QUALITY EVALUATION OF PARACETAMOL SPLITTING TABLETS AVAILABLE IN COMMUNITY PHARMACIES IN JAFFNA MUNICIPAL COUNCIL AREA, SRI LANKA

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Abstract

Paracetamol is a widely used over-the-counter medicine which is an analgesic and antipyretic. It is frequently subjected to splitting for giving accurate doses to children. Not only whole tablets but also half tablets should have equivalent good quality to ensure the safety, efficacy and cost-effectiveness of treatment. This study evaluated the quality of whole and split tablets from ten brands of paracetamol 500mg tablets available in the Jaffna municipal council area. The tablets were examined for physical characteristics and hardness, friability and disintegration tests according to British pharmacopoeia (BP) 2017 specifications. Further, the half tablets obtained after splitting by hand and tablet cutter were subjected to weight variation, friability, disintegration and uniformity of content tests adopted from British Pharmacopoeia (BP) 2017 specifications. Furthermore, splitting tablets were checked for compliance with the subdivision test prescribed by European Pharmacopoeia and the loss of weight requirement prescribed by the United States, Food and Drug Regulatory Authority (US FDA). All hand and tablet cutter split tablets failed to comply with BP 2017 weight variation standards. All splitting tablet products met the friability specification where friability percentages range of hand and tablet cutter split tablets ranges were 0.07-1.0 and 03-1.0 %. Also, the hand and cutter split tablets of different brands' disintegration time ranges were 072-4.68 to 0.83-6.23 minutes respectively. Four brands of hand split tablets failed to comply with both the subdivision requirement and the US FDA weight loss requirement. No significant difference was observed between weight loss of tablet splitting and the hardness of whole tablets in the tablet splitter ($p=0.3861$) and hand splitting method ($p=0.3162$). Further, all cutter split paracetamol tablets failed to meet pharmacopeial and FDA standards. Only four brands of hand split tablets out of ten brands complied with weight variation and weight loss tests. Appropriate split cutter should be used to split the tablets accurately.

Keywords: Paracetamol, quality, tablet splitting

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INTRODUCTION

Paracetamol is a widely used over-the-counter medicine that is considered an analgesic and antipyretic. In particular, it is abundantly subjected to tablet subdivision to treat children in developing countries. Even though the paracetamol liquid form is available, the tablet form is cost-effective and helpful to circumvent problems related to portability and stability (Hosary et al., 2016). Not only whole tablets but also half tablets should have equivalent good quality to ensure the safety, efficacy and cost-effectiveness of treatment. This study aims to evaluate the quality of paracetamol-splitting tablets available in the Jaffna municipal council area.

METHODOLOGY

It is a laboratory-based experimental study which was conducted to evaluate the quality of split tablets of Paracetamol. Ten different brands of paracetamol available in the pharmacies of the Jaffna municipal area were collected. These tablets were subjected to quality evaluation. Then, whole tablets were split by the nurse who worked in the Pediatric Ward of Teaching Hospital, Jaffna. A Consent form was obtained from the nurse before the study. Ethical clearance for the study was obtained from the Ethical Review Committee, Faculty of Medicine, University of Jaffna.

Three hundred and fifty tablets of ten different brands of paracetamol were collected from the same community pharmacies. They were coded as P1, P2, P3, P4, P5, P6, P7, P8, P9 and P10.

Assessment of physical properties and hardness of whole tablets

Samples were examined for their shape and presence of scoreline. Ten tablets in each product were subjected to the hardness test. The load required to break the tablet was recorded. The average hardness values were calculated as kg/cm^2 (Hettiarachchi et al., 2015).

Tablet splitting

Each Paracetamol tablet was split by both hand and tablet cutter splitting methods by a nurse who worked in the Pediatric Ward in Jaffna Teaching Hospital. The nurse split 240 tablets from each product by both methods. Resultant splitting tablets were assigned as 1st half and 2nd half and packed in well-zipped bags with clearly mentioned labels to avoid interchange.

Weigh variation test

Thirty tablets of each product were split by hand and tablet splitter separately. The average percentage deviation of 1st and 2nd half tablets from different splitting methods was calculated. According to British Pharmacopeia 2017, the acceptable limit for the deviation of weight for tablets that have an average weight of 250 mg or more should not exceed 5%.

Friability test

According to BP 2017, twenty tablets from each sample were accurately weighed and placed in the drum of the friabilator and subjected to rotation for 4 minutes at 25 rpm. The tablets were dedusted and weighed. The friability percentage loss was determined. This procedure will be triplicated. Twenty tablets were split by splitting two methods separately. Then, resultant 1st and 2nd halves were subjected to a friability test.

Uniformity of content

Twenty tablets of Paracetamol were split by a tablet cutter and the average weight of the resultant 1st and 2nd halves of tablets were determined separately. Then, the twenty tablets of 1st and 2nd halves were powdered separately. Then, equivalent powder containing about 0.20g Paracetamol was added to 50ml of 0.1M NaOH and diluted with 100ml of distilled water and shaken for 15 min in a beaker. Then, the mixture was transferred into a 250ml volumetric flask. 50ml of water was then added and

then transferred into a 250ml volumetric flask. Then, 50 ml of 0.1 m of NaOH was added to dissolve the powder and shaken for 15min. The volume was made up to 250 ml with purified water. The prepared solution was filtered through filter paper. 10ml of the resulting solution was then added to 10ml of 0.1m NaOH and made up to 100ml with water. The absorbance was read at 257nm. This test was triplicated. The same procedure was followed for half tablets made by hand splitting.

Disintegration test

Splitting tablets were made by hand and tablet splitter, and they were subjected to determine disintegration time at 37 ±2ºC distilled water by using disintegration apparatus. The disintegration time was measured when there were no granules of tablets remaining in the mesh. This test was triplicated for each product. The same procedure was followed for the hand and tablet cutter split half tablets one time.

Subdivision test

Sub-division test was conducted according to European Pharmacopoeia. Sixty halves of tablets obtained from both splitting methods were weighed individually. The percentage of the mass of each half tablet versus the theoretical weight of the split portion was calculated. According to European Pharmacopoeia, the splitting tablets should comply with the subdivision test; if not, more than one individual mass is outside the limits of 85% to 115%. The test is failed when more than one individual mass of the splitting tablet is outside these limits or if one individual mass is outside the limits of 75% to 125% of the average mass.

Weight loss

The weight loss of Paracetamol tablet products was determined by calculating a weight loss obtained by splitting 30 tablets by hand and using the splitter respectively. Thirty tablets were split for a loss of weight less than 3.0% for 60 individual split tablet portions when compared to the whole tablet according to US FDA guidance (U.S. Department of Health and Human Services, FDA, 2013).

Statistical analysis

Data were entered into MS Excel 2010 and the calculations were done. SPSS version 20 was used to perform an independent t-test and one sample t-test.

RESULTS AND DISCUSSION

Each product shape, presence of score line, hardness, disintegration time and the friability % were depicted in Table 1.

The study results showed that none of the hand split tablets and tablet cutter split tablets complied with BP 2017 weight variation specification. Also, tablet cutter split tablet portions showed more weight deviation percentages compared to hand-split tablets. All cutter-split tablets and hand-split tablets of different brands of Paracetamol tablet passed the friability test. In this study, the friability ranged from 0.07% to 0.15%. According to BP 2017, the whole tablets showed a friability percentage of less than 1%. The split tablets showed an increased friability percentage compared to whole tablets but within standard limits. In this study, the splitting tablets showed a high friability percentage than their whole tablets.

Table 1 - Physical characteristics and hardness, disintegration time and friability percentage of different Paracetamol whole tablet products

Product code	Shape	Score line	Hardness (kg/cm^2) (M+/-SD)	Intact tablet Friability % (M+/-SD)	Intact tablet disintegration time minute (M+/-SD)
P1	Oblong	Absent	6.16+/-0.332	0.13+/-0.0002	3.466+/-0.404
P2	Oblong	Present	10.86+/-0.496	0.11+/-0.0001	4.378+/-0.863
P3	Oblong	Present	4.65+/-0.432	0.07+/-0.0002	3.239+/-0.327
P4	Round	Present	6.08+/-0.44	0.13+/-0.0004	6.150+/-0.102
P5	Oblong	Present	11.98+/-0.665	0.06+/-0.0000	2.022+/-0.171
P6	Oblong	Present	10.32+/-0.776	0.03+/-0.0001	1.322+/-0.284
P7	Round	Present	10.40+/-1.331	0.07+/-0.0001	2.056+/-0.908

P8	Oblong	Absent	6.00+/-0.396	0.05+/-0.0001	4.828+/-0.158
P9	Oblong	Present	5.26+/-0.783	0.09+/-0.0001	4.394+/-0.813
P10	Oblong	Present	4.15+/-0.229	0.15+/-0.0001	3.439+/-0.264

(M-Mean, SD-Standard Deviation)

Tablet splitting could increase friability and fragmentation (Abbood & Layka, 2017). Friability of split tablets showed a high friability percentage compared to corresponding whole tablets but it was within 1% in this study. Studies by Seong et al., (2019) and Shah et al., (2010) also reported the same findings.

The mean and SD of the active pharmaceutical ingredient (API) percentage are given in Table 2. One-side portions of P2, P3, P8, P9 and P10 brands resulting from tablet splitter and one-side portions of P1, P7 and P8 brands resulting from hand splitting only complied with uniformity of content specification of BP 2017. In this study, splitting tablets were considered as whole tablets and conducted uniformity tests for whole tablets. One-side portions of P2, P3, P8, P9 and P10 brands resulting from tablet splitter and one-side portions of P1, P7 and P8 brands resulting from hand splitting only complied with BP 2017 in uniformity of content. Hand splitting of P5 and P6 passed the content uniformity test.

None of the tablets split by cutter complied with the European Pharmacopeial requirement of the subdivision test. Only seven hand-split Paracetamol products, out of ten, complied with European pharmacopoeia subdivision test requirements. This study indicated that P4, P7, P9 and P10 showed significant differences between weight losses in both split techniques. In the present study, six products demonstrated significant differences in weight loss between hand and tablet splitting device split methods. All tablet cutter split tablets failed to comply with the subdivision test of European Pharmacopoeia. However, seven hand-split products met the subdivision test of European Pharmacopoeia compared to tablet cutter split tablets.

The hand-split tablets indicated a significant difference in the API amount between the API in splitting tablet and label claimed API amount of split tablets. Some of the hand-split tablet products only complied with subdivision tests of European Pharmacopoeia and US FDA requirement of loss of mass.

The drug content of P4, P6, P8 and P9 products is significantly different from the label claim (250mg). An independent t-test was conducted to determine whether weight loss between tablet splitting by tablet cutter and by hand for each Paracetamol product. Based on the results, P4, P7, P9 and P10 products showed no significant difference between weight loss during table cutter split and hand split methods.

The independent t-test was conducted to determine whether weight loss of different Paracetamol products during tablet cutting and hand splitting methods with corresponding tablet products' hardness. In this case, tablet hardness between 4 $kgcm^{2-}$ to 7 $kgcm^{2-}$ is considered as ‘optimum hardness and hardness greater than 7 $Kgcm^{2-}$ is considered as 'more hardness'. There is no significant difference between hardness tablets and weight loss of splitting tablets by both methods with different hardness occurring irrespective of splitting methods.

This study showed that disintegration time of all half tablets from the tablet splitter and hand were complied with BP 2017. In this study, Paracetamol products divided by the tablet-splitting device did not comply with European Pharmacopoeia weight variation requirements. The tablet device type that was used in this study may impact the splitting of tablets. A study on the accuracy, precision and sustainability of different techniques for subdivision demonstrated that the uniformity of weight of tablet halves broken by a different type of tablet cutters impacts on compliance with the European Pharmacopeial specification (Van Riet-Nales et al., 2014). Although six tablet products were split by hand, they met the specification of the European Pharmacopoeia for weight variation requirement. The results showed seven tablet cutter-splitting and six hand-splitting tablet products only complied with U.S.FDA weight loss requirements. Both P4 and P7 Paracetamol round tablet products did not comply with the US.FDA weight loss requirements in both splitting methods.

Unscored oblong shaped tablet products (P1 and P8) showed weight loss of less than 3% in both splitting methods. Based on this study, the presence of a score line does not impact on weight loss in tablet cutter and hand-splitting methods. In this study tablet cutter split caused less weight loss compared to hand split. Seong et al., (2019) found that the use of a splitter facilitates getting a more uniform tablet with less weight loss than hand breaking because the tablet hand-splitting method failed to exert uniform pressure on tablets, thus causing serrated cut lines and thereby creating greater weight variation in comparison to use of a splitter.

The present study compared the drug content of tablet cutter and hand-split tablets of different products with label-claimed drug content. A significant difference was observed in drug content between P4, P6, P8 and P9 tablet cutter split tablets and label claimed drug content for half tablet. In the case of hand-splitting tablets, other than P1 and P10 products, all other hand-split products showed significant differences from label claimed drug value.

In this study, weight loss is not significantly different with the hardness of tablets which were split by both tablet cutter splitting and hand splitting (Van Riet-Nales et al., 2014). Except for P4, P7, P9 and P10 products, all other products showed significant differences between weight loss in cutter and hand-split tablets in the same product.

Based on the study, both hand and cutter methods failed to meet regulatory requirements for the splitting tablets. Cutter splitting produces poor-quality split tablets compared to hand-split tablets. Splitting of tablets affects their quality parameters such as disintegration time and it is consistent with the study done on Nebivolol tablets. Further, cutter splitting tablets produce poor quality compared to hand-splitting tablets. This result was consistent with a previous study (Diana A. van Riet-Nales et al., 2014). Splitting methods of tablets cause inaccurate dosing and it results in sub-therapeutic doses and adverse effects of drugs. Methods of splitting tablets should be regularised to give accurate doses of drugs to the patients.

CONCLUSION AND RECOMMENDATIONS

All the splitting tablets by hand and cutter from different Paracetamol brands did not comply with all pharmacopeial standards. In this study, most Paracetamol tablet products indicated significant differences between their weight loss during tablet cutter split and hand split methods. The quality parameters of splitting tablets were changed due to splitting methods. The hand-splitting method is comparatively better than the tablet cutter-splitting method in most of the pharmacopeial tests. However, compared to cutter splitting of tablets, the hand-splitting tablets showed a significant difference between their content of active pharmaceutical ingredients with the label claimed amount. An appropriate cutter needs to be designed for accurate splitting of tablets.

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