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Research Paper

FORMULATION DEVELOPMENT AND EVALUATION OF FLOATING DRUG DELIVERY OF GELUCIRE BEADS OF RAMIPRIL

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For better absorption and enhanced bioavailability of some drugs, prolongation of retention time of the dosage form in the stomach is essential. This problem can be solved by preparation of gastro-retentive drug delivery systems. An attempt is made to prepare lipid based floating beads of Ramipril a poor water soluble drug, using Gelucire by increasing the drug loading. Gelucires are a family of relatively inexpensive materials, comprising mixtures of mono-, di-, and triglycerides and also poly (ethylene glycol) esters of fatty acid. In the present investigation, a multiparticulate delivery system of Ramipril capable of providing controlled release was prepared using Gelucire 43/01. The release profiles of Ramipril from beads made from Gelucire 43/01 showed that Gelucire 43/01 employed yielded a sustained Ramipril release.

Key Words: - Floating tablets, Gelucires beads, bioavailability, drug release, Validation.

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the Ease of administration, patient compliance and flexibility in formulation, etc. It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in the stomach for a prolonged and predictable period of time exists today in academic and industrial research groups (Logsdon, 2000). One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time(GRT).Dosage forms with a prolonged GRT, i.e. gastro retentive dosage forms (GRDFs), will provide us with new and important therapeutic options (Chandel, 2012).

GRDFs extend significantly the period of time over which the drug may be released. Thus, they not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage forms (Siripuram, 2010).

Drugs that are required to be formulated into gastro retentive dosage forms include.

1. Drugs acting locally in the stomach.

2. Drugs that are primarily absorbed in the stomach.

3. Drugs that is poorly soluble at alkaline pH.

4. Drugs with a narrow window of absorption.

5. Drugs rapidly absorbed from the GI tract and

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

6. Drugs that degrade in the colon. (Shah, S. 2009).

Floating drug delivery systems (FDDS) can be formulated by employing various excipients of natural or synthetic origin. Several floating dosage forms that have been explored may include granules, powders, capsules, tablets, laminated films, hollow microspheres, etc. (Adebisi, A. 2011)

MATERIALS AND METHODS

Materials

Gift sample of Ramipril was received from Oniosome healthcare Pvt .Ltd. Gift sample of Gelucire 43/01 was received from Gattefosse. Tween 80 and Oleic acids received from Molychem.

Drug-excipient compatibility studies

To study the compatibility between Polymer and Ramipril solid admixtures were prepared by mixing the drug with each formulation excipient separately in the ratio of 1:1 and stored in air tight containers. The solid admixtures were characterized using Fourier transform infrared spectroscopy (FTIR) (Shimpi, S. 2004).

Preparation of standard curve of Ramipril

An accurately weighed amount of Ramipril was transferred into a 100 ml volumetric flask containing 0.1N HCl to dissolve and then the volume was made up to the mark with 0.1N HCl. From this stock solution necessary dilutions were made to give solutions with concentrations ranging from 1 - 10 µg/ml. The absorbances of the volumetric solutions were recorded at 210 nm. by using the UV-Spectrophotometer using 0.1N HCl as the blank. Then a graph was plotted by taking concentration on X-axis and absorbance on Y-axis which gives a straight line (Jain, S.K. 2009; Thakkar, V.T. 2008).

Preparation of Gelucire floating 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 5ml/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. Various other vehicles such as Olive oil, light liquid paraffin, Ethanol, isopropyl myristate, Coconut oil and isopropyl alcohol separately and in different combination ratio were used as dispersion medium (Rani 2014; Jain, SK. 2006).

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Table 1: Composition of Ramipril beads

S.No.	Formulation Code	Ramipril (mg)	Lipid	Amount of Lipid (mg)	Name of Solvent
1	F1	2.5	Gellucire 43/01	100	Isopropoanol
2	F2	2.5	Gellucire 50/13	100	Isopropoanol
3	F3	2.5	Compritol 888 ATO	100	Isopropoanol
4	F4	2.5	Stearic Acid	100	Isopropoanol
5	F5	2.5	Gellucire 43/01	100	Ethanol
6	F6	2.5	Gellucire 43/01	100	light liquid paraffin
7	F7	2.5	Gellucire 43/01	100	Isopropyl myristate,
8	F8	2.5	Gellucire 43/01	100	Olive oil
9	F9	2.5	Gellucire 43/01	100	Coconut oil
10	F10	2.5	Gellucire 43/01	200	Isopropoanol
11	F11	2.5	Gellucire 43/01	300	Isopropoanol
12	F12	2.5	Gellucire 43/01	400	Isopropoanol
13	F13	2.5	Gellucire 43/01	500	Isopropoanol
14	F14	2.5	Gellucire 43/01	600	Isopropoanol

EVALUATION OF GELUCIRE FLOATING BEAD

Percent Drug Entrapment and Percent Yield

1. The Ramipril content in Gelucire 43/01 beads was determined by dispersing accurately 50 mg formulation in 10 ml of Hcl 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 210 nm using UV–visible spectrophotometer after suitable dilutions. The experiment was performed in triplicate. Percent entrapment was calculated by using following formula (Sanjay, S 2009; Du Quing, 1996).

$$\%\text{Drug entrapment} = \frac{\text{Calculated drug content}}{\text{theoretical drug content}} \times 100$$

Percent yield was calculated by using following formula:

$$\%\ \text{yield} = \frac{\text{Weight of beads collected}}{\text{Weight of all non volatile components used for the preparation}} \times 100$$

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Floating Behavior

Floating beads (20 in numbers) were placed in 100 ml of the simulated gastric fluid (SGF; pH 2.0) 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 (Kumar, K 2004; Stockwell, A.F. 1986). In-vitro evaluation of alginate gel systems as sustained release drug delivery systems .J.Control.Release, 3: 167-175.). The determination was performed in triplicate.

The percentage of floating beads was calculated according to the following equation:

$$F\ (\%) = \frac{NF}{NT} \times 100$$

Where:

F= Floating percent

NF = Number of floating beads

NT = Total number of beads

In- Vitro Drug Release Study

The release of Ramipril from floating beads was determined in a USP paddle type (XXIII) dissolution apparatus. A weighed amount of beads equivalent to 2.5 mg drug was placed in the dissolution rate apparatus. Nine hundred milliliters of the SGF (pH 2.0). 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 at 210 nm (Soberanez,J. 2011; Shah, A. 2005; H R Chueth, 1999).

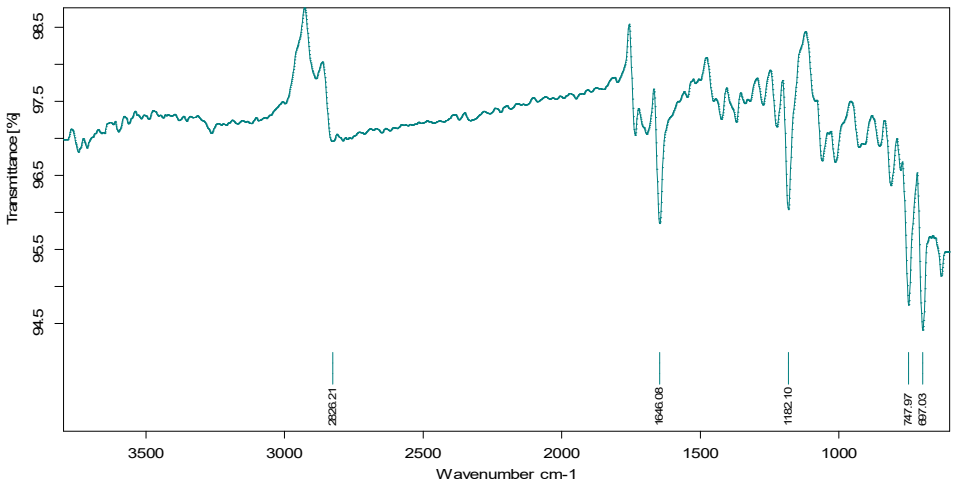

Fig 1: FTIR Spectra of Ramipril Pure Drug

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

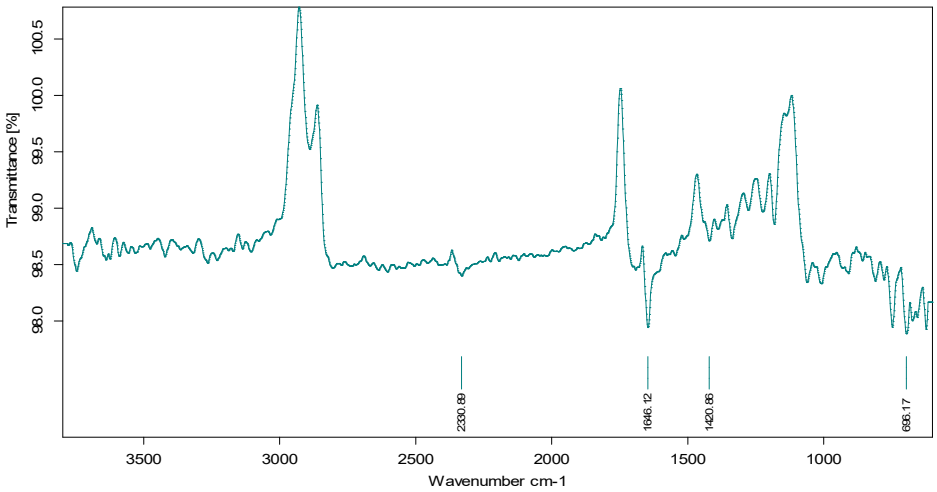

Fig. 2: FTIR Spectra of Ramipril with Gelucire 43/01

Table 2: Percentage Drug Entrapment and yield of the formulations (F1-F5)

S.No.	Formulation Code	% Drug Entrapment	% Yield
1	F1	14.19 ±0.38	82 ±1.86
2	F2	26.15 ±1.20	93 ±2.00
3	F3	70 ±1.28	93.45 ±0.48
4	F4	47 ±0.42	89.10 ±0.26
5	F5	24.10 ±0.85	68.15 ±0.10

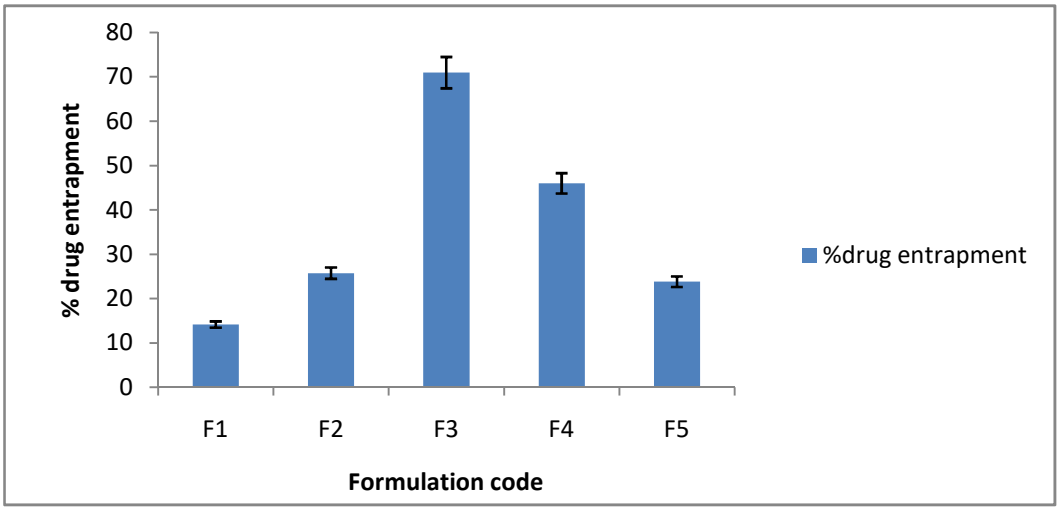

Figure 3: % drug entrapment of the formulations (F1-F5)

RESULTS AND DISCUSSION

Compatibility Study

The Infrared spectra of Ramipril solid admixtures of drug and excipients were recorded between 400 and 4000cm^{-1} on FTIR. No significant change occurred in the characteristics peaks of Ramipril in all the solid admixtures. The spectrum shown in (Fig. 1,2).

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Percentage yield and Drug Entrapment

Fourteen batches of Ramipril were evaluated for their entrapment efficiency, % floating, and %Yield for the optimization of Gelucire, Solvent and Lipid concentration. The % entrapment efficiency for the final formulations was determined using 0.1N HCl. For formulation from F1 to F5 the percent drug entrapment was

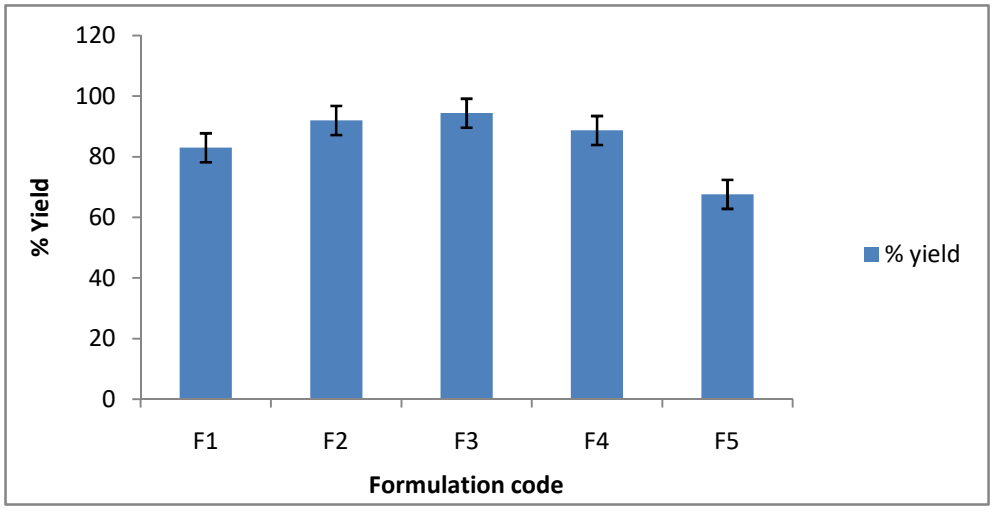

Figure 4: %Yield of the formulations (F1-F5)

Table 3: Percentage Drug Entrapment and yield of the formulations (F6-F10)

S. No.	Formulation Code	% Drug Entrapment	%Yield
1	F6	44.27±0.27	65.1±0.38
2	F7	44±0.31	62.71±0.22
3	F8	42.10±0.42	60.52±0.29
4	F9	86.03±0.15	65.2±0.22
5	F10	65.42±0.42	65.46±0.18

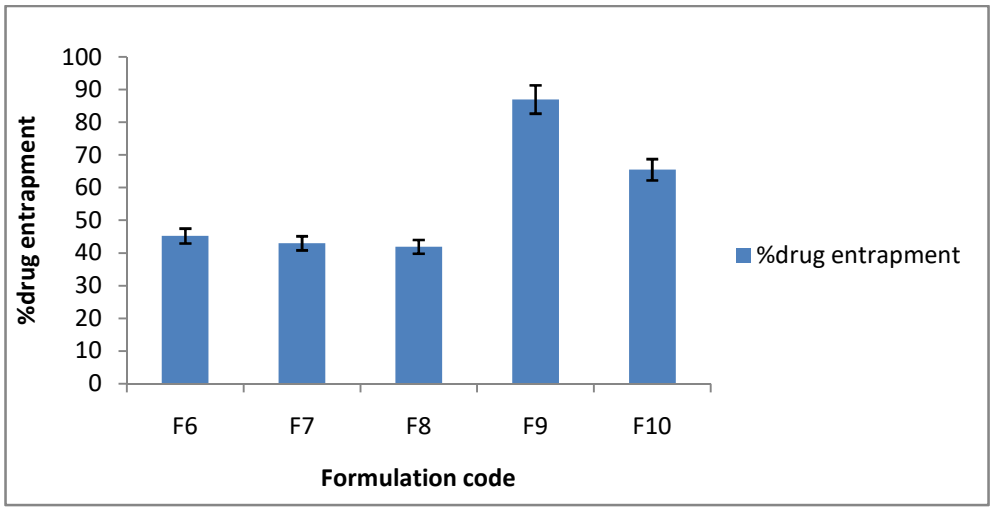

Figure 5: % drug entrapment of the formulations (F6-F10)

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

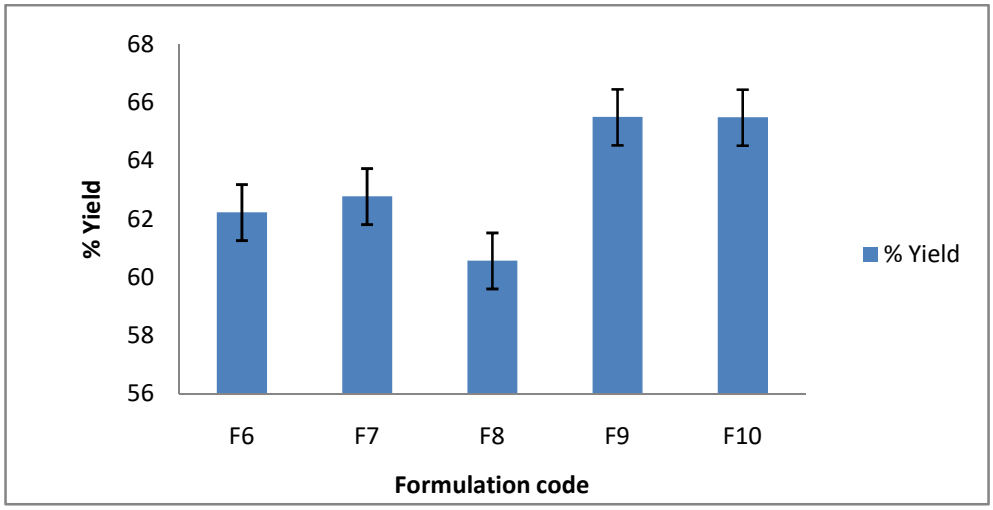

Figure 6: %Yield of the formulations (F6-F10)

Table 4: Percentage Drug Entrapment and yield of the formulations (F11-F14)

S.NO.	Formulation Code	% Drug Entrapment	%Yield
1	F11	88.05	66.52
2	F12	49	62
3	F13	35	61
4	F14	34	62

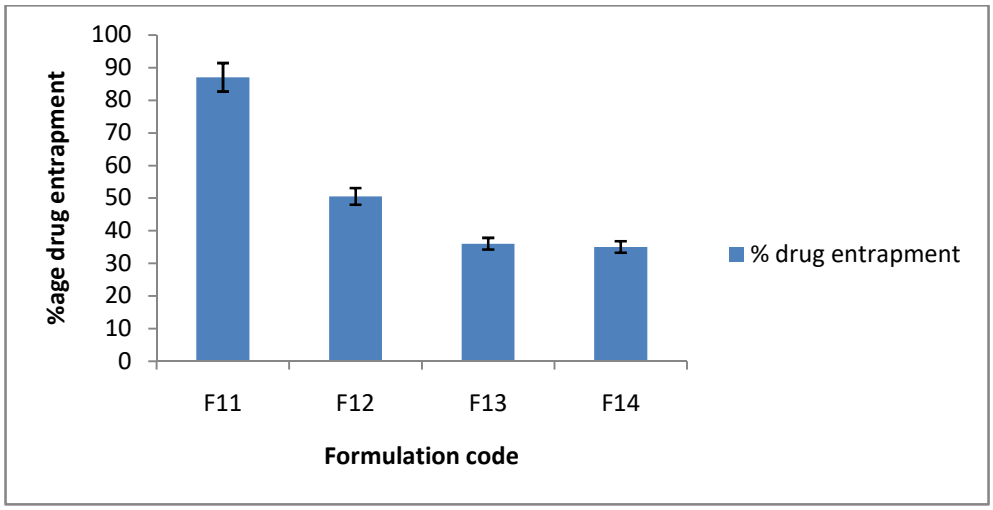

Figure 7: % drug entrapment of the formulations (F11-F14)

found to be in the range of 14.19%- 70% and the percentage yield of beads was in the range of 68.15%- 93.45%. For formulation from F6 to F10 the percent drug entrapment was found to be in the range of 42.10%- 86.03% and the % yield of beads was in the range of 60.52%- 65.46%.For formulation from F11 to F14 the percent drug entrapment was found to be in the range of 34%- 88.05% and the % yield of beads was in the range of 61%- 66.52%.

ISSN 2249-3875

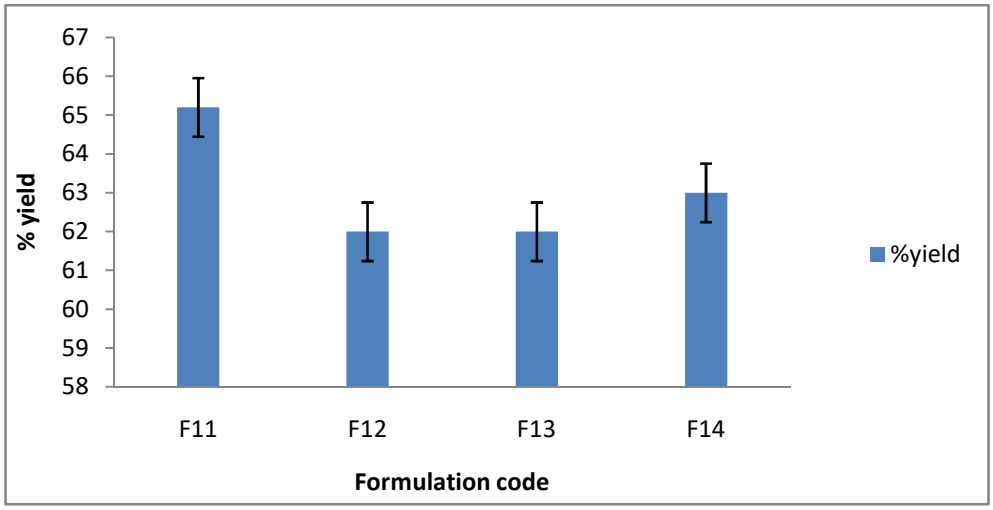

Figure 8: %Yield of the formulations (F11-F14)

In vitro Floating study

In-vitro percentage floating of selected formulations was given in a table 15.

Table 5: Percentage floating of different Formulations

S.No.	Formulation Code	Percentage Floating
1	F3	100
2	F9	100
3	F10	100
4	F11	100
5	F12	100
6	F13	100
7	F14	100

The results show that all formulations remain floating up to 8 h, reflects excellent floating ability of beads (Table 5). 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). On the basis of result of above parameters Formulation F11 was selected for further in-vitro drug release study.

In-vitro Drug release study

The in-vitro cumulative drug release of Formulation F11, Conventional tablet and pure drug was given in a table 6.

The in-vitro cumulative drug of lipid based floating bead was found to be more as compare to conventional tablet that showed the effect of lipid matrix of Gelucire in drug release property.

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. The release profiles of Ramipril from beads made from Gelucire 43/01 showed that Gelucire 43/01 employed yielded a sustained Ramipril release. 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

ISSN 2249-3875

International Journal of Pharmaceutical Erudition

Table 6: Percentage In-vitro drug release of Formulation F11, Conventional tablet and pure drug

S.NO.	Time (hr)	% drug release of F11	% drug release of Tablet	% drug release of pure drug
1	0	0±0	0±0	0±0
2	0.5	12.40±0.14	25.62±0.027	21.46±0.38
3	1	15.71±0.22	43.24±0.64	35.42±0.40
4	2	26.00±0.10	63.10±0.24	42.00±0.52
5	3	29.63±0.022	78.64±0.84	52.46±0.11
6	4	32.27±0.032	88.92±0.62	76.11±0.27
7	5	48.17±0.27	94.03±0.80	91.69±0.69
8	6	51.40±0.39	95.86±0.87	93.84±0.86
9	7	57.25±0.27	96.99±0.80	94.92±0.78
10	8	68.13±0.52	97.90±0.64	95.99±0.82
11	9	82.46±0.17	98.09±0.95	96.90±0.32

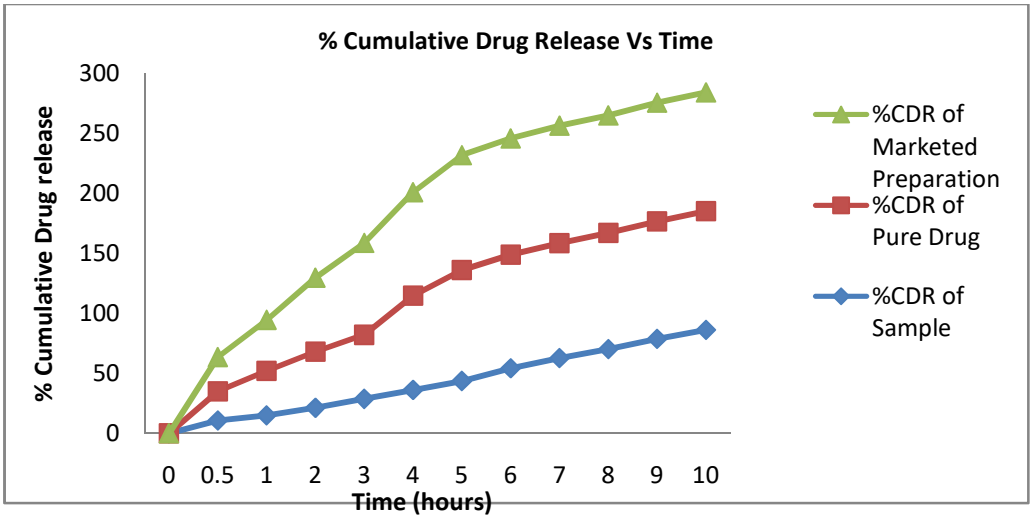

Fig 9: In-Vitro Drug release of Ramipril loaded Gelucire floating beads, conventional tablet and pure drug

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.

CONCLUSION

From the results, we conclude 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 Ramipril showed excellent buoyancy ability. Prepared formulation showed better controlled release behavior when compared with its conventional dosage form and comparable release profile with pure drug

Thus, Gelucire 43/01 can be considered as an

ISSN 2249-3875

effective carrier for the design of a gastroretentive multiparticulate drug delivery system.

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