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Research Article

Development of Gelucire 43/01 Beads of Metformin Hydrochloride for Floating Delivery

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Abstract. The objective of this study was to prepare and characterize beads of Gelucire 43/01 for floating delivery of metformin hydrochloride (MH). The beads were evaluated for particle size, surface morphology, percent drug entrapment, percent yield, differential scanning calorimetry (DSC), *in vitro* floating ability, and *in vitro* drug release. Aging effect on storage was evaluated using hot stage microscopy (HSM), DSC, scanning electron microscopy, and *in vitro* floating ability. The formed beads were sufficiently hard and spherical in shape. Photomicrographs show that the surface was porous in nature. The average particle diameter of beads was found to be in the size range of 3.85 to 3.95 mm, and percent entrapment was 83.07% to 86.13%. The beads demonstrated favorable *in vitro* floating ability. The analysis of DSC thermograms revealed no physical interaction between the lipid and the drug in the prepared beads. Prepared formulations showed better controlled release behavior when compared with its conventional dosage form and comparable release profile with marketed sustained release product. HSM photomicrograph showed presence of some unmelted portion even at 43°C and completely melts on 51°C in aged sample. It was found that there was no significant effect on floating ability of aged beads since it remains floats up to 8 h study period. Thus, it is concluded that beads of Gelucire 43/01 could be serve as an effective carrier for highly water-soluble antihyperglycemic drugs like MH for the controlled delivery.

KEY WORDS: aging effect; beads; floating drug delivery; Gelucire 43/01; metformin HCl.

INTRODUCTION

Diabetes is one of the major causes of death and disability in the world. The global figure of people with diabetes is set to rise from the current estimate of 150 million to 220 million in 2010 and 300 million in 2025. Most cases will be of type II diabetes, with a sedentary lifestyle and obesity (1). A plethora of antidiabetic drugs are used in clinic, of which metformin hydrochloride (MH) is a very widely accepted drug. MH, a model drug for this study, is an oral antidiabetic drug. It has elimination half-life of 6.5 h (2). In spite of its favorable clinical response and lack of significant drawbacks, chronic therapy with MH suffers from certain specific problems of which the most prominent being the high dose (1.5–2.0 g/day), low bioavailability (60%), and high incidence of gastrointestinal (GI) side effects (30% cases). Therefore, there are continued efforts to improve the pharmaceutical formulation of MH in order to achieve an optimal therapy. These efforts mainly focus on controlled/slow release of the drug including the sophisticated gastroretentive systems (3).

Gastric floating drug delivery system (GFDDS) is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments. The GFDDS is able to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug (4). Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients (5–9). Jain *et al.* (6–8) has discussed *in vitro* and *in vivo* characterization of calcium silicate-based floating microspheres of repaglinide and orlistat. They have also reported preparation and evaluation of calcium silicate-based floating granular delivery system of repaglinide and ranitidine hydrochloride (9,10).

Lipids are considered as alternative to polymer in the design of controlled drug delivery systems due to their advantages like (a) low melt viscosity, thereby obviating the need of organic solvents for solubilization, (b) the absence of toxic impurities such as residual monomers catalyst and initiators, and (c) the potential biocompatibility and biodegradability and prevention of gastric irritation by forming a coat around the gastric irritatic drug (11,12). 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 acid. Gelucires

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are available with a range of properties depending on their hydrophilic lipophilic balance (HLB; 1–18) and melting point (33–65°C) range (13–16). Gelucires containing only polyethylene glycol (PEG) esters (Gelucire 55/18) are generally used in the preparation of fast-release formulations, while Gelucires 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 (17,18). 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 (19).

Kumar *et al.* (20) reported floating glycerol monooleate single-unit lipid matrix containing high drug/excipient ratio (1:30) to achieve sustained drug release. Shimpi *et al.* (21) reported diltiazem HCl-Gelucire 43/01 floating granules prepared by melt granulation. Sutananta *et al.* (22) reported sustained release single-unit matrices using Gelucire 43/01, where only 1.7% theophylline was released over a period of 20 h. The objective of the study was to prepare and characterize beads of Gelucire 43/01 for floating delivery of MH. The obtained beads were evaluated for size analysis, surface morphology, percent drug entrapment, percent yield, *in vitro* floating ability, and *in vitro* drug release study. The effect of aging on floating beads was also observed.

MATERIALS AND METHODS

Materials

Metformin HCl was supplied as a gift sample by M/s Cadila Pharmaceuticals Ltd. (Jammu, India). Gelucire 43/01 (waxy solid, melting point 43°C, HLB=01, lot no. 6E2606-2) was obtained as gift sample from M/s Gattefosse (St Priest, Cedex, France). Isopropyl alcohol (IPA) was purchased from S. D. Fine Chemical Ltd. (Mumbai, India). All other chemicals were of analytical reagent grade and were used as received.

Preparations of Beads

Lipid (Gelucire 43/01) was melted at 50°C, and the finely powdered drug was gradually added with uniform mixing to form dispersion. The resultant dispersion was dropped via a 23-guage syringe needle (0.65 mm internal diameter) into 100 ml of prechilled (4°C) IPA at a rate of 5 ml/min. The distance from the needle tip to the IPA was 5 cm. The content was stirred at 100 rpm using magnetic stirrer for 15 min. The beads were collected after filtration through Whatman filter paper (# 41), washed three times with distilled water, and subsequently dried to their constant weight in vacuum desiccator for 24 h to ensure complete removal of solvents. Beads were evaluated every 6 h for their weight (Tarsons Products, Pvt. Ltd., Kolkata, India). The drug/lipid ratios used to prepare the different formulations were 1:5, 1:10, and 1:15. Various other vehicles such as olive oil, light liquid paraffin, heavy liquid paraffin, sesame oil, coconut oil, isopropyl myristate, and isopropyl alcohol separately and in different combination ratio were used as dispersion medium and at different temperature conditions employed to prepare beads (data not shown).

Particle Size and Surface Morphology

The average particle size of beads was determined with a micrometer (Mittotuyo micrometer, NSK Co., Japan) and calculated as the average value of size of 100 beads. The surface morphology of selected beads was visualized by scanning electron microscopy (SEM; JSM 6100, JEOL, Tokyo, Japan). The sample for SEM was prepared by sticking the beads on a double adhesive tape, which stuck to an aluminum stub. The stubs were then coated with gold to a thickness of about 300 Å using a sputter coater (6). These samples were then randomly scanned and photomicrographs were taken.

Percent Drug Entrapment and Percent Yield

The MH content in Gelucire 43/01 beads was determined by dispersing accurately 100 mg formulation in 100 ml of distilled water followed by heating at 65°C and agitation at 50 rpm with a magnetic stirrer and allowed to cool at room temperature. The lipid was solidified and the drug solution was filtered through a Whatman filter paper (# 41). The sample was analyzed for drug content by UV spectrophotometry at 233 nm using UV–visible spectrophotometer (Systronics, India) after suitable dilutions. The experiment was performed in triplicate. Percent entrapment was calculated by using following formula:

$$\%\ \text{Drug entrapment} = [\text{Calculated drug content}/\text{Theoretical drug content}] \times 100.$$

Percent yield was calculated by using following formula:

$$\%\ \text{Yield} = \left[\begin{array}{l}\text{Weight of beads collected}\\ /\text{Weight of all nonvolatile components}\\ \text{used for the preparation}\end{array}\right] \times 100.$$

Floating Behavior

Floating beads (20 in numbers) were placed in 100 ml of the simulated gastric fluid (SGF; pH 2.0) containing 0.02% wt/vol of Tween 20 at room temperature. The mixture was stirred at 100 rpm with a magnetic stirrer. After 8 h, the layer of buoyant beads was pipetted and separated by filtration. Beads in the sinking particulate layer were separated by filtration. Beads were dried in a vacuum desiccator until constant weight was achieved. Both the fractions of beads were counted and buoyancy was determined by the count the ratio of floating beads to the sum of floating and sinking beads (21). The determination was performed in triplicate.

Differential Scanning Calorimetry

The differential scanning calorimetry (DSC) analyses of pure drug, Gelucire 43/01, and the formulation prepared were carried out using a Diamond DSC (Perkin Elmer, USA) to evaluate any possible drug–lipid interaction. Samples of 2–6 mg were placed in aluminum pans (Al-Crucibles, 40 Al) and sealed. The probes were heated from 25°C to 250°C at a rate of 5°C/min under nitrogen atmosphere.

In Vitro Release Study

The release of MH from floating beads was determined in a USP paddle type (XXIII) dissolution apparatus. A weighed amount of beads equivalent to 100 mg drug was placed in the dissolution rate apparatus. Nine hundred milliliters of the SGF (pH 2.0) containing 0.02% wt/vol of Tween 20 was used as the dissolution medium. The dissolution fluid was maintained at 37±0.5°C at a rotation speed of 100 rpm. Perfect sink conditions prevailed during the drug release study. Five-milliliter samples were withdrawn at specified intervals, passed through a 0.25-μm membrane filter (Millipore, USA), and the initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal. Samples were analyzed using a UV–visible spectrophotometer (Systronics, India) at 233 nm. The release profile of marketed formulations, i.e., conventional tablet of MH, Glyciphage (Franco-India Pharmaceutical Pvt. Ltd.) coded as CONV and sustained release tablet of MH, Glyciphage SR (Franco-India Pharmaceutical Pvt. Ltd.) coded as S.R., were also determined by the same procedure as followed earlier.

Statistical Treatment of Dissolution Data

Differences in *in vitro* drug release of MH from prepared formulations and marketed formulations (CONV and S.R.) were statistically analyzed by one-way analysis of variance (ANOVA) with Dunnett's multiple comparison test. Statistically significant differences between *in vitro* MH releases from formulations were defined as $P<0.05$ and $P<0.01$ as very significant. Calculations were performed with Graphpad-Instat Software program (Graphpad Software Inc, San Diego, CA, USA).

Model Fitting of Release Study

Five kinetic models including the zero order (Eq. 1), first-order (Eq. 2), Higuchi matrix (Eq. 3), Peppas–Korsmeyer (Eq. 4), and Hixon–Crowell (Eq. 5) release equations were applied to process the *in vitro* release data to find the equation with the best fit using PCP Disso V 3.0 software (India) (23,24).

$$R = k_1 t \tag{1}$$

$$\log \mathrm{UR} = \frac{k_2 t}{2.303} \tag{2}$$

$$R = k_3 t^{0.5} \tag{3}$$

$$R = k_4 t^n \tag{4}$$

or

$$\log R = \log k_4 + n \log t$$

$$(UR)^{1/3} = k_5 t \tag{5}$$

where R and UR are the released and unreleased percentages, respectively, at time (t); k_1, k_2, k_3, k_4, and k_5 are the rate constants of zero-order, first-order, Higuchi matrix, Peppas–Korsmeyer, and Hixon–Crowell model, respectively.

Effect of Aging

Two types of samples were prepared for the physical evaluation of Gelucire 43/01:

1. Fresh samples: Placebo beads were prepared and stored for 6 h at room temperature (25°C, 60% relative humidity) in order to avoid effects due to their low melting temperature.

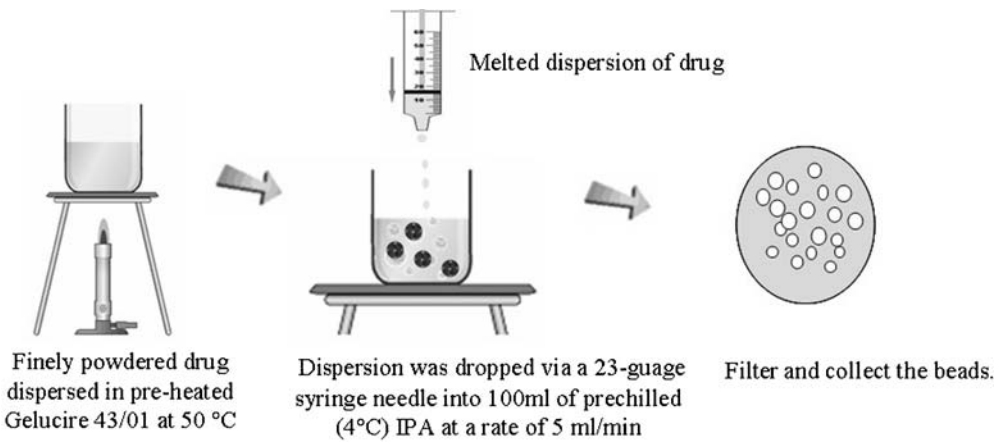

Fig. 1. Schematic presentation of method of preparation of Gelucire 43/01 beads of metformin HCl

2. Aged samples: Placebo beads were prepared and stored up to 45 days at room temperature (25°C, 60% relative humidity).

The above-mentioned samples were studied for aging effect of Gelucire 43/01 by hot stage microscopy (HSM), SEM, DSC, and *in vitro* buoyancy test (11,21).

Hot Stage Microscopy

HSM was conducted using HCS410 hot and cold stage microscope (INSTEC, Arapahoe Avenue, USA). Freshly prepared and aged placebo samples were observed under the microscope at scanning speed of 2°C/min. Changes in the samples morphology (melting crystallization) were noted as a function of temperature.

Differential Scanning Calorimetry

Thermograms of placebo fresh and aged Gelucire 43/01 beads were obtained using a Diamond DSC (Perkin Elmer, USA). Samples of 2–6 mg were placed in aluminum pans (Al-Crucibles, 40 Al) and sealed. The probes were heated from 30°C to 55°C at a rate 5°C/min under nitrogen atmosphere.

Scanning Electron Microscopy

The surface morphology of fresh and aged beads was observed by SEM to study the aging effect.

Buoyancy Behavior

Effect of aging on floating ability was studied on fresh beads and aged beads to detect any changes in buoyancy behavior of aged product.

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.

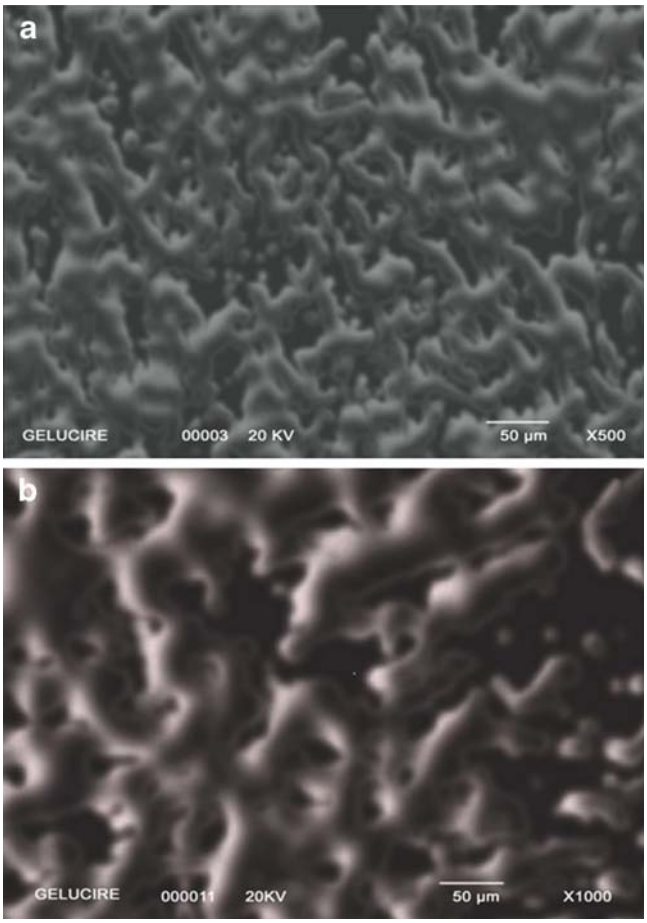

Fig. 2. Scanning electron photomicrograph of MHG-15 at **a** ×500 and **b** ×1,000

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

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

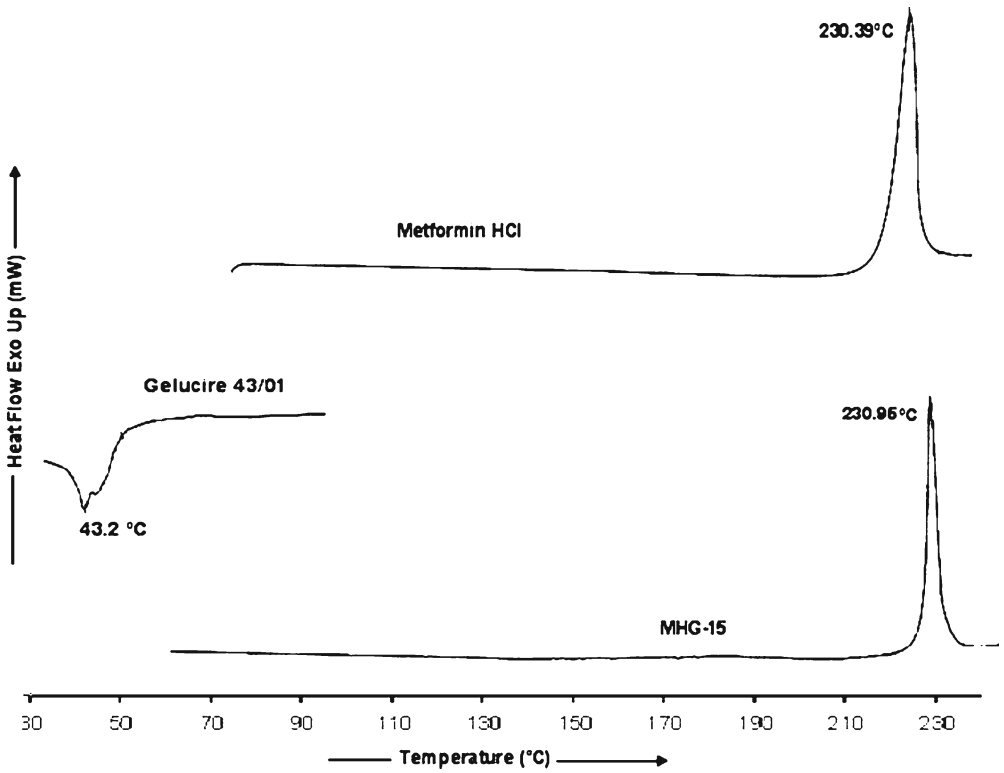

Fig. 3. DSC thermograms of pure drug (MH), Gelucire 43/01, and optimized formulation (MHG-15)

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.

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

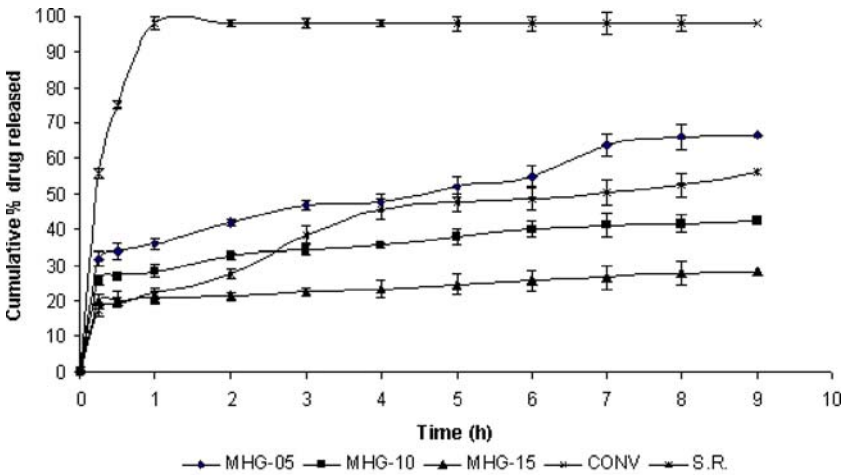

Fig. 4. *In vitro* drug release profile of MH from different formulation batches (based on drug/lipid ratio) and marketed formulations (CONV and S.R.) in SGF (pH 2.0). *MHG* floating beads of Gelucire 43/01 containing metformin HCl, *CONV* conventional tablet of metformin HCl, *S.R.* sustained release tablet of metformin HCl

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

	Zero order model		First order model		H-M model		P-K model		H-C model	
Formulation	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

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

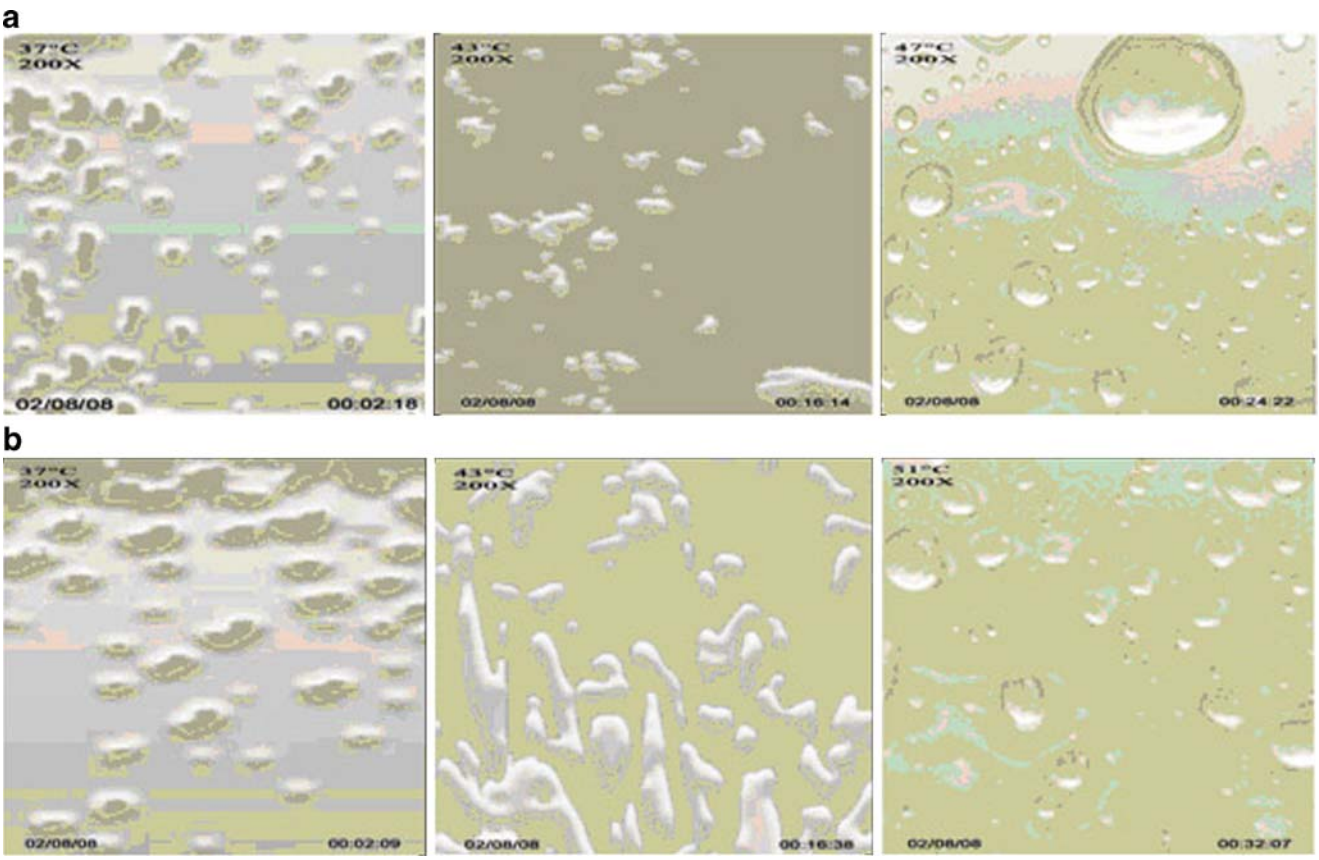

Fig. 5. Hot-stage photomicrograph of **a** fresh beads and **b** aged beads of Gelucire 43/01 at different temperatures (×200)

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.

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).

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

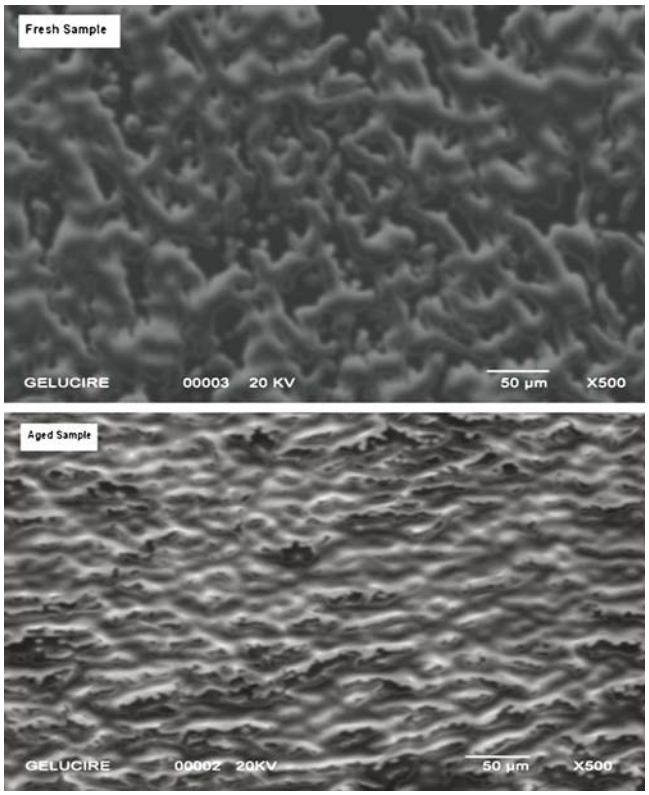

Fig. 7. Scanning electron photomicrographs of fresh beads and aged beads of Gelucire 43/01 (×500)

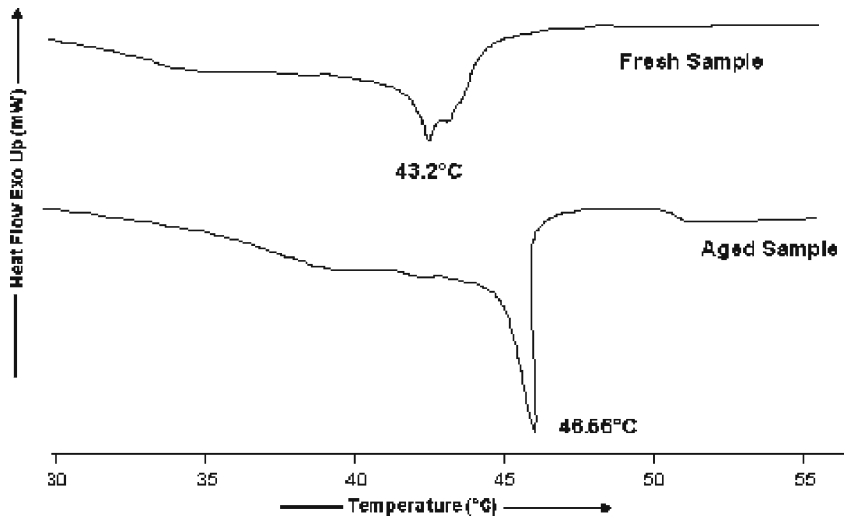

Fig. 6. DSC thermograms of fresh beads and aged beads of Gelucire 43/01

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.

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.

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 behavior 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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