Formulation and Evaluation of Gastroretentive Floating Matrix Tablets of Metronidazole using a Novel Non-effervescent Technique

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Abstract: The aim of this study was to formulate a novel non-effervescent gastro-floating drug delivery system of metronidazole using non-effervescent (sublimation and sintering) technique. Granules were prepared by wet granulation technique using varying concentration of *Grewia mollis* gum; 2,4,6,8% w/w admixed with 1%w/w acrylate methacrylate copolymer (Eudragit® RL100) and extra 2%w/w batch without the addition of Eudragit® RL100. Ammonium bicarbonate (30%w/w) was used as the sublimating agent. The granules were characterized for micromeritic properties. Thereafter, the granules were compressed at 30 units on the arbitrary scale load of a single punch tableting machine and the physicotechnical properties were determined. The metronidazole tablet was then sintered at 70ºC for 12 h. Drug-excipient compatibility study was done using Fourier Transform Infra-red Spectroscopy (FTIR). All granules were free flowing and compressible. The metronidazole tablets had no floating lag time showing that tablets floated instantaneously. The *in vitro* buoyancy test of metronidazole tablet formulated using varying concentrations of *Grewia mollis* gum and Eudragit® RL100 was > 12 hr. The % maximum release (m_∞) and time to achieve it i.e. (t_∞) for metronidazole tablets were ≥88% and ≥10 h respectively. FTIR studies showed that the excipients and the Active Pharmaceutical Ingredient (API) i.e. metronidazole were compatible. *Grewia mollis* gum has been investigated in the formulation of gastroretentive floating matrix tablet of metronidazole using sublimation and sintering technique (Non-effervescent method) which may find useful application in sustained release drug delivery particularly for drugs with short biological half-life that require frequent administration.

Keywords: Non-effervescent, floating, Grewia mollis, metronidazole, ammonium bicarbonate and sublimation.

INTRODUCTION

Gastroretentive drug delivery systems (GRDDS) are controlled drug delivery systems that are formulated to float and remain buoyant on top of the gastric for a long period of time and have been an area of interest in terms of their potential for sustained drug release [1]. Over the years, several gastroretentive drug delivery approaches have been designed and formulated, including high density (sinking) systems that are retained in the bottom of the stomach, low-density (floating) systems that remains afloat in the gastric fluid, swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach and mucoadhesive systems that causes bio adhesion to mucin-epithelial surface of stomach [2].

Several attempts have been made to formulate a floating system that could prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract for local or systemic effects. The system basically floats in the gastric fluid because of its lower bulk density compared to that of the aqueous medium [3]. Various approaches have been used to formulate this particular type of drug delivery system, such as the effervescent floating drug delivery systems that generates carbon (iv) oxide in presence of gastric fluid which imparts buoyancy on the dosage form, gas-filled floatation, and raft-forming systems [4]. However, some challenges exist from the available floating mechanisms; for example, in the effervescent systems, it takes some time for the floating dosage form to float from the bottom of the beaker to the top when immersed in a simulated gastric fluid (floating lag time). Consequently, a novel and non-complicated technique offering short or no floating lag time would be beneficial to formulate.

Metronidazole has a bitter taste and darkens when exposed to light. It is soluble in water, slightly soluble in alcohol, and sparingly soluble in chloroform. It is an anti-amoebic, anti-protozoan, antibacterial, anti-parasitic and anti-trichomonal agent [5].

Grewia polysaccharide gum grows abundantly in the middle belt region of Nigeria where it is found growing wild or cultivated and is used as a food delicacy by the local people. The gum is obtained by extraction from the inner stem bark of the edible plant *Grewia mollis*, Juss, (Fam. Tiliaceae). The polysaccharide gum consists of glucose and rhamnose as the main monosaccharide components and galacturonic acid as the main sugar acid [6]. The binding, bioadhesive and mechanical [7] properties of the gum have been reported. However, its use as a matrix former in the formulation of non-effervescent floating drug delivery system has not been investigated.

The aim of this study is to formulate a novel non-effervescent gastro floating drug delivery system of metronidazole using non-effervescent (sublimation and sintering) technique. This technique offers no floating lag time as compared to the effervescent method. Floating of the dosage form on top of the gastric fluid is the rate-limiting and very important step in the release of the active ingredients from the dosage form hence; this technique eliminates the barrier to the efficient release of drugs from the dosage form compared to the delay in floating (floating lag) time commonly experienced in the effervescent method [1].

MATERIALS AND METHODS
Materials

Metronidazole (Cipla Ltd, Goa, India) was used in this study as the drug model, acrylate methacrylate copolymer (Eudragit® RL100) was received from Rhoma Pharma, Darmstadt, Germany, *Grewia mollis gum* was used as a matrix former and was extracted by method described previously [7]. Ammonium carbonate was purchased from Riedel-de Haen (Seelze, Germany) and was used as the sublimating agent. All other chemicals were of analytical grade.

Methods
Granulation and flow properties of the granules:

Gastroretentive floating matrix granules (GFMG) of metronidazole were prepared using the wet granulation method. Four batches were prepared using *Grewia mollis* gum at varying concentrations (2, 4, 6 and 8 $\%^w/_w$) with 1 $\%^w/_w$ of Eudragit® RL100. One extra batch was also prepared without the addition of Eudragit® RL100 at 2 % $^w/_w$ concentration.

In each formulation, the lactose, ammonium carbonate and metronidazole were mixed in the dry state in a mortar using the geometric mixing method. Then the binder mixtures of the gum and Eudragit® RL100 were used to wet mass the powder in the mortar. The damp mass formed was forced through a sieve mesh of 850 µm and dried at 60 ℃ for 30 min. It was then sieved using a sieve mesh of 710 µm. The packing properties were obtained by measuring the bulk density

(BD) and tapped density (TD) using standard procedures [8] and values were obtained using equations 1 and 2 respectively. From the resulting data, Carr's Index (CI) [9] was determined using the equation 3:

$$\text{Bulk density}\left(g/cm^3\right) = \frac{\text{mass of granules}}{\text{initial volume of granules}} \quad - \quad - \quad 1$$

$$\text{Tap density } (g/cm^3) =$$

$$\frac{\text{mass of granules}}{\text{tapped volume of granules}} \quad - \quad - \quad 2$$

$$CI = \frac{TD - BD}{TD} x\,100 - - - - - - - - - - - - 3$$

The flow properties of the granules were determined by measuring the angle of repose formed when a sample of the granules (15 g) was allowed to fall freely through the stem of a funnel onto a plain bench surface [10]. The angle of repose was determined using equation 4. Talc was then incorporated extragranularly and the granules compressed into tablets using a single punch tableting machine.

$$\theta = \text{Tan}^{-1}h/r \quad - \quad\quad - \quad\quad 4$$

Where,

θ is the angle of repose, h is the height of powder heap in cm, r is the radius of base of the heap in cm.

Tableting Technique

The composition of tablet formulae is shown in Table-1. A Manesty Single Punch Tableting Machine (Type F3 Manesty Machine UK) was used to formulate the tablets. The NEFMG equivalent to 400 mg of metronidazole were placed in the die and compressed at a pressure of 30 arbitrary units on the tableting load scale. A constant pressure was maintained for all the batches of metronidazole produced. The resulting tablets were collected, dusted and stored in an air tight jar containing activated silica gel as a desiccant. The formulated tablets were then sintered (heated) in a hot-air oven at 70℃ for 12 h and this resulted in the sublimation of the ammonium carbonate creating pores in the tablets.

Evaluation of Non-Effervescent Floating Matrix Tablets (NEFMTs)
Tablet hardness and friability

The tablet hardness was determined by diametrical compression using the Campbell Electronics Hardness tester machine (HT-30/50, India). The pressure required to fracture a tablet placed in the anvil of the hardness tester was determined. Five (5)

tablets were used for the determination. The mean value and standard deviation were recorded. Ten tablets (10) were randomly selected for the friability test using the Roche Friabilator (Erweka Germany). The initial weight of the tablets was obtained before they were placed in the friabilator. The friabilator was operated for 4 min at a revolution of 25 rpm giving 100 revolutions after which the final weight of the tablets was also determined and recorded. These values were used to calculate the percentage friability using equation 5.

$$\% \, Friability = \frac{W1-W2}{W1} \, x \, 100 ----- 5$$

Where,

w_1 and w_2 are initial and final weights of the tablets.

Floating lag time (FLT) and *in vitro* buoyancy test
The method described previously by Rosa *et al* [11] was adopted. A 1000 ml beaker was filled with 900 ml simulated gastric fluid (0.1 N HCl). A tablet was immersed and the medium kept stagnant and maintained at 37 ± 2^oC. The time taken for the tablet to rise to the surface and float was obtained as the FLT. The time duration for which the tablet floats and remains afloat without fracturing was determined as *in vitro* buoyancy time.

ic *In vitro* **dissolution studies and drug release kinetics**
The basket technique was used and dissolution studies were performed using 900 ml of 0.1 N HCl as the dissolution medium maintained at 37 ± 2^oC. One tablet was placed in a cylindrical basket which was immersed in the dissolution medium. The dissolution fluid was agitated at 100 rpm with a single blade Gallen Kamp stirrer (Model APP No 4B 5784A). At predetermined time intervals (5, 10, 15 and 30 min; 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 h), 5 ml samples of the leaching fluid was withdrawn using a pipette fitted with a cotton wool plug. Equal amount of fresh dissolution medium without the drug kept at the same temperature, was used to replace the withdrawn fluid. The withdrawn samples were filtered, diluted and their absorbance determined with a UV/Visible spectrophotometer (Model Spectronic 21D, Bausch and Lomvb, USA) at a maximum wavelength (λ_{max}) of 276 nm. The determination was done in triplicate and the mean results reported. The corresponding amount of metronidazole released at any time t, was determined.

The data obtained from the dissolution studies of the NEFMT of metronidazole were subjected to various drug release kinetics to determine the pattern of release kinetics. The models include: zero order, first order and Higuchi square root of time relationship [12]. The mechanism of drug release from the formulation was determined using Korsmeyer and Peppas model [13,14]. The linear regression coefficient (r^2) for each rate order was computed. The dissolution profile was considered to have followed a specific release order if the r^2 value was >0.95 [15].

Compatibility studies
Compatibility studies were carried out using Fourier Transform Infra-Red (FTIR) spectrophotometer and the spectra of the pure drug, admixture of metronidazole, grewia gum plus other ingredients and the optimized tablet formulation containing 8%w/w grewia gum were studied.

STATISTICAL ANALYSIS
The data obtained were recorded as mean $\pm$ standard deviation (SD). All the data were subjected to Student t- test statistical analysis to test for significance of difference. $P < 0.05$ was considered to be significant.

RESULTS AND DISCUSSION
Micromeritic properties of the NEFMG
The micromeritic properties of the NEFMG formulated by different concentrations of *Grewia mollis* gum (GMG) are shown in Table 2. It was observed that all the granules produced with GMG had angle of repose ranging from 27.5 – 30.2^o while Carr's indices ranged from 09 – 11%. The Hausner's ratio was between 1.10 - 1.13. These results show that all the NEFMG exhibited good flow which is very important in ensuring weight and content uniformities during tableting. The evaluation of these parameters can provide a means of monitoring batch to batch variation.

Table-1: The formula table for the NEFMT.

S/N	Ingredients	Quantity
1	Metronidazole powder	400 mg
2	*Grewia mollis* gum	2, 4, 6, 8 %w/w
3	Eudragit RL® 100	1%
4	Ammonium carbonate	30%
5	Talc	1%
6	Lactose	Qs

Table-2: Micromeritic properties of the Non-effervescent floating matrix granules of metronidazole prepared with *Grewia mollis* gum (n=3)

G. mollis: Eudragit® RL$_{100}$ (%w/w)	Bulk Density (g/cm^3)	Tap Density (g/cm^3)	Angle of repose (°)	Carr's index (%)	ausner's Ratio
GMG1	0.50±0.02	0.56±0.01	27.5±1.0	11±1.7	.12±0.02
GMG2	0.49±0.01	0.55±0.02	29.2±1.1	11±1.0	.12±0.01
GMG3	0.49±0.01	0.53±0.02	28.5±1.1	0.8±1.0	.10±0.01
GMG4	0.49±0.02	0.56±0.01	28.1±1.2	11±1.7	.13±0.03
GMG5	0.45±0.01	0.50±0.02	30.1 ±1.1	10±1.0	.11±0.02

Where; GM1 (GMG alone), GMG2 (2:1), GMG3 (4:1), GMG4 (6:1), GMG5 (8:1)

Table-3: Some Physic technical properties of metronidazole tablets (Hardness and Friability, n=3)

G.mollis : Eudragit® RL$_{100}$ (% w/w) Formulation	Hardness (kg/cm^2)	Drug Content (%)	Friability (%)
GMG1	6.0 ± 0.12	96	0.70 ± 0.01
GMG2	6.5 ± 0.10	94	0.74 ± 0.01
GMG3	7.0 ± 0.13	91	0.78 ± 0.02
GMG4	7.2 ± 0.10	88	0.82 ± 0.01
GMG5	8.5 ± 0.11	85	0.90 ± 0.02

Table-4: Floating lag time and *In vitro* buoyancy values of NEFMTs using GMG

Formulation concentration of GMG: Eudragit® RL$_{100}$	GMG1	GMG2	GMG3	GMG4	GMG5
Floating lag time (s)	0	0	0	0	0
Buoyancy time without rupture of tablet (h)	5 min	>12	>12	>12	>12

Table-5: Dissolution parameters of NEFMTs formulated with *Grewia mollis* gum (m_∞ %), (t_∞ hr), (m_∞/t_∞)

GMG: Eudragit® RL$_{100}$ (%w/w)	m_∞ (%)	t_∞ (h)	m_∞/t_∞ (%h^{-1})
GMG1	98	4	24.5
GMG2	93	6	15.5
GMG3	91	9	10.1
GMG4	84	10	8.4
GMG5	87	10	8.7

Where, m_∞ (%) is maximum release, t_∞ (h) is time to attain maximum release, m_∞/t_∞ (%h^{-1}) is dissolution rate

Table-6: Correlation coefficient and release kinetics of NEFMTs of metronidazole (n=3) prepared with varying concentrations of GMG

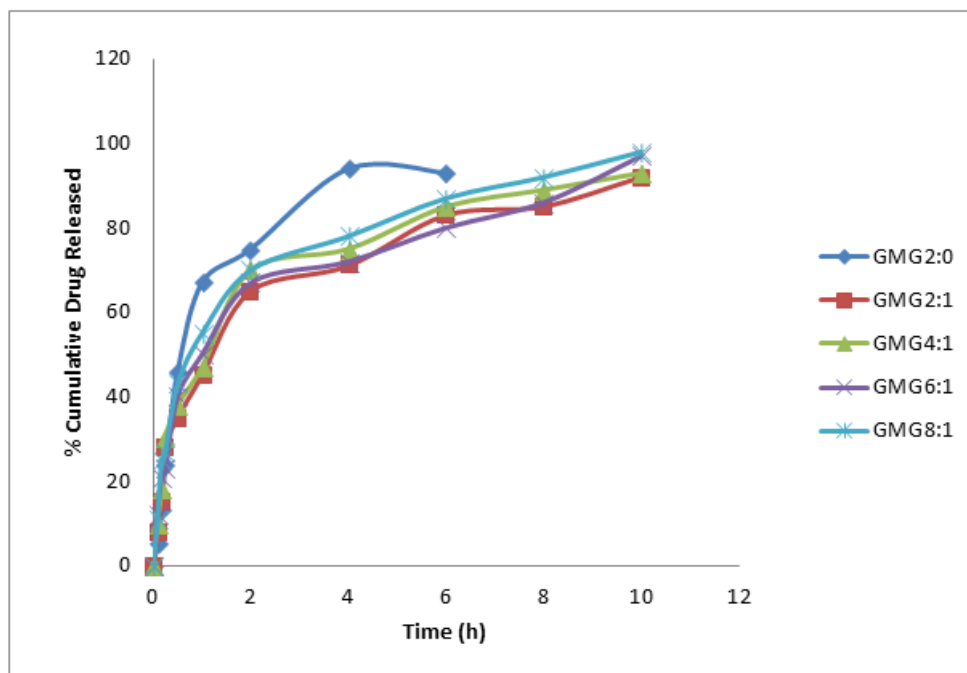| Models	Zero		First		Higuchi		Korsmeyer and Peppas	
Formulations	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n
GMG1	0.72	15.13	0.91	-0.22	0.90	43.13	0.29	0.58
GMG2	0.79	8.30	0.95	-0.10	0.94	29.99	0.33	0.48
GMG3	0.77	8.35	0.96	-0.11	0.93	29.69	0.30	0.46
GMG4	0.79	8.21	0.90	-0.13	0.93	28.95	0.27	0.42
GMG5	0.76	8.31	0.97	-0.13	0.92	29.72	0.26	0.42

Fig-1: Drug release profiles of NEFMT of metronidazole prepared using different concentrations of GMG, where GMG1 (GMG alone), GMG2 (2:1), GMG3 (4:1), GMG4 (6:1), GMG5 (8:1).
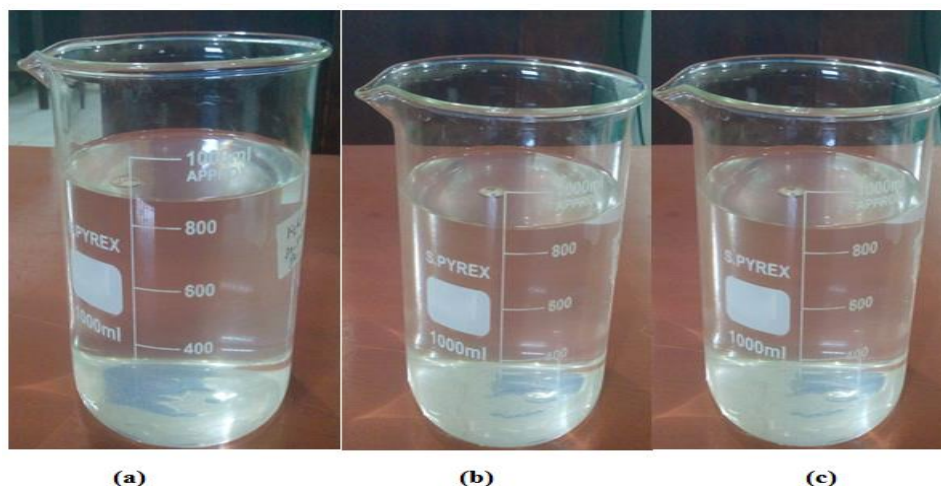

Fig-2: (a) Photographs showing the *in vitro* buoyancy characteristics of NEFMTs of metronidazole. (b) Photograph taken immediately after placing the tablet into the beaker indicating a no floating lag time and (c) Photograph taken after the tablet floated for 2 and 4 hours respectively.
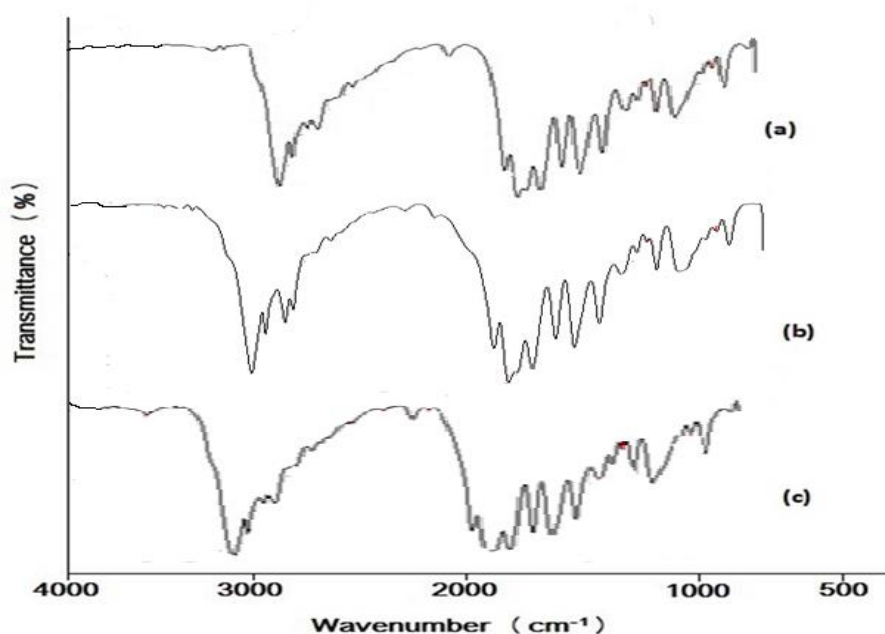
Fig-3: FTIR Spectra of a) Pure Metronidazole Sample (b) 8%w/w tablet formulation. (c) Admixture of metronidazole, grewia gum etc.

Post Compression Parameters of the NEFMTs
Tablet Hardness, Friability and Drug Content

Hardness of the formulated tablets in the various formulations GMG1-GMG5 varied from 6.0 ±0.1 to 7.5±0.1 Kpa indicating good mechanical strength with an ability to withstand physical and mechanical stress while handling, storage and transportation. The loss in total weight of the tablets due to friability was in the range of 0.7±0.1 to 0.8±0.2% in all the formulations and the value was less than 1% which ensures that the formulated tablets were mechanically stable to withstand fracture and abrasion due to handling, transportation and storage. The drug content in the different tablet formulations was uniform and ≤ 85% which is within the permissible limits of the British Pharmacopoeia [16] (Table 4).

Floating lag time and *In vitro* buoyancy of NEFMTs

The result of the *in vitro* buoyancy study is presented in Table-4 shows that all the tablet formulations had no floating lag time (0 s) as they floated instantaneously when placed on the simulated gastric fluid (0.1 N). The mechanism of floating was due to the sublimation of the ammonium carbonate from the tablets during the sintering (heating) process thereby creating pores in the tablets which enable the tablets to float freely on top of the simulated gastric fluid and the sublimation of the ammonium carbonate also reduces the bulk density of the tablets less than that of the simulated gastric fluid thus conferring buoyancy [1, 2].

Batch GMG1 (2%w/w grewia gum without Eudragit RL100) showed buoyancy duration without

rupture of 5 min while the other batches showed buoyancy duration of >12 h. However, the floating time of GMG1 was quite short as the tablets disintegrated or eroded during the test because the medium gradually penetrated into the 'uncoated' porous tablets, resulting in drowning. This was due to the fact that Eudragit® RL100 was not incorporated in batch GMG1 as this acrylate methacrylate copolymer helps to maintain the integrity of the tablets thereby imparting more buoyancy time for the tablets formulations to remain afloat over a long period of time. The indication is that the addition of Eudragit® RL100 helped to increase the integrity of the tablet formulations and imparted more buoyancy time for the tablets formulations (GMG2-GMG5) and also sustained the drug release. The illustrative view of the *in vitro* buoyancy characteristic of NEFMT formulated with GM gum is presented in Figure 1.

Release profile of NEFMTs of Metronidazole

The *in vitro* drug release profiles of the NEFMT of metronidazole formulated using GM gum are shown in Figure-2. The drug release from the floating metronidazole tablet of 2%w/w *Grewia mollis* gum without Eudragit® RL100 (batch GMG1) showed a faster release of drug content compared to the other batches (GMG2-GMG5) containing Eudragit® RL100 this is because Eudragit® RL100 helps in maintaining the integrity of the tablet and sustaining the drug release from the tablet formulations. It was also observed that there was a decrease in the rate of release of the drug content as the concentration of the gum increased. Batch GMG1 tablets displayed a faster release of drug content compared to the other batches containing

Eudragit® RL100. For example, batch GMG1 released about 98% of its drug content within 2 h while batches GMG2 – GMG5 released about 75 - 95% of the drug contents for up to 8 h. Thus, there was a more sustained release of drugs from batches GMG2 – GMG5. This shows that the release profile of the tablet was concentration dependent. The higher the concentration of the gum, the more retarded the release of drug content from the matrix of the tablet [5]. This perhaps may be due to low permeability which acts as a rate controlling factor in retarding of drug release from matrix systems. It was also observed that the time to attain maximum release in the floating tablets also reduced as the concentration of the gum increased. Drug release from the matrix tablet resulted from slow diffusion of dissolved drug molecules through aqueous filled channel in the polymeric matrix network. The dissolution parameters are presented in Table 5. For instance, maximum drug released (m_∞), time to achieve maximum release (t_∞) and dissolution rate (m_∞/t_∞) for batch GMG1 was 98%, 2 h and 49% h^{-1} respectively while the corresponding values for batch GMG5 was 88%, 10h and 8.8% h^{-1}. The higher the concentration of the gums, the slower the drug release from the matrix system studied. This reveals that the drug release from the GRFMTs depended on the concentration of the gum. It was also observed that there was a significant prolongation in the rate of drug release from the NEFMTs as concentration of the gums increased [5].

Release kinetics and mechanism of drug release from the NEFMTs

In order to determine the drug release kinetics of the different formulations of metronidazole tablets, the data were subjected to zero order (cummulative percentage of drug released vs. time), first order (log cumulative percentage of drug remaining vs. time), Higuchi's (cumulative percentage of drug released vs. square root of time) and Korsmeyer and Peppas (log cumulative percentage of drug released vs. log time) equations. The results of the various release kinetics for floating metronidazole tablets are represented in Table-6.

The release kinetics of the formulations did not follow a zero order release pattern as the plot showed poor linearity with regression values ranging from 0.72-0.79. This shows that the formulation did not obey the zero order, where the amount of drug released is expected to be constant irrespective of the concentration. Although the desired release model for controlled drug delivery system is zero order, this was not attained. Generally, linear regression coefficient (r^2) values were higher for first order when compared to zero order.

Data obtained were plotted according to the first order equation which showed a fair linearity with regression values r^2 ranging from 0.91-0.97. This

implies that the amount of drug released was dependent on the amount of drug left in the formulation. The *in vitro* release profiles of the floating metronidazole tablet was best expressed by Higuchi's equation as the plot showed a high linearity with r^2 values of 0.90-0.94. The release kinetics was more consistent with this model since it gave a higher correlation when compared to other models analysed. This shows that the drug released from the matrix tablet were mainly by Higuchi's model which states that the amount of drug released is dependent on the square root of time [17, 18].

The data obtained were fitted into Korsmeyer and Peppas equation in order to confirm the mechanism of release. The formulation showed poor linearity with r^2 values ranging 0.26-0.30. Since the R^2 values were consistent with Higuchi's model, it was expected that the mechanism of drug release from matrix tablet was diffusion controlled. The release exponent (n) for the floating metronidazole tablets ranged from 0.42-0.58. Formulations GMG1 to GMG3 have their release exponent (n) > 0.45; hence their release mechanism was by Non-Fickian diffusion while formulations GMG4-GMG5 have their release exponent (n) < 0.45; hence their release mechanism was by Fickian diffusion. This indicates that diffusion was the dominant mechanism of drug release.

Compatibility studies

The results of the compatibility studies are presented in Figure-3. It was observed that there were no obvious changes in peaks due to the presence of other excipients and also due to compression to final tablets. This indicates that the API (metronidazole) and the other excipients were compatible.

CONCLUSION

Gastroretentive floating non-effervescent matrix tablets of metronidazole were formulated using the sublimation and sintering techniques. The floating metronidazole tablets were successfully formulated in this study using *Grewia mollis* gum in addition with Eudragit® RL100 to prolong gastric retention time and subsequently sustain drug release for up to ten (10) h.

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