In Vitro Dissolution of Metronidazole (400 Mg) Tablets: Effects of Lubricants on The Dissolution of Tablets

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ABSTRACT

The aim of the study was to evaluate the effect of different lubricants on pharmaceutical effectiveness of metronidazole tablets determined by the rate of release of drug from the dosage form. Different lubricants, like magnesium stearate, talc and the combination of both were used to prepare metronidazole tablets by direct compression method. The tablets were tested for quality control parameters such as uniformity of weight, thickness, diameter, contents assay, hardness, friability and disintegration time. Formulations were tested for the releasing pattern of drug from tablets by in-vitro dissolution test. Better results were achieved from formulation having magnesium stearate as lubricant based on compression force value. The content uniformity for all the three formulations was found in the range of 96.71 to 99.61%, while hardness was in the range of 7.39±0.341 to 10.375±0.95 Kg. The formulated tablets were also analyzed for dissolution profile which was more than 85% within 20 minutes. Then it was compared with dissolution profile of marketed products for quality and similarity analysis. Lubricant plays a key role in successful manufacturing of pharmaceutical solid dosage forms. Many failures in pharmaceutical manufacturing operations, directly or indirectly, can be controlled by appropriate screening of lubricants.

Keywords: Metronidazole; effects of lubricants; in-vitro dissolution; quality control analysis; magnesium stearate.

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INTRODUCTION

To obtain a therapeutic response against the disease, it is important that the suitable amount of the active drug must be delivered to the site of action. The most critical point in this regard is the release of appropriate amount of drug substance from its dosage form. In the formulation designing many efforts have been put to make a clear framework for selecting different compounds with minimum ambiguity that impacts the quality of the drug products.

Different processes are used to produce compressed tablets containing precise amount of an active pharmaceutical ingredient (API) and excipients at high speed in the proper form. The selection of method depends upon the number of factors, the most important being the properties and the dose of the drug. The excipients behave differently, depending upon the vendor and the quality. The differences in the density of API and excipients cause the segregation that lead to a problem of weight variation and content uniformity. Lubricants have prominent effects on the filler, which may lead to the softening of the mass resulting in capping or lamination of the tablets, adhesion or sticking of powder material with punch tips, etc.

Metronidazole was the first clinically effective 5-nitromidazole drug that received widespread therapeutic use in the treatment of various infections. It is an antimicrobial drug that is primarily active against obligate anaerobic microorganisms both bacteria and protozoa. The bioavailability of oral metronidazole approaches 99-100%. Bioavailability and pharmacokinetics parameters of drugs depend upon number of physiochemical, formulation and physiological factors. In this regard, several studies in which serum concentration / time data from oral / intravenous infusions of metronidazole were analyzed and significant variation in these parameters was found among individual patient or volunteers. The rate of absorption and physiological availability of drug administered orally in solid form is the function of their rate of dissolution in gastrointestinal fluids. Certain formulation and processing factors such as lubricants, disintegrants, their concentration and also the granulation methods apparently affect the dissolution rate of the drugs contained in tablets.

The objective of the present study was based on the formulation of metronidazole tablets containing different lubricants such as magnesium stearate, talc and both talc and magnesium stearate, followed by direct compression method. The study was conducted to evaluate the effect of different lubricants on the rate of disintegration and dissolution profile of the tablets. Then the formulated tablets dissolution profiles were compared with commercially available tablets of the same strength for the similarity scrutiny.
MATERIALS AND METHOD

Material
Metronidazole was a kind gift sample from Abbott Laboratory Pakistan Limited, Karachi. Six different brands of metronidazole tablets were obtained from a retailer of Karachi (Pakistan) markets. All material and solvents such as avicel pH 101 of Gujarat Microwax (India) origin, cross povidone of Switzerland origin, magnesium stearate of BHD (Malaysia), talc powder and hydrochloride acid, used were of pharmaceutical grade and distilled water was freshly prepared for tablets processing and dilution.

Preparation of tablets
Direct compression method was used to prepare the tablets. Total three types of formulas (tablets) were prepared with two different lubricants having the same quantity (400mg) of active drug. All the three formulations were compressed at the same pressure and 1000 tablets per batch of metronidazole were produced. Each batch went through official and unofficial testing.

To prepare tablets, Metronidazole (AI) was mixed by geometric dilution method with cross-povidone K-30 and avicel pH101. Sieved with sieve # 20 then mixed in a polythene bag for 12 minutes. Lubricants (magnesium stearate, talc powder and magnesium stearate + talc powder) were added separately in each formulation batches and mixed for further 2 minutes and were sifted through mesh # 40 manually one by one. The blended powders were then compressed on Single Punch Tablet Press (Model TDP) on round shaped punches having bisect line on one side and plain from the other at theoretical weight of 750 mg ± 5% (Table-1)

| Materials            | Formulation Code (mg/tablet) | F1 | F2  | F3 |
|----------------------|------------------------------|----|-----|----|
| Metronidazole        | 400                          | 400| 400 |    |
| Avicel               | 302                          | 302| 326 |    |
| Povidone             | 8                            | 8  | 8   |    |
| Talc                 | 40                           | ---|     | 8  |
| Magnesium Stearate   | ----                         | 40 | 8   |    |
| Total Weight         | 750                          | 750| 750 |    |

F1 = formulation have 40 mg talc as lubricants, F2 = Formulation have 40 mg magnesium stearate as lubricants, F3 = formulation have 8mg magnesium stearate + 8 mg talc

In vitro evaluation of tablets
The dose uniformity of tablet can be determined by two different general approaches, weight variation and drug content uniformity. The USP permits the later approach in all cases including
the coated tablets. Weight uniformity can only be applied to uncoated tablets which contain 50mg or more of single active ingredient. For weight variation 20 tablets were selected randomly from each batch and were weighed individually as well as on an average. Average weight, range, standard deviation and variances were calculated.

USP Content Uniformity test is designed to establish the homogeneity of the batch. Ten tablets were assayed individually. USP criteria are met if the content uniformity lies within 85% to 115% of the label claim [10]. The amount of metronidazole per tablet was determined by established Pharmacopeial method. Ten tablets were selected randomly from each batch, and the tablets were weighed and crushed into fine powder with the help of mortar and pestle individually. An amount of powder equivalent to 100 mg of metronidazole was transferred in a 100ml volumetric flask. Added 50-60 ml of 0.1N HCl and was shaken for 45 minutes. The volume was made up to the mark with the same solvent and filtered through Whatmann filter paper. One ml of the filtered solution was diluted to 100 ml with 0.1N HCL solution (10µg/ml) and absorbance was measured at 277nm. The standard solution for content uniformity was prepared by weighing 20.0 mg of metronidazole (B.P) reference standard accurately which was transferred into 100ml volumetric flask. It was then dissolved in 50-60 ml of 0.1N HCl and the volume of 100 ml was made. Five ml of the solution was diluted with 100 ml of the 0.1N HCl. The concentration of resulting solution was 10µg/ml. The absorbance of the standard solution was measured at the wavelength λ = 277 nm. Hydrochloric acid 0.1N was used as blank to obtain zero base line.

Disintegration is very important test as it provides the in-vitro simulation of drug disintegration and dispersion after intake. In present study an Erweka GmbH disintegration apparatus type ZT-2 was used for the measurement of the disintegration time. Disintegration medium for Metronidazole tablet was 0.1N HCl. The disintegration time for uncoated tablets should be NMT 15 minutes. All of the tablets were disintegrated completely within the time limit.

Dissolution is a qualitative tool that provides in vitro measurement of the bioavailability of a drug as well as demonstration of bioequivalence. Hydrochloric acid (0.1N) was used as dissolution medium. One tablet was placed in each basket (USP apparatus I) and immersed in a vessel containing 900 ml of dissolution medium previously warmed to 37 ± 0.5°. The vessel was covered to prevent the evaporation of the medium. The rotational speed of the basket was adjusted at 100 rpm. Ten milliliters samples were collected at predetermined time intervals 5, 10, 20, 30, 45 and 60 minutes and filtered (millipore) to remove any insoluble excipients. Five milliliters of the filtrate was diluted to 200ml with the same dissolution medium. Ten milliliters of medium that was already equilibrated to 37± 0.5° was replaced into dissolution vessel after each sampling in order
to maintain sink condition. Six tablets per formulation (F1, F2, and F3) as well as the six marketed brands were used for the study. The diluted samples were analyzed by the UV-spectrophotometric method at $\lambda = 277$nm. The concentration and the percentage release in each time interval was determined. The standard solution for the analysis of tablets dissolution was prepared by weighing 22.22 mg of metronidazole (BP) reference powder accurately. It was then dissolved in 40-60 ml of dissolution medium to make the volume of 100 ml. Five ml of the solution was diluted with 100 ml of the dissolution medium. The concentration of resulting solution was $11.11\mu g/ml^{12}$.

Along with official some non-official tests were also performed to evaluate the pharmaceutical quality of the formulated tablets. The ability of a tablet to withstand the shock of handling, packing and shipping has been the traditional measure of tablet strength requirement. For the determination of hardness of a tablet a Fugiwara hardness tester was used. Ten tablets were selected randomly and separately from each of the batches formulated. Hardness of the tablets should be not less than 4 kg. Ten (10) more tablets were designated separately from each formulated batch for the measurement of surface brittleness of tablets. D2800 BREMEN type EU 44E2/114 apparatus was used to determine the friability of tablets. After weighing, the tablets were placed in a plastic chamber and allowed to revolve for 4 minutes (i.e. 100 revolutions). Tablets were reweighed and percentage weight loss was calculated (Limit = NMT 1%).

Six Marketed brands were also picked from retail pharmacy and evaluated for drug release profile and quality control parameters. This study was carried out to compare the similarity level in dissolution pattern between formulated and marketed tablets (Tablet-2).

RESULTS AND DISCUSSION

Numbers of pharmaceutical companies are engaged in producing and marketing the metronidazole tablets. Along with national, international brands are also present in the market of Karachi. Sometime the same active substance prepared by different companies gives different pharmacological index because each brand has different composition of excipients. This study was carried out to understand the effect of lubricant on the in vitro dissolution release of drug from tablets formulated in the Lab with different composition and types of lubricants.

The oral route of drug administration is the most convenient for patients, with tablets emerging as the most popular solid oral dosage form used today. A wide range and diversity of ingredients are often included in tablet formulations. Jinjiang and Yongmei in 2014 reviewed that lubricant plays a key role in successful manufacturing of pharmaceutical solid dosage forms; critical selection of
lubricants are required for the achievement of robust formulations. Although many failures in pharmaceutical manufacturing operations such as hardness, release of drug from dosage form, are directly or indirectly related to the amount and use of inappropriate lubricants.

In the present study two different lubricants, magnesium stearate and talc were used in different proportion to evaluate their effects on the physiochemical properties as well as on the release pattern of drug from tablets. During the study three (3) different batches of oral tablet were formulated with different concentrations of talc, magnesium stearate and combination of magnesium stearate + talc as per Table-1. The composition of tablets was determined by preliminary screening. Tablets were prepared by direct compression method and inspected visually for shape and color.

The appearances of all tablets were elegant, round in shape and white in color. Average weight of all three formulations felt in the range of 755.2 ± 1.43 to 757.2 ± 1.66 mg with lower limit of 738 mg and upper limit of 790 mg as shown in Table-3. The weight of the tablets must be adequately controlled to assure the content uniformity. The diameters of formulated tablets were controlled between 8.4-9.9 mm while the thickness was 4.8 to 5.8 mm.

### Table-2: Pharmaceutical evaluation of six (6) commercial Formulations

| Formulation | Weight variation Mean ± SD | Content Uniformity (%) | Disintegration time (min) | Hardness (Kg) | Friability (%) |
|-------------|-----------------------------|------------------------|--------------------------|---------------|---------------|
| Com 1       | 758.5 ± 38.26              | 101.98± 0.66           | 10.10                    | 17.87 ± 1.22  | 0.064         |
| Com 2       | 643.2 ± 10.75              | 99.94± 1.03            | 8.54                     | 16.74 ± 2.11  | 0.15          |
| Com 3       | 733.8 ± 26.36              | 101.36± 0.89           | 7.32                     | 13.14 ± 0.73  | 0.18          |
| Com 4       | 721.2 ± 12.41              | 100.1± 0.77            | 7.45                     | 10.16 ± 0.22  | 0.012         |
| Com 5       | 769.9 ± 28.16              | 100.6± 1.23            | 3.49                     | 22.82 ± 1.03  | 0.098         |
| Com 6       | 750 ± 52.58                | 99.67± 0.83            | 13.20                    | 14.28 ± 2.45  | 0.027         |

### Table 3: Weight variation for three different Formulations (1-3)

| No. of Tablets | Weight of Formulation 1(mg) | Weight of Formulation 2 (mg) | Weight of Formulation 3 (mg) |
|----------------|-----------------------------|-----------------------------|-------------------------------|
| 1              | 780                         | 748                         | 738                           |
| 2              | 756                         | 760                         | 750                           |
| 3              | 766                         | 755                         | 770                           |
| 4              | 745                         | 750                         | 740                           |
| 5              | 742                         | 740                         | 760                           |
| 6              | 748                         | 750                         | 760                           |
| 7              | 758                         | 790                         | 754                           |
| 8              | 765                         | 768                         | 750                           |
| 9              | 768                         | 758                         | 764                           |
| 10             | 744                         | 750                         | 766                           |
| Mean           | 757.2                       | 756.9                       | 755.2                         |
| SD             | 12.54149                    | 13.90803                    | 10.75794                      |
| %RSD           | 1.66                        | 1.84                        | 1.43                          |
SD = Standard Deviation
RSD is relative standard deviation

The basic quality parameters namely disintegration time, hardness and friability analysis of the formulation # 1-3 showed that formulation # 2 of metronidazole tablet, containing magnesium stearate (5.34%) as lubricant showed better result than formulation # 1 that having talc (5.34%) as shown in Table 4. Whereas the ease of ejection of the tablets from the die were observed much better when the combination of talc + magnesium stearate (1.5% of each) were used in formulation # 3. In the present study the lubricant efficacy was observed by smooth ejection of tablets from dies. It was calculated by compression force value and the force value is influenced by the nature of lubricant. For tablet formulations, it is important that it must show good mechanical strength with sufficient hardness in order to handle shipping and transportation. Pharmacopeias do not directly define the limit of hardness. It is usually expressed in term of disintegration time and friability as dependent variables. The friability of tablets is a tool to assess the tendency of a solid substance to break into smaller pieces under duress or contact during transportation after manufacturing till its final delivery to the patient. Hardness or breaking force of tablets for all three formulations was found in the range from 7.39 ± 0.341 to 10.375 ± 0.95 Kg. whereas the friability values were found between 0.25min - 0.82max % as presented in Table-4.

Table-4: Pharmaceutical quality analysis of Formulated Batches

| Formulation | Disintegration time (min)a | Hardness (Kg)b | Friability (%)b |
|-------------|----------------------------|----------------|-----------------|
| Formulation 1 | 1.0                        | 7.39 ± 0.341   | 0.82            |
| Formulation 2 | 1.45                       | 10.375 ± 0.95  | 0.25            |
| Formulation 3 | 0.55                       | 8.678 ± 0.86   | 0.55            |

a= results based on 6 tablets
b = results based on 10 tablets

The disintegration test measures the time required for tablets to break into particles. This is one of the important parameter especially for oral tablets where the disintegration time is supposed as the predictor for release of drug, as it could be the rate-determining step in the process of drug dissolution and absorption. The result showed that formulation # 3 were disintegrated in average of 0.55 min having the combination of two lubricants that are magnesium stearate and talc with very minimum standard deviation ± 0.03 as shown in Table-4. Theoretically rapid disintegration of tablets gives a sense of quick onset of action and good sign for bioavailability. Formulation # 1 having talc as lubricant showed a rapid disintegration of tablets (≤ 1min). It has the ability to reduce friction and quickly disintegrate the tablets by absorption method but the weak binding of
SiO₂ in its structure makes it softer and influence the ejection efficacy of tablets from dies. The friability was also highest among the three formulations. Whereas the formulation # 2 was comprised on magnesium stearate showed the best result for disintegration (1.45min) and friability (0.25%). Magnesium Stearate is the most widely used lubricant. It is typically added to the blend a few minutes (2-5 minutes) prior to the conclusion of the blending period. Even if it is used in low concentrations (0.2%-1.5%), it is often the cause of many issues experienced with solid oral dosage forms¹⁴-¹⁷.

Ten (10) tablets from each formulation were selected randomly and measured individually for content uniformity test and it was found well within the acceptance limits defined by the USP (NLT 85% and NMT 115%). The content uniformity for all the three formulations was found in the range of 96.71 to 99.61% (Fig. 1). This result also indicated the uniformity of active ingredient in the formulation blends.

### Table-5: Dissolution Profile of Formulated Tablets

| Tablets   | % Drug Dissolved In Minutes |
|-----------|----------------------------|
|           | 0 | 5 | 10 | 20 | 30 | 45     |
| Formulation -1 | 0 | 50.52 | 82.2 | 102.86 | 102.67 | 103.01 |
| Formulation -2 | 0 | 48.79 | 75.52 | 96.49 | 99.04 | 101.23 |
| Formulation -3 | 0 | 53.18 | 88.21 | 107.29 | 106.54 | 106.98 |

**Figure 1: Content Uniformity for Formulated tablets (Batches # 1-3)**

Formulation-1 have content percentage from 96.71-98.44%, formulation-2 have content assay from 97.5499.61%, formulation-3 have content uniformity between 96.87 to 97.99%, SD is standard deviation and RSD is relative standard deviation
A dissolution test simulates the availability of active substance and allows the prediction of the time for complete release of the material from the dosage form. The dissolution test defined in the USP-34 was performed on all the three formulated batches. As shown in Table-5 percent dissolution was calculated to evaluate the release of drug as per the acceptance criteria of USP-34. Under appropriate test conditions, a multipoint dissolution profile can characterize the product more precisely than a single point dissolution test. According to FDA a dissolution profile comparison helps to assure the similarity in product performance and bioequivalence\textsuperscript{18}.

The drug releasing profiles of formulated tablets were assessed by using DD solver (Microsoft Excel) which indicated that the release of drug from tablets were rapid i.e. more than 85% only within 20 minutes (Table-5). Tablets dissolution versus time plots, obtained by calculating the equation with a computer (Weibull reliability curve), gave a S-shaped curve between the dissolution curve for particles starting at time zero and the curve for particles starting at the tablet disintegration time. The joint influences of disintegration and particle dissolution on the overall tablet dissolution profile were examined. $\beta > 1$ indicated that the failure rate is increasing with time (Table-6).

Table-6: Dissolution Models parameters of F1, F2 and F3

| Parameter               | F1      | F2      | F3      |
|-------------------------|---------|---------|---------|
| Zero Order – Model      |         |         |         |
| $k_0$                   | 3.149   | 3.035   | 3.282   |
| $R^2$                   | 0.7865  | 0.8140  | 0.7753  |
| First Order – Model     |         |         |         |
| $k_1$                   | 0.148   | 0.130   | 0.167   |
| $R^2$                   | 0.9926  | 0.9973  | 0.9887  |
| Hixson-Crowell Model    |         |         |         |
| $kHC$                   | 0.033   | 0.032   | 0.034   |
| $R^2$                   | 0.9864  | 0.9942  | 0.9795  |
| Weibull Model           |         |         |         |
| $\alpha$                | 43.071  | 6.058   | 62.710  |
| $\beta$                 | 1.853   | 1.041   | 2.105   |
| $Ti$                    | -0.284  | 2.166   | -0.262  |
| $R^2$                   | 0.9996  | 0.9999  | 0.9981  |

$K_0$ = Zero Order rate constant, $R^2$ = linear regression, $K_1$ = first Order rate constant, and $kHC$ = Hixson-Crowell rate constant

The dissolution data were subjected to different kinetic models such as zero order, first order, Hixson-Crowell, and Weibull Model as presented in Table-6. The Table-6 shows that all the three batches (F1-F3) failed to obey the zero order kinetics. First-order, Hixson-Crowell and Weibull models described the drug release with $r^2$ value $\leq 1$ that provides the qualitative information about
diffusion and disintegration processes of the dosage form. Weibull is considered as a good model in determination of difference among various formulations. Review of literature study showed that in the tablet formulation and process development “in terms of Quality-by-Design” lubricants play a vital rule\textsuperscript{19, 20}.

**Figure 2: Drug dissolution profile of marketed and formulated tablets**

\*n = 6 tablets

Graphical method to assess the similarity of dissolution profiles. The pattern of release of drug from formulated tablets was same as that of immediate release tablet of metronidazole available in local market.

In the proposed study the dissolution profile of formulated tablets were also compared with six (6) brands of metronidazole tablets along with innovator brand that were collected from local market and all these tablets were within their expiry date. This comparison was used as quality control tool to demonstrate the consistency and similarity of formulated tablets with different formulations (Figure 2).

**CONCLUSION**

Thus the conclusion was made that the proposed study evaluated the effect of two different lubricants i.e. magnesium stearate, talc and their combination that was used in different proportion to assess their effects on pharmaceutical properties as well as on the release pattern of drug from tablets. The magnesium stearate showed better quality control result than that of talc. Whereas the ejection of the tablets from the die were much better when the combination of talc + magnesium stearate was used in formulation. The results of the study concluded that the ejection of tablets
(upward and downward movement) from tabletting machine is corresponding to the peculiar behavior of the powder mixture mainly on the quantity and mechanism of the lubricant used. Hence the performance of lubricant was observed by compression force value.

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