Effect of Shape on Physico-Chemical Properties of Metronidazole Tablet

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Received: 15-Sep-2021; Accepted: 08-Mar-2022.

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HIGHLIGHTS

- Metronidazole is selected for this study because it is a poorly compressed drug.
- This study is based on the comparison of various physicochemical parameters of round and oblong shape tablets.
- Different statistical results showed that round shape is more stable form for poorly compressed drugs like metronidazole.

Abstract: This work was aimed to analyze metronidazole tablet for its properties by explaining the role of compaction and compression related to its process of manufacturing in round and oblong shape tablets. The desirable features of a tablet that includes a known value of hardness, friability, disintegration, weight variation and dissolution was carefully evaluated. The weight variation test performed on different days for round and oblong shape tablets. All tablets of round shape were within limits of +/- 5% (USP, BP) however some of oblong shape tablets deviating from +/-5% limit. The hardness and friability tests indicate that oblong shape tablets are more prone to breaking during handling and transportation while round shape tablets are well within limits of hardness and friability tests i.e. within 1% and 0.8% (USP, BP). The disintegration time of both round and oblong shape tablets are nearly same and within the limits. The dissolution profile of both round and oblong shape tablets were determined according to USP. The obtained dissolution profile of both
shaped tablets were evaluated and compared using two different statistical methods, the fit factor (f1 and f2) and the dissolution efficiency (DE) model. The values obtained were 9 and 64 for f1 and f2 respectively. The DE was found to be 63 and 72 for round and oblong shapes. The experimental findings showed that change in shape of tablet affect different physicochemical parameters. In addition, tablet shape enhances tablets mechanical properties, packaging, handling ease and the aesthetic appearance of the tablet.

**Keywords:** Geometric Shape; metronidazole tablets; physico-chemical characteristics.

**INTRODUCTION**

Metronidazole [1-(2-hydroxyethyl)-2-methyl5-nitroimidazole] is a nitroimidazole compound, available for use in clinical practice for over 25 years and belongs to chemical class same as tinidazole and ornidazole. Compound of metronidazole was discovered in the late 1950s [1].

Tablet is that type of pharmaceutical solid dosage form which contains drug substance with diluents which are suitable and prepared either by molding or compression methods. The manufacturing of tablet involve granules, powders and pellets [2]. Normally, powder is compressed into compact mass to form tablet [3]. For tabletting of a material, good compressibility is imperative. Powder mixture for successful compression must have low segregation with high value of flowability and compaction while pretreatment of powder before compaction is done when it lack the above properties. The pretreatment involve the agglomeration of the excipient particles and primary drug(s) into secondary particles which are larger with the higher value of porosity as compared to the primary one [4].

The role of compression and compaction is related to manufacturing of tablet formulation. The physical and mechanical characteristics such as density, strength (hardness or friability) of tablets are defined by the compaction while, integrity and bioavailability of dosage forms are attributed to compression [5]. Some of the elements changes certain properties i.e size of the particle, distribution of size, crystallinity, amorphism, pseudomorphism of compression [6, 7]. Simple compression of powder or granulate into tablet is also known to be influenced by deformation behavior of particles, the rate at which force is transfer, and forces of adhesion in between particles [8]. In drugs having high doses with poor compressibility profile, compression physics has gained importance because in high drug doses tensile strength of tablet and compression force exhibit a relationship which is non-linear. This condition provides an inclination towards problems of tableting which include lamination, sticking, capping and picking. So structure failure occurs as a result of variation in various process related factors, composition proportion and type. Some drugs having high doses and/or poor compressibility are reported in the literature which includes paracetamol [9] ibuprofen [10] mefenamic acid [11] acetazolamide [12] metformin [13] and hydroxyapatite [14]. Such complication can be reduced by identification of problems related to tabletting and by establishing their relation with parameters of compaction.

The compaction behavior of some of the drugs and excipients having poor compression characteristics is improved by improving the compaction behavior either of the excipients and or active pharmaceutical ingredients by adopting different strategies. So by explaining the rational of various shape of oral dosage form, manufacturer should not neglect the importance of designing a proper shape tablet with optimum therapeutic profile because there is a direct relationship between the quality and shape of the tablet. While designing a dosage form of optimum quality one should consider temperature sensitivity, compressibility, picking, sticking, capping, lamination and abrasive behavior of the product [15]. Different shape tablet have different tensile strength due to difference in compressibility character. The profiles of drug release from tablet is also known to be affected by tablet shape and size [16, 17]. Tablet shape is also important in regulation of time required for the drug release [18] and also for controlling its release from a tablet or formulation of specific shape [19]. Moreover selection of optimum shape for a tablet also enhances the quality of tablet formulation. Keeping in view all the above facts relating to tablet shape it is compulsory for the manufactures not to miss any single concerned point related to shape that will in turn affect the quality of tablet end product. Hence importance is given to the geometric shape of tablets, to design a product of optimum quality with beneficial outcomes. Tablet geometric shape has an important role in drug release profile because any change in it is consider to cause changes in tablet various physical parameters i.e. hardness values if changes as a result of change in geometric shape, then there may be a change in other physical parameters of the tablet such as friability of tablet and also its disintegration as well as its dissolution [20, 21].
MATERIAL AND METHODS

Instruments

Analytical balance Ohaus USA, Tablet hardness tester Curio, Friablerator Curio (Model: FB2020), Disintegration apparatus Dawn (Model: DT08), Dissolution (Model: DIS/6B), Glass wares (local manufactured), UV/Visible spectrophotometer (Model: CE CECIL USA).

Materials and reagents

Reference sample of metronidazole were gifted by Stanley Pharma Ltd. Similarly, the round shape and oblong shape tablets of metronidazole were manufactured by Stanley Pharma according to the established pharmacopeial procedures for this study.

Weight variation test USP

The purpose of this test is to make sure that the entire tablets under observation have uniformity in weight and have the required amount of labeled drug. 20 tablets will be selected randomly and will be weighed individually on the analytical balance Ohause, USA. The percent deviation from the average weight will be then determined.

Tablet Hardness test USP

Hardness of tablet is also known as crushing strength of tablet. Hardness will be measured by placing the tablet between the two jaws of hardness tester and then start moving one jaw towards the other until the tablet fracture. The reading from display on the hardness tester will be noted. Then the tablet average hardness will be calculated.

Tablet friability test USP

A friabilator is used to assess the capability of tablets to combat abrasion after its post manufacturing process during its handling and packing. For each operation of friability test, 10 tablets will be selected, dedusted and weighed initially. The tablets will be then put in friabilator and will be operated for four minutes at 25 rpm. Tablet will be removed and then weighted again. Then weight of the tablet before and after friability will be putted in the formula to measure the % loss in weight.

Tablet Disintegration test USP

In disintegration test, the tablets undergo conversion into granules from the parent drug. This is measured in rate or per unit time. Six tablets will be taken randomly and putted in tubes separately in basket rack assembly. Movement of basket rack assembly causes the tablet in the tubes to disintegrate. The time will be noted from the display of the disintegration apparatus when the tablet is completely disintegrated.

Tablet dissolution test USP

Dissolution test of tablet is usually performed to determine the availability of known amount of drug product. Dissolution test involve the quantitative analysis of drug product by assessing the rate at which the ingredient is liberated from the tablet under specific circumstances. The apparatus used will be Dissolution apparatus DIS/6B. In this study the apparatus used will be USP and BP apparatus I (basket) for metronidazole tablet and will be then analyzed on UV/Visible spectrophotometer.

Dissolution Test procedure for apparatus (I)

Rotating basket method is adopted for metronidazole tablet. Hydrochloric acid will be used as a dissolution medium. Temperature was maintained at 37°C. Dissolution apparatus for metronidazole will run for 60 minutes at 100 rpm. Then samples will be taken from each basket and the amount of metronidazole dissolved will be determined by using UV visible spectrophotometer at 278 nm. For comparison metronidazole standard dissolved in the same medium will be used. The readings will be noted and putted in the formula given below for dissolution assay.

\[
\text{Assay} \% = \frac{\text{absorption of sample}}{\text{absorption of standard}} \times \frac{\text{weight of standard}}{\text{weight of sample}} \times 100
\]
RESULTS

Weight variation test for different shape tablets

There were total of ten series of round and oblong metronidazole tablets tested for weight variation. Each series consisted of twenty tablets of metronidazole. The average of all series is shown in Figure 1. The graph also composed of the upper and lower limits in addition to the average weights of all series of round and oblong shape metronidazole tablet.

![Graph showing weight variation test of round shape metronidazole tablets.](image)

Figure 1. Weight variation test of round shape metronidazole tablets.

The results indicated that all the round shape tablets of metronidazole are complying with BP and USP weight limits. The results of weight variation of all series of oblong shape metronidazole tablets are shown in Figure 2.
Hardness test for different shape tablets

The oblong shapes tablets are under higher stress state and hence break easily as compared to the round shapes. This trend can be comprehended from all the hardness reading in Figure 3 given here for metronidazole round and oblong shape tablets.

Figure 3. Comparison of Hardness tests of metronidazole round and oblong shape tablets.

Friability test for different shape tablets

The tablet having high value of hardness may have lesser value of friability so the amount of material loss in percentage have been determined for different shape metronidazole tablets experimentally and shown in Figure 4.
Figure 4. Comparison of Friability test (%loss) of metronidazole round and oblong shape tablets.

Disintegration test for different shape tablets
The disintegration of different shaped tablets was determined experimentally to declare which shape has greater impact on disintegration time. The shape along with the disintegration time is given in Figure 5.

Figure 5. Comparison of Disintegration test of metronidazole round and oblong shape tablets.

Dissolution test for different shape tablets
The dissolution profile of round and oblong shape metronidazole tablets and percent amount of drug released from each shape of metronidazole tablet is determined as shown in Figure 6.
DISCUSSION

Shape and Weight variation relationship

All tablets of metronidazole in round shape are within the weight limits specified by BP/USP however some of the oblong shape tablets are deviating from the limits (+/-5%, USP and BP) as shown by the curve above in Figure 2, indicating the fact that poorly compressed powder is difficult to mould into oblong shape tablets. While on the other hand round shape metronidazole tablets easily pass the weight variation test.

Shape and hardness relationship

To investigate the effect of shape on hardness and crushing strength of the tablets, both round and oblong tablets were tested by the hardness tester. The results showed that the oblong shape is very much closer to the lower limit of hardness and prone to easily breakage. It can be noticed from the Figure 3 above that round shape tablets are inherited with higher hardness as compared to the oblong shapes. One of the reasons behind the elevated hardness in case of round shape is that more area is in contact with the jaws of the hardness tester. The higher the contact area higher is the resistance against the crushing/breaking of the tablet. According to mechanics and force analysis, higher area decreases the stress on the tablet. So in many cases hardness is used as a surrogate measurement of compression force. So the results of our study reports that the round shape of metronidazole tablet which has greater compression forces than the oblong shape metronidazole will have higher hardness value and will need larger compression pressure than the oblong shape tablet to be broken.

Shape and friability relationship

It was observed from the experimental results of the friability tests that oblong shape tablets have higher friability (near to 1%) as compared to the round shape tablets friability which is around 0.3%. In other words, the oblong shape is more susceptible to lose the material/fragments than the round shape tablets because of its high friability values. In addition, the round shape tablets are harder as explained in the last section pertaining to the hardness performance evolution of both round and oblong shapes. So this study reports that the amount of material loss in percentage for round shape tablet metronidazole is less as compared to the oblong shape metronidazole tablets.

Shape and disintegration relationship

The experimental results of this study shows that the round shape tablet of metronidazole has higher disintegration value than that of the oblong shape tablets, so the oblong shape tablets will disintegrates quickly than the round. This fast disintegration make the oblong shape tablet not a preferable shape because if the drug is disintegrating at a faster rate than the body is unable to receive the therapeutic amount of drug.
Shape and dissolution relationship

In the literature [21, 23], different methods which can be used to compare dissolution profiles data have been reported. However, in this study the two most important and widely used methods have been used: the fit factors and dissolution efficiency (D.E). The fit factors can be expressed by two approaches: f1 (the difference factor) and f2 (the similarity factor). Table 1 indicates the dissolution efficiency (D.E) data calculated from the mean dissolution profiles. Oblong shape metronidazole tablets revealed D.E greater than the round shape tablets. Results obtained for f1 and f2 are also shown in Table 1. Values less than 15 and higher than 50 were obtained for similarity (f1) and difference (f2) factors, respectively.

The results in table 1 suggested that there is no significant difference in the release profile however the oblong shape tablet of metronidazole have shown slight increased rate of dissolution than the round shape metronidazole so we can say that the round shape tablet has increase compression profile. This is the reason that if the compression force during the compression of the tablets increase, definitely those tablets will have slower rate of dissolution (longer time). One of the reasons for slow dissolution of round shape tablet is that increase in compression force also increases the hardness of the tablet due to high compact arrangement of the granules in the tablet, so the tablet requires more time and effort to get dissolve in the dissolution medium. Also if compression force increases, the tablet wettability decreases in the dissolution medium thus making the penetrability of the dissolution medium into the tablet core at slow pace, and ultimately it will slows down the dissolution of the tablet. So the round shape tablet is preferred to obtain dissolution profile of drug in order to get therapeutic drug dosage and to prevent toxicity by drugs that are dissolving at increase rate.

Table 1. Mathematical results obtained from the dissolution profiles data for round and oblong shape metronidazole tablets by model-independent analyses.

| Parameter                  | Formulation  |   |
|----------------------------|--------------|---|
| Dissolution efficiency (%) | Round tablet | 63|
|                           | Oblong tablet| 72|
| Difference factor (f1)     | Round tablet | 9 |
|                           | Oblong tablet|   |
| Similarity factor (f2)     | Round tablet | 64|
|                           | Oblong tablet|   |

CONCLUSION

It is concluded from this study that for drugs having poor compressibility it is very important to compress that drug in proper shape. Metronidazole is a poorly compressed drug therefore it can best be compressed into round shape tablet as compare to oblong shape to have the desired quality product. It is evident from the results that the round shape tablets have more desirable results in terms of weight variations, hardness, friability, disintegration and dissolution. If the drug is compressed in improper shape it will lead to many problems resulting in loss of drugs during handling and transportation thus ultimately affecting the efficacy of the drug and health of the patient.

Funding: This research received no external funding.

Acknowledgments: The authors acknowledge the support provided by Stanley Pharmaceutical Pvt Ltd Pakistan.

Conflicts of Interest: “The authors declare no conflict of interest.”

REFERENCES

1. Trivedi M, Patil S, Shettigar H, Bairwa K, Jana S. Spectroscopic Characterization of Biofield Treated Metronidazole and Tinidazole. Med Chem. 2015;5:340-4.
2. Peck G, Baley G, McCurdy V, Banker G, Lieberman H, Lachman L, et al. Pharmaceutical Dosage Forms: Tablets. Ed HA Lieberman, L Lachman and JB Schwartz, Marcel Dekker, Inc, New York. 1989:105-8.
3. Joiris E, Di Martino P, Berneron C, Guyot-Hermann AM, Guyot JC. Compression behavior of orthorhombic paracetamol. Pharm Res. 1998 Jul;15(7):1122-30.
4. Sun CC, Himmelspach MW. Reduced tabletability of roller compacted granules as a result of granule size enlargement. J Pharm Sci. 2006 Jan;95(1):200-6.
5. Leuenberger H, Leu R. Formation of a tablet: a site and bond percolation phenomenon. J Pharm Sci. 1992 Oct;81(10):976-82.
6. York P. Crystal engineering and particle design for the powder compaction process. Drug Dev Ind Pharm. 1992;18(6):677-721.
7. Sun C, Grant DJ. Influence of crystal shape on the tableting performance of L-lysine monohydrochloride dihydrate. J Pharm Sci. 2001 May;90(5):569-79.

8. Garekani HA, Ford JL, Rubinstein MH, Rajabi-Siahboomi AR. Effect of compression force, compression speed, and particle size on the compression properties of paracetamol. Drug Dev Ind Pharm. 2001 Oct;27(9):935-42.

9. Akande OF, Ford JL, Rowe PH, Rubinstein MH. The effects of lag-time and dwell-time on the compaction properties of 1:1 paracetamol/microcrystalline cellulose tablets prepared by pre-compression and main compression. J Pharm Pharmacol. 1998 Jan;50(1):19-28

10. Pawar AP, Paradkar AR, Kadam SS, Mahadik KR. Crystallo-co-agglomeration: a novel technique to obtain ibuprofen-paracetamol agglomerates. AAPS PharmSciTech. 2004 Jun 19;5(3):e44. doi: 10.1208/pt050344. PMID: 15760077; PMCID: PMC2750267.

11. Adam A, Schrimpl L, Schmidt PC. Factors influencing capping and cracking of mfenamic acid tablets. Drug Dev Ind Pharm. 2000 May;26(5):489-97.

12. Di Martino P, Scoppa M, Joiris E, Palmieri GF, Andres C, Pourcelot Y, Martelli S. The spray drying of acetazolamide as method to modify crystal properties and to improve compression behaviour. Int J Pharm. 2001 Feb 1;213(1-2):209-21.

13. Gohe MC, Jogani PD. Exploration of melt granulation technique for the development of coprocessed directly compressible adjuvant containing lactose and microcrystalline cellulose. Pharm Dev Technol. 2001 May;51(3):249-57.

14. Gad SC. Pharmaceutical manufacturing handbook: production and processes: John Wiley & Sons; 2008.

15. Reynolds TD, Mitchell SA, Balwinski KM. Investigation of the effect of tablet surface area/volume on drug release from hydroxypropylmethylcellulose controlled-release matrix tablets. Drug Dev Ind Pharm. 2002 Apr;28(4):457-66.

16. Siepmann J, Kranz H, Peppas NA, Bodmeier R. Calculation of the required size and shape of hydroxypropyl methylcellulose matrices to achieve desired drug release profiles. Int J Pharm. 2000 May 25;201(2):151-64.

17. Colombo P, Catellani P, Peppas N, Maggi L, Conte U. Swelling characteristics of hydrophilic matrices for controlled release new dimensionless number to describe the swelling and release behavior. Int J Pharm. 1992;88(1-3):99-109.

18. Deshpande A, Rhodes C, Shah N, Malick A. Controlled-release drug delivery systems for prolonged gastric residence: an overview. Drug Dev Ind Pharm. 1996;22(6):531-9.

19. Gökçe EH, Ozyazici M, Ertan G. The effect of geometric shape on the release properties of metronidazole from lipid matrix tablets. J Biomed Nanotechnol. 2009 Aug;5(4):421-7.

20. Vemula SK. Formulation and pharmacokinetics of colon-specific double-compression coated mini-tablets: Chronopharmaceutical delivery of ketorolac tromethamine. Int J Pharm. 2015 Aug 1;491(1-2):35-41.

21. Vemula SK, Veerareddy PR. Development, evaluation and pharmacokinetics of time-dependent ketorolac tromethamine tablets. Expert Opin Drug Deliv. 2013 Jan;10(1):33-45.

22. Veerareddy PR, Vemula SK. Formulation, evaluation and pharmacokinetics of colon targeted pulsatile system of flurbiprofen. J Drug Target. 2012 Sep;20(8):703-14.

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