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Development of Novel Drug Delivery System Using Calcium Silicate

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***Abstract*—** *The process of dissolution plays a vital role in liberation of a drug from its dosage form and making it bioavailable for subsequent gastrointestinal absorption. This piece of work was initiated to characterize microparticles obtained by adsorption of poorly water-soluble drug, metronidazole, on a porous calcium silicate (Florite) to improve the dissolution properties of metronidazole. Metronidazole was adsorbed on the Florite in 3 proportions (1:0.5,1:1,1:3), by fast evaporation of solvent from drug solution containing dispersed Florite. Metronidazole tablets were prepared by direct compression and compared with Florite adsorbed tablets. The tablets were evaluated for mechanical and release properties of friability, hardness; disintegration test and dissolution test as evaluation parameters respectively. The prepared tablets were compared with Flagyl as standard drug. All the prepared tablets showed acceptable mechanical properties of hardness values ranging from 2.25 -2.45 kg/cm2 which implies that the tablets are less hard than Flagyl tablets having hardness of 2.75kg/cm2. The friability test results were less than 1% with values ranging from 0.21- 0.23 % for compressed tablets. For the release properties, disintegration times of the prepared tablets were 50 secs for B1 tablets, 61 secs for B2 tablets, 63.82 secs for B3 tablets and 62 secs for metronidazole tablets compressed without calcium silicate (B4). The results suggest FLR provides a large surface area of drug adsorption in a smaller ratio resulting in improved drug dissolution.*

***Keywords*—** *Calcium silicate, Metronidazole, Solvent evaporation method, Mechanical and release properties*.

I. INTRODUCTION

The oral route is the most common route of administering drugs, both conventional and orthodox medicines; and among the oral dosage forms, tablets of various types, formed by the compression of a powder held within a confined space, are the most common (Alderson, 20023). The tablet is undoubtedly the most popular mode of presentation of metronidazole as solid dosage form intended for oral administration. Even though metronidazole is classified according to biopharmaceutics classification system (BCS) as class 1 drug i.e., highly soluble and highly permeable (Fatima *et al*., 2017), this research work deals with enhancing the dissolution of metronidazole further by adsorption on a Florite (FLR) carrier, a pharmaceutical excipient. Owing to a wide range of useful properties, porous carriers such as calcium silicate have been used in pharmaceuticals for many purposes including development of novel drug delivery systems such as floating drug delivery systems and sustained drug delivery systems; improvement of solubility of poorly soluble drugs; and enzyme immobilization (Sharma *et al*., 2005).

Calcium silicate, a porous carrier, is a white free-flowing powder. It can be derived from naturally occurring limestone and diatomaceous earth, a siliceous sedimentary rock. It is one of a group of compounds that can be produced by reacting calcium oxide and silica in various ratios (Taylor, 1990). It has a low bulk density and high physical water absorption. Calcium silicate is an excipient with a promising drug porous carrier owing to its excellent biocompatibility, good bioactivity and high drug-loading capacity. In recent years, studies have been carried out on the synthesis of calcium silicate and their applications in drug delivery, where very interesting results and important insights have been documented (Zhu and Sham, 2014). Florite (FLR) is easily dispersible in all aqueous fluids and has been used to adsorb oily and other drugs, as a compressive agent in pharmaceuticals, and to improve solubility (Sharma *et al*., 2005).

Owing to a wide range of useful properties, porous carriers have been used in pharmaceuticals for many purposes including development of novel drug delivery systems such as floating drug delivery systems and sustained drug delivery systems; improvement of solubility of poorly soluble drugs; and enzyme immobilization. Examples of pharmaceutically exploited porous carriers include porous silicon dioxide (Sylysia), polypropylene foam powder (Accurel), magnesium aluminometa silicate (Neusilin), and porous ceramic (Sameer *et al*., 2005). A relatively newer group of carriers include porous carriers, which are low-density solids with open or closed pore structure and that provide large exposed surface area for drug loading. Their hydrophobicity varies from completely hydrophilic carriers, which immediately disperse or dissolve in water, to completely hydrophobic ones, which float on water for hours.

Micro particulate drug delivery system contains microparticles which are particulate dispersion or solid particles with 1-1000µm in size range. The microparticles system allow entrapping the active drug within the matrix, which eliminates the environmental stability problems, minimize the adverse effects regarding drug, increase the bioavailability, as well as enhance the patient compliance (Galatage *et al*., 2019). Micro particles are widely used in the pharmaceutical and other sciences to mask tastes or odours, impart stability to drug molecules, improve bioavailability, and as multi-particulate dosage forms to produce controlled or

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targeted drug delivery (Aduri *et al*., 2018). It is therefore a rapidly expanding technology for achieving immediate-release dosage forms, the micro particles being produced by the solvent fast evaporation method.

Metronidazole is a nitroimidazole antibiotic. It inhibits nucleic acid synthesis by disrupting the DNA of microbial cells. This function only occurs when metronidazole is partially reduced, and because this reduction usually happens only in anaerobic bacteria and protozoans, it has relatively little effect upon human cells or aerobic bacteria.

This study was aimed at mainly investigating Florite as a substance capable of improving dissolution rate of metronidazole and hence its bioavailability. Metronidazole was adsorbed over Florite using solvent evaporation technique and the resultant microparticles were evaluated using surface, infrared radiation (IR) micromeritics studies and dissolution studies. Microparticles were formulated into a tablet followed by evaluation of its mechanical and release properties.

II. Materials and Methods

Materials

Calcium silicate (Florite®) was a gift from Tomita Pharmaceutical Co. Ltd, Japan), polyvinylpyrrolidone (PVP (Kollidon® VA 64 Fine Ludwigshafen Germany), lactose (Granulac® 140 MEGGLE Group Wasserburg, Germany). All other reagents and chemicals were obtained commercially as analytical grade.

Methods

Preparation of microparticles

Adsorption of metronidazole over Florite

Metronidazole (6 g) was weighed accurately and put in a 1000ml conical flask. Ethanol (936 mL) was used to dissolve the drug, and weighed quantity of Florite (calcium silicate) was dispersed with shaking into drug solution. Florite was used in 3 different quantities to produce 1:0.5, 1:1 and 1:3 drug: Florite ratios on the weight basis, respectively. Ethanol was evaporated in a DKZ shaking water bath (model DKZ shaking water bath, laboratory oven (TT-9053 Techmel & Techmel, USA) at a constant temperature of 90°C, and evaporation was terminated when dried powder started flowing freely along the surface of the conical flask. Collected microparticles were dried for 48 hours in an oven at a temperature of 50°C for complete removal of ethanol.

Preparation and characterization of tablets

Microparticles with sodium lauryl sulphate (5% $^{w}/_{w}$), PVP-K30 (6% $^{w}/_{w}$), and lactose IP (quantity sufficient) were geometrically mixed, lubricated with 2% $^{w}/_{w}$ magnesium stearate and directly compressed using a single punch tableting press (Cadmach Machinery Co. PVT. Ltd, Ahmedabad-45, India) fitted with 12.5mm fitted face punches. The machine was adjusted to produce tablets of 400mg weight with hardness of ~ 2.0 ± 0.5 kg/cm^2. Also, metronidazole tablets were prepared without calcium silicate using same procedure. This formulation was used to compared with those containing FLR. The composition of compressed tablets is as shown in Table 1.

Bulk and tapped densities

The weights of the microparticles were determined using an electronic weighing balance (OHAUS electronic balance No: B423673727, USA). Microparticles (10g) was placed in a 100ml clean, dry measuring cylinder and the volume, occupied by the sample before tapping (bulk volume), was noted. The tapped volume was obtained by mechanically tapping the graduated cylinder containing the sample until further volume changed was observed. The bulk and tapped densities were calculated as the ratio of weight (mass) to volume.

TABLE 1: Composition of compressed tablets

Ingredients	B1 (1:0.5)	B2 (1:1)	B3 (1:3)	B4 (pure metronidazole tablets)
Metronidazole (mg)	6000	6000	6000	6000
Calcium silicate (mg)	3000	6000	18,000	___
Ethanol (ml)	936	936	936	___
Sodium lauryl sulphate ($\%^{w}/_{w}$)	5	5	5	5
PVP ($\%^{w}/_{w}$)	6	6	6	6
Magnesium stearate ($\%^{w}/_{w}$)	2	2	2	2
Lactose (mg)	1440	500	500	4,440

Carr's compressibility index

Carr's compressibility index was calculated by using the equation below:

Carr's index= tapped density-bulk density/tapped density (1)

Hausner's ratio

Hausner's ratio was calculated as the ratio of the tapped density to the bulk density for each batch of microparticles.

Hausner's ratio =tapped density/bulk density (2)

Evaluation of tablets properties

Mechanical properties

Hardness test

Hardness test was done using the Monsanto hardness tester, India (MHT-20). Four tablets from each batch were used. Each tablet was placed diametrically between the jaws of the tester and the force needed to just crush the tablets was noted.

Friability test

Ten tablets from each batch were selected, dusted, weighed and placed in separate drums of a Roche friabilator, England (DT-2D). The tablets were tumbled for 4 minutes at a speed of 25 revolutions per minute. The tablets were then removed, dusted and reweighed. The friability of the tablets was expressed as a percentage using the formula below:

$$\text{Friability} = \frac{W1 - W2}{W1} \times 100 \quad (3)$$

Weight uniformity test

To study weight uniformity,10 tablets were obtained from each of the batch of the formulation and weighed individually using an electronic balance, and the average weight determined. The mean and standard deviation was determined for each batch.

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Thickness

The thickness of the tablets was determined by using a micrometer screw gauge (0.25 × 0.01mm). Four tablets from each batch of the formulation were randomly selected and the thickness measured.

Diameter

The diameter of the tablets was determined by using a micrometer screw gauge (0.25 × 0,01mm). Four tablets from each batch of the formulation were selected and their individual diameters determined.

Release properties

Disintegration test

The BP Disintegration Apparatus containing distilled water at 37±2°C was used to run the test. Four (4) tablets from each batch were placed individually in each of the cylinder of the disintegration apparatus and a guided disc placed on each of the tablets. The apparatus was then started and a stopwatch was used to monitor the time taken for all fragments of the four tablets to pass through the screen.

Dissolution test

Preparation of dissolution medium

Phosphate buffer (pH 7.4) (900 mL) was prepared by dissolving 34g of potassium dihydrogen phosphate and 5g of 98.0% sodium hydroxide pellets in a little quantity of distilled water. The volume was made up to 900 mL with distilled water.

In vitro dissolution test

In vitro dissolution study was carried out using the USP basket method in the tablet dissolution test apparatus (DA-6D), at 100rpm (revolution per minutes), in 900 mL of the dissolution medium containing phosphate buffer, maintained at 37°C ± 0.5°C. 5 mL aliquot was withdrawn every 5 minutes interval (5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 min) and replacing an equal volume of fresh medium into each dissolution media after each sampling. Drug release in the medium was determined using the L7 Double Beam UV-VIS spectrophotometer (UV Shanghai China). The assay was done at a wavelength of 380 nm, where metronidazole exhibits peak absorbance. For comparison, a commercial tablet was also simultaneously studied.

III. Results and Discussion

Process design

Metronidazole has a very poor solubility even in polar organic solvents such as ethanol and methanol (Seedher and Bhatia, 2003). Ethanol was selected as a solvent in which metronidazole showed moderate solubility. Because of the porous nature of FLR, it possesses a low density and hence to limit bulk volume, the ratio of drug: FLR was restricted to a maximum of 1:3. Preliminary studies to obtain microparticles were performed using 3 different drug: FLR ratios (1:0.5, 1:1, 1:3).

Characterization of microparticles

SEM showed microsized drug crystals as well as agglomerates of pure methronidazole and irregular Florite particles with numerous pores on surface (Figure 1). Drug adsorption over Florite particles can be seen in surface topography of microparticles

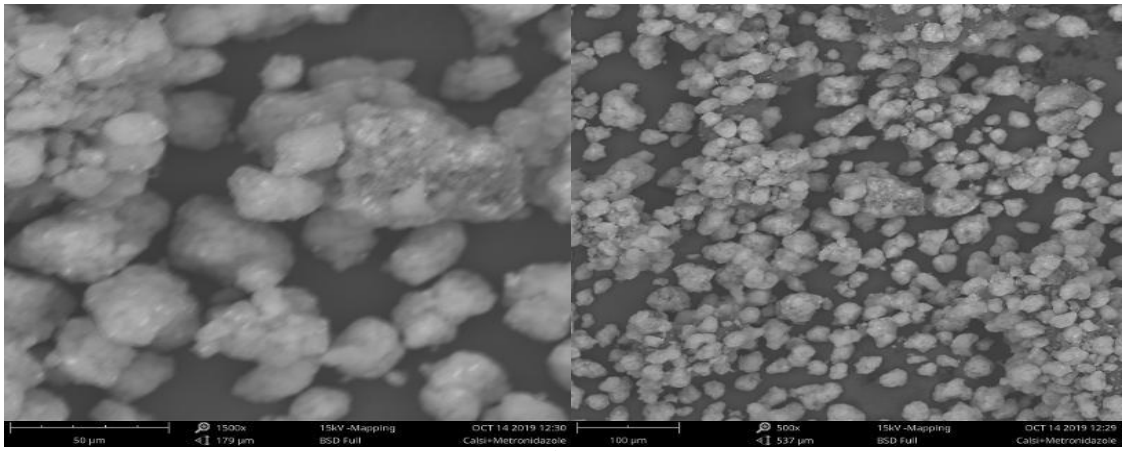

Figure 1. SEM photographs of metronidazole adsorbed Florite

Physicochemical properties of microparticles

The results of the tapped density (TD), bulk density (BD), Hausner's ratio (HR), Carr's index (CI) are presented in Table 2. The results are interpreted on the basis of the FLR ratio. From the study, the bulk density was between (0.26-0.42), and the tapped density between (0.31-0.56). Because bulk density is an important micromeritic property in the characterization, handling, processing of a powder system, it is dependent on its particle size distribution which in turn influences flowability of the powder. Thus, the microparticles obtained was said to have good flowability. The ranking of the bulk density and tap density was B3 > B2 > B1. The compressibility index and Hausner ratio are measures of the products ability to settle, and permit an assessment of the relative importance of inter-particulate interactions. In a free-flowing powder, these interactions are less significant and the bulk and tapped densities will be closer in value. For poorly flowing particles, there are greater interparticulate interactions and a greater difference between the bulk and tapped densities. The differences are reflected in the Carr's compressibility index

and Hausner ratio. The smaller the value of the Carr's index, the better the flow property of the powder and the higher the particle size, the smaller the Carr's index.

From the study, the Carr's compressibility was between (18.8-26.04). Indicating that all the batches possessed a fair flow character. From the Hausner's ratio which was between (0.06-0.15), the study result indicates a good flow property. The ranking of the Carr's index and Hausner's was B3 > B2 > B1.

Mechanical properties of tablets

Weight uniformity, hardness, diameter, thickness and friability

The weight uniformity, hardness, diameter, thickness, and friability of formulated tablets were compared with those of Flagyl tablets as presented in Table 3.

Tablet hardness

Hardness influences the compaction of substances in the tablets; the higher the hardness, the higher the compaction (Savjani *et al*., 2012). Because these are immediate release tablets, it should have a low compaction indicating a decrease in porosity of the matrix. The study shows that the FLR concentrations affected the hardness of the tablet; B1 with the lowest concentration of FLR was less hard than B2 and B3; whereas metronidazole tablets compressed without FLR was least hard. From the result, the hardness values ranged from 2.25 – 2.4 kg/cm^2 which implies that the tablets are less hard than metronidazole tablets compressed without FLR and Flagyl tablets of hardness values 2.45 kg/cm^2 and 2.75 kg/cm^2 respectively, and would yield immediate release of active pharmaceutical ingredient. Tablet hardness may influence tablet disintegration and more significantly, it would affect the dissolution rate.

TABLE 2. Results of tapped density, bulk density, Hausner's ratio and Carr's index of microparticles

Parameters	B1	B2	B3
Bulk density (g/cm^3)	0.26 ± 0.006	0.34 ± 0.01	0.42 ± 0.01
Tap density (g/cm^3)	0.31 ± 0.006	0.43 ± 0.01	0.56 ± 0.006
Carr's index (%)	18.80 ± 1.72	20.94 ± 0.49	26.04 ± 1.28
Hausner's ratio	0.06 ± 0.006	0.09 ± 0.002	0.15 ± 0.006

TABLE 3: Mechanical properties and disintegration time of formulated and Flagyl tablets

Samples	Weight variation (n=10) Mean ± SD	Thickness (mm) Mean ± SD (n=4)	Diameter (mm) Mean ± SD (n=4)	Hardness (kg/cm^2) Mean ±SD(n=4)	Friability (%) Mean ±SD (n=3)	Disintegration time (secs) Mean± SD
B1	0.38 ± 0.011	2.61 ± 0.43	12.64 ± 0.056	2.25 ±0.17	0.21 ± 0.18	50 ± 3.49
B2	0.39 ± 0.021	2.52±0.024	12.58 ± 0.054	2.3± 0.27	0.23 ± 0.09	61 ± 4.51
B3	0.41 ± 0.038	2.46 ± 0.24	12.64 ± 0.084	2.4± 0.44	0.25 ± 0.39	63.82 ± 2.06
B4	0.46 ± 0.02	2.27 ± 0.11	12.61 ± 0.01	2.45±0.04	0.23 ± 0.01	62 ±3.42
Flagyl Tablets	0.52 ± 0.011	2.63±0.051	11.22 ± 0.033	2.75± 0.71	0.24 ± 0.06	64.23 ± 3.02

Tablet friability

Friability test measures the ability of the tablet to withstand mechanical hazards in packing, shipping and handling. The normal limit for friability is less than or equal to 1% (BP, 2008). As the particle size decreases and the polymer concentration increases, it brings about a corresponding increase in the friability of the tablets. From the result of the study, all the batches passed friability test. The ranking of friability test was B1 < B2 < B4 < B3.

Weight uniformity

Weight uniformity ensures consistency of dosage units during compression (Felton, 2012) as well as the uniformity of the dose of the drug. The results suggest that the smaller the quantity of FLR, the more uniform the weight of the tablet. The weight uniformity test indicated no significant difference in the weights of tablets from all the batches including the commercial tablets. Hence, this indicates that the tablets possessed a good uniformity in weight and dose and it conforms to the British Pharmacopoeia specification; which states that for tablets weighing greater than or equal to 250mg, not more than two of the individual weights should deviate from the average weight by more than ±5% and none should deviate by more than ±10% (BP, 2008). Also, FLR is seen to impart an effect of weight reduction on the API and other excipients.

Tablet diameter and thickness

These parameters influence the weight uniformity of the tablets and subsequently dose uniformity. From the result, the particle size had no significant influence on the diameter and thickness of the tablet. The values obtained from the diameter are above 12.5mm, the pharmacopoeia standard. The deviation of diameter of the tablets may either be due to an uneven feeding of particles into the die or may be due to the irregular movement of power punch. Tablet thickness is determined by the die of the tableting machine and may vary as a result of the speed of tablet compression. Tablet thickness is generally controlled to minimize appearance problems. Although tablet thickness is not in the pharmacopeia standards, it is important to be evaluated as it is one of the methods to control the quality for packaging. The thickness values obtained were; 2.61mm, 2.52mm, 2.46mm and 2.27mm for B1, B2, B3 and B4 tablets respectively.

Release properties

The results of the disintegration and dissolution tests are represented in Table 4 and Figure 1 respectively.

Tablet disintegration

The tablet disintegration test is a useful means of assessing the potential significance of formulation and process variables on the biopharmaceutical properties of the tablet, and as a control procedure to evaluate the quality reproducibility of the tablet during production. The disintegration test is an *in-vitro* procedure and does not necessarily bear a relationship to the *in-vivo* action of solid dosage forms. Specified disintegration time for immediate release tablets in official compendia stipulates 15 min for uncoated tablets. The results obtained were 50 secs, 61 secs, 63.82 secs, and 62 secs for B1, B2, B3

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and B4 compressed tablets respectively. The compressed tablets were seen to disintegrate faster than Flagyl tablets with Flagyl tablets having 64.23 sec. The ranking of disintegration times was B1 < B2 < B4 < B3.

In vitro dissolution studies

Samples were taken as follows: 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60 min intervals The drug released was for 1hour for all the compressed batches. The drug release profile as shown in Figure 2 indicated that at the end of 1hour, B1, B3 and Flagyl tablets had dissolved completely. Dissolution rate of drug from microparticles was significantly rapid compared with pure drug, and the dissolution rate increases with increase in proportion of Florite. B1, B2, showed extended drug dissolution may be due to lower quantity of Florite for drug adsorption.

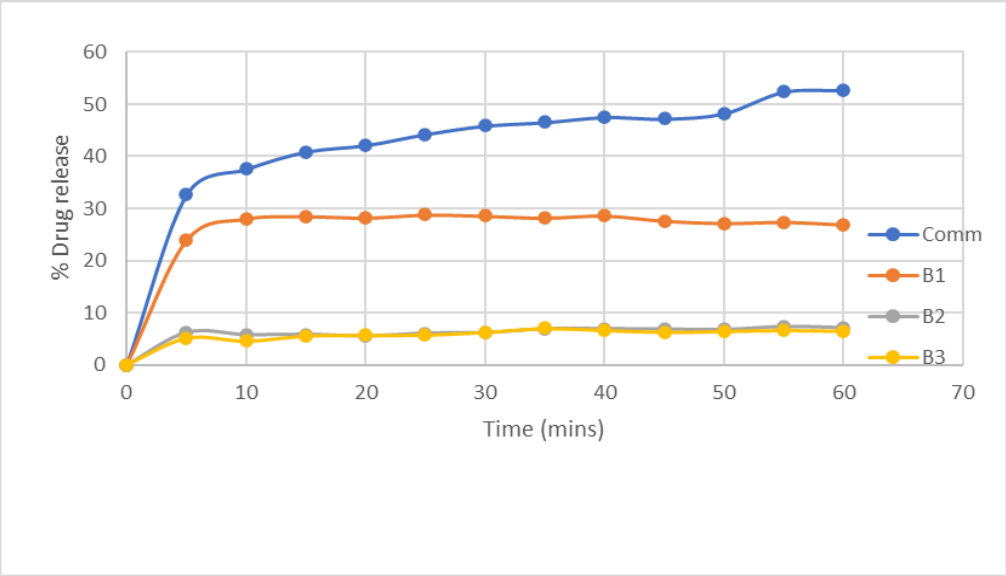

Figure 2. The release profile of tablets compressed with FLR and Flagyl tablet

IV. Conclusion

Calcium silicate was employed in developing a novel drug delivery system in this research work. It was used formulate an immediate-release drug dosage form with improved dissolution rate as well as bioavailability. Tablet microparticles were prepared by adsorbing metronidazole on calcium silicate (Florite) to enhance the dissolution rate of metronidazole; and evaluating the mechanical and release properties of these tablets were determined to follow the standard in pharmacopeia. The FLR adsorbed tablets were compared with metronidazole tablets compressed without FLR and Flagyl tablets. The results obtained indicated that FLR can be used as a potential pharmaceutical excipient in improving the dissolution rate of metronidazole and thus its bioavailability. This is possible because, calcium silicate (FLORITE), for its biocompatibility and high drug- loading capacity providing a large surface area for drug adsorption and reducing crystallinity resulting in improved drug dissolution, has shown to be a promising drug carrier excipient in this study.

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