Impact of formulation variables on weight uniformity of scored tablets using factorial design

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Abstract: Maintaining safety and efficacy is an important task when splitting a tablet. This Pharmacy practice affords the patient with unavailable required dose, easy swallowing, and cost-saving measure. To access the role of formulation variables on the weight uniformity test of halves tablets. Uncoated and coated placebo tablets were prepared using wet granulation technique. After compression, hardness, disintegration time, friability and weight variation were evaluated according to the USP test. Both coated and uncoated tablets were dived and the obtained halves were weighed and the uniformity of halves was assessed for each kind of tablets. Despite the hardness, size, tablet shape (oval, disc, capsule), all of them passed the splitting test except for the disc shape which showed %RSD higher than 6%. However, hardness and the coating had a generally positive trend on tablet breaking since they gave low% RSD. These findings suggest that the disc shape particle is not suitable for breaking. In addition, film coating, as well as high hardness may give better uniformity of the obtained halves, since a decrease in the calculated %RSD was observed.

Keywords: Tablet, weight uniformity, halves, manufacturing, factorial design.

INTRODUCTION

Recently, pharmaceutical quality by design QbD is becoming a very important approach in the development of pharmaceutical dosage forms. It starts with predetermined objectives and highlights process and product perspectives based on robust scientific evidence and quality risk management (Amidon *et al*., 2014, Hu *et al*., 2017). In fact, the United State Food and Drug Administration (FDA) encourages the use of this approach since the increased number of tests in quality control does not automatically enhance the final quality of the product (Yu, Lawrence *et al*., 2019). The approach begins with the determination of the quality target product profile (QTPP) and recognition of the critical quality attributes (CQAs) of the final products depending on the severity of harm to a patient that results from failing to demonstrate that quality attribute of the final pharmaceutical product. Tablet weight uniformity is considered as one of the most important CQAs. Accordingly, the pharmaceutical companies exert important efforts to meet this attribute (US Food Drug Administration, 2009).

The legitimate question that has been raised by many researchers and regulatory bodies around the globe is what happens to the weight uniformity when tablets are divided. In fact, the failure of achieving equal halves would mean a failure in keeping this important CQA and this may cause safety or inefficacy problems. Accordingly, tablet splitting has been handled in many pharmacopeial standards. For example, the European Pharmacopeia (EP) currently applied standards for accurate subdivision of scored tablets and has also enclosed standards for variation of weight content, mass loss and uniformity of achieved halves. On the other hand, the United States Pharmacopeia (USP) proposed criteria for mass loss and accuracy of subdivision for split tablets (Berg *et al*., 2009, Juszkiewicz *et al*., 2018).

Recently, the Center for Drug Evaluation and Research (CDER) of the FDA was engaged in many drug safety-related regulatory efforts as well as activities to identify priority gaps that could be addressed through targeted research projects. In 2009 the CDER's drug safety oversight discussed how doctors and especially insurance companies are more and more encouraging that patients divide tablets, either to modify or adjust the patients' dose or as a procedure for cost-saving. Accordingly, internal research on tablet splitting has been conducted by the agency to assess if there are any safety issues, particularly when tablets aren't assessed for splitting of tablets. The Agency's burden regarding tablet splitting included variations in the tablet weight, content, disintegration, or dissolution, that may change the amount of drug available in the obtained tablet halves and then present for absorption. Furthermore, stability problems with splitting tablets may arise (Juszkiewicz *et al*., 2018, Zidan *et al*., 2010).

Therefore, the FDA requires that a pharmaceutical company should apply a series of guidelines and criteria on a scored tablet as a part of the review process of the

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New Drug Application (NDA) and Abbreviated New Drug Application (ANDA) in order to guarantee the splittability of the produced scored tablet. Only in this way the scored tablet product could state on the label of the product the important statement of functional scoring (Food Drug Administration, 2013).

Accordingly, this would be a challenge for many pharmaceutical companies, since obtaining equal halves is not an easy task. In fact, many published papers reported the failure of the functional splitting or the achievement of equal halves after tablet splitting, which may result in a failure in the safety and efficacy of the product (Gurst *et*

Table 1: General characteristics of tablets and % RSD of obtained halves from oval shape tablets.

Run	Weight	Hardness	Coating	% RSD
1	Oval 600	18	Coated	2.1
2	Oval 600	18	Uncoated	2
3	Oval 600	9.5	Coated	2
4	Oval 600	9.5	Uncoated	4
5	Oval 300	10.5	Coated	2.4
6	Oval 300	10.5	Uncoated	2.8
7	Oval 300	4.5	Coated	4.8
8	Oval 300	4.5	Uncoated	5

Table 2: General characteristics of tablets and % RSD of obtained halves from round shape tablets

Run	Weight	Hardness	Coating	% RSD
1	Round 550	13	Coated	5.8
2	Round 550	13	Uncoated	9.23
3	Round 550	6.4	Coated	4
4	Round 550	6.4	Uncoated	8
5	Round 200	5.7	Coated	2.1
6	Round 200	5.7	Uncoated	7
7	Round 200	3.8	Coated	4.3
8	Round 200	3.8	Uncoated	13

Table 3: General characteristics of tablets and % RSD of obtained halves from capsule shape tablets

Run	Weight	Hardness	Coating	% RSD
1	Capsule 1100	14	Coated	2.1
2	Capsule 1100	14	Uncoated	2.2
3	Capsule 1100	7.5	Coated	4.3
4	Capsule 1100	7.5	Uncoated	4.5
5	Capsule 550	14	Coated	1.9
6	Capsule 550	14	Uncoated	2
7	Capsule 550	7.9	Coated	2.9
8	Capsule 550	7.9	Uncoated	5

Table 4: 2^3 factorial design with two variables in each shape placebo tablets

Run	Level of Change		
	Hardness X 1	Size X2	Coating X 3
1	-1	1	-1
2	-1	-1	1
3	1	-1	-1
4	1	-1	1
5	1	1	1
6	1	1	-1
7	-1	-1	-1
8	-1	1	1

x1, x2 and x3 represent the hardness and the size of the tablets respectively. Note that all variables are changed simultaneously in a controlled way, to ensure that every experiment in each design is a unique combination of variable levels.

al., 1998, Song *et al*., 2002, Mehuys *et al*., 2011, Biedrawa *et al*., 2018).

Therefore, finding the way or the trick to produce scored tablets that pass the weight uniformity test would be very useful for the industrial pharmacy. To the best of our knowledge, only two published studies were conducted on this topic. The first one focused only on the speed of rotation and the tableting machine (Van Vooren *et al*., 2005), while the second suggested a relationship between the formulation parameters and the splitting of the scored tablets into two equal halves (Zaid and Ghosh, 2011).

However, this last study was conducted on products available in the pharmaceutical market which have many other variables such as active pharmaceutical ingredient (API), excipients and manufacturing procedures. Accordingly, our study was conducted in order to minimize this variable to access the role of hardness and friability, tablets size, shape and film coating on the weight uniformity test of obtained halves tablets.

MATERIALS AND METHODS

Materials

Microcrystalline Cellulose (Avicel pH 101) was bought from FMC Corp (Ireland), Plasdone was bought from ISP (Switzerland), Aerosil was obtained from Evonik, (Germany), sodium starch glycolate (DMV-Fonterra, Holland) and magnesium stearate (Magnesia, Germany), Lactose monohydrate (Friesland foods, Netherland), Starch from (Galam, Israel). Sodium hydroxide (Merck, KgaA, and Darmstadt, Germany) monobasic potassium phosphate (Merck, KgaA, Darmstadt, Germany) and all the used chemicals were obtained from commercial origin and were of analytical grade. The film coating material was white opadry and was bought from Colorcon GmbH (Germany), Propylene Glycol (The Dow Chemical Co.). Ethanol (Gadot Chemical Co.).

Instruments

An electronic balance (Precisa 205 ASCS) was used to assess the halves tablet weights. Vernier caliper (TA-100 Erweka) was used to control thickness and diameter, hardness tester (Pharma test PTB311E) was used to assess the hardness, friability tester (Copley Type FR 1000, United Kingdom) was used to test the friability of the obtained tablets, while a disintegrator tester (Electrolab (USP), ED-2L, India) was used assess the disintegration time of the manufactured tablets. The coating was conducted using conventional coating pan (Erweka GmbH., type UG, Frankfurt, Germany) provided with an external dryer and spray gun (Type: Ceccato air compressor S.p.A, mod:8566 Mfg by CDA Engineering Sdn Bhd-Malaysia.

Method of preparation of placebo tablets

Uncoated and coated placebo tablets were prepared at JPharm PLC (Palestine). Precisely, all used excipients were meticulously weighed and passed through 24 mesh sieves. The core tablets consist of lactose monohydrate, avicel pH 101, starch, plasdon, sodium starch glycolate, aerosil, and magnesium stearate. Wet granulation method was used as preparation process; the granules were dried and lubricated using magnesium stearate. A Manesty tableting machine (Liverpool, UK) was used to compress the flowable granules. After compression disintegration time, friability, hardness and weight variation of uncoated tablets were assessed based on the USP tests (United States Pharmacopeia, 2017). After that, the tablets were dived and the obtained halves were weighed and the uniformity of halves was assessed for each kind of tablets. In addition, all the above tests were conducted on the coated tablets to assess the role of the coating on weight uniformity of the obtained halves.

Preparation of opadry for film coating

250g of Opadry white powder (containing HPMC as coating polymer, PEG as a plasticizer, talc and titanium dioxide as opacifiers), was accurately weighed and added to 2000 ml of water stirred with propeller mixer to form a whirlpool without drawing air into the liquid. Opadry was added in a slow steady stream to avoid powder flotation, as well as clumping. After all, Opadry powder had been added, the speed of the mixer was reduced to practically eliminate the whirlpool and mixing was kept for around 45 minutes. The aqueous dispersion of Opadry was sieved through a 177 µm sieve just before starting the process of coating. In addition, the aqueous film coating dispersion was maintained under continuous stirring during the entire coating process. The core tablets were placed in the coating pan. Tablet cores were pre-heated to about 40°C by introducing warm air (around 55°C) into the coating pan using a dryer and air compressor. This step was kept for the whole process of coating. The spray gun was loaded with the opadry aqueous dispersion and run at a suitable flow speed. The pan was set into appropriate rotation and the film coating was sprayed on to the falling uncoated tablets. The air heater was switched off and tablets were appropriately dried for nearly 25 minutes in the coating pan. The core tablets aquired 3±2% weight after coating with Opadry.

Hardness and mechanical strength

A tablet hardness tester was used to test the hardness of the coated tablets. This test was carried out according to the USP (United States Pharmacopeia, 2017). Precisely, 20 tablets from each study batch were randomly selected and weighed. The tablet resistance to stress was also assessed by using the friability test and hardness. These tests indicate the ability of tablets to withstand mechanical shocks of handling by the patient, handling during manufacturing, packaging and shipment. To carry out the friability test, a sample of entire tablets equal to 6.5 g (a sample of 10 whole tablets for tablets with a unit weight of more than 650mg), the sample was weighed before the test (Wi) and then placed in the drum of the tester (Copley

Type FR 1000, United Kingdom). The drum was set to rotate at a moderate speed (25±1) revolution per minute (rpm) for 100 revolutions. The tablets were then de-dusted and re-weighed (W_f) and the percentage of friability was assessed using.

$$\%F = \frac{Wi - Wf}{Wi} \times 100\% \qquad \text{Equation 1}$$

Where %F stands for percentage of friability, W_i stands for the weight of the sample before testing, and W_f stands for the weight of the sample after testing (United States Pharmacopeia, 2017).

Disintegration test

The tablet cohesiveness and resentence to fluid disintegration capacity was also assessed. The test was accomplished by placing 6 tablets into the tubes of the rack assembly of a disintegration tester (Electrolab (USP), ED-2L, India). The assembly was suspended in 1000mL simulated gastric fluid (pH 1.2) and maintained at 37°C. After that, the apparatus was run (raising and immersing) in the fluid at constant frequency rate between 29 and 32 cycles per minute until no fragments of the tablets, except fragments of insoluble coating, was observed on the screen of the test apparatus.

Tablets splitting test

Firstly, the whole tablets were assessed for weight uniformity. 30 tablets were randomly selected and each one was weighed and the mean weight of each tablet product was calculated. The tablets were judged to fail the test when more than one individual weight was outside the range of 85-115% of the average weight, or if any individual weight was outside the range 75-125% of the average weight. In addition, the percentage standard deviation was calculated. The tablets were divided by hand along their scored line; each part of each tablet was weighed for the test. Each one of the obtained parts was weighed independently, the average weight for each product was computed and the relative standard deviation was also calculated.

STATISTICAL ANALYSES

The weight uniformity of the halves was analyzed as per ANOVA of 2^3 Factorial design to find the significance of the individual and combined effects of three Factors (size, hardness and coating) involved in the uniformity of the obtained tablet halves of placebo tablets. In fact, the objective of the present study is to assess the formulation factors that may affect the splitting of scored tablets into two equal halves using 2^3 factorial design to achieve tablets halves within the recommended pharmacopoeial specification and using a relative standard deviation SRD less than 6%. Design-Expert version 8.0.7.1 was applied for performing the experimental design and the data analysis.

RESULTS

Various shapes of placebo core tablets were successfully prepared, with two levels of hardness, friability and weights using the same excipients and tablet procedure (tables 1, 2 and 3). In addition, all the obtained tablets were successfully coated using the same coating materials and process (tables 1, 2 and 3).

DISCUSSION

Tablet splitting is one of the most important practices that encounter healthcare providers. In fact, it can provide dose flexibility, especially for elderly, children and those requiring titrating or tapering doses (Elliott, Mayxay *et al*. 2014). Also, it is considered a cost-saving measure, especially in low-income countries. Another important advantage is the ease of swallowing, especially in case of too large size tablets or oral solid dosage forms (Zaid and Ghosh 2011).

However, weight uniformity of tablet halves is becoming a challenge in pharmaceutical industries since it becomes a requirement of the FDA to register facial scored tablets. In fact, because of the importance of having uniform dose after tablet splitting in order to ensure the safety and efficacy of the treatment, the CDER's Drug Safety Oversight Board introduced a special guidance for the pharmaceutical industries on tablet scoring, nomenclature, labeling and data for evaluation (Food and Administration 2013). In this guidance, the CDER recognized the requirement of consistent scoring between the generic tablet product and the related original brand. In fact, consistent scoring should enable the patient to switch between these products without affecting negatively the safety and efficacy since inconsistent scoring may result in under or overdosing. In addition, may cause unintentional drug exposure due to the loss of tablet fragments during the splitting process. Accordingly, the pharmaceutical companies should pay huge attention during the stage of development and production of these scored tablet products.

To the best of our knowledge, few studies have been conducted to assess the factors that may influence the splitability of tablets (Van Vooren *et al*., 2005, Rajan *et al*., 2016, Sa-Barreto *et al*., 2017, Zaid and Ghosh, 2011).

The first one was conducted by De Spiegeleer, Van Vooren *et al.* to assess the impact of some operational compression parameters such as speed and force on the weight variabilities of half- and quarter-tablets using two types of cross-scored round tablets that have identical composition but different in size. De Spiegeleer confirmed that the mass units, will remain approximately identical for round tablets and hence the RSD of quarter-tablet weights will always be higher when breaking half-tablets into quarter-tablets. Unfortunately, the author did

not report the operational variables that may affect the uniformity of the obtained halves. Recently, two studies have been conducted to assess the key technical aspects that may influence the accuracy of tablet splitting. However, these studies were conducted on generic products and the related brands that are available in the pharmaceutical market (Sá-Barreto *et al*., 2017, Zaid and Ghosh, 2011).

Therefore, it would be difficult to fix the reason behind obtaining uniform halves since these products are different and several variables are present between them such as excipient content, shape, disintegration, friability, size, and APIs. Another attempt was carried out to evaluate the impact of manufacturing parameters and splitting between the content and weight uniformity of Atenolol tablets. In this study, two strengths of Atenolol tablets (100 and 50 mg) were prepared under the same manufacturing conditions and using the same excipients. The author concluded that physical factors such as tablet hardness, diameter, may be involved in achieving both weight and content uniformity in the obtained tablet halves. However, this manuscript included neither tablet shape nor tablet coating (Zaid and Ghoush 2011). This is the first one that has been conducted in order to assess most of the formulation tablet characteristics that may be involved in the achievement of equal halves.

These variables were tablet shapes, size of tablets, hardness, friability, and coating. All tested tablets were prepared using the same formula and the same tableting procedure to minimize these effects on our final results. To assess the first variable (shape), three different shapes, oval, disc, and capsule, were manufactured and each one was produced with two levels of hardness (low and high) and in two sizes (large and small). Despite the hardness level and the size of tablets, all shapes passed the splitting tests except for the disc shape which showed % RSD higher than 6%. In the second part of this study, the impact of hardness, and size of tablets on weight uniformity of the split halves was evaluated. Moreover, the effect of film coating on this practice was also investigated. For all these purposes, a three-levels, 2^3 full factorial design was selected. Four variables were chosen, namely, hardness (x1), the size as (x2) and coating (x3). Each independent variable had 2 levels which were coded as –1 (low and +1 (high) respectively The coded values of independent variables were given to the software as shown in table 1. The 8 runs for each shape placebo tablets in a design matrix of 2^3 full factorial designs are set up by randomization. A multiple regression, first-degree model was used to express the response as a function of the selected three factors (Neamati *et al*., 2014).

8 experiments (2^3) were suggested to calculate the main effects and the interaction effects from the factorial design as summarized in table 4.

Concerning the size or weight of tablets, it showed a positive trend, however, this trend has no significant effect on the uniformity of the obtained splits (*p*-value > 0.05) (table 5).

Regarding hardness, it is clear that there is always a positive effect and in two tablet shapes (oval and capsule) was significant (p-value <0.05) as reported in table 5.

In general, higher the hardness lowers the % of RSD and better the uniformity of the obtained halves. In fact, this may be explained since higher hardness may result in better cohesiveness between the powder or granules that form the tablets and this does not permit easy loose of these dusts or bad breaking. Moreover, this would permit the breaking of the tablet from it is the weaker part which is the scoreline. Accordingly, it could be suggested the use of excipients with high capacity that give high harness without impacting negatively disintegration time of the obtained tablets (i.e., CC). In same time, a processing technique such as granulation and the slower rotation speed of the rotary tableting machine may give the desired hardness. In addition, suitable shape like oval or capsule-like shape tablets could be beneficial for this issue as all tablets (large and small) passed this test. Therefore, in an additional attempt to confirm this hypothesis we decided to coat the same tablets. In fact, we believe that coating ma protects tablets from losing their parts and again would permit splitting from the weak part of the tablet. In fact, among the studied three shapes, only the disc or round shape showed failer of the splitting test as shown in runs 2, 4 and 6 (table 4). In fact, all these three experiments were uncoated tablets and all of them passed the splitting test once they were coated, a significant decrease in the % RSD was observed. This may suggest a positive significant effect of the coating on obtaining uniform halves. Accordingly, we can deduce that film coating may provide additional value to its existing benefits in pharmaceutical manufacturing since it may be helpful in obtaining uniform halves. Regarding the friability, as well as hardness of tablets, it is considered one of the quality control tests that are used to assess the capacity of the tablet to retain its powder components. The USP stated that good conventional tablet should not loss more than 1% of its initial weight when subjected to the friability test (United States Pharmacopeia, 2017). This is to ensure that the obtained tablets are don not lose fragments which may decrease the therapeutic response and may express human subjects to unintentional drug exposure. In addition, low friability is also important when tablets are subjected to stresses like transportation and in case of a subsequent coating.

Accordingly, it may play a positive rule as well as hardness and coating in achieving weight uniformity halves. In fact, the results showed a generally positive (but not significant) trend on tablet breaking since low

friability results in low %RSD as well as hardness and coating. In addition, the disintegration time of all obtained tablets was within the accepted criteria of the USP which may encourage pharmaceutical companies that desire to produce functional scoring to focus on these variables without concerns about the disintegration time wich should remain low since it usually affects the final release of drugs from tablets.

CONCLUSION

The aim of the presenting research was to examine the impact of formulation parameters (Hardness, Size, Film coating) on weight uniformity of scored tablet. Size or weight had no significant effect on the uniformity of the obtained tablet halves. In addition, high hardness and low friability had a positive effect and significant (disc and capsule shape). Meanwhile, coating gives significant and positive effect even on disc shape tablets which failed the splitting test. These findings suggest that the disc shape particle is not suitable for breaking. In addition, film coating, as well as high hardness and low tablets friability, may give better uniformity of the obtained halves, since a decrease in the calculated % RSD was observed.

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