Verzamelde literatuurstudies
over voor- en nadelen
van het breken respectievelijk delen van tabletten

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International Journal of Pharmaceutics 466 (2014) 44–51

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

The accuracy, precision and sustainability of different tec"hniques for tablet subdivision: Breaking by hand and the use of tablet splitters or a kitchen knife☆

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ARTICLE INFO

Article history:
Received 7 November 2013
Received in revised form 13 February 2014
Accepted 15 February 2014
Available online 21 February 2014

Keywords:
Medication
Pharmaceutical development
Tablet splitting
Break mark
Weight uniformity

ABSTRACT

Introduction: Tablets are frequently subdivided to lower the dose, to facilitate swallowing by e.g. children or older people or to save costs. Splitting devices are commonly used when hand breaking is difficult or painful.
Methods: Three techniques for tablet subdivision were investigated: hand breaking, tablet splitter, kitchen knife. A best case drug (paracetamol), tablet (round, flat, uncoated, 500 mg) and operator (24-year student) were applied. Hundred tablets were subdivided by hand and by three devices of each of the following types: Fit & Healthy, Health Care Logistics, Lifetime, PillAid, PillTool, Pilomat tablet splitter; Blokker kitchen knife. The intra and inter device accuracy, precision and sustainability were investigated. The compliance to (adapted) regulatory requirements was investigated also.
Results: The accuracy and precision of hand broken tablets was 104/97% resp. 2.8/3.2% (one part per tablet considered; parts right/left side operator). The right/left accuracies of the splitting devices varied between 60 and 133%; the precisions 4.0 and 29.6%. The devices did not deteriorate over 100-fold use. Only hand broken tablets complied with all regulatory requirements.
Conclusion: Health care professionals should realize that tablet splitting may result in inaccurate dosing. Authorities should undertake appropriate measures to assure good function of tablet splitters and, where feasible, to reduce the need for their use.

1. Introduction

Breaking or splitting tablets is common practice in inpatient and outpatient settings as it increases dosing flexibility, facilitates swallowing and allows cost savings for both patients and health-care providers (Dormuth et al., 2008; Ekedahl, 2013; Freeman et al., 2012b; Quinzler et al., 2006; Rodenhuis et al., 2004).

However, patients have indicated that it may be difficult and painful to break tablets by hand (Ekedahl, 2013; van Santen et al., 2002). This is especially true for patients with impaired hand function such as (school) children and older people (patient populations who often need lower doses or dose titrations) or patients suffering from rheumatic diseases (Barends et al., 2005; Ekedahl, 2013; Mehuys et al., 2012; Wilson et al., 2001). Ekedahl for example concluded that 31% of Swedish adult patients experienced

Abbreviations: EMA, European Medicines Agency; EDQM, European Directorate for the Quality of Medicines; MEB, Medicines Evaluation Board; SmPC, Summary of product characteristics; Ph. Eur., European pharmacopoeia; KNMP, Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie (Royal Dutch Society for the advancement of Pharmacy); FDA, US Food and Drug Administration.

☆ Disclaimer: The opinions in this article are only those of the authors. This article is not intended to reflect the opinion of the Medicines Evaluation Board in the Netherlands (MEB) nor any of the working parties or scientific committees of the European Medicines Agency (EMA).

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http://dx.doi.org/10.1016/j.ijpharm.2014.02.031
0378-5173/

difficulties subdividing tablets, Mehuys et al. concluded that 29.7% of home dwelling older adults experienced difficulties when they had to subdivide tablets and Barends et al. concluded that older Dutch people were far less able to break tablets by hand than healthy adult volunteers. Wilson et al. reported a mean pain score of 3.2 out of 10 for generic anti-diabetic tablets when hand broken by older American citizens.

As breaking tablets by hand is often considered problematic, the use of tablet splitters is common. This is especially true for tablets that do not have a break mark. Other splitting devices such as kitchen knives or scissors may be applied as well (Ekedahl, 2013; Quinzler et al., 2009; Tahaineh and Gharaibeh, 2012).

Indexed publications on the accuracy and precision of tablet splitters, kitchen knives or other devices that may be applied to subdivide tablets (all further referred to as "splitting devices") generally show limitations as e.g. uncertainties about the type of device, operator or weight measurements applied; random selection of the device and tablet types; only small numbers of tablets/devices tested and the lack of data comparison between tablets subdivided with a splitting device and those broken by hand. Consequently, it is not yet possible to draw a firm conclusion on the suitability e.g. accuracy, precision, sustainability of splitting devices as an alternative to breaking tablets by hand.

In addition, the conclusion of Freeman's review that tablet splitters may not subdivide tablets into equal doses and that the accuracy of tablet splitters may depend on the type of splitter, tablet or operator applied needs further consideration as the review shows methodological shortcomings such as no information on search profile, data extraction and data analysis and no quality evaluation of the included publications (Freeman et al.,2012a).

Therefore, the primary objective of this study was to evaluate the accuracy, precision and sustainability of commercially available tablet splitters and a kitchen knife as an alternative to breaking tablets by hand. The secondary objective was to evaluate if tablets subdivided with a splitting device were likely to comply with current regulatory requirements for break marked tablets (European Directorate for the Quality of Medicines (EDQM), 2013; European Union, 2001; US Department of Health and Human Services, FDA, 2011).

2. Material and methods

2.1. Study design

In this experiment three techniques for tablet subdivision were compared: hand breaking, tablet splitter, and kitchen knife. A hundred paracetamol tablets were hand broken by a single operator, by three devices of several types of tablets splitters or by three kitchen knives of the same type. The suitability of the techniques was compared by evaluation of the accuracy, precision, sustainability and regulatory compliance of the weight measurements. The experiment did not require ethical approval according to the Dutch Medical Research Involving Human Subjects Act (WMO). The study protocol was approved by the Committee on Clinical Practice of the Medicines Evaluation Board in the Netherlands.

2.2. Methodology

All data were collected between November 2012 and February 2013.

Splitting devices: Tablet splitters were included if these were available in the standard assortment of at least two community pharmacies or drug stores in Utrecht, the Netherlands. The pharmacies were identified via a list of the Dutch Society for the Advancement of Pharmacy (KNMP) whereas drug stores were identified via the Dutch Trading Register or the internet. Thirty five pharmacies and 59 drug stores were identified, selling 15 types of tablet splitters. Five tablet splitters were excluded because these were not in the pharmacy's standard assortment and another four because these were sold in one establishment only. Six types of tablet splitters were included. The kitchen knife was purchased at a household warehouse in Utrecht (national chain) (Fig. 1).

Drug compound and tablet trade mark: Marketing authorisations for round, flat, uncoated, break marked 500 mg paracetamol tablets were identified with help of the database of the Medicines Evaluation Board in the Netherlands (MEB). The retrieved tablet authorisations were categorized in groups with authorisations for tablets sharing the same manufacturer and

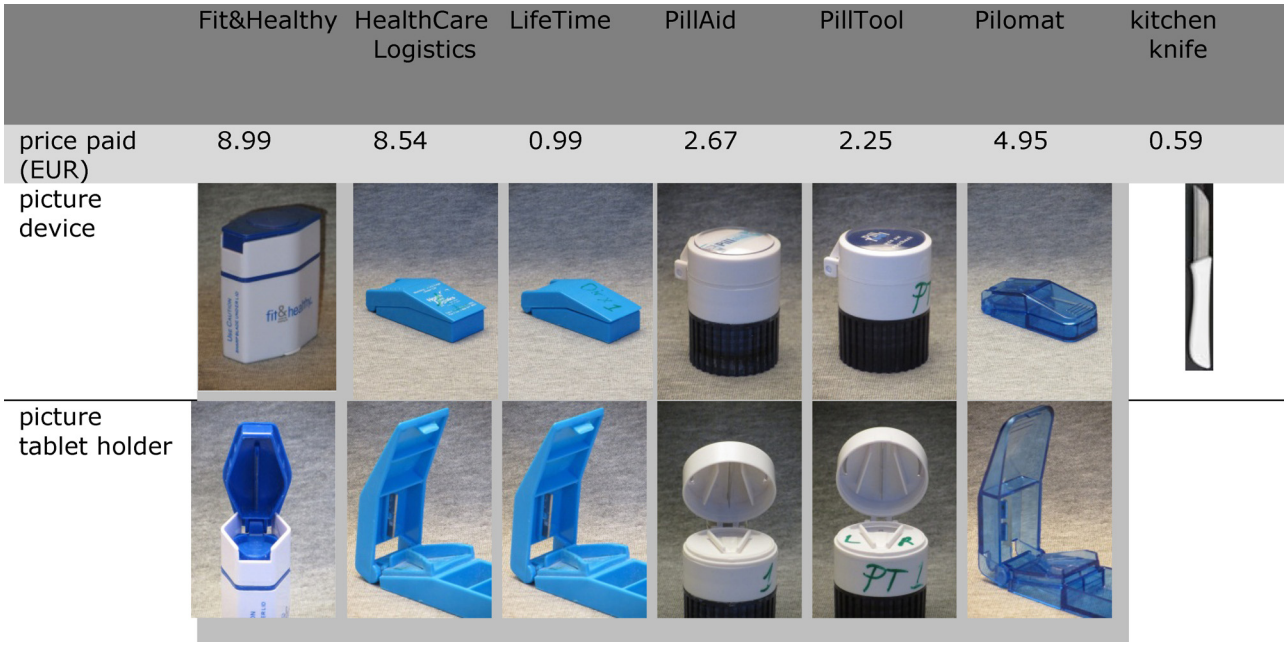

Fig. 1. Characteristics splitting devices.

excipient composition. For each group, the diameter and thickness (household vernier calliper gauge) and resistance to crushing (Heberlein diametral compression test apparatus; 2E/205 Schleuniger Productronic AG, Solothurn, Switserland) of the commercially available tablets was assessed ($n = 10$). The results from all groups were compared and a tablet with "average" characteristics i.e. Paracetamol Centrafarm RVG 53055 was selected.

Operator: A best case operator with adequate understanding of the study principles and good hand function was selected i.e. a healthy, female, 24-years old master student in her 5th year of pharmaceutical sciences at Utrecht University (MD).

Weight measurements: The weight of 100 intact tablets was determined (Mettler Toledo AG64 analytical balance). The average weight (further referred to as "theoretical intact tablet weight") and standard deviation were 619.775 mg; 4.152 mg. The theoretical weight of a tablet part was calculated as half the theoretical intact tablet weight i.e. 309.888 mg.

2.3. Data collection

The key characteristics of each tablet splitter (name, appearance, shape tablet holder, position tablet holder, shape knife, price), kitchen knife (name, appearance) were extracted. The weights of both parts of each subdivided tablet were determined (Mettler Toledo AG64 analytical balance). It was recorded whether a tablet part resulted from the right or left side of the splitting device or the operator's hands.

2.4. Data analysis: accuracy, precision, sustainability

Five approaches were used to the selection of the tablet parts to be considered in the data analysis: 1) The intra device accuracy was calculated as the percent of the average weight of 100 parts obtained from the right side of a splitting device (where the parts from the left side were rejected) versus the theoretical weight of a tablet part. The inter device accuracy was calculated in the same way as the average weight of 300 parts obtained from the right side of the three devices of the same type (where the parts from the left side were rejected). The intra and inter precision were calculated likewise as the relative standard deviations of the weight measurements; 2) As approach 1, however now the left sides were considered and the right sides rejected; 3) As approach 1, however the tablet parts were no longer grouped depending on the side of the splitting device these originated from, but in those weighing the least or most following subdivision. The tablets with the lowest weight were considered (and those with the highest weight rejected); 4) As approach 3, however now the tablets with the highest weight were considered (and those with the lowest weight rejected); 5) As approach 1, however now both parts from each tablet were considered.

All results were compared with those of tablets broken by hand (multiple t-tests; analysis of variance with type of splitting device and device as factors, with the latter nested within the former, followed by Dunnett's posthoc analysis). The sustainability of the splitting devices over 100-fold use was inspected visually (integrity of the device, trends in weight variability).

2.5. Regulatory requirements

Uniformity of weight of tablet parts as adapted from Ph. Eur. 478 subdivision of tablets: Both parts of the same tablet were considered. It was evaluated if the weight of the parts complied with the following criterion "at least 194 of 200 parts resp. 582 of 600 parts should be within 85–115% and all parts within 75–125% of the theoretical weight of a tablet part" (European Directorate for the Quality of Medicines (EDQM), 2013).

Simulated assay as adapted from Directive 2001/83/EC: It was evaluated if the mean weight of parts obtained from the same side of the operators hands or a splitting device would be within 95.0–105.0% of the theoretical weight of a tablet part i.e. if the accuracy would be 95.0–105.0% (European Union, 2001).

Loss of mass as adapted from FDA: For each tablet, the loss of mass was calculated by subtracting the weight of the right and left part of a tablet from the theoretical intact tablet weight. The loss of mass of each tablet should be smaller than 3.0% (US Department of Health and Human Services, FDA, 2011).

3. Results

3.1. Accuracy, precision, sustainability

The intra and inter accuracies of tablets broken by hand or a splitting device are displayed in Table 1. The accuracy of hand broken tablets was 104/97% (right/left side operator i.e. R/L); 96/104% (lowest/highest weight i.e. L/H); 100% (both sides). The accuracies of the splitting devices varied between 60 and 133% (R/L); 59 and 133% (H/L); 94 and 100% (both). The largest difference between sampling R/L versus L/H was observed for the Fit & Healthy device 1: 96.3/93.6% (R/L) resp. 81.4/108.5% (L/H). Results for the intra and inter precision are displayed in Table 2. The precision for hand broken tablets varied between 2.4% (lowest parts considered) and 4.7% (both parts considered). The precision of tablets subdivided by a splitting device was 29.6% at the maximum when parts from one side were considered only (Fit & Healthy device 2; left parts). Overall, the accuracy and precision of three types of tablet splitters (Fit & Healthy, Lifetime, PillAid) were less favourable than the kitchen knife.

Comparing all parts derived from the same side of a splitting device with those broken by hand from the corresponding side of the operator, Dunnett's posthoc analysis showed a statistical difference in the following cases when the tablets were grouped per side of device: Lifetime (both $p < 0.000$), PillTool ($p = 0.032$; $p = 0.001$), Health Care Logistics ($p = 0.002$; $p < 0{,}000$), PillAid (right $p = 0.001$) and Fit & Healthy splitter (left $p \leq 0\,0.000$).

Visual evaluation of the splitting devices did not show any deterioration over 100-fold use and the devices still worked. In one single case (PillAid device 2) the knife detached from the device during the experiment. The knife was put back again anticipating that this approach would also be carried out by patients. No trends in weight variability of the tablet parts were observed over 100-fold use (Fig. 2).

3.2. Regulatory requirements

The uniformity of weight of tablet parts broken by hand or subdivided by the Health Care Logistics or PillTool splitter types complied with the adapted Ph. Eur. test. The other types of devices did not comply (Table 3).

The accuracy of tablet parts broken by hand and those subdivided by the Health Care Logistics, PillAid, PillTool or Pilomat tablet splitter complied with the simulated assay criteria of 95.0–105.0% when the parts were sampled from the same side of the operator and when the overall type of tablet splitter was considered (Table 3). When the 21 devices were considered separately and when all five approaches to the selection of the tablet parts were taken into consideration, then only tablets broken by hand and by the Health Care Logistics splitter complied in every case (Table 2).

Tablets broken by hand complied with the adapted FDA test for loss on mass of maximum 3% (Table 3) whereas no of the seven types of splitting devices complied. When the 21 devices were considered separately, also tablets subdivided by the Pilomat device 1 complied (data not shown).

Table 1
Intra and inter accuracy of paracetamol tablets broken by hands ($n = 100$), several types of tablet splitters or a kitchen knife ($n = 100$ per device; three devices per type investigated).

Splitting technique		Number device tested	Accuracy (%) for five different approaches to the selection of the tablet parts to be considered				
			Right side only	Left side only	Lowest weight of both parts only	Highest weight of both parts only	Both sides
Hand broken		nap	103.8	96.6	96.3	104.1	100.2
Tablet splitter	Fit & healthy	1	96.3	93.6	81.4	108.5	95.0
		2	108.0	80.5	74.6	113.9	94.2
		3	102.5	86.9	80.2	109.2	94.7
		all	102.3	87.0	87.8	101.5	94.6
	Health care logistics	1	99.2	100.3	96.4	103.1	99.8
		2	95.6	103.5	95.1	104.1	99.6
		3	98.5	100.6	96.2	102.9	99.5
		all	97.8	101.5	95.9	103.4	99.6
	Lifetime	1	69.0	125.0	69.0	125.0	97.0
		2	78.3	115.6	78.3	115.7	97.0
		3	113.1	82.6	82.6	113.2	97.9
		all	86.8	107.7	86.8	107.7	97.3
	PillAid	1	59.9	132.5	59.3	133.1	96.2
		2	117.2	77.6	76.8	118.0	97.4
		3	119.6	78.3	77.2	120.7	98.9
		all	98.9	96.1	95.7	99.3	97.5
	PillTool	1	98.2	100.8	95.4	103.6	99.5
		2	100.3	99.1	94.8	104.6	99.7
		3	98.9	100.9	96.0	103.8	99.9
			99.1	100.3	95.4	104.0	99.7
	Pilomat	1	101.2	98.1	94.9	104.4	99.7
		2	101.5	98.0	95.3	104.2	99.8
		3	101.5	97.5	94.7	104.3	99.5
		all	101.4	97.9	97.9	101.3	99.6
Kitchen knife	Blokker own brand	1	100.4	94.0	87.5	106.9	97.2
		2	98.34	94.5	83.2	109.6	96.4
		3	104.9	92.6	88.3	109.2	98.7
		all	101.2	93.7	93.3	101.6	97.5

Table 2
Intra and inter precision of paracetamol tablets broken by hands ($n = 100$), several types of tablet splitters or a kitchen knife ($n = 100$ per device; three devices per type investigated).

Splitting technique		Number device tested	Precision (% RSD) for five different approaches to the selection of the tablet parts to be considered				
			Right parts only	Left parts only	Lowest weight of both parts only	Highest weight of both parts only	Both parts
Hand broken		nap	2.78	3.15	2.74	2.43	4.66
Tablet splitter	Fit & healthy	1	20.31	20.74	21.31	8.52	20.52
		2	16.90	29.59	25.81	9.91	26.79
		3	16.69	23.14	20.58	10.04	21.33
		all	18.47	25.06	24.56	19.46	22.99
	Health care logistics	1	4.52	4.62	3.48	2.78	4.59
		2	4.46	3.99	3.96	3.18	5.78
		3	4.42	4.36	3.48	2.37	4.50
		all	4.73	4.54	3.70	2.85	4.98
	Lifetime	1	14.55	5.68	14.47	5.65	30.28
		2	12.84	6.06	12.75	6.00	21.28
		3	6.72	8.75	8.71	6.69	17.39
			24.42	18.13	24.42	18.13	23.54
	PillAid	1	25.67	11.16	24.94	9.16	40.96
		2	13.56	24.72	23.67	12.58	27.22
		3	8.76	14.24	11.13	6.63	23.60
		all	31.37	31.21	31.12	31.40	31.30
	PillTool	1	5.22	5.45	3.90	3.40	5.49
		2	5.43	6.20	3.69	2.64	5.84
		3	5.02	5.03	3.68	2.96	5.11
			5.29	5.61	3.80	3.05	5.48
	Pilomat	1	6.04	6.20	4.51	3.81	6.31
		2	5.99	5.99	4.70	3.92	6.24
		3	6.03	6.35	4.86	3.89	6.49
		all	6.00	6.12	6.45	5.91	6.40
Kitchen knife	Blokker own brand	1	11.88	15.10	11.97	7.47	13.85
		2	18.59	19.23	18.40	8.25	18.96
		3	12.39	14.82	12.79	8.48	14.88
		all	14.70	16.50	17.71	13.24	16.03

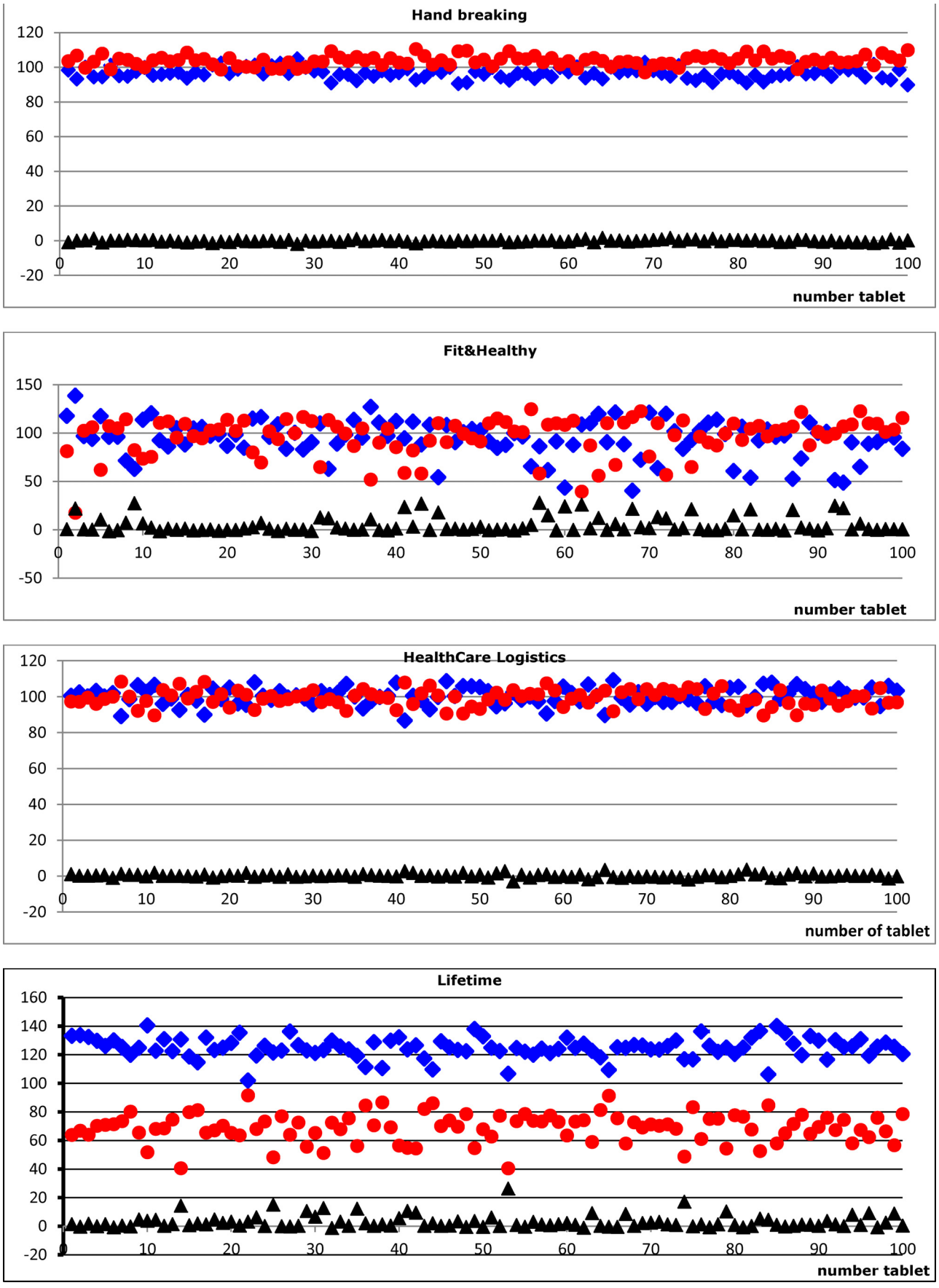

Fig. 2. Percent active substance for tablets subdivided by hand and three different types of tablet splitters (red left parts, blue right parts, black loss of mass). For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.

Table 3
Compliance to regulatory requirements of paracetamol tablets following subdivision by three techniques: hand breaking, tablet splitter and kitchen knife (100 tablets subdivided by hand; 300 tablets subdivided per type of device).

Splitting technique		Uniformity of weight as adapted from Ph. Eur. 478 subdivision of tablets[a]						Assay simulated as adapted from Directive 2001/83/EC[b]			Loss of mass as adapted from FDA[c]	
		Number of tablet parts (from both sides) in the specified range					Complies	Mean weight parts from				
		<75% (*n*=)	75–85% (*n*=)	85–115% (*n*=)	115–125% (*n*=)	>125% (*n*=)		Right side (%)	Left side (%)	Complies	>3.0% (*n*=)	Complies
Hand broken		0	0	200	0	0	yes	103.8	96.6	yes	0	yes
Splitting devices	Fit & Healthy	110	46	360	58	26	no	102.3	87.0	no	128	no
	Health care logistics	0	2	598	0	0	yes	97.8	101.5	yes	7	no
	Lifetime	148	91	173	126	62	no	86.8	107.7	no	88	no
	PillAid	149	91	149	88	123	no	98.9	96.1	yes	83	no
	PillTool	0	2	598	0	0	yes	99.1	100.3	yes	6	no
	Pilomat	1	8	584	7	0	no	101.4	97.9	yes	5	no
Kitchen knife	Blokker own brand	48	47	460	38	7	no	101.2	93.7	no	74	no

[a] Both parts of the same tablet were considered. Not less than 194 parts of 200 parts and 582 of 600 parts should be within 85–115% and all parts within 75–125% of the theoretical (nominal) halved tablet weight (Ph. Eur. requirements: break 30 tablets by hand; take 30 parts at random and reject the other parts; not less than 29 parts should be within 85–115% and all parts within 75–125%).
[b] Only parts from right / left side of the operators hands or from the right / left side of the device were considered. The average weight of the 100/300 parts should be 95.0–105.0% of the theoretical halved tablet weight.
[c] Loss of mass of each tablet not more than 3.0% of the theoretical intact tablet weight.

4. Discussion

The accuracy, precision and sustainability of three techniques for the subdivision of paracetamol tablets were investigated: hand breaking ($n=1$ operator), tablets splitter ($n=6$ types, 3 devices for each type tested), kitchen knife ($n=1$ type, 3 devices tested). The results showed large differences and were generally best for hand broken tablets. It was also tested whether the tablet parts complied with three regulatory requirements adapted to the conditions of this experiment: Ph. Eur. subdivision of tablets; assay; FDA loss of mass. Only hand broken tablets complied with all three tests. The devices did not deteriorate over 100-fold use. Any impact of the type of operator or tablet characteristics on the superiority of hand breaking over the use of a splitting device is left for future research.

The methodology was specifically developed for the aim of this experiment. In order to limit bias to the selection of the types of tablet splitters to be considered, we evaluated all splitters that were likely to be used by patients living in a specified region of the Netherlands (Utrecht) and those that could be purchased form either a community pharmacy or a drug store. Currently, tablet splitters are not considered as a medical device. This implies that their manufacture is outside the control of a Notified Body i.e. the consistent performance between several devices of the same type may not be adequately assured. Therefore, we decided to evaluate three devices of the same type i.e. to study the intra as well as the inter device accuracy and precision. In addition, there is also no assurance that the devices will not deteriorate over repeated use. We therefore decided to evaluate the performance of each device over common dispensing periods and dosing frequencies i.e. 100 tablets (equalling 3 months twice daily dosing and 2 months trice daily dosing of a half tablet).

Paracetamol was selected as the drug of choice because it is frequently used by a wide variety of patients in the Netherlands; because the dose for children and older people is often achieved by subdivision of the "standard" 500 mg immediate release tablet; because the geometry of this "standard" tablet (round, flat, uncoated) favours easy breaking and because the handling of large numbers of paracetamol tablets would not involve a risk to the operator's health (van der Steen et al., 2010). In order to avoid any bias due to the evaluation of a paracetamol tablet with outlier "characteristics", we carefully selected a trade mark with "average characteristics".

There is substantial evidence that tablets may not always break into two parts i.e. that tablets may break into several pieces or show grinding. In such cases the difference in the weight of one tablet part to the half of the intact tablet weight may differ from the other part and consequently, the accuracy and precision may depend on the selection of the tablet parts that are considered in the data analysis. In order to evaluate any impact of the selection of the tablet parts on the results of this experiment, we decided to evaluate five pre-defined approaches. These approaches were based on the following considerations 1) the possibility to study any impact of the key characteristics of the splitting devices on the accuracy, precision, sustainability of the devices; 2) current clinical practices where large numbers of tablets are broken at the same time and put back into the container as if they were single dose units; 3) current clinical practices where both parts from the same tablet may not be given to the same patient.

In this experiment, the accuracies and precisions were calculated on basis of the theoretical weight of an intact tablet rather than the weight of each tablet itself prior to subdivision. This approach was considered acceptable in view of the low variability in the weight of 100 intact tablets (0.7%).

The differences in the accuracy and precision of the tablet splitters could not be explained by their design and price: although some splitters looked the same, their accuracy and precision were quite different and the most expensive tablet splitters were not always the best. One of the tablet splitters had a knife that was sharp on one side only. By visual examination, it turned out that the sharp end was at the left side for two splitters and at the right side for the third splitter. A correction for this aspect was implemented in the General Linear model and Dunnet's analysis.

This experiment showed that tablet splitters and a kitchen knife may not accurately and precisely subdivide tablets into equal parts. This result is consistent with findings from other authors (Freeman et al., 2012a; Shah et al., 2010; Tahaineh and Gharaibeh, 2012). However, in contrary to their studies, this experiment tested several types of tablet splitters and a kitchen knife over 100-fold use applying a best case drug, tablet and operator, and allowing comparison of the results with those of tablets broken by hand. In addition, three devices of each type were considered as well as the impact of five different approaches to the selection of the tablet parts.

Health care professionals may consider to study the dosing accuracy and precision of a specific type of tablet splitter in relation to a specified medicine if such a medicine must be subdivided by a splitting device. However, such studies will only be of any value to the patient when the results show consistent and acceptable intra

device accuracies and precisions and when the results do not depend on the selection of the tablet parts that were considered in the data analysis. This investigation showed that these conditions were only met by the Health Care Logistics splitter when applying a range of 95.0–105.0 for accuracy and a maximum of 5.0% for precision, and also by the PilTool and Pilomat splitter when applying a slightly lower treshold for accuracy of 94.7% and a higher threshold of 6.5% for the precision.

This experiment has some limitations. Firstly, only a "best case" tablet with "average" hardness was studied. It was assumed that smaller, convex, very soft or very hard tablets would be more difficult to break into two equal parts by hand than the selected paracetamol tablets and that such smaller, convex, very soft, or very hard tablets would also be more difficult to subdivide with a splitting device. The included tablet splitters were dispensed without any restrictions to the type of tablets for which the splitters could be used. We therefore considered that the tablet splitters and the kitchen knife should be suitable for any tablet type, especially "best case". Thus, the impact of tablet geometry and hardness on the accuracy and precision of splitting devices is left for future research for those with adequate accuracy and precision with a best case tablet only.

Secondly, this experiment was conducted by a "best case" operator. However, the ability to break tablets by hand and correctly use a splitting device is known to decline with certain patient characteristics such as impaired hand function, limited visibility or mental retardation. It is unlikely that the effect of such changes on the accuracy and precision of tablet subdivision will show a similar pattern between the three techniques e.g. people with trembling hands may be well able to use a tablet splitter but not a kitchen knife. The evaluated tablet splitters were dispensed without any restrictions to the operator. In the Netherlands, tablet splitters and kitchen knives are commonly used by health care professionals and caregivers who need to subdivide large numbers of tablets. We therefore considered that splitting devices should be suitable for any patient population. Thus the impact of patient characteristics on the accuracy and precision of splitting devices is left for future research for those showing adequate accuracy and precision with a best case operator only.

None of the splitting devices meet the regulatory requirements as adapted for this experiment. As our criteria are reasonable and our results cannot be explained by a poor performing operator, we consider that the device industry should develop better tablet splitters.

In view of the high potential of intended or unintended off-label breaking, we advise the pharmaceutical industry to assure precise and accurate breaking of all break marked tablets irrespective of their posology and user instruction i.e. irrespective as to whether breaking needs to be approved by the regulatory authorities or not. In addition, the pharmaceutical industry is recommended to assure that the majority of the indicated patient populations will be able to break tablets by hand without any relevant difficulties or discomfort.

We urge authorities to undertake measures to assure that only tablet splitters with an acceptable accuracy, precision and sustainability can enter the market. In addition, the ease, accuracy and precision of breaking tablets by hand should be evaluated during the licensing process (new applications) and appropriate measures should be considered for break mark tablets that are already on the market. The development of a standardised methodology for the ease of tablet breaking would be welcomed. Such a test may be included in the Ph. Eur. In addition, incentives may be aimed at the development and authorisation of additional dosage forms that allow flexible dosing and easy swallowing such as oral liquids, sprinkles and mini-tablets (Klingmann et al., 2013; van Riet-Nales et al., 2013).

The development of an international harmonized methodology for the subdivision of tablets with a tablet splitter is recommended also. As this experiment showed that the accuracy and precision may depend on the selection of the tablet parts to be considered in the data analysis, such a test preferably includes a predefined approach to the selection strategy.

Health care professionals, patients and caregivers should realize that tablet splitting may result in dosing inaccuracies, which may have an effect on clinical outcomes. They should also remember that the subdivision of tablets is likely to go with any loss of mass and that even a small loss ("dust") may be potentially harmful to the patient's environment depending on the type of active substance that the tablet contains e.g. in case of subdivision of mercaptopurin tablets for paediatric dosing in a domestic setting (Breitkreutz et al., 2007). Thus, patients should tell their nurses, doctors and pharmacists that they have difficulties (hand) breaking or swallowing tablets. Together they should consider alternative treatment options. These considerations may result in the continuation of the tablet splitter, however if so, the best available device should be used.

5. Conclusions

The accuracy and precision of none of the investigated tablet splitters and kitchen knife was equivalent to hand breaking when applying a best case drug, tablet and operator. Health care professionals and patients should realize that tablet splitting may result in inaccurate dosing. Authorities should undertake measures to assure good function of tablet splitters and, where feasible, to reduce the need for their use. The devices did not deteriorate over 100-fold use.

Financial disclosure

This study was sponsored by the Medicines Evaluation Board in the Netherlands.

Conflicts of interest

Yechiel Hekster, Bart van den Bemt are members of the Committee on Clinical Practice of the Medicines Evaluation Board in the Netherlands. Yechiel Hekster, Agnes Nicia, Kim Notenboom and Diana van Riet are all experts for the European Medicines Agency (EMA).

Contributor statement

- Bart van den Bemt: Dr. Van den Bemt supervised the conceptualization, design and data analysis of the study, reviewed the manuscript and approved the final version as submitted.
- Myrthe Doeve: Mrs. Doeve assisted in the design of the study, took the role to break, split and weigh the tablets, analysed the data, assisted in the drafting of the original manuscript and approved the final manuscript as submitted.
- Yechiel Hekster: Prof. Hekster initiated this study, supervised the conceptualization, design and data analysis of the study, reviewed the manuscript and approved the final version as submitted.
- Agnes Nicia: Mrs. Nicia was involved in the design of the study, supervised the identification of the tablets and tablet splitters, provided support to the data analysis, assisted in the drafting of the original manuscript and approved the final version as submitted.
- Kim Notenboom: Mrs. Notenboom provided support to the design of the study, reviewed the manuscript and approved the final version as submitted.
- Diana van Riet-Nales: Mrs. Van Riet initiated this study, coordinated the conceptualization, design and data collection

of the study, provided support to the data analysis, drafted the original manuscript and approved the final version as submitted.
- Steven Teerenstra: Dr. Teerenstra supervised the data analysis, reviewed the manuscript and approved the final version as submitted.

Acknowledgements

We like to acknowledge the contribution of Dr. Christien Oussoren for her support to MD.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.aca.2013.12.001 http://dx.doi.org/10.1016/j.aca.2013.12.001.

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International Journal of Pharmaceutics 545 (2018) 57–63

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

How close is the dose? Manipulation of 10 mg hydrocortisone tablets to provide appropriate doses to children

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ARTICLE INFO

Keywords:
Hydrocortisone
Tablet
Manipulation
Age-appropriate

ABSTRACT

This study explores the methodology advised by healthcare professionals and the methods used by parents/carers to identify whether there is a best practice method for manipulation of 10 mg hydrocortisone tablets to provide an accurate dose to children. Bespoke surveys were used to identify methods recommended and used in manipulation of tablets. Hydrocortisone tablets were manipulated to provide a specified dose by both naïve participants and parents/carers. The accuracy of manipulation was assessed using HPLC analysis. Competed surveys were received from 159 parent/carers reporting doses that ranged from 0.25 to 15 mg. Parents/carers most commonly reported splitting the tablet and administering the solid fraction; however more than 30% of those reporting physically splitting tablets were preparing doses that were not simply halving or quartering tablets. In a naïve population the dose accuracy, defined as percent of doses within 20% of the theoretical dose ranged from 57 to 58% depending on the tablet brand and the method of manipulation used. Almost three-quarters (74.1%) of parent/carers (n = 27) were able to produce a dose within 20% of the theoretical value and the most accurate method was to split tablets and administer the solid fraction. This study shows that a lack of age-appropriate medicines results in children being at risk of sub-optimal dosing.

1. Introduction

The lack of age-appropriate medicines that are specifically designed for children results in the need to manipulate adult medicinal products to provide the required dose to children (Kayitare et al., 2009; Skwierczynski and Conroy, 2008). The manipulation of medicines (e.g. crushing of tablets) renders its use unlicensed. Previous reports state that up to 29% of medicines are manipulated within ward and home settings (Venables et al., 2015). There is limited evidence and a lack of understanding about the range of manipulations that occur in practice (Richey et al., 2017). The risks of error to neonatal and paediatric patients, as a result of manipulation has previously been highlighted (Conroy et al., 2007).

In this study the term manipulation is defined as the physical alteration of a tablet for the purpose of extracting the required proportion of the drug dose. Previously different definitions of "modification" and "manipulation" have been used (EMA, 2013; Ernest et al., 2012). There is currently no standard method(s) for an acceptable and safe way to manipulate tablets, although guidance is available from several sources. Medicines for Children is a partnership between Wellchild; Royal College of Paediatrics and Child Health and Neonatal and Paediatric Pharmacists Group; that provides advice for parents on giving a part dose from a tablet or capsule (http://www.medicinesforchildren.org.uk/part-dose-tablet-or-capsule, accessed 15th November 2017). MODRIC: Manipulation of Drugs Required in Children provides guidance for health care professionals (http://www.alderhey.nhs.uk/wp-content/uploads/MODRIC_Quick_Reference_Guide.pdf, accessed 26th March 2018). The NEWT Guidelines provide advice to healthcare professionals on the administration of medication to patients with enteral feeding tubes or swallowing difficulties and can provide advice on manipulation of solid dosage forms (www.newtguidelines.com, accessed 26th March 2018 (subscription required)).

Although guidelines exist for healthcare professionals, the methods that parents use to manipulate tablets may vary depending upon: the

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https://doi.org/10.1016/j.ijpharm.2018.04.054
Received 24 January 2018; Received in revised form 24 April 2018; Accepted 25 April 2018
Available online 26 April 2018
0378-5173/

dose required; the advice provided by their consultant or other health care professional; the product(s) they are provided with; and the equipment they have to hand. Inter-individual variability may also occur, where different carers use different techniques for the same patient.

Tablets can be manipulated using different methods; splitting, crushing or dispersing. Verrue et al., compared tablet splitting devices and demonstrated that splitting devices were superior to knives or scissors yet there were still large dose deviations (Verrue et al., 2011). The accuracy of tablet splitting may vary with different devices, users, and tablet shapes (Abu-Geras et al., 2017; van Riet-Nales et al., 2014). Size, shape, and the presence or absence of tablet score lines can affect the content uniformity and weight variation of split tablets (Ciavarella et al., 2016). European pharmacopoeial guidelines on subdivision of tablets require that the parts meet the following criteria "at least 194 of 200 parts resp. 582 of 600 parts should be within 85–115% and all parts within 75–125% of the theoretical weight of a tablet part" (EDQM, 2013).

Dispersion of tablets into a known volume of liquid then withdrawal of the required volume is also associated with variability in dosing (Abu-Geras et al., 2017). Insoluble drugs can be particularly challenging as the drug needs to be homogeneously dispersed within the liquid as it will not form a solution. Issues with unhomogenous liquids produced by dispersion of insoluble drugs was highlighted by Standing and Tuleu; they suggested that inclusion of a suspending agent would be beneficial rather than mixing directly with water (Standing and Tuleu, 2005). Even dispersible aspirin tablets were not superior to crushing and dispersing a conventional aspirin tablet as inconsistent doses were found when sampled from different depths within the liquid produced following dispersion of the tablet (Broadhurst et al., 2008). It has previously been reported that scored hydrocortisone tablets are harder than an unscored alternative and therefore do not disperse as readily (Saimbi et al., 2016).

Changes in the bioavailability of crushed or split tablets that are designed to be swallowed whole has been well documented (e.g. (Argenti et al., 2001; Cleary et al., 1999; Dodds Ashley et al., 2007; McNeely et al., 2013; Nunn, 2003)). Bioavailability of tablets can be affected by their manipulation in cases where integrity of formulation is essential for controlled release of the drug substance. For immediate release tablets this is less significant yet changes in the overall surface area of the solid dosage form can change the rate of dissolution of medicines. Furthermore manipulations that require crushing or splitting a tablet can affect the overall exposure due to inaccuracies in the dose obtained. Thus, there is a risk of under- or over- dosing due to imprecise measurements within a manipulation and the change in physical dimensions of the resulting product.

Orally administered hydrocortisone is used widely in paediatric endocrinology for the treatment of primary adrenal disorders such as congenital adrenal hyperplasia (CAH), adrenal hypoplasia and Addison's disease and secondary adrenal insufficiency due to hypothalamic and pituitary disorders. Hydrocortisone replacement therapy is essential in children with CAH and adrenal insufficiency to control androgen excess and optimise their growth and development. Hydrocortisone is used to mimic glucocorticoid levels of a healthy child and the best therapy will be one that matches the circadian rhythm of cortisol (Ng and Stepien, 2017). The rapid half-life of hydrocortisone means that frequent administration of low doses best matches the normal physiological endogenous cortisol levels. Hydrocortisone is administered to children according to body surface area three to five times daily (Bornstein et al., 2016). The dose is carefully titrated and the low doses involved mean that dosing accuracy becomes important in providing optimised glucocorticoid levels for these children. There is currently a wide range of oral hydrocortisone treatment regimens administered to neonates, infants and children with adrenal insufficiency, with the dosages varying from 0.5 to 5 mg; the most common being 1 and 2 mg per dose (Whitaker et al., 2015). There are long term consequences of poor hydrocortisone therapy in childhood as adult CAH patients who remain short may have been underexposed as children (Han et al., 2014).

During this research project only hydrocortisone tablets were licensed for use in children to treat endocrine disorders (BNF-C, 2017), however, there are "Special" liquid products prepared as a suspension although these have short shelf-lives and can be costly. Many children used manipulated 10 mg hydrocortisone tablets to obtain the necessary dose (Richey et al., 2013). The unmet need for a licensed infant preparation of hydrocortisone which allows dosing from 0.5 mg up to 2 mg has previously been identified based on both dose and poor palatability of the crushed tablets (Kauzor et al., 2014; Orlu-Gul et al., 2013; Whitaker et al., 2015). In December 2017 a novel hydrocortisone formulation was approved 0.5 mg, 1.0 mg, 2.0 mg and 5.0 mg granules in capsules for opening (EMA, 2017).

Many studies that have investigated the accuracy of manipulated tablets have used medical/pharmacy students, nurses, pharmacists as the population yet an experienced person may be better able to prepare an accurate dose from a manipulated tablet (Abu-Geras et al., 2017). This study seeks to explore current methods of manipulation reported and used by parents and carers to identify whether there is a method that is more likely to provide the most accurate dose. A population of naïve adults will be compared to experienced parents/carers to note any differences in results based on population.

2. Aims and objectives

The aim of this study was to determine whether parents/carers can prepare accurate doses of hydrocortisone for the child in their care from manipulation of 10 mg tablets.

The objectives of this study included; identification of the methods recommended to parents and carers by health care professionals to manipulate hydrocortisone tablets to deliver the appropriate dose for the child in their care; determination of the methods (and tools) used by parents and carers in preparing doses of hydrocortisone for the child in their care; and to quantify the accuracy of doses obtained by naïve adults and parents/carers of children who require hydrocortisone in the preparation of doses of following manipulation of a 10 mg hydrocortisone tablet. The impact of tablet score lines was also explored.

3. Methods

3.1. Survey method

Bespoke surveys were developed based on key questions that were identified by a multidisciplinary team (three paediatric endocrine consultants; one paediatric endocrine specialist nurse, pharmaceutical researcher; parents of children with adrenal insufficiency) to collect information on strategies that health care professionals advise and that parents currently use or have used previously to manipulate hydrocortisone tablets to provide the appropriate dose for children.

Three surveys were developed for: (i) Paediatric endocrinologists; (ii) Endocrine nurses; and (iii) parents/carers of children who require treatment using hydrocortisone. Key areas of interest included: strategies used to manipulate 10 mg hydrocortisone tablets; the tools used to manipulate tablets and instructions provided for manipulation. Although the questions were different in each survey there was some overlap allowing comparison of data between the three groups. Draft questionnaires were reviewed by the multidisciplinary team to assess ease of completion and ensure that questions were phrased unambiguously. Bristol Online Survey, (www.onlinesurveys.ac.uk) was deemed most appropriate software as it is specifically designed for academic research and public sector organisations and is fully compliant with UK data protection laws. A non-probability based convenience sampling method was selected and participants were left with a choice to "opt in" to the questionnaire following an invitation. A

target sample size was not set as this was a consultation and not research therefore statistical powering is not relevant. The surveys used in this study were approved by South Central – Oxford B Research Ethic Committtee REC reference: 17/SC/0048 (HRA/ IRAS Ref: 217947). The final surveys are included as Supplementary files.

Potential parent/carer participants were recruited via distribution of the survey uniform resource identifier (Ocal et al., 2010) via parent groups associated with CLIMB, Addison's Disease Self-Help Group and the child growth foundation (http://www.livingwithcah.com; www.addisons.org.uk; http://www.childgrowthfoundation.org). The inclusion criteria were that the survey participant identifies as caring for a child who has taken oral hydrocortisone and has been required to manipulate tablets to provide a dose (no exclusion criteria).

Questionnaires were distributed to paediatric endocrinologists and endocrine nurses at UK tertiary centres for paediatric endocrinology via personal contacts of the author team.

3.2. Accuracy of manipulated 10 mg hydrocortisone tablets

The variability in dose resulting from the manipulation of a 10 mg hydrocortisone tablet was quantified. Manipulations were undertaken by naïve study participants as well as parents/carers who routinely manipulate hydrocortisone for their children. The difference between the measured and theoretical dose was calculated and the overall accuracy of dosing assessed. This study was approved by South Central – Oxford B Research Ethic Committtee REC reference: 17/SC/0048 (HRA/ IRAS Ref: 217947).

3.2.1. Naïve study

The participants were given either a 10 mg hydrocortisone tablet with score lines marking quarters (brand was Auden McKenzie; batch 16B11/H) or an unscored 10 mg tablet (brand was AMDIPHARM; batch 6066492). Images of the tablets are provided in Supplementary material 1. The participants then received brief instructions on how to manipulate the 10 mg hydrocortisone tablet to obtain a 2.5 mg dose. They manipulated their tablet by one of two methods: (i) quartering the tablet, a tablet splitter (PillMate Pill Cutter) was available if they wanted to use this OR (ii) crushing the whole tablet between two spoons, dispersing the powder in 10 mL of water and then drawing up a 2.5 mg dose. For method (ii) two spoons, a cup, water and a 10 mL syringe (Medicina 10 mL home oral/enteral syringe, Ref: HE10) were provided. After manipulation the prepared dose was collected and analysed within 7 days of sample collection. The solid fractions were stored in individual airtight universal tubes and refrigerated prior to analysis; the liquid samples were stored in airtight universal tubes and frozen at −20 °C prior to analysis. Previous literature suggested that hydrocortisone is stable for up to 14 days at room temperature (Chappe et al., 2015). In this study a dispersion of a single tablet in water was stored for 14 days and measure on 5 occasions; there was no change in the measured hydrocortisone concentration over time.

3.2.2. Parent/carer study

Parents/carers were provided with a 10 mg scored Auden McKenzie hydrocortisone tablet (batch 16B11/H) and requested to prepare the smallest dose of hydrocortisone that they would usually give to their child as part of their treatment regimen as they would in a home setting. All participants were provided with tools including: differing sized spoons; medicine spoons; tablet crushers/splitters; syringes and other items identified in the survey. The samples were anonymised with only the intended dose and the method of preparation recorded. The prepared samples was collected and stored as per the naïve samples prior to quantitative analysis.

3.2.3. Quantitative analysis via HPLC

The hydrocortisone content was analysed according to the current European Pharmacopoeial method. In brief, a stationary phase end-capped octadecylsilyl silica gel column 250 × 4.6 mm i.d., 5 µm particle size. Elution was established with a mobile phase composition of acetonitrile and water (40:60 v/v) at a flow rate of 1.0 mL/min. The chromatographic signal was monitored at 254 nm with an injection volume of 20 µL.

The drug content of the tablet batches used was assessed to determine their actual content compared to the labelled content of 10 mg. Ten individual tablets from each manufacturer (Auden McKenzie and AMDIPHARM) tablets were weighed and then each dissolved in 100 mL of mobile phase to ensure complete dissolution of the hydrocortisone.

Hydrocortisone samples prepared by participants within the study required further manipulation prior to analysis. The solid tablet fractions were weighed and then dissolved in 50 mL of mobile phase (acetonitrile and water (40:60 v/v)), samples were sonicated for 10 min to ensure full dissolution of hydrocortisone. The liquid samples of dispersed tablets were defrosted, weighed then dissolved at a ratio of 1:10 with the mobile phase and sonicated for 10 min to ensure complete dissolution of hydrocortisone (to prepare a solution from the suspension) prior to analysis. For HPLC a small volume (20 µL) of this solution was taken for analysis.

4. Results

4.1. Survey data

4.1.1. Healthcare professionals

Completed surveys were received from 32 paediatric endocrinologists and 20 endocrine nurses. Both endocrinologists and endocrine nurses were comfortable in recommending dispersed, cut and crushed hydrocortisone tablets to children. Interestingly, more endocrinologists were comfortable in recommending the use of half a 10 mg tablet (90.6%) compared to a quarter of a tablet (46.9%) as a manipulation. When endocrine nurses were asked directly what advise they would provide to parents/carers to prepare a dose of 2.5 mg the results were split evenly between dispersing the tablet in 10 mL water and drawing up 2.5 mL and quartering the tablet.

4.1.2. Parents/carers

Surveys were received from 159 parents/carers. The age range of children and young people was 3 months to 23 years with a mean age of 8.7 years. The total number of doses reported was 476 ranging from 0.25 mg to 15 mg. When the doses for those children under six year of age were separated the total number of doses analysed was 191 and the range from 0.25 to 7.5 mg; the percentage of those doses divisible by 2.5 mg was 43.2%, meaning > 50% of doses could not be prepared from quartering tablets.

Seventy-three percent of respondents reported receiving instructions on how to prepare a dose, of which the majority reported receiving instructions from a nurse, only 6.8% received instructions from a pharmacist. Of those who reported receiving instructions, 63.1% reported this being more than a year ago with only 10.6% reporting to have received an update on instructions for manipulation since diagnosis with adrenal insufficiency. Seventy-four percent of parents/carers reported that they had trained between one and ten other people on the preparation of hydrocortisone dose from a 10 mg tablet.

Seventy percent of parents/carers reported using the method that was recommended to them by their healthcare professional; discrepancies typically related to those advised to disperse the tablet yet choosing to cut the tablet and administer a solid portion. The methods used by parents/carers to prepare doses for the child in their care are shown in Fig. 1a. The most common method reported was to cut the tablet and administer the cut portion as a solid.

More than 60% of parents/carers reported cutting the 10 mg tablet and then administering the cut portion as a solid. Of those cutting tablets 19.6% were administering a dose not divisible by 2.5 mg. Doses reported to be prepared by cutting included 0.5, 2, 4, 6 and 14 mg.

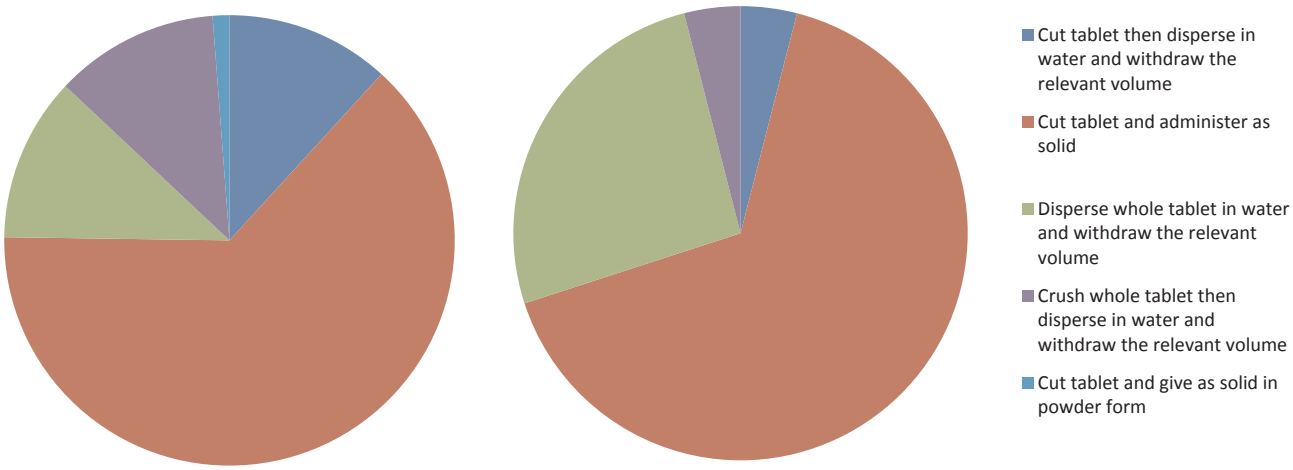

Fig. 1. Methods of manipulation of a 10 mg hydrocortisone tablet (a) reported by parents/carers (n = 119) to achieve an appropriate dose for the child in their care and (b) undertaken by parents/carers within this study (n = 27).

Hydrocortisone tablets are available from a wide range of manufacturers. However, in the UK it is only the Auden Mackenzie brand that have score lines to produce quarters on the tablet. Seventy-four percent of those who reported cutting tablets were using the scored tablets.

It was important to determine the tools used by parents/carers to manipulate the tablet so that we could replicate the typical utensils used for the dose preparation aspect of this study. The most popular tool used in manipulation was either a tablet cutter or knife (> 40%); followed by a syringe, cup and water (> 15%). Many parents/carers reporting splitting the tablets with their hands; due to the small size of hydrocortisone tablets this is more likely to be the scored tablets.

4.2. Accuracy of manipulated 10 mg hydrocortisone tablets

A calibration curve was produced which was linear with an R^2 value of 0.99 over the range 0–0.20 mg/mL. The tablets both showed uniform content with a mean content of 9.98 mg for the Auden Mackenzie brand and 10.01 mg for the Amdi brand tablets.

4.2.1. Naïve study

A total of 30 naïve participants were recruited from events held at the University of Birmingham using posters or word of mouth at engagement events. Naïve participants were invited to prepare 2.5 mg doses from tablets that were scored or unscored using either tablet splitting or dispersing the tablet in 10 mL of water and withdrawing the relevant volume.

The hydrocortisone content from each of the methods was measured and the results are shown in Fig. 2. There were no statistically significant differences (ANOVA $p > 0.05$) in the dose produced based either on the method or brand of tablet investigated.

The weights of the quartered tablets ranged from 0.0369 to 0.0888 g for the scored tablet and 0.0428–0.0781 g for the unscored tablets; both data sets were normally distributed. The mean and standard deviations were 0.068 ± 0.015 g and 0.065 ± 0.009 g for the scored and unscored tablets respectively. There was a linear relationship between the weight of the quarter and the dose that was contained within the tablet fragment. This demonstrates that the weight may be used as a surrogate for content in comparing these hydrocortisone tablet brands.

The total volume used to disperse the tablet was not recorded, this was suggested to be 10 mL and the syringe has an accuracy of ± 0.5 mL. The volume of liquid removed from the ~10 mL dispersion was weighed to examine the variability in volumes withdrawn from the dispersion. Assuming a density of 1 g/mL the weight should have been close to 2.5 g. The weights of the volume withdrawn from the scored tablet dispersion ranged from 1.95 to 2.94 g with a mean and standard deviation of 2.32 ± 0.22 g. The weights of the volume withdrawn from the unscored tablet dispersion ranged from 1.44 to 3.93 g with a mean and standard deviation of 2.36 ± 0.42 g. The volume withdrawn did not relate to the dose delivered; the liquid prepared was a suspension rather than a solution which can explain this lack of correlation.

The accuracy was better for the non-scored tablets with 70% and 87% being within the 20% limits (2–3 mg) compared to 57% and 67%

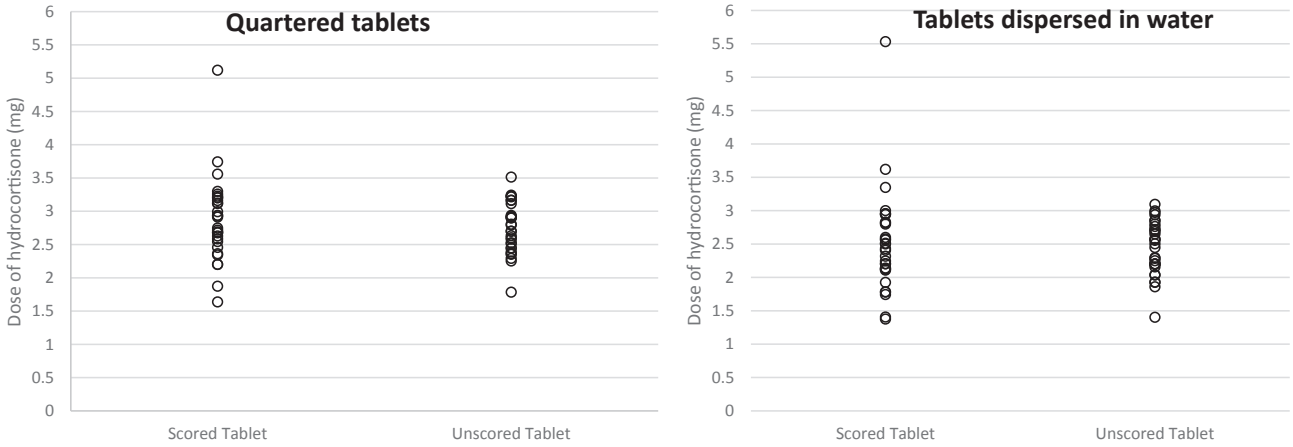

Fig. 2. Comparison of the dose produced when non-scored and scored tablets were manipulated by naïve adults. The data points show each manipulation (n = 30 in each group). The target dose was 2.5 mg.

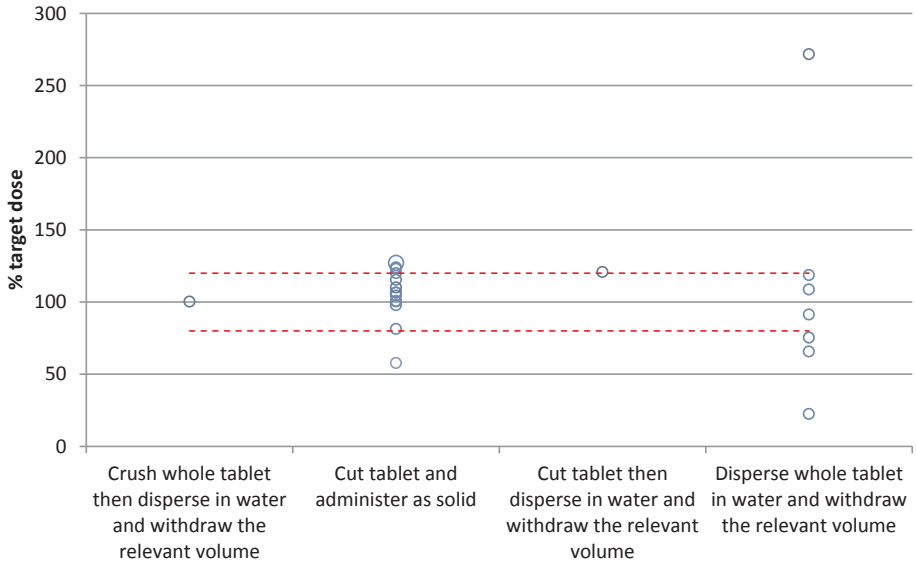

Fig. 3. The accuracy of methods used by the parents/carers, the dashed red lines show ± 20%.

for the scored tablets for the quartered vs dispersed tablets respectively.

4.3. Parent/carer study

Parent/carers were recruited from paediatric endocrinology clinics held at Birmingham Children's Hospital. A total of 27 parents/carers were recruited to this study. The target doses they prepared ranged from 0.5 to 7.5 mg.

The methods used by the parents/carers within this study were representative of those reported by the 119 parents/carers within the survey. This is shown in Fig. 1b. The most common method in both cases was to cut the tablet and administer the cut portion as a solid.

The accuracy of dosing of parent/carers is shown in Fig. 3.

Based on this data and the small sample size the most suitable methods included (i) crushing the tablet prior to dispersion and withdrawing the relevant volume and (ii) cutting the tablet. Dispersing the tablet in water without first crushing gave the widest range of doses with one dose being greater than 250% of the target dose.

4.4. Comparison of the parent/carers vs naïve participants

Table 1 compares the percentage of parents/carers versus the percentage of naïve participants who were able to produce a dose that was within 20% of the required dose.

When quartering tablets a greater proportion of the parent/carers were able to generate accurate doses for the child in their care. However, when dispersing tablets the parent/carers were less able to generate doses that were within 80–120% of the target dose.

Overall 74.1% of the parents/carers prepared doses that were within 20% of the stated dose of hydrocortisone using the scored (Auden Mackenzie brand of tablets). This suggests that parent/carers are somewhat better at obtaining accurate doses for the child in their care. However, it is important to support parents/carers at diagnosis as they will be naïve when preparing the initial doses for the child in their care.

Table 1
The percentage of participants that prepared a dose within 20% of the target dose based on the population, method and tablet brand used.

	Quartered Tablets		Dispersed Tablets	
	Scored	Unscored	Scored	Unscored
Number of naive participants	30	30	30	30
% within 80–120% target dose	56.7	70	66.7	86.7
Number of parent/carers	18		7	
% within 80–120% target dose	83.3		42.9	

5. Discussion

This study supports other work (Orlu-Gul et al., 2013; Whitaker et al., 2015) which have highlighted the need for age-appropriate hydrocortisone formulations. Parents and carers of children are required to manipulate tablets to provide an appropriate dose for the child in their care. The techniques described in this study reflect common practice across the UK as they are reported by those involved in the manipulation of hydrocortisone tablets. Although new formulations of low dose hydrocortisone are now available in the UK this study has relevance to the many other manipulations that parents undertake. Hydrocortisone, as a poorly soluble drug where dosing accuracy greatly improves therapy is a useful example to consider as it represents a "worse-case" scenario.

The results from the naïve study showed that hydrocortisone tablets without score lines gave more accurate results compared to those with score lines when producing a 2.5 mg dose. The reason for this is unknown and in the case of the tablet splitting was unexpected as the presence of score lines was anticipated to generate superior data (Ciavarella et al., 2016). This study was limited to hydrocortisone tablets that were split into quarters either using score lines or using a tablet splitter on a circular tablet. Extrapolation of this data to other products should be undertaken with caution as the shape and hardness of tablets have previously been demonstrated to affect accuracy following tablet splitting (Abu-Geras et al., 2017; Saimbi et al., 2016; van Riet-Nales et al., 2014).

Dispersion of the tablets to provide an accurate dose relied on participant crushing the tablet adequately prior to mixing with the water then withdrawal of a suspension of the hydrocortisone within the liquid. Greater errors were anticipated in this method due to the number of processing steps involved and the equipment available. The 10 mL water volume was withdrawn typically using a 10 mL syringe with graduations every 1 mL which has an accuracy of ± 0.5 mL. This water was then combined with the 10 mg tablet, typically this had been crushed between two teaspoons and stirred for a period from a few seconds up to 2 min. A 2.5 mL sample was withdrawn using the same 10 mL syringe (with the same error of ± 0.5 mL) which was used for subsequent analysis. The weight of the liquid volumes was measured to

note the variability in volumes withdrawn (assuming equal density in all cases). In the naïve study the mass of the volume withdrawn ranged from 1.3 to 3.0 g showing large variability in volume; however when this was correlated to dose there was limited correlation between the mass and the dose provided.

This study compared the ability of parents and carers (with experience of manipulating hydrocortisone tablets) to naïve participants in their ability to manipulate tablets to prepare a fixed dose. The results showed that a higher percentage of parents/carers were able to manipulate a tablet to provide a dose that was within 20% of the specified dose when simply cutting tablets. There are more processing steps involved in the dispersion of tablets method, therefore where possible an age appropriate dosage form or dose increment of 2.5 mg should be prescribed for children who require hydrocortisone from a 10 mg tablet. One of the parent/carer target doses prepared by dispersion of a tablet was 0.5 mg; a small change in the measured dose equates to a large percentage change due to the very low target dose. It is not possible to prepare such a low dose by cutting the solid tablet and this example illustrates the variability and issues in dosing very low doses to children from manipulation of a tablet. Many parent/carers have never received formal training on the use of syringes and are unaware of their limitations in terms of accuracy. It would be prudent to ensure that parent/carers are appropriately trained and have access to a range of syringes if manipulation via dispersion of a poorly soluble drug in a tablet form is their only means of generating the appropriate dose for the child in their care. From the parent/carer data there is insufficient evidence to promote a particular manipulation process yet where possible simply cutting tablets along score lines appeared to give a more accurate dose. Where possible, health care professionals should recommend cutting solid dosage forms rather than dispersing them when extracting a dose.

Provided that parents/carers have access to a tablet splitter there is no need to specify scored tablets on the prescription as the dose accuracy was not compromised in the naïve data set; this may also result in cost savings to the healthcare provider or payer. The NHS indicative price for the scored tablets is £84.45 for 30 × 10 mg tablets whereas the unscored are £41.22 (BNF-C, 2017). However, this is only applicable to dosing multiples of 2.5 mg. For lower doses dispersions are still required yet there should be training provided to all those involved in administration of manipulated medicines to children to ensure that the most suitable tools are being used. This may involve providing several syringes with a range of graduations.

6. Conclusions

More than 25% of children are at risk of receiving doses of hydrocortisone that are not within 25% of the prescribed dose which is likely to have a significant clinical impact. Hydrocortisone is used to mimic typical glucocorticoid levels therefore ideal treatment will match circadian rhythms. Optimizing glucocorticoid therapy during childhood is critical to prevent adrenal crisis, optimise linear growth, body composition, cardiovascular and bone health and ensure normal progression through puberty (Webb and Krone, 2015).

In the absence of 2.5 mg age-appropriate hydrocortisone formulations a 10 mg hydrocortisone tablet should be cut and the dose administered as a solid as this has shown good dose accuracy and avoids the poor palatability associated with dispersions of crushed tablets.

Funding source declaration

This work was funded by an education grant from and the British Society of Paediatric Endocrinologists (for support of a Summer studentship to Cameron Watson).

Acknowledgements

The authors would like to thank Diurnal for funding this study; the British Society of Paediatric Endocrinologists (for support of a Summer studentship to Cameron Watson); the Child Growth Foundation, CLIMB and the Addisons society self-help group for distribution of the parent/carer questionnaire; Birmingham Children's Hospital, in particular the Wellcome Trust CRF for support and for hosting the study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijpharm.2018.04.054.

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ORIGINAL RESEARCH ARTICLE

Pharmacoeconomics 2002; 20 (5): 339-346
1170-7690/02/0005-0339/$25.00/0

The Practice of Splitting Tablets

Cost and Therapeutic Aspects

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Abstract

Background: Tablet splitting is used in pharmacy practice to adjust the dose to be administered. It is also being advocated as a method of reducing prescription drug costs.

Methods: The potential for using this practice as a cost-saving method was examined. The top 200 prescription products in Canada were evaluated for their potential for tablet splitting to reduce costs.

The assessment was based on the dosage form (only tablets could be split), availability of dosages in multiples, whether the drug was used for long-term therapy, whether the product was packaged suitably (e.g. oral contraceptives in a therapeutic package), whether pricing structure would allow substantial saving, and the physical nature of the tablets (e.g. whether there were special dose-release characteristics). The products most commonly split in three Canadian pharmacies were compared with the products that had a substantial savings potential. Costs for splitting tablets in the pharmacy and costs of instructing patients to split tablets were calculated.

Results: Savings could be generated from tablet splitting for only 15 of the 200 products. There was little overlap between these 15 products and the products that were most frequently split in the three pharmacies. The costs associated with tablet splitting in the pharmacy were approximately 0.1 Canadian dollars ($Can) per tablet. The cost of instructing a patient to split the tablets was approximately $Can1.

Conclusions: Tablet splitting appears to have limited usefulness as a cost-reduction strategy. Only a small proportion of products are suitable for splitting and have the potential for savings. There are also costs arising from splitting tablets in the pharmacy, or instructing patients to do so, and from wastage of product. There are also issues such as patient compliance and the risk of an incorrect dose being taken that should be considered.

Tablet ('pill') splitting is an accepted practice in dispensing medication. It has been used when a dosage form of the required strength is not available commercially. This is a common clinical problem in prescribing low-dose therapy for elderly patients.[1] More recently, the practice has been used in some countries as a method to control prescription expense. With the increasing cost of medication this practice may become more common.

Splitting tablets for the purpose of providing a lower dose is done under various circumstances, including providing medication for a child or older person when the dosage form is not available in the prescribed strength, when tapering a dose, or when titrating the dose. Tablet splitting is one of many

techniques used by pharmacists and nurses to provide medication in the proper dosage.

A number of medications are used at doses much smaller than those traditionally used. For example, hydrochlorothiazide is commonly used at a dose of 12.5mg, but the lowest dose tablet currently available is 25mg. Thus, patients need to split tablets in order to receive the smaller dose. This approach contributes to a more cost-effective approach to treating hypertension.[2]

Slow titration refers to starting a medication at a low dose and slowly increasing the dose to the target level. One example of the benefits of tablet splitting for slow titration is in patients post-myocardial infarction (MI). Often patients post-MI cannot tolerate full doses of β-blockers used in clinical trials and are often given a very small initial dose of a β-blocker, such as metoprolol 12.5mg, in order to see how they tolerate the drug. If the patient tolerates this dose, the dosage is gradually increased to reach the dosage used in comparative clinical trials. However, the smallest dose metoprolol tablet is 50mg, which requires that the tablet be split into quarters to provide the 12.5mg dose. The procedure of splitting tablets thereby allows for ease of dosage management by the patient, because only one tablet dosage is required. If several different dosages of tablet were used, this would have the potential of increasing the errors in taking medication, as well as increasing the cost of the medication to the patient.

Patients who are receiving anticoagulation therapy with warfarin may require frequent dosage changes to maintain an appropriate level of anticoagulation, especially when starting therapy. Patients are often prescribed warfarin 2mg tablets when therapy is initiated. This allows for modification of dosage by using one or more tablets, or breaking the tablets in half for smaller increments. Instead of purchasing numerous different dosage tablets, the patient would purchase one dosage of tablet, and then adjust the dosage as directed.

The accuracy that can be achieved in splitting tablets varies with the size of the tablet and its characteristics.[3,4] For example, when halving small tablets there was a variation in weight of more than 20 for 44% of the tablet halves. This is outside the compendial limits of variation for tablets. It appears that for reasonable accuracy in dosage, tablet splitting should be restricted to large or scored tablets. This has been confirmed in an evaluation of a commercial product for splitting tablets. The Pill Splitter (LGS Health Products, Beachwood OH) was found to be effective in splitting all the tablets tested, with best results from large tablets (tablets approaching 0.5cm in size take longer to position for cutting) and those that were coated (film rather than sugar coated, for example).[5]

In one small study comparing tablets that were split (40mg atorvastatin) with an equal dose of the formulated product (20mg), there were no differences in clinical outcomes, as measured by low-density lipoprotein cholesterol levels, in patients followed for 12 weeks.[6] This study also demonstrated that there were no significant clinical implications relating to compliance/adherence with therapy when tablets are split.

The patient may be required to perform the tablet splitting and this would be indicated in the label directions, or verbally by the pharmacist. Alternatively, the tablets may be split by the pharmacy staff at the time of dispensing. There do not appear to be any problems of compliance or patient acceptance of therapy when split tablets are used.[7]

Some countries have specifically set out instructions for splitting tablets; for example, Barbados, through the Barbados National Drug Formulary.[8] Some health management organisations (HMOs) in the US also have guidelines for the splitting of tablets to effect savings. An instruction sheet from one HMO entitled 'Half-tablets: cost-effective and easy to do!' states that the purpose is to save money.[9]

The cost savings achieved through tablet splitting may accrue either to the patient, where they must pay for their own medications out of pocket, or to a drug benefit programme. For many drugs, generic products are available at reduced cost. For newly marketed medications that do not yet have generic equivalents (e.g. an HMG-CoA reductase inhibitor, or 'statin'), the splitting of tablets may

provide substantial cost savings for the patient. They may be able to obtain a full prescribed dose of the medication at a fraction of the cost, by obtaining tablets containing twice the required dose and splitting them.

Tablet splitting has several drawbacks.

- *Unsuitability of some dosage forms:* Controlled release tablets have been designed to release the medication in a predictable manner over time. To do this a variety of methods have been used. Some methods, such as the use of coated granules, may be suitable for tablet splitting. Other dosage forms, however, would have their designed features impaired by splitting. The difficulty in assessing the suitability of each controlled dosage form and the probability of impairing their function makes it impractical to include these tablets for tablet splitting.
- *Wastage:* Because of poor technique or tablet characteristics, the tablets may crumble or shatter when splitting is attempted. This leads to wastage of the product, as the tablet fragments cannot be used because of dose inaccuracy. The loss from tablet wastage may significantly decrease the benefits of tablet splitting.
- *Incorrect dose:* For the reasons mentioned above, the patient may split tablets unevenly, resulting in an incorrect dose being administered. This would be a significant concern if it occurred with a drug with a narrow therapeutic index, such as digoxin. While 0.25mg tablets are available, it would be dangerous to have the patient split tablets to provide 0.125mg. It may also be difficult to split irregularly shaped tablets evenly.
- *Confusion/noncompliance:* Even patients who have excellent records of compliance may become confused about their regimen, especially if their medication dose is frequently adjusted or requires splitting tablets. In one reported case, a patient receiving two and a half 1mg warfarin tablets was prescribed 0.5mg warfarin tablets and continued to take two and a half tablets, not realising the difference in dose.[10] A patient may not read the label accurately and take a full tablet instead of splitting the tablet. If the pharmacy supplies the tablets already split, the patient may not realise that the tablets are already split and choose to split the half tablets again, thereby receiving only 50% of the prescribed dose. Patients who require a regimen including split tablets need to be counselled about how to administer and split the tablets. Compliance may be increased by having the pharmacy staff split the tablets and dispense them in an appropriate form of compliance packaging. This would increase the cost of providing the medication.

Older patients or patients with disabilities may have difficulty splitting tablets, either manually or with a tablet splitter.[11,12] Those with vision or manual dexterity problems may find tablet splitting very difficult. In a study of acute geriatric patients, 94 (78.3%) were unable to open a container or break a scored tablet.[11] Even using tablet-splitting devices may be challenging for these patients, because good eyesight and manual dexterity are essential to place the tablet in the cutting device, line it up appropriately, and ensure the tablet is evenly split before administering the product. Patients may also have difficulty splitting tablets if the tablets are not scored.

If they do not receive assistance, patients may become frustrated to the point that they become nonadherent to the prescribed regimen. They may try to adapt their regimen to their abilities, by taking a full tablet every other day. However, this type of alternate-day regimen can be dangerous. Patients must be continually encouraged, counselled and monitored if they are to succeed on a regimen that involves splitting tablets. This requirement for more professional time is a cost that will offset some of the economic gains from tablet splitting.

With the use of tablet splitting as a means of reducing prescription costs, there is a need to analyse the potential benefits and drawbacks to this practice. This paper sets out some of the potential savings available from the practice of tablet splitting, based on the top 200 products on the Cana-

dian market, and factors that constrain the possible savings.

Methods

Cost-Saving Potential

The top 200 prescription drugs in Canada, based on number of prescriptions, were selected to determine the potential for tablet splitting as a mechanism to reduce prescription price.[13] The proportion of tablets suitable for splitting and the cost of the tablets for each dosage were determined for each drug.

The suitability for splitting was determined based on the dosage form (only tablets could be split), availability of dosages in multiples, whether the drug was used for long-term therapy, whether the product was packaged suitably (e.g. oral contraceptives in a therapeutic package), whether the pricing structure would allow substantial saving (more than $Can0.10 per tablet – roughly the salary expense for a pharmacy staff member to split the tablets; 2000 values), whether they had special dose-release characteristics and the nature of the tablets (e.g. spherical or irregular tablets are difficult to split). The cost of a tablet-splitting device ranges from $Can6 to $Can10.

Comparison with Current Practice

Information was sought on the pharmaceutical products that are routinely split in practice. To identify these products, three Canadian (Edmonton) pharmacy managers specialising in geriatric services were asked to prepare a list of products they commonly split. These were then compared with the top 200 products list.

Time Required to Split Tablets in Pharmacy

The time required to split tablets in the pharmacy was determined by using a stopwatch. Two pharmacy students used a tablet splitter to split 20 tablets of four different products selected as a convenience sample. The average time was calculated from these data and was used to calculate the cost to cover the added time cost in tablet splitting. This would be done in cases where the patient was unable to split the tablets accurately.

Time to Counsel Patients on Tablet Splitting

A pharmacy student counselled eight actual patients on tablet splitting. The procedure was timed by the pharmacy student using a stop watch.

Results

Cost-Saving Potential

The top 200 products had a variety of dosage forms, of which 148 were tablets. These tablets consisted of various tablet forms (sugar- or film-coated, sustained-release, sublingual). A number of products were found to be unsuitable for splitting because of their therapeutic characteristics or presentation. This reduced the potential number of products to 127. About 70 of the products were generic or low-cost products that would yield little saving from tablet splitting. For the remaining products, many had dosages that were not in multiples that could be used for tablet splitting, for example a 10mg and a 25mg tablet.

By narrowing the list to medications that are for long-term therapy, tablets that can be easily split and those for which there is a gain of at least 10 cents, the number of drugs was reduced to 15 [enalapril (Vasotec®[1]), warfarin (Coumadin®), simvastatin (Zocor®), pravastatin (Pravachol®), atorvastatin (Lipitor®), lisinopril (Zestril®), fosinopril (Monopril®), lisinopril (Prinivil®), quinapril (Accupril®), risperidone (Risperdal®), sumatriptan (Imitrex®), alendronate (Fosamax®), nefazadone (Serzone®), cilazapril (Inhibace®) and lovastatin (Mevacor®)]. They represent only 14 chemical entities and include four statins and five ACE inhibitors (table I).

The potential savings from tablet splitting for these products are substantial. Many of the products have similar prices for each of the dosages, so

1 Use of tradenames is for product identification only and does not imply endorsement.

Table I. Potential cost savings from tablet splitting of 15 products

Drug	Dose (mg)	Price per tablet (Canadian dollars; 2000 values)	Dose (mg)	Price per tablet	Saving (%)
Quinapril (Accupril®)	5	0.82	10	0.82	50
	20	0.82	40	0.82	50
Cilazapril (Inhibace®)	2.5	0.68	5	0.79	41
Fosinopril (Monopril®)	10	0.79	20	0.95	40
Enalapril (Vasotec®)	2.5	0.68	5	0.68	50
	5	0.68	10	0.96	29
	10	0.96	20	1.16	40
Lisinopril (Zestril®)	5	0.67	10	0.87	34
Lisinopril (Prinivil®)	10	0.87	20	1.05	40
Atorvastatin (Lipitor®)	10	1.16	20	2	38
	20	2	40	2.15	46
Lovastatin (Mevacor®)	20	1.73	40	3.19	8
Pravastatin (Pravachol®)	10	1.15	20	1.79	22
	20	1.79	40	2.15	40
Simvastatin (Zocor®)	5	0.9	10	1.78	1
	10	1.78	20	2.2	38
	20	2.2	40	2.2	50
	40	2.2	80	2.2	50
Risperidone (Risperdal®)	0.25	0.42	0.5	0.7	17
	0.5	0.7	1	0.96	31
	1	0.96	2	1.92	0
	2	1.92	4	3.83	0
Nefazadone (Serzone®)	50	0.73	100	0.8	45
	100	0.8	200	0.93	42
Alendronate (Fosamax®)	5	1.38	10	1.76	42
Sumatriptan (Imitrex®)	50	12.95	100	14.27	45
Warfarin (Coumadin®)	1	0.32	2	0.34	47
	2	0.34	4	0.42	38
	2.5	0.33	5	0.36	45
	5	0.36	10	0.57	19

savings of up to 50% are possible. Most savings are in the range of 30 to 50%. Maximum savings are obtained for quinapril, for which all dosages are priced the same.

Comparison with Current Practice

The list of tablets that were reported to be commonly split in three Edmonton pharmacies is as follows: amlodipine, atenolol, benztropine, calcium (unspecified), carbamazepine, clonazepam, Dyazide®, hydrochlorothiazide, indapamide, loxapine, methylphenidate, metoprolol, oxybutynin, paroxetine, risperidone, sildenafil, sotalol, Stresstabs® (a high potency multivitamin product classified as a dietary supplement), warfarin and zopiclone (table II). The lists from each pharmacy had little overlap. They represent routine medication for chronic disease.

For the listed products that were reported as being split in Edmonton, there is an overlap of only two products from the top 200 products: risperidone and warfarin. Savings were not substantial, with only 4 of 19 showing savings of more than $Can10 for an average prescription representing a 1-month supply of medication. Six of the products did not have double-strength products that would generate savings by splitting.

Time Required to Split Tablets in Pharmacy

The results are presented in table III. The products used for timing were Desyrel® 50mg (trazodone), Norvasc® 10mg (amlodipine besylate),

Novo-cimetine® 600mg (cimetidine) and Apo-Trimip® 25mg (trimipramine maleate).

The cost associated with tablet splitting was based on an hourly rate of $Can60, which is representative of charges for pharmaceutical services in Canada.[14] Based on an average time for tablet splitting of 5 seconds per tablet (table III), the service cost of splitting was $0.0833 per tablet. This indicates that a cost of almost 10 cents per tablet would be incurred to cover the pharmacy cost of splitting tablets. The use of technicians or trained staff to split tablets may reduce the cost. If the patients split the tablets themselves, this pharmacy cost is avoided.

Other costs would be incurred in implementing a tablet-splitting procedure. The first of these is the product expense resulting from wastage when the tablets shatter or break unevenly. This cost is one that both pharmacy and patient might incur. Additional salary cost to cover the added calculation and record keeping is required.

Time to Counsel Patients on Tablet Splitting

Counselling time for eight patients on tablet splitting ranged from 37 to 80 seconds (table IV). The patients ranged in age from 54 to 68 years. For the four patients who had split tablets previously, the average time was 57.5 seconds. The four patients who had not split tablets previously required an average of 64 seconds. Overall, the average time for counselling was 60.75 seconds. At an hourly cost of $Can60, the counselling expense would be about $Can1.00.

Discussion

From this limited sample it appears that in current practice, tablet splitting is more likely to be for clinical, than for economic, reasons. However, there appears to be some benefit in using tablet splitting as a means of reducing drug costs, and the procedure is used widely, both in Canada and elsewhere. The procedure can generate savings, not only for new, expensive products, but also for many products that have moderate costs. In Barbados, a small study of six drugs used in cardiovascular disease showed prescription savings from tablet splitting in the range of 15 to 35% (personal communication, Pamela Payne, 2001 Aug).

Similarly, HMOs in the US seek out savings and insist on tablet splitting for many products. The

Table II. Potential cost savings from tablet splitting in 3 pharmacies

Drug	Dose (mg)	Price per table ($Can; 2000 values)	Dose (mg)	Price ($Can; 2000 values)	Average no. of tablets/prescription	Saving ($Can)
Amlodipine	5	1.23	10	1.82	44	14.08
Atenolol	100	0.11			51	
Benztropine	2	0.02			35	
Carbamazepine controlled release	200	0.21	400	0.42	92	0
Clonazepam	0.05	0.12	1	0.19	49	1.23
Dyazide[a]	0.05				40	
Hydrochlorothiazide	25	0.04	50	0.04	51	1.02
Indapamide	1.25	0.19	2.5	0.3	50	2
Loxapine	50				45	
Metoprolol	50	0.12	100	0.22	111	1.11
Oxybutynin	5				62	
Paroxetine	10	1.49	20	1.59	38	26.41
Risperidone	0.5	0.7	1	0.96	38	8.36
Sildenafil	50	10.8	100	10.8	6	32.4
Sotalol	80	0.59	160	0.65	78	20.67
Warfarin	2	0.34	4	0.42	62	8.06
Zopiclone	75	0.47			34	

a A combination product containing triamterene 50mg and hydrochlorothiazide 25mg; **$Can** = Canadian dollars.

Table III. Average time (sec) to split four different products

Product	Student 1	Student 2
Trazodone (Desyrel®) 50mg	4.05	4.35
Amlodipine (Norvasc®) 10mg	5.4	5.0
Cimetidine (Novo-cimetine®) 600mg	5.5	6.0
Trimipramine (Apo-Trimip®) 25mg	4.1	4.4
Mean time (sec)	4.76	4.94

avoidance of expense by tablet splitting is recommended in the US by various nonprofit groups such the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, as well as the publication Consumer Reports. An incentive for patients to economise is the requirement that they pay the full cost, or a substantial portion of the costs, of medication that is not covered by a drug benefit programme.

In countries where medication is dispensed in the original treatment pack (thus creating an obstacle to pharmacists splitting tablets for patients), it is possible for patients to realise savings as long as the pricing structure results in similar prices for varying doses. The disincentive for this to occur in many European countries is the extensive health insurance coverage for medication, which requires patients to pay only a portion of the cost. For this reason the use of tablet splitting as a method of generating health cost savings may be appropriate only for some countries.

The potential for using this method to reduce costs is severely restricted by the small number of products suitable for tablet splitting. The practice is largely dependent on the actions and policies of pharmaceutical manufacturers. Changes in pricing policies could create a substantial reduction in possible savings. Pharmaceutical firms also have the capacity to encourage or hinder the practice of tablet splitting by the dosage forms they produce. The number of dosages available, the characteristics of the tablet, the use of controlled-release dosage forms and packaging all have an effect.

Errors involving split tablets are likely to result in double or half the dose being taken, which can be harmful to the patient. Widespread use of tablet splitting may increase the inappropriate use of medication, a problem that is now serious and in need of redress. To minimise problems, there is a need for effective instruction by pharmacy or other healthcare personnel, as well as some form of continual monitoring of drug use to detect inappropriate dosages being taken.

Patients have a major role in understanding the relationship of dosage to dosage forms, so that they are not confused by the splitting of tablets. They should be able to split the tablets easily, either by hand or with a tablet splitter. To achieve the therapeutic and economic benefits from tablet splitting, patients need to be educated on the rationale and procedures of tablet splitting. This process takes time and incurs a cost. For instruction on tablet splitting, counselling takes only about 1 minute. If more detailed counselling were required, based on dosage or disease factors, the time would be longer.

In cases where medication is prepared by the pharmacist, there is less problem with an inappropriate dose being used in an institutional setting, or if the medicine is dispensed in compliance pack-

Table IV. Time required to counsel patients on tablet splitting

Patient age (y)/gender	Drug	Repeat treatment?	Time (sec)
57 M	Hydrochlorothiazide 25mg	Yes	37
61 M	Hydrochlorothiazide 25mg	No	80
67 M	Atenolol 50mg	Yes	69
54 M	Atenolol 50mg	Yes	49
61 M	Atenolol 50mg	No	60
62 M	Paroxetine 20mg	Yes	75
68 F	Paroxetine 20mg	No	57
65 F	Metoprolol 50mg	No	59

F = female; **M** = male.

aging (weekly medication boxes or bubble packs) for ambulatory use. For ambulatory patients, medication provided without compliance packaging would require some patient instruction. There is, however, a cost generated by the preparation of the medication. At a cost of 10 Canadian cents per tablet for tablet splitting, a prescription of 100 tablets would cost an additional $Can10.00. Compliance packaging would also incur additional costs.

Private or public drug benefit programmes have the greatest potential gain from a general trend towards tablet splitting to save on pharmaceutical expenditures. They can select products where savings will be realised and set out guidelines for the tablet-splitting procedure. There may be substantial cost savings for some expensive products. This is best realised for long-term therapies where the patients can consistently and accurately split the tablets. But it should be realised that major saving on a few products has little effect on the overall expenditure level.

A policy of attempting to implement tablet splitting on a widespread basis as a general approach to cost cutting, however, would be likely to create problems of inappropriate drug use, with resultant toxicity, decreased compliance with therapy and less attention to patient instruction and monitoring. In many cases, the costs incurred in following this approach for some products would be greater than the saving and make the healthcare system less efficient. The combination of administrative policymaking, product evaluation, implementation of procedures and monitoring could lead to substantial administrative overhead costs that would limit savings and increase programme complexity.

Limitations to the generalisability of this study result from local costs and practices that may not be comparable to those in other countries. Local conditions may be conducive to a widespread use of tablet splitting in one area and not in another.

Conclusion

Tablet splitting has a major role in dosage adjustment in a variety of therapeutic situations. However, its potential for cost saving is limited and it is better suited to specific situations than as a method of general cost reduction in pharmaceutical programmes.

Acknowledgements

Research funding was obtained from the Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Canada. Information on the leading products and their average monthly prescription quantity was provided by IMS Health. There is no declared conflict of interest in this study by the authors.

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AAPS PharmSciTech, Vol. 18, No. 4, May 2017 (© 2016)
DOI: 10.1208/s12249-016-0615-y

Research Article

Key Technical Aspects Influencing the Accuracy of Tablet Subdivision

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Received 16 June 2016; accepted 10 August 2016; published online 1 September 2016

Abstract. Tablet subdivision is a common practice used mainly for dose adjustment. The aim of this study was to investigate how the technical aspects of production as well as the method of tablets subdivision (employing a tablet splitter or a kitchen knife) influence the accuracy of this practice. Five drugs commonly used as subdivided tablets were selected. For each drug, the innovator drug product, a scored-generic and a non-scored generic were investigated totalizing fifteen drug products. Mechanical and physical tests, including image analysis, were performed. Additionally, comparisons were made between tablet subdivision method, score, shape, diluent composition and coating. Image analysis based on surface area was a useful tool as an alternative assay to evaluate the accuracy of tablet subdivision. The tablet splitter demonstrates an advantage relative to a knife as it showed better results in weight loss and friability tests. Oblong, coated and scored tablets had better results after subdivision than round, uncoated and non-scored tablets. The presence of elastic diluents such as starch and dibasic phosphate dehydrate conferred a more appropriate behaviour for the subdivision process than plastic materials such as microcrystalline cellulose and lactose. Finally, differences were observed between generics and their innovator products in all selected drugs with regard the quality control assays in divided tablet, which highlights the necessity of health regulations to consider subdivision performance at least in marketing authorization of generic products.

KEY WORDS: generic product; image analysis; score; tablet subdivision; tablets subdivision method.

INTRODUCTION

The division of oral tablets into two or more parts before intake is a fairly common practice (1). This procedure is performed many times by patient's own initiative or following physician or pharmacist recommendations for dose adjustments, dose titration, swallowing facilitation or even treatment cost reduction (2–4).

The main problem related to this practice is the wide dosage variation of the tablet fragments, which could result either in a subtherapeutic or toxic dose, particularly in cases of drugs with narrow therapeutic index (4–9). Additionally, formulations with modified pharmaceutical performance can be impaired by the subdivision process, leading to hazardous outcomes (10,11). Elderly and paediatric tablet consumers are especially affected by tablet subdivision due to the high frequency with which they use this procedure and the commonly vulnerable health condition of these target groups (5,10,12).

Although scored tablets imply the possibility of subdivision, such characteristic is currently not regulated in many countries. As so, mechanical behaviour after subdivision is not considered for registration, and generic drug products have not been required to have similarity with the innovator one with regard to this aspect (13).

The available literature is not sufficient to precisely determine which production technical aspects impact most on tablet subdivision, although relevant differences have been observed between different types of tablet splitters. In fact, influence of shape, surface, composition or coating on tablet subdivision is discordant, and whether the presence of scoring is a favourable factor for the accuracy of tablet subdivision is still a controversial issue (8,14–17). Consensus is also not reached regarding the best procedure to subdivide tablets. Although, in daily practice, breaking by hand or using of a tablet splitter are still the most common subdivision methods, other means for tablet fraction have been described as the use of scissors and kitchen knife (4,14,18).

Considering this scenario and the relevance of the subject, this study was designed to determine the key

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technical aspects of tablet production (i.e. tablet shape, the presence of score and coating and composition) in the subdivision accuracy of five different drugs and three drug products of each drug (innovator, scored generic, non-scored generic) using two different methods for tablet subdivision (a commercial tablet splitter and a kitchen knife).

MATERIAL AND METHODS

Material

Immediate-release oral tablets of five different drugs, which are often subdivided in clinical practice by elderly patients, were selected—atenolol 50 mg, captopril 25 mg, hydrochlorothiazide 25 mg, losartan 50 mg and sertraline 50 mg. For each of these drugs, three sorts of drug products marketed in Brazil were chosen: the innovator drug product and two generics randomly selected (one scored and another non-scored), totalling 15 different drug products (Table I). The studies were conducted using the same batch for each product for all tests.

Study Protocol

Tablets were subdivided using a commercial tablet splitter (Inconterm, Brazil) and a kitchen knife (Fig. 1). New tablet splitters were acquired for this study and used within the usage limit established by Van Riet-Nales and col. of up to hundred times without changes in its performance (19). The different products were submitted to image analysis followed by mechanical and physical tests to assess the subdivision impact on weight, hardness, friability and disintegration. Comparisons were built based on method for tablet subdivision (knife and tablet splitter), score (scored and non-scored tablets), shape (round and oblong) and coating (uncoated and coated tablets). A qualitative analysis of the tablet diluents starch, lactose monohydrate, microcrystalline cellulose (MCC) and dibasic phosphate dehydrate (DPD) (presence and absence) was also performed. The study protocol is outlined in Fig. 2.

Mechanical and Physical Characterization of Tablets

Weight

Twenty tablets of each drug product were individually weighed using an analytical balance Shimadzu model AUY 220, before and after subdivision. Weight variation was measured by the difference between the experimental weight of half tablets and the theoretical value, which was the whole tablet weight divided by two. Weight loss was calculated as the difference between the weight of the whole tablet and the sum of their half tablets.

Hardness

The hardness of ten whole tablets or halves of each drug product was obtained using a durometer Nova Etica model 298-AT. The results were expressed as hardness variation, which was calculated by the difference between the hardness of whole tablets and half tablets. Halves were measured in durometer in a way the force was applied parallel to the direction of division.

Friability

Tablet friability was measured as the percentage of weight loss of twenty whole tablets or halves of each drug product tumbled in a friabilometer Nova Etica model 300 operating at 25 rpm for 4 min. The results were expressed as friability variation of whole and half tablets.

Disintegration Time

Tablet disintegration time was measured in water at 37°C in a disintegration tester Nova Etica model 301-6. For each variable of the study, six randomly selected tablets were tested. The results were expressed as disintegration time variation of whole and half tablets.

Table I. Description of the 15 Drug Products Selected for the Study

Drug	Brand product	Authorization number	Batch number	Shape	Score	Coat
Atenolol	Astra Zeneca	MS 1.1618.0003.003-0	34214	Round	Yes	No
	EMS	MS 1.0235.0458.019-6	679174	Round	Yes	No
	PratiDonaduzzi	MS 1.2568.0146.005-4	14H79T	Round	No	No
Captopril	Medley	MS 1.4107.0025.014-8	23042	Round	Yes	No
	Pharlab	MS 1.0181.0329.013-1	14020322	Round	Yes	No
	PratiDonaduzzi	MS 1.2568.0153.010-9	13L14M	Round	No	No
Hydrochlorothiazide	Sanofi Aventis	MS 1.2033.0013.005-0	215803	Round	Yes	No
	EMS	MS 1.0235.0792.015-1	492665	Round	Yes	No
	Medquímica	MS 1.0917.0093.001-8	09624S	Round	No	No
Losartan	MSD	MS 1.0029.0007.007-4	MK043	Oblong	Yes	Yes
	Biositética	MS 1.1213.0321.003-0	1408572	Round	Yes	Yes
	EMS	MS 1.0235.0810.054-7	499210	Round	No	Yes
Sertraline	Pfizer	MS 1.0216.0004.001-1	10472001A	Oblong	Yes	Yes
	Medley	MS 1.0181.0537.002-7	14051035	Oblong	Yes	Yes
	EMS	MS 1.0235.0700.020-4	546879	Round	No	Yes

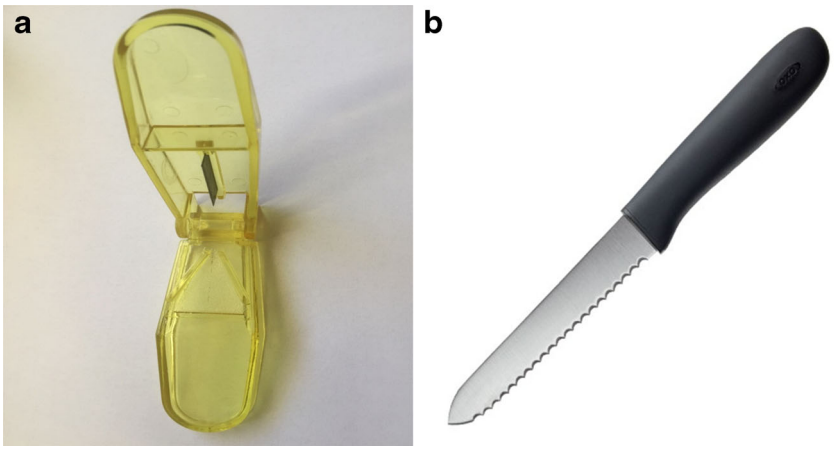

Fig. 1. Tablet subdivision devices: tablet splitting (**a**) and kitchen knife (**b**)

Image Analysis

Ten tablets from each sample were analysed using a stereomicroscope Stereo Zoom Microscope XTL connected to a video camera. The images were captured with software ISCapture version 2.5.1 and processed with software Image-Pro Plus version 4.5.0.29. Tablet surface area was measured and compared.

Statistical Analysis

Statistical analysis was performed taking into account the subdivision tablet method, differences between generics and innovator and information related to the technical characteristics of tablets such as drug, shape, surface, presence of score, presence of coating and excipients. Statistical analysis was performed using SPSS® version 20.0 and Prism version 5.0 software. Mechanical and physical characterization of tablet data was expressed as the mean ± standard error of the mean, and $p < 0.05$ was considered statistically significant. Quantitative variables were tested for normal distribution with the Shapiro-Wilk test. Possible differences among groups were investigated by performing an ANOVA or Kruskal-Wallis test, followed by Tukey's or Dunn's multiple comparison tests. When two groups were compared, we used Student's *t* test or Mann-Whitney *U* test. All correlations between the characterizations of tablet data were determined using Pearson product-moment estimates (*r*). Reference values for each quantitative variable were 7.49 for weight variation, 0.76 for weight loss, 54.94 for hardness variation, 0.37 for friability variation, 12.52 for disintegration time variation and 10.85 for surface area variation.

RESULTS AND DISCUSSION

In general, the subdivision process compromised the mechanical strength of tablets (Table II). A reduction of subdivided tablets hardness (approximately 50%) was noticed in comparison to whole tablets, which may be, at least in part, influenced by the size and shape of the tablets (20). The practical implication of such result is that once a tablet is divided, the sparing half should be kept and handled with even more care, as the risk of disintegration and partial losses is increased. Indeed, tablet halves were 0.7% more friable than whole tablets, which is consistent with a previous study (5). This is because tablet subdivision weakens the dosage form structure by generating sharp corners that are easily eroded by the mechanical friction during the disintegration test. For ordinary tablets, the maximum value accepted by US pharmacopoeia for the friability assay is 1.0% (21). In the present study, several drug products remained outside this limit after the subdivision, namely hydrochlorothiazide (innovator, scored, subdivided by knife) with 3.1%, captopril (generic, scored, subdivided by knife) with 2.3%, captopril (innovator, scored, subdivided by knife) with 2.3%, hydrochlorothiazide (generic, non-scored, both subdivided by knife and tablet splitter) with 1.6%, sertraline (generic, non-scored, subdivided by knife) with 1.6% and captopril (innovator, scored, subdivided by tablet splitter) with 1.0%. Based on the difficulty of keeping the pharmacopoeia limits after subdivision, US health agency (FDA) has recommended the extension of the friability limit to 3% for tablets after subdivision (22). However, there is no scientific evidence to support the safety of changing the acceptable limit for this assay.

Tablet halves disintegration was approximately 20% faster to whole tablets (Table II). This could be explained by the irregular distribution of lubricants in tablets (23),

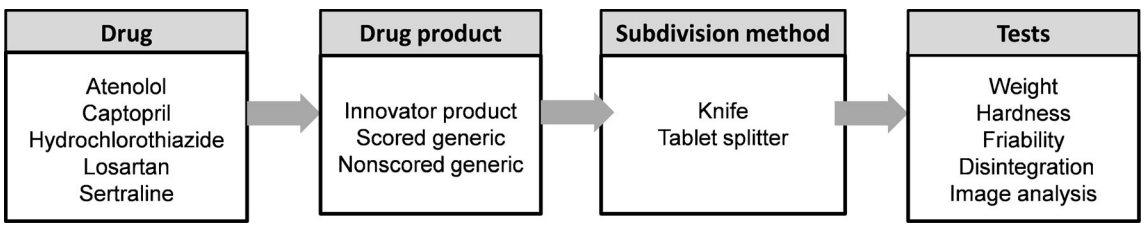

Fig. 2. Flowchart of the experimental protocol to study the tablet subdivision process

Table II. Mean and Standard Deviation of Mechanical and Physical Tests

		Hardness variation	Friability variation	Disintegration time variation	Weight loss	Weight variation	Surface area variation
Overall mean for all studied tablets		53.3 ± 15.8	0.7 ± 0.7	22.3 ± 32.8	2.3 ± 3.9	9.9 ± 10.0	15.2 ± 14.1
Atenolol	Innovator	66.9 ± 2.4	0.2 ± 0	0 ± 0	0.9 ± 0.2	5.0 ± 0.5	13.6 ± 2.3
	Scored generic	54.4 ± 3.8*,#	0.3 ± 0	40.8 ± 4.1*,#	2.7 ± 0.7#	8.7 ± 1.0	13.7 ± 3.5
	Non-scored generic	62.0 ± 2.7*	0.2 ± 0	13.2 ± 0*	0.7 ± 0.3	6.0 ± 0.8	10.8 ± 1.7
Captopril	Innovator	43.4 ± 5.0	1.5 ± 0.6	0.0 ± 0	4.8 ± 0.9	16.3 ± 1.5	19.2 ± 3.8
	Scored generic	53.8 ± 3.0*,#	1.2 ± 0.9	11.9 ± 0*,#	5.3 ± 1.0*,#	11.7 ± 1.4	23.3 ± 4.7
	Non-scored generic	41.4 ± 4.0	0.5 ± 0.0	36.4 ± 0	1.7 ± 0.4	11.8 ± 1.5	17.1 ± 2.3
Hydrochlorothiazide	Innovator	48.8 ± 3.9	1.6 ± 1.4	29.7 ± 1.6	1.2 ± 0.4	9.1 ± 1.2	9.3 ± 1.8
	Scored generic	58.7 ± 3.6	0.1 ± 0.0*,#	33.7 ± 3.3*,#	1.1 ± 0.4*,#	10.4 ± 1.3	22.1 ± 4.0*
	Non-scored generic	60.2 ± 2.4	1.4 ± 0.0	109 ± 63.6	6.6 ± 1.2	10.6 ± 1.0	20.0 ± 2.9*
Losartan	Innovator	48.6 ± 2.7	0.2 ± 0.0	4.9 ± 4.4	0.9 ± 0.2	10.4 ± 0.7	3.5 ± 0.6
	Scored generic	48.5 ± 4.2	0.6 ± 0.1	9.3 ± 6.6*,#	3.4 ± 1.1*,#	6.1 ± 1.0*,#	16.8 ± 3.0*
	Non-scored generic	55.0 ± 2.2	0.4 ± 0.2	0.0 ± 0.0	0.6 ± 0.1	16.1 ± 1.6	18.6 ± 2.8*
Sertraline	innovator	42.1 ± 2.1	0.1 ± 0.0	6.7 ± 0.0	0.3 ± 0.1	3.5 ± 0.6	6.4 ± 0.9
	Scored generic	54.3 ± 1.4*,#	0.5 ± 0.1*,#	39.1 ± 0.0*,#	0.8 ± 0.1*,#	5.2 ± 0.8*,#	6.6 ± 1.0*,#
	Non-scored generic	60.7 ± 2.8*	1.1 ± 0.5*	0.0 ± 0.0*	2.2 ± 0.6*	18.9 ± 2.2	26.3 ± 3.8

Statistical significance between innovator and generic is indicated by asterisks, and difference between scored or non-scored generics is designated by octothorpes ($p < 0.05$)

which might be concentrated on the tablet surface and, due to its lipophilic characteristics, hinder tablet disintegration. Tablet subdivision creates a new face without lubricant in the dosage form, exposing the tablet core, which accelerates the disintegration of tablet halves. Disruption of tablet aesthetic coat, in addition to specific surface increase, can also justify the fast disintegration of subdivided tablets (24). In absolute terms, however, changes in these parameters represent a maximum of 4.5 min (in the case of atenolol—generic, scored, subdivided by splitter tablet), which might have little impact on the dissolution and bioavailability of most products.

The weight loss related to tablet fragmentation and crumbling caused by subdivision was less than 2% (Table II). These data seem to be compatible with other studies that have found values of average weight loss ranging from 0.2 to 3.8% (7,9,17,25,26). Still, the high coefficient of variation for this test is noteworthy. Some studies noted individual weight loss as high as 23.5 and 19.4% (7). In the present study, the highest values were found for sertraline (generic, non-scored, subdivided by knife) with a weight loss of 38.9% and hydrochlorothiazide (generic, non-scored, subdivided by knife) with 19.1% of weight lost. The reduction in tablet mechanical strength after subdivision, observed by the decrease in hardness and the increase in friability, is probably the main cause of weight loss variation. As might be expected (16), there was a strong positive correlation between this response (weight loss) and the friability variation ($r = 0.432$; $p = 0.001$).

Weight variation is one of the most important variables to set the security of a subdivision process because it is directly related to dose when the active substance is uniformly distributed within the tablet mass. Our data showed a mean weight variation of 9.9% ± 10.0. Some drug products present weight variations of nearly 50%. These data are in accordance with others in the literature, which identified an average weight variation of 7%, with some products having a weight variation of up to 40% when evaluating different techniques for tablet division (27). Other studies have described variations higher than 10% on the expected weight of halved tablets on a portion of tested drug products ranging from 16 to 41% (7,8,17,24). Weight variations greater than 20% are described for approximately 12% of the tested tablets in two of these studies (7,8). Except for drugs with a wide therapeutic index, such magnitude of dose variation can lead to serious consequences for the health of consumers.

Image analysis quantified variations in the specific surface of subdivided tablets (15.2%; Table II) and related them to the weight variation (Fig. 3). As expected, there was a statistical correlation between these parameters ($r = 0.169$; $p = 0.001$). Considering the lack of specific quality control tests to evaluate the tablet subdivision process, the image analysis used in this work proved to be a simple and useful analytical tool in the evaluation of the subdivision process.

The Brazilian health agency (ANVISA) follows international parameters similar to the USA (FDA) and European member states (EMA) health agencies concerning the regulation of generic drugs. Generic drugs must be

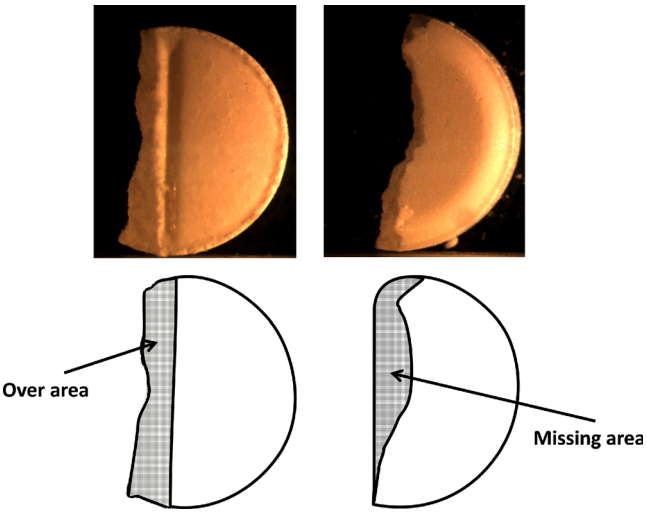

Fig. 3. Scheme of the image analysis test performed to determine the difference between the expected theoretical area and the area found in the subdivided tablets

bioequivalent to the innovator drug product (27). The five drugs studied showed significant differences between the innovator and their generics in at least three control assays (Table II). With regard to the subdivision performance, innovator drug products are not equivalents to their generics. Additionally, the two generics evaluated for each drug also presented a different performance from each other. These differences were associated not only with the presence of scoring, as all five drugs showed significant differences considering only the scored tablets (innovator drug product and scored generic). This issue was also reported by Wilson and col., who did not find equivalence in subdivision for generic and innovator glyburide tablets (28).

In this sense, the concept of functional score established by the FDA and the European Pharmacopoeia (22,29) could solve this problem. Those guidelines for tablets containing a score with subdivision purpose require that the behaviour in the subdivision process is assessed. Nevertheless, the recommended tests are only for tablets divided by hand and do not cover the use of tablet splitter and knife, which are very used

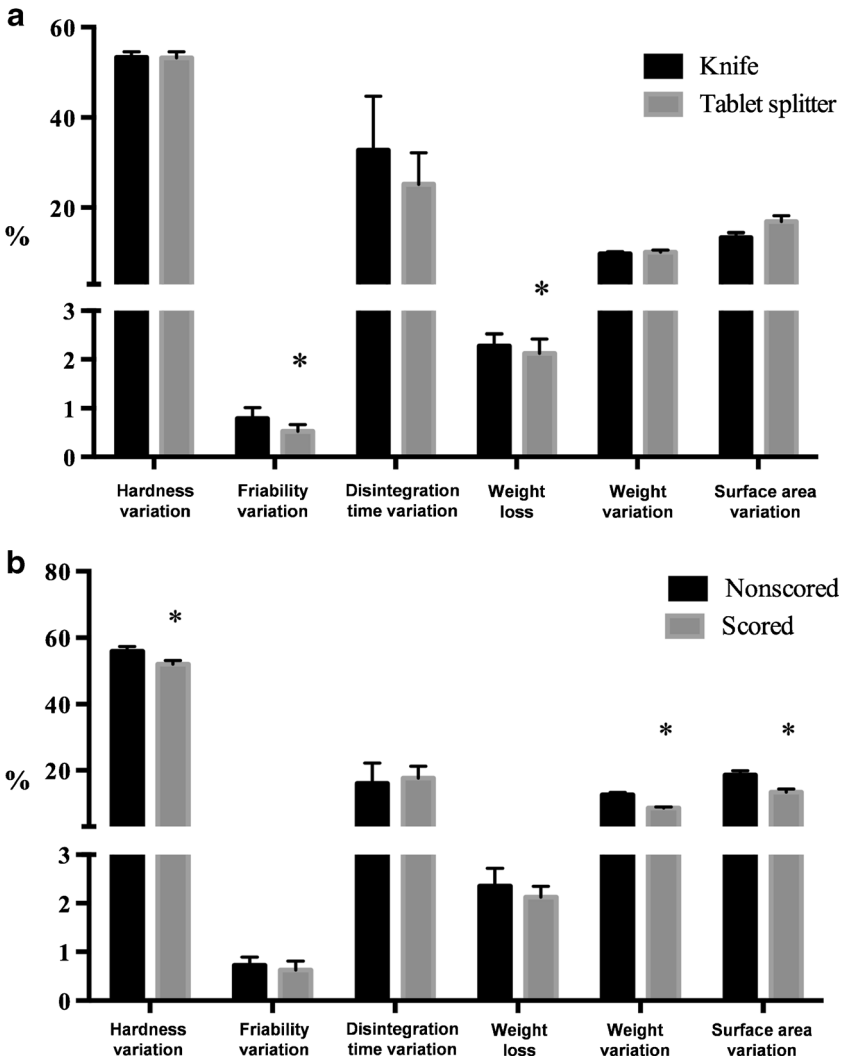

Fig. 4. Data for subdivided tablets depending on the tablet subdivision method (**a**) and on the presence of tablet score (**b**), expressed in percentage as the mean. *Bars* represent the standard error values, and *asterisks* indicate a significant difference between groups ($p < 0.05$)

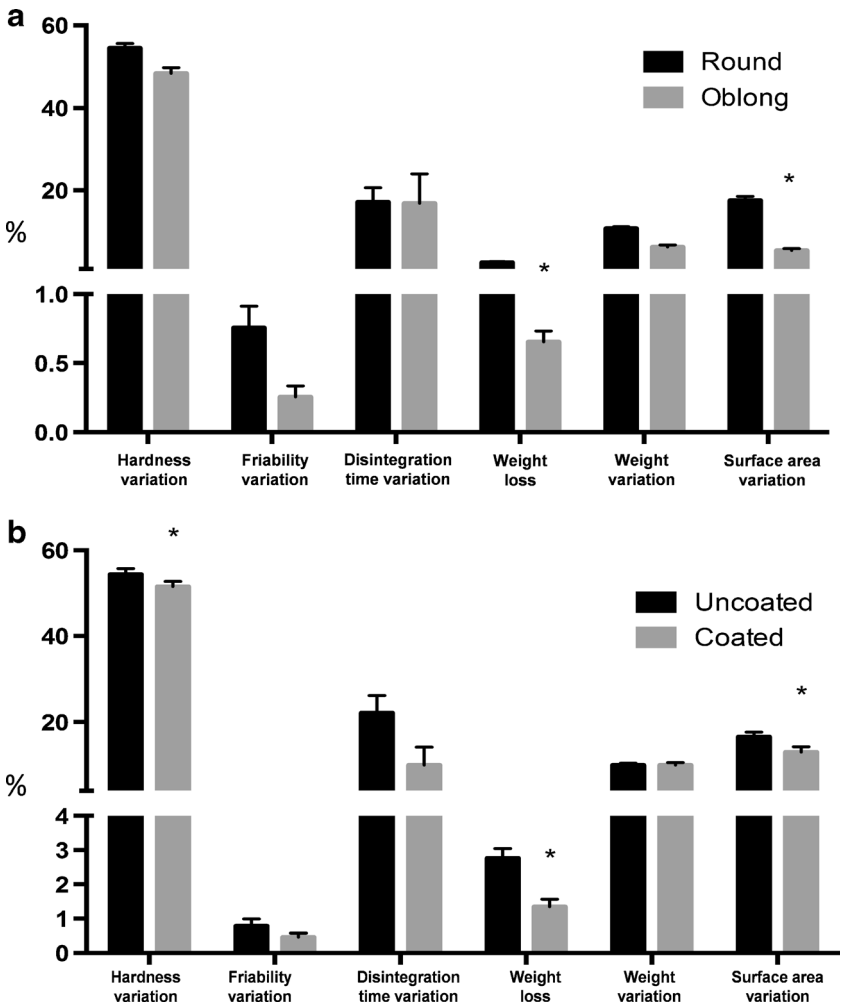

Fig. 5. Data of subdivided tablets depending on the tablet shape (**a**) and on the presence of coating (**b**) expressed in percentage as the mean. *Bars* represent the standard error values, and *asterisks* indicate significant differences between groups ($p < 0.05$)

especially to subdivide small tablets or tablets without break mark (19).

In our studies, the most pronounced differences between innovator and generic drug product occurred with sertraline (Table II), which showed significant differences in all evaluated parameters ($p < 0.05$). In the specific case of this antidepressant drug, side effects such as nausea, insomnia and diarrhoea could be exacerbated due the subdivision process (30). Hence, a better understanding of subdivision tablets is the first step in designing a more suitable tablet for this propose.

According to Fig. 4a, Mann-Whitney U test noted that the splitter tablet produced lower weight loss and friability variation than a knife ($p < 0.001$ and $p = 0.002$, respectively). In theory, a tablet splitter helps centralize the tablet and allow a section in a most appropriate place. The literature shows contradictory conclusions about this issue. Some researchers have indicated better performance using a tablet splitter than a knife (4,18,31). Nonetheless, Boggie and col. found no difference between manual breaking and a tablet splitter, whereas Teng and col. showed superior results in subdivide tablets using a razor blade instead of manual subdivision (14,32). A recent study showed that hand breaking presented superior results in tablet subdivision than tablet splitter. In addition, the authors pointed out that subdivision process is highly influenced by the type of tablet splitter (19).

Figure 4b shows the responses obtained from subdivision in scored and non-scored tablets. Scored tablets presented a lower weight variation (8.6% ± 0.4, $p = 0.000$) than non-scored tablets (12.6% ± 0.7), which is in accordance with the findings of other studies (8,16,17,33). The score delimits the region to be sectioned, providing a more precise division of the tablet. Moreover, this element reduces the thickness of the tablet in the cutting region, facilitating the process.

Following the weight variation results, Fig. 4b also shows a higher variation in the surface area of non-scored tablets (18.6 ± 1.3%, $p = 0.000$) than scored ones (13.4 ± 1.0%). Hardness variation was also lower for scored tablets (52.0% ± 1.2) than non-scored tablets (55.9% ± 14.6, $p = 0.031$). A possible reason for this behaviour may be the more regular forms of split scored tablets. The statistical relationship between surface area variation and hardness variation support this inference ($r = 0.101$; $p = 0.013$).

Tablet shape is usually chosen considering aesthetics and marketing over technical aspects. However, this variable showed a significant effect in two of the six evaluated

parameters (weight loss and surface area variation, $p = 0.000$ for both) (Fig. 5a). Round tablets exhibited weight loss (2.6% ± 0.2), and surface area variation (17.6% ± 1.0) was noticeably higher than those obtained for oblong tablets (0.7% ± 0.8 and 5.5% ± 0.5, respectively). These results agree with other studies which have also shown facility and better outcomes by subdivide oblong rather than round tablets (7,33). The surface contact area for subdivision, which is smaller in oblong tablets, could explain the better results obtained with oblong tablets (33). Hardness and weight variations showed statistical relevance initially, but this result was attributed to the presence of coating. There were no differences for the responses comparing only coated round and coated oblong tablets ($p = 0.811$ and $p = 0.523$, respectively).

Coating provides advantages for tablets submitted to subdivision (Fig. 5b). Coated tablets presented lower weight loss ($p = 0.000$), hardness ($p = 0.022$) and surface area ($p = 0.009$) variations with values of 1.4% ± 0.2, 51.5% ± 1.2 and 13.0% ± 1.2, respectively, than uncoated tablets, which presented 2.8% ± 0.3, 54.4% ± 1.3 and 16.6% ± 1.1, respectively. Coating confers inherent strength and elasticity and consequently holds the core together after subdivision, reducing weight loss and hardness variation, which is connected to film properties (7,34,35).

Finally, the qualitative composition of the studied drug products was identified to analyse the possible influence of diluents on tablet subdivision. The following diluents were found in the selected studied tablets: starch, lactose, MCC and DPD. Figure 6 shows the assessment made for the parameters that showed statistical significance.

Regarding hardness, as expected, the presence of materials with plastic behaviour—MCC and lactose—showed better performances (absence of lactose 57.2% ± 1.3, presence of lactose 51.3% ± 1.2, $p = 0.010$; absence of MCC 57.0% ± 1.7, presence of MCC 51.4% ± 1.1, $p = 0.004$). However, for important responses, such as weight change and weight loss, lactose and MCC have a negative effect on subdivision, increasing weight variation (absence of lactose 7.6% ± 0.6, presence of lactose 11.1% ± 0.4, $p = 0.0001$; absence of MCC 7.3% ± 0.5, presence of MCC 11.3% ± 0.5, $p = 0.0001$) and weight loss (absence of lactose 1.0% ± 0.1, presence of lactose 2.8% ± 0.3, $p = 0.0001$; absence of MCC 1.5% ± 0.3, presence of MCC 2.6% ± 0.3, $p = 0.0056$). In contrast, tablets containing starch and DPD have a beneficial effect on weight variation (absence of starch 11.1% ± 0.5, presence of starch 8.3% ± 0.5, $p = 0.000$) and weight loss (absence of DPD 2.7% ± 0.3, presence of DPD 1.0% ± 0.2, $p = 0.000$).

Excipient also plays an important influence on compressibility factors and on the consolidation behaviour of each material (36). MCC and lactose predominantly present plastic deformation, whereas starch and DPD show fragmentation and elastic conduct (37–39). In this study, the latter group seems to be more suitable for the subdivision process. It is possible that materials that demonstrate predominantly plastic deformation when subjected to pressure, culminating in the rupture of structure, may collapse and cause major variations in weight compared to materials that can undergo elastic deformation and fragmentation that are able to subdivide without suffering major structural damage (5,26).

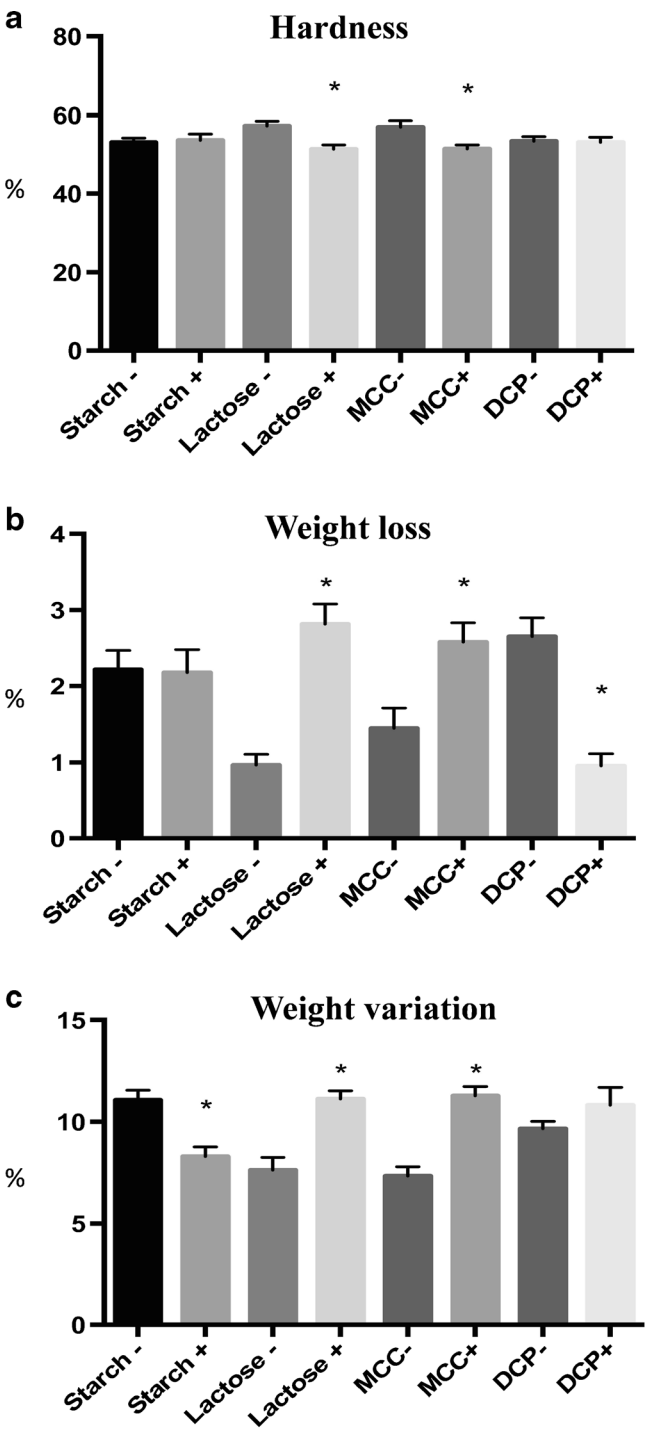

Fig. 6. Impact of the presence (+) or absence (−) of diluents in the hardness (**a**), weight loss (**b**) and weight variations (**c**), expressed in percentage as the mean. *Bars* represent the standard error values, and *asterisks* indicate significant differences between groups ($p < 0.05$)

CONCLUSION

According to this study, a tablet should have the following desirable characteristics to be securely subdivided—oblong shape, scored and coating. Better subdivision in terms of friability and weight loss considering the drug products studied were achieved using the tablet splitter instead of a kitchen knife. As a significant reduction of hardness and resistance of subdivided

tablets has been noticed in all cases, it would be prudent to recommend consumers to immediately use the drug products in halves. In addition, differences in quality control assays found between all generic products and innovator counterparts indicate the necessity of reviewing the health regulations for marketing authorization of generic drug products, at least for new applications. The evaluation of the subdivision capacity of tablets with score, including mechanical assessments of subdivided tablets, currently demanded by the FDA and European Pharmacopoeia, could be an option to solve this issue.

ACKNOWLEDGMENTS

This research was supported by Brazilian agency FAP-DF project number 0193.001023/2015.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest The authors declare that they have no conflict of interest.

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AAPS PharmSciTech, Vol. 19, No. 7, October 2018 (© 2018)
DOI: 10.1208/s12249-018-1144-7

Rapid Communication

The Effects of Fillers and Binders on the Accuracy of Tablet Subdivision

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Received 9 June 2018; accepted 6 August 2018; published online 17 August 2018

Abstract. The effects of excipients on the accuracy of tablet subdivision are severely underinvestigated. In this study, placebo tablets were prepared using a combined mixture design of fillers and binders to evaluate the effect of these excipients on subdivision accuracy. The responses assessed were mass loss, mass variation, tablet fragmentation, and increased friability. Dicalcium phosphate dihydrate (DCP) gave rise to more uniform and denser tablets than microcrystalline cellulose (MCC), thus resulting in greater subdivision accuracy. The binder type, hydroxypropylcellulose (HPC) or polyvinylpyrrolidone (PVP), did not affect the subdivision of DCP tablets. On the contrary, the structural similarity between HPC and MCC led to improved subdivision accuracy for MCC tablets. A less accurate subdivision was observed in tablets prepared with a DCP–MCC combination; this finding could be attributed to irregular binder distribution in this matrix. An optimized response was built using desirability analysis. This study helps to illuminate the relationship between fillers and binders to guide formulation scientists in the development of tablets with better subdivision performance.

KEY WORDS: tablet splitting; binder distribution; cellulose excipients; matrix homogeneity.

INTRODUCTION

Tablets are frequently divided by patients or health professionals for dose adjustment, swallowing facilitation, and cost reduction [1,2]. This procedure is often related to the wide variations in drug dosage and can result in irregular plasma drug concentrations and unpredicted clinical outcomes [1,3].

Most published studies on this subject evaluate the accuracy of tablet subdivision by using drug products that are available on the market [1,3]. The subdivision patterns obtained from these studies reveal that certain characteristics of the tablet, such as oblong format, coating, and scored lines, lead to better subdivision results [1]. Nevertheless, consensus shows that tablet composition is the key to achieving successful subdivision and that excipients play a main role in determining the accuracy of tablet subdivision [4].

Despite this consensus, studies on the effect of pharmaceutical excipients on tablet subdivision are still scarce [4–7]. Until now, the effects of pharmaceutical excipients on tablet subdivision had been described in terms of matrix density, matrix homogeneity, and tablet hardness. A more uniform and denser tablet structure favors subdivision accuracy [4–7]. An appropriate level of tablet hardness can also determine the success of tablet subdivision [4]. What remains to be understood is the role of excipient interaction on subdivision accuracy. To clarify this point, it is important to control the highest number of physical properties of the tablet. In the present study, tablets with different compositions were prepared with the same hardness and thickness by using the wet granulation method. A combined mixture design was applied to determine the effect of fillers and binders on the subdivision accuracy to understand the possible interactions between these materials and their repercussions on the subdivision process. Nonscore tablets were prepared to better discriminate the effects and interactions of excipients on tablet subdivision allowing for their rational use in the development of formulations that are designed to be split.

MATERIAL AND METHODS

Materials

Klucel® ELF (hydroxypropylcellulose (HPC), 40,000 Da) and polyvinylpyrrolidone (PVP)K-30® (58,000 Da) were kindly donated by Ashland (São Paulo, Brazil). Microcrystalline cellulose (MCC) pH 101 and dicalcium phosphate dihydrate (DCP) were obtained from Mingtai (Taiwan). Colloidal silicon dioxide, magnesium stearate, and sodium croscarmellose were purchased from Evonik Degussa GmbH (Essen, Germany) and ValdequímicaProdutosQuímicosLtda (São Paulo, Brazil), respectively.

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Table I. Formulations in the Experimental Design

Formulation	Composition (%, m/m)			
	MCC	DCP	PVP	HPC
1	91	0	0	4
2	91	0	2	2
3	91	0	4	0
4	45.5	45.5	0	4
5	45.5	45.5	2	2
6	45.5	45.5	4	0
7	0	91	0	4
8	0	91	2	2
9	0	91	4	0

All formulations had croscarmellose (3%, m/m), colloidal silicon dioxide (1%, m/m), and magnesium stearate (1%, m/m)

Methods

Experimental Design

A combined mixture design was employed using the filler and binder as input variables. The fillers (91%, *w*/*w*) used were MCC, DCP, or an MCC–DCP mixture at a 1:1 mass ratio. Similarly, HPC, PVP, or their 1:1 mixture was used as binder (4%, m/m). A total of nine different tablet formulations were prepared (Table I). Croscarmellose (3%, m/m), colloidal silicon dioxide (1%, m/m), and magnesium stearate (1%, m/m) were kept constant for all formulations. Three batches of each formulation were produced. Mass loss, mass variation, increased friability, and fragmentation were considered output variables. Design Expert® software 7.1.3 (Stat-Ease Inc., Minneapolis, MN) was used to evaluate the data. The optimized response was calculated by taking all obtained responses into consideration.

Wet Granulation and Tablet Preparation

The different amounts of binder solution prepared with ethanol (30%, m/m) were used to granulate each formulation to reach approximately 75% of the granulation holding capacity [8]. Therefore, the binder concentrations were adjusted accordingly to follow the experimental design. Formulations were wetted, and the resulting mass was granulated (1.0 mm), dried at 60°C, and calibrated (0.85 mm).

Tablets were obtained in a rotary machine using round flat 11.5 mm punches. A worst-case scenario (nonscored and noncoated tablet) was chosen in an attempt to better discriminate the effects of the excipients. The compaction force was adjusted to keep the tablet hardness at the same

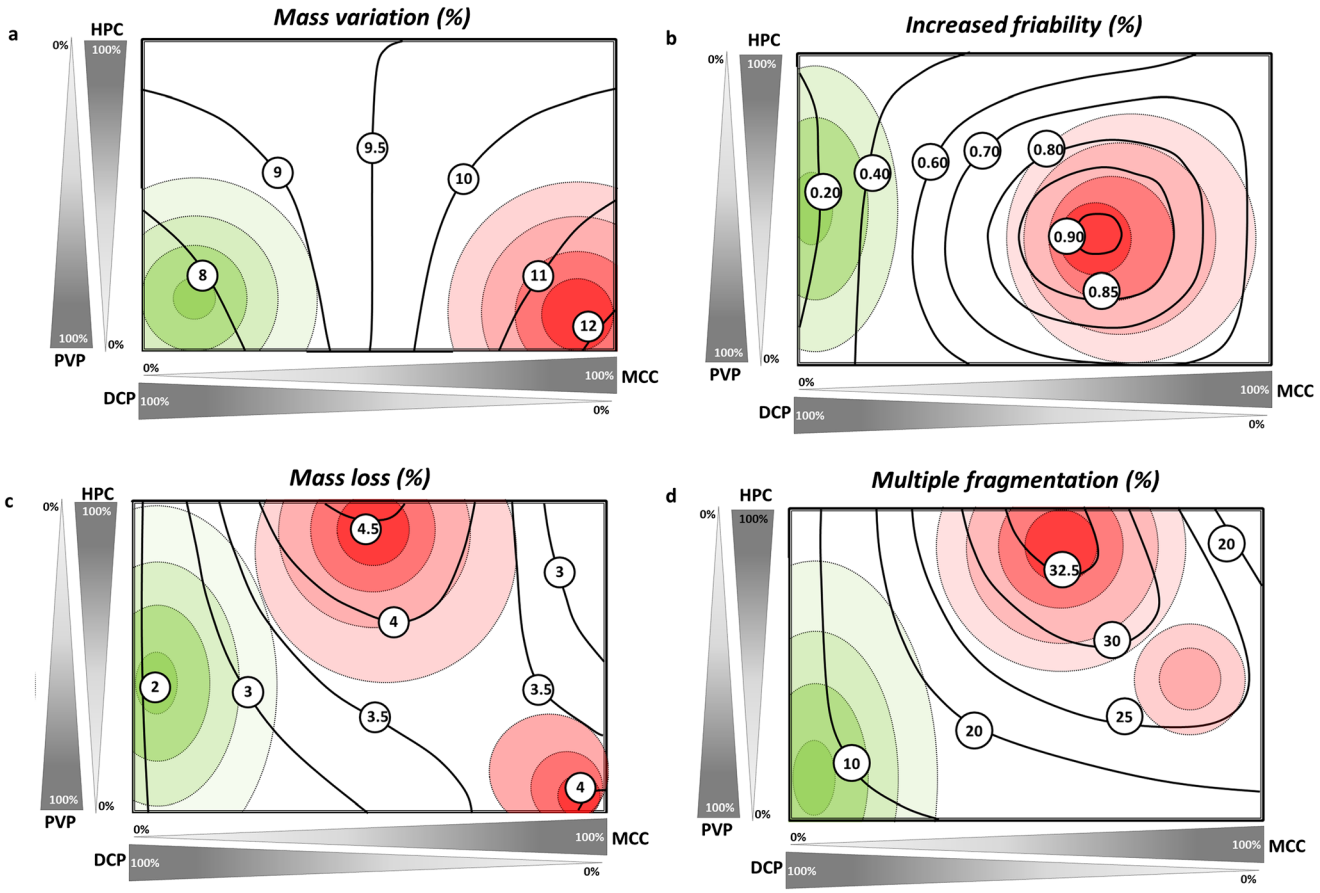

Fig. 1. Response surfaces for mass variation (**a**), increased friability (**b**), mass loss (**c**), and frequency of multiple fragmentations (**d**) of subdivided tablets according to a combined mixture design. The green marks show favorable formulations for subdivision, and the red marks indicate formulations with unfavorable subdivision behavior

Table II. Statistical Parameters of the Mixture Design and the Predictive Equation for Each Studied Response

Fitted model	Mass variation (%) Linear-linear	Increased friability (%) Quadratic-quadratic	Mass loss (%) Quadratic-linear	Multiple fragmentation (%) Quadratic-quadratic
p value	0.0031	0.0002	0.0031	< 0.0001
Adeq. precision	8.1	8.7	5.7	9.3
Predictive equation		=+ 0.7 MCC/HPC		=+ 11.8MCC/HPC
	=+ 9.6MCC/HPC	+ 0.6 MCC/PVP	=+ 1.8 MCC/HPC	+ 17.8 MCC/PVP
	+ 12.4MCC/PVP	+ 0.2 DCP/HPC	+ 4.1 MCC/PVP	+ 2.7 DCP/HPC
	+ 9.4 DCP/HPC	+ 0.3 DCP/PVP	+ 1.9 DCP/HPC	+ 6.5 DCP/PVP
	+ 6.8 DCP/PVP	+ 0.9 MCC/DCP/PVP	+ 1.9 DCP/PVP	+ 103.1 MCC/DCP/HPC
		− 0.6 DCP/HPC/PVP	− 10.9 MCC/DCP/HPC	+ 37.3 MCC/HPC/PVP
		+ 6.0 MCC/DCP/HPC/PVP		

level (64 N ± 2 N). Similarly, the tablet thickness was maintained at 4.46 mm ± 0.03 mm by adjusting the tablet weight.

Tablet Characterization and Subdivision

The tablets were subdivided using a commercial tablet splitter (Inconterm, Brazil) [1]. Thirty tablets from each batch were split. Mass variation was calculated as the difference between the mass of each half and the whole tablet mass divided by two. Mass loss was calculated as the difference between the mass of the whole tablet and the sum of the halves. Friability was calculated as the percentage of mass loss of 20 whole or half tablets of each product tumbled at 25 rpm for 4 min in a friabilometer.

RESULTS AND DISCUSSION

Figure 1 and Table II show the response surfaces of the responses studied and their statistical evaluations and predictive equations. The studied responses show that DCP tablets had superior subdivision behavior to MCC tablets (lower coefficients of predictive equations in Table II; green areas of response surfaces in Fig. 1). The mean values of mass variation and mass loss of the DCP tablets were 7.2 and 1.7%, respectively, compared with 12.7 and 3.8% for the MCC tablets, respectively. The DCP tablet results for these responses were below the mean values reported by other studies [1]. Furthermore, the increase in the friability of the DCP tablets after subdivision was only 0.2%, and multiple fragmentations occurred in less than 5% of the samples. For MCC tablets, the increase in friability exceeded 0.6%, and multiple fragmentations occurred in more than 18% of the samples. The friability data of the halves is a relevant factor in determining the quality of the divided tablets because the halves are handled by the patients and are stored for later use, which can cause further mass loss and compromise therapeutic outcomes. Therefore, DCP tablets showed not only the best subdivision accuracy but also produced halves with superior mechanical properties.

The morphological evaluation of the DCP tablet cross sections revealed a regular and uniform structure that contrast drastically with the looser and more irregular MCC tablets (Fig. 2). Literature shows that subdivision accuracy is improved in uniform and denser matrices [5,7], thus corroborating the present results.

The ionic nature of DCP favors its interaction with the polar groups of binders (ion–dipole interaction), thus explaining the good performance of the tablets prepared with this filler and the two binders tested (green area of the response surfaces in Fig. 1). Similarly, Gupta *et al.* [6] concluded that the subdivision of DCP tablets was not influenced by the binder type. The affinity of binders for the DCP increases the mechanical strength of this material, thus correcting its tendency to fragment. Sovany *et al.* [4] stated that stronger interparticulate bonding and elastic behavior lead to more accurate tablet subdivision.

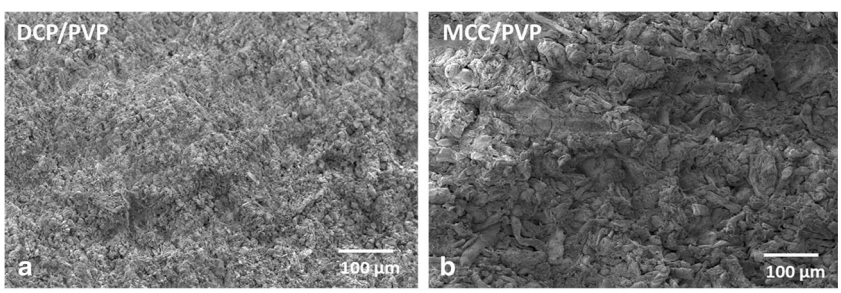

Fig. 2. Cross-sectional view of subdivided tablets by SEM at 150× magnification. MCC–PVP tablets (**a**); DCP–PVP tablets (**b**)

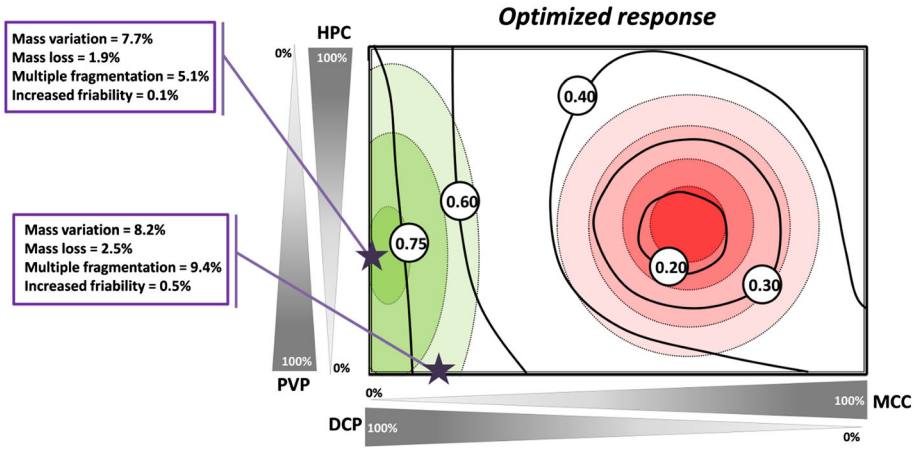

Fig. 3. Response surfaces for the optimized response considering mass variation, increased friability, mass loss, and frequency of multiple fragmentations of subdivided tablets, together with the predicted results of two possible formulations. The green marks show formulations with higher desirability, and the red marks indicate formulations with unfavorable subdivision behavior

The opposite situation was observed in tablets produced exclusively with MCC as filler, in which the binder plays an important role in the subdivision process; this result corroborates the findings of Shah *et al.* [5]. MCC, which has several free hydroxyls, shows more affinity for binding with HPC because of its higher structural similarity, *i.e.*, MCC has the possibility of establishing more hydrogen bonds and dipole–dipole interactions when binding with HPC than when binding with PVP. In fact, the PVP solution gave rise to weaker films, lower binder ingress, and less distribution into the MCC granules; these results have been reported in a previous study [9]. Similarly, Joneja *et al.* [10] reported that HPC gave rise to tablets with higher fracture toughness than PVP. Moreover, MCC tablets produced with PVP showed a higher propensity to break into several pieces [10]. Table II shows that the coefficient values of MCC–PVP are higher than MCC–HPC in three of the four studied responses.

It is important to note the drastic worsening in subdivision results in tablets produced using the combination of MCC and DCP as filler and HPC as binder, particularly for mass loss and multiple fragmentation responses (red central areas of Fig. 1 c, d). The MCC–DCP–HPC coefficients for these responses showed values up to 50 times higher than the other coefficients (Table II). The explanation for this behavior may be in the heterogeneous distribution of the fillers in the granules [9,11]. The great affinity of HPC for MCC produces an irregular distribution of the binder in the granule. Furthermore, the consequent lack of binder action in DCP causes the manifestation of a brittle behavior, thus leading to the higher rates of crumbling and multiple fragmentations of the tablet.

An optimized response was built by considering all studied responses (Fig. 3). Tablets prepared with 100% DCP as filler and a mixture of HPC and PVP at a 0.35:0.65 ratio should provide the best performance in terms of tablet subdivision (desirability of 0.8). It is important to consider that the elastic properties of DCP may limit its use as an exclusive filler in the formulation. Figure 3 also shows areas in which the mixtures of DCP/MCC could be used with acceptable results, such as a 0.75:0.25 DCP:MCC ratio with a desirability of 0.64.

The findings of this study shed light on one of the most relevant aspects in the manufacturing of tablets intended for subdivision, namely, composition. Therefore, it is expected that improving our understanding of the relationships that guide the use of fillers and binders could help in the development of tablets with better subdivision performance. It is important to consider that the active pharmaceutical ingredient and other inert excipients (disintegrants, lubricants, glidants) can affect subdivision performance. Our findings do not exclude the need for developing separate tablet formulations to achieve the best subdivision performance for a given product.

ACKNOWLEDGMENTS

This research was supported by the Brazilian agency CAPES.

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tion histories that must be taken per year, or 90 per day; this amounts to one history every 16 minutes.

The number of pharmacists needed to successfully implement a medication reconciliation system in the ED is also a significant concern and is further complicated by the national pharmacist shortage. There were over 2.4 million registered nurses recorded by the U.S. Bureau of Labor Statistics, compared with 239,920 pharmacists in May of 2006.[3]

ED pharmacists must make definitive decisions on how the specialty is to develop. Medication reconciliation cannot be relied upon to sustain ED pharmacy. It is a foot in the door, but ED pharmacy has much more to offer. The complexity of and time required for medication reconciliation make it prohibitive for pharmacists to take exclusive ownership of this process. Claiming such ownership may prevent ED pharmacists from performing other vital roles.

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The authors have declared no potential conflicts of interest.

DOI 10.2146/ajhp080199

Influence of tablet characteristics on weight variability and weight loss in split tablets

Tablets are often manufactured with a score line in the center to assist in splitting into smaller portions to meet individual needs and to better adjust dosage. Splitting tablets is now being used to save on medication costs. The weight variability in split tablets is well documented.[1-4] However, there is no available literature documenting the influence of the tablet score line, the hardness, and the formulation components (e.g., filler, binder, disintegrating agent) on the weight variability of split tablets. We assessed these influences on verapamil hydrochloride tablets prepared under identical conditions with and without a score line.

A 2^5 full-factorial design was used to evaluate the influence of five variables of verapamil tablets: (1) filler (lactose monohydrate[a] or dibasic calcium phosphate[b]; 600 mg/tablet), (2) binder (hydroxypropyl-methyl cellulose[c] or polyvinyl pyrollidone[d]; 32 mg/tablet), (3) disintegrating agent (sodium carboxy-methyl cellulose[e] or microcrystalline cellulose[f]; 80 mg/tablet), (4) tablet hardness (low or high), and (5) tablet surface (with or without score line). We studied the effect of these variables on the weight variation of split tablets and on tablet weight resulting from splitting. The verapamil hydrochloride[g] content was kept constant at 80 mg/tablet.

Granules were prepared by the fluid-bed wet granulation method and compressed into tablets on an instrumented tablet press[h] fitted with a single 12-mm cylindrical die and flat-faced punch set. The upper punch produced no score line or a single, v-shaped, 0.1-mm deep score line. One hundred tablets were compressed at each of the 32 combinations of the 5 variables. The thickness of resulting tablets varied between 5 and 6 mm. Ten tablets for each combination were randomly selected and weighed individually on an analytical balance[i] before being split with a commercially available tablet splitter.[j] The resulting tablet halves were weighed to determine the weight variability between them. The difference between the tablet weight before splitting and the sum of the weights of the two halves after splitting was used to calculate the weight loss during tablet splitting. Statistical analysis of the data was performed using the analysis of variance function in the JMP software.[k] The a priori level of significance was 0.05.

Weight variability between halves ranged from 10 to 75 mg and, weight loss ranged from < 1 mg to 25 mg/tablet. No significant influence of tablet hardness and binder type was observed on weight variability or weight loss. Scored tablets exhibited a significantly lower mean ± S.D. weight variation (23.5 ± 9.5 mg) and weight loss (2.4 ± 0.8 mg/tablet) as compared to the unscored tablets, for which the corresponding values were 48.0 ± 12.8 mg and 10.3 ± 5.7 mg/tablet, respectively ($p < 0.0000001$ for both comparisons). Tablets prepared with dibasic calcium phosphate as the filler and those prepared with microcrystalline cellulose as the disintegrating agent also showed a significantly lower weight variability and weight loss upon splitting as compared to the tablets prepared with either lactose monohydrate as the filler ($p < 0.005$ for both endpoints) or sodium carboxymethyl cellulose as the disintegrating agent ($p < 0.015$ for both endpoints).

A number of other factors, including mass production techniques and use of different drugs and excipients may influence the weight variability and weight loss because of tablet splitting. However, the study highlights the importance of score line on the tablet surface in limiting the weight variability among split tablets and weight loss during the tablet splitting when compared to the unscored tablets prepared from the same formulation under identical conditions. The practice of splitting tablets when they are not scored should be discouraged for better therapeutic outcomes. A careful selection of

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excipient and processing methods may yield tablets that can be split appropriately when scored.

[a]Foremost Farms USA, Rothschild, WI, lot 8505121710
[b]Di-Cafos, CFB KG, Budenheim, Germany, lot A64000A
[c]Methocel E15 LV, Dow Chemical, Midland, MI, lot 507368
[d]Kollidon 30, BASF Corp, Florham Park, NJ, lot G52297PT0
[e]Emcocel 50M, JRS Pharma, Cedar Rapids, IA, lot E5D6B12
[f]Ac-di-sol, FMC Biopolymer, Newark, DE, lot TN05814969
[g]Fermion Oy, Espoo, Finland, lot 1053328
[h]Minipress, GlobePharma, New Brunswick, NJ.
[i]Mettler-Toledo, Inc., Columbus, OH.
[j]Safety shield tablet cutter, Apothecary Products, Inc., Burnsville, MN.
[k]JMP Software, ver 6.0, SAS institute Inc., Cary, NC.

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The authors have declared no potential conflicts of interest.

DOI 10.2146/ajhp080371

Bias in *AJHP* supplements

For some time, we have noticed bias in *AJHP* supplements that are based on industry-sponsored symposia held during the ASHP Midyear Clinical Meeting.[1] Up until now, we have withheld comments about *AJHP*'s editorial integrity, but after reading the August 1, 2008, supplement, we feel compelled to be more pointed in our criticism.

In that supplement, Dobesh et al.[2] discuss antithrombotic therapy in acute coronary syndrome (ACS). The abstract and the section summarizing the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial results are written in a way that favors the supplement sponsor's product, enoxaparin (Lovenox, sanofi-aventis, U.S.). The OASIS-5 investigators studied enoxaparin and fondaparinux (Arixtra, GlaxoSmithKline), and it was the largest ACS trial to date with about 20,000 patients.[3] The supplement's abstract states, "Since fondaparinux use in patients undergoing PCI [percutaneous coronary intervention] has been associated with an increased risk for catheter-related thrombosis, the use of fondaparinux in PCI patients should be limited." Dobesh et al. discuss OASIS-5 day-9 endpoints and dedicate two paragraphs to describing complications of cardiac catheterization and explaining the lower bleeding rate associated with fondaparinux, compared with enoxaparin. Dobesh et al. fail to mention compelling 180-day outcomes or to include an unbiased discussion of catheter-related complications.

In OASIS-5, fondaparinux was associated with a significantly lower frequency of the composite endpoint of death, myocardial infarction, refractory ischemia, or major bleeding at 180 days, compared with enoxaparin. In addition, other investigators have found fondaparinux to be associated with a statistically lower frequency, compared with enoxaparin, of blood transfusion and bleeding that required surgical intervention.[4]

Details of enoxaparin- and fondaparinux-related catheter complications in OASIS-5 were published before the symposium on which the supplement was based, and catheter-related complications were not prespecified endpoints.[5] In addition, fondaparinux was associated with a statistically lower frequency of complications at vascular access sites, pseudoaneurysms, and large hematomas than enoxaparin. The frequency of catheter thrombosis was not statistically significant between the two medications. In both the enoxaparin and fondaparinux groups, catheter clotting was associated with higher rates of recurrent myocardial infarction but not death. After the investigators adjusted the protocol to give heparin to the fondaparinux group during PCI, there was only one catheter thrombus in a fondaparinux-treated patient who received a suboptimal heparin dose of 5 units/kg.

The OASIS-5 trial was a major step forward in enrolling patients with severe renal impairment. Fondaparinux-associated reductions in death and bleeding were greatest in patients with a glomerular filtration rate less than 58 mL/min/1.73 m^2.[6] Few trials enroll such patients, yet 25–50% of cardiac patients have moderate or severe renal impairment.[7]

We do not blame supplement authors for bias. We have assumed *AJHP* supplements undergo the usual peer review. According to *AJHP*'s website, "Sole-sponsored supplemental issues of *AJHP* may be purchased for $90,000" and are "peer-reviewed by the manuscript development editors."[8] These editors may not have the subject-matter expertise to recognize subtle or even obvious bias. If *AJHP* depends on supplement revenue, it should disclose its review process in the supplement itself or change supplements'

Asia Oceania Journal of Nuclear Medicine & Biology
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Comparison of Treatment Response Achieved by Tablet Splitting Versus Whole Tablet Administration of Levothyroxine in Patients with Thyroid Cancer

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ARTICLE INFO

Article type:
Original article

Article history:
Received: 10 Oct 2017
Revised: 30 Dec 2017
Accepted: 15 Jan 2018

Keywords:
Differentiated thyroid cancer
Levothyroxine
Suppressive therapy
Tablet splitting
TSH

ABSTRACT

Objective(s): TSH suppression by Levothyroxine consumption is a mainstay of thyroid cancer treatment. Tablet-splitting is a worldwide approach in dose adjustment in patients. However, it is highly recommended to evaluate the validity of tablet splitting for each distinctive drug by clinical trials before routinely using tablet halves in clinical practice. In this study we compared the effect of 150 µg dose of Levothyroxine by use of a100 and a 50 µg tablets or one and half 100 µg tablets in Differentiated thyroid cancer (DTC) patients.

Methods: One hundred DTC patients treated with one and half 100 µg Levothyroxine tablets were randomly divided into two groups. The first group continued taking medication as before and the second group received the same daily dose by taking one 100 and one 50 microgram Levothyroxine tablets. The mean changes in TSH and T3 levels and patients weight were compared between the groups.

Results: 91 patients completed the study. Levothyroxine consumption pattern, age, gender distribution, weight and TSH levels were comparable between groups at the beginning of the study. The mean change of body weights, serum levels of T3 and TSH showed no significant difference between groups in different time points during the study (P>0.05).

Conclusion: This study showed similar efficacy of tablet splitting and two tablets administration for Levothyroxine; however, patients preferred two tablets at the end of the study. It can be concluded that tablet splitting can be used as an alternative way when the 50 µg tablet is not available.

▶ Please cite this paper as:
Ashrafpour R, Ayati N, Sadeghi R, Zare Namdar S, Ayati N, Ghahremani S, Zakavi SR. Comparison of Treatment Response Achieved by Tablet Splitting Versus Whole Tablet Administration of Levothyroxine in Patients with Thyroid Cancer. Asia Ocean J Nucl Med Biol. 2018; 6(2): 108-112. doi: 10.22038/aojnmb.2018.26793.1187

Introduction

Differentiated thyroid cancer is the most common malignancy of endocrine system (1-3) and its prevalence is increasing worldwide. As this pathology mostly occurs in the middle age population and it has excellent prognosis, the patients are expected to live for a long time after

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diagnosis. Replacement or suppressive therapy with Levothyroxine is the standard therapeutic protocol in these patients following total thyroidectomy and radioactive iodine therapy. The suggested dose of Levothyroxine in an adult DTC patient is 1.6 to 2 microgram per kilogram of body weight (μg/kg) (3), equivalent to 100 to 200 micrograms of Levothyroxine on a daily basis.

Tablet splitting is a popular way of daily dose adjustment with better social acceptability, more convenience, and cost saving for the patient and society compared to simultaneous use of two tablets with different doses.(4, 5) However, this method is not suitable in all patients or for all drugs and it may result in inaccurate dosing.(6) It has been strongly recommended to access the splitting impact of each individual medication by clinical trials before their routine use.(7) This issue is of greater concern in the medications with narrow therapeutic index such as Levothyroxine. Although lots of trials have been done on appropriateness of tablet splitting in different medications (8-13) and different underlying diseases (14-19), to the extent of our knowledge, there is no published study regarding the clinical impact of Levothyroxine tablet splitting in the literature. Only an in-vitro assessment has been done on uniformity content of splits tablets of Levothyroxine Sodium which showed high probability of uniformity failure in tablet halves. (20) The aim of this study is to compare the effectiveness of tablet splitting with taking two tablets of Levothyroxine in DTC patients.

Methods

One hundred differentiated thyroid cancer patients who were under suppressive therapy with one and a half 100 μg levothyroxine sodium tablets were included in the study. The serum TSH and T3 levels were measured in all patients at baseline, and then they were randomly divided into two groups. The first group continued taking medication as before and the second group received the same daily dose by taking one 100 and one 50 microgram Levothyroxine tablets. Thyroid function tests were repeated at least three weeks later and the results were compared. To ensure consistency of used drug in patients, all tablets used in these patients were produced by the same company (Iran-hormone Company) that is the most common generic form in Iran. Consumption pattern of Levothyroxine tablet and plasma levels of TSH and T3 and the patients' weight were recorded at the beginning and the end of the study and the mean changes in TSH and T3 levels and weight in both groups were compared. Confounding variables such as time of using medication, and other used medicines were recorded and compared between two groups.

For evaluation of normal distribution of the study variables, Kolmogorov-Smirnov test was used. For comparison of study variables between groups, independent sample t-test was used and level of significance was set at $P<0.05$.

Results

One hundred DTC patients, 29 male (29%) and 71 female (71%) with the age range of 18 to 76 years (mean±SD =41.9±13.3) were included in the study. Among these 100 patients, 9 (2 cases from group 1 and 7 cases from group 2) were excluded from the study. The cause of exclusion of patients from the first group was discontinuation of drug for repeating radioactive iodine therapy in one of patients and decision for performing diagnostic whole body iodine scan in the other one. The cause of exclusion of patients from second group was discontinuation of drug for treatment evaluation in off-T4 status (2 cases), patient's decision to leave the study (2 cases), no referral after two months and change it to previous form of drug usage (2 cases) and changing the Levothyroxine dose by endocrinologist (1 case). Consequently, 48 patients (52.7%) in group 1 (daily intake of 1.5 levothyroxine 100 μg tablets) and 43 (47.3%) in group 2 (daily consumption of one 50 μg tablet and one 100 μg tablet) completed the assessment.

The mean time interval between two assessments was 78.5 (26 to 175 days) with the standard deviation of 33.6.

All variables in the study had normal distribution and independent sample t-test was used for comparison of variables between groups. 12 (25%) patients in the first and 14 (32.6%) patients in the second group were male ($P=0.42$). The age distribution and initial measured quantities including patients' weight, blood level of TSH and time interval between two tests were similar between the two groups at the beginning of the study (Table 1). T3 plasma level was statistically different between two groups ($P=0.01$) (Table 1).

The Levothyroxine consumption pattern was unchanged in both groups at the first and at the end of the study.

Table 2 shows the dependent variables at baseline and end of study and the comparison of changes between the groups. The mean changes of patients' weight and serum levels of TSH and T3 were not statistically different between two groups and the p values were 0.28, 0.29 and 0.74

Table 1. Comparison of initial variables between two groups

	Range	Group 1 (mean±SD)	Group 2 (mean±SD)	*P value*
Age (year)	18-76	42.3±13.4	41.5±13.1	0.75
Initial Weight (Kg)	36-101	71.9±9.1	73.0±11.9	0.07
Initial TSH (mU/L)	0.005-3.58	0.31±0.43	0.38±0.66	0.6
Initial TT3 (mU/L)	78-264	130.0±27.3	152.2±36.5	0.01
Time interval between two tests (days)	26-175	82.2±40.9	74.6±23.7	0.29

Table 2. Comparison of variables change at the beginning and end of the study between two groups

	Group 1 (Mean±SD)	Group 2 (Mean±SD)	*P value*
Weight (Kg)			
W_0	71.9±9.1	73.0±11.9	
W_1	72.2±8.9	72.8±12.4	0.28
ΔW (W_0-W_1)	-0.36±2.37	0.28±1.73	
Serum TSH (mU/L)			
TSH_0	0.31±0.43	0.38±0.66	
TSH_1	0.21±0.34	0.41±0.69	0.29
ΔTSH (TSH_0-TSH_1)	0.10±0.30	-0.03±0.86	
Serum TT3 (mU/L)			
$TT3_0$	130±27.3	152±36.5	
$TT3_1$	138±33.2	155±38.9	0.74
$\Delta TT3$ ($TT3_0$-$TT3_1$)	-7.3±39.8	-3.4±52.6	

TSH: Thyroid Stimulating Hormone, TT3: Total T3

respectively (Table 2).

At baseline, twenty patients (25.6%), including ten patients in the first group (23.3%) and ten patients in the second group (28.6%) declared that they prefer using two tablets instead of tablet splitting which was statistically similar between the two groups (P=0.31). The same question was repeated at the end of the study, which the result was unchanged in group 1 while in the second group 78.6% of patients preferred the use of two tablets (instead of tablet splitting) and this time, the difference between two groups in their consumption preference was statistically significant (P<0.001). Considering the increasing cost of medicines by using two tablets instead of tablet splitting at the rate of 3$ per year, the question was repeated and there was no change in the preferences of patients (Table 3).

Table 3. Patients preference about method of Levothyroxine consumption at the beginning and end of the study

	No comments	Two tablets (One 100 + one 50 µg LT4 tablets)	Tablet Splitting (1.5 tablets of 100 µg LT4)
Beginning of the study			
All Patients	59%	15.4%	25.6%
Group 1	55.8%	20.9%	23.3%
Group 2	62.9%	8.6%	28.6%
End of the study			
All Patients	37.6%	13%	49.4%
Group 1	55.8%	20.9%	23.3%
Group 2	19%	78.6%	2.4%

Discussion

This study was done to compare the performance of using 1.5 tablets of 100 µg Levothyroxine and the simultaneous using of one 100 and one 50 µg tablets in patients with DTC. To the extent of our knowledge, this is the first study which assessed the efficacy of tablet splitting for Levothyroxine Sodium in clinical practice.

The size, shape and hardness of each kind of drug have influence on uniformity of tablet pieces and stability of blood levels of that medicine (18, 21-23). There is only one study in the literature which evaluated the uniformity of Levothyroxine halves as well as their stability in the laboratory. (20) The study showed similar stability between half and whole Levothyroxine tablets. However as the chemical imaging analysis revealed heterogeneous distribution of content, the potential likelihood of under or over dosage using tablet halves remained a clinical concern. The current study verified the same clinical effect of using each of these two methods in a large group of DTC patients. This finding is of great clinical significance in daily practice from two different aspects including acceptability of tablet splitting for this specific medication (Levothyroxine) as well as its appropriateness in this specific population of thyroid cancer patients. As DTC patients are routinely on suppressive therapy with Levothyroxine, the nervousness and anxiety are common complaints among them (24) which have the potential of interfering with accurate tablet splitting. However, this study showed no significant impact of underlying disease and its complications on tablet splitting accuracy.

Changing in patients' preference after taking levothyroxine in new way (using two tablets) was an interesting observation and showed that among the 22 patients in group 2 which initially had no preferred route of administration, 14 people (63%), preferred it to tablet splitting method after experiencing two tablets taking. This observation was in contrary with previous data which mentioned the convenience consumption as an obvious advantage of tablet splitting.(25-27)

Another mentioned advantage for tablet splitting in the literature is reducing health expenses (4); however at the moment, this point is not important issue for patients in our country due to slight difference in drug costs between these two methods of administration.

Because the patients were assessed under the administration of Levothyroxine, T4 hormone level was not assessed and TSH and T3 levels as well as patients' weight were used as quantitative variables. A limitation of this study was unchecked fT3 and fT4 levels in patients.

There was no statistically significant difference between two groups in terms of laboratory tests interval; however, the lesser mean interval in the second group is probably due to the limited number of new tablets we provided and personal sensitivity due to being faced with new method of Levothyroxine taking.

In this study, significant change was observed in patient preference after taking two tablets however as the patients were provided with new Levothyroxine tablets (50 microgram) by department without charging, some key preference factors such as cost and availability were not available for assessment.

Conclusion

This study showed similar efficacy of tablet splitting and taking two tablets of Levothyroxine with different doses in DTC patients. It can be concluded that tablet splitting can be used as an alternative way of Levothyroxine administration when the 50 µg tablet is not practically available.

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BMJ Paediatrics Open

Content uniformity of quartered hydrocortisone tablets in comparison with mini-tablets for paediatric dosing

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To cite: Madathilethu J, Roberts M, Peak M, *et al*. Content uniformity of quartered hydrocortisone tablets in comparison with mini-tablets for paediatric dosing. *BMJ Paediatrics Open* 2017;**2**:e000198. doi:10.1136/bmjpo-2017-000198

Received 22 August 2017
Revised 27 November 2017
Accepted 29 November 2017

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ABSTRACT

Objectives Children requiring cortisol replacement therapy are often prescribed hydrocortisone doses of 2.5 mg, but as this is commercially unavailable 10 mg tablets, with functional break lines, are split commonly in an attempt to deliver the correct dose. This study aimed to determine the dose variation obtained from quartered hydrocortisone tablets when different operators performed the splitting procedure and to ascertain whether better uniformity could be attained from mini-tablets as an alternative formulation.

Methods Hydrocortisone 10 mg tablets were quartered by four different operators using a standard pill splitter. Hydrocortisone 2.5 mg mini-tablets (3 mm diameter) were formulated using a wet granulation method and manufactured using a high-speed rotary press simulator. The weight and content uniformity of the quartered tablets and mini-tablets were assessed according to pharmacopoeial standards. The physical strength and dissolution profiles of the mini-tablets were also determined.

Results More than half of all quartered 10 mg tablets were outside of the ±10% of the stated US Pharmacopoeia hydrocortisone content (mean 2.34 mg, SD 0.36, coefficient of variation (CV) 15.18%) and more than 40% of the quartered tablets were outside the European Pharmacopoeia weight variation. Robust mini-tablets (tensile strengths of >4 MPa) were produced successfully. The mini-tablets passed the pharmacopoeial weight and content uniformity requirements (mean 2.54 mg, SD 0.04, CV 1.72%) and drug release criteria during in vitro dissolution testing.

Conclusion This study confirmed that quartering 10 mg hydrocortisone tablets produces unacceptable dose variations and that it is feasible to produce 3 mm mini-tablets containing more accurate doses for paediatric patients.

What is already known on this topic?

- Children often require a hydrocortisone dose of 2.5 mg but there is no suitable, licensed, formulation available.
- Hydrocortisone 10 mg tablets, with functional break lines, are split commonly in an attempt to deliver the correct dose.
- Mini-tablets are an alternative and acceptable oral dosage form for children as young as 6 months old.

What this study hopes to add?

- Quartering 10 mg hydrocortisone tablets produces unacceptable dose variations.
- Additional variability in dosing could be introduced by different operators.
- It is feasible to produce 3 mm hydrocortisone mini-tablets that meet pharmacopoeial requirements of weight and dose uniformity.

INTRODUCTION

Hydrocortisone is the preferred cortisol replacement therapy in childhood, because it is of lower potency than the synthetic glucocorticoids and may be associated with fewer side effects.[1] Hydrocortisone doses of 8 mg/m^2/day,[2] given in three to four divided doses, are thought to be adequate for cortisol replacement therapy in childhood. Higher, supraphysiological doses of 10–15 mg/m^2/day are used to treat patients with congenital adrenal hyperplasia (CAH),[3] in whom the goal of treatment is to achieve suppression of adrenocorticotropic hormone (ACTH) drive to the adrenal gland, while avoiding the adverse effects of glucocorticoid excess.

Liquid hydrocortisone formulations, such as a 1 mg/mL oral suspension, are only available as unlicensed specials and in addition to the general limitations of transport, storage and stability there are potential concerns relating to the bioavailability of liquid hydrocortisone formulations.[4] In paediatric practice, 2.5 mg hydrocortisone doses are prescribed frequently and to achieve these doses, it is recommended that tablets are divided or crushed.[3] Crushing and dissolving tablets may result in unacceptably high variability of dosing[2 3] and it may be preferable to quarter 10 mg tablets. The hydrocortisone 10 mg tablets licensed for oral administration are quarter scored, allowing them to be

divided into equal halves or quarters.[5] However, despite the presence of functional break lines, splitting may result in unequal parts thereby producing unequal doses and loss of mass due to crumbling.[6]

To date, most data relating to the medium-term/long-term outcomes of children with CAH report features more likely to represent over, rather than under, dosing: obesity, insulin resistance, elevated leptin levels, dyslipidaemia and impaired glucose metabolism.[7–10] However, working memory performance is lower in children with CAH than in unaffected relatives,[11] and health-related quality of life is also reported to be reduced, with boys and girls equally affected, suggesting that this is not simply related to androgen excess in girls and associated disorders of sex development.[12] Erratic and inadequate doses of hydrocortisone may contribute to these adverse effects.

No current licensed oral hydrocortisone formulation adequately meets the dosing requirements of children. Mini-tablets provide an alternate to standard tablets and oral liquids mainly for paediatric patients, ≥4 years of age. Variations exist in the defined size of mini-tablets in literature, but a diameter of ≤3 mm is commonly compatible with paediatric patients.[13] Mini-tablets can be administered to paediatric patients as young as 6 months old with their food/beverages and recent studies have demonstrated mini-tablets to be more acceptable than oral syrups.[14–16]

AIMS AND OBJECTIVES

The aim of this study was to manufacture 3 mm mini-tablets to provide a 2.5 mg dose of hydrocortisone and to compare the content uniformity of the mini-tablets against quartered hydrocortisone tablets. The content uniformity of hydrocortisone mini-tablets and the quarters of commercial hydrocortisone tablets was also determined. The tensile strength of the mini-tablets and their compliance with the pharmacopoeial tests for dissolution and uniformity of mass were also assessed.

MATERIALS AND METHODS

Materials

Hydrocortisone (10 mg) tablets (Auden Mckenzie Pharma Division, UK) were used for the dose uniformity study. Analytical grades of hydrocortisone (Sigma Aldrich, UK); water (Liverpool John Moores University, Liverpool, UK); Methanol (Sigma Aldrich) and Acetonitrile (Fischer Scientific UK, Loughborough, UK) were used for high-performance liquid chromatography (HPLC) analysis.

Mini-tablets were manufactured using hydrocortisone European Pharmacopoeia (Ph. Eur.; Courtin and Warner, UK), Microcrystalline cellulose (Avicel PH101; FMC, Brussels, Belgium), lactose (Pharmatose 200M; DFE Pharma, Goch, Germany), hydroxypropyl methyl cellulose 603 (Shin-Etsu Chemicals, Tokyo, Japan), croscarmellose sodium (Ac-Di-Sol; FMC Europe NV, Brussels, Belgium), silicon dioxide (Aerosil 200; Degussa-Hüls AG, Frankfurt, Germany) and magnesium stearate (BDH Laboratory Supplies, Poole, UK).

Table 1 Composition of the mini-tablets

Component	% per batch
Hydrocortisone	16.67
Microcrystalline cellulose	22.40
Lactose monohydrate	51.60
Hydroxypropyl methyl cellulose	3.00
Croscarmellose sodium	5.00
Colloidal silicon dioxide	0.33
Magnesium stearate	1.00

Formulation and manufacture of mini-tablets

The mini-tablet formulation was prepared using a wet granulation technique to ensure uniformity of die fill, since adequate flowability of a formulation is essential for the manufacture of mini-tablets due to the small size of the die orifice.[17] All of the excipients listed in table 1 (with the exception of the glidant (Aerosil) and the lubricant (magnesium stearate) were blended with hydrocortisone for 5 min using a Turbula Shaker Mixer type 2C (Willy A. Bachofen, Basel, Switzerland) at 42 rpm. The blended powder mixture was then transferred to a Model KM330 series planetary mixer (Kenwood, UK). Water (0.48 mL per g of powder) was added uniformly during mixing by spraying with an atomiser from a distance of 10–15 cm from the powder bed over a period of 15 min. The wet powder mass was screened evenly onto a flat, stainless steel tray and oven-dried overnight at 40°C. Dry granules were screened using a 1 mm aperture sieve prior to separation into size fractions using a laboratory shaker (Endecotts, UK). Granules in the size range 125–355 µm were subsequently blended with glidant (5 min) and lubricant (2 min) using the Turbula Shaker Mixer. The bulk density (ρB) of the granules in the size range of 125–355 µm was determined by filling a measuring cylinder with a known weight of granules. The tapped density (ρT) was determined by dropping the volumetric cylinder 250 times from a height of 2.5 cm using a dropbox. The tapping procedure was repeated until there was no change in the volume of the granule giving the tapped density. The % Carr's Compressibility Index (equation 1) and Hausner ratio (equation 2), both indicators of flowability[18] in fluencing key tablet parameters such as mechanical strength and weight uniformity, were calculated.

$$\text{Carr's } (\%) = \frac{\rho T - \rho B}{\rho T} \times 100 \quad (1)$$

$$\text{Hausner Ratio} = \frac{\rho T}{\rho B} \quad (2)$$

The mini-tablets were produced using a Stylcam 100R rotary press simulator (Medel'Pharm, Beynost, France) fitted with 3 mm flat-faced, single-tip tooling at a speed of 20 rpm. A compression force of 1–2 kN

(compression pressure of 140–280 MPa) was maintained with a fill height of 7.10 mm.

Tensile strength

The dimensions of 10 mini-tablets were measured using a digital micrometer (Mitutoyo, Tokyo, Japan) and their crushing strengths were determined with a 6D Tablet Tester (Schleuniger, Germany). Values were used to calculate the tensile strength, σ, using equation 3,[19] where P is the crushing strength (N), D is the diameter (mm) and T is the tablet thickness (mm).

$$\sigma = \frac{2P}{\pi DT} \quad (3)$$

Content uniformity analysis of hydrocortisone tablets and mini-tablets

An Agilent 1200 series with Variable Wavelength Detector (Agilent Technologies, UK) set to 254 nm was used with a 4.6 mmx15 cm column containing 5 µm packing of octadecyl silane chemically bonded to porous silica (Phenomenex, HyperClone 5µ ODS C18). The mobile phase (degassed 50:25:25 mixture of water, acetonitrile and methanol) flow rate was 1 mL/min and an injection volume of 10 µL was used. Chemstation open lab CDS software for LC and LC-MS Rev C.01.05 (Agilent Technologies) were used for all data analysis.

Standard solutions of hydrocortisone (0%–0.2% w/v) were prepared and filtered into HPLC vials using a 0.45 µm PTFE filter (Agilent Technologies) and 5 mL syringe. The peak area–concentrations response was acceptably linear (R^2=0.9985), and thus a 0.01% w/v was used as a single-point calibration for the assays. The retention time of hydrocortisone was 4.0 (±0.2) min. The active content of whole hydrocortisone 10 mg tablets was determined by weighing and dispersing individual tablets into 100 mL mobile phase by sonification. Each tablet was analysed in duplicate. The hydrocortisone content of quartered tablets was determined, each individual tablet was weighed and, using a Deluxe Pill Splitter (W+W Medsystems, UK), cut into quarters. Each quarter was weighed and dispersed into 25 mL mobile phase by sonification. Each tablet quarter was analysed in duplicate. Four individuals each quartered five tablets to account for interoperator variability. The operators, comprising two students and two academics, had no previous experience of tablet splitting. The quarters were then weighed and assayed.

The active content of the 2.5 mg hydrocortisone mini-tablets was determined by weighing and dispersed individual mini-tablets into 25 mL mobile phase by sonification. As per US Pharmacopoeia (USP) 905 (uniformity of dosage units), 10 whole mini-tablets were analysed per batch.[20] Each mini-tablet was analysed in duplicate. All solutions were filtered into HPLC vials using a 0.45 µm PTFE filter (Agilent Technologies) and 5 mL syringe prior to analysis.

According to USP (905) uniformity of dosage units, the acceptance value (AV) is calculated using equation 4, where X is the sample mean as a % of label claim, k is 2.4 for L1 criteria and s is the SD of the sample.[20] M is dependent on the sample mean and if X ≥98.5% and ≤101.5% of the label claim then M=X and, as in the present study, (M–X) becomes zero. The L1 criteria states that 10 samples should be tested and the AV should be ±15%.[20]

$$Aceptance\ Value = \left(M - X\right) + ks \quad (4)$$

Weight uniformity analysis of hydrocortisone tablets and mini-tablets

The Ph. Eur. monograph 'Uniformity of mass of single-dose preparations' method[21] was employed to determine the uniformity of weight of the 2.5 mg mini-tablets, and quartered 10 mg hydrocortisone tablets. Twenty tablets and mini-tablets were weighed individually and their mean weights calculated. The products failed if >2 of the individual tablets' weight deviated by more than 10% (mini-tablets) or 7.5% (tablets) from the average weight and if one tablet weight deviated by >20% (mini-tablets) or 15% (tablets) from the average weight.[21] For quartered tablets, the mean weight was calculated and the percentage of samples that failed to meet the same weight variation criteria as mini-tablets was calculated.

Drug release from hydrocortisone mini-tablets

The dissolution method from USP monograph for hydrocortisone tablets was used,[22] using a Varian VK 7010 dissolution apparatus (Agilent Technologies) attached to UV spectrophotometer (Cary 50 UV spectrophotometer) at 248 nm. USP apparatus 2 (paddle apparatus), with a paddle speed of 50 rpm and 900 mL of water as the dissolution media (at 37°C) were used for the test.[23]

Statistical analysis

The weight and content uniformity of tablet quarters (data were normally distributed) were compared by one-way analysis of variance using the Minitab V.17.1.0 statistical software package (Minitab, USA). A P value of less than 0.05 was considered significant. Regression analysis was used to determine the correlation coefficient (R^2 value) between weight and content of quartered hydrocortisone tablets.

RESULTS

Splitting of hydrocortisone tablets

The tablets used for the study were convex, diamond shaped and quarter scored allowing them to be divided into equal halves or quarters.[5] The assay of the whole hydrocortisone tablets gave >98% recovery, which is within the specified 90%–110% limits of the USP monograph for hydrocortisone tablets.[22] The mean weight of whole hydrocortisone tablets was 244.18 mg (SD 1.70 mg, coefficient of variation (CV) 0.7%).

The recovered weights of the quartered tablets indicated that approximately 2% mass was lost during the subdivision process. The expected weight for each tablet quarter was 61.05 mg, based on the mean whole tablet

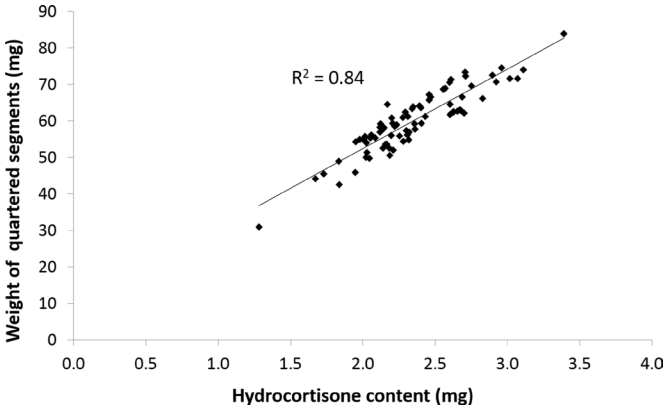

Figure 1 Correlation between weight and content of quartered hydrocortisone tablets.

weight. The obtained weight was 59.83 mg (SD 8.45 mg). However, 33 of the 80 (41%) quartered tablets failed to meet the Ph. Eur. monograph specification.[21] Based on the mean mass of 59.83 mg, the criteria would allow quartered tablets to have a mass in range 53.85–65.81 mg.

The mean content of hydrocortisone in all of the quartered tablets (n=80) was 2.34 mg (94% of 2.5 mg target dose), with a CV of 15%, range 1.28 (51%) to 3.39 mg (136%). Of the 80, 43 quartered tablets (54%) failed to achieve ±10% (2.25–2.75 mg) of the target 2.5 mg dose.

Figure 1 shows the correlation between quartered tablet weight and hydrocortisone content, which explains the large number of substandard hydrocortisone doses in the quarters, as content is directly related to weight.

Operator bias

The data obtained by the four individual operators when performing the tablet quartering is summarised in table 2. Although there was no significant difference in the mean weights (P=0.206) or mean hydrocortisone content (P=0.253) of the quartered tablets produced by the different operators, there were marked differences in the ranges obtained. All four operators produced quartered tablets outside of the weight variation limits specified. Splitting by operator A resulted in a mean hydrocortisone content of 2.40 mg (96% of the target dose) but had the largest variation between the quantities; 51%–136% of the target 2.5 mg dose per quarter. Operators B and C obtained a mean quarter content of 2.23 and 2.22 mg (89% of 2.5 mg target dose), respectively, and operator C had a much narrower range for the hydrocortisone content in quartered tablets at 78%–103%. Operator D on the other hand obtained a mean hydrocortisone content of 2.51 mg (100.4% of target) but the range was relatively high at 73%–124% of the target dose. The mean hydrocortisone contents for operators B and C were outside of the ±10% limit stated in the USP.[20] In addition to this, each of the operators had individual quarters that had hydrocortisone contents outside of the ±10% limit.

Mini-tablets

Hydrocortisone mini-tablets were manufactured successfully under simulated rotary press production conditions. The tapped density of granules used for the manufacture of the mini-tablets was determined as 0.48 g/mL and the Carr's Index value of 16% and Hausner ratio of 1.19 indicated a fair flowability. The Stylcam is a high precision, single station press capable of producing up to 2400 tablets per hour using an automatic feeder operates using a mechanical cam, which produces a biaxial compaction profile analogous to that of a rotary tablet press.

Although mini-tablets were produced at a relatively high compression speed of 20 rpm (equivalent to a rotary press production rate of approximately 80 000 tablets per hour[24]), the flow of the granules from the hopper into the narrow die orifice during manufacture was satisfactory and all mini-tablets met the pharmacopoeial specification for uniformity of mass.[21] Consistent and high tensile strengths were also achieved throughout the batch as shown in table 3, indicating a good compactibility of the granules. Figure 2 illustrates that hydrocortisone was released rapidly and consistently from mini-tablets under in vitro dissolution conditions. The full dose was released within 10 min from all mini-tablets, thus passing the dissolution specification for immediate release dosage forms.[23]

Content uniformity analysis carried out on 10 mini-tablets gave an AV of 4.37% when using equation 4, thus meeting the USP (905) Uniformity of Dosage L1 criteria. Furthermore, mini-tablets obtained a mean hydrocortisone content of 2.54 mg (101.68% of target dose) which is compliant to the USP.[22] These weight and content uniformity data for hydrocortisone mini-tablets demonstrate clear superiority over quartered 10 mg hydrocortisone tablets and, unlike manipulated tablets, mini-tablets did not fail compliance with any of the USP requirements.

Table 2 Weight and content uniformity of hydrocortisone tablet quarters (n=20 for each operator)

Operator	Mean weight, mg (SD)	CV (%)	Range (mg)	Mean hydrocortisone content, mg (SD)	CV (%)	Range (mg)
A	59.67 (11.49)	19.26	31.00–83.90	2.40 (0.46)	19.06	1.28–3.39
B	60.18 (8.63)	14.34	44.20–73.40	2.23 (0.31)	13.92	1.67–2.71
C	60.14 (4.39)	7.30	54.30–69.00	2.22 (0.18)	7.95	1.95–2.57
D	59.33 (8.38)	14.13	42.50–74.00	2.51 (0.36)	14.23	1.84–3.11

CV%, coefficient of variation.

Table 3 Weight (n=20), strength and content (n=10) of 3 mm hydrocortisone mini-tablets

Mean weight, mg (SD)	CV (%)	Mean tensile strength, MPa (SD)	Mean content, mg (SD)	Mean content as a percentage of 2.5 mg target dose (%)	CV (%)
16.40 (0.64)	3.93	4.45 (0.50)	2.54 (0.04)	101.68	1.72

CV%, coefficient of variation.

DISCUSSION

The availability of age-appropriate medicines for children as solid dosage forms remains a pressing need. The European Medicines Agency (EMA) Paediatric Committee's Formulation Working Group recommends that for younger patients, those aged 6–8 years, tablets of 6–7 mm with appropriate shape are acceptable.[25] Growing evidence suggests that some children may have already acquired the ability to swallow tablets from an earlier age or can be taught using behavioural training interventions, especially those with severe diseases,[26] such as children with HIV as young as 3 years who were prescribed stavudine as a solid dosage form.[27]

There is limited evidence to support the use of dosage from manipulation to obtain an intended dose in paediatric practice.[28] A study in UK hospitals reported that in paediatric practice, 42%–62% of manipulations involved tablets and 6% of total manipulations were steroid drugs.[29] In the absence of an age-appropriate solid dosage form of hydrocortisone, parents/carers, young people and healthcare professionals are required to manipulate 10 mg tablets to derive an intended dose for use in paediatric practice. The data presented in this report clearly demonstrate that children treated with 2.5 mg doses of hydrocortisone derived from quartered 10 mg tablets are subject to unacceptable variability in hydrocortisone doses.

While minor fluctuations in doses may be of little significance, as hydrocortisone pharmacokinetics are influenced by a number of factors, including fasting status[30] puberty[31] and the time of day,[32] the lowest doses obtained from quartered tablets may be associated with symptoms of cortisol deficiency, and in patients with CAH, loss of ACTH suppression.

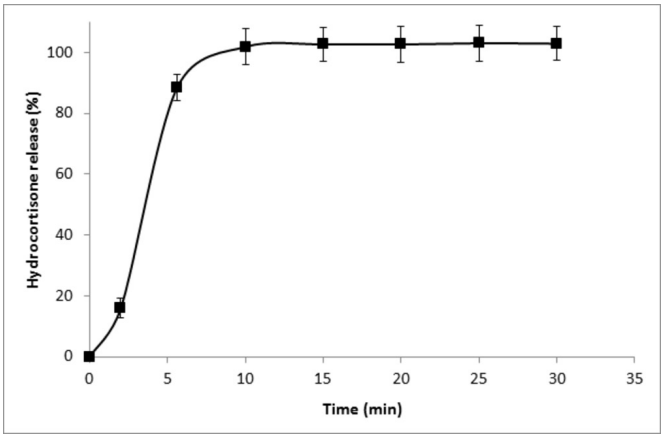

Figure 2 Hydrocortisone release from mini-tablets in water at 37°C (mean±SD, n=6).

As hydrocortisone doses are reduced in a drive to address the long-term morbidity associated with glucocorticoid excess, the margin for error in dosing is lower, and patients are at increased risk for the adverse effects of underdosing due to formulation issues.

Clinical markers of glucocorticoid excess, such as slow growth or excess weight gain, require observation over an extended period, while features of cortisol insufficiency, such as tiredness, nausea or poor concentration may be subjective and difficult to assess in the young child. For this reason, some clinicians advocate the use of 24-hour profiles of cortisol and, in patients with CAH, 17α-hydroxyprogesterone (17-OHP) as a tool to determine the adequacy of treatment, and to titrated doses. However, the application of the data obtained from these studies relies on the assumption that hydrocortisone doses are reliable and reproducible over time. Clearly, this is not the case during treatment with quartered 10 mg tablets and this unpredictability makes interpretation of clinical symptoms or biochemical measures unreliable and dose titration and optimisation extremely difficult.

The Ph. Eur. monograph[21] states that a 10% deviation from the mean mass is allowed for tablets weighing ≤80 mg is allowed with no more than 2 out of the 20 individual masses deviating from the mean mass by 10%. Based on the mean mass of 59.83 mg, the criteria would allow quartered tablets to have a mass in range 53.85–65.81 mg. However, 33 of the 80 (41.25%) quartered tablets failed to meet this specification.

This signifies the importance of the technique employed during tablet splitting, as there will be inevitably variation from person to person during the operation. Given the relationship between quartered tablet weight and hydrocortisone content (figure 1), it is unsurprising that the coefficients of variation for these data are very similar (table 2).

In a recent study,[33] 8 mm tablets were halved and their weight variation was compliant with pharmacopoeial standards, but the tablets were split by an experienced pharmacist while in reality the process may not always be performed by a qualified healthcare professional. For example, parents or carers may be required to split tablets on a regular basis and the data in this study highlight the variations, which could be obtained if an untrained operator performs the subdivision of doses. Other previous studies have also highlighted the

potential interoperator variation obtained when splitting scored tablets.[34 35]

It is not possible to replicate the physiological, diurnal pattern of cortisol secretion using standard formulations of hydrocortisone, and patients experience highly non-physiological cortisol profiles, with periods when cortisol concentrations are excessively high, shortly after a dose of hydrocortisone and prolonged periods of hypocortisolaemia between doses.[36 37]The half-life of hydrocortisone is short, requiring three to four doses a day, and concordance with treatment can be particularly difficult during adolescence. A future aim should be to produce alternative modified-release dosage forms to provide more consistent and tailored hydrocortisone release profiles, and a reduced frequency of dosing.

CONCLUSIONS

This study confirms that quartering of 10 mg hydrocortisone tablets by untrained operators produces an unacceptable variation in the weight of the quartered segments with 41% of the quartered tablets failing to meet the weight variation limits. In addition, 54% of the quartered tablets were outside of the ±10% stated active pharmaceutical ingredient (API) content (2.5 mg for the quartered tablets) proving that under and over dosing is a major risk in formulations manipulated in this way. The feasibility of industrial production of 3 mm mini-tablets with allowing delivery of more accurate doses of hydrocortisone than quartered tablets has been demonstrated.

Contributors All authors planned the study, were involved in study design and critically revised the manuscript. MR, RP, JM and MP collected the data. All authors participated in the analysis and interpretation of the data. MR, MP, JLF and JB drafted the manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or not- for-profit sectors.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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P8 COMPARISON OF HYDROCORTISONE 10 MG TABLETS: TABLET HARDNESS OPTIMISED FOR ADULT USE HAS NEGATIVE CONSEQUENCES FOR PAEDIATRIC USE

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10.1136/archdischild-2016-311535.17

Background Children's medicines are not always readily available as an age appropriate product and manipulation of adult products is often required. Recently the commercial manufacturing process for 10 mg hydrocortisone tablets has changed and the compression force increased due to tablets fracturing on removal from the blister pack. However, this change led to parents of children requiring hydrocortisone reporting that the tablets were more difficult to manipulate.

This study evaluated 10 mg hydrocortisone tablets for their suitability for manipulation in order to deliver an appropriate dose to children (2 mg dose). The physical properties of tablets with the old and new compression force were compared as well as the accuracy of obtaining the paediatric dose.

Methods The tablets compared were hydrocortisone Auden 10 mg tablets (Brand A, PL16876/002)-these are the newer, harder tablets- and hydrocortisone 10 mg tablets (Brand B, PL17507/0097). Tablet physical properties including friability (Copley FRV200) and tablet hardness (Copley TBF1000) were compared. The accuracy of split doses (halve and quarter tablets) were recorded on a Sartorius analytical balance. The accuracy of the 2 mg paediatric dosing was assessed by crushing the tablet, adding 10 mL of water and extracting 2 mL. The concentration was measured using UV analysis (Jenway Genova Plus) according to a calibration curve (wavelength=246 nm). Two devices were used to crush the tablets: a spoon onto a plate and a commercially available crushing device (Apothecary Ezy Crush Pill Crusher With Ergo Grip).

Results As anticipated Brand A tablets were harder (51.85 ±5.1 N) compared to Brand B (30.99±4.1 N). Brand A tablets passed the friability testing with <1% weight loss whereas Brand B failed as 5 tablets broke during testing.

The accuracy of split doses using the score lines to halve and quarter the tablets showed that Brand A were generally better with smaller ranges for both halves (Range for A=41–55%; B=29–70%) and quarters (Range for A=17–35%; B=12–42%) compared to Brand B.

The 2 mg dosing accuracy was better for Brand B tablets compared to A and crushing tablets using a commercial device improved the accuracy of dosing for both brands of tablets. When crushing using a spoon the mean dose obtained was 1.3 mg for Brand A and 1.7 mg for Brand B; the commercial crushing device gave values of 1.9 mg for Brand A and 2.1 mg for Brand B.

Conclusion Parents or carers who are required to manipulate 10 mg hydrocortisone tablets to administer a dose to children dispersed in water should be advised to crush the tablet into a fine powder where possible to improve the likelihood of administering an accurate dose. This is particularly important since the introduction of new hydrocortisone Auden tablets which are known to be harder tablets and therefore more force is required to crush these.

Acknowledgements Some of the experimental work within this project was conducted by Andrew Hackett and Kameron Paul-Thaper whilst at the University of Birmingham on work experience from Arden Sixth Form, Station Rd, Knowle, Solihull, West Midlands, B93 0PT.

JPP JOURNAL OF Pharmacy and Pharmacology
ROYAL PHARMACEUTICAL SOCIETY
JPP Journal of Pharmacy And Pharmacology
Research Paper

Accuracy of tablet splitting and liquid measurements: an examination of who, what and how

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Keywords
accuracy; general population; liquid measurement; pharmacy students; tablet splitting

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Received August 22, 2016
Accepted November 6, 2016

doi: 10.1111/jphp.12671

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Abstract

Objective To examine factors that might affect the ability of patients to accurately halve tablets or measure a 5-ml liquid dose.

Methods Eighty-eight participants split four different placebo tablets by hand and using a tablet splitter, while 85 participants measured 5 ml of water, 0.5% methylcellulose (MC) and 1% MC using a syringe and dosing cup. Accuracy of manipulation was determined by mass measurements.

Key findings The general population was less able than pharmacy students to break tablets into equal parts, although age, gender and prior experience were insignificant factors. Greater accuracy of tablet halving was observed with tablet splitter, with scored tablets split more equally than unscored tablets. Tablet size did not affect the accuracy of splitting. However, >25% of small scored tablets failed to be split by hand, and 41% of large unscored tablets were split into >2 portions in the tablet splitter. In liquid measurement, the syringe provided more accurate volume measurements than the dosing cup, with higher accuracy observed for the more viscous MC solutions than water.

Conclusion Formulation characteristics and manipulation technique have greater influences on the accuracy of medication modification and should be considered in off-label drug use in vulnerable populations.

Introduction

The splitting of a tablet into halves is a common medication modification (MM) technique for providing a prescribed dose of medicines to children.[1,2] Tablet splitting may also help a young child swallow a solid medication, thereby aiding medication compliance. However, tablet splitting when inaccurately performed has the potential to impact on the safety and efficacy of a medication. Presently, there is inadequate published research on the clinical safety of tablet splitting, perhaps because the additional expenditure required for conducting the clinical trials is not balanced with clear incentives and direction from the regulatory authorities.[3,4] Studies have shown that the ability of a person to split a tablet into two accurate halves is influenced by factors that include the tablet characteristics (shape, size, thickness and score line), technique used for splitting (by hand, or using a knife or tablet splitter) and personnel characteristics, which include previous experience with tablet splitting, visual acuity, hand dexterity and strength, and cognitive function.[5–9] There is no clear consensus on which technique produces greater accuracy in tablet splitting. In one study involving fifth-year pharmaceutical science students, the splitting of paracetamol (500 mg) tablets by hand produced greater accuracy, precision and sustainability than the use of a tablet splitter or kitchen knife.[5] In another study in which five volunteers were asked to split eight tablets of different sizes and shapes, the use of a tablet splitter was shown to provide the highest accuracy for the MM.[6]

The measurement of a liquid medication is another common manipulation associated with the provision of a correct dose of medication to paediatric patients. Liquid medications are often prescribed for younger children with perceived difficulties with swallowing tablets. As with tablet splitting, the accuracy of a measured liquid dose has been

found to be dependent on participant demographics, although the liquid viscosity, the measuring device and patient education are also important factors.[10–12] Caregivers may use a measuring cup, oral syringe, oral dropper, a medicine spoon or even a household spoon to measure out the liquid dose for a child.[10] Of these devices, the oral syringe has been found to consistently provide the most accurate doses.[10–12] However, the preference for non-calibrated household spoons amongst some caregivers,[10] and for manufacturers of liquid medicines to still supply a dosing cup, dropper or spoon,[13] even though these devices have been associated with significant overdosing errors,[10–12] are issues of concern.

The aim of this study was to examine the interplay of formulation, manipulation technique and personnel factors on the accuracy of tablet splitting and liquid dose measurements. While there has been a plethora of studies examining the accuracy of tablet splitting and liquid dose measurement, this is a first in-depth controlled study on the interaction of factors. This study would provide a more holistic insight into a person's ability to accurately split a tablet or measure a prescribed volume of liquid formulation. Factors investigated for the tablet splitting experiments included tablet characteristics (size, presence of a score line) and splitting technique (by hand and using a tablet splitter). Factors investigated for the liquid measurement experiments included liquid viscosity and measuring device (measuring cup or oral syringe). Subject demographics (pharmacy students vs general population, age, sex, prior experience) were also examined in both the tablet splitting and liquid measurement experiments. The generated data may aid manufacturers in designing more appropriate medicated tablets and liquid formulations, as well as inform healthcare providers to adopt appropriate practices for accurate dose delivery.

Materials and Methods

Subjects

Subjects for this study were recruited from students enrolled in the Master of Pharmacy program at the University of Western Australia (UWA) in 2015, visitors who attended the Pharmacy booth at the UWA Open Day 2015, and friends and relatives of the researchers. Each subject who agreed to participate in the study was provided with the study objectives and other relevant information, assigned a unique identification number, and was required to sign a consent form prior to participation. Participants were assigned to the tablet splitting group, liquid measuring group or both, depending on which experiments were being conducted at the point of recruitment.

Ethics approval

Approval to conduct this research has been provided by the University of Western Australia Human Research Ethics Committee (RA/4/1/7617).

Tablet splitting

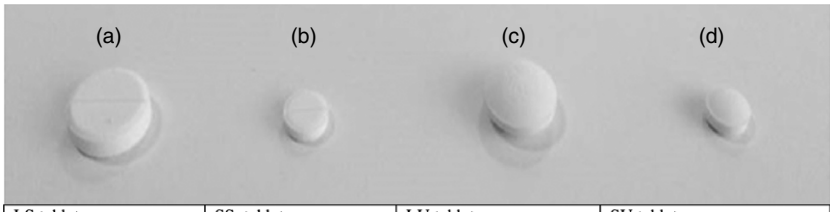
Round placebo tablets manufactured in April 2015 from the same composition of corn starch and microcrystalline cellulose (Avicel 102) were kindly supplied by Jalinous Pharmaceutical Company (Tehran, Iran). The morphology and quality control data for the four batches of tablets are given in Figure 1a. For ease of discussion, the batches are denoted as LU (large, unscored), LS (large, scored), SU (small, unscored) and SS (small, scored) tablets. The scored tablets (LS and SS) were flat, while the unscored tablets (LU and SU) were convex in shape. The manufacturer was unable to supply tablets of the same shape for the scored and unscored tablets.

Each tablet was individually weighed and the weight recorded on a zip-lock bag into which the tablet was placed and later presented to a participant for splitting. Following written consent, and indicating on the form whether they had prior experience with splitting tablets, participants were provided with written instructions and a role-play scenario to split the tablets as they would normally do in a household setting. Duplicate tablets, in the order SU, SS, LU and LS, were then presented to the participants for splitting by hand. The tablet presentation sequence was repeated for the participants to split the tablets using a domestic tablet splitter (SurgiPack; Tatham Pty Ltd, Rydalmere, NSW, Australia) (Figure 1b). All portions of the split tablet were returned to the corresponding zip-lock bags for weighing in the laboratory. A total of 16 tablets were split by each participant. Where a participant was unable to split a tablet, or where a tablet was split into more than two portions, these were recorded accordingly. No time limit was set for splitting the tablets.

Liquid measurements

Three liquids of different viscosities, namely water, 0.5% w/v methylcellulose (MC) and 1% w/v MC, both dissolved in water, were employed within 48 h of manufacture for this study. Deionised water was used throughout. MC (viscosity of 5000 cPs at 2% w/v in water at 20 °C) was purchased from PCCA (NSW, Australia) and compounded according to the Australian Pharmaceutical Formulary and Handbook[14] into a 2% w/v mucilage containing 1% v/v propylene glycol and preserved with 0.08% w/v methyl hydroxybenzoate and 0.02% w/v propyl hydroxybenzoate. The mucilage was diluted two- and fourfold with water to

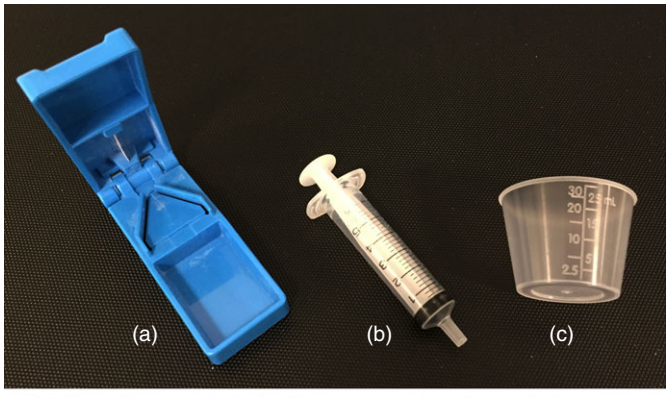
(a)



LS tablet	SS tablet	LU tablet	SU tablet
Weight: 390–400 mg	Weight: 100 mg	Weight: 400 mg	Weight: 100 mg
Size: 12 mm, flat	Size: 7 mm, flat	Size: 12 mm, convex	Size: 7 mm, convex
Hardness: 60–90 N	Hardness: 80–110 N	Hardness: 50–80 N	Hardness: 60–80 N
Thickness: 3.1–3.3 mm	Thickness: 2–2.3 mm	Max thickness: 5–5.2 mm	Max thickness: 2.7 – 2.9 mm
Disintegration time: 15 s	Disintegration time: 4 - 9 min	Disintegration time: 2 - 5 min	Disintegration time: 4 - 8 min

(a) LS is a large, flat tablet with a score line; (b) SS is a small, flat tablet with a score line; (c) LU is a large, convex, unscored tablet; and (d) SU is a small, convex, unscored tablet.

(b)



(a) Tablet splitter; (b) 5-mL dosing syringe; and (c) 30-mL dosing cup.

Figure 1 (a) Characteristics of tablets for splitting; (b) devices employed for tablet splitting and liquid measurements. [Colour figure can be viewed at wileyonlinelibrary.com]

yield the 1% and 0.5% MC solutions, respectively. All three liquid samples were lightly coloured with the addition of two drops/100 ml of pink food colouring (Queen Fine Foods, Alderley, Qld, Australia) to aid volume measurement. Freshly prepared liquid samples were presented in 200-ml labelled amber bottles to the participants.

Participants were provided with written instructions and a role-play scenario following written consent and indicating in the signed form whether they had prior experience with using a dosing cup and syringe for measuring liquid medications. The devices are shown in Figure 1b. They were then presented with the three bottles of liquids and instructed to measure 5 ml of each liquid twice, proceeding from water to 0.5% MC to 1% MC, first using the dosing cup (Huhtamaki, South Windsor, NSW, Australia), followed by the syringe (Terumo Philippines Co., Laguna, Philippines). This gave a total of 12 measurements by each participant. No time limit was set for measuring the liquids. To avoid bias, participants were not given assistance with reading the scale on either measuring device. They were asked to transfer each measured liquid sample from the measuring device into a preweighed zip-lock bag to simulate the administration of the measured liquid to a patient. The bag was ascertained to be non-leaking, and was labelled with the name of the liquid, the measurement method and the participant's unique identification number.

Storage and weight determination

Tablet samples before and after splitting, as well as the measured liquid samples, were stored at ambient temperatures in 90 mm × 65 mm zip-lock bags obtained from Anysaleau Pty Ltd, Australia. Weighing of samples was conducted within 72 h of manipulation. Sample weights were measured on one of four calibrated weighing balances – Sartorius Extend, C64 and CP224S balances (Goettingen, Germany), and Shimadzu AUW220 balance (Kyoto, Japan). Where a tablet was split into more than two portions, the portions were combined to give a size as close as possible to the corresponding tablet halves, and the weight of the

portions was subsequently recorded. The rationale was that it reflected not a uncommon practice of combining fractured tablets to deliver a prescribed dose to a patient in the home setting. After each liquid sample had been weighed, its volume was calculated as a ratio of the mass to its density.

Data input

The weights of the zip-lock bags, tablets (before and after splitting) and liquid samples were entered into an Excel data file. The weights of the tablet segments were recorded in separate columns for the larger and smaller tablet segments, and expressed as a percentage deviation from the expected half-tablet weight (DA) (Table 1). The expected half-tablet weight for each tablet was calculated based on the tablet weight measured prior to splitting. Due to the large number of data points, the researchers worked in pairs to cross-check all weight measurements and data entry.

Statistical modelling

The variables in the data are listed in Table 1. All data analyses were performed using the R statistical software (http://www.R-project.org).

Table 1 The categorical and continuous variables considered in this study to have an impact on accuracy in tablet splitting and liquid measurements

Variable	Detail
Demographics	
Subject	Categorical: pharmacy student or general population
Age	Continuous
Sex	Categorical: male or female
Prior experience	Categorical Yes: experience using a tablet splitter or bare hands to split a tablet or Experience measuring liquids using a measuring cup or syringe No: no previous experience
Tablet characteristics	
Size	Categorical: small or large
Scoring	Categorical: unscored or scored
Method	Categorical: hand or tablet splitter
NegDevPerc	The deviation from the expected weight of the smaller half as a percentage (%)
PosDevPerc	The deviation from the expected weight of the larger half as a percentage (%)
Split	Categorical: yes or no, indicating whether the subject was able to or not able to split the tablet
Liquid characteristics	
Liquid	Categorical: water, 0.5% methylcellulose or 1% methylcellulose
Method	Categorical: measuring cup or syringe

Separate linear models were fitted for the tablet data and liquid data. Two models were fitted to the tablet data, one for the smaller part and one for the larger part of the tablet segments. This allows investigation of the level of underdosing or overdosing. As each person performed two trials for the tablet splitting using each method, these trials were not independent. In such situations, significant variation between participants could be expected. However, a mixed-effects model with participant (person) as a random factor, along with the other variables when fitted to the tablet splitting data,[15] revealed no significant difference in variation within participants for both the positive DA (large tablet segment) and negative DA (small tablet segment) indicating a lack of a 'person' effect. A similar model was fitted to analyse the volumes measured of the three liquids.

More specifically, the model for the larger segment of the tablet data was:

$$\begin{aligned}\text{PosDevPerc} = {} & \beta_0 + \beta_1\text{Pharmacy} + \beta_2\text{Age} + \beta_3\text{Male} \\ & + \beta_4\text{PriorYes} + \beta_5\text{SizeSmall} + \beta_6\text{Scored} \\ & + \beta_7\text{MethodHand} + \beta_8\text{SplitYes} + \text{Error}\end{aligned} \quad (1)$$

Each of the categorical variables was binary, taking only one of two possible values. In the model Equation (1), only one of the levels (values) of the categorical variable appeared. Thus, for example, the coefficient β_3 for male indicated the average difference in PosDevPerc between the male and female participants. In general, the number of terms for a categorical variable was $k - 1$, where k was the number of levels in the variable. The coefficients gave the mean difference between the corresponding level and the omitted level. The final term was a random variation (or error) term which was assumed to be normally distributed. The model equations for the other analyses were similarly written.

It should be noted that in complex data such as this, which contained several categorical variables, significant interactions between the variables could be expected. Equation (1) does not show the interaction terms, but they had been included in the modelling of the data.

Additionally, a logistic regression model was fitted to the variable 'split' (indicating if the participant had been able to split the tablet), with a view to determining the factors that affect whether a participant could split a given tablet.[16] The logistic regression model equation was:

$$\begin{aligned}\log\left(\frac{p}{1-p}\right) = {} & \beta_0 + \beta_1\text{Pharmacy} + \beta_2\text{Age} + \beta_3\text{Male} \\ & + \beta_4\text{PriorYes} + \beta_5\text{SizeSmall} + \beta_6\text{Scored} \\ & + \beta_7\text{MethodHand} + \beta_8\text{SplitYes}\end{aligned} \quad (2)$$

This equation has a similar interpretation to Equation (1). It should be noted that the left-hand side of the

equation is the log of the odds ratio, where p is the probability of splitting a tablet. Again interaction between variables could be expected and was included in the actual model.

Results

Demographics

A total of 158 participants were recruited for the study, of whom 85 were volunteers from the general population and 73 were UWA students (Table 2). In both groups, there were more females (>65%) than males. In the pharmacy student cohort, most participants were between the ages of 21 and 40 (90.4%), while the participants from the general public were divided mainly between the age groups of 12 and 20 (40.0%), 21 and 40 (11.8%) and 41 and 60 (32.9%) years. Overall, less than 5% of the participants were aged less than 12 years or above 60 years. Eighty-eight participants, of whom 41 were UWA pharmacy students, were recruited for the tablet splitting experiments. More than half of the participants, 61.7% in the general population and 58.5% of the student groups, had prior experience with tablet splitting. Eighty-five participants, of whom 40 were UWA pharmacy students, took part in the liquid measurement experiments. The majority, 95% of the general population and 86.7% of the student participants, had prior experience with using the dosing cup while a smaller majority, 67.5% of the general population and 57.8% of the student participants, had prior experience with using the syringe to measure liquid medications. Fifteen participants, including five pharmacy students, took part in both the tablet splitting and liquid measurement experiments.

Tablet splitting

Figure 2 shows the boxplots of the deviations from expected half-tablet weights for the smaller segment (negative DA), and the larger segment (positive DA) of the tablets. For all four tablet types, the mean negative and positive DA values were similar, and they were all under 10%. However, there were a few participants who incurred errors of greater than 50% for the positive and negative DA, particularly for the small tablets. When all tablets were considered (Table 3), the negative DA had a median value of 7.35% and a maximum value of 83.85%. The positive DA had a median value of 7.19% and a maximum value of 66.18%.

Table 3 shows the significant variables ($P = 0.05$) in the two models for the DA data for the smaller half and larger half of a split tablet when all variables (tablet characteristics, splitting technique and demographics) were considered. Examination of the residuals from the fitted models indicated that there was no reason to doubt the assumption of normality. Once a tablet was split, and only the smaller segment was considered, the general population demonstrated significantly greater DA compared to the pharmacy students ($P < 0.0001$), but the age, gender and previous tablet splitting experience of the participant had no significant effects on the DA. If the tablets were scored, the DA was significantly lower compared to the corresponding unscored tablets ($P = 0.0003$). The splitting technique was also important, with hand splitting incurring a greater DA than using a tablet splitter ($P = 0.0009$). However, the tablet size did not contribute to a significant difference in DA. Similar effects were observed for the positive DA. Once a tablet was split, and only the larger segment was considered, scored tablets again gave rise to significantly lower DA ($P = 0.0125$), while greater DA was incurred when participants were asked to split the tablets by hand than using a tablet splitter ($P < 0.00001$). The general population also demonstrated greater DA compared to pharmacy students ($P < 0.00001$), and the age, gender and previous experience of individual participant again had no significant effect on the DA for the larger tablet segment.

Figure 3 shows the number of tablets that could not be split, as well as the number of tablets that were split into more than two portions in the study. Hand splitting was mainly achievable for the large tablets, with all the LS tablets successfully split into two segments and only a small number of the LU tablets failing to be split (1.3%) or splitting into more than two portions (3.2%). In contrast, more than a quarter of the SS tablets (26.3%) and about one in eight of the SU tablets (12.3%) could not be split by hand. Where the SS tablets could be split by hand, about 4% were split into more than two portions, a phenomenon not observed with the hand-split SU tablets. The logistic regression model revealed that the probability of being able to split a tablet was lower for participants in the above 60-year-old age category and for splitting the SS tablets by hand.

When the tablet splitter was employed, most of the scored tablets could be split into halves, with only a small number of the SS and LS tablets unable to be split (1.1% and 0.7%, respectively) or splitting into more than two portions (1.1% and 0.6%, respectively). In the case of the unscored tablets, all were also successfully split using the tablet splitter; however, a significant number of the SU tablets (21.8%) and even more of the LU tablets (41.4%) were split into more than two portions.

Liquid measurements

The per cent deviation (PercDev) from expected volumes was collated for all participants who measured 5 ml of the three liquids (water, 0.5% w/v MC and 1% w/v MC) using

Table 2 The demographical profiles of participants in the study. (A) Overall demographics. (B) Demographics of participants in the tablet splitting study. (C) Demographics of participants in the liquid measurement study

Age in years	<12	12–20	21–40	41–60	>60
(A) Total number of participants = 158					
Number of participants	7	38	76	31	6
Gender	Male = 48			Female = 110	
Pharmacy students = 73					
Number of participants	0	4	66	3	0
Gender	Male = 19			Female = 54	
General population = 85					
Number of participants	7	34	10	28	6
Gender	Male = 29			Female = 56	
(B) Total number of participants = 88					
Number of participants	3	20	44	17	4
Gender	Male = 28			Female = 60	
Prior experience with tablet splitting	Yes = 53			No = 35	
Pharmacy students = 41					
Number of participants	0	3	36	2	0
Gender	Male = 10			Female = 31	
Prior experience with tablet splitting	Yes = 24			No = 17	
General population = 47					
Number of participants	3	17	8	15	4
Gender	Male = 18			Female = 29	
Prior experience with tablet splitting	Yes = 29			No = 18	
(C) Total number of participants = 85					
Number of participants	4	21	40	18	2
Gender	Male = 25			Female = 60	
Prior experience with using:					
1. Medicated measuring cup only	25				
2. Oral syringe only	1				
3. Both cup and syringe	52				
No experience with using cup or syringe	7				
Pharmacy students = 40					
Number of participants	0	1	37	2	0
Gender	Male = 13			Female = 27	
Prior experience with using:					
1. Medicated measuring cup only	11				
2. Oral syringe only	0				
3. Both cup and syringe	27				
No experience with using cup or syringe	2				
General population = 45					
Number of participants	4	20	3	16	2
Gender	Male = 12			Female = 33	
Prior experience with using:					
1. Medicated measuring cup only	14				
2. Oral syringe only	1				
3. Both cup and syringe	25				
No experience with using cup or syringe	5				

the 30-ml measuring cup and 5-ml syringe. No significant difference in PercDev was found between participants from the general population and those from the UWA pharmacy cohort when measuring 5 ml volumes of each liquid with either measuring device. Age, gender and having previous experience with either or both of the measuring devices also did not significantly affect the PercDev of the measured volumes. However, a significant interaction was observed between the measuring device and the liquid viscosity ($P < 10^{-13}$). As illustrated in the interaction plot in Figure 4, the syringe gave rise to smaller PercDev for all three liquids measured compared to the dosing cup. In addition, while the higher-viscosity MC liquids were measured with greater accuracy when using the syringe, with the dosing cup, the accuracy decreased with increasing liquid viscosity. The mean PercDev associated with the cup

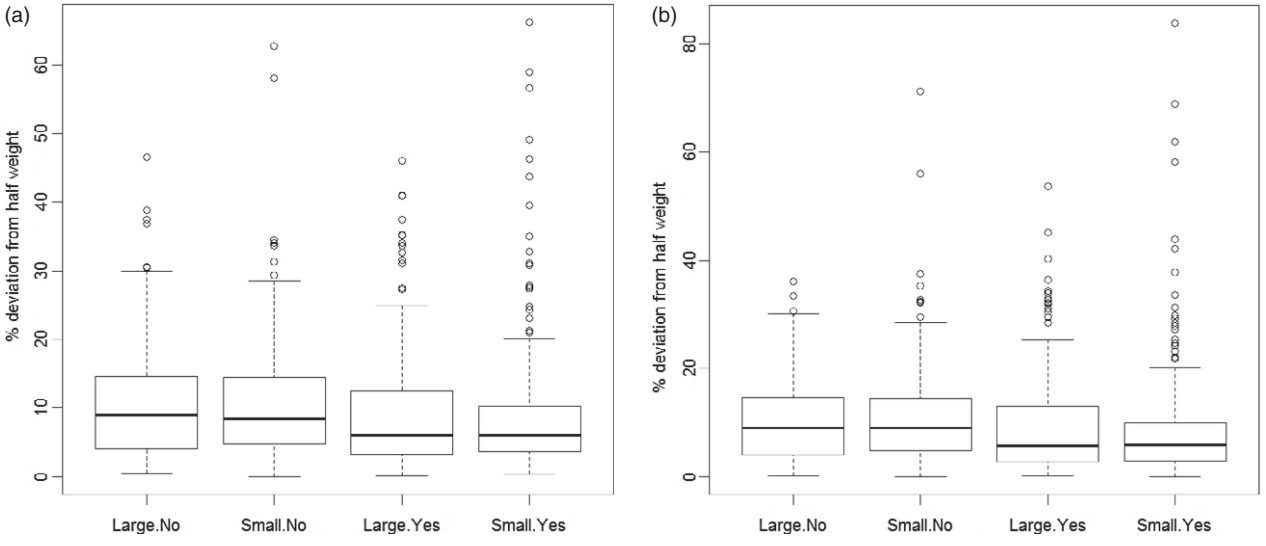


Figure 2 The deviations from expected half-tablet weights for (a) the smaller half (negative deviation) and (b) the larger half (positive deviation) of the split tablet. The bold line in the boxes represents the medians, and the edges of the boxes represent the lower and upper quartiles correspondingly. The ends of the 'whiskers' represent 1.25× interquartile range from the upper (lower) quartile, or the maximum (minimum) value, whichever is smaller (larger). Points that lie beyond the whiskers are plotted as circles.

Table 3 Distribution of deviation values from expected half-tablet weights for the smaller half and the larger half of all tablets that were split, and the variables that contributed to significantly higher deviation from expected half-tablet weights for the smaller half and the larger half of a tablet that was split

Minimum	Lower quartile	Median	Mean	Upper quartile	Maximum
Deviation from expected half-tablet weight for smaller half tablet (negative DA, %)					
0.00	3.46	7.35	9.71	13.52	83.85
Deviation from expected half-tablet weight for larger half tablet (positive DA, %)					
0.00	3.73	7.19	9.65	13.08	66.18

	Smaller half tablet		Larger half tablet	
Variable	Coefficient	*P* value	Coefficient	*P* value
General population	0.021	<0.00001	0.031	<0.00001
By hand	0.018	0.0009	0.035	<0.00001
No score line on tablet	−0.022	0.0003	−0.013	0.0125

ranged from 7.1% when measuring water to 23.7% when measuring the 1% MC. By contrast, the syringe showed a mean PercDev of 2.8% when it was used to measure water, and a tendency towards underdosing, by about 0.9% and 1.5%, respectively, when measuring the more viscous 0.5% and 1% MC solutions.

Discussion

Caregivers of young children are expected to split tablets or measure liquids to obtain the correct medication dose for their charges. The techniques employed in this study for tablet splitting and liquid measurement reflect common practices in Australia. The four batches of tablets were manufactured using standard tablet manufacturing equipment and processes, while the three liquids are common vehicles encountered in liquid medicinal formulations.[14] The data are therefore representative of how well a caregiver may split a medicated tablet or measure a liquid medication in a home setting. Nonetheless, it is recognised that caregivers often have to perform the MM in a more stressful environment than that set up in the study, although the associated disadvantage may be offset by the accumulated experience of the caregivers, in particular parents of chronically ill children, in performing the MM. It would be ideal to randomise the order of tablets to be split and liquids to be measured. However, with more than 50% of participants in the general population group recruited on a busy university Open Day, it was decided to present the tablets and

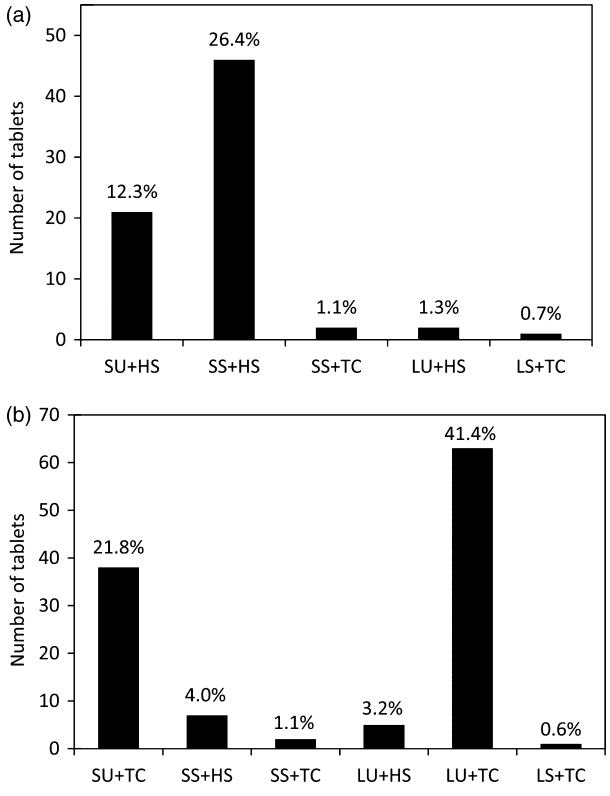


Figure 3 Number of tablets that (a) could not be split and (b) were split into more than two pieces.

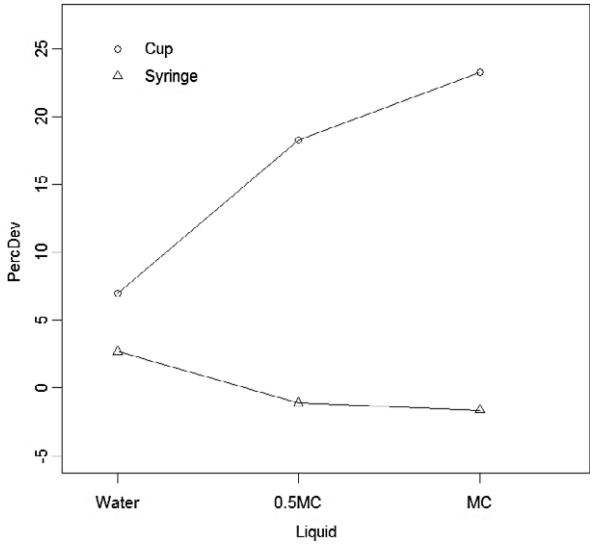


Figure 4 Interaction plot of deviation (PercDev) (%) from the expected 5 ml volume with respect to liquid type and the measuring device.

liquids in a specific order to maintain procedural consistency and ensure all 28 manipulations were allocated to each participant. Compared with published studies on MM accuracy,[5–8,10–13] this study had a larger sample size; it afforded interindividual comparisons rather than the intra-individual comparisons seen in some studies and examined the effects of prior experience on the accuracy of the MM. It therefore provides a more holistic insight into the range of factors that affect an individual's capacity to split a tablet or measure a liquid volume accurately.

Overall, the deviation had a mean of 9.7% and an upper quartile of around 13% from the expected mass for the split half tablets. This is reassuring, as it implies that 75% of the split half tablets would be within the 25% deviation limits set by the Ph.Eur 478 for a tablet part split from scored tablets, beyond which the scored tablets would fail the test for uniformity of mass.[17] However, it should be noted that more than 50% of the split half tablets would fail the more stringent European Directive 2001/83, which requires the split half tablets to be within 95.0–105.0% of the theoretical half-tablet weight.[18] A more disconcerting observation was the maximum deviation determined for the smaller and larger tablet segments, at 83.85% (splitting of small tablet by hand) and 66.18% (splitting of small tablet using the tablet splitter), respectively. These errors were committed in the small tablets, which are normally associated with potent, low-dose drugs. To put this into perspective, a 250-mcg digoxin tablet would after splitting yield a small tablet segment containing 20 mcg of digoxin or a large tablet segment containing 208 mcg of digoxin at these maximum error levels. Although only a small number of participants had incurred such large errors, the implications for the patient can be dire for potent drugs.[19] Dosing error is further compounded when we consider that drug content uniformity may be breached in the split tablet segments.

While age, gender and prior experience with splitting a tablet were not significant contributory factors, the general population was less adept at splitting the tablets accurately than the pharmacy students. It could be that the educational background of the pharmacy students had better prepared them to perform the MM with greater care. Also, the general population cohort included more children and teenagers, who might not have understood the significance of having to split a tablet accurately, as well as middle-aged members many of whom found it challenging to align the tablets in the tablet splitter for splitting. The wide age range of participants in the general population is, however, a realistic reflection of practice, as children, particularly teenagers, may take on the responsibility of administering medications to themselves.[20] The lower probability of participants above 60 years of age being able to split a tablet warrants

further investigation, given the small proportion (4%) of participants aged above 60 years in the study. There is growing importance of tablet splitting as a cost-cutting measure in the treatment of elderly patients,[21,22] and the expectations that the motor and cognitive capabilities of geriatric patients may determine their ability to accurately split a tablet.[9,23] Friends and relatives of the pharmacy students made up 35% of the participants in the general population group. It can reasonably be expected that these participants were not different to other individuals in the general population with respect to the demographic characteristics of interest, such as age, education and prior experience. Care was taken to ensure none of the friends and relatives were associated with the pharmacy profession.

This study shows that using a tablet splitter and having a score line on the tablet provided greater accuracy in splitting a tablet into halves. The tablet size per se did not influence the DA once the tablet was split. However, more of the small tablets, in particular, and somewhat surprisingly, those that were scored, failed to be split by hand. It could be that the small tablets (7 mm ∅) were harder to grip by hand than the large tablets (12 mm ∅) and that the convex shape of the unscored tablets mitigated the poor grip to a certain extent. Using the tablet splitter enabled all tablets to be split more efficiently. However, the tendency for the unscored tablets, both large and small, to be split into more than two portions by the tablet splitter is undesirable. It accentuates dosing inaccuracy, when the patient or caregiver arbitrarily chooses portions to make up a half of the tablet, or wastage, when they decide to discard the multiple split portions. Tablet shape could again be a factor, as the convex unscored tablets might have fitted poorly in the groove of the tablet splitter compared with the flat scored tablets. Further studies using scored and unscored tablets of the same shape would have to be conducted to confirm this. In addition, this study did not establish whether the tablet splitting conformed to the FDA's recommendations that the loss of mass following tablet splitting be limited to less than 3% of the initial tablet weight and that the split tablets possessed the same finished product characteristics as a whole tablet of equivalent strength.[24]

In the case of the measured volumes of liquids, data from this study support literature evidence suggesting the greater accuracy of the oral syringe as a measuring device, especially for liquids of higher viscosity.[10–13] The dosing cup was less accurate in measuring all three liquids compared to the syringe, but the differential in accuracy was considerably narrowed for liquids of lower viscosity. Unlike tablet splitting, the participant demographics (pharmacy students or general population, age, sex, prior experience with liquid measuring device) did not significantly influence the accuracy of liquid measurements using either device. This finding affords confidence in caregivers and patients being able to accurately administer medicated liquids in a home or self-care setting. While the FDA provides guidelines on the design of the dosing cup for OTC liquid medications,[25] it does not prescribe an acceptable dosing accuracy. If a dosing accuracy of 5.0 ± 0.5 ml (i.e. 10% accuracy) was adopted for this study, the mean PercDev obtained when using the dosing cup to measure the MC solutions would not have been acceptable. The oral syringe would, however, provide 5 ml volumes of acceptable accuracy for all three liquids.

Conclusions

In summary, while patients and caregivers of young children may be as competent as a healthcare professional in measuring the dose of a liquid medication, manufacturers and pharmacists can significantly enhance the accuracy of these measurements by supplying an oral syringe rather than a dosing cup, especially when the liquid medication is viscous. On the other hand, the splitting of tablets into halves may be more accurately performed by pharmacists using a tablet splitter. Manufacturers can facilitate the accuracy of tablet splitting by providing appropriate tablet size, and possibly shape, and a score line in the tablet, particularly for tablets of drugs with narrow therapeutic indices, where small dosing errors can cause serious adverse outcomes. Given that tablet splitting has the potential to alter drug safety and efficacy by destroying critical design function in a tablet, for example an enteric coat or controlled drug release mechanisms, it is prudent for future studies to also examine the clinical responses to the split tablets of a potent medication.

Declarations

Funding

Funding is provided by the University of Western Australia.

Acknowledgements

The authors gratefully acknowledge the gift of the placebo tablets from Jalinous Pharmaceutical Company (Tehran, Iran), and the assistance of Edith Tang, Minh Nguyen, Wendy Chen and Brad Zhang towards this study.

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Tablet Splitting: Is It Worthwhile? Analysis of Drug Content and Weight Uniformity for Half Tablets of 16 Commonly Used Medications in the Outpatient Setting

Sally A. Helmy, PhD, CPHQ

ABSTRACT

BACKGROUND: Tablet splitting is a well-established medical practice in clinical settings for multiple reasons, including cost savings and ease of swallowing. However, it does not necessarily result in weight-uniform half tablets.

OBJECTIVES: To (a) investigate the effect of tablet characteristics on weight and content uniformity of half tablets, resulting from splitting 16 commonly used medications in the outpatient setting and (b) provide recommendations for safe tablet-splitting prescribing practices.

METHODS: Ten random tablets from each of the selected medications were weighed and split by 5 volunteers (2 men and 3 women aged 25-44 years) using a knife. The selected medications were mirtazapine 30 mg, bromazepam 3 mg, oxcarbazepin 150 mg, sertraline 50 mg, carvedilol 25 mg, bisoprolol fumarate 10 mg, losartan 50 mg, digoxin 0.25 mg, amiodarone HCl 200 mg, metformin HCl 1,000 mg, glimepiride 4 mg, montelukast 10 mg, ibuprofen 600 mg, celecoxib 200 mg, meloxicam 15 mg, and sildenafil citrate 50 mg. The resulting half tablets were evaluated for weight and drug content uniformity in accordance with proxy United States Pharmacopeia (USP) specification (95%-105% for digoxin and 90%-110% for the other 15 drugs). Weight and drug content uniformity were assessed by comparing weight or drug content of the half tablets with one-half of the mean weight or drug content for all whole tablets in the sample. The percentages by which the weight and drug content of each whole tablet or half tablet differed from sample mean values were calculated. Other relevant physical characteristics of the 16 products were measured.

RESULTS: A total of 52 of 320 half tablets (16.2%) and 48 of 320 half tablets (15.0%) fell outside of the proxy USP specification for weight and drug content, respectively. Bromazepam, carvedilol, bisoprolol, losartan, digoxin, and meloxicam half tablets failed the weight and content uniformity test; however, the half tablets for the rest of the medications passed the test. Mean percent weight loss after splitting was less than 1.5% for all drugs. Bromazepam, carvedilol, and digoxin showed the highest powdering loss during the tablet-splitting process.

CONCLUSIONS: Tablet splitting could be safer and easier when drug- and patient-specific criteria have been met. Tablet size, shape, and hardness may also play a role in the decision to split a tablet or not. Tablets containing drugs with a wide therapeutic index and long half-life might be more suitable candidates for division. Dose variation exceeded a proxy USP specification for more than one-third of sampled half tablets of bromazepam, carvedilol, bisoprolol, and digoxin. Drug content variation in half tablets appeared to be attributed to weight variation due to fragment or powder loss during the splitting process.

J Manag Care Pharm. 2015;21(1):76-86

What is already known about this subject

- Tablet splitting is a well-established medical practice in clinical settings, especially within the geriatric and psychiatric communities, as a means of reducing medication dose and/or cost and providing for ease of swallowing. However, it does not necessarily result in weight-uniform half tablets.
- Most studies have assessed drug content uniformity only as variation in half tablet weights. However, a few studies have explored the drug content of half tablets.
- United States Pharmacopeia guidelines for the drug content of split tablets have yet to be established. To date, no available guidelines regulate the tablet-splitting practice in Egypt.

What this study adds

- This research was conducted to recommend initiating a database that could be accessed electronically for safe tablet-splitting prescribing practices.
- Recommendations are provided for what tablets can or cannot be divided depending on the effect of different tablet characteristics on weight and content uniformity of the selected medications.

Various cost-saving strategies have been used in order to alleviate rising prescription drug costs, including the use of generic medications, selection of more cost-effective medications, formulary restrictions, and tablet splitting.[1] Tablet splitting is a well-established medical practice in clinical settings, especially within the geriatric and psychiatric communities, as a means of reducing medication dose and/or cost.[2,3] Many prescription drugs are available at increased dosages for the same or similar costs as smaller dosages. Physicians frequently write prescriptions for half- and quarter-tablets in order to achieve doses less than the smallest available manufactured strength. Besides the cost-saving potential,[4] tablet splitting has a number of advantages, including providing proper dosage in cases where slow dose titration and dose tapering are necessary, such as with antihyperlipidemic or antihypertensive drugs.[5] Another important advantage of scored tablets for geriatric and pediatric patients is ease of swallowing.[6]

A score on a tablet, however, can be misleading because not all scored tablets are suitable for splitting.[7] Accordingly, uneven

TABLE 1 Characteristics of Study Volunteers

Volunteer	Gender	Age (years)	Training Level	Splitting Experience
1	F	32	Physician	No
2	F	42	Nurse	Yes
3	F	44	Laboratory technician	No
4	M	19	Pharmacy student	No
5	M	25	Community pharmacist	Yes

splitting may result in the administration of an inaccurate dose, which can be of significant risk if the split medication is a narrow therapeutic index medication.[3] Several studies have reported weight differences among split medications.[7-13] Most of these studies have assessed drug content uniformity only as a variation in half tablet weights. However, a few studies have explored the drug content of half tablets.[8] United States Pharmacopeia (USP) guidelines for the drug content of split tablets have yet to be established. These studies adapted the USP guidelines to ensure that actual drug content was equivalent to manufacturer-labeled drug content and indirectly measured half tablet drug content by measuring half tablet weight.[10]

Although tablet splitting may be frequent in long-term care facilities, little is known about actual patterns of tablet splitting, particularly in ambulatory settings in Egypt. In addition, tablet splitters are not commonly used and not even available in all pharmacies in Egypt. Accordingly, the objective of this study was to investigate the effect of tablet characteristics on weight and content uniformity of half tablets resulting from splitting 16 products that are commonly split and used for long-term therapy in different clinical settings in Egypt. Furthermore, this study sought to provide recommendations for safe tablet-splitting prescribing practices. Factors that affect accuracy of tablet splitting, including tablet shape, size, hardness, presence of score line, and depth of score line, were also determined.

Methods

Sixteen commonly split drugs available in the Egyptian market were studied. These products included a narrow therapeutic index medication, medications that require tapering, and medications that could be administered when needed. Medications with extended-release formulations were excluded, since altering the physical properties of these medications by splitting could negatively impact their pharmacokinetics. The products included in this study are as follows: Remeron (mirtazapine 30 millgrams (mg), Schering-Plough, Netherlands); Calmepam (bromazepam 3 mg, GlaxoSmithKline, United Kingdom); Trileptal (oxcarbazepin 150 mg, Novartis, Switzerland); Lustral (sertraline 50 mg, Pfizer, United Kingdom); Dilatrend (carvedilol 25 mg, Roche, Germany); Concor (bisoprolol fumarate 10 mg, Merck, Germany); Cozaar (losartan 50 mg, Merck Sharp & Dohme, Netherlands); Lanoxin (digoxin 0.25 mg, GlaxoSmithKline, United Kingdom); Cordarone (amiodarone HCl 200 mg, Sanofi-Synthelabo, France); Glucophage (metformin HCl 1,000 mg, Merck, Germany); Amaryl (glimepiride 4 mg, Sanofi-Aventis, Germany); Singulair (montelukast 10 mg, Merck, United States); Brufen (ibuprofen 600 mg, Abott, United States); Eurocox (celecoxib 200 mg, Amriya, Egypt); Mobic (meloxicam 15 mg, Boehringer Ingelheim, Germany); and Viagra (sildenafil citrate 50 mg, Pfizer, United States).

Twenty whole tablets were randomly selected from each medication lot for each of the 16 products. All of them were weighed individually using a sensitive balance (Sartorius, Goettingen, Germany), and the average weight per tablet was calculated. Tablet characteristics including diameter, thickness, and score depth were measured using a micrometer. Tablet hardness was measured using a hardness tester (Erweka, Heusenstamm, Germany).

Ten of the 20 randomly selected tablets were split using a knife with a sharp stainless steel blade that was commonly available in pharmacies and houses. The dimensions of the blade were measured at the midpoint using a micrometer; the length of the blade was 10.3 centimeters (cm), and the width of the blade at the nonsharpened end was 0.13 cm. The length of the edge of the sharpened end was 0.1 cm. Tablets were split on a glassine weighing paper placed on a flat surface.

Five volunteers (2 men and 3 women aged 25-44 years) were recruited to perform the splitting. Volunteer details are shown in Table 1. All of the volunteers were right handed with no physical disability affecting the ability to split tablets. Each volunteer split 4 randomly selected tablets of each medication. They were instructed to hold the knife in their right hands, place the sharp end along the middle of the tablet, and apply incremental force on the nonsharpened end of the knife using the left hand until the tablet split.[13] The weights of the half tablets were then measured.

The 10 whole tablets and 20 half tablets for each of the 16 products were then dissolved separately in an appropriate diluent adapted from respective USP official monographs. All tablets were assayed for content uniformity in accordance with USP methodology[14] via an ultraviolet spectrophotometer (JASCO V-530 UV/VIS spectrophotometer, Tokyo, Japan).

The criteria for assessing weight and content uniformity were adapted from Hill et al. (2009).[8] Hill et al. adapted their methodology from USP Chapter 905 (2005) and hypothesized that the drug content and weight of half tablets would deviate from USP specifications for drug content and weight of whole tablets (proxy USP specification).[15] In the present study, the target drug content and weight of a half tablet was defined as equal to half of the mean drug content and weight, respectively, for all whole tablets in a sample of 16 commonly split medications. Furthermore, the acceptability of variation in the half tablets was assessed as the percentage by which each individual whole tablet and half tablet differed from the sample mean values.[8]

Measured Weight

The weight of each whole tablet (n = 10) was compared with the target weight for whole tablets, defined as the mean measured weight for all whole tablets in the sample. Target weight for individual tablets (measured mean weight per tablet) was found using the following equation:

$$\text{Whole tablet target weight} = \frac{\Sigma \text{ weight for whole tablets}}{\text{number of whole tablets}}$$

The target weight of each half tablet (n = 20) was compared with one-half of the target weight for whole tablets, defined as one-half of the mean measured weight for all whole tablets in the sample.

$$\text{Half tablet target weight} = \frac{\Sigma \text{ weight for half tablets}}{\text{number of half tablets}}$$

The measured weight expressed as a percentage of the target weight was calculated for each tablet or half tablet using the following equation:

$$\% \text{ Target weight} = \frac{\text{measured weight for whole or half tablets}}{\text{target weight of whole or half tablets}} \times 100$$

The proxy USP specification for weight is the measured weight of whole or half tablets within 95%-105% of the target weight for half tablets for digoxin and within 90%-110% of target weight for half tablets for the other medications.

The percentage of weight loss due to fragmenting and/or powdering during the splitting process was calculated for each tablet using the following equation:

$$\% \text{ Weight loss} = \frac{\text{measured weight of whole tablet} - \text{measured weight of both half tablets}}{\text{measured weight of whole tablet}} \times 100$$

Measured Drug Content

The drug content for each whole tablet (n = 10) was compared with the target drug content for whole tablets, defined as the mean measured drug content for all whole tablets in the sample.

$$\text{Whole tablet target drug content} = \frac{\Sigma \text{ drug content for whole tablets}}{\text{number of whole tablets}}$$

The target drug content for each half tablet (n = 20) was compared with the target drug content for whole tablets, defined as one-half of the mean measured drug content for all whole tablets in the sample.

$$\text{Half tablet drug content} = \frac{\Sigma \text{ drug content for half tablets}}{\text{number of half tablets}}$$

To account for tablet powdering or fragmenting and the inability to split tablets into perfectly equal halves, the target drug content for each half tablet (n = 20) was adjusted for the weight of the fragment. The adjustment formula assumed that within a single half tablet of known weight, the half tablet's proportion of the whole tablet drug content should equal the half tablet's proportion of the whole tablet weight.

$$\text{Weight-adjusted target drug content} = \frac{\text{measured half tablet weight} \times \text{target drug content for whole tablets}}{\text{measured whole tablet weight}}$$

Nonscored drug tablets (n = 60; montelukast, ibuprofen, and sildenafil citrate) were compared with the 13 other scored drug tablets (n = 260) on 2 outcome measures: half tablet drug content and half tablet weight. The measured drug content expressed as a percentage of target drug content was calculated for each tablet or half tablet using the following equation:

$$\% \text{ Target drug content} = \frac{\text{measured drug content for whole or half tablets}}{\text{target drug content for whole or half tablets}} \times 100$$

The percentage by which weight-adjusted drug content differed from target drug content was calculated using the following equation:

$$\% \text{ Weight-adjusted target drug content} = \frac{\text{measured half tablet drug content}}{\text{weight-adjusted target drug content for half tablet}} \times 100$$

Because no USP criteria for drug content uniformity of half tablets have yet been established, this study applied the proxy USP specification for whole tablets to half tablets. Proxy USP specifications were chosen for weight and content uniformity: 95%-105% of target weight and content for half tablets for digoxin and within 90%-110% of target weight and content for half tablets for the other medications, rather than 85%-115% used in other studies.[11,13]

Relative standard deviation expressed as a percentage (%RSD), which is a ratio of the standard deviation (SD) to the mean of the variable being analyzed, was calculated for whole tablets (drug content and weight) and for half tablets (drug content, weight-adjusted drug content, and weight). The %RSD is widely used to assess the repeatability and precision of the assays used to analyze drug content. Individual medication lots for whole tablets are targeted to have a %RSD less than 6% (proxy USP specification for %RSD).

Results

This study identified 16 commonly split medications in outpatient settings. Of these medications, many are used for treatment of psychiatric disorders, hypertension, cardiovascular diseases, diabetes, asthma, and pain. In addition, sildenafil, a drug for erectile dysfunction, was included.

Basic Characteristics of Products

The basic characteristics of the 16 products studied are listed in Table 2. Of the 16 medications, 8 tablets were oblong; 1 tablet was oval; 3 tablets were round; 1 tablet was rounded and diamond shaped; 1 tablet was heart shaped, 1 tablet was rectangular; and 1 tablet was pentagonal. The 16 medications comprised scored (81.25%) and unscored (18.75%) tablets. The

TABLE 2 Tablet Characteristics of Study Medications (Mean ± SD)

Drug	Weight (gm) n = 20	Dimensions (mm), n = 20				Score (mm), n = 20		Score Depth/Total Thickness × 100 (%)	Flat-Faced Tablet	Hardness (kg/inch^2) n = 5
		Diameter	Thickness	Width	Length	Score Depth	Score Mark			
Mirtazapine	0.32 ± 0.012	—	3.4 ± 0.004	6.2 ± 0.001	12.1 ± 0.01	0.12 ± 0.03	1-sided	3.52	No	8.7 ± 0.06
Bromazepam	0.236 ± 0.004	—	3.8 ± 0.01	9.0 ± 0.01	—	0.31 ± 0.07	1-sided	8.15	No	4.7 ± 0.02
Oxcarbazepin	0.209 ± 0.004	—	3.2 ± 0.0	5.8 ± 0.001	11.8 ± 0.005	0.82 ± 0.06	2-sided	51.25	No	7.8 ± 0.01
Sertraline	0.151 ± 0.001	—	2.9 ± 0.001	4.9 ± 0.0	11.0 ± 0.0	0.11 ± 0.02	1-sided	3.79	No	6.8 ± 0.03
Carvedilol	0.093 ± 0.001	7.5 ± 0.002	2.1 ± 0.0	—	—	0.18 ± 0.03	2-sided	8.57	Yes	4.5 ± 0.1
Bisoprolol	0.173 ± 0.002	7.5 ± 0.001	2.2 ± 0.001	—	—	0.10 ± 0.03	2-sided	9.09	No	4.0 ± 0.02
Losartan	0.17 ± 0.02	—	3.3 ± 0.0	5.7 ± 0.00	10.5 ± 0.02	0.16 ± 0.04	1-sided	4.84	No	8.21 ± 0.2
Digoxin	0.112 ± 0.002	7.0 ± 0.01	2.7 ± 0.02	—	—	0.17 ± 0.05	1-sided	6.29	No	6.0 ± 0.12
Amiodarone	0.346 ± 0.004	10.5 ± 0.02	2.8 ± 0.001	—	—	0.48 ± 0.1	1-sided	17.14	No	9.15 ± 0.48
Metformin	1.071 ± 0.015	—	5.1 ± 0.01	11.1 ± 0.03	18.9 ± 0.1	0.92 ± 0.1	2-sided	36.07	No	10.1 ± 0.48
Glimepiride	0.170 ± 0.004	—	3.2 ± 0.0	5.6 ± 0.0	11.0 ± 0.02	0.85 ± 0.09	2-sided	53.12	Yes	7.5 ± 0.3
Montelukast	0.21 ± 0.0	—	3.2 ± 0.001	7.9 ± 0.002	7.9 ± 0.004	—	—	—	No	12.0 ± 0.5
Ibuprofen	0.981 ± 0.005	—	3.9 ± 0.01	9.9 ± 0.005	21.1 ± 0.02	—	—	—	No	12.2 ± 0.48
Celecoxib	0.614 ± 0.006	—	5.2 ± 0.0	8.5 ± 0.1	17.0 ± 0.0	0.19 ± 0.03	1-sided	3.65	No	12.1 ± 0.88
Meloxicam	0.191 ± 0.01	10.4 ± 0.0	4.8 ± 0.0	—	—	0.21 ± 0.02	1-sided	4.37	Yes	6.0 ± 0.35
Sildenafil	0.305 ± 0.004	—	3.5 ± 0.001	8.3 ± 0.002	11.0 ± 0.003	—	—	—	No	10.5 ± 0.1

gm = gram; kg = kilogram; mm = millimeter; SD = standard deviation.

unscored medications were montelukast, ibuprofen, and sildenafil. Among the scored tablets, 5 had a score line along 2 faces of the tablet (oxcarbazepin, carvedilol, bisoprolol, metformin, and glimepiride).

Bromazepam, carvedilol, and bisoprolol tablets had the lowest hardness values (approximately 4 kilogram [kg]/inch^2). Metformin, montelukast, ibuprofen, celecoxib, and sildenafil tablets had the highest hardness values (approximately 10-12 kg/inch^2). Metformin, ibuprofen, and celecoxib had the highest weight (1.071, 0.981, and 0.614 grams [gm], respectively) and the highest hardness (>10 kg/inch^2). Oxcarbazepin, metformin, and glimepiride had the highest score depth, which represented 51.25%, 36.07%, and 53.12% of the total thickness, respectively.

Weight Uniformity

The results of the weight uniformity test performed on whole and half tablets of the 16 products are shown in Table 3. For all whole tablets studied, measured weight expressed as a percentage of target weight fell within the proxy USP specification for weight and met the proxy USP specification for %RSD (Table 3). All half tablets passed the weight uniformity test except bromazepam, carvedilol, bisoprolol, losartan, digoxin, and meloxicam. At least 5 half tablets for each of these medications fell outside the proxy USP specification. A total of 52 of 320 half tablets (16.2%) fell outside of the proxy USP specification for weight; these included bromazepam (45%), carvedilol (60%), bisoprolol (40%), losartan (30%), digoxin (60%), and meloxicam (25%). Mean percent weight loss, after splitting, was less than 1.5% for all drugs (Table 3). Bromazepam, carvedilol, and digoxin showed the highest powdering loss during the tablet-splitting process. Amiodarone, montelukast, and celecoxib were split with the lowest powdering loss.

Content Uniformity

For all whole tablets studied, measured drug content expressed as a percentage of target drug content fell within the proxy USP specifications (Table 4). The measured drug content expressed as a percentage of target drug content for half tablets fell outside of the proxy USP specification for at least 5 half tablets of bromazepam, carvedilol, bisoprolol, losartan, digoxin, and meloxicam. A total of 48 of 320 half tablets (15.0%) fell outside of the proxy USP specifications for drug content: bromazepam (40%), carvedilol (60%), bisoprolol (40%), losartan (25%), digoxin (50%), and meloxicam (25%). These results coincided with the weight uniformity results.

Weight-adjusted drug content, expressed as a percentage of target drug content for half tablets, fell outside of the proxy USP specification for at most 2 half tablets of bromazepam, carvedilol, bisoprolol, losartan, digoxin, and meloxicam (Table 4). After weight adjustment, a total of 8 of 320 half tablets (2.5%) fell outside of the proxy USP specification for drug content; these included bromazepam (5%), carvedilol (10%), bisoprolol (10%), losartan (0%), digoxin (10%), and meloxicam (5%).

Scored Versus Nonscored Tablets

For the selected nonscored medications, all half tablets passed the proxy USP specifications for weight and drug content

TABLE 3 Weight Variation Analysis for Study Medication Whole and Half Tablets

Drug	Whole or Half Tablets	Target Weight (gm)	Measured Weight Mean (gm)	%RSD	Mean Percent Weight Loss (SD)	Percentage of Target Weight Range	Outside of Proxy USP Specification[a]	Result
Mirtazapine	Whole (n = 10)	—	0.320	3.75	—	98.8-101.1	0	Accept
Bromazepam	Whole (n = 10)	—	0.236	1.694	—	97.4-102.1	0	Accept
Oxcarbazepin	Whole (n = 10)	—	0.209	1.913	—	99.4-103.3	0	Accept
Sertraline	Whole (n = 10)	—	0.151	0.662	—	99.8-102.0	0	Accept
Carvedilol	Whole (n = 10)	—	0.093	1.075	—	97.8-102.1	0	Accept
Bisoprolol	Whole (n = 10)	—	0.173	1.156	—	98.8-102.3	0	Accept
Losartan	Whole (n = 10)	—	0.170	1.176	—	99.1-102.1	0	Accept
Digoxin	Whole (n = 10)	—	0.112	1.785	—	98.2-103.5	0	Accept
Amiodarone	Whole (n = 10)	—	0.346	1.156	—	98.5-102.0	0	Accept
Metformin	Whole (n = 10)	—	1.071	1.437	—	99.1-101.2	0	Accept
Glimepiride	Whole (n = 10)	—	0.170	2.352	—	99.4-103.0	0	Accept
Montelukast	Whole (n = 10)	—	0.210	0.0	—	99.5-100.9	0	Accept
Ibuprofen	Whole (n = 10)	—	0.981	0.509	—	99.1-103.1	0	Accept
Celecoxib	Whole (n = 10)	—	0.614	0.977	—	98.1-102.3	0	Accept
Meloxicam	Whole (n = 10)	—	0.191	5.235	—	98.2-101.1	0	Accept
Sildenafil	Whole (n = 10)	—	0.305	1.311	—	99.0-101.9	0	Accept
Mirtazapine	Half (n = 20)	0.160	0.151	6.0	0.17 (0.42)	97.3-107.5	0	Accept
Bromazepam	Half (n = 20)	0.118	0.108	12.0	1.40 (1.2)	90.9-118.1	9 (45%)	Reject
Oxcarbazepin	Half (n = 20)	0.104	0.101	5.7	0.25 (0.2)	91.1-108.9	0	Accept
Sertraline	Half (n = 20)	0.075	0.074	3.9	0.20 (0.1)	101.4-109.7	0	Accept
Carvedilol	Half (n = 20)	0.046	0.040	17.6	1.50 (1.0)	80.0-112.5	12 (60%)	Reject
Bisoprolol	Half (n = 20)	0.086	0.082	12.9	0.58 (0.33)	86.4-112.0	8 (40%)	Reject
Losartan	Half (n = 20)	0.085	0.081	11.0	0.47 (0.21)	87.5-114.7	6 (30%)	Reject
Digoxin	Half (n = 20)	0.056	0.051	12.3	1.30 (0.05)	89.2-117.8	12 (60%)	Reject
Amiodarone	Half (n = 20)	0.173	0.173	2.1	0.03 (0.02)	98.2-104.0	0	Accept
Metformin	Half (n = 20)	0.535	0.531	2.3	0.21 (0.01)	99.7-103.1	0	Accept
Glimepiride	Half (n = 20)	0.085	0.083	4.2	0.10 (0.03)	96.3-108.4	0	Accept
Montelukast	Half (n = 20)	0.105	0.101	5.9	0.02 (0.01)	92.3-105.7	0	Accept
Ibuprofen	Half (n = 20)	0.490	0.489	4.8	0.31 (0.02)	97.1-106.1	0	Accept
Celecoxib	Half (n = 20)	0.307	0.307	5.8	0.04 (0.02)	97.2-103.0	0	Accept
Meloxicam	Half (n = 20)	0.095	0.091	12.1	0.24 (0.12)	88.2-116.2	5 (25%)	Reject
Sildenafil	Half (n = 20)	0.152	0.153	5.2	0.30 (0.06)	96.0-110.0	0	Accept

[a]*Number of whole or half tablets with measured weight NOT within 95%-105% of target weight for digoxin or 90%-110% of target weight for the other medications and NOT within %RSD < 6.*

gm = gram; SD = standard deviation; USP = United States Pharmacopeia; %RSD = percentage of relative standard deviation.

(Table 5). However, 52 of 260 (20.0%) half tablets and 48 of 260 (18.4%) half tablets of scored medications fell outside of the proxy USP specifications for weight and drug content, respectively (Table 5). The number of half tablets for scored (nonscored) drugs falling outside of the range for weight were 71 (15) for 95%-105%, 47 (0) for 90%-110%, 35 (0) for 85%-115%, and 12 (0) for 75%-125%. The numbers of half tablets for scored (nonscored) drugs falling outside of range for drug content were 68 (13) for 95%-105%, 44 (0) for 90%-110%, 34 (0) for 85%-115%, and 10 (0) for 75%-125%.

Discussion

Tablet splitting is a widespread, international practice in all sectors of health care.[14,16] The practice of tablet splitting is considered compounding of a medication that is not commercially available in the desired dosage by a pharmacist.[17,18] Although cost savings might be accomplished, the tablet-splitting technique used could result in unpredictable effects on the stability of the drug, loss of drug due to powdering, uneven doses, lack of physical strength, and dexterity.[19] Different splitting techniques can be used to cut a tablet into 2 halves, such as hand, splitting device, scissors, razor blades, or kitchen knife. Less weight loss can be achieved by using a splitting device compared with the other methods.[20] With greater precision and accuracy, tablet-splitting devices generally provide more consistency in half tablet doses. However, tablet splitters are not commonly used and are not even available in all pharmacies in Egypt. Splitting by hand or with sharp instruments, such as

TABLE 4 Drug Content for Study Medication Whole and Half Tablets

Drug	Whole or Half Tablets	Target Drug Content (mg)	Measured Drug Content Mean (mg)	%RSD	Percentage of Target Drug Content-Range	Outside of Proxy USP Specification[a]	Results
Mirtazapine	Whole (n = 10)	—	29.83	2.32	95.0-102.5	0	Accept
Bromazepam	Whole (n = 10)	—	3.014	2.54	96.3-104.0	0	Accept
Oxcarbazepin	Whole (n = 10)	—	151.8	1.218	100.0-103.3	0	Accept
Sertraline	Whole (n = 10)	—	50.4	2.1	98.4-104.8	0	Accept
Carvedilol	Whole (n = 10)	—	25.02	3.64	96.1-108.2	0	Accept
Bisoprolol	Whole (n = 10)	—	10.23	3.7	99.0-109.0	0	Accept
Losartan	Whole (n = 10)	—	51.3	3.64	97.6-16.2	0	Accept
Digoxin	Whole (n = 10)	—	0.253	3.12	98.0-108.1	0	Accept
Amiodarone	Whole (n = 10)	—	200.6	1.11	99.2-102.1	0	Accept
Metformin	Whole (n = 10)	—	1000.1	3.1	99.9-104.2	0	Accept
Glimepiride	Whole (n = 10)	—	4.05	1.97	99.7-105.0	0	Accept
Montelukast	Whole (n = 10)	—	10.1	1.71	99.8-104.0	0	Accept
Ibuprofen	Whole (n = 10)	—	599.9	2.4	99.8-103.3	0	Accept
Celecoxib	Whole (n = 10)	—	201.2	1.2	99.2-102.5	0	Accept
Meloxicam	Whole (n = 10)	—	15.1	1.25	99.3-103.3	0	Accept
Sildenafil	Whole (n = 10)	—	50.6	2.43	97.6-106.0	0	Accept
Mirtazapine	Half (n = 20)	14.91	15.4	5.76	90.6-110.0	0	Accept
Bromazepam	Half (n = 20)	1.507	1.315	11.41	86.6-113.3	8 (40%)	Reject
Oxcarbazepin	Half (n = 20)	75.9	76.4	4.23	92.0-109.3	0	Accept
Sertraline	Half (n = 20)	25.2	24.85	4.1	94.6-104.0	0	Accept
Carvedilol	Half (n = 20)	12.51	11.84	12.4	80.8-116.3	12 (60%)	Reject
Bisoprolol	Half (n = 20)	5.11	4.72	9.64	82.5-106.9	8 (40%)	Reject
Losartan	Half (n = 20)	25.65	24.02	10.5	84.2-112.0	5 (25%)	Reject
Digoxin	Half (n = 20)	0.126	0.131	12.3	80.0-132.0	10 (50%)	Reject
Amiodarone	Half (n = 20)	100.3	100.2	2.97	95.0-104.1	0	Accept
Metformin	Half (n = 20)	500.05	499.0	3.1	98.9-107.5	0	Accept
Glimepiride	Half (n = 20)	2.02	2.03	4.7	94.5-109.0	0	Accept
Montelukast	Half (n = 20)	5.06	5.01	4.61	94.0-107.1	0	Accept
Ibuprofen	Half (n = 20)	299.95	298.7	5.1	92.1-108.3	0	Accept
Celecoxib	Half (n = 20)	100.6	100.2	4.9	95.2-104.0	0	Accept
Meloxicam	Half (n = 20)	7.55	73.8	10.6	80.1-120.0	5 (25%)	Reject
Sildenafil	Half (n = 20)	25.3	25.2	5.2	95.4-108.1	0	Accept
Mirtazapine	Half wt adj (n = 20)	—	14.09	5.14	92.1-108.7	0	Accept
Bromazepam	Half wt adj (n = 20)	—	1.37	9.13	89.0.1-99.1	1 (5%)	Reject
Oxcarbazepin	Half wt adj (n = 20)	—	73.35	3.1	96.6-102.8	0	Accept
Sertraline	Half wt adj (n = 20)	—	24.69	3.9	96.4-102.7	0	Accept
Carvedilol	Half wt adj (n = 20)	—	10.76	10.5	86.5-110.9	2 (10%)	Reject
Bisoprolol	Half wt adj (n = 20)	—	4.84	8.8	88.8-104.2	2 (10%)	Reject
Losartan	Half wt adj (n = 20)	—	24.44	7.1	93.0-104.8	0	Reject
Digoxin	Half wt adj (n = 20)	—	0.126	10.1	88.0-108.0	2 (10%)	Reject
Amiodarone	Half wt adj (n = 20)	—	100.3	2.0	99.2-102.1	0	Accept
Metformin	Half wt adj (n = 20)	—	500.0	2.7	99.2-104.1	0	Accept
Glimepiride	Half wt adj (n = 20)	—	1.97	4.1	97.4-102.5	0	Accept
Montelukast	Half wt adj (n = 20)	—	4.88	3.91	95.9-103.0	0	Accept
Ibuprofen	Half wt adj (n = 20)	—	299.1	4.5	95.3-104.1	0	Accept
Celecoxib	Half wt adj (n = 20)	—	100.6	3.11	99.2-102.5	0	Accept
Meloxicam	Half wt adj (n = 20)	—	7.19	9.8	89.5-113.4	1 (10%)	Reject
Sildenafil	Half wt adj (n = 20)	—	25.38	4.1	97.9-104.3	0	Accept

[a]Number of whole or half tablets with measured drug content NOT within 95%-105% of target drug content for digoxin or 90%-110% of target drug content for the other medications and NOT within %RSD < 6.

mg = milligram; USP = United States Pharmacopeia; wt adj = weight adjusted; %RSD = percentage of relative standard deviation.

TABLE 5 Comparison of Scored and Nonscored Half tablets: Weight and Drug Content

Tablet Type	Percentage of Mean-Range	Outside of Proxy USP Specification[a]	Number (%) of Half tablets with Measured Weight/Drug Content			
			Out of Range (95%-105%)	Out of Range (90%-110%)	Out of Range (85%-115%)	Out of Range (75%-125%)
Weight						
Scored (n = 260)	80.0-118.1	52 (20.0%)	71 (29.5%)	47 (19.5%)	35 (14.5%)	12 (5.0%)
Nonscored[b] (n = 60)	92.3-110.0	0	15 (25.0%)	0	0	0
Drug Content						
Scored (n = 260)	80.0-132.0	48 (18.4%)	68 (28.3%)	44 (18.3%)	34 (14.1%)	10 (16.6%)
Nonscored (n = 60)	92.1-108.3	0	13 (21.6%)	0	0	0

[a]*Number of half tablets with measured weight or drug content NOT within 95%-105% of target weight or drug content for digoxin or 90%-110% of target weight or drug content for the other medications and NOT within %RSD < 6.*

[b]*The unscored medications were montelukast, ibuprofen, and sildenafil.*

USP = United States Pharmacopeia.

knives and razor blades, are also commonly used techniques in the outpatient setting. Although splitting tablets by hand produce cleaner splits with less tablet crumbling, tablets split by hand show less uniformity than tablets split using knives and razor blades.[9,20] Accordingly, splitting with a knife was used in this study.

To date, no available guidelines regulate tablet splitting in Egypt. Accordingly, this research was conducted to recommend initiating a database that could be accessed electronically and that would specify what tablets could or could not be divided, depending on the presence of score lines, depth of the score lines, tablet hardness, and other relevant characteristics. Many medications available in Egypt are imported from the United States and Europe. Therefore, tablet-splitting information could be quoted and applied to such products. In addition, the U.S. Food and Drug Administration issued a draft guidance for industry regarding tablet scoring that should be applied by Egyptian drug manufacturers.[21]

The USP has not created a method for assessing half tablet drug content uniformity; thus, previous studies assessing half tablet drug content uniformity used adapted USP methods for assessing weight variability as a means of estimating drug content uniformity.[8,11,13] The selected medications in this study are commonly split during the dosage titration or tapering process either for unavailability or for cost-saving reasons. They shared relatively wide therapeutic windows except digoxin, long half-lives, and potential for cost savings.

Physical properties of medications such as scoring, shape, and size can affect the ease and accuracy of splitting.[22] Metformin, glimepiride, and oxcarbazepin tablets were ideal for accurate and uniform splitting. This might be due to large tablet thickness (3.2-5.1 millimeters [mm]), high crushing strength (7.5-10.1 kg/inch^2), and the deepest score line on the 2 tablet surfaces with a flat face, in case of glimepiride (Table 2). Also, the amiodarone tablet showed an excellent splitting uniformity among the studied round tablets. This could be due to the large diameter (10.5 mm), large size (0.346 gm), suitable crushing strength (9.15 kg/inch^2), and the obvious score line (Table 2). The large size of the celecoxib tablet (0.614 gm) and the oblong shape of the mirtazapine and sertraline tablets might explain their good splitting behavior.

Conversely, carvedilol, bisoprolol, and digoxin tablets showed the lowest splitting uniformity and accuracy. They easily crumbled upon splitting. Digoxin tablets had the smallest diameter (7.04 mm), low weight (0.112 gm), and a biconvex face, along with the score line only on 1 face (Table 2). In addition to the low crushing strength (6 kg/inch^2), these characteristics seem to provide digoxin tablets with poor splitting accuracy and uniformity. The carvedilol tablet was unsuitable for splitting because of small weight (0.093 gm) and diameter (7.5 mm) and low crushing strength (4.5 kg/inch^2; Table 2). These characteristics could lead to tablet fracture at the score with moderate powdering upon splitting, despite the presence of a flat surface and double score lines on the 2 faces of the tablet. The irregular shape, small diameter, and the low crushing strength (4-4.7 kg/inch^2) of the bromazepam and bisoprolol tablets might also contribute to the poor splitting accuracy and uniformity of those tablets. The meloxicam tablet was expected to split accurately because of the large tablet diameter (10.4 mm); however, the opposite happened, which could be due to its circular shape and a relatively low crushing strength (6 kg/inch^2; Table 2). Also, the small size (0.17 gm) and length (10.5 mm) of the losartan tablet might cause the poor splitting behavior it exhibited (Table 2).

The relationship between tablet characteristics and splitting behavior has been previously studied.[8,11,13] The effect of resistance to crushing on predicting the ease of subdivision of scored tablets has also been reported.[13] The results from these previous studies suggest that crushing strength is the most important contributor to good splitting behavior, followed by diameter, score mark (1- or 2-sided), and shape (flat or biconvex).[13] These findings coincided with the finding that

tablets with high crushing strength values (approximately 10-12 kg/inch^2), such as metformin, montelukast, ibuprofen, celecoxib, and sildenafil tablets, showed a much better splitting uniformity than tablets with low crushing strength values (approximately 4 kg/inch^2), such as bromazepam, carvedilol, and bisoprolol tablets. Accordingly, a large crushing strength was expected to improve the accuracy and uniformity of tablet splitting.[23] Conversely, other researchers found opposite results regarding the effect of crushing strength on tablet-splitting behavior.[11] Thus, achieving a high degree of splitting accuracy and uniformity was not a result of a single characteristic but, rather, depended upon a number of tablet characteristics. Such results can be of clinical significance in cases of narrow therapeutic index medications such as digoxin, where small dose changes might result in sub- or supratherapeutic doses.[24]

Six of the 16 (37.5%) tested split medications (bromazepam, carvedilol, bisoprolol, losartan, digoxin, and meloxicam) fell outside of the proxy USP specification for weight and content (Tables 3 and 4). There was a wide variation of weight among these 6 medications (%RSD > 6%), despite the presence of score lines that could improve the accuracy of splitting.[7] Carvedilol had the greatest degree of drug content variability (%RSD = 2.4%), which could be attributed to the greatest amount of weight loss from splitting (1.5%).

Dose variation exceeded a proxy USP specification for more than one-third of the sampled half tablets of bromazepam, carvedilol, bisoprolol, and digoxin. This variation might have been affected by the inability of the tablet-splitting device to accurately split medications into 2 equal halves. Additionally, a greater percentage of drug content variation could be attributed to tablet formulation, especially content, shape, and coating.

Variation in half tablet drug content was greatest with bromazepam, digoxin, and carvedilol, which had tablet halves ranging from 80%-132% of the target drug content for half tablets. Thus, when tablet splitting was performed for these 3 products, patients might have received daily doses that varied by as much as 50%. This finding was likely a result of weight loss due to tablet powdering and inaccuracy of tablet splitting devices and persons operating the devices. This argument is supported by the weight-adjusted data (Tables 3 and 4).

When half tablet drug content was adjusted for weight, a large reduction in drug content variation was found. Thus, half tablet weight appeared to be directly correlated with drug content. When compared with the target drug content of a perfectly split tablet half, 48 of 320 half tablets (15.0%)—but only 8 of 320 weight-adjusted half tablets (2.5%)—fell outside of proxy USP specifications for drug content.

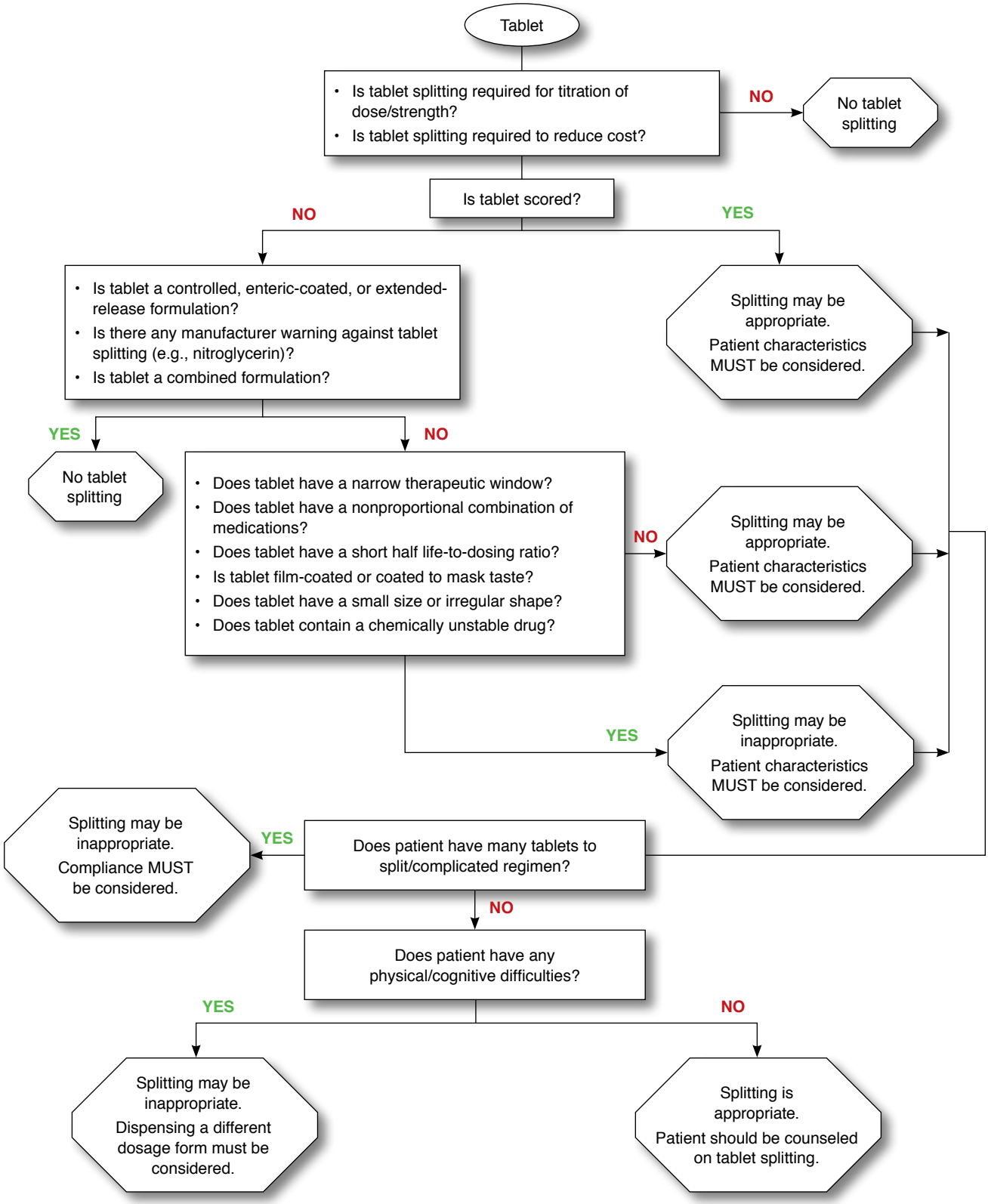
It was also observed that the %RSD for weight-adjusted drug content for all medications was reduced in comparison with nonweight-adjusted drug content. Carvedilol, bisoprolol, and digoxin accounted for the majority of weight-adjusted half tablets falling outside of proxy USP specifications for drug content (2 of the 20 half tablets). This finding could be explained by the nonuniform dispersion of drug content within a single whole tablet. Thus, drug content variation in half tablets appeared to be attributable primarily to weight variation occurring when tablets fragmented during the splitting process. As such, equal daily doses could be determined by the ability of patients to split tablets perfectly in half.

Conversely, in the selected medications, the data suggested greater variability in half tablet drug content and weight for scored medications than for nonscored medications. More scored half tablets were found to have drug content and weight out of the ranges of 85%-115% and 75%-125%. Although montelukast, ibuprofen, and sildenafil tablets are unscored, they exhibited good splitting with minimal powder loss and less tablet crumbling upon fracture into 2 equal halves. The mean percent weight loss values were 0.02%, 0.31%, and 0.3% for montelukast, ibuprofen, and sildenafil tablets, respectively. These findings suggest that when a tablet-splitting knife is used, dose administration might be more accurate and consistent, depending on not only the score line but also other characteristics, such as hardness, size, thickness, and shape of the tablets. The selected nonscored tablets were ideal for accurate and uniform splitting. The crushing strength and tablet thickness might explain their good splitting behavior. The studied nonscored tablets had the highest crushing strength (approximately 10-12 kg/inch^2) compared with other scored tablets, such as carvedilol, bisoprolol, bromazepam, and digoxin tablets (< 6 kg/inch^2). The relatively large thickness (3.2-3.9 mm) and the high tablet weight, especially with ibuprofen—which had the highest weight (0.981 gm) among all the tested medications—seemed to provide the nonscored tablets with good splitting accuracy and uniformity. However, a larger sample of scored and nonscored tablets is needed to determine if there is a significant difference between scored and nonscored tablets.

Tablet splitting is safe when drug- and patient-specific criteria have been met.[1] Although cost savings might be achieved, fears of inaccurate dosing, noncompliance, poor cognitive function or memory, and physical inability to effectively split tablets might discourage physicians and patients from adopting this practice.[8,25] A tool for evaluation of the appropriateness of tablet splitting, taking product and patient characteristics into account, is presented in Figure 1.

Not all of the tablets used in this study were suitable for splitting. Medications should not be split if there is potential for adverse pharmacologic outcomes. Splitting of enteric-coated, sustained, and controlled-release formulations could increase the risk of side effects and compromise effectiveness.[26] The pharmacokinetics seem to dictate if splitting will have a clinical impact on long-term patient outcomes. Medications with short half-lives should not be split if inaccurate splitting could result in fluctuations in plasma concentrations. Once-daily sertraline, with a half-life of 25 to 26 hours, is an example of a

FIGURE 1 *Is Tablet Splitting Appropriate? Tablet and Patient Characteristics*



medication with a substantial pharmacokinetic buffer against inaccurate tablet splitting.[27] Mirtazapine, bromazepam, sertraline, and montelukast are agents with long durations of action, in which minor dose variation should have no significant impact on steady state plasma concentrations. The splitting of montelukast was appropriate as long as the split tablet was used within a week of splitting. Lastly, antihypertensive drugs are administered over an extended period of time. Thus, daily fluctuations in dose would not be expected to affect blood pressure measurements and side effects and long-term clinical end points. In contrast, caution should be used when splitting narrow therapeutic index medications such as digoxin because of the potential for significant adverse events with minimal change or fluctuations in daily dose.

Tablet splitting is an accepted practice in managed care pharmacy for suitable drugs if performed by patients without physical disabilities under a pharmacist's guidance.[28] A patient's state of health might affect the ability to properly split tablets.[29] In particular, certain patients might have increased difficulty splitting tablets, such as the elderly and patients with arthritis, movement disorders, poor eyesight, or poor cognitive function.[17,30] These patients should be instructed by pharmacists in how to accurately split tablets manually or how to use a tablet-splitting device.

Concerns also have been expressed regarding patient adherence. There is a fear that patients may not be willing to take the time to split a tablet before taking it. However, 1 study reported that splitting tablets had no effect on adherence.[4] It was further suggested that tablet splitting might increase adherence by reducing the cost barrier faced by some patients.[4]

Limitations

The only tablet-splitting technique used in this study was a knife. However, splitting by hand or with sharp instruments such as splitting devices or razor blades are commonly used techniques in the outpatient setting and may lead to greater variability than that observed in this study. This research did not permit clinical conclusions, since no clinical end points were assessed.

Conclusions

Tablet splitting can be a cost-saving practice when implemented judiciously using drug- and patient-specific criteria aimed at clinical safety. A patient's state of health might affect the ability to properly split tablets. A special precaution should be written on a medication's package indicating if dividing tablets is considered appropriate. In addition, pharmacists should instruct patients in how to accurately split tablets manually or how to use a tablet-splitting device. The criteria used to evaluate weight and drug content uniformity were derived from the criteria set for whole tablets and were applied for half tablets. Not all tablets were suitable for splitting. Medication characteristics suitable for tablet splitting include long half-life; scored; flat, oblong, or oval; large size; and broad therapeutic window. Medication characteristics unsuitable for tablet splitting include enteric-coated or extended-release formulations, frequent dosing changes, small size, easily crumbles or breaks, bitter taste, and narrow therapeutic window. More studies should be performed that assess the clinical impact of half tablet regimens for the selected 16 medications.

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DISCLOSURES

The author declares no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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Saudi Pharmaceutical Journal (2014) **22**, 454–459

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ORIGINAL ARTICLE

Accuracy of tablet splitting: Comparison study between hand splitting and tablet cutter

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Received 24 September 2013; accepted 14 December 2013
Available online 25 December 2013

KEYWORDS

Salbutamol;
Tablets;
Low dose;
Weight variation;
Drug content;
Electron microscopic scan;
Hand splitting;
Tablet cutter;
Tablet splitter;
Half tablets

Abstract *Background:* Tablet splitting is often used in pharmacy practice to adjust the administered doses. It is also used as a method of reducing medication costs.

Objective: To investigate the accuracy of tablet splitting by comparing hand splitting vs. a tablet cutter for a low dose drug tablet.

Methods: Salbutamol tablets (4 mg) were chosen as low dose tablets. A randomly selected equal number of tablets were split by hand and a tablet cutter, and the remaining tablets were kept whole. Weight variation and drug content were analysed for salbutamol in 0.1 N HCl using a validated spectrophotometric method. The percentages by which each whole tablet's or half-tablet's drug content and weight difference from sample mean values were compared with USP specification ranges for drug content. The %RSD was also calculated in order to determine whether the drugs met USP specification for %RSD. The tablets and half tablets were scanned using electron microscopy to show any visual differences arising from splitting.

Results: 27.5% of samples differed from sample mean values by a percentage that fell outside of USP specification for weight, of which 15% from the tablet cutter and 25% from those split by hand fell outside the specifications. All whole tablets and half tablets met the USP specifications for drug content but the variation of content between the two halves reached 21.3% of total content in case of hand splitting, and 7.13% only for the tablet cutter. The %RSDs for drug content and weight met the USP specification for whole salbutamol tablets and the half tablets which were split

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Peer review under responsibility of King Saud University.

ELSEVIER Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2013.12.014

by tablet cutter. The halves which were split by hand fell outside the specification for %RSD (drug content = 6.43%, weight = 8.33%). The differences were visually clear in the electron microscope scans.

Conclusion: Drug content variation in half-tablets appeared to be attributable to weight variation occurring during the splitting process. This could have serious clinical consequences for medications with a narrow therapeutic-toxic range. On the basis of our results, we recommend to avoid tablet splitting whenever possible or the use of an accurate tablet splitting device when splitting cannot be avoided.

1. Introduction

Although it is most common to use the whole tablets in therapy, they can be divided into halves (Duman et al., 2000; Verrue et al., 2011). Dividing a solid dosage form offers the advantages of ease of administration to the elderly, children or patients who have difficulty in swallowing (Duman et al., 2000), to achieve doses less than the smallest available manufactured strength and it is also being advocated as a method of reducing prescription drug costs .The cost of some medication regimens can be decreased by as much as 50% (McDevitt et al., 1998).

Uneven breaking of a tablet may result in significant fluctuations in the administered dose. This may be clinically significant for drugs with a narrow therapeutic range, such as warfarin or digoxin. For many drugs, however, especially those with long half-lives and/or a wide therapeutic range, dose fluctuations are unlikely to be clinically significant.

Unless breaking tablets where dosage is not a major issue such as vitamins or analgesics, splitting tablets is not a good idea. If breaking tablets is necessary, a special tablet splitting gadget can be used. Splitting of tablets should not be prescribed for serious medical conditions, extended-release or enteric-coated tablets and tablets without a score line.

There are many different ways to split tablets in half. One way is to purchase a tablet splitter from your local pharmacy (see Fig. 1). These tablet splitters are safe and easy to use. All you need to do is to place the tablet in the proper place and then when the splitter is closed, a steel blade cuts the tablet in halves. Some tablets are scored and have a line dividing the dose in half and may be able to be snapped in half using your fingers. Other alternatives used are splitting by hands (for scored tablets) or with scissors (for unscored tablets), or with a kitchen knife (Verrue et al., 2011).

Tablets with score line allow the administration of a portion of the tablet, which can then be considered as the unit dosage of the drug. However, actual dosages of hand-split tablets may deviate by more than 20% (McDevitt et al., 1998) and it may pose a serious risk for tablet uniformity and differ in the content of the two halves resulting in high or low blood levels which may affect the cure of the disease (Duman et al., 2000; Teng et al., 2002) especially if the dose is critical in disease treatment.

Few reports compared the bioavailability and dissolution of whole vs. half of the tablets and little effort has focus on the scoring effect on the uniform tablet divisibility (Duman et al., 2000). Properly scored tablets are necessary to divide the tablets into two equal halves (Duman et al., 2000). Besides the manufacturers' decision on tablet scoring, human factors (physical and psychological) affect the final performance of the scored tablet (Duman et al., 2000). Nonetheless, a literature review concluded that the available literature was limited to adequately address the safety of this practice (McDevitt et al., 1998).

Salbutamol tablet was used as a model in this study. Salbutamol or albuterol is a short-acting β2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma (one of the most common chronic diseases in Saudi Arabia), and chronic obstructive pulmonary disease.

The aim of the current study is to investigate the drug content and weight of the split half tablet by hand vs. use of tablet cutter comparing with whole tablet for Salbutamol using the drug assay analysis.

2. Materials and methods

2.1. Materials

Salbutamol 2 mg and 4 mg tablets were studied (Table 1). This drug was chosen because it is widely used in Saudi Arabia for the treatment of asthma and its low dose (4 mg) as well as the presence of whole tablet (2 mg) which will be as standard for

Figure 1 Different design of tablet splitter.

Table 1 Description of salbutamol tablets studied.

Drug	Tablet description	Scored	Observations[a]
Salbutamol 4 mg	Pink, non-coated, circular tablet	Yes	Minimal powdering with tablet splitter, fractured at score
Salbutamol 2 mg	Orange, non-coated, circular tablet	Yes	Minimal powdering with tablet splitter, fractured at score

[a] Observation of tablet characteristics were made during the tablet splitting process.

measurement. All other chemicals and solvents used were of pharmaceutical grade.

2.2. Methods

2.2.1. Spectrophotometric scanning of salbutamol sulphate

47.8 mg of salbutamol sulphate (equal to 39.83 mg of salbutamol) was dissolved in 100 ml of 0.1 N HCl. Then the samples of resulting solution were scanned for UV absorption (in range between 200 and 400 nm) via a UV system using a double-beam spectrophotometer Shimadzu (UV-160A) and matched 1-cm optical quartz cell to determine maximum absorption wavelength.

2.2.2. Calibration curve of salbutamol sulphate in 0.1 N HCl at (225 and 276.5 nm)

A standard curve was created for salbutamol sulphate, using pure drug powder diluted to 3 known concentrations (range between 0.0096 and 0.0478 mg/ml). These standard curves were established to verify accurate analysis of the drug.

2.2.3. Scanning electron microscope

A scanning electron microscope (SEM) is a type of electron microscope that images a sample by scanning it with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the atoms that make up the sample producing signals that contain information about the sample's surface topography, composition, and other properties such as electrical conductivity. SEM studies were done by research centre of the dentistry college, KSU.

2.2.4. Weight variation

A total of 20 whole tablets were randomly selected from salbutamol 4 mg and another 20 whole tablets from salbutamol 2 mg. Ten of the 20 randomly selected tablets of salbutamol 4 mg were split in halves using a Locking Tablet Cutter (Apothecary Products, Inc.) and the other 10 tablets were split in half by hand. All 20 whole tablets from 2 mg and 40 half tablets from 4 mg were weighted using a Mettler Toledo Aj150 (Mettler Toledo, Inc., Columbus, Ohio) analytical balance. The individual weight was compared with an average weight. Not more than two of the individual weights deviated from the official standard (limit $\pm 7.5\%$). Assay parameters for each drug were taken directly from USP monographs.

2.2.5. Content uniformity

First the 10 whole tablets of 2 mg and 20 half-tablets selected from 40 halves were dissolved individually using a combination of shaking and sonication techniques in 25 ml of 0.1 N HCl. Then the samples were mixed well before filtration through a membrane filter. All tablets were assayed in accordance with developed and validated spectrophotometric method for determining content uniformity for whole tablets. Assay parameters for each drug were taken directly from USP monographs. The samples of each solution were assayed for drug concentration via UV system using a spectro UV-UIS Dual beam (uvs-2800, labomed, Inc.). The drug content was quantified by calculating the concentrations from the absorbance readings obtained through UV analysis of whole and half-tablet samples.

To assess the amount and acceptability of variations in drug content and weight, several measures were calculated. The measured drug content expressed as a percent of label claim was calculated for both whole and half-tablets. Individual values for whole tablets should be in the range of 85–115% for the drugs studied (proxy USP specification for drug content). Relative standard deviation expressed as a percentage (%RSD), was calculated for whole tablets (drug content and weight) and for half-tablets (drug content and weight). The %RSD is widely used to assess the repeatability and precision of the assays used to analyse drug content. Individual medication lots for whole tablets are targeted to have a %RSD less than 6% (proxy USP specification for %RSD).

3. Results and discussion

3.1. Spectrophotometric scanning of salbutamol sulphate

The spectrophotometric scanning of salbutamol sulphate in 0.1 N HCl showed that there are two maximum absorption wavelengths at 225 and 276.5 nm (Fig. 2).

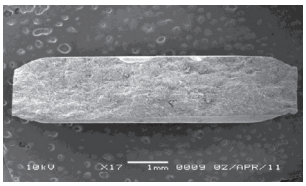
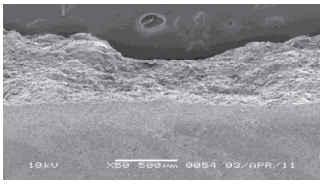
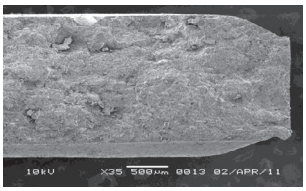
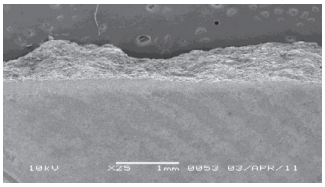
3.2. Calibration curve of salbutamol sulphate in 0.1 N HCl at (225 and 276.5 nm)

A linear relationship between the absorbance and the concentration of salbutamol sulphate in 0.1 N HCl at (225 and 276.5 nm), in the concentration range of 0.0096–0.0478 mg/ml was observed. The regression equation is $Y = 20.688\ X + 0.0096$ and the correlation coefficients (r) of the linear regression of the calibration curves is 0.9999.

3.3. Scanning electron microscope

The image shows that after breaking, the tablet produces some of the terrain to either increase or decrease in the fracture. It has been noted that these features exist in both cases (hand and splitter) and more clearly when using the hand. The followings are some of the SEM photographs showing this.

Salbutamol tablet split by hand:

Salbutamol tablet split by splitter:

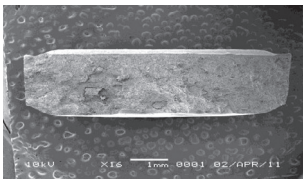
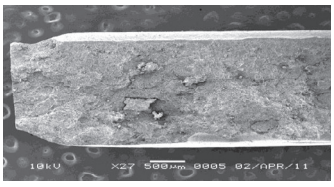
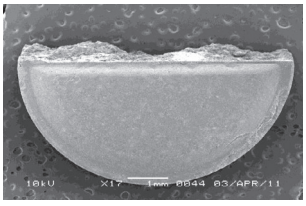
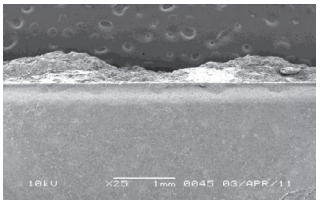





Table 2 Weight variation test for whole tablets.

No.	Weight (g)	Difference from the mean	%RSD
1	0.1175	−0.0029	−2.39
2	0.1170	−0.0010	−0.85
3	0.1214	0.0010	0.85
4	0.1218	0.0014	1.18
5	0.1184	−0.0020	−1.64
6	0.1179	−0.0025	−2.06
7	0.1190	−0.0014	−1.14
8	0.1195	−0.0009	−0.73
9	0.1215	0.0011	0.93
10	0.1164	−0.0040	−3.30
11	0.1192	−0.0012	−0.98
12	0.1263	0.0059	4.92
13	0.1214	0.0010	0.85
14	0.1204	0.0000	0.02
15	0.1155	−0.0049	−4.05
16	0.1241	0.0037	3.09
17	0.1201	−0.0003	−0.23
18	0.1217	0.0013	1.10
19	0.1237	0.0033	2.76
20	0.1247	0.0043	3.59

Mean = 0.1204 g.
SD = 0.0029.
%RSD = 2.41.

3.4. Weight variation test

For all whole tablets studied, measured tablet weight expressed as a percent of target weight (see Table 2) was found to fall within the proxy USP specification percentage range. The weight variation increased significantly after splitting compared to the intact tablets (see Tables 3 and 4). Measured weight expressed as a percent of target weight for half-tablets fell outside the proxy USP specification for weight for at least 3 half-tablets when cutter was used (15%), while the number increased when tablet was split by hand to 8 half-tablets (25%).

3.4.1. Statistical analysis

3.4.1.1. t-Test. The mean of weight variation test for half tablets split by hand is 0.0606, while the mean of weight variation test for half tablets split by splitter is 0.0608. The *t*-value calculated is 1.8964 with a degree of freedom of 38; meanwhile, the *t*-value tabulated is 2.02 at 95% confidence interval. The *t*-value calculated is less than the *t*-value tabulated so there is no different between the two means.

3.4.1.2. F-test. The SD of tablets split by hand is 0.005 and the SD of tablets split by splitter is 0.0031. Accordingly, the *F*-value calculated is 2.604 with a degree of freedom of 19; meanwhile, the *F*-value tabulated is 2.17 at 95% confidence interval. Accordingly, the *F*-value calculated is more than the tabulated *F*-value and that gives evidence of unequal population variances.

3.5. Drug content

The measured drug content was expressed as a percent of target drug content for all whole tablets and half tablets met the proxy USP specification for %RSD (see Tables 5–7). While the percentage of content variation between the two halves can reach 21.3% of total content in case of hand splitting; using the Locking Tablet Cutter gave a maximum variation of only 7.13%.

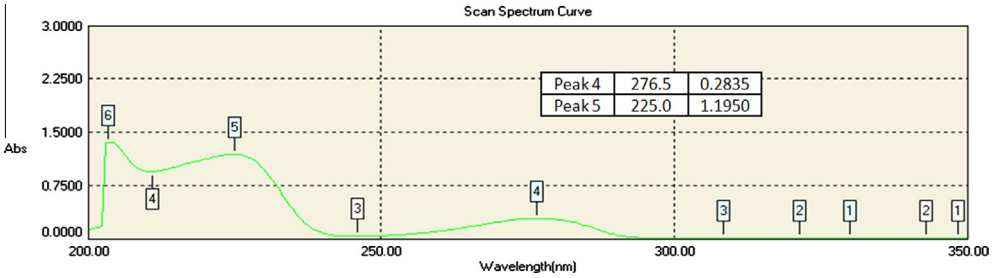


Figure 2 Absorption spectrum of salbutamol sulphate in 0.1 N HCl.

Table 3 Weight variation test for half tablet split by hand.

No.	Weight (g)	Difference from the Mean	%RSD
1	0.0710	0.0104	17.17
2	0.0550	−0.0056	−9.23
3	0.0640	0.0034	5.62
4	0.0588	−0.0018	−2.96
5	0.0547	−0.0059	−9.73
6	0.0631	0.0025	4.13
7	0.0623	0.0017	2.81
8	0.0600	−0.0006	−0.98
9	0.0610	0.0004	0.67
10	0.0599	−0.0007	−1.15
11	0.0571	−0.0035	−5.77
12	0.0640	0.0034	5.62
13	0.0536	−0.0070	−11.54
14	0.0606	0.0000	0.01
15	0.0550	−0.0056	−9.23
16	0.0680	0.0074	12.22
17	0.0526	−0.0080	−13.19
18	0.0672	0.0066	10.90
19	0.0593	−0.0013	−2.14
20	0.0647	0.0041	6.77

Mean = 0.0606.
SD = 0.0050.
%RSD = 8.33.

Table 4 Weight variation test for half tablet split by splitter.

No.	Weight (g)	Difference from the Mean	%RSD
1	0.0629	0.0021	3.54
2	0.0589	−0.0019	−3.05
3	0.0598	−0.0010	−1.56
4	0.0604	−0.0004	−0.58
5	0.0625	0.0017	2.88
6	0.0588	−0.0020	−3.21
7	0.0614	0.0006	1.07
8	0.0671	0.0064	10.45
9	0.0585	−0.0023	−3.70
10	0.0625	0.0017	2.88
11	0.0574	−0.0034	−5.51
12	0.0593	−0.0015	−2.39
13	0.0633	0.0025	4.20
14	0.0590	−0.0018	−2.88
15	0.0630	0.0023	3.70
16	0.0601	−0.0007	−1.07
17	0.0550	−0.0058	−9.47
18	0.0649	0.0041	6.83
19	0.0557	−0.0051	−8.31
20	0.0645	0.0038	6.17

Mean = 0.0608.
SD = 0.0031.
%RSD = 5.11.

3.5.1. t-Test

The mean of drug content for half tablets split by hand is 98.44, while the mean of drug content for half tablets split by cutter is 98.00. The *t*-value calculated is 0.201485 with a degree of freedom of 18. The *t*-value tabulated is 2.1 at 95% confidence interval. The *t*-value calculated is less than the *t*-value tabulated so there is no different between the two means.

Table 5 Salbutamol 2 mg whole tablets drug content.

No.	Weight	Content%
1	0.1175	102.01
2	0.1170	100.10
3	0.1214	103.36
4	0.1218	104.00
5	0.1184	100.89
6	0.1179	101.06
7	0.1190	103.10
8	0.1195	102.11
9	0.1215	104.94
10	0.1164	100.65
Mean	0.1190	102.22
SD	0.0020	1.59
%RSD	1.65	1.56

Table 6 Drug content for half tablets split by hand.

No.	Weight	Content (% of label claim)		
		Half tablet	Whole tablet	Range
1	0.0710	111.20	100.54	21.31
2	0.0550	89.89		
3	0.0640	102.37	99.29	6.17
4	0.0588	96.21		
5	0.0547	89.50	95.27	11.55
6	0.0631	101.05		
7	0.0623	100.70	99.05	3.29
8	0.0600	97.41		
9	0.0610	100.43	98.05	4.75
10	0.0599	95.67		
Mean	0.0610	98.44		
SD	0.0047	6.33		
%RSD	7.69	6.43		

Table 7 Drug content for half tablets split by tablet cutter.

No.	Weight	Content (% of label claim)		
		Half tablet	Whole tablet	Range
1	0.0629	94.55	95.85	2.60
2	0.0589	97.15		
3	0.0598	96.90	98.25	2.70
4	0.0604	99.59		
5	0.0625	99.30	98.06	2.50
6	0.0588	96.81		
7	0.0614	97.02	100.58	7.13
8	0.0671	104.15		
9	0.0585	94.36	97.26	5.80
10	0.0625	100.16		
Mean	0.0613	98.00		
SD	0.0026	2.91		
%RSD	4.28	2.97		

3.5.2. F-test

The SD for the tablets split by hand is 6.33, and the SD for tablets split by splitter is 2.91. Accordingly, the calculated *F*-

value is 4.7317 with a degree of freedom of 9; meanwhile, the tabulated *F*-value is 3.18 at 95% confidence interval. Accordingly, the *F*-value calculated is more than the tabulated *F*-value and that gives evidence of unequal population variances.

4. Conclusion

Tablet splitting may not have adverse clinical consequences and can reduce costs for both patients and institutions (Verrue et al., 2011), but using a whole tablet is the safest way to ensure accurate dosing. However, not all formulations are suitable for splitting, and even when they are, it may lead to dose deviations. This could have serious clinical consequences for medications with a narrow therapeutic-toxic range. On the basis of our results, which demonstrated that using accurate tablet cutter is superior to hand splitting, we recommend the use of an accurate splitting device when splitting cannot be avoided (i.e. for example when the prescribed dose is not commercially available, or when there is no alternative formulation, such as a liquid). Nursing home staff performing the splitting should also be educated in splitting as accurately as possible, and should be aware of the possible clinical consequences of dose deviations. As for policy implications, we concur with previous scientific recommendations (Teng et al., 2002) that manufacturers make it possible to avoid splitting, by introducing a wider range of tablet doses or liquid formulations.

Acknowledgement

The authors would like to thank Al-Kayyali chair of pharmaceutical industry for hosting the work, and supplying the materials and equipment.

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Iatrogenic Cushing Syndrome in a Child With Congenital Adrenal Hyperplasia: Erroneous Compounding of Hydrocortisone

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Context: Patients with 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) require lifelong treatment with glucocorticoids. In growing children, the drug of choice is hydrocortisone. Commercially available hydrocortisone tablets do not conform to very low doses prescribed to infants and toddlers, and compounded hydrocortisone is often dispensed to meet therapeutic needs. However, safety, efficacy, and uniformity of compounded products are not tested. We report a case of Cushing syndrome in a child with CAH who was inadvertently receiving excessive hydrocortisone in compounded form.

Design: A 20-month-old girl with CAH developed growth deceleration, excessive weight for length, irritability, increased facial fat, plethora, and excess body hair while receiving hydrocortisone from a local compounding pharmacy. The signs and symptoms persisted despite decreasing hydrocortisone dose. Iatrogenic Cushing syndrome was suspected. The prescribed hydrocortisone capsules were sent for analysis to the Sports Medicine Research & Testing Laboratory, where testing revealed that each 1-mg hydrocortisone capsule contained five to 10 times the dose prescribed and listed on the label.

Conclusion: Physicians must be aware that errors in compounded medications may lead to unanticipated adverse effects. Iatrogenic Cushing syndrome should be suspected in any child receiving compounded glucocorticoid treatment who develops growth arrest and excess weight gain. (***J Clin Endocrinol Metab*** **103: 7–11, 2018)**

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders characterized by impaired cortisol synthesis, and in ~75% of cases, impaired aldosterone synthesis. The treatment of CAH is challenging. The goal of therapy is to reduce excessive androgen secretion by replacing the deficient hormones. Proper treatment with glucocorticoids and mineralocorticoids prevents adrenal crisis, and allows for normal growth and development. During childhood, the preferred glucocorticoid is hydrocortisone because its short half-life minimizes the adverse side effects of more potent longer-acting glucocorticoids, especially growth suppression and excess weight gain (1).

During early infancy, reduction of markedly elevated adrenal sex hormones often requires hydrocortisone doses up to ~30 mg/m^2/d, but typical childhood maintenance dosing is 10 to 15 mg/m^2/d (1). The usual starting hydrocortisone dose for neonates is 2.5 mg three times daily, with adjustments made within the first few weeks of life, most often to lower doses. As commercially available tablet sizes (5 mg, 10 mg) do not conform to dosages below 2.5 mg, common practice is to provide crushed, weighed hydrocortisone tablets from a compounding pharmacy. Such products are not subject to regulatory processes. Periodic consistently timed testing of serum adrenal steroid levels, electrolytes, regular assessment of

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 14 July 2017. Accepted 19 September 2017.
First Published Online 28 September 2017

Abbreviations: 17-OHP, 17-hydroxyprogesterone; CAH, congenital adrenal hyperplasia; FDA, Food and Drug Administration.

patients' length/height, weight, blood pressure, and physical examination are means by which clinicians monitor for adverse effects and efficacy of treatment.

We report a case of an infant with CAH and iatrogenic Cushing syndrome resulting from inadvertent excess administration of compounded hydrocortisone.

Case

A 2-year-old girl with classic salt wasting CAH was born at full term with atypical genitalia. The diagnosis of 21-hydroxylase deficiency was confirmed by hormonal and genetic tests. Peak serum 17-hydroxyprogesterone (17-OHP) was 402 nmol/L (13,300 ng/dL) following adrenocorticotropic hormone stimulation. *CYP21A2* genotype showed a paternal 30 kb deletion in trans with maternal Arg357Trp. Treatment was begun on day 2 of life with hydrocortisone 2.5 mg three times daily (~31 mg/m^2/d), fludrocortisone 0.1 mg twice daily, and sodium chloride 250 mg four times per day. Serum 17-OHP, testosterone, androstenedione, and renin plasma activity were measured periodically by liquid chromatography-mass spectrometry.

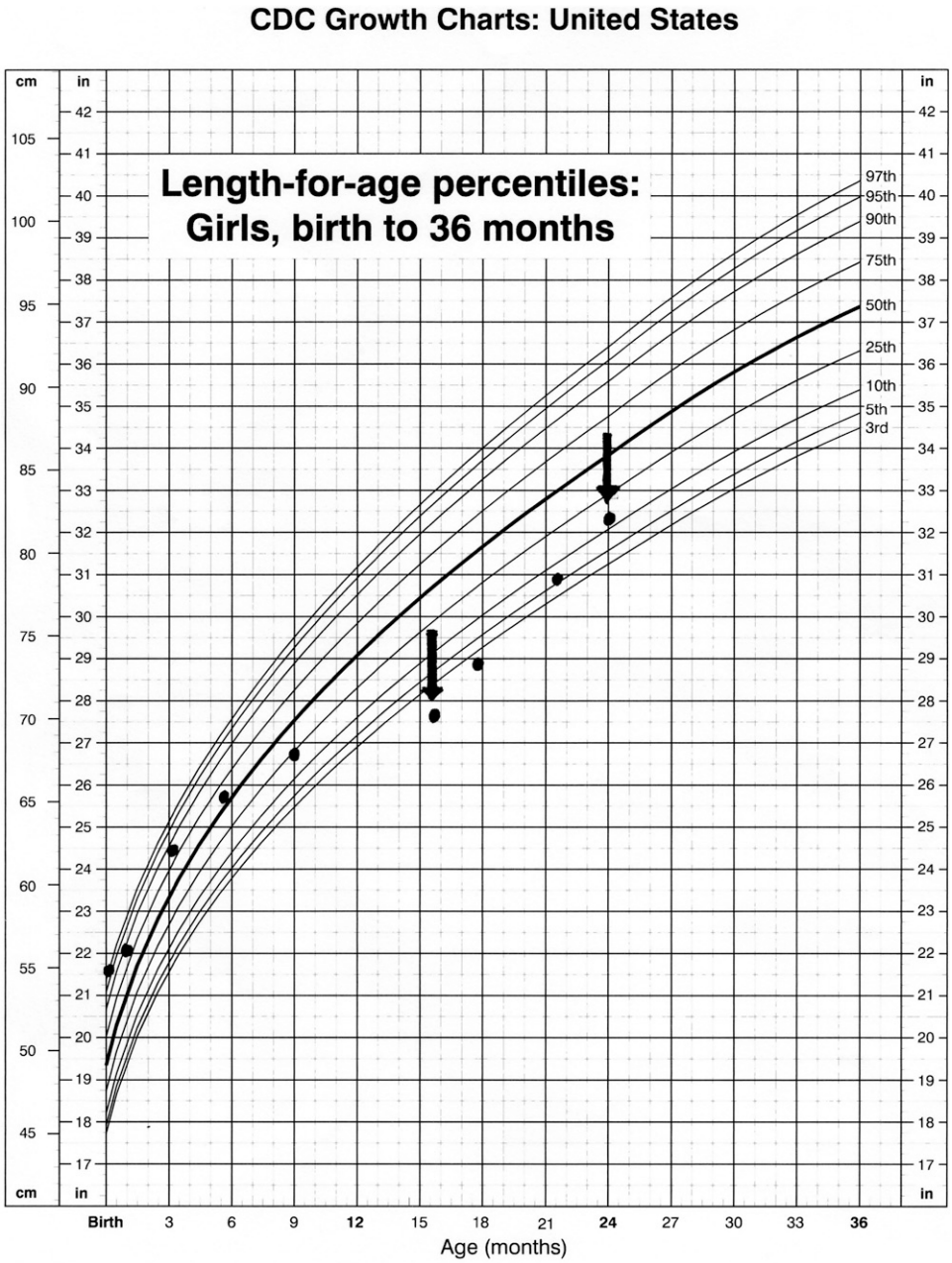

Figure 1. Arrows showing growth deceleration to the first percentile at age 16 months. At this point, compounded hydrocortisone was obtained from a different pharmacy. At age 24 months, the patient showed catch up growth to the 13th percentile on the new drug formulation (2). Centers for Disease Control and Prevention. Use of the World Health Organization and CDC growth charts for children aged 0-59 months in the United States. *MMWR Recomm Rep.* 2010;59(RR-9);1–15. Accessed 18 September 2017. https://www.cdc.gov/growthcharts/data/set1/chart06.pdf.

Hydrocortisone and fludrocortisone doses were weaned by 6 weeks of age, when her hydrocortisone was decreased to a total of 5 mg daily (~17 mg/m^2/d) in three divided doses given as crushed and weighed hydrocortisone tablets in capsules from a local compounding pharmacy. The infant had been tracking at the 90th percentile for length for the first several months of life, but began to show growth deceleration at 6 months of age, and by 16 months of age she had fallen to the first percentile for length (Fig. 1) (2). Her weight for length was excessive at the 91st percentile (Fig. 2) and physical examination was notable for irritability, increased facial fat, plethora, and excess body hair (2). Even with a low dose of hydrocortisone, 1 mg three times daily or 7.5 mg/m^2/d, her adrenal profile showed persistent suppression of 17-OHP and androstenedione. Imaging for an adrenal tumor proved negative. Due to strong suspicion of iatrogenic Cushing syndrome, the hydrocortisone capsules were sent for analysis at the Sports Medicine Research & Testing Laboratory in Salt Lake City, Utah. Liquid chromatography coupled with tandem mass spectrometry revealed that each hydrocortisone capsule contained as much as five

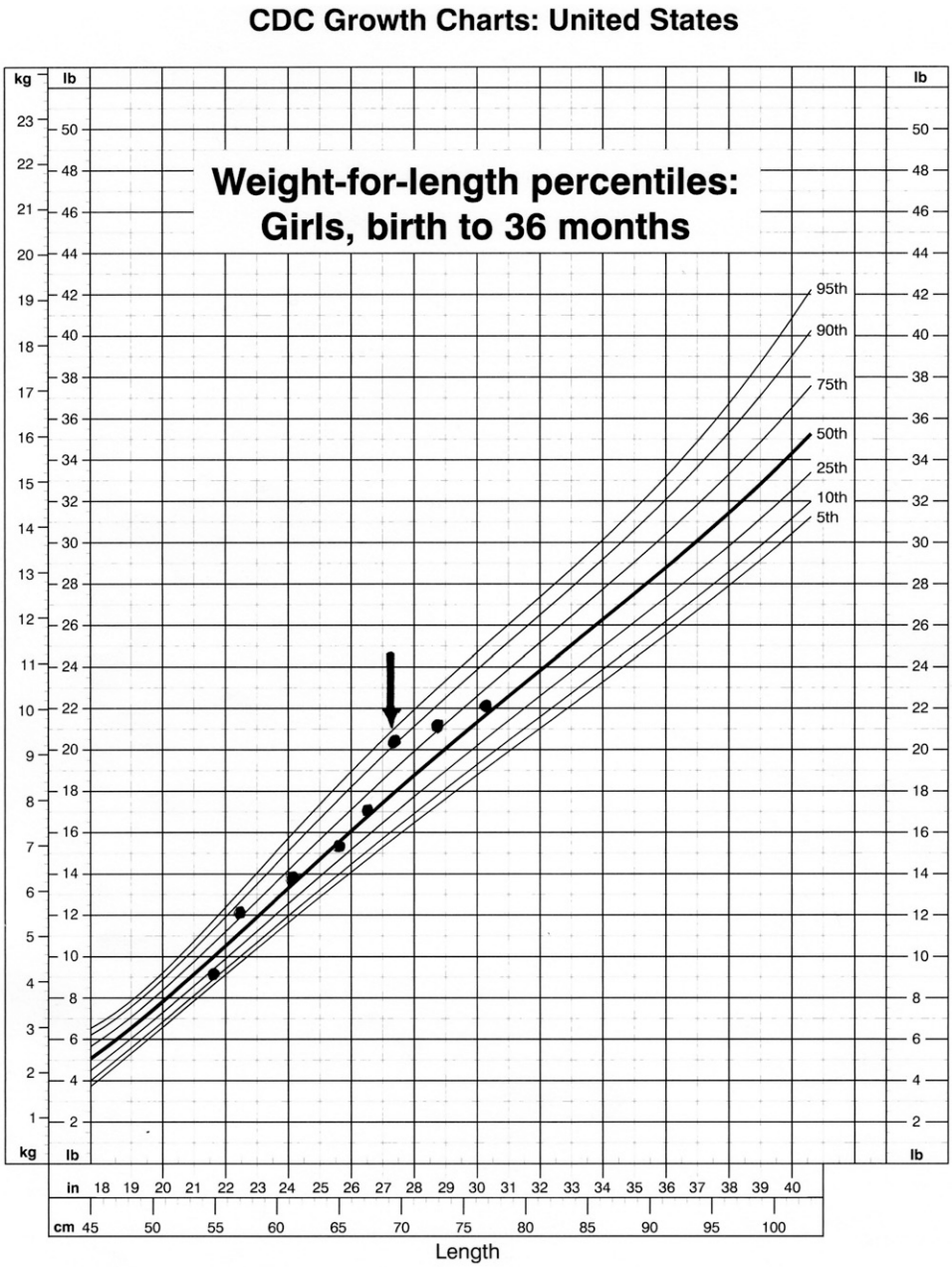

Figure 2. Arrow showing excessive weight for length at the 91st percentile at 16 months of age, with improvement after changing to a different compounding pharmacy (2). Centers for Disease Control and Prevention. Use of the World Health Organization and CDC growth charts for children aged 0-59 months in the United States. *MMWR Recomm Rep*. 2010;59(RR-9);1–15. Accessed 18 September 2017. https://www.cdc.gov/growthcharts/data/set1/chart12.pdf.

to 10 times the dose indicated on the label (1 mg or 2 mg prescribed), thus delivering a supraphysiologic dose of hydrocortisone. No anabolic steroids were detected. Once the medication was obtained from another pharmacy, the child's growth rate improved, and the Cushingoid features gradually resolved. This case has been reported to the Food and Drug Administration's (FDA) MedWatch (RCT-24696), and is under continuing investigation.

Discussion

Pharmacy compounding plays a valuable role in providing access to medication for individuals with unique medical needs that cannot be met with a commercially available product (3). FDA-approved drugs are produced under Good Manufacturing Practice regulations, federal statutes that govern pharmaceuticals. Pharmacy compounding involves making a "new" drug whose safety and efficacy has not been demonstrated according to FDA standards.

In our patient's case, because the actual prescribed dose quantities were 1 mg and 2 mg, halving or quartering 5-mg tablets using a pill cutter would not have worked. In retrospect, altering the doses and using a pill cutter might have been reasonable. However, except for a very recent European report (4), errors in steroid dose compounding have not been described in the literature. This is an instance in which an infant developed Cushing syndrome attributable to iatrogenic hydrocortisone overdose. In many other countries, the lowest dose hydrocortisone tablet is 10 mg resulting in an even greater need to use compounding pharmacies than in the United States. Thus, this is a potential problem worldwide.

Because hydrocortisone suspension was withdrawn from the US market due to inconsistent concentrations (5), there have been newer suspending agents that may allow compounding of suspensions with satisfactory stability (6–9). The development of a new immediate release, multiparticulate granule formulation of hydrocortisone with taste-masking was shown to be well tolerated, easy to administer to neonates, infants, and children, with good absorption, and cortisol levels at 60 minutes similar to physiologic cortisol levels in healthy children (10). However, these preparations are as yet commercially unavailable. Another potential alternative to hydrocortisone compounding might be prednisolone syrup, which is widely available. This drug preparation is up to 15 times the potency of hydrocortisone and longer-acting. A direct comparison of prednisolone syrup with conventional hydrocortisone treatment in nine children (six with CAH) showed improved adrenal control, but growth suppression was also observed (11).

Pediatric endocrinologists must balance possible growth suppressive effects of carefully titrated prednisolone vs risks of unreliable dosing from a compounded hydrocortisone preparation, the increased expense of compounded medication, or lack of access to a reliable compounding pharmacy.

Conclusion

This case report should raise awareness of the possibility of iatrogenic Cushing syndrome in patients inadvertently receiving supraphysiologic doses of compounded hydrocortisone. When using individualized drug preparations to meet patients' needs, one must query the product's identity, strength, quality, and purity, particularly in the setting of side effects or inability to achieve disease control. Furthermore, this serious adverse event highlights the need for development of pediatric-specific glucocorticoid formulations, including dosing forms that would obviate frequent dose administration.

Acknowledgments

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Disclosure Summary: The authors have nothing to disclose.

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BijnierNET

Verzamelde literatuurstudies
over voor- en nadelen
van het breken respectievelijk delen van tabletten