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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☆

Diana A. van Riet-Nales [a,*], Myrthe E. Doeve [a], Agnes E. Nicia [a], Steven Teerenstra [a,c], Kim Notenboom [b], Yechiel A. Hekster [a,c], Bart J.F. van den Bemt [c,d]

[a] Medicines Evaluation Board, Department of chemical pharmaceutical assessment (DAR/AN/MD) resp. Pharmacotherapeutic Group 3 (ST) resp. Scientific Board (YH), Utrecht, The Netherlands
[b] National Institute for Public Health and the Environment (RIVM), Centre for Health Protection (GZB), Department of Public Health Effects, Bilthoven, The Netherlands
[c] Radboud University Medical Centre, Department of Health Evidence (ST) resp. department of clinical pharmacy (YH, BB), Nijmegen, The Netherlands
[d] Sint Maartenskliniek, Department of pharmacy, Nijmegen, The Netherlands

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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).

* Corresponding author at: Medicines Evaluation Board Department of Chemical Pharmaceutical Assessment (CFB) Graadt van Roggenweg 500 P.O. Box 8275, 3503 RG, Utrecht, The Netherlands. Tel.: +31 88 224 8217/6 527 56 462.
E-mail address: da.v.riet@cbg-meb.nl (D. A. van Riet-Nales).

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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

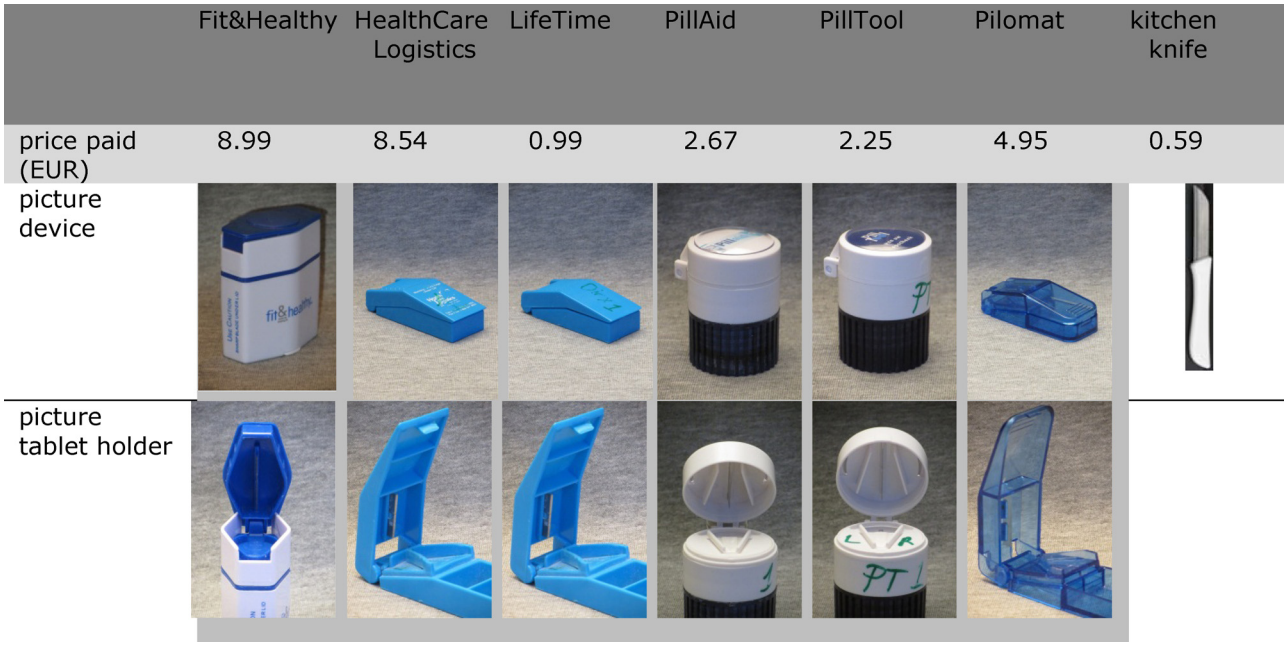

Fig. 1. Characteristics splitting devices.

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

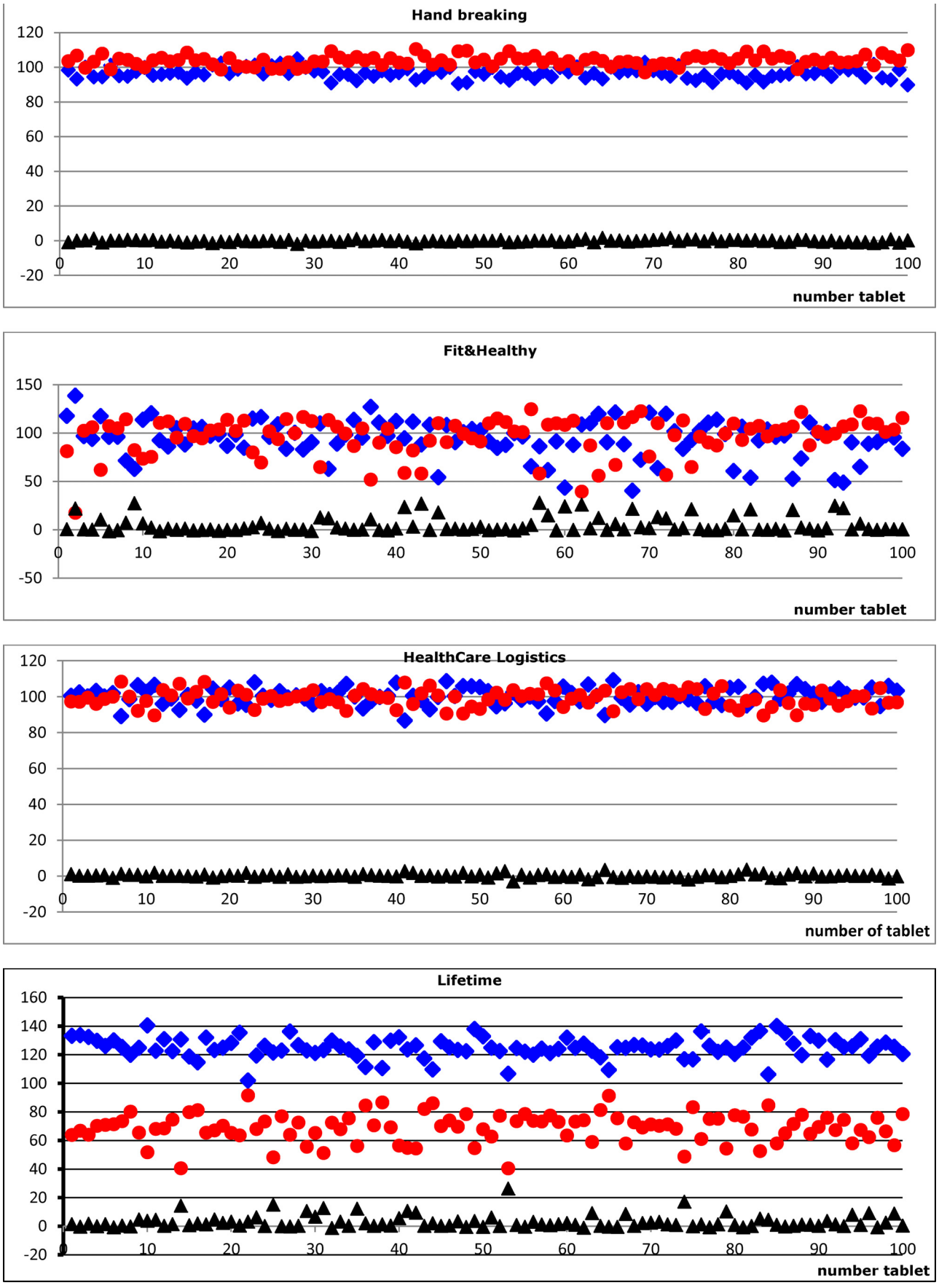

Fig. 2. Percent active substance for tablets subdivided by hand and three different types of tablet splitters (red left parts, blue right parts, black loss of mass). For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.

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.

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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.

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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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