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SUSTAINED RELEASE BEHAVIOR OF FAMOTIDINE FROM FLOATING GELUCIRE FORMULATIONS

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ABSTRACT

The aim of the present study was to prepare floating sustained release formulations of famotidine (FM) using a blend of Gelucire 43/01 (GL 43/01) and Gelucire 44/14 (GL 44/14) in different concentrations. These formulations were intended to be retained in the stomach and prolong the drug release to improve bioavailability and reduce frequency of administration. Granules and beads were prepared by melt-granulation technique and melt-solidification technique, respectively. The formulations were evaluated for surface morphology, flowability, *in-vitro* floating ability, and *in-vitro* drug release. In case of beads, process yield, drug loading, encapsulation efficiency, and particle size were also investigated. Differential scanning calorimetry (DSC) and infrared spectroscopy (IR) were used to investigate the possibility of drug-lipid interactions. The obtained beads had smooth surfaces, while the granules showed rough surfaces. Both formulations showed free flowing properties and excellent floating characteristics. There was no interaction between the drug and Gelucires used in the formulation. *In-vitro* drug release of FM from the prepared granules and beads was studied in 0.1 N HCl (pH 1.2) for up to 12 hrs. The drug released in a sustained manner in pH 1.2 from both formulations with no significant difference between granules and beads.

INTRODUCTION

Famotidine (FM) is a potent histamine H2-receptor antagonist used to treat peptic ulceration, reflux esophagitis, Zollinger–Ellison syndrome, and other conditions where reduction of gastric acid is benef-icial [1]. The usual oral dosage regimen is 20 mg twice daily for 6 weeks in gastroesophageal reflux disease, 20 mg every 6 h in hypersecretory conditions, and 40 mg for 4-8 weeks in gastric ulcer[2]. It has a low bioavailability (40-45%) and short biological half life (2.5-4.0 hrs) following oral administration. It is not absorbed uniformly throughout the GI-tract but mainly at a specific absorption site leading to incomplete and variable absorption[3]. Moreover, being a weak base, famotidine with a pKa of 7.06 has pH dependant solubility and its gastric retention would allow adequate time for its dissolution, the rate-limiting step in drug absorption[4]. A traditional oral sustained-release formulation releases most of the drug at the colon; thus, the drug should have an absorption window either in the colon or throughout the GI-tract. Hence, clinically acceptable sustained-release dosage forms of FM prepared with conventional technology may not be successful. The gastroretentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the GI-tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. It is also reported that oral treatment of gastric disorders with an H2-receptor antagonist like ranitidine or famotidine used in combination with antacids promotes local delivery of these drugs to the receptor of the parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the drugs' ability to reduce acid secretion [5]. This principle may be applied for improving systemic as well as local delivery of FM, which would efficiently reduce gastric acid secretion. Therefore, a once-daily sustained-release gastroretentive formulation of famotidine can reduce the frequency of administration and improve patient compliance.

Different approaches have been proposed to retain the dosage form in the stomach. These include bioadhesive systems [6], swelling and expanding systems[7,8] and floating systems[2,4,9]. Large single-unit dosage forms undergo significant swelling after oral administration, and the swollen matrix inhibits gastric emptying even when the pyloric sphincter is in an uncontracted state. But with swelling and expanding systems there is a risk of permanent retention. Bioadhesive systems may cause problems such as irritation of the mucous layer owing to high localized concentration of the drug[9]. Hydrodynamically balanced systems, designed using effervescent mixtures, have achieved commercial success but require a high drug:excipient ratio, have unpredictable bioavailability, and are unsuitable for drugs degrading in basic pH because of the alkaline microenvironment. Single-unit systems such as tablets or capsules may exhibit the all-or-none emptying phenomenon, which may be overcome by the design of multiunit systems[10]. Multiunit dosage forms such as pellets and granules may be more suitable because they claim to reduce the intersubject variability in absorption and lower the probability of dose dumping[10].

Gastric floating drug delivery systems (GFDDS) are particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. They are able to prolong the retention time of a dosage form in the stomach, which would reduce drug waste, improve solubility for drugs that are less soluble in a high pH environment, and hence improve oral

bioavailability[11]. It has applications also for local drug delivery to the stomach and proximal small intestines.

Lipids are considered as good alternatives to polymers in the design of controlled drug delivery systems due to their advantages like low melt viscosity, thereby obviating the need of organic solvents for solubilization, the absence of toxic impurities such as residual monomers catalyst and initiators, the potential biocompatibility and biodegradability and prevention of gastric irritation by forming a coat around the gastric irritating drug[12, 13].

Among waxy materials, Gelucires are a family of relatively inexpensive materials, comprising mixtures of mono-, di-, and triglycerides and also poly (ethylene glycol) esters of fatty acids. They are available with a range of properties depending on their hydrophilic lipophilic balance (HLB; 1–18) and melting point (33-65°C) range[14-17]. Gelucires containing only polyethylene glycol (PEG) esters (Gelucire 55/18) are generally used in the preparation of fast-release formulations, while those containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in the preparation of sustained-release formulations[18, 19].

The presence of both hydrophobic glycerides and more hydrophilic PEG esters results in a wide range of hydrophobicity and drug release rates. This versatility makes their use very promising as base materials for the production of sustained-release formulations[20]. Gelucire 43/01 is a highly hydrophobic lipid with an HLB value of 1 and a melting point of 43°C. The extreme hydrophobicity of Gelucire 43/01 provides release-retarding properties and floating behavior[12]. Gelucire 44/14 is a semi-solid excipient with an HLB value of 14 and a melting point at 44°C. The hydrophilic property of Gelucire 44/14 is useful in dissolution enhancement as well as in controlled-release formulations[21]. Many lipid-based sustained release matrix systems are discussed in the literature[22-24].

The objective of this study was to prepare and characterize floating formulations of FM for sustained delivery using Gelucires (GL 43/01 and GL 44/14). The obtained formulations (granules and beads) were evaluated for surface morphology, drug-Gelucires compatibility, and different *in-vitro* characteristics.

EXPERIMENTAL

MATERIALS

Famotidine (FM) was kindly supplied by Memphis Co. (Cairo, Egypt). Gelucire 43/01 (GL 43/01) and Gelucire 44/14 (GL 44/14) were obtained as gift samples from Gattefosse (Saint-Priest, Cedex, France), all other chemicals were of analytical grade.

Preparation of FM granules

Floating granules containing FM were prepared using the melt granulation technique. The lipid (GL 43/01 alone or mixed with 25% or 30% GL 44/14) was melted at 50°C, and the calculated amount of drug was added to produce the required drug : lipid ratio (1:1, 1:2, and 1:3), mixed well using a magnetic stirrer, and cooled to room temperature. The solidified mass was passed through a 14-mesh sieve (1.2 mm) to obtain uniform-sized granules. Table 1 shows the composition of FM-GL granules.

Table 1: Composition of FM-GL granules (G1-G11) and beads (B1- B5).

Code	FM (mg)	GL 43/01 (mg)	GL 44/14 (mg)
G1, B1	100	100	-
G2, B2	100	200	-
G3, B3	100	300	-
G4, B4	100	150	50
G5, B5	100	140	60
G6	100	120	80
G7	100	100	100
G8	100	225	75
G9	100	210	90
G10	100	180	120
G11	100	150	150

Preparation of FM beads

Floating FM beads were prepared using the melt-solidification technique. The lipid (GL 43/01 alone or mixed with 25% or 30% GL 44/14) was melted at 50°C, and the drug was gradually added with uniform mixing. Using a pipette this melt was dropped into water of ambient temperature (under stirring at 750 rpm), resulting in beads solidification upon cooling. The beads were separated by filtration, washed with distilled water, and subsequently dried for 24 hrs. The drug:lipid ratios used to prepare the beads were 1:1, 1:2 and 1:3 and the GL 44/14 concentrations were selected based on the results obtained with granules. The composition FM-GL beads is shown in Table 1.

Evaluation of FM granules and beads

Entrapment efficiency, drug loading, and yield

The entrapment efficiency (in case of beads) or drug content (in case of granules) was determined using the method reported in the literature[23]. Gelucire granules or beads equivalent to the dose of FM were added to 100 ml of 0.1 N HCl, heated to 60°C, and allowed to cool to room temperature. Upon cooling, the Gelucire solidified, and the drug in 0.1 N HCl was filtered through a 0.45-µm membrane filter. The drug content was estimated by UV spectrophotometry at 266 nm (Shimadzu-50-02, Kyoto, Japan) after sufficient dilution with HCl buffer (pH 1.2). Blank formulations were treated similarly. None of the ingredients used in the formulations interfered with the assay. The results were expressed as the mean of three experiments.

Percent entrapment (or drug content) was calculated by using the following formula:

$$\%\text{Drug entrapment} = [\text{Calculated drug content}/\text{Theoretical drug content}] \times 100 \quad \ldots\ldots(1)$$

For FM beads, the percent drug loading and percent yield were also calculated. The percent drug loading was calculated by dividing the amount of drug in the sampled beads by the weight of beads.

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Percent yield was calculated by using the following formula

% yield = [weight of beads collected/weight of all components used for the preparation] × 100 ... (2)

Particle size determination of FM beads

The average particle size of beads was determined with a micrometer (Mitutoyo micrometer, NSK Co., Japan) and calculated as the average value of the size of 50 beads.

Floating properties of FM granules and beads

A weight of granules or beads equivalent to 40 mg of FM was placed in 900 ml of 0.1 N HCl in a vessel maintained at 37±0.5°C and stirred at 50 rpm in USP XXIII dissolution apparatus (Erweka DT- D6, Duesseldorf, Germany). The percentage of floating granules or beads up to 12 hrs was determined [20,25]. The floating portion of granules was recovered, then they were dried and weighed. Floating percentage was calculated as the ratio of the weight of the granules or beads that remained floating and the total mass:

% floating = [Weight of floating granules or beads / Total weight] × 100 ..... (3)

Each experiment was carried out in triplicate

Flowability of FM granules and beads

The flow properties were investigated by measuring the angle of repose (θ) of drug loaded granules and beads using the fixed funnel method. Granules or beads were allowed to fall freely through a funnel fixed at 1cm above the horizontal flat surface until the apex of the conical pile just touches to the tip of the funnel. The height and diameter of the cone was measured and angle of repose was calculated by using the following formula:

Tan (θ) = height / radius ..... (4)

Each experiment was carried out in triplicate

Scanning electron microscopy (SEM)

The surface characteristics of the prepared formulations were examined with a scanning electron microscope (Joel, JSM-5400 LV, Japan) operated at an acceleration voltage of 15 kV. FM-GL granules and beads were coated with gold palladium foil (54 nm) by sputter coater unit (SPI, sputter, USA) prior to examination.

In-vitro drug release studies

The release profiles of FM from granules and beads were studied in 0.1 N HCl (pH 1.2). The dissolution process was carried out by using a USP XXIII dissolution apparatus (Erweka DT- D6, Duesseldorf, Germany). The drug loaded lipid granules or beads (equivalent to 40 mg of drug) were placed into the dissolution vessel containing 900 ml of the release medium which was stirred at a constant speed of 100 rpm and maintained at a temperature of 37±0.5°C and the test was performed for 12 hrs. At scheduled time intervals, the samples (5 ml) were withdrawn and replaced with same volume of fresh medium. The withdrawn samples were filtered through a 0.45μm membrane filter and then estimated for FM concentration spectrphotometrically at 266 nm after appropriate dilution. None of the ingredients used in the formulation interfered with the assay. The results were expressed as the mean of three experiments.

The drug release data were fitted to different kinetic models (zero-order, first-order, and Higuchi) to evaluate the kinetics of drug release from the granules and beads.

Dissolution efficiency (DE) is used to compare the results of dissolution tests of different formulations [26]. DE is defined as the area under the dissolution curve up to time t expressed as a percentage of the rectangle described by 100% dissolution in the same time.

$$\text{Dissolution efficiency } (DE_t\ \%) = \frac{\int_0^t y\,dt}{y100t} \times 100 \quad \ldots(5)$$

Where yt is the percentage of drug dissolved at any time t, $y100$ denotes 100% dissolution, and the integral represents the area under dissolution curve between time zero and t. Time t in this study was selected at the midpoint of the dissolution experiment (6 hrs). Another dissolution parameter, mean dissolution time (MDT), which is a measure of the rate of the dissolution process, was calculated using the following equation:

$$MDT = \frac{\sum_{i=0}^{i=n} tmid \times \Delta M}{\sum_{i=0}^{i=n} \Delta M} \quad \ldots(6)$$

Where i is the dissolution sample number, n is the number of observations, $tmid$ is the midpoint time between t and $i-1$, and ΔM is the additional amount of drug dissolved between t and $i-1$ [27]. As the MDT increases, the drug release rate decreases.

Infrared spectroscopy (IR)

Samples (FM, GL 43/01, GL 44/14 and FM : GL 1:2 containing 30% GL 44/14) were mixed with KBr and compressed into disc using hydrolic pump (Shimadzu IR-470, Japan) under pressure of about 5 ton. The spectra were recoded over a range of 4000-300 cm^{-1}.

Differential scanning calorimetry (DSC)

Thermograms of the samples (FM, GL 43/01, GL 44/14 and FM : GL 1:2 containing 30% GL 44/14) were obtained using differential scanning calorimetry (DSC-60, Shimadzu, Japan). Thermal analysis data were recorded using a TA 50I PC system with Shimadzu software programs. Indium standard was used to calibrate the DSC temperature and enthalpy scale. The samples (3-5 mg) were sealed in aluminum pans and heated at a constant rate of 10°C /min, over a temperature range of 25-200°C. Inert atmosphere was maintained by purging nitrogen at a rate of 30 ml/min.

Statistical analysis

Statistical analysis of the obtained results was performed by the Student's t-test.

RESULTS AND DISCUSSION

Preliminary characterization

The drug content of the Gelucire granules was in the range of 97.9–99.7±0.1% indicating good content uniformity of prepared granules.

The initial formulations prepared in ratios of 1:1, 1:2, and 1:3 FM-GL 40/13 (G1–G3) exhibited excellent *in-vitro* floating characteristics in agreement with reported findings [12, 20, 22] (Table 2). The granules remained floating for 12 hrs with no lag time. However the granules prepared in a 1:1 drug : GL 40/13 ratio were friable and showed high percentages of fines during sieving. Therefore, drug : GL 43/01 ratios of 1:2 and 1:3 were selected as the basic formulation ratios for further studies.

Table 2: Flowability and % floating of FM-GL granules and beads.

Code	Angle of repose (θ°)	% Floating
G1	23.33 ± 0.77	92.9 ± 0.4
G2	23.87 ± 0.65	99.6 ± 0.2
G3	25.53 ± 0.63	99.7 ± 0.5
G4	24.11 ± 0.54	97.4 ± 0.6
G5	24.34 ± 0.65	96.4 ± 0.9
G6	23.65 ± 0.88	78.6 ± 1.5**
G7	23.77 ± 0.68	75.7 ± 1.7**
G8	26.21 ± 0.73	98.1 ± 0.3
G9	26.78 ± 0.77	96.4 ± 0.5
G10	25.86 ± 0.67	82.5 ± 0.9**
G11	25.24 ± 0.54	77.7 ± 1.2**
B2	20.14 ± 0.64	99.7 ± 0.3
B3	20.55 ± 0.72	99.3 ± 0.6
B4	21.73 ± 0.44	98.5 ± 0.9
B5	20.12 ± 0.36	98.1 ± 0.7

Mean ± SD, n=3

** Highly significant value compared to corresponding formula containing no GL 44/14 ($P < 0.01$).

Various concentrations of GL 44/14 affected the *in-vitro* floating ability of granules (formulations G4–G11, Table 2). As the amount of GL 44/14 increased beyond 30% in both ratios (1:2 and 1:3), the granules showed decreased floating characteristics (differences were statistically significant). This may be due to variation in the density of GL 44/14 compared with GL 43/01. However, granules with GL 44/14 at concentrations below 30% showed good floating properties for 12 hrs. Apart from hydrophobicity, density of Gelucire 43/01 (true density 0.0856 g/cm^3) [23] also plays an important role in floating ability of beads. In contrast to most conventional floating systems (including gas-generating ones), these beads floated immediately upon contact with the release medium showing no lag time in floating behavior because the low density was prevailed from the beginning (t = 0). Shimpi *et al.* [23] prepared floating granules of diltiazem hydrochloride-GL 43/01. The surface hydrophobicity imparted to the drug particle by the hydrophobic lipid coat was responsible for floating behavior. But all low HLB excipients did not ensure floating, as similar granules prepared using Compritol and glyceryl monostearate separately did not show floating properties.

FM-GL 43/01 beads were prepared using drug : lipid ratios of 1:1, 1:2, and 1:3 (B1-B3). Beads prepared with a 1:1 FM-GL 43/01ratio (B1) were elongated or irregular in shape, therefore, only beads prepared with drug : GL 43/01 ratios of 1:2 (B2) and 1:3 (B3) were evaluated. GL 44/14 was used in two concentrations only (25 and 30%) based on the floating behavior results of the granules. It was incorporated in the beads prepared with 1:2 drug : GL 43/01 ratio based on the release data of GL 43/01 beads.

The mean particle diameter, % yield, practical drug loading and encapsulation efficiency of the obtained FM-GL beads prepared by the melt-solidification method are given in Table 3. The average particle diameter of beads was found to be in the size range of 1.27 ± 0.12 -1.33 ± 0.13 mm and it was not affected significantly by increasing GL ratio. The practical drug loading and encapsulation efficiencies were high for different formulated beads with no significant difference between them. Process yield was high ranging from 88.7 ± 0.45 to 90.5± 0.40%.

Similar to granules, formulations prepared with ratios of 1:2 and 1:3 FM : CL 40/13 (B2 and B3) exhibited excellent *in- vitro* floating characteristics for up to 12 hrs. As the GL 44/14 concentrations were below 30% the floating properties were maintained for beads B4 and B5 (Table 2).

Flowability of FM-GL granules and beads

Flowability study showed that the prepared granules had good flow properties as seen from the values of the angle of repose (Table 2). There was no significant difference between the different granules regarding the angle of repose indicating that the lipid content did not affect the flow properties. Beads also showed good flowability. The values of the angle of repose of all beads formulations were less than those of granules. However, both are in the same range of good flow properties (20°-30°). Beads had slightly better flow properties due to their perfect spherical shape (described in the next section).

Table 3: Various characteristics of FM-GL beads.

Code	Yield (%)	Drug loading (%)	Entrapment efficiency (%)	Mean particle diameter (mm)
B2	90.5 ± 0.40	32.2 ± 0.31	97.2 ± 0.24	1.27± 0.12
B3	88.1 ± 0.36	19.3 ± 0.44	96.7 ± 0.33	1.24 ± 0.18
B4	88.7 ± 0.45	20.9 ± 0.22	94.5 ± 0.28	1.33 ± 0.13
B5	90.3 ± 0.70	30.8 ± 0.35	95.2 ± 0.39	1.30 ± 0.13

Mean ± SD, n=3

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Scanning electron microscopy (SEM) of FM-GL granules and beads

The produced granules were nearly spherical in shape. The SEM photomicrograph of surface of the granules shows the rough nature of surface with few cracks (Fig. 1a). Beads were spherical showing smooth porous surface with many small pores (Fig. 1b).

In-vitro drug release studies

The *in-vitro* drug release studies revealed that granules of GL 43/01 alone showed high retardation of drug release in 0.1 N HCl. As the amount of GL 43/01 in the formulations increased, the release rate decreased (Figure 2). This is in agreement with Patel *et al.* [20]. The FM released from formulations G1, G2, and G3 after 12 hrs was about 55.11%, 26.43%, and 20.33%, respectively. Figure 3 shows FM release from granules of 1:2 and 1:3 drug-GL 43/01 with various concentrations of GL 44/14. It indicates that as the proportion of GL 44/14 in the formulation increased, the release increased for both ratios studied. This is because GL 44/14 is more hydrophilic than GL 43/01. This effect is also evident from dissolution efficiency (DE) and mean dissolution time (MDT) values for different formulations (Table 4). It can be seen from the table that the changes in these dissolution parameters were statistically significant.

Similar results were obtained for beads (Table 4), as drug release was retarded from beads of GL 43/01. Increasing the lipid ratio decreased the drug release. Incorporation of GL 44/14 enhanced the drug release from the beads significantly ($P < 0.05$). Increasing GL 44/14 from 25 to 30% resulted in further increase in drug release and dissolution parameters. The difference between beads and granules regarding drug release was insignificant ($P > 0.05$). Figure 4 shows the *in-vitro* drug release profiles from the prepared beads.

Slow drug release observed for formulations having high amounts of GL 43/01 is due to the hydrophobic nature of GL 43/01, which might have reduced the wetting of drug and thus the dissolution. It has been suggested that, because of the high hydrophobicity of lipid materials, the release medium is not able to diffuse through the matrix and can progress in the dosage form by dissolving the grains of drug in contact with it. The dissolution of the drug particles on the surface of the matrix allows the formation of channels, from which the drug is slowly released [28].

The regression coefficients of drug release profiles according to different kinetic models are presented in Table 5. It is evident from the results that the regression coefficient values of Higuchi plots were close to one indicating the release from both granules and beads was through a diffusion mechanism. The release exponent (n values) of the Korsmeyer-Peppas model were between 0.45 and 0.89 suggesting that drug release from the granules and beads followed an anomalous non-Fickian diffusion mechanism.

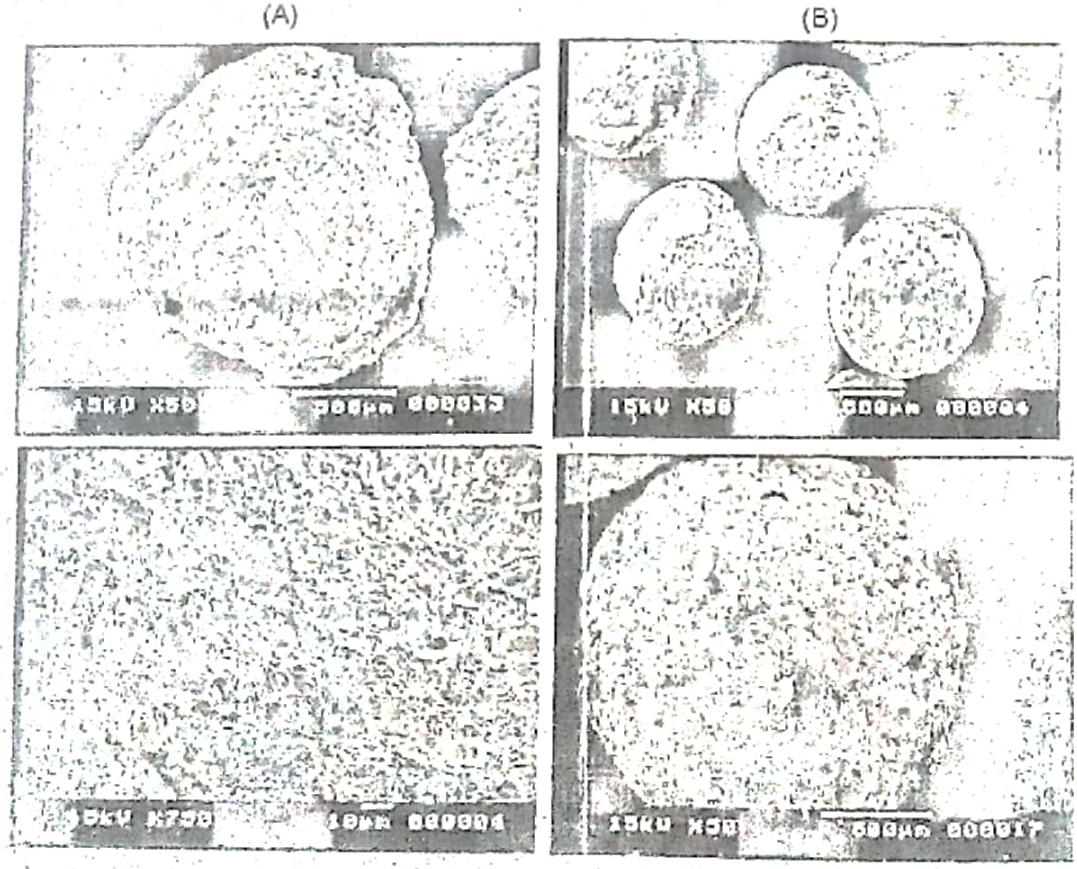

Fig. 1: SEM microphotographs of (A): FM-GL granules, (B): FM-GL beads.

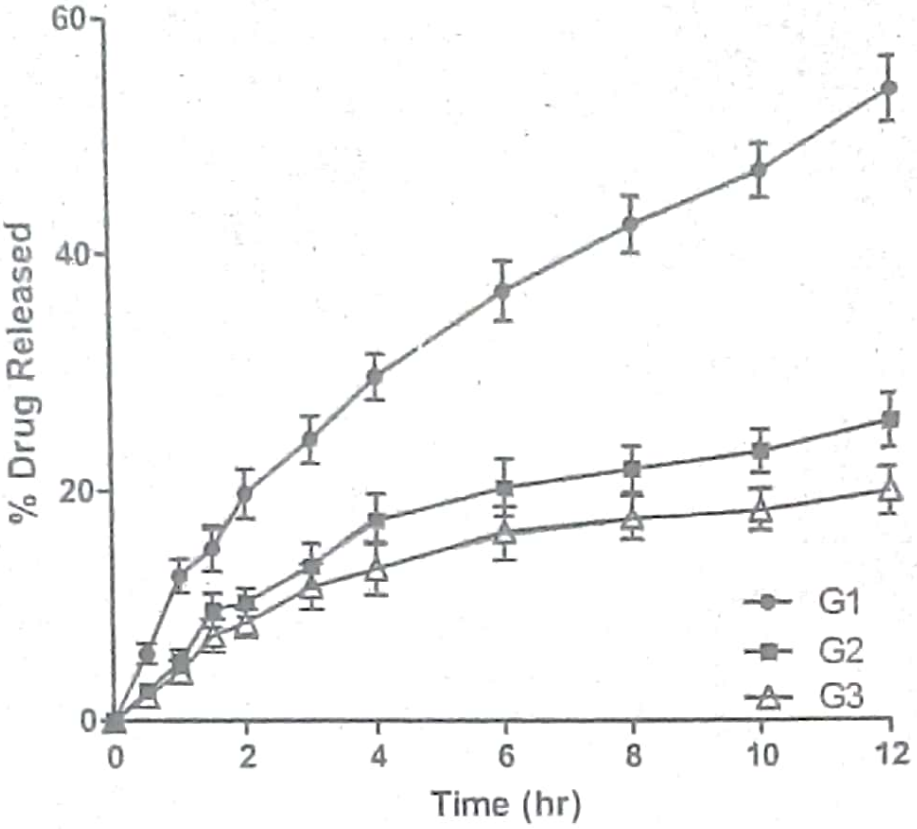

Fig. 2: *In-vitro* release profiles of FM from GL 43/01 granules of different drug: GL 43/01 ratios in 0.1 N HCl. Each point is the average of 3 experiments.

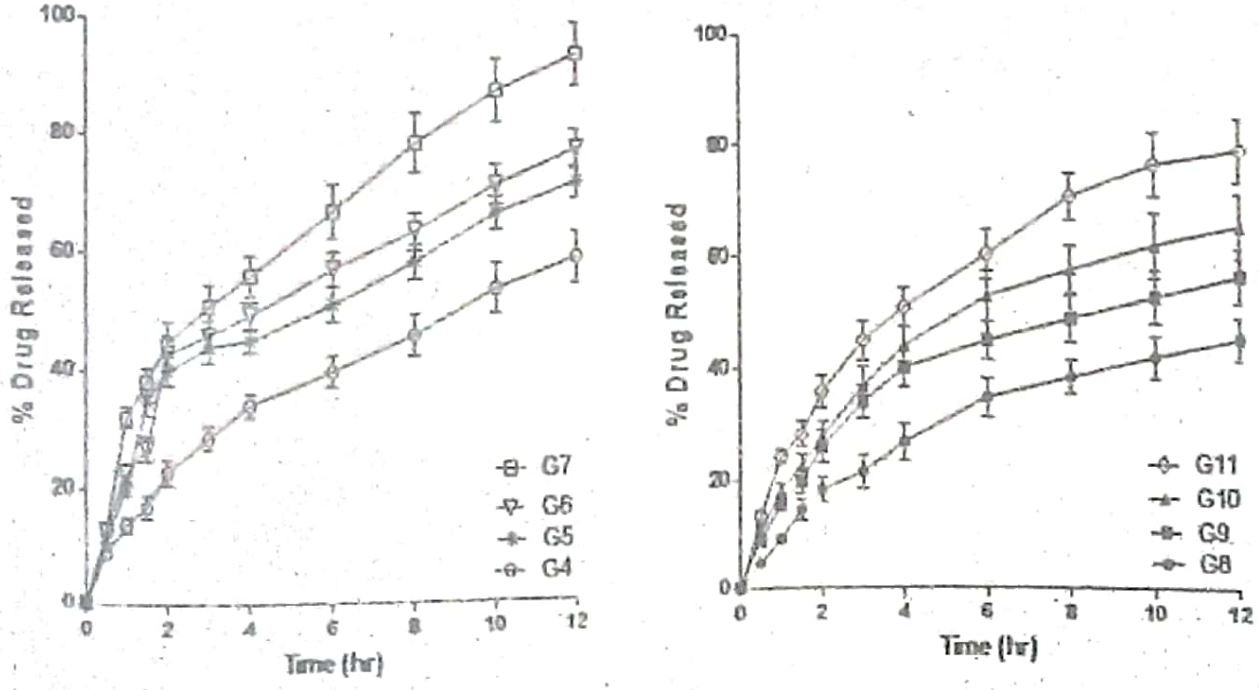

Fig. 3: *In-vitro* release profiles of FM from granules of 1: 2 and 1: 3 drug: GL 43/01 with various concentrations of GL 44/14 in 0.1 N HCl. Each point is the average of 3 experiments.

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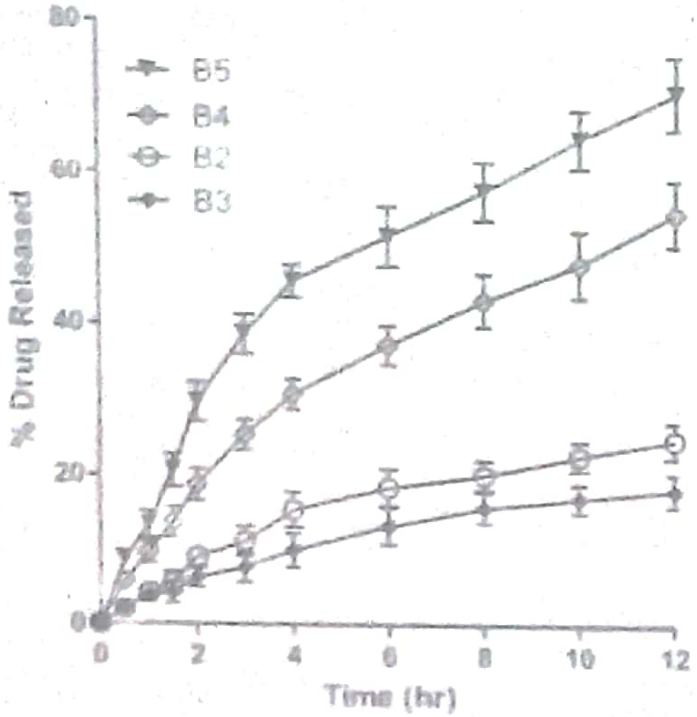

Fig. 4: *In-vitro* release profiles of FM from different GL 43/01 beads with or without GL 44/14 in 0.1 N HCl. Each point is the average of 3 experiments.

Table 4: Dissolution parameters of prepared FM GL granules and beads

Code	MDT (hr)	DE, %	Q_6
[illegible]	6.44 ± 0.21	[illegible] 2.58 ± 1.93	17.55 ± 2.56
[illegible]	7.21 ± 0.16	12.78 ± 1.32	20.63 ± 3.46
[illegible]	7.69 ± 0.14	10.19 ± 1.45*	16.53 ± 2.67
[illegible]	8.18 ± 0.15*	25.96 ± 3.11**	39.55 ± 2.56
[illegible]	8.22 ± 0.12*	31.40 ± 2.14**	50.84 ± 2.96
[illegible]	8.51 ± 0.11**	30.56 ± 2.17**	56.75 ± 2.96
[illegible]	8.53 ± 0.13**	47.60 ± 2.43**	66.34 ± 4.50
[illegible]	8.04 ± 0.14*	19.21 ± 1.35*	34.63 ± 3.46
[illegible]	8.43 ± 0.15*	28.59 ± 1.98**	44.84 ± 3.51
[illegible]	8.61 ± 0.13**	37.68 ± 1.96**	52.86 ± 4.26
[illegible]	8.79 ± 0.14**	40.17 ± 2.23**	60.34 ± 4.54
[illegible]	[illegible]	[illegible]	18.63 ± 2.11
[illegible]	[illegible]	8.91 ± 1.05	14.63 ± 2.56
[illegible]	[illegible]	21.24 ± 1.87*	37.55 ± 2.97
[illegible]	[illegible]	34.36 ± 1.79*	51.84 ± 3.55

Values in SD, n=3
DE_{15}: dissolution efficiency at 15 hr
MDT: Mean dissolution time
Q_6: Percent drug released at 6 hr
* Significant value compared to corresponding formula containing no GL 44/14 ($P < 0.05$)
** Highly significant value compared to corresponding formula containing no GL 44/14 ($P < 0.01$)

Table 5: Regression coefficient of FM release profiles from granules and beads according to different kinetic models

Code	Zero order	First order	Higuchi	n
G1	0.9956	0.9543	0.9996	0.543
G2	0.9937	0.9578	0.9994	0.588
G3	0.9931	0.9698	0.9992	0.605
G4	0.9754	0.9655	0.9985	0.592
G5	0.9884	0.9435	0.9985	0.566
G6	0.9873	0.9552	0.9973	0.497
G7	0.9766	0.9135	0.9979	0.410
G8	0.9877	0.9468	0.9982	0.558
G9	0.9743	0.9199	0.9985	0.489
G10	0.9787	0.8977	0.9976	0.582
G11	0.9788	0.9122	0.9974	0.576
B2	0.9921	0.9587	0.9996	0.545
B3	0.9892	0.9701	0.9989	0.587
B4	0.9766	0.9729	0.9987	0.602
B5	0.9879	0.9557	0.9992	0.524

n: Peppas release exponent.

Differential scanning calorimetry (DSC)

DSC thermograms of pure drug, GL 43/01, GL 44/14, and the drug-GL solidified melt are presented in Figure 5. An endothermic peak at 163°C corresponding to the melting point of pure drug was prominent in the optimized formulation with respect to GL 43/01 and GL 44/14 peaks, which clearly suggests that the drug was present in an unchanged form.

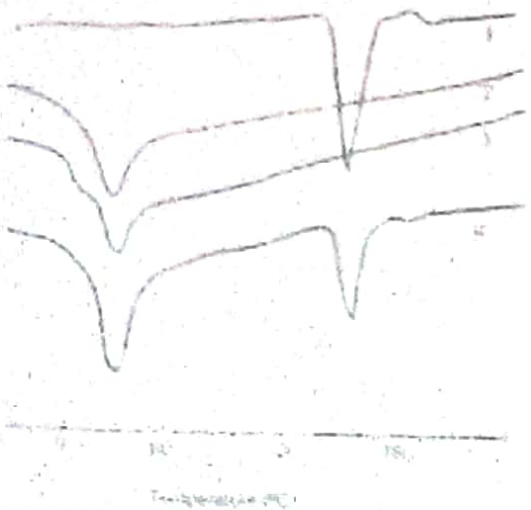

Fig. 5: DSC thermograms of (1) famotidine, (2) Gelucire 43/01, (3) Gelucire 44/14, and (4) FM: GL-1:2 containing 30% GL 44/14.

Infrared spectroscopy (IR)

In order to evidence the possible chemical interaction of drug with the Gelucires, IR analysis was used. Figure 6 shows the IR spectra of FM: GL 43/01, GL 44/14, and the drug-GL solidified melt. Pure drug shows characteristic peaks at 3395, 3240 cm^{-1} (NH$_2$ asymmetric stretching), 2970 cm^{-1} (C-H stretching), 1630 cm^{-1} (C=N stretching), 1595 cm^{-1} (N-H bending). GL 43/01 and GL 44/14 show important bands at 1741 and 1735 cm^{-1}, respectively, which are indicative of C=O stretching of the ester group. Peaks at 1172 and 1100 cm^{-1} can be assigned to the C-O stretch of alcohols (primary or secondary). The IR spectrum of the optimized formulation displays the characteristic peaks of both drug and Gelucires. Overall, there was no alteration in the characteristic peaks of drug and Gelucires suggesting that there was no interaction between them.

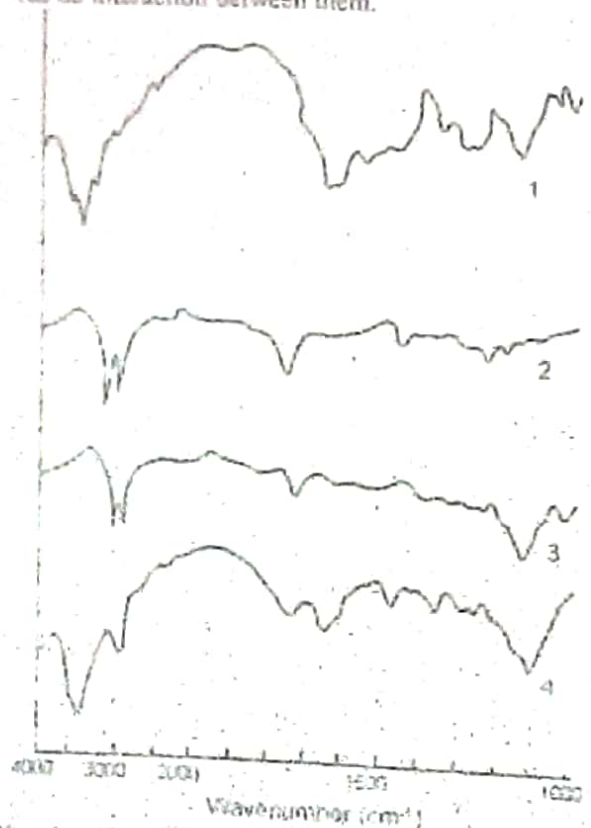

Fig. 6: IR spectra of (1) FM, (2) GL 43/01, (3) GL 44/14 and (4) FM: GL-1: 2 containing 30% GL 44/14.

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CONCLUSION

GL 43/01 may be an appropriate carrier for the preparation of sustained-release floating formulations of FM because of its extreme hydrophobicity and low density. GL 44/14, a high HLB excipient, acted as a dissolution enhancer in the formulations studied (granules and beads). The Gelucires showed good compatibility with the drug (FM). Both developed formulations showed excellent *in-vitro* floating ability and retarded drug release with no significant differences between them indicating successful development of a sustained-release floating drug delivery system of FM. Formulation procedures of both granules and beads were reproducible with minimum drug loss. However, granules obtained by melt-granulation were relatively easier to scale up.

REFERENCES

1. Dollery, C In: Therapeutic Drugs, volume *1*, 2nd edition, Churchill Livingstone, Edinburgh London New York Philadelphia San Francisco Sydney Toranto (1999).
2. Jaimini, M., Rana, A.C. and Tanwar, Y.S., **Current Drug Delivery**, 4: 51-55 (2007).
3. Hui, Y. F., Kolars, J., Hu, Z. and Fleisher, D., **Biochem. Pharmacol.**, 48: 229-231 (1994).
4. Fell, J. T., Whitehead, L. and Collet, J. H., **Pharm. Technol.**, 24: 82-87 (2000).
5. Patel, D. M., Patel, N. M., Patel, V. F. and Bhatt D. A., **AAPS PharmSciTech**, 8 (2): Article 30, E1-E7 (2007).
6. Dave, B. S., Amin, A. F. and Patel, M. M., **AAPS PharmSciTech**, 5 (2): 1-6 (2004).
7. Santus, G., Lazzarini, G., Bottoni, G., Sandefer, E.P., Page, R.C., Doll, W.J., Ryo, Y.U. and Digenis, G.A., **Eur. J. Pharm. Biopharm.**, 44: 39-52 (1997).
8. Deshpande, A.A., Rhodes, C.T., Shah, N.H. and Malick, A.W., **Drug Dev. Ind. Pharm.**, 22: 531-539(1996).
9. Akash, Y., Jain, D.K. and Neelam, B., **The Pharma Research**, 1: 133-141 (2009).
10. Efentakis, M., Koutlis, A. and Vlachou, M., **AAPS PharmSciTech**, 1: E34 (2000).
11. Singh, B.N. and Kim, K.M., **J. Control. Release**, 63: 235-259 (2000).
12. Chauhan, B., Shimpi, S., Mahadik, K.R. and Paradkar, A., **Drug Dev. Ind. Pharm.**, 31: 851-860 (2005).
13. Bowtle, W., **Pharm. Tech. Europe**, 12: 20-30 (2000).
14. Ainaoui, A. and Vergnaud, J.M., **Int. J. Pharm.**,169: 155-162 (1998).
15. Ainaoui, A., Ouriemchi, E.M., Bidah, D., El Amrani, M.K. and Vergnaud, J.M., **J. Polym. Eng.**, 17: 245-257 (1997).
16. Sutananta, W., Craig, D.Q.M. and Newton, J.M., **Int. J. Pharm.**, 111: 51-62 (1994).
17. Sheu, M.T., Hsia, A. and Ho, H.O., **Chin. Pharm. J.**, 53: 107-111 (2001).
18. Barker, S.A., Yap, S.P., Yuen, K.H., McCoy, C.P., Murphy, J.R. and Craig, D.Q.M., **J. Control. Release**, 91: 477-488 (2003).
19. Dennis, A.B., Farr, S.J., Kellaway, I.W., Taylor, G. and Davidson, R., **Int. J. Pharm.**, 65: 85-100 (1990).
20. Patel, D.M., Patel, N.M., Patel, V.F. and Bhatt, D.A., **AAPS PharmSciTech.**, 8 (2): Article 30 (2008).
21. Roussin, P. and Laforet, J.P., **Fram. Vestn.**, 48: 260-261 (1997).
22. Kumar, K., Shah, M.H., Ketkar, A., Mahadik, K.P. and Paradkar, A., **Int. J. Pharm.**, 272: 151-160 (2004).
23. Shimpi, S., Chauhan, B., Mahadik, K.R. and Paradkar, A., **AAPS PharmSciTech.**, 5(3): Article 43, 1-6 (2004).
24. Sutananta, W., Craig, D.Q.M. and Newton, J.M., **J. Pharm. Pharmacol.**, 47: 182-187 (1995).
25. Iannuccelli, V. Coppi, G., Bernabei, M.T. and Cameroni, R., **Int. J. Pharm.**, 174: 47-54 (1998).
26. Banakar, U.V., Pharmaceutical Dissolution Testing, 1st ed., Marcel Dekker: New York, pp. 191-194 (1992).
27. Barzegar-Jalali, M., Maleki, N., Garjani, A., Khandar, A.A., Haji-Hosseinloo, M., Jabbari, R. and Dastmalchi, S., **Drug Dev. Ind. Pharm.**, 28: 681–686 (2002).
28. Sanker, C. and Mishra, C., **Acta Pharm.**, 53: 101-110 (2003).

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الانطلاق الممتد لعقار الفاموتيدين من صياغات الجلوسير الطافية

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تهدف هذه الدراسة الى صياغة عقار الفاموتيدين فى صياغات طافية باستخدام خليط من الجلوسير ٠١/٤٣ والجلوسير ١١/٤٤ بتركيزات مختلفة وذلك بهدف بقائها لفترة أطول فى المعدة وإطالة فترة إنطلاق العقار مما يحسن التوافر الحيوى ويقلل من عدد مرات تناول العقار. تم تحضير صياغات فى شكل حبيبات باستخدام طريقة تحبيب المصهور وفى شكل كريات باستخدام طريقة تصلب المصهور. تم تقييم الصياغات المحضرة باستخدام المسح المجهرى الإلكترونى لدراسة السطح كما تم تقييم خصائص التدفق، قدرتها على الطفو، وكذلك انطلاق العقار من الصياغات المختلفة. فى حالة الكريات تم بالإضافة إلى ذلك تعيين نسبة الانتاجية ونسبة تحميل العقار وكفاءة إدخال العقار داخل الصياغات وكذلك قياس حجم الكريات. تم استخدام مقياس التفاضل السعرى الحرارى والتحليل الطيفى بالأشعة تحت الحمراء لدراسة احتمالية أى تداخل بين الجلوسير بنوعيه والعقار. أظهرت النتائج أن الصياغات المحضرة فى صورة كريات كانت ذات شكل كروى كامل وسطح أملس بينما كانت الحبيبات كروية إلى حد ما وذات سطح خشن. كانت الصياغات المحضرة ذات خصائص تدفق جيدة كما كان لها خصائص طفو ممتازة ولم يظهر أى تداخل كيميائى أو فيزيائى للجلوسير مع العقار. كما أظهرت النتائج أن إنطلاق العقار من الحبيبات والكريات فى وسط له درجة حموضة ١,٢ كان ممتدا لمدة اثنى عشرة ساعة ولم تكن الفروق بينهما ذات دلالة إحصائية.