

## Formulation and evaluation of multiple tablets as a biphasic gastroretentive floating drug delivery system for fenoverine

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A biphasic gastroretentive drug delivery system of fenoverine was developed to maintain constant plasma concentration. The delivery system consisted of a loading-dose tablet and a floating multiple matrix tablet prepared by the direct compression process. The drug release from biphasic GRDDS in 0.1 mol L<sup>-1</sup> HCl and SGF (enzyme free) was sustained over 12 h with buoyant properties. Stability studies showed no significant change in dissolution profiles ( $f_2$  value > 50). Based on the release kinetics, it can be concluded that the floating multiple matrix tablet containing HPMC was a particularly suitable gastroretentive drug delivery system with a zero-order release profile.

*Keywords:* biphasic release, gastroretention, multiple matrix tablet, release kinetics

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A unique problem frequently encountered with the therapeutically advantageous oral sustained release dosage forms is their inability to reside in stomach and the proximal part of small intestine for a prolonged period of time. This led to the development of various gastroretentive drug delivery systems (GRDDS). The various approaches cited in the literature (1–4) include floatation, mucoadhesion, sedimentation, swelling or expansion, modified shape systems, or simultaneous administration of pharmacological agents that delay gastric emptying.

Among the various attempts made, the floating drug delivery systems offer the most effective and rational protection against early and random gastric emptying compared to the other methods proposed for prolonging the gastric residence time of solid dosage forms (4). However, the problems such as all or nothing emptying of single unit floating dosage forms made them unreliable and irreproducible in prolonging the gastric residence time, which led to the development of multiple unit floating systems (5). The development of mini-matrices is a promising area concerned with high control over the release rate of the drug combined with high flexibility of the adjustment of both the dose and the release of a drug or drugs (6). The concept of multiple units is characterized by

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the fact that the dose is administered as a number of subunits, each one containing the drug. The dose is then the sum of the quantity of the drug in each subunit and the functionality of the entire dose is directly correlated with the functionality of individual subunits (7). Like other multiple unit systems, multiple tablets can be filled into hard gelatin capsules that release these subunits after disintegration.

Fenoverine is an anti-spasmodic agent that restores smooth muscle motility and relieves the distressing symptoms associated with irritable bowel syndrome and primary dysmenorrhoea (8).

In the present study, biphasic GRDDS of fenoverine, as model drug, comprising an immediate release loading dose tablet (LDT) and sustained release floating multiple matrix tablets (FMMT) were developed and characterized for *in vitro* performance.

## EXPERIMENTAL

### Materials

Fenoverine and Spasmopriv™ 200 mg capsules were generous gifts from Eurodrugs, India. HPMC K4M and HPMC 100 LV were obtained from ISP, India. Sodium bicarbonate, anhydrous citric acid and magnesium stearate were purchased from S.D. Fine-Chem Ltd, India. Purified talc was purchased from E. Merck, India. All other chemicals used were of analytical grade.

### Methods

*Preparation of the biphasic gastroretentive drug delivery system.* – The total dose of fenoverine for twice daily sustained release formulation was calculated based on pharmacokinetic data (9). The loading dose and the maintenance dose were 74 mg and 126 mg of fenoverine, respectively. The total dose of GRDDS was 200 mg.

Preliminary formulations were studied to optimize the drug to polymer ratio and effervescent composition (data not shown). Then, the FMMT was prepared with an optimized concentration of effervescent composition. All formulation ingredients of FMMT and LDT were sifted through a 420- $\mu$ m aperture size sieve, homogeneously blended in a mortar separately and directly compressed using 6-mm flat punches on a rotary compression machine (Riddhi, India). The GRDDS marked 1, 2, 3, 4 comprising LDT and FMMT marked 1, 2, 3, 4 equivalent to 200 mg of fenoverine, respectively, were placed in hard gelatin capsules size 0 and evaluated. The qualitative and quantitative composition of FMMT and LDT are shown in Table I.

*Physical characterization of the blend and compressed FMMT and LDT.* – Physical properties such as bulk density ( $\rho_b$ ), tapped density ( $\rho_t$ ), compressibility index and the angle of repose of the final blend of FMMT were determined.

Compressed multiple tablets were characterized for mass and thickness variation ( $n = 20$ ). Crushing strength ( $n = 6$ ) was measured with a Monsanto tester Campbell Electronics (India), friability ( $n = 6$ ), with a Roche type friabilator. The drug content in

Table I. Composition of the biphasic fenoverine gastroretentive drug delivery system

Ingredient (mg per tablet)	FMMT1	FMMT2	FMMT3	FMMT4	LDT
Fenoverine	42.00	42.00	42.00	42.00	74.00
HPMC K 4M	63.00	47.25	31.50	15.75	–
HPMC K 100 LV	–	15.75	31.50	47.25	–
Sodium bicarbonate	20.00	20.00	20.00	20.00	–
Citric acid	5.00	5.00	5.00	5.00	–
Talc	2.00	2.00	2.00	2.00	2.00
Magnesium stearate	2.00	2.00	2.00	2.00	2.00
Cross carmellose sodium	–	–	–	–	13.00
Lactose	–	–	–	–	44.00
Total tablet mass (mg)	134.00	134.00	134.00	134.00	135.00

each formulation was determined by triturating 20 tablets in a mortar and powder equivalent to the average mass was added in 100 mL of 0.1 mol L<sup>-1</sup> hydrochloric acid, followed by shaking for 30 minutes. The sample was analyzed by the HPLC method (10).

*Tablet density.* – The density of the tablets (in g cm<sup>-3</sup>) was calculated from tablet height, diameter and mass using the equation:

$$D = W / [(m/2)^2 \times \pi \times h]$$

where  $W$  is the mass of a tablet,  $m$  is the tablet diameter,  $\pi$  is the circular constant, and  $h$  is the tablet height.

*Floating behavior.* – Buoyancy lag time and duration of buoyancy were determined in the USP dissolution apparatus II (11) with 0.1 mol L<sup>-1</sup> HCl and simulated gastric fluid (enzyme free SGF). The time between the tablet introduction into the medium and its buoyancy in the medium was taken as the buoyancy lag time and the duration of the tablet remaining buoyant was observed visually.

*In vitro drug release studies.* – The release of fenoverine from FMMT and biphasic GRDDS was studied using a USP (11) dissolution apparatus II (Labindia, India). The dissolution media were 900 mL 0.1 mol L<sup>-1</sup> HCl and SGF (enzyme free) maintained at 37 ± 0.5 °C and rotation speed of 50 rpm. Aliquots of 5 mL were collected at predetermined time intervals, filtered through a 0.45-µm membrane filter and replenished with an equivalent volume of fresh medium. Drug contents in the samples were determined by HPLC after suitable dilutions.

*Drug release modeling.* – The suitability of several equations, reported in the literature to identify the mechanism(s) of fenoverine release (12, 13), was tested with respect to the release data.

The release profiles were compared by a statistically derived mathematical index, similarity factor ( $f_2$ ) (14) using theoretical profile as reference. The two dissolution pro-

files are considered to be similar if  $f_2$  value is higher than 50 (between 50 and 100). The dissolution efficiency (DE) (15) at 2, 6 and 8 h,  $t_{50\%}$  and  $t_{75\%}$  were also determined from the dissolution profiles for each formulation.

*Stability studies.* – Optimized formulation was kept in the humidity chamber (LabTop, India) maintained at 40 °C and 75 % relative humidity for 3 months. At the end of studies, the formulation was subjected to a drug assay, floating behavior testing and *in vitro* dissolution studies. For the comparison of release profiles of initial and aged samples, the similarity factor  $f_2$  was calculated.

## RESULTS AND DISCUSSION

### *Physical properties of the final blend and compressed FMMT and LDT*

The floating multiple matrix tablets of fenoverine were prepared by the effervescent technique using methocel (K4M, K100LV). The combination of two different grades of HPMC was utilized to obtain the desired buoyant characteristics and to maintain the FMMT integrity for 12 h. The blend of the final batches showed bulk density of  $0.55 \pm 0.08$  g cm<sup>-3</sup> and tapped density of  $0.64 \pm 0.10$  g cm<sup>-3</sup> indicating desirable flow properties. Further, the angle of repose showed a value of < 30°, compressibility below 15 %, indicating good flow properties of the formulations.

Physical characteristics of the loading dose tablet and floating multiple matrix tablets are shown in Table II. The drug content of FMMT and LDT was  $101.1 \pm 1.1$  and  $100.4 \pm 1.6$  %, respectively ( $n = 3$ ).

### *Buoyancy and density*

The density of FMMT formulations was 1.202, 1.195, 1.225 and 1.234 g cm<sup>-3</sup>, respectively. Though the density of formulated tablets was higher than 1.0 g cm<sup>-3</sup>, they remained buoyant for 12 h with a lag time of 4.16 to 5.22 minutes. The optimized concentration of the effervescent mixture (sodium bicarbonate and citric acid) contributed to the buoyancy of all tablets.

Table II. Physical characteristics of multiple tablets

Formulation	Mass (mg) <sup>a</sup>	Crushing strength (kg cm <sup>-2</sup> ) <sup>b</sup>	Friability (%) <sup>b</sup>	Drug content (mg) <sup>c</sup>	Floating lag time (min) <sup>c</sup>
FMMT1	134.3 ± 1.0	4.1 ± 0.3	0.8 ± 0.1	42.3 ± 1.1	4.16 ± 0.3
FMMT2	133.5 ± 1.6	4.3 ± 0.4	0.6 ± 0.1	41.9 ± 1.5	5.22 ± 0.7
FMMT3	135.4 ± 1.7	5.1 ± 0.1	0.5 ± 0.1	42.6 ± 0.3	4.93 ± 0.3
FMMT4	136.0 ± 2.2	4.5 ± 0.2	0.6 ± 0.1	43.1 ± 0.9	4.74 ± 0.6
LDT	134.2 ± 2.8	5.3 ± 0.3	0.5 ± 0.1	74.3 ± 1.6	–

Mean ± SD: <sup>a</sup>  $n = 20$ , <sup>b</sup>  $n = 6$ , <sup>c</sup>  $n = 3$ .

### In vitro release studies

Ideally, a sustained release formulation should release the required quantity of drug with predetermined kinetics in order to maintain an effective drug plasma concentration. To achieve this, the delivery system should be formulated so that it releases the drug in a predetermined and reproducible manner. The release of fenoverine from biphasic GRDDS was analyzed by plotting the cumulative percent drug released against time. Figs. 1a and b show the *in vitro* drug release profile of fenoverine in 0.1 mol L<sup>-1</sup> HCl and SGF (enzyme free) from biphasic GRDDS. The biphasic GRDDS remains buoyant in dissolution media with liberation of FMMT and LDT after 10–15 minutes. There was an initial burst release of fenoverine from the gastroretentive system, which can be attributed to the LDT, and release of fenoverine from FMMT was sustained over 12 h compared to conventional commercial capsules which released the complete drug within 30 minutes. The initial burst release of 47.2 ± 1.8 % in 0.1 mol L<sup>-1</sup> HCl and 41.5 ± 1.6 % in SGF (enzyme free) from GRDDS was found during the first hour. The amount of drug released after 12 h (Q<sub>12</sub>) from biphasic GRDDS was found to be 102.4 ± 1.6 % in 0.1 mol L<sup>-1</sup> HCl and 98.5 ± 2.2 % in SGF (enzyme free). The drug release from FMMT was sustained for a prolonged period of time due to the viscous nature of the HPMC matrix through which drug diffuses. Replacement of HPMC 100LV grade with HPMC K4M helped increase the drug release within 12 h and maintained the integrity and buoyancy of the FMMT formed. The increased drug release from FMMT with high concentration of HPMC K100LV compared to the FMMT containing its smaller amount may be due to matrix erosion in the former and swelling diffusion and a slight erosion mechanism in the latter. However, the matrix containing a high viscosity grade of polymer with large molecular mass mainly results in swelling properties with little erosion and *vice versa*. Integrity and floating properties of FMMT were thus maintained.

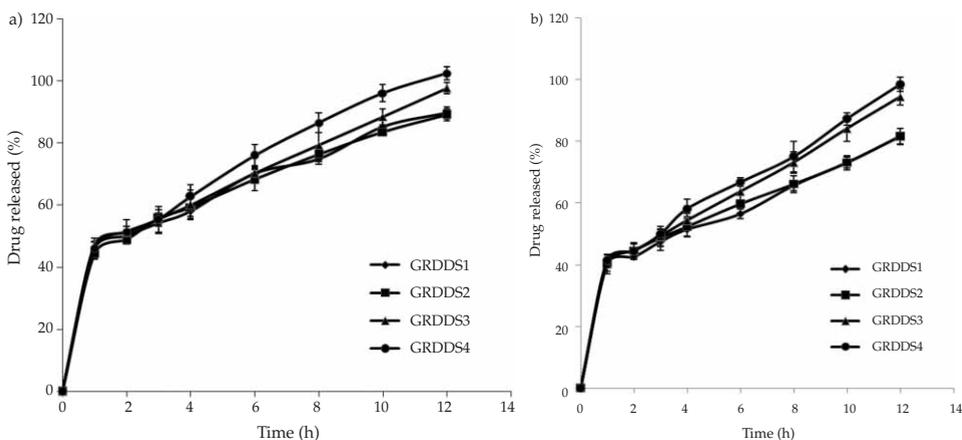


Fig. 1. Dissolution profiles of fenoverine from biphasic GRDDS in: a) 0.1 mol L<sup>-1</sup> HCl, b) SGF (enzyme free) (mean ± SD, n = 6).

### Drug release pattern from GRDDS

The results of kinetic models for fenoverine release from biphasic GRDDS are shown in Table III. The coefficient of determination ( $R^2$ ) was used as an indicator of the best fitting for each of the models considered. The results reveal that all formulations of biphasic GRDDS best fit in the zero-order model, in both 0.1 mol L<sup>-1</sup> HCl and SGF (enzyme free). The mechanism of drug release from these tablets was found to be diffusion, as seen from high  $R^2$  values of the Higuchi model.

The optimized GRDDS formulation was selected based on the similarity factor ( $f_2$ ) values of all GRDDS and other dissolution parameters such as dissolution efficiency ( $DE$ ) at 2, 6 and 8 h,  $t_{50\%}$  and  $t_{75\%}$  and characteristics of GRDDS3 (Table IV). The similarity factor ( $f_2$ ) of GRDDS3, when compared to the theoretical release profile in 0.1 mol L<sup>-1</sup> HCl, was observed to be 91.5, which was higher than for the other formulations, and 61.4 in SGF, which was well above 50 indicating that the drug release pattern was similar to the theoretical release profile. The other independent model parameters, such as dissolution efficiency, also revealed that the drug release profile from GRDDS3 was similar to the theoretical profile.

### Influence of media on drug release

The fenoverine release in 12 h from optimized biphasic GRDDS3 in 0.1 mol L<sup>-1</sup> HCl and SGF (enzyme free) was found to be 97.7 and 94.4 %, respectively. *t*-Test indicated no statistically significant difference in drug release between the two media. However, the similarity factor ( $f_2$ ) of the drug release from GRDDS3 in 0.1 mol L<sup>-1</sup> HCl and SGF was found to be 59.4, thus indicating that the drug release in both media was similar.

Table III. In vitro release kinetics of fenoverine biphasic gastroretentive drug delivery systems

Formulation	$Q_{12}$ release (%) <sup>a</sup>	$R^2$		
		First-order	Zero-order	Higuchi
0.1 mol L <sup>-1</sup> HCl				
GRDDS1	89.7 ± 0.1	0.975	0.990	0.980
GRDDS2	89.1 ± 0.1	0.965	0.990	0.994
GRDDS3	97.7 ± 0.1	0.991	0.999	0.974
GRDDS4	102.4 ± 0.1	0.970	0.991	0.983
SGF (enzyme free)				
GRDDS1	81.7 ± 1.1	0.992	0.996	0.964
GRDDS2	81.6 ± 0.4	0.986	0.998	0.980
GRDDS3	94.4 ± 0.2	0.991	0.999	0.970
GRDDS4	98.5 ± 0.3	0.983	0.996	0.969

<sup>a</sup> Drug released in 12 h. Values represent mean ± SD,  $n = 3$ .

Table IV. Dissolution parameters and  $f_2$  factor of GRDDS

Formulation	$t_{50\%}$ (h)	$t_{75\%}$ (h)	DE (%)			$f_2$ factor
			2 h	6 h	8 h	
0.1 mol L <sup>-1</sup> HCl						
Theoretical release	2.0	7.0	50	70	80	–
GRDDS1	2.0	8.0	55.9	78.2	83.6	80
GRDDS2	2.1	7.6	55.0	76.6	85.8	85
GRDDS3	1.7	7.0	52.4	72.0	81.1	92
GRDDS4	1.6	5.8	50.2	74.1	84.5	70
SGF (enzyme free)						
GRDDS1	3.6	10.4	52.1	69.2	80.4	50
GRDDS2	3.3	10.5	54.6	73.1	81.0	53
GRDDS3	3.0	8.3	47.2	67.5	77.5	61
GRDDS4	3.0	8.0	45.1	67.8	76.2	68

DE – dissolution efficiency

### Stability studies

In view of the potential utility of the formulation, stability studies were carried out at 40 °C and 75 % RH for three months (for accelerated testing) to assess their long-term stability. Analysis of the dissolution data (Fig. 2), after storage for three months, showed no significant change in the release pattern indicating that the two dissolution profiles were similar ( $f_2 > 50$ ). The other parameters evaluated were comparable with initial values.

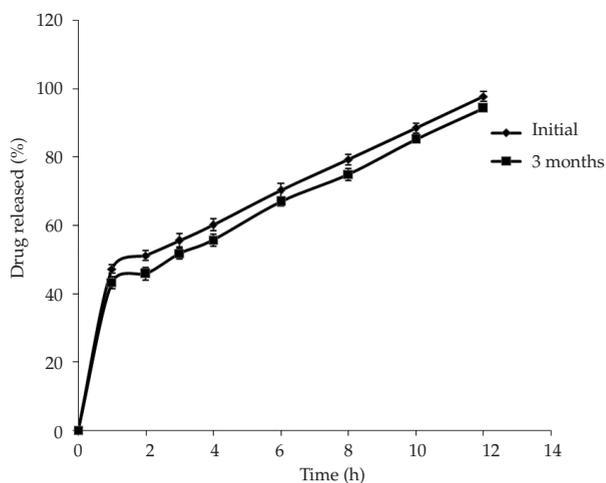


Fig. 2. Dissolution profile of GRDDS3 after storage at 40 °C and 75 % RH (mean  $\pm$  SD,  $n = 6$ ).

## CONCLUSIONS

On the basis of buoyancy and *in vitro* release kinetics, it was concluded that the optimized formulation containing 200 mg of fenoverine is a suitable GRDDS. FMMT was observed to be rigid, buoyant and initially showed no fragmentation because of its physical characteristics; it became soft at the end of the drug release studies. Biphasic GRDDS is characterized by the initial burst release (LDT) followed by a slow zero-order release pattern (FMMT) that shows high flexibility in modulating the delivery of the initial loading dose and the sustained dose. A further *in vivo* study has to be carried out to assess the bioavailability of the drug form biphasic GRDDS.

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## S A Ž E T A K

### Priprava i evaluacija dvofazičnih plutajućih tableta fenoverina

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U radu je opisan razvoj bifazičnog sustava za isporuku fenoverina s produljenim zadržavanjem u želucu radi održavanja konstantne koncentracije lijeka u plazmi. Sustav je dobiven metodom izravne kompresije, a sastoji se od tablete za inicijalno doziranje i matriksne tablete za plutanje. Oslobođanje lijeka iz bifazičnog GRDDS u 0,1 mol L<sup>-1</sup> HCl i SGF (bez enzima) bilo je produljeno više od 12 h, a sustav je pokazao plutajuća svojstva. Ispitivanja stabilnosti pokazala su da nema značajne promjene u profilu oslobađanja ( $f_2 > 50$ ). Na temelju kinetike oslobađanja može se zaključiti da su plutajuće višeslojne matriksne tablete s HPMC posebno pogodan sustav za isporuku fenoverina u želucu s kinetikom oslobađanja nultog reda.

*Ključne riječi:* bifazično oslobađanje, zadržavanje u želucu, višeslojne matriksne tablete, kinetika oslobađanja

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