ORIGINAL RESEARCH PAPER

Volume-8 | Issue-2 | February-2019 | PRINT ISSN No 2277 - 8179

INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

DISINTEGRATION BEHAVIOR OF METRONIDAZOLE TABLETS CONTAINING DIFFERENT RATIOS OF CO-PROCESSED *ABELMOSCHUS ESCULENTUS* GUM AND *MANIHOT ESCULENTA* STARCH.

Pharmaceutical

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ABSTRACT

This study examines the disintegration behaviour, over 3 months, of metronidazole tablets formulated with co-processed *Abelmoschus esculentus* gum to *Manihot esculenta* starch. The gum and starch were extracted from *Abelmoschus esculentus* fruits and *Manihot esculenta* tubers respectively. The gum and starch extracts were co-processed in 4 different ratios of gum to starch; 0.50:99.5, 1.00:99, 1.25:98.75 and 1.50:98.5. These 4 co-processed excipients, and standard microcrystalline cellulose, were used in formulating 5 different batches of metronidazole granules as disintegrant. The metronidazole granules from these batches were analysed for chemical compatibility and micrometric properties. The FT-IR analysis of the co-processed excipients and metronidazole showed no chemical incompatibility, and the granules exhibited good flow properties. The granules were compressed to tablets, and the tablets physicochemical properties determined and evaluated. The tablets all passed tablet per cent friability, hardness, and disintegration time tests. The dissolution of metronidazole from tablet after I hour was over 60 % for all the batches. The disintegration properties of the tablets over 3 months were then determined and statistically analysed. The two Way ANOVA analysis showed that the difference in disintegration time of the metronidazole tablets with different test excipients, after 3 months of storage is significant at 5 % level. It can be concluded that the different excipient combinations had different effect on disintegration time on storage. The metronidazole tablets formulated with 0.5:99.5 ratio of co-processed *Abelmoschus esculentus* gum and *Manihot esculenta* starch gave the best disintegration time as metronidazole formulated with standard microcrystalline cellulose disintegrant.

KEYWORDS

Abelmoschus esculentus gum, *Manihot esculenta starch*, Co-processed.

INTRODUCTION

A limited number of solid active substances can be easily compressed to tablets either purely or with simple addition of disintegrant and lubricant. The majority of solid drug actives, however, have poor flow and poor compressive ability and may require additional treatment to first convert them to free flowing compressible granules. The conversion of powder solid drug actives to free flowing compressible granules may require complex multi-stage processing with a number of therapeutically inert excipients (Moreton, 2013). The various therapeutically inert excipients which may be combined with powdered drug active in tablet granulation formula include starch, lactose, microcrystalline cellulose, magnesium stearate, talc, and a host of others (Patel, Shah, & Upadhyay, 2011). These excipients, in correct proportion, may function as wetting agents, diluents, adhesives, absorbents, disintegrants or lubricants among others in tablet design.

There is an increasing shift towards the use of plant based therapeutically inert excipient in tablet formulations. This is because, among other advantages, plant based excipients are non-toxic, biocompatible, biodegradable, and relatively cheap in comparison with synthetic products (Emeje et al., 2011). Starch is the most commonly used plant-based excipient in solid dosage design. Starch can serve as diluent, binder, lubricant or disintegrant depending on the quantity used, stage and state of application in formulation of powdered drug actives to granules. The proportion of native starch required to exert certain satisfactory functional property in granules formation may negatively affect the granules compressive abilities and other physicochemical properties of the tablet. In other to overcome the drawbacks of proportion and functionality of native starch, various modified forms of starch and combinations have been produced. Modification of starch has been used to create starch of functional specificity with reduced drawback effect. Physically, chemically, genetically, combination of these methods, or co-processing techniques with other modified forms or with different excipients have been used to create novel excipients with enhanced functional properties. Some novel excipients with enhance functionality has been processed using particle engineering by co-processing. Corn starch and microcrystalline cellulose have been co-processed for direct compression of aspirin, and had relative to corn and microcrystalline cellulose alone, improved hardness and disintegration time (Builders et al., 2010). Corn starch and gelatin with tensile strength and disintegration time suitable for direct compression (Apeji et al., 2018). Pregelatinized corn starch and acacia have been evaluated for direct compression application (Olowosulu, Oyi, Isah & Ibrahim, 2011). Mixture of corn starch and pregelatinized starch have been co-processed to StarCap 1500 that exhibits good physical, chemical and microbiological stability (Mahmoudi, Do and Rajabi-Siahboomi, 2010). Starch-1500 (pregelatinized starch) is a combination of intact and partially hydrolyzed starches, and is used as disintegrant at a range of 5 – 10 %, and also as filler and binder similar to modified *Manihot esculenta* starch Okafor, Ofuefule and Udeala (2011). Production of *Cedrela odorata* Gum Co-Processed with Plantain Starch and Microcrystalline Cellulose with decreased degree of agglomeration, and increased compressibility in direct compression have also been done (Adetunji and Odeniyi, 2016). These co-processed excipients, by combining two excipients of different degree of functionality in one compact form, exhibit multipurpose functionality (Olowosulu, Oyi, Isah & Ibrahim, 2011).

In this work, co-processed *Abelmoschus esculentus* gum and *manihot esculenta* starch will be used as excipient in formulating metronidazole tablet. Modified *Manihot esculenta* is reported to have disintegration binding and properties in tablet formulation (Nnamani & Okonkwo, 2017). Gum obtained from *Abelmoschus esculentus* fruit has been reported to have binding, disintegration, sustain release, suspending and emulsifying properties in different pharmaceutical dosage formulations (Onunkwo & Udeala, 2003; Emeje et al., 2011). Metronidazole is an antimicrobial and antiprotozoal drug active used alone or in combination with other antimicrobial agents to treat bacterial vaginosis disease, pelvic inflammatory disease, endocardiatis, amebiasis and others. Metronidazole is available in tablets, creams and intravenous preparations. Metronidazole tablets are available in 200 – 750 mg. The aim of this research is to co-process *Abelmoschus esculentus* gum and *Manihot esculenta* starch and evaluate for application in formulation of metronidazole tablet.

MATERIALS

Abelmoschus esculentus fruits were obtained from Agricultural Development Project (ADP) Farm, Ibusa, Delta State, Nigeria. Metronidazole powder BP and Corn starch were gifts from Dizpharm Pharmaceutical Nigeria Limited. All other reagents and solvents were of analytical grade and procured from local chemical shops.

METHODS

Extraction of *Abelmoschus Esculentus* Gum

Modifying the method of Nagpal et al. (2017), debris were removed from the *Abelmoschus esculentus* fruits, and the fruits were washed

with water to clean. The clean fruits were sliced and meshed into 2 % v/v glacial acetic acid solution to form slurry. The slurry was poured into a 1000 ml beaker and equal volume (1:1) of warm water (at 65^0 C) was gradually poured into the beaker of slurry over 5 minutes with the magnetic stirrer operating at 500 r.p.m. The slurry was allowed to stir for 45 minutes more to extract gum. After extraction, the slurry was filtered through a muslin cloth to remove debris. Excess acetone was then added to the slurry to precipitate the gum. The precipitated gum was removed and dropped into excess acetone again to purify further. The precipitate was then soaked in ethanol and placed inside a fridge 4^{0}C for 12 hours, removed and dried at 80^{0}C for 2 hrs. The dried gum obtained was ground in a porcelain mortar, passed through a 0.22 mm sieve and stored in an air tight glass container.

EXTRACTION OF *MANIHOT ESCULENTA* STARCH

Using the method of Nnamani and Okonkwo (2017), the *Manihot esculenta* tubers were peeled, washed, rasped and grated to mesh. The mesh was immersed in water, stirred and then screened through a muslin cloth. The filtrate was allowed to stand for 4 hours to sediment the starch. The supernatant was drained of and water was added again to the sediment and stirred and allowed to stand, to wash the starch further. The supernatant was the drained off and the slurry sediment poured into a cloth bag and squeezed to release water using hydraulic press. The semi-solid mass was then dried in the oven (Kottermanns Company, Germany) at 80^{0}C for 24 hours. The dried starch lumps were then milled, passed through a 0.22 mm stainless sieve and stored.

Preparing Co-processed Excipient of *Abelmoschus esculentus* gum and *Manihot esculenta starch* (MAGMES)

To prepare 100 g of any of the ratio of Abelmoschus esculentus gum to Manihot esculenta starch (0.50:99.5, 1.00:99, 1.25:98.75 and 1.50:98.5) MAGMES excipients, the respective gum and starch proportions were weighed separately and then blended in a mortar. The blend was placed in a 200 ml beaker and gradually made up to 100 ml with distilled water, while stirring gently. The mixture was then stirred vigorously for 5 minutes at 50 ℃ to create a homogenous viscous mixture. Excess acetone was then poured into the viscous mixture and stirred for 5 minutes to precipitate off the MAGMES. The MAGMES was dehydrated and immersed in acetone again to precipitate further. The decanted precipitate was then dried at 70 ℃ for 12 hours. The dried MAGMES mass was ground, passed through 0.22 mm stainless steel sieve, and stored.

CHEMICAL COMPATIBILITY TEST OF METRONIDAZOLE AND MAGMES USING FOURIER TRANSFORMS INFRARED SPECTROSCOPY (FT-IR)

The FT-IR of metronidazole raw active, and a mixture of metronidazole active with 1:1 MAGMES (1:1 ratio of *Abelmoschus esculentus* gum and *Manihot esculenta starch*) excipient samples were conducted. Using potassium bromide (KBr) method, the samples were made to 200 mg with KBr to produce 1 % dispersion, pulverised, dried in a vacuum oven at 110 ℃ for 2 h, allowed to cool. Then 80 mg of the dried mixture was fed into 13 mm diameter pellet-forming die and compressed by pressure gauge at 8 tons for 3 min to produce 80 mg pellet. The FT-IR readings of the pellets were determined at different wavelength using Schimadzu FTIR-8400S Fourier transmission Infrared Spectrophotometer.

PREPARATION OF METRONIDAZOLE GRANULES

The formula in Table 1 was used to prepare the batches A, B, C, D, E, and F. For each batch, the metronidazole and lactose were blended in a glass mortar first. Cold water was used to disperse starch in a beaker, and the Hot water (at 90 ℃) was poured once into the starch dispersion to form paste. The hot paste was poured into the glass mortar containing metronidazole-lactose and blended for 4 mins to get a homogenous mass. The MCC or MAGMES (depending on the batch) is then added to the mass and blended for 4 mins. The blend was then passed through a 0.44 mm stainless sieve, and dried in a hot air oven at 110 ℃ for 10 mins. The dried granules was passed through the 0.44 mm sieve again, and then blended with the magnesium stearate and stored.

Table 1: Formula For Preparing 150 Tablets Each Of 200 Mg Metronidazole.

	WEIGHT (G)					
FORMULAR	A	B	C	D	E	F
Metronidazole	30	30	30	30	30	30
Lactose	12	12	12	12	12	12
Starch	4.8	4.8	4.8	4.8	4.8	4.8
Cold water	4	4	4	4	4	4
Hot water	4	4	4	4	4	4
MCC	1.8	0	0	0	0	0
MAGMES 0.0	0	1.8	0	0	0	0
MAGMES 0.5	0	0	1.8	0	0	0
MAGMES 1.0	0	0	0	1.8	0	0
MAGMES 1.25	0	0	0	0	1.8	0
MAGMES 1.5	0	0	0	0	0	1.8
Magnessium stearate	0.5	0.5	0.5	0.5	0.5	0.5
TOTAL (Less water)	49.1	49.1	49.1	49.1	49.1	49.1

EVALUATION OF METRONIDAZOLE GRANULES

1.ASSAY OF METRONIDAZOLE GRANULES (DRUG LOADING AND ENTRAPMENT EFFICACY)

Using the USP Monograph (2010 USP29-NF24 P 154) and metronidazole active for range of 1 – 20 µg / ml in deionized water the UV spectrophotometer absorbance at 342 nm and standard Beers plot of metronidazole were obtained. Then, 491 mg of metronidazole granules was weighed and put in a 200 ml volumetric flask, and made up to volume with dilute hydrochloric acid (1 in 100) and mixed. Then 10 ml of the solution was taking out with a pipet and transferred to a 1000 ml volumetric flask, and made up to volume with the dilute hydrochloric acid (1 in 100). Using a UV spectrophotometer, the absorbance of metronidazole in the solution at 342 nm was determined. Using standard beers plot, the concentration of metronidazole was estimated. Using equations 1 and 2, the granules loading and entrapment efficacy of metronidazole was calculated.

2.MICROMERITIC EVALUATION OF METRONIDAZOLE GRANULES

(2a) Bulk and tapped density

Using the method of Sinko (2011) for determining bulk and tapped volumes and densities to calculate Carr's index and Hausner ratio, the metronidazole granules was passed through a 0.33 mm sieve and 20 g each was poured into a 100 ml dry glass cylinder. The cylinder was dropped at 2 seconds interval unto a wooden surface three times from a height of 1.0 cm and the bulk volume was read and recorded. The cylinder was then dropped at 2 seconds interval from a height of 5 cm repeatedly until there was no further reduction in volume. Each test was repeated three times. The bulk and tapped densities were then calculated from these readings using equations 1 and 2 respectively.

$$\text{Bulk density} = \frac{sample\ weight}{bulk\ volume} \quad \text{..... Equation 1}$$

$$\text{Tapped density} = \frac{sample\ weight}{tapped\ volume} \quad \text{..... Equation 2}$$

(2b) Carr's index and Hausner ratio

The Carr's index and Hausner ratios were calculated from the bulk and tapped densities obtained using equations 3 and 4.

$$\%\ \text{Carr's index} = \frac{tapped\ density - bulk\ density}{tapped\ density} \times 100 \quad \text{..... Equation 3}$$

$$\text{Huasner ratio} = \frac{tapped\ density}{bulk\ density} \quad \text{..... Equation 4}$$

(2c) Flow properties (flow rate and angle of repose)

The flow rate and angle of repose were determined using 20 g sample, a funnel fastened to a triple stand at 20 cm from table surface. With the funnel end blocked with a flat stopper, 20 g sample was poured into the funnel. The stopper was removed and the time taken for all the granules to leave the funnel recorded and used to calculate the flow rate (equation 5). The height and diameter of the heap of granules were measured and used to determine angle of repose (equation 6a and 6b).

$$\text{Flow rate} = \frac{weight\ of\ granules\ (grams)}{time\ of\ flow\ (seconds)} \quad \text{..... Equation 5}$$

$$\text{Tan}\ \theta = \frac{height\ of\ granules\ heap}{radius\ of\ granules\ heap} = \gamma \quad \text{..... Equation 6a}$$

$$\theta = \text{Tan}^{-1}\ \gamma \quad \text{..... Equation 6b}$$

Where γ is the coefficient of friction, and θ is the angle of repose.

Compression Of Metronidazole Granules To Tablets

A Type F3 single punch machine (Manesty Machines Limited,

England) with a 10.30 mm concave punches and die set to produce 327 mg tablets. The machine was operated at compression pressure of 4.0 metric tonnes, and speed number 2. The formulated granules were separately poured into the hopper of the tableting machine and operated to compress 150 tablets of 327 mg of metronidazole tablet that should be equivalent to 200 mg metronidazole active per tablet.

Evaluation Of Metronidazole Tablets

Content Uniformity Test

Two tablet of metronidazole was crushed and 327 mg was taken and made up to 200 ml with dilute hydrochloric acid. Then 10 ml of the mixture was made up to 1000 ml with dilute hydrochloric acid and assayed at 342 nm in a UV spectrophotometer. The concentration of metronidazole was then extrapolated from the metronidazole standard beers plot.

WEIGHT UNIFORMITY TEST

Using the USP (2010) method, 20 tablets from each batch was weighed in bulk, and then each tablet individually.

HARDNESS TEST

The Monsanto hardness tester (Model MHT-20, Thermonik, Campbell Electronics, India) the crushing strength of 10 tablets from each batch was determined.

FRIABILITY TEST

Using a single drum friabilator (PTF 10 E, Pharma Test Instruments India Pvt., Limited, India) the friability of 10 tablets as a bulk was determined at 25 r.p.m for 4 min (100 revolutions). The test was done in triplicates.

DISINTEGRATION TIME TEST

Disintegration test was performed on 6 tablets from each batch using a disintegration tester (Model MK4, Manesty Machine Limited, India) operated at 30 cycles/min with 0.1 N HCl at 37 C. The time taken for the tablets to disintegrate was recorded. The test was repeated three times.

DISSOLUTION RATE TEST

Using the USP-NF (2010) method, a dissolution apparatus (Caleva Company Limited, England), 0.1 N HCl and a 1000 ml dissolution flask at 37 C, the dissolution of 5 tablets from each batch was extracted time intervals and determined using the UV spectrophotometer and calculated from the Metronidazole Beers plot.

RESULTS

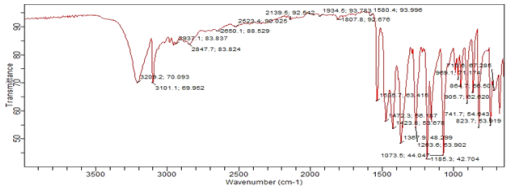

Figure 1 : FT-IR Spectrum of Metronidazole Pure Sample

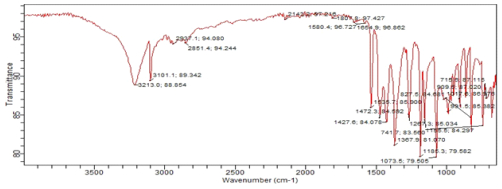

Figure 2 : FT-IR Spectrum of Metronidazole in Ratio 1:1 Solid Dispersion with

Table 2: Interpretation of FT - IR Stretching Vibrations Absorption Frequency of Metronidazole

		Absorption band (cm-1)	
Functional group	Vibration mode	MTZ	MTZ + MEGMES
aliphatic alcohol	O-H stretch (H-bonded)	3209	3213
alkyl group	C-H stretch (saturated)	3101	3101
alkyl group	C-H stretch (saturated)	2937	2918
imino group	C=N stretch	2847	2851
nitro group	N=O stretch	1807	1807

Table 1: Micrometric Properties of Metronidazole Granules

Batch		Bulk Density	Tapped Density	Huasner ratio	% Carrs Index	Angle of Repose	Flow Rate (g/s)
MCC	A	0.45	0.53	1.16	13.64	32.07	9.45
MAGMES 0.0	B	0.47	0.61	1.30	23.26	30.82	8.81
MAGMES 0.5	C	0.51	0.56	1.08	7.69	32.27	9.80
MAGMES 1.0	D	0.53	0.61	1.15	13.16	28.20	11.06
MAGMES 1.25	E	0.53	0.56	1.06	5.26	27.74	10.79
MAGMES 1.5	F	0.50	0.54	1.08	7.50	31.67	9.68

Table 2: Physicochemical Properties Of Metronidazole Tablets

	Batch	Hardness KGF	Friability %F	Disintegration Time (sec)	Dissolution Rate (% D60)
MCC	A	5.5	0.48	6.65	65.9
MAGMES 0.0	B	6.5	0.56	5.26	64.5
MAGMES 0.5	C	2.6	1.73	2.82	68.7
MAGMES 1.0	D	2.6	1.32	5.16	66.9
MAGMES 1.25	E	3.5	1.43	6.30	64.3
MAGMES 1.5	F	3.6	1.39	4.42	68.6

Key:
%D60 = per cent drug released after 60 min.

Table 3: Disintegration Properties Of Metronidazole Tablets Stored Over 3 Months

MONTHS	A	B	C	D	E	F
0	6.13	4.16	2.47	4.13	3.41	2.90
1	6.59	3.04	2.91	4.32	6.33	3.51
2	7.02	7.38	3.40	5.52	7.29	4.11
3	7.11	7.26	3.54	7.10	8.21	7.29

KEY:
A= Metronidazole granues with microcrystalline test excipient
B= Metronidazole with starch as text excipient
C= Metronidazole with 0.5:99.5 ratio of *Abelmoschus esculentus* gum and *Manihot esculenta* starch text excipient
D= Metronidazole with 1.0:99.0 ratio of *Abelmoschus esculentus* gum and *Manihot esculenta* starch text excipient
E= Metronidazole with 1.5:98.5 ratio of *Abelmoschus esculentus* gum and *Manihot esculenta* starch text excipient
F= Metronidazole with 2.0:98.0 ratio of *Abelmoschus esculentus* gum and *Manihot esculenta* starch text excipient

GRAPH ANALYSIS

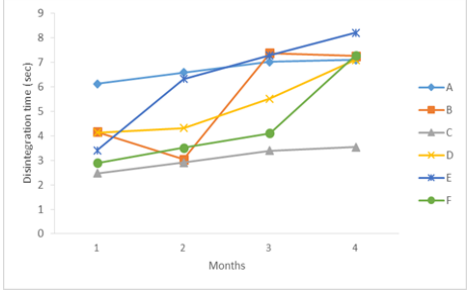

Figure 3: Disintegration Time Profile of Metronidazole Tablets

Key:
A= Metronidazole granules with microcrystalline test excipient
B= Metronidazole with starch as text excipient
C= Metronidazole with 0.5:99.5 ratio of *Abelmoschus esculentus* gum and *Manihot esculenta* starch text excipient
D= Metronidazole with 1.0:99.0 ratio of *Abelmoschus esculentus* gum and *Manihot esculenta* starch text excipient
E= Metronidazole with 1.5:98.5 ratio of *Abelmoschus esculentus* gum and *Manihot esculenta* starch text excipient
F= Metronidazole with 2.0:98.0 ratio of *Abelmoschus esculentus* gum and *Manihot esculenta* starch text excipient

Statistics Analysis Of Metronidazole Disintegration Time

Using the Kothari and Gaurav (2014) statistical Two Way ANOVA analysis, the disintegration time of the metronidazole tablets with the test excipients over 3 months showed significant difference. The calculated F value of 4.85 is higher than the table value of 2.9 at 5 % level with degree of freedoms being $V_1 = 5$ and $V_2 = 9$, and hence could not be due to chance. We reject the null hypothesis and conclude that the difference in disintegration time over the 3 months was due to the different test excipients (Microcrystalline cellulose and the Co-processed *Abelmoschus esculentus* gum and *Manihot esculenta* starch text excipient

DISCUSSION

The mixture of Metronidazole with *Abelmoschus esculentus* gum and *Manihot esculenta* starch did not introduce any new functional group to the metronidazole, as seen in the FT-IR readings and interpretation table of Metronidazole and metronidazole blend. The flow properties of metronidazole granules prepared with microcrystalline cellulose and those with combinations of co-precipitated *Abelmoschus esculentus* gum and *Manihot esculenta* starch text excipients all showed good flow and compressibility properties (Table 1). Tablets compressed from these granules gave passable friability, hardness and disintegration time properties (Table 2). After 60 min, all the metronidazole tablets of the test batches released over 60 % of metronidazole into the dissolution medium. The per cent friabilities of metronidazole granules with ratio of *Abelmoschus esculentus* gum and *Manihot esculenta* starch text excipients were higher than metronidazole tablets produced with microcrystalline cellulose. The disintegration time of Metronidazole tablets with 0.5:99.5 ratio of *Abelmoschus esculentus* gum and *Manihot esculenta* starch was fastest, and remained the fastest after 3 months (Table 3 and Figure 3).

CONCLUSION

All through 3 months storage, tablets compressed from metronidazole granules containing 0.5:99.5 ratio of co-processed *Abelmoschus esculentus* gum and *Manihot esculenta* starch text excipient gave good tablet properties comparable to tablets compressed from metronidazole granules containing standard microcrystalline cellulose excipient.

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