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Formulation Development And Characterization Of Gelucire Beads Of Antihypertensive Drug For Floating Drug Delivery System

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ABSTRACT
Oral delivery is the preferred method for drug administration due to its ease of use, low cost, and high patient compliance. However, conventional oral drug delivery systems have drawbacks such as quick gastric emptying time and low bioavailability due to incomplete absorption and degradation in the gastrointestinal tract. To address these issues, controlled drug delivery systems have been developed, such as the gastroretentive drug delivery system. This system allows dosage forms to remain in the stomach for extended periods without impacting gastric transit time. Various types of polymers have been used to distribute drugs to specific regions in the gastrointestinal tract. Gelucire, a preferred excipient in these systems, is derived from mono, di, and triglyceride mixtures of polyethylene glycol fatty acid esters. Ramipril, an inhibitor of the long-acting non-sulfhydryl angiotensin converting enzyme (ACE), is an extremely lipophilic active antihypertensive medication with 28-35% absolute bioavailability.

Keywords: Floating drug delivery system, Gelucire, Ramipril, Tween 20, Solubility Enhancement, Percentage drug release, Factorial design.

INTRODUCTION:
Oral delivery is the favored path for the administration of drugs due to with its ease of use, low cost, and high compliance with patients. Some drawbacks related to quick gastric emptying time and low bioavailability of certain drugs due to incomplete absorption and degradation in the gastrointestinal tract (GIT) have been demonstrated by most conventional oral drug delivery systems [1]. To overcome this complication, controlled drug delivery system is designed to improve the pharmacological activity of a therapeutic agent or active pharmaceutical ingredients by increasing the drug solubility, bioavailability, stability, reducing side effects, and enhancing the selective delivery of drug with a predictable rate and mechanism [2].

The gastroretentive drug delivery system is one novel approach in this field. Dosage forms that can be retained in the stomach for prolong period of time are called gastroretentive drug delivery system [3]. Numerous approaches to gastroretentive drug delivery such as high density systems (i.e., retained in the bottom of the stomach [4]), low-density systems (reason for buoyancy in gastric fluid [5-7], mucoadhesive systems (which causes bioadhesion to stomach mucosa [8]), unfoldable, extendible or swellable systems (which limits emptying of the dosage forms through the pyloric sphincter of stomach)[9,10], and superporous hydrogel systems [11] and magnetic system have been design and developed [12]. Buoyancy in gastric fluid, floating system (dynamically controlled) allows it to float over contents of gastric and stay floating in stomach without impacting the gastric transit time [13]. Various types of polymers used to formulate floating drug delivery systems are designed to distribute drugs to particular regions in the GIT [14]. Much focus has recently been on the use of fats and fatty acids as carriers in drug delivery systems in which Gelucire is one of the preferred excipients.

Gelucire is derived from mono, di, and triglyceride mixtures of polyethylene glycol fatty acid esters [17]. Different types of Gelucire can be identified by two digits, where the first and second digit signifies the melting point of the base and the hydrophilic-lipophilic balance (HLB) value of water to fat soluble parts in each Gelucire, respectively. The melting point of Gelucire has a variance of 33–65°C and HLB variance of 1–14. Hence, if we consider Gelucire 43/01, 43 would be the melting point, and 1 its HLB [18]. Ramipril is an inhibitor of the long-acting non-sulfhydryl angiotensin converting enzyme (ACE) that was developed about a decade ago for clinical use. Ramipril is a drug which is de-esterifies to form ramiprilat, its active metabolite, in the liver [19]. It is an extremely lipophilic active antihypertensive medication (Log p=3.32), a poorly water-soluble drug with 28–35% absolute bioavailability [20]. In the earlier, mildto-moderate essential hypertension in 85% of patients was effectively treated with ramipril 2.5 or 5 mg/day. Hence, it is a useful alternative for ACE inhibitor where positive effect of the drug was seen in patients who had heart failure, post-acute myocardial infarction, shows clinical studies. So far, patients with established asymptomatic left ventricular dysfunction (or heart failure), it is safe to assume, ramipril will be worth it [21].

MATERIALS AND METHODS:

Materials Drug (Ramipril), Tween 20, Span 80, and dimethyl sulfoxide (DMSO) were obtained as a gift sample from Emcure Pharmaceutical Limited Pune, India. Gelucire43/01, Gelucire 50/13, and Gelucire 48/16 were obtained as a gift sample from Gattefosse India Pvt. Ltd, Mumbai, India. All other chemicals used were of analytical grade.

Drug-excipient compatibility study: Fourier-transform infrared (FTIR) spectroscopy was carried out to check the compatibility between drug and polymer. The spectra of drug with polymers were compared with the standard spectrum of the pure drug [22].

FTIR analysis: Pure drug and physical mixtures between 400 cm1 and 4000-1 cm have been performed with the infrared spectroscopy.

Ultraviolet (uv) scan of ramipril: λmax required to prepare calibration curve was derived by performing a scan using UV spectrophotometer between 200 and 400 nm. For this, a drug sample concentrated at 10 µg/ml was used. Calibration curve of Ramipril in 0.1 N HCl A standard plot of the drug was prepared in 0.1 N HCl to determine the drug content of ramipril. Stock solution of the ramipril having concentration of 100 µg/ml was prepared and diluted serially to attain a concentration range between 5 and 30 µg/ml. These were spectrophotometrically analyzed using UV spectrophotometers at 210 nm.

Preparation of Gelucire beads: Lipid (Gelucire) has melted to 50°C and gradually the fine powdered drug has been added to form dispersion with the uniform mixture. The resulting dispersion was dropped to 100 ml Prechilled (4°C) water at a rate of 5 drop/min through 23-guage syringe needle (0.65 mm inner diameter). The distance between the tip of the needle and water was 5 cm in 100 rpm with the magnetic stirrer for 15 min, the contents were stirred. The beads were then collected through a Whatman filter paper (#41), 3 times washed with distilled water and then dried up in the vacuum desiccator for duration of 24 h to ensure that the solvents had been completely removed. Beads for their weight were measured every 6 h. Separated and combined for dispersion medium are used in a number of other vehicles such as olive oil, light liquid paraffin, ethanol, isopropyl myristate, coconut oil, and isopropyl alcohol [23].

Preliminary screening of lipid carrier and dispersing media: To assess three different grades of lipid, the preliminary screening was carried out as a carrier- Gelucire 48/16, Gelucire 50/13, and Gelucire 43/01 using various drug-to-carrier ratio (1:10, 1:20, 1:30, and 1:40) in various vehicles such as water, olive oil, light liquid paraffin, ethanol, isopropyl myristate, coconut oil and isopropyl alcohol separately, and in combination ratio were used as dispersion medium.

Optimization of Gelucire 43/01 beads using a 32 factorial experimental design with Drug loading agent concentration: To evaluate the collective effect of Gelucire 43/01 and Tween 20 on the drug release from the beads a full factorial design was used. Factorial experiments 3n (n factors each at three levels) is of historical

interest and software's are usually used to analyze the outcome of factorial experiments. Ramipril-Gelucire beads were prepared using a 32 factorial experimental design in order to investigate the main effects as well as interaction of formulation and process variables using Design Expert® software (8.0.6). In this design, two factors are evaluated, each at three levels and experimental trials are performed at all nine possible combinations. For this study, the formulation variables were Gelucire 43/01 concentration (X1) and Tween 20 (X2). The percent drug released after 1 (Y1), after 6 (Y2), and after 12 h (Y3) was selected as the dependent variables. Tables 1 and 2 illustrate the composition of the prepared beads. A statistical model incorporating interactive and polynomial terms that correlate the independent variables and response is described by Equation (1);

$$Y = b0 + b1\ X1 + b2\ X2 + b12\ X1\ X2 + b11\ X1\ X1 + b22\ X2\ X2$$

Where b0 is the arithmetic mean response of the 9 runs; b1 and b2 are the estimated coefficients for X1 and X2 , respectively; and b12 is the estimated coefficients for interaction terms (X1 X2). The model used for main effects of the variables X1 and X2 represent the changing variable each at a time. The second-order interaction (X1 X2) shows that how the value of X1 amplifies or downplays the effect on the response of a change in X2 . The polynomial terms were included to investigate nonlinearity [24].

Morphology study (scanning electron microscopy [SEM]): SEM used to study the surface morphology and inner textures of the optimized formulation.

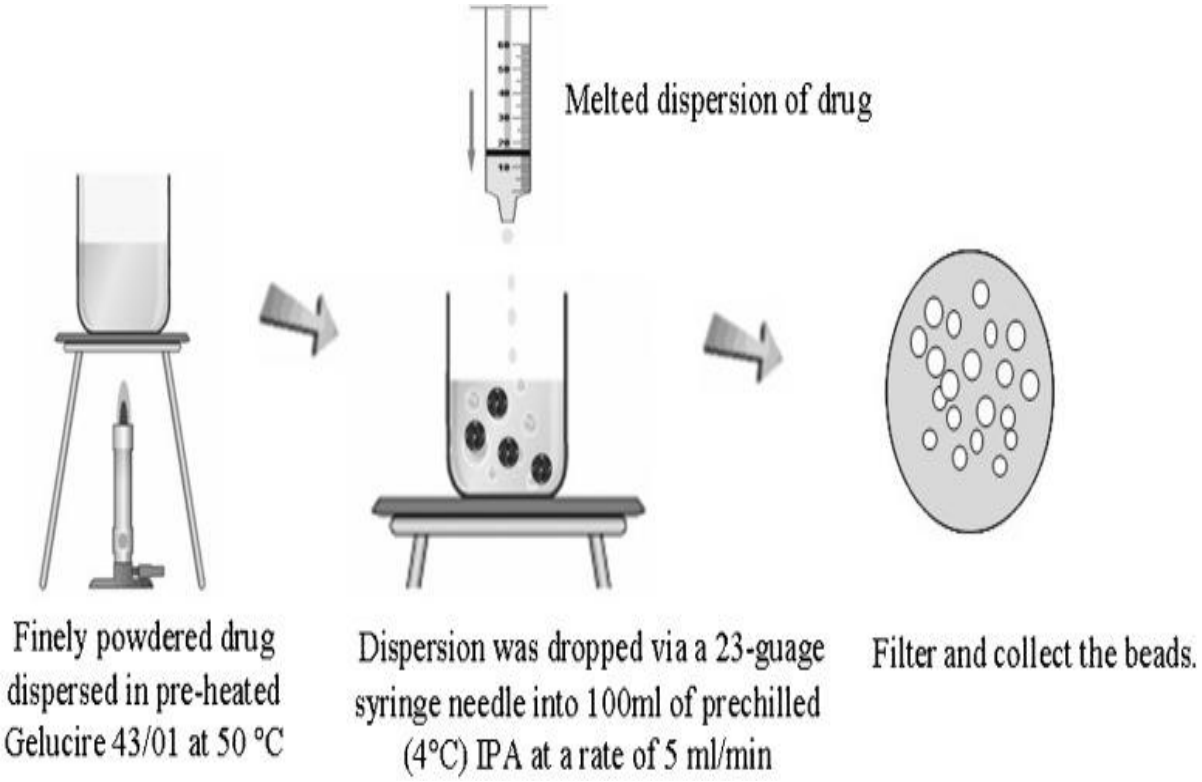
In vitro drug release study: Using USP paddle type II dissolution apparatus, the release of ramipril from the floating beads was determined. In the dissolution apparatus, a weighted amount of beads equal to 5 mg of drug was place in 900 ml of 0.1N HCl (pH 2.0) dissolution media. At a rotation Speed of 50 rpm, the dissolution media were held at 37±0.5°C. During the analysis of drug release, optimal sink conditions maintained for that 5 ml samples were removed at every 1 h, passed through a membrane filter and the initial volume of the dissolution media was preserved by adding 5 ml of fresh dissolution fluid after each removal. Using a UV-Visible spectrophotometer at 210 nm λmax, samples were analyzed. The release profile of marketed formulation, that is, conventional tablet of ramipril (Ramgee-5, German Remedies Pharmaceuticals pvt. ltd) was also determined by the same procedures as followed earlier [25].

In vitro drug release kinetics: The release kinetic was studied by various kinetic models as zero-order, first-order, Higuchi model, and Korsmeyer–Peppas equation. The value of correlation coefficient (R2) nearly 1, verified the most suitable model. The zero-order model describes where the drug is released independent of its concentration and is commonly identified as the matrix based drug with low solubility. Information obtained from drug releases in vitro has been obtained as percentage cumulative drug releases verses time to know correlation coefficient. The first-order equation describes the systems in which releases depended on the concentration of the drug and is commonly identified as water-soluble drugs in the porous matrix. The data obtained were plotted as log cumulative percentage of drug retained verses time. The Model Higuchi model is based on Fickian diffusion that explains the drug's release of an insoluble matrix linearly linked to the square root of time. Graph between cumulative percentages drug released and root square of time was obtained.

RESULT AND DISCUSSION

Preparations of Beads

In the present investigation, a multiparticulate delivery system of MH capable of providing controlled release was prepared using Gelucire 43/01. Beads were not formed when using olive oil, sesame oil, light liquid paraffin, heavy liquid paraffin, and coconut oil as dispersion medium. Uniform and compact beads were formed with IPA but not with some other oils and organic solvents used. IPA is used as surface active agent and cross-linking agent. So might be these properties play an important role in uniform bead formation. Schematic of preparation of beads is shown in Fig. 1. Formulations containing 1:5, 1:10, and 1:15 ratio of drug/Gelucire 43/01 were assigned batch code as MHG-05, MHG-10, and MHG-15, respectively (Table I). The method of preparation of beads was found to be simple and reproducible.



Schematic presentation of method of preparation of Gelucire 43/01 beads of metformin HCl

Table I. Composition of Beads and Their Assigned Batch Codes, Bead Diameter, Bulk Density, Porosity, Yield (percent), Drug Entrapment (percent), and Buoyancy (percent) of Different Formulation Batches

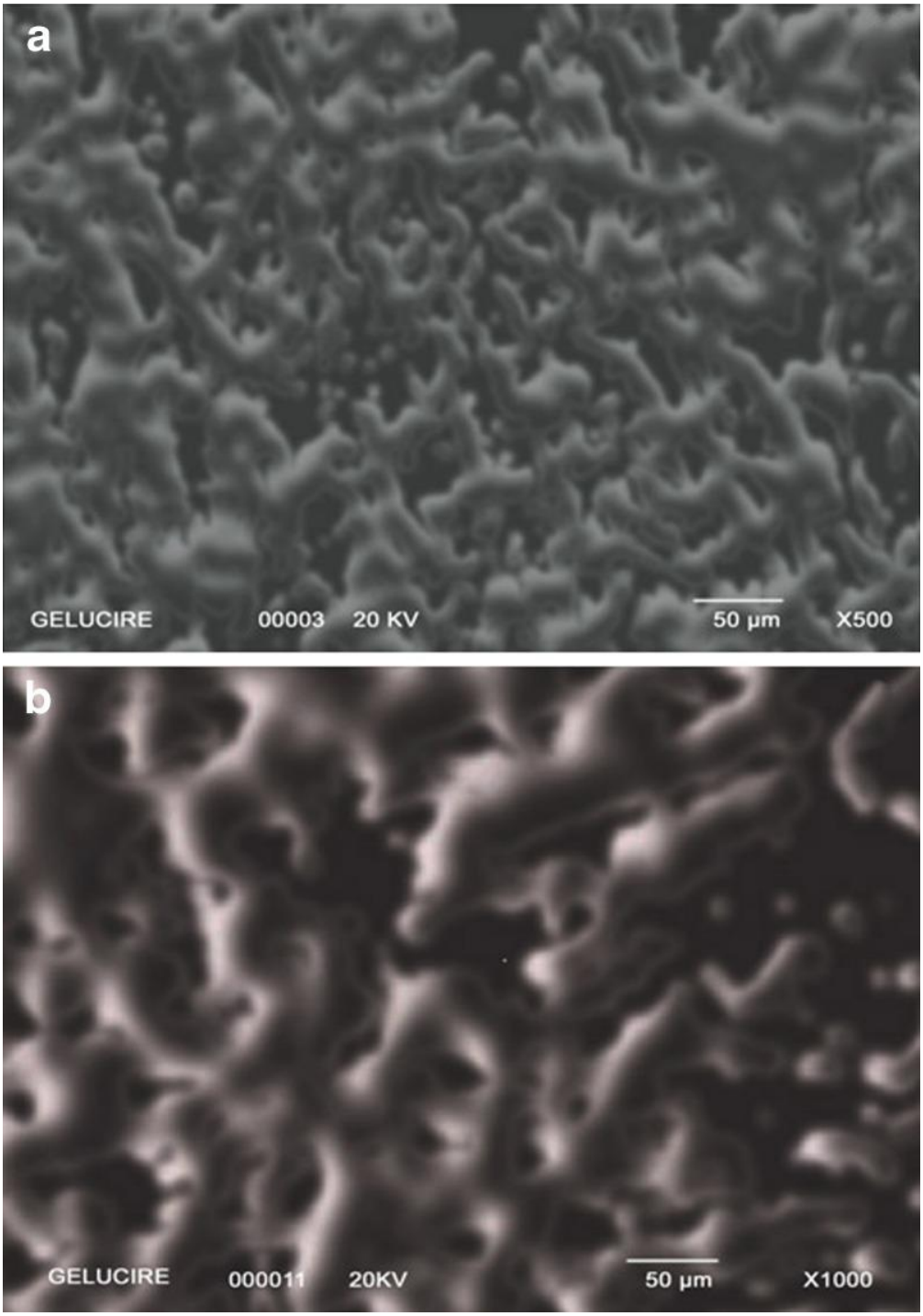
Ratio (MH/Gelucire 43/01)	Formulation code	Average particle diameter (mm)	Bulk density (g/cm^3)	Porosity (%)	Yield (%)	Drug entrapment (%)	Buoyancy (%)
1:05	MHG-05	3.85 ± 0.13	0.74 ± 0.02	51.7 ± 2.4	96.83 ± 1.32	83.07 ± 0.37	100
1:10	MHG-10	3.95 ± 0.21	0.75 ± 0.03	50.9 ± 4.5	97.66 ± 0.57	84.3 ± 0.54	100
1:15	MHG-15	3.87 ± 0.18	0.79 ± 0.02	55.0 ± 1.6	97.94 ± 1.04	86.13 ± 0.24	100

Values are mean ± standard deviation (n = 6)

***MH* metformin HCl, *MHG* floating beads of Gelucire 43/01 containing metformin HCl**

Particle Size and Surface Morphology

The average particle diameter of beads was found to be in the size range of 3.85 ± 0.13, 3.95 ± 0.21, and 3.87 ± 0.18 mm with varying drug/Gelucire 43/01 ratio from 1:5, 1:10, and 1:15, respectively (Table I). The average particle size of Gelucire 43/01 beads were not affected significantly by increasing Gelucire 43/01 ratio. The formed beads were sufficiently hard and spherical in shape. Surface morphology of developed beads was determined using scanning electron microscopy. Photomicrographs (Fig. 2a, b) show the surface was porous in nature. As can be seen in the photomicrographs, there were many small pores on the surface of beads which made them float on the SGF.



Scanning electron photomicrograph of MHG-15 at **a** ×500 and **b** ×1,000

Percent Drug Entrapment and Percent Yield

The percent drug entrapment was found to be 83.07 ± 0.37%, 84.30 ± 0.54%, and 86.13 ± 0.24% for MHG-05, MHG-10, and MHG-15, respectively (Table I). These results explain that no significant effect on percent entrapment efficiency of beads was observed with increasing lipid concentration. The surface adsorbed drug and released drug from beads during washing process were analyzed spectrophotometrically (data not shown). It was found to be 8 ± 2%. The fact that encapsulation efficiency was below 100% for all batches may also be due to the solubility of MH in IPA (11.8 ± 1.2 mg/ml) at the time of preparation before solidification of beads (25). With varying MH/Gelucire 43/01 ratio from 1:5, 1:10, and 1:15 and analyzed for the percent yield, it was found to be 96.83 ± 1.32%, 97.66 ± 0.57%, and 97.94 ± 1.04%, respectively (Table I). The results obtained show no significant changes on percent yield on increasing lipid ratio. Percent yield was found to good for all the prepared beads.

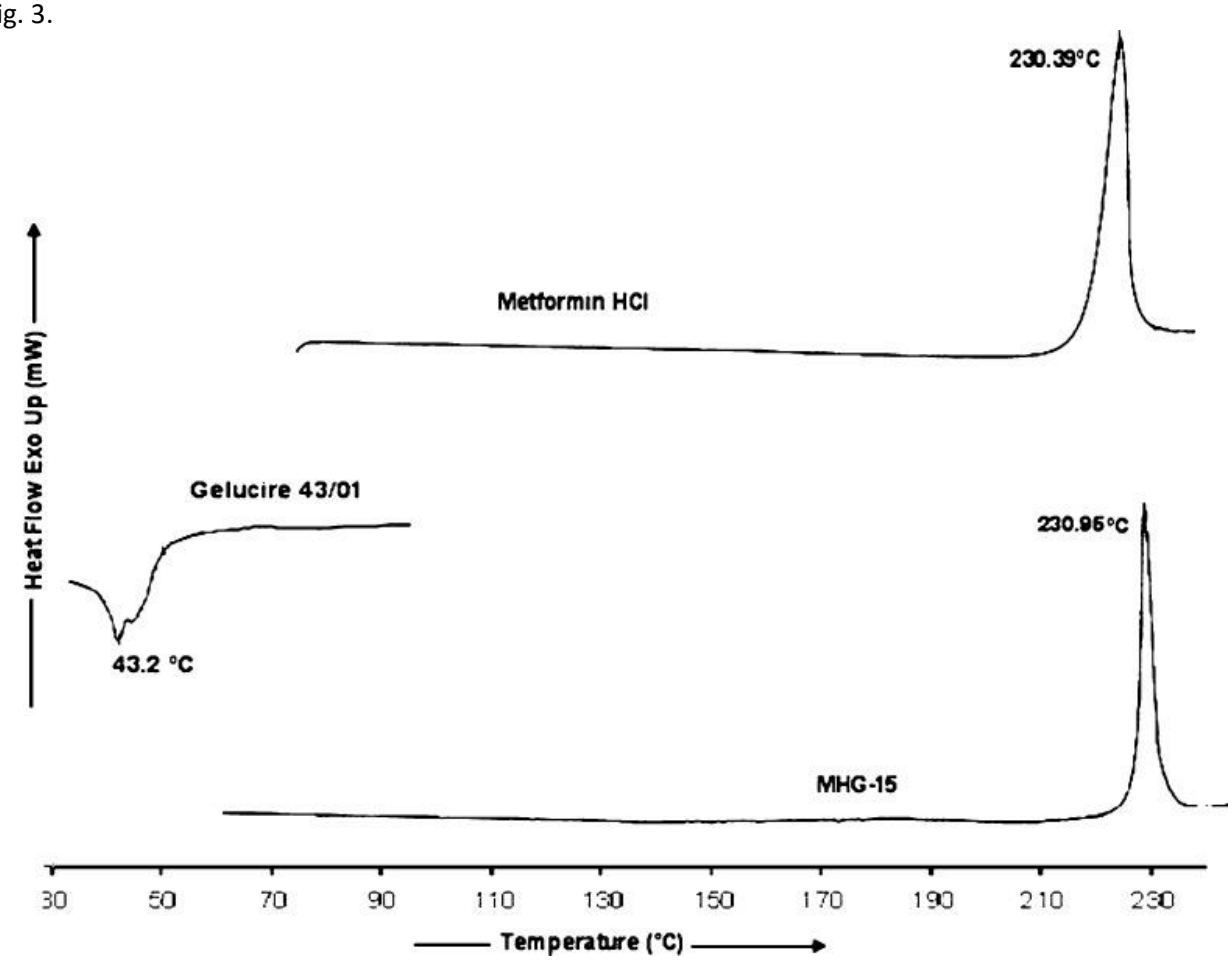
Floating Behavior

The results show that all formulations remain floating up to 8 h, reflects excellent floating ability of beads (Table I). Apart from hydrophobicity, density of Gelucire 43/01 (true density 0.0856 g/cm^3) also plays an important role in floating ability of beads. Tween 20 (0.02% *w*/*v*), added to SGF, counteracted the downward pulling at the liquid surface by lowering surface tension of SGF and increasing the surface area at the air fluid interface (6). 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.* (21) prepared floating granules of diltiazem hydrochloride-Gelucire 43/01 by melt granulation and evaluated the buoyancy behavior of granules up to 6 h, and the floating times were measured by visual observation. The surface hydrophobicity imparted to the drug particle by the hydrophobic lipid coat was responsible for floating behavior. But all low HLB excipient did not ensure floating, as similar granules prepared using Compritol and glyceryl monosterate separately did not show floating property. The floating properties of beads may be attributed to the low bulk density (0.76 ± 0.13 g/cm^3) and the porosity of the beads (52.5 ± 3.0%), implying that the beads will have the propensity to exhibit excellent buoyancy effect *in vivo*.

Differential Scanning Calorimetry

In an effort to investigate the possible physical and chemical interactions between drug and lipid, samples were analyzed: (a) pure MH, (b) fresh Gelucire 43/01, and (c) the prepared beads using modulated DSC (Fig. 3). The DSC thermogram showed a sharp endothermic peak at 230.39°C for pure MH, near to the melting point of the drug. For fresh Gelucire 43/01, thermal transition at 43.2°C can be seen, which is attributed to its melting point. In the DSC thermogram of the prepared beads, the endothermic peak was observed at 230.95°C also near to the melting point of the drug. The analysis of thermograms revealed no physical interaction between the lipid and the drug in the prepared beads.

Fig. 3.

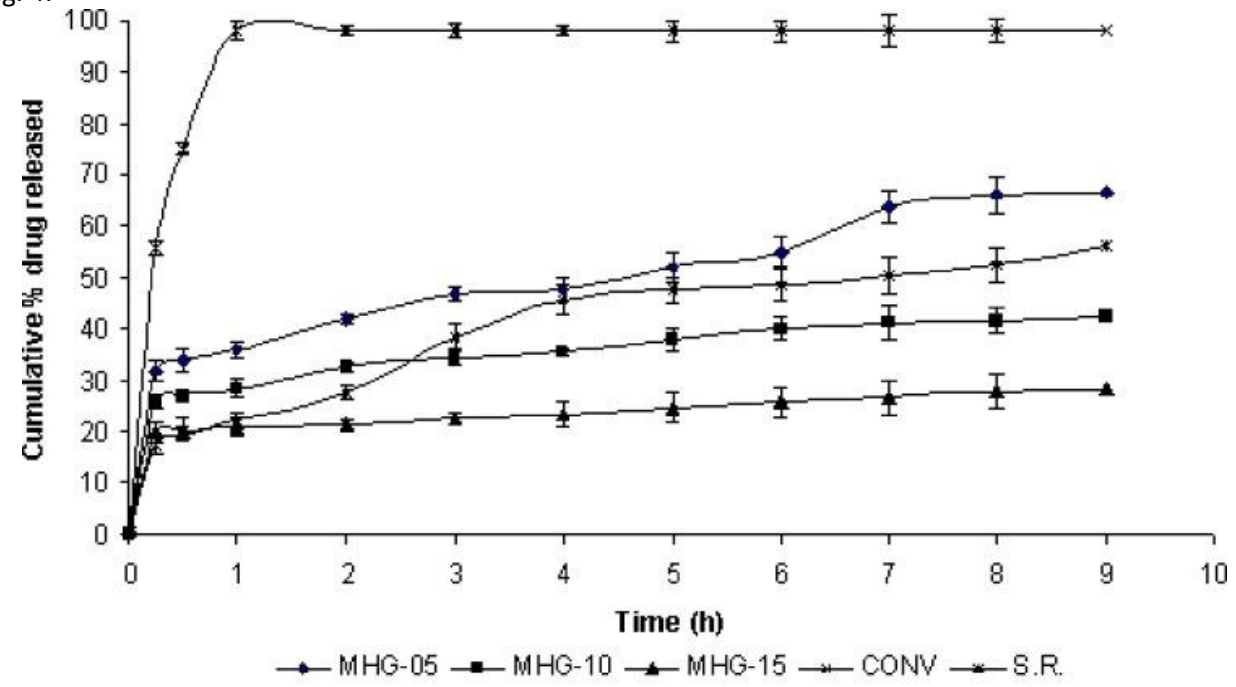


DSC thermograms of pure drug (MH), Gelucire 43/01, and optimized formulation (MHG-15)

***In Vitro* Release Study**

The *in vitro* drug release profiles of floating beads of MH were evaluated in SGF (pH 2.0). The release of MH from different prepared formulations (MHG-05, MHG-10, and MHG-15) and marketed formulations (CONV and S.R.) followed the order: CONV > MHG-05 > SR > MHG-10 > MHG-05 (Fig. 4). It was found that approximately 67%, 42%, and 28% drug released after 9 h from MHG-05, MHG-10, and MHG-15, respectively. The pattern provides an idea about the effect of concentration of Gelucire 43/01 on drug release from beads, i.e., the higher the Gelucire 43/01 content, better the controlled drug release. This could be attributed to the increase of lipid matrix density and in the diffusion path length which the drug molecules have to transverse (26,27).

Fig. 4.



In vitro drug release profile of MH from different formulation batches (based on drug/lipid ratio) and marketed formulations (CONV and S.R.) in SGF (pH 2.0). *MHG* floating beads of Gelucire 43/01 containing metformin HCl, *CONV* conventional tablet of metformin HCl, *S.R.* sustained release tablet of metformin HCl

The release was biphasic and characterized by an initial fast (31.75 ± 0.28%, 25.70 ± 0.15%, and 19.64 ± 0.17% for MHG-05, MHG-10, and MHG-15, respectively) in 15 min followed by a period for constant release. The fast effect, namely the amount of encapsulated compound released at short times, is normally related to the drug embedded into or near the beads surface. Modulation of the short-term release can be a very interesting tool in on-field applications because many controlled release systems are characterized by an exceedingly slow initial release that can result in ineffective doses. Murata *et al.* (28) prepared floating alginate gel beads for stomach-specific drug delivery and evaluated the *in vitro* release profile. The data generated shows that the 20% of metronidazole had been released 10 min after exposure of the alginate gel bead containing chitosan to the solution, and all had been released by about 90 min. The controlled release of MH could be the consequence of the preparation conditions because MH was dispersed into the molten Gelucire 43/01 as a micronized powder and the resulting beads were formed by a dispersion of MH particles through the waxy matrix. The release profiles of MH from beads made at different Gelucire 43/01 concentrations showed that the increase in the amount of Gelucire 43/01 employed yielded a slower MH release. These behaviors can be explained in terms of release mechanism of the entrapped compound from the lipid beads. 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 (26).

When the release data of marketed formulation, sustained release tablet of MH (S.R.) was compared with developed formulations, i.e., MHG-05, MHG-10, and MHG-15 by one-way ANOVA (Dunnett's multiple comparison test), the difference in *in vitro* release in SGF from MHG-05, MHG-10, and MHG-15 was found to be insignificant ($P > 0.05$), and when the release data of marketed formulation, conventional tablet of MH (CONV) was compared with developed formulations, i.e., MHG-05, MHG-10, and MHG-15 by one-way ANOVA (Dunnett's multiple comparison test), the difference in *in vitro* release in SGF from MHG-05, MHG-10, and MHG-15 were found to be very significant ($P < 0.01$). Therefore, it was concluded from *in vitro* drug release study that prepared formulation shown better controlled release behavior when compared with its conventional dosage form (CONV) and comparable release profile with marketed sustained release product (S.R.). The release pattern of all developed formulation (MHG-05, MHG-10, and MHG-15) and marketed formulation (CONV) followed Peppas–Korsmeyer model and the marketed formulation (S.R.) followed Higuchi matrix model (Table II). When plotted with Korsmeyer's equation, the formulations irrespective of drug concentration showed high linearity ($R^2 > 0.99$) with a comparatively high slope (n) value within the range of 0.100–0.357. If $n < 0.43$, a Fickian diffusion (case I), $0.43 < n < 0.85$, a non-Fickian transport, and $n > 0.85$, a case II transport (zero order) drug release mechanism dominates. These n values, however, appear to indicate a coupling of diffusion—so-called Fickian diffusion. Formulation MHG-15 was selected for further stability studies due to its better buoyancy and controlled release behavior as compared to MHG-05 and MHG-10.

Table II.

The Regression Coefficients and Rate Constants for Release of MH from Different Formulations in SGF (pH 2.0)

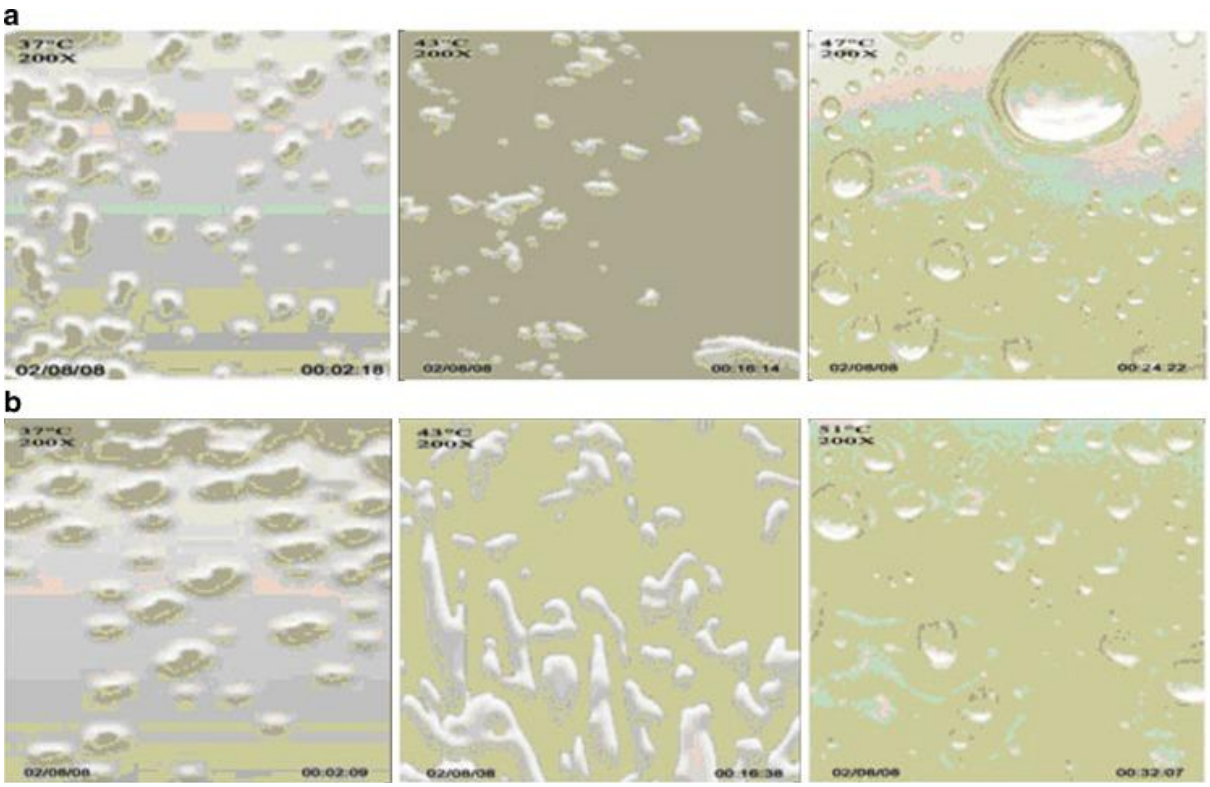
Formulation	**Zero order model**		**First order model**		**H-M model**		**P-K model**		**H-C model**	
	R	**k_1**	**R**	**k_2**	**R**	**k_3**	**R**	**k_4**	**R**	**k_5**
MHG-05	0.780	25.292	0.898	1.878	0.934	14.308	0.936	1.588	0.867	4.219
MHG-10	0.601	21.326	0.688	1.892	0.789	14.213	0.969	1.476	0.660	4.278
MHG-15	0.504	15.390	0.554	1.925	0.680	11.092	0.872	1.329	0.538	4.387
CONV	0.350	64.143	0.975	2.078	0.993	25.299	0.999	1.587	0.993	4.533
S.R.	0.857	15.798	0.916	1.928	0.970	52.249	0.963	1.402	0.898	4.387

MH metformin HCl, *MHG* floating beads of Gelucire 43/01 containing metformin HCl, *CONV* conventional tablet of metformin HCl, *S.R.* sustained release tablet of metformin HCl, *R* correlation coefficient, k_1, k_2, k_3, k_4, k_5 rate constants of zero order, first order, Higuchi matrix, Peppas-Korsmeyer and Hixon-Crowell model, respectively, *H-M* Higuchi matrix, *P-K* Peppas-Korsmeyer, *H-C* Hixon-Crowell

Effect of Aging

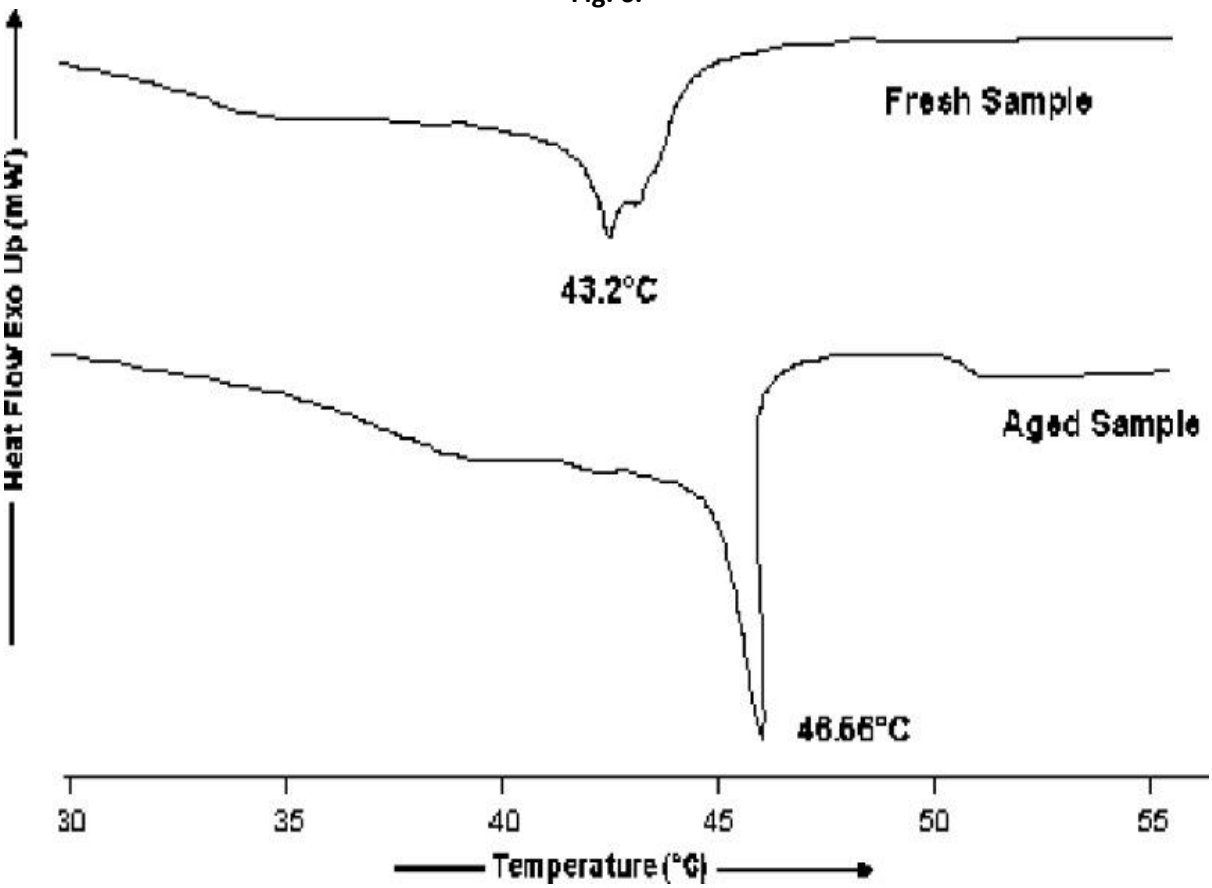
HSM photomicrographs of fresh and aged placebo samples are shown in Fig. 5. It has been observed that complete melting of the Gelucire occurs at 47°C. HSM photomicrograph showed presence of some unmelted portion even at 43°C and completely melts on 51°C in aged sample. The energy required for melting increased with aging, which might be attributed to phase transformation due to crystallization of glycerides during aging. The similar result was also reported by Chauhan *et al.* (11). Thermograms of fresh and aged samples have shown significant difference. The melting endotherm of fresh sample was at 43.2°C which might be associated with low melting glycerides present in the sample, but in case of aged sample, the melting endotherm was 46.56°C which might be due to crystallization of glycerides (Fig. 6). The similar observations were reported by Shimpi *et al.* (21). The SEM photomicrographs of fresh and aged beads are shown in Fig. 7. The SEM photomicrograph of surface of the fresh beads did not show any crystalline structure but shows rough and porous nature of surface. After aging, sample showed significant change in the surface and there was less pores and cracks on surface, possibly owing to crystallization of glycerides. Effect of aging on floating ability was studied on sample stored for 45 days, and it was found that there was no significant effect on floating ability of beads since it remains floats up to 8 h study period.

Fig. 5.



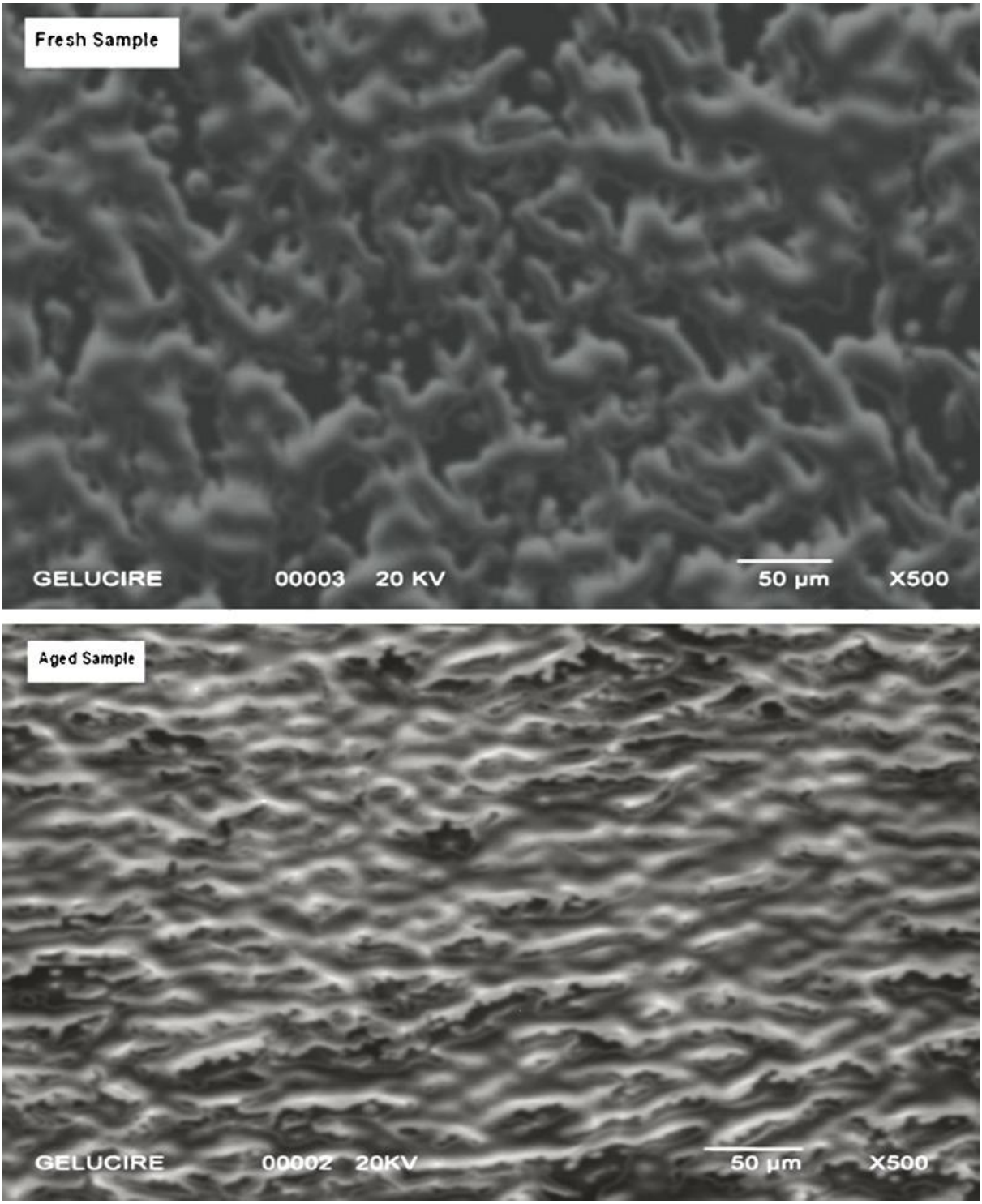
Hot-stage photomicrograph of a fresh beads and b aged beads of Gelucire 43/01 at different temperatures (×200)

Fig. 6.



DSC thermograms of fresh beads and aged beads of Gelucire 43/01

Fig. 7.



Scanning electron photomicrographs of fresh beads and aged beads of Gelucire 43/01 (×500)

CONCLUSION

It is concluded that the method of preparation of beads was found to be simple, reproducible, and provides good yield. The *in vitro* data obtained for floating beads of metformin HCl showed excellent buoyancy ability. Prepared formulation showed better controlled release behaviour when compared with its conventional dosage form and comparable release profile with marketed sustained release product of metformin HCl. Thus, Gelucire 43/01 can be considered as an effective carrier for the design of a gastroretentive multiparticulate drug delivery system of highly water-soluble antihyperglycemic drugs like metformin HCl for the effective management of type 2 diabetes mellitus.

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References

1.Zimmet P. Diabetes epidemiology as a trigger to diabetes research and care. Diabetologia. 1999;42(5):499–518. doi: 10.1007/s001250051188. [DOI] [PubMed] [Google Scholar]

2.Davis SN, Granner DK. Insulin, oral hypoglycemic agents and the pharmacology of the endocrine pancreas. In: Hardman JG, Limbrid LE, editors. Goodman & Gilman's the pharmacological basis of therapeutics. 10. USA: McGraw-Hill Medical Publishing Division; 2001. pp. 1705–1706. [Google Scholar]

3.Patel A, Ray S, Thakur RS. In vitro evaluation and optimization of controlled release floating drug delivery system of metformin hydrochloride. Daru. 2006;14(3):57–69. [Google Scholar]

4.Singh BN, Kim KM. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J Control Release. 2000;63:235–259. doi: 10.1016/S0168-3659(99)00204-7. [DOI] [PubMed] [Google Scholar]

5.Baumgartner S, Kristel J, Vreer F, Vodopivec P, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm. 2000;195:125–135. doi: 10.1016/S0378-5173(99)00378-6. [DOI] [PubMed] [Google Scholar]

6.Jain SK, Awasthi AM, Jain NK, Agrawal GP. Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: preparation and in vitro characterization. J Control Release. 2005;107:300–309. doi: 10.1016/j.jconrel.2005.06.007. [DOI] [PubMed] [Google Scholar]

7.Jain SK, Agrawal GP, Jain NK. A novel calcium silicate based microspheres of repaglinide: in vivo investigations. J Control Release. 2006;113:111–116. doi: 10.1016/j.jconrel.2006.04.005. [DOI] [PubMed] [Google Scholar]

8.Jain SK, Agrawal GP, Jain NK. Evaluation of porous carrier-based floating microspheres for gastric delivery. AAPS PharmSciTech. 2006;7(4):Article 90. doi: 10.1208/pt070490. [DOI] [PMC free article] [PubMed] [Google Scholar]

9.Jain SK, Agrawal GP, Jain NK. Porous carrier based floating granular delivery system of repaglinide. Drug Dev Ind Pharm. 2007;33:381–391. doi: 10.1080/03639040600920655. [DOI] [PubMed] [Google Scholar]

10.Jain AK, Jain SK, Yadav A, Agrawal GP. Controlled release calcium silicate based floating granular delivery system of ranitidine hydrochloride. Curr Drug Del. 2006;3(4):367–372. doi: 10.2174/15672010778559083. [DOI] [PubMed] [Google Scholar]

11.Chauhan B, Shimpi S, Mahadik KR, Paradkar A. Preparation and evaluation of floating risedronate sodium–Gelucire 43/01 formulations. Drug Dev Ind Pharm. 2005;31:851–860. doi: 10.1080/03639040500271837. [DOI] [PubMed] [Google Scholar]

12.Bowtle W. Lipid formulations for oral drug delivery. Pharm Tech Europe. 2000;12:20–30. [Google Scholar]

13.Ainaoui A, Vergnaud JM. Modeling the plasma drug level with oral controlled release forms with lipidic Gelucire. Int J Pharm. 1998;169:155–162. doi: 10.1016/S0378-5173(98)00105-7. [DOI] [Google Scholar]

14.Ainaoui A, Ouriemchi EM, Bidah D, El Amrani MK, Vergnaud JM. Process of drug release with oral dosage forms with lipidic gelucire matrix. J Polym Eng. 1997;17:245–257. [Google Scholar]

15.Sheu MT, Hsia A, Ho HO. Polyglycolized saturated glycerides as carrier and enhancer for drug penetration. Chin Pharm J. 2001;53:107–111. [Google Scholar]

16.Sutananta W, Craig DQM, Newton JM. The effects of ageing on the thermal behavior and mechanical properties of pharmaceutical glycerides. Int J Pharm. 1994;111:51–62. doi: 10.1016/0378-5173(94)90401-4. [DOI] [Google Scholar]

17.Barker SA, Yap SP, Yuen KH, McCoy CP, Murphy JR, Craig DQM. An investigation into the structure and bioavailability of α-tocopherol dispersion in Gelucire 44/14. J Control Release. 2003;91:477–488. doi: 10.1016/S0168-3659(03)00261-X. [DOI] [PubMed] [Google Scholar]

18.Dennis AB, Farr SJ, Kellaway IW, Taylor G, Davidson R. In vivo evaluation of rapid release and sustained release Gelucire capsule formulations. Int J Pharm. 1990;65:85–100. doi: 10.1016/0378-5173(90)90013-T. [DOI] [Google Scholar]

19.Patel DM, Patel NM, Patel VF, Bhatt DA. Floating granules of ranitidine hydrochloride-Gelucire 43/01: formulation optimization using factorial design. AAPS PharmSciTech. 2008;8(2):Article 30. doi: 10.1208/pt0802030. [DOI] [PMC free article] [PubMed] [Google Scholar]
20.Kumar K, Shah MH, Ketkar A, Mahadik KP, Paradkar A. Effect of drug solubility and different excipients on floating behavior and release from glyceryl mono-oleate matrices. Int J Pharm. 2004;272:151–160. doi: 10.1016/j.ijpharm.2003.12.025. [DOI] [PubMed] [Google Scholar]
21.Shimpi S, Chauhan B, Mahadik KR, Paradkar A. Preparation and evaluation of Diltiazem Hydrochloride-Gelucire 43/01 floating granules prepared by melt granulation. AAPS PharmSciTech. 2004;5(3):Article 43. doi: 10.1208/pt050343. [DOI] [PMC free article] [PubMed] [Google Scholar]
22.Sutananta W, Craig DQM, Newton JM. An evaluation of the mechanisms of drug release from glycerides bases. J Pharm Pharmacol. 1995;47:182–187. doi: 10.1111/j.2042-7158.1995.tb05775.x. [DOI] [PubMed] [Google Scholar]
23.James E, Singh G, Larry L, Vinod P. Methods to compare dissolution profiles and a rationale for wide dissolution specification for metoprolol tartrate tablets. J Pharm Sci. 1997;86:690–700. doi: 10.1021/js960473x. [DOI] [PubMed] [Google Scholar]
24.Wu PC, Tsai MJ, Huang YB, Cheng JS, Tsai YH. In vitro and in vivo evaluation of potassium chloride sustained release formulation prepared with saturated polyglycolyed glycerides matrices. Int J Pharm. 2002;243(1–2):119–124. doi: 10.1016/S0378-5173(02)00264-8. [DOI] [PubMed] [Google Scholar]
25.Quaglia F, Barbato F, Rosa GD, Granata E, Miro A, Rotonda MI. Reduction of the environmental impact of pesticides: waxy microspheres encapsulating the insecticide carbaryl. Agric Food Chem. 2001;49(10):4808–4812. doi: 10.1021/jf010418w. [DOI] [PubMed] [Google Scholar]
26.Sanker C, Mishra C. Development and in vitro evaluations of gelatin microspheres of ketorolac tromethamine for intranasal administration. Acta Pharm. 2003;53:101–110. [PubMed] [Google Scholar]
27.Jain SK, Jangde M. Lectin conjugated gastro-retentive multiparticulate delivery system of clarithromycin for the effective treatment of helicobacter pylori. Mol Pharm. 2009;6(1):295–304. doi: 10.1021/mp800193n. [DOI] [PubMed] [Google Scholar]
28.Murata Y, Sasaki N, Miyamoto E, Kawashima S. Use of floating alginate gel beads for stomach specific drug delivery. Eur J Pharm Biopharm. 2000;50:221–226. doi: 10.1016/S0939-6411(00)00110-7. [DOI] [PubMed] [Google Scholar]