eISSN: 2231-0541 CAS CODEN: PHARN8 An ELSEVIER Covered Journal

PHARMANEST

An International Journal of Advances in Pharmaceutical Sciences

Volume 4 | Issue 4 | July-August 2013 | Pages 587-601

Original Research Article

FORMULATION AND DEVELOPMENT OF FLOATING MULTIPARTICULATE DRUG DELIVERY SYSTEM OF ANTIDIABETIC DRUG BY HOT MELT TECHNIQUE

ARIJIT BARAL*, PRASHANT UPADHYAY, TANMOY DE

School of Pharmaceutical Sciences, IFTM University, Lodhipur, Rajput, Moradabad, UP, 244 001, INDIA

Author for Correspondence: arijitdj@gmail.com

Received: 02-06-2013 Revised: 06-06-2013

Accepted: 13-06-2013 Available online: 01-09-2013

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 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 favourable in vitro floating ability. After the addition of sodium alginate a change in the drug release pattern was observed, the sustained nature of the drug increased and the drug followed a zero order release kinetic. 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 behaviour when compared with its conventional dosage form and comparable release profile with marketed sustained release product. It was found that there was no significant effect on floating ability of aged beads since it remains floats up to 8 hrs 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: Gastro retentive Drug Delivery system, floating drug delivery, Gelucire 43/01, metformin HCl, Sodium Alginate.

INTRODUCTION

Multiparticulate drug delivery system is mainly related to the multiple particles such as pellets, beads, microspheres and microcapsules. Nowadays multiparticulate dosage forms or microparticles have achieved a greater popularity for a variety of reasons [1]. A lot of research efforts have been performed on oral sustained or controlled release multiparticulate drug delivery system due to its advantages over monolithic dosage forms. Multi-particulate drug delivery systems are mainly oral dosage forms consisting of a multiple numbers of small discrete units, where each unit exhibits some desired characteristics. In these multiparticulate systems, the dosage of the drug substances is divided into different types of subunits, typically consisting of thousands of spherical particles with a diameter of around 0.05-2.00mm. For this reason, the multiparticulate dosage forms are pharmaceutical Formulations in which the active substance is present as a number of small independent subunits. Now to administer the recommended dose, these subunits are filled into a sachet and encapsulated or compressed into a tablet or bead [2]. The floating multiparticulate oral sustained release drug delivery system have advantages like efficient absorption and enhanced bioavailability of the drugs due to its high surface to volume ratio, which therefore increases the intimate contact with the mucus layer and the beads thereby helping in specific targeting of drugs to the absorption site.

Characterises of floating multiparticulates drug delivery system [2-4]

- Improve stability
- Taste masking
- Increase therapeutic efficiency
- Sustain release or prolong release medication
- Increase solubility or dispersability

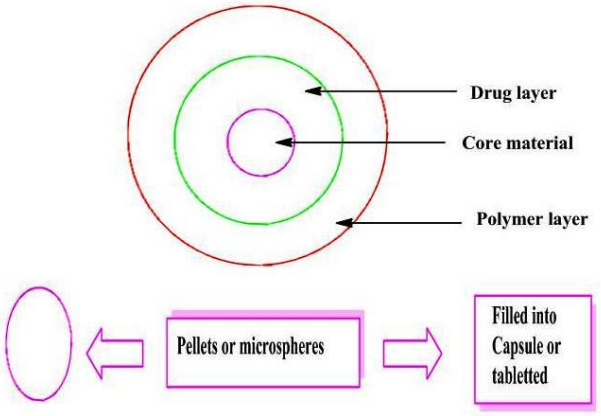


Fig.1. Structure of a drug Formulation

FLOATING DRUG DELIVERY SYSTEMS:

Floating systems [5] are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation in plasma drug concentration. After release of drug, the residual system is emptied from the stomach. These results in an increased gastric retention time (GRT) [6] and a better control of the fluctuations in plasma drug concentration.

APPLICATIONS OF FLOATING MULTIPARTICULATES [7]

Sustained Drug Delivery:

Multiparticulates of non-steroidal anti inflammatory drugs are very effective for controlled release as well as it reduces the major side effect of gastric irritation.

Solubility Enhancement:

Multiparticulates are especially effective in delivery of sparingly soluble and insoluble drugs. It is known that as the solubility of a drug decreases, the time available for drug dissolution becomes less adequate and thus the transit time becomes a significant factor affecting drug absorption. For weakly basic drugs that are poorly soluble at an alkaline pH, hollow microspheres may avoid chance for solubility to become the rate-limiting step in release by restricting such drugs to the stomach.

Pharmacokinetic advantages and future potential

As sustained release systems, floating dosage forms offer various potential advantages evident from several recent publications. Drugs that have poor bioavailability because their absorption is restricted to the upper GI tract can be delivered efficiently thereby maximizing their absorption and improving their absolute bioavailability.

MATERIAL AND METHODLOGY

Materials

Metformin was a gifted sample from Sohan Healthcare Pvt. Ltd**,** Ankleshwar, Gujrat, India. All grades of Gelucire (Gelucire39/01, Gelucire43/01, and Gelucier50/13) were purchased from St.Prist, France. Isopropyl alcohol, calcium chlorides were purchased from CDH.

Experimental analysis

Determination of Absorption Maxima: An UV absorption maxima was determined by scanning a 1%w/v solution of Metformin in 0.1 N HCl solution (pH 1.2), and Metformin in 0.1 N HCl between 200 (λ max) nm – 400 (λ max) nm.

Media for Preparation of Standard Curve:

Preparation of 0.1 M HCl Solution: Approximately 8.5 ml of Hydrochloric acid was dissolved in sufficient purified water to produce 1000 ml.

Preparation of standard Calibration curve: Metformin exhibited peak absorbance at 213 (λ max) nm in 0.1 N HCl.

Instruments used: Shimadzu (UV-1800) UV-Visible spectrophotometer

Procedure

- **Standard solution:** Accurately weighed 100 mg of Metformin was separately taken into 100 ml volumetric flasks and dissolved in small quantity of 0.1 N HCl; the volume was made up with the methanol, to get a solution containing 1mg/ml.
- **Stock solution:** From the standard solution, a stock solution was prepared by pipette out 1 ml of above standard solution in to another 100 ml volumetric flasks and volume was made with the 0.1 N HCl, to give a solution containing 100 µg/ml
- **Preparation of working standard solution:** Aliquots of 2, 4, 6, 8, and 10 ml of stock solution were pipette out into 10 ml volumetric flasks. The volume was made up to the mark with 0.1 N HCl. These dilutions give 2, 4, 6, 8 and µg/ml Concentration of metformin. The absorbance of prepared solutions of Metformin in 0.1 N HCl was measured at 213 (λ max) nm respectively using Shimadzu UV-1800 spectrophotometer against an appropriate blank (0.1 N HCl). The absorbance data for standard calibration curves of Metformin was given in **Table 3** respectively.

Methodology

Preparations of Floating Beads (Metformin + Gelucire)

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, washed three times with distilled water, and subsequently dried to their constant weight in vacuum desicator for 24 h to ensure complete removal of solvents. 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.

Table.1. Different ratios of drug and polymer in Formulation 'F' (Metformin + Gelucire)

Formulation code	Metformin (mg)	Gelucire (39/01)	Gelucire (43/01)	Gelucire (53/01)
F_1	400	400	0	0
F_2	400	0	400	0
F_3	400	0	0	400
F_4	400	200	200	0
F_5	400	0	200	200
F_6	400	200	0	200
F_7	400	133.33	133.33	133.33

Preparation of Floating Beads (Metformin + Sodium alginate + Gelucire)

Floating alginate beads were prepared by ionotropic gelation technique. Briefly, a solution of sodium alginate containing metformin was extruded with the help of 18 ml hypodermic syringe, into calcium chloride ($CaCl_2$) and glacial acetic acid (4% v/v). The beads were allowed to remain in the same solution for 10 to 20 min. to improve their mechanical strength. The formed beads were separated by filtration and washed with deionised water and dried at 35^0C in hot air oven, for 12hrs, and kept in a desicator for another 12hr before further experiments.

Table.2. Different ratios of drug and polymer in Formulation 'S' (Metformin + Sodium alginate + Gelucire)

Formulation code	Metformin (mg)	Gelucire (39/01)	Gelucire (43/01)	Sodium alginate (%)
S_1	400	400	0	4
S_2	400	0	400	4
S_3	400	200	200	4

Excipient incompatibility study especially by DSC and FTIR:

In this any drug-excipient reaction is detected by DSC. In this 1:1 ratio of drug and excipient will be prepared and finally will be evaluated by this procedure.

Fourier transform infrared (FTIR) spectra will be taken on a instrument to investigate any possible chemical reactions between the drug and the polymer. FTIR spectra of the pure drug, placebo beads, and drug-loaded beads will be obtained. All the samples will be crushed with KBr to get the pellets by applying a pressure. Analysis will be done to detect any drug excipient – interactions.

Size, surface morphology and drug uniformity

In this size of the multiparticulate will be determined by the stage micrometer microscope**.** The mean diameter of multiparticulate will be determined by sieving. The collected fractions will be weighed and the average particle size will be determined. External surface and cross sections of multiparticulate will be studied with a scanning electron microscope.

Partition Coefficient

Partition coefficient is a measure of a drug's lipophilicity and an indication of its ability to cross cell membrane in systems such as octanol/water and chloroform/water.

It is defined as "the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium"

$$P_{o/w} = (C_{oil}/C_{water})\ \text{equilibrium}$$

Drugs having values if p much greater than 1, are classified as lipophilic, whereas those with partition coefficient much less than 1, are indicative of a hydrophilic drug.

Determination of Drug Entrapment Efficiency

The drug entrapment efficiency of each Formulation was determined by extracting the crushed beads with 0.1M HCl (pH 1.2) for 45 min at 37^0C and then centrifuged at 5000 rpm. The supernatant layer was taken and suitably diluted with 0. 1M HCl, quantifying the amount of drug UV spectrophotometrically at 2133(λ max) nm for Metformin. The entrapment efficiency (EE) was calculated according to relationship:

$$EE = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Release kinetics

The results of in vitro release profiles obtained for the best Formulation was fitted into four models of data treatment as follows

1. Cumulative percent drug release virus time (zero order kinetic model).
2. Log cumulative percent drug remaining virus time (first order kinetic model)
3. Cumulative percent drug released versus square root of time (Higuchi's model)

4. Log cumulative percent drug release versus log time (Korsmeyer-peppas equation)

RESULTS

Standard calibration curve of Metformin base was prepared by 0.1N HCL at wavelength 278nm using U.V-visible Spectrophotometer. The absorbance data of Metformin was found to obey Beer's Law within the specific range as indicated by statistical analysis undertaken. The observations are presented in **Table-3** and in **Table-4**. The data were found to have nearly perfect correlation coefficient and was found to be linear in nature. The reproducibility of the method was tested by reputing the procedure. The standard curve is shown in **Fig-2.**

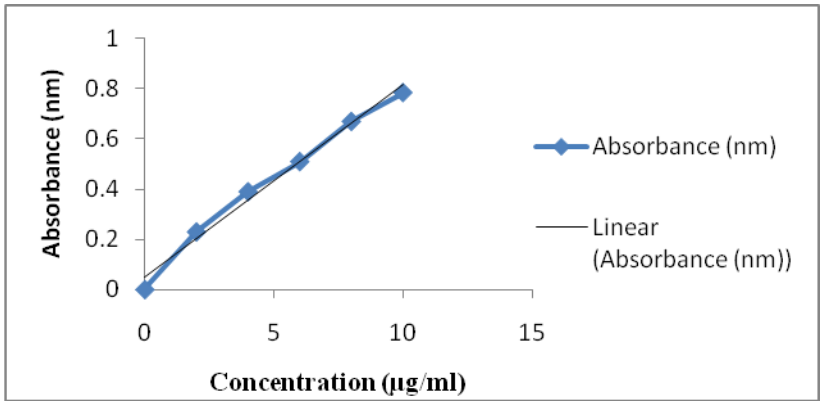


Fig.2. Standard calibration curve of Metformin base

Table.3. Calibration curve data for Metformin in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
2	0.23
4	0.39
6	0.51
8	0.67
10	0.785

Table.4.Statistical parameter related to the standard curve of Metformin

Parameters	Values
Regression coefficient	0.987
Intercept on y- axis	0.047
Equation of line	y= 0.076x + 0.047

Determination of partition coefficient: The partition coefficient of the Metformin was determined using equal volume of n-octanol as the oil phase and 0.1N HCL as the aqueous phase. The two phases were mixed in equal quantities in separating funnel. The mixture was shaking by hand shaking method until equilibrium was reached and after that separating funnel kept aside for 15 min.

The partition coefficient of Metformin HCl was found to be 0.1337, which shows that the drug is highly hydrophilic in nature that means the drug is soluble in aqueous solution of 0.1N HCl.

Drug Entrapment Efficiency (%EE) of Metformin Beads: The Metformin entrapment efficiency of each Formulation was determined by extracting the crushed beads with 0.1M HCl (pH 1.2) for 45 min at 37 ^{0}C and then centrifuged at 5000 rpm. The supernatant layer was taken and suitably diluted with 0.1M HCl, quantifying the amount of drug UV spectrophotometrically at 213 (λmax) nm. The entrapment efficiency of various PEC beads varied from 40.31%to 71.51%. The beads prepared without sodium alginate exhibits greater drug entrapment efficiency (F). Incorporation of Sodium alginate to the Gelucire Formulations resulted in significant improvement in the net drug release but the drug entrapment gradually decreased. It was also observed that, drug entrapment efficiency seems to be dependent upon gelucire concentration, however, the difference was found to be insignificant. As the concentration of drug was increased in F batch Formulations, entrapment efficiency also significantly increased ($p<0.05$, F_1 compared to F_2 and F_3; F_5 compared to F_7). This could be attributed to increase in micro viscosity of Formulations, which in turn, resulted in increased resistance to the diffusion of drug in to the acidic gelation medium during curing of the beads.

Thermal characterization: In an effort to investigate the possible physical and chemical interactions between drug and lipid, samples were analyzed: (a) pure Metformin, (b) the Formulation containing drug + gelucire **(F_2)** and the Formulation

containing drug + gelucire + sodium alginate **(S_2)** beads using modulated DSC **(Fig.3, 4, 5)**. The DSC Thermogram showed a sharp endothermic peak of at 230.95°C for pure Metformin, near to the melting point of the drug. In the DSC Thermogram of the prepared beads, the endothermic peak of F_2 Formulation was observed at 232.27°C and that of S_2 Formulation was observed at 233.23°C, thus the endothermic peaks found for the above two Formulation containing two different polymers lie near to the melting point of the drug, therefore the analysis of Thermogram revealed that there is no physical interaction between the lipid and the drug in the prepared beads.

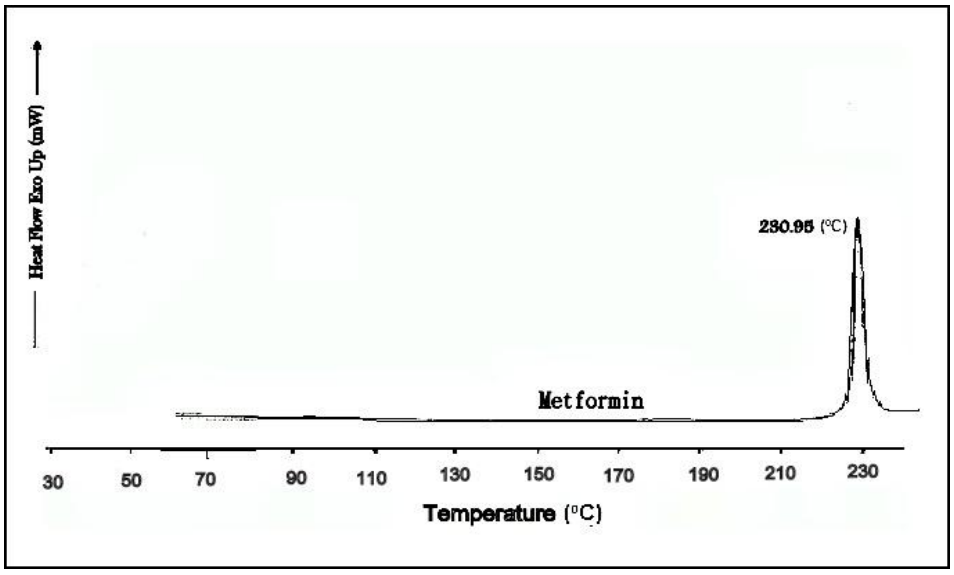


Fig.3. DSC Thermogram of Metformin

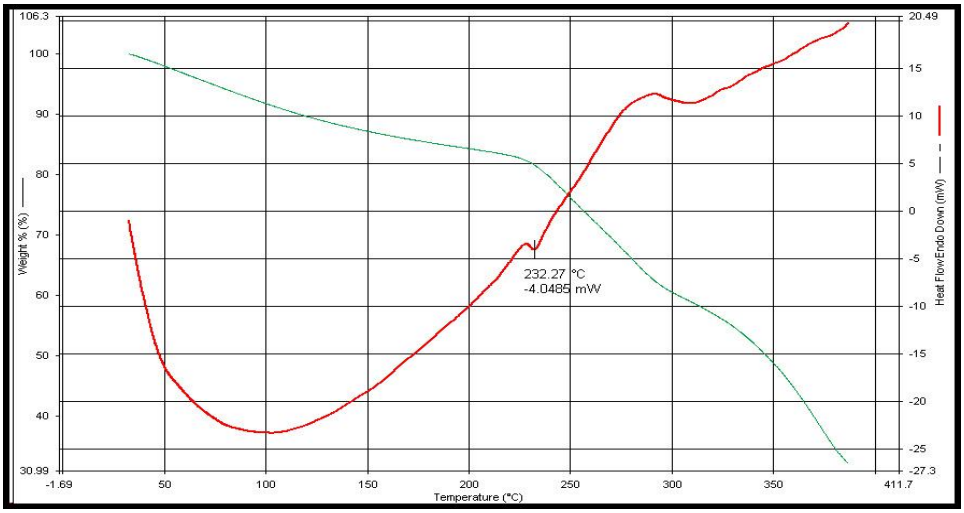


Fig.4.DSC Thermogram F_2 Formulation

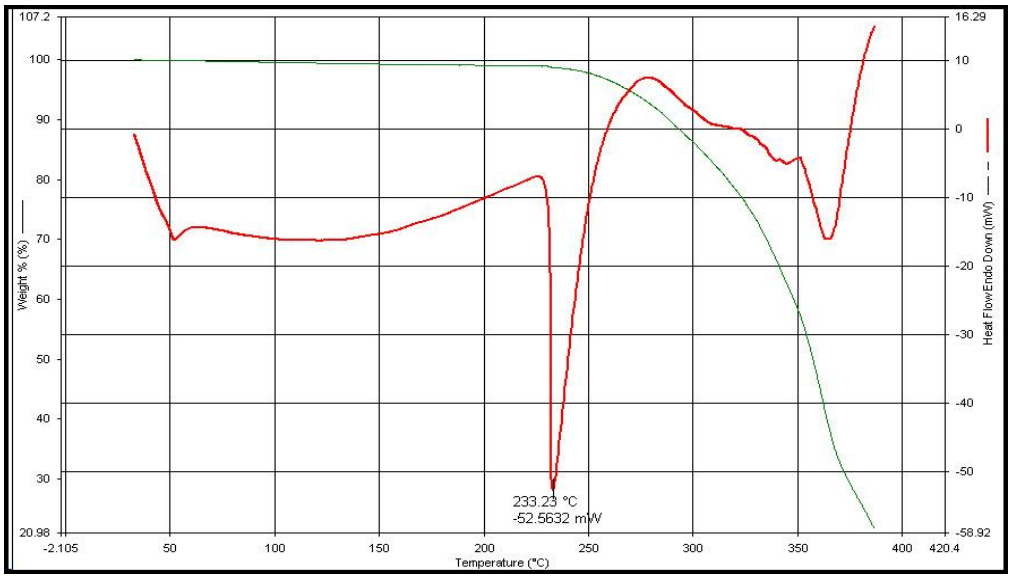
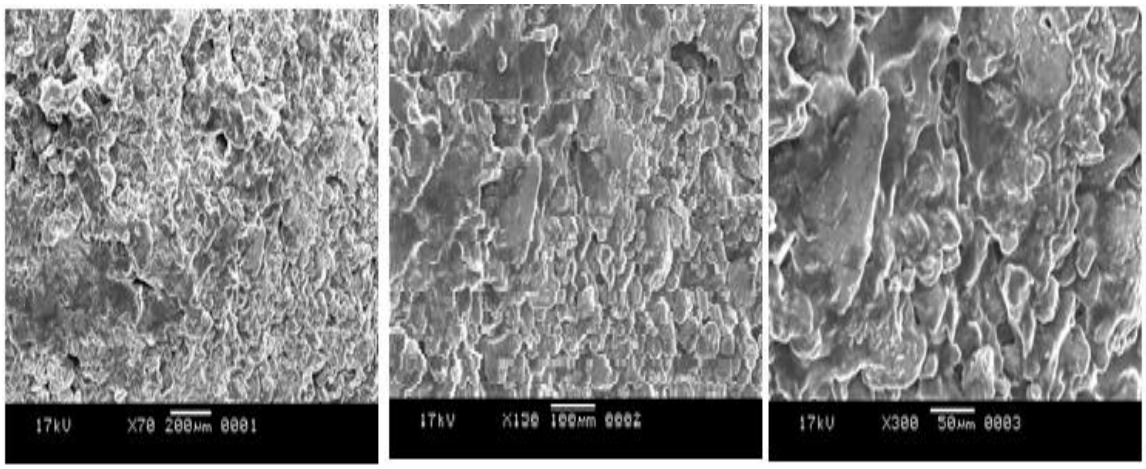


Fig.5.DSC Thermogram of S_2 Formulation

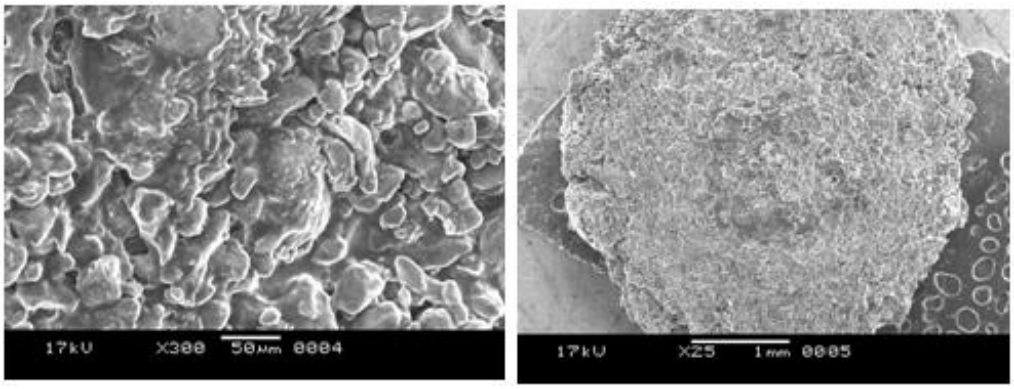
Scanning Electron Microscopic (SEM) Characterization of beads

The scanning electron micrographs (SEM) of various Metformin beads are shown in the Figures below. The SEM results revealed that all beads were spherical shape with rough outer surfaces. The transverse section of floating metformin beads of Formulations F_2 and S_2 shows numerous internal pores, attributed to the use of a gas generating agent. The transverse section of floating beads of Gelucire showed a various types of dimensions in different magnifications. This is attributed to the less dense internal structure of the Gelucire beads.

SEM of F_2 Formulation : Images shown below in Fig.6.



a b c

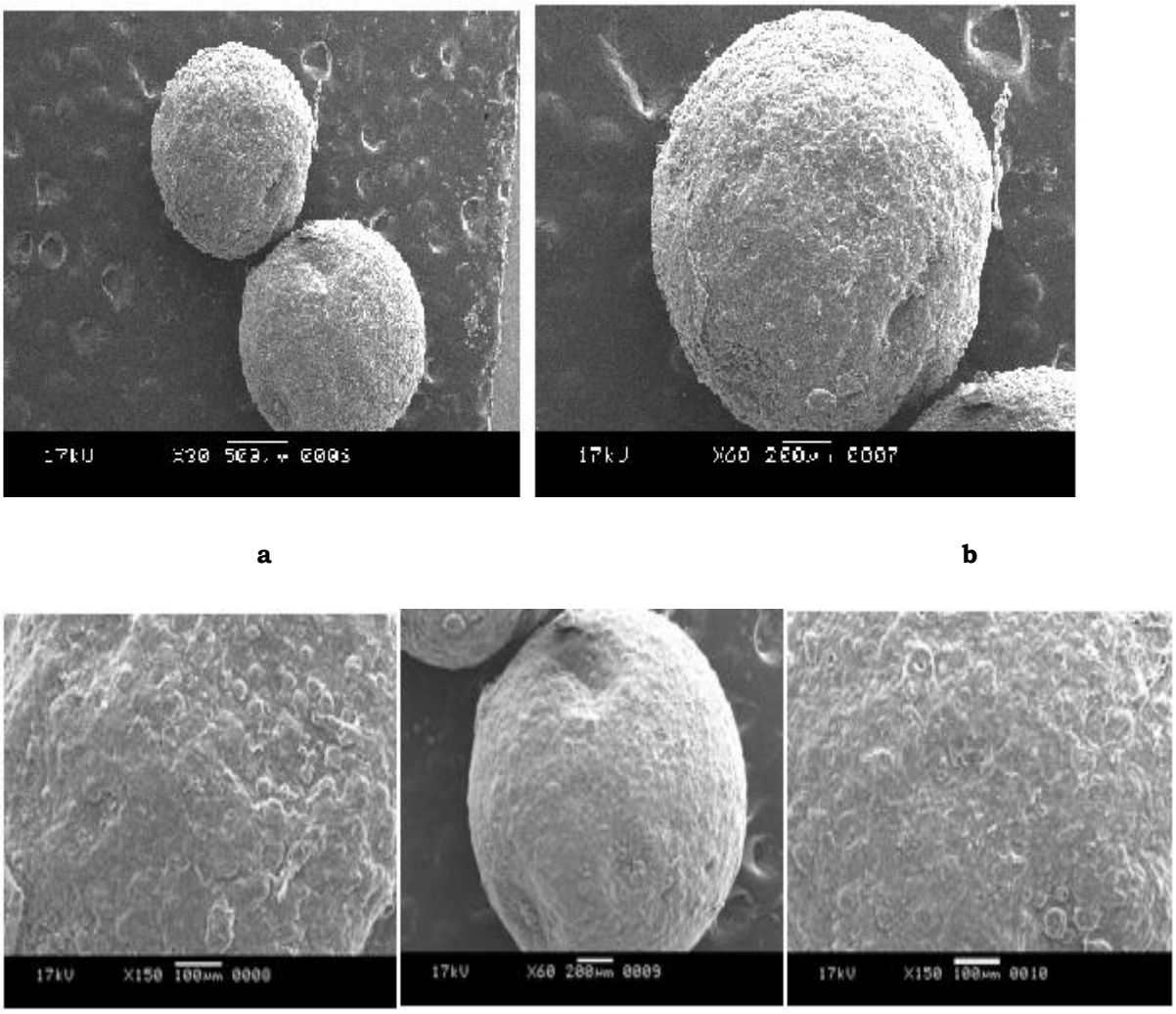


d e

a. magnification 70X and a diameter of 200µm
b. magnification 150X and a diameter of 100µm
c. magnification 300X and a diameter of 50µm
d. magnification 300x and a diameter of 50µm
e. magnification 25x and a diameter of 1mm

Fig.6. SEM of Formulation F_2 at different magnification

SEM of S_2 Formulation – Images shown below in Fig.7.



a. magnification 30X and a diameter of 500µm
b. magnification 60X and a diameter of 200µm
c. magnification 150X and a diameter of 100µm
d. magnification 60x and a diameter of 200µm
e. magnification 150x and a diameter of 100µm

Fig.7. SEM of Formulation S_2 in different magnifications

In-vitro Drug Release:

For beads containing Drug + Gelucire:

The In vitro drug release from prepared Formulations was performed in 0.1 M HCl (pH 1.2) using USP type II apparatus at 50 rpm .The drug release from beads containing Metformin and Gelucire (39/01, 43/01, and 50/13) in different ratios varied

from grade to grade i.e. in F_1 Formulation there is controlled way of drug release but with the increase in grade the drug release varied. An increase in drug release was observed for F_2 and F_4.

When combination of polymers are used (i.e. in F_4, F_5, F_6, F_7) the change in drug release found was not so significant.

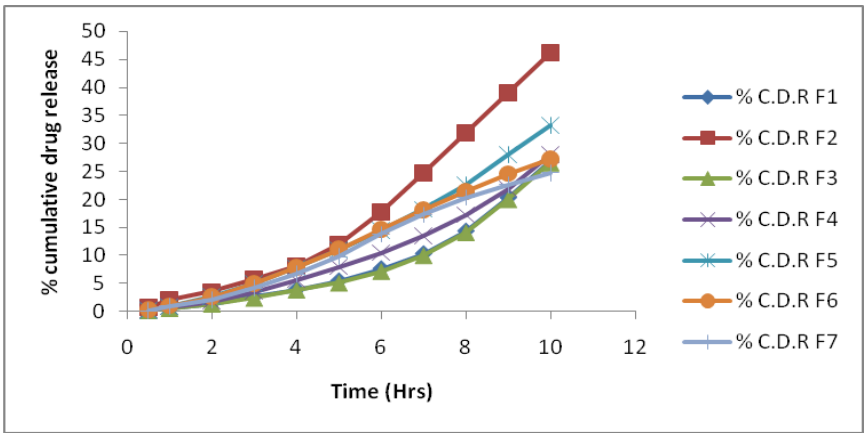


Fig.8. Zero order drug release pattern for batch type "F" (Metformin + Gelucire)

For beads containing Drug + Gelucire + Sodium alginate:

The In vitro drug release from prepared Formulations was performed in 0.1 M HCl (pH 1.2) using USP type II apparatus at 50 rpm .The drug release from Metformin, Gelucire and Sodium alginate **(S)** varied from grade to grade of gelucire. But the release of drug increased by the addition of sodium alginate to each of the Formulation, their seemed to be minute difference in each of the three Formulations. With the addition of sodium alginate the beads have shown excellent drug release behaviour for extended time period.

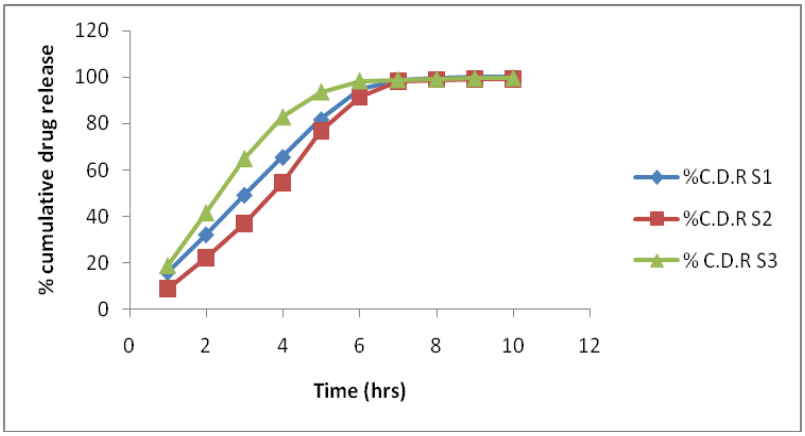


Fig.9. Zero order drug release pattern for batch type "S" (Metformin + Gelucire + Sodium alginate)

Release mechanism: The *in-vitro* release pattern of various Formulations was analyzed by fitting the dissolution data into various kinetic models. The r^2 values for Formulations F_1, F_2, F_4, F_5, F_6 and F_7 were found to be higher when fitted to zero order release kinetics, which describes the systems where the release rate is independent of the concentration of the dissolved species. The rate constant (K) values ranged from 0.0288-0.0392. The MDT value ranged from 6.4-8.66. All the Formulations seemed to have followed super case II release kinetics, only the F_3 Formulation seemed to have a lesser r value than the other.

In the next batch of Formulations S_1, S_2, and S_3 has got there r values were lesser than 1, suggesting mechanism of drug release as non-fiction transport. This model is used to analyze the release from pharmaceutical polymeric dosage forms when the release mechanism is not well known or when more than one type of release phenomena are involved.

Table.5. R values for "F" series of Formulations

Formulation	Zero order	First order	Higuchi		Korsemeyer	Rate constant (k)	MDT (hrs)
	R value				n		
F1	0.8811	0.8495	0.6993	0.9829	1.499	0.0288	8.66
F2	0.942	0.908	0.7754	0.977	1.3357	0.0608	7.59
F3	0.8213	0.8023	0.6581	0.8763	1.552	0.0158	7.12
F4	0.9433	0.9194	0.7795	0.9959	1.524	0.0313	8.011
F5	0.972	0.9335	0.8219	0.996	1.6354	0.0392	7.31
F6	0.9916	0.9855	0.8658	0.9963	1.5518	0.0345	6.80
F7	0.9864	0.9816	0.8583	0.9875	1.6238	0.0316	6.4

Table.6. R values for "S" series of Formulations

Formulation	Zero order	First order	Higuchi	Korsemeyer		MDT
	R value				n	(hrs)
F1	0.865	0.945	0.943	0.958	0.816	4.015
F2	0.885	0.940	0.910	0.956	1.099	4.367
F3	0.747	0.965	0.919	0.886	0.705	3.315

CONCLUSIONS

In the present study floating Metformin beads were formulated with use of two main polymers i.e Gelucire 39/01, 43/01 and 50/13, following lattice square design and Sodium alginate, following ionotropic gelation technique. Drug release pattern of different batches of Formulations were observed and were fitted to pharmacokinetic mathematical modelling. Metformin and Gelucire (Batch F) on simple lattice square design Formulation pattern formed seven combinations while second with ionotropic gelation technique formulated three batches of Metformin, Gelucire and Sodium alginate (Batch S). After observing all the n values of the formulated batches it was seen that batch no F seems to follow super case II release which is not preferable in sustained release Formulation but with the addition of sodium alginate the release mechanism followed zero order non-fickian which is good for a sustained release Formulation. Optimized Formulations were further characterized for DSC and SEM studies.

More over it was concluded that use of sodium alginate could add in sustained release pattern in combination with gelucire along with floating ability for more hydrophilic drug like metformin.

REFERENCES

1. Gattani YS, Floating multiparticulates drug delivery systems: An overview. International journal of pharma and bio-sciences. 2010; 1(2):1-14.
2. Masaki I, Sum W, and Yasuo M, A New Multiple-Unit Oral Floating Dosage System: Preparation and In Vitro Evaluation of Floating and Sustained-Release Characteristics, Received December 1**,** 1989, from the Pharmaceutical Research Laboratories, Research and Development Division, Eisai Company, Lid., 7-3 Tokodai 5-Chome, Tsukuba-Shi, Ibaraki, 1991; 300-26.
3. Sharma BS, Das TD, Hayak KV, Nayak MG, and Jain NK, Floating multiparticulate oral sustained release drug delivery system. Journal of Chemical and Pharmaceutical Research. 2011;3(1):536-547.
4. Deniz BB, Karim A, Andre JM, Preparation of Controlled-release Coevaporates of Dipyridamole by loading natural pellets in a fluidized Bed Coating System. Pharmaceutical research. 1995;12(9):12691272.
5. Patel A, Ray S, Thakur RS, In vitro evaluation and optimization of controlled release floating drug delivery system of metformin hydrochloride. Daru Journal of pharmaceutical Sciences. 2006; 14(3):57–69.
6. Singh BN, Kim KM, Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. Journal of Control Release. 2000; 63:235–259.
7. Whitehead L, Fell JT, Collett JH, Development of a gastro-retentive dosage form. European Journal of Pharmaceutical Sciences. 1996; 4:S182.