ORIGINAL ARTICLE

# Formulation and Evaluation of Floating Capsules of Diltiazem Hydrochloride Prepared by Semisolid Matrix Filling Technology

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## Abstract

**Objective:** The objective of this research work is to prepare and evaluate the sustained release semisolid matrix capsules of diltiazem hydrochloride (diltiazem HCl) developed using different grades of Gelucire in alone and in combination, to construct the calibration curve of diltiazem HCl in 0.1 N HCl, to prepare diltiazem HCl capsule using different Gelucire grades such as Gelucire 43/01, Gelucire 50/02, and Gelucire 50/13 and performing evaluation tests for all the prepared capsules (formulations). **Materials and Methods:** Various formulation of diltiazem HCl has been developed to reduce the frequency of dosing in chronic therapy. In the present study, the suitability of different grades of glycerides based excipients like Gelucires to formulate floating capsules by the method of semisolid matrix filling capsule technology. In the present research, different grades of Gelucires such as Gelucire 43/01, Gelucire 50/02, and Gelucire 50/13 were used to develop floating capsule of diltiazem HCl formulations developed and evaluated for the *in vitro* drug release and to evaluate gastric residence time by radiographic studies. **Results:** The *in vitro* drug release studies were conducted for all the formulations, that is, F1-F15 with 0.1 N HCl for 12 h. Among them, F10 showed 96.03 ± 3.15 in a sustained manner and showed gastric residence time of about 6 h. **Conclusion:** In the present study, an attempt was made to formulate a sustained release formulation of diltiazem hydrochloride using different grades of Gelucires. The Gelucire grades having high lipophilicity could retard release rate than that of the grades with high hydrophilicity. Gelucire grades having hydrophilicity could enhance dissolution rate. The combination of both lipophilic and hydrophilic grades used for successful formulation of sustained release matrix capsules of diltiazem HCl.

**Key words:** Diltiazem hydrochloride, gastroretentive drug delivery system, Gelucire, lower pH, semisolid matrix filling

## INTRODUCTION

Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery system, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms though have some limitationssuch as (a) drugs with short half-life require frequent administration which increases the chance of missing dose, leading to poor patient compliance, (b) a typical peak valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult, (c) the unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the $C_{ss}$ value fall or rise beyond the therapeutic range, and (d) the fluctuating drug concentration levels may lead to precipitation of adverse effect, especially of a drug with a small therapeutic window, whenever overmedication occurs.[1,2] Various controlled drug

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delivery systems have been designed which can overcome these problems and release the drug to maintain its plasma concentration for longer period of time. One such drug delivery system is gastroretentive drug delivery system (GRDDS).[3] After its administration, the drug would remain in the stomach and release the drug in a controlled manner; hence, the drug could be supplied continuously to its relative absorption sites in the gastrointestinal tract. Dosage forms that can be retained in the stomach are called GRDDS.[4]

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric retention time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in high pH environment. GRDDS can also be used for local drug delivery to the stomach and proximal part of small intestine.[5]

Hypertension is one of the risk factors for stroke, myocardial infarction, heart failure, and arterial aneurysm, and is a leading cause of chronic kidney failure. High blood pressure is a chronic medical condition in which the systemic arterial blood pressure is elevated. Some of the antihypertensive drugs are nifedipine, diltiazem hydrochloride, amlodipine, enalapril, hydrochlorothiazide, losartan, etc., used to control the high blood pressure. Among many antihypertensive agents, one suitable for floating drug delivery was selected to carry out research work. To prolong the retention time of the drug in the stomach, floating capsules were prepared in this work, based on a hydrodynamically balanced controlled release delivery system.

Diltiazem hydrochloride undergoes an extensive biotransformation, mainly through cytochrome P-450 CYP3A, which results in <4% of its oral dose being excreted unchanged in urine. Bioavailability of diltiazem hydrochloride is ~30–40% due to an important first-pass metabolism. It has an elimination half-life of 3.5 h and has an absorption zone from the upper intestinal tract. Efficacy of the administered dose may get diminished due to incomplete drug release from the device above the absorption zone. Diltiazem hydrochloride requires multiple daily drug dosage to maintain adequate plasma concentrations. Therefore, it is a suitable model candidate for gastroretentive formulation.[6]

Semisolid capsule filling is a novel method to incorporate liquid solution or suspension of drug into a hard gelatin capsules using a hydrophilic carriers. In this method, as the drug is dispersed molecularly in hydrophilic carriers, it results in the enhancement of solubility and dissolution rate. Studies reported the improved rate of dissolution of nimodipine semisolid capsules using Plasdone as polymer.[5] Semisolid matrix filling into hard gelatin capsules is a new technique and is being used more often because it has several advantages such as weight and content uniformity, improvement in the dissolution of poorly water-soluble drugs, and creation of dust-free manufacturing process with minimal number of manufacturing steps.[7]

Gelucire containing only glycerides or a mixture of glycerides and polyethylene glycol esters (Gelucire 30/01 and 43/01) are used in the preparation of sustained release formulation. Due to their extreme hydrophobicity and low density, Gelucire 39/01 and 43/01 are considered as appropriate carriers for designing sustained release floating drug delivery system.[8-10]

The present work was aimed in preparing and evaluating sustained release semisolid matrix capsules of diltiazem HCl using different Gelucire grades in alone and in combination, to construct the calibration curve of diltiazem HCl in 0.1 N HCl, to perform Fourier transform infrared (FTIR) studies for the optimized formulation. To perform differential scanning calorimetry (DSC) studies for optimized formulation and to evaluate the *in viv*o residence time of optimize formulation by X-ray studies formulations of diltiazem HCl capsule were developed using different Gelucire grades such as Gelucire 43/01, Gelucire 50/02, and Gelucire 50/13, and selection of the best batch (optimized formulation) of capsules was done based on th*e in vitr*o drug release studies and from th*e in vitr*o drug release kinetics data.

## MATERIALS AND METHODS

### Materials

Diltiazem hydrochloride was gift sample from Novartis, Hyderabad, India. Gelucire 43/01, Gelucire 50/02, and Gelucire 50/13, gift sample from Gattefosse India, hard gelatin capsules, and hydrochloric acid were purchased from SD Fine Chemical, Mumbai, India.

### Drug: Excipient compatibility studies by FT-IR analysis

FT-IR spectrum of pure drug and physical mixture of drug with polymer was recorded in the range of 4000–400 $cm^{-1}$. FT-IR study revealed that pure diltiazem HCl has the stretching frequency of the amide group at 1676 $cm^{-1}$, ester group at 1741 $cm^{-1}$, C-O of acid at 1215 $cm^{-1}$, C-N aliphatic at 1025 $cm^{-1}$, and C = C aromatic at 1606 $cm^{-1}$ gave peaks at respective wave numbers [Tables 2, Figures 2 and 3].

### Identification of diltiazem HCl melting

Infrared absorption spectrum: The infrared absorption spectrum of diltiazem was recorded with a UV spectrophotometer over the wave number 4000–400 $cm^{-1}$.

### Differential Scanning Calorimetry (DSC)

Thermograms of granules were obtained using a Universal V4. 5A TA Instrument. Indium or zinc standards were used to calibrate the DSC temperature and enthalpy scale.

The sample of granules was hermetically sealed in an aluminum pan and heated at a constant rate of 10°C/min, over a temperature range of 0°C–300°C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50 ml/min [Figure 4].

### Preparation of diltiazem hydrochloride semisolid matrix capsules

All semisolid matrix capsules, each containing 90 mg of diltiazem hydrochloride, were prepared. Weighed amount of lipid carrier was taken in beaker and heated to 10°C above the melting point of carrier at constant temperature on a water bath. To this molten base, the required quantity of drug was added with continuous stirring for some time until the drug was uniformly distributed in the molten carrier. The molten mixtures were then filled in the hard gelatin capsules No. 2 with a dropper, to a weight equivalent to 90 mg diltiazem hydrochloride and allowed to solidify at room temperature for 24 h before conducting evaluation tests.[11,12] In the formulations prepared the release retardants used are different grades of Gelucires, Gelucire 44/01, Gelucire 50/02, and Gelucire 50/13 were used. Drug polymer ratios 1:1, 1:1.5, and 1:2 were used to study their effect on release of drug form the capsules prepared [Table 1].

### Construction of standard graph of diltiazem hydrochloride in 0.1 N HCl

About 100 mg of diltiazem hydrochloride was weighed accurately and dissolved in 0.1 N HCl and make up the volume to 100 ml with 0.1 N HCL in 100 mL volumetric flask. From this, transfer 10 ml from stock solution into 100 mL volumetric flask and make up the volume to 100 ml with 0.1 N HCL. From this, 0.2, 0.4, 0.6, 0.8, 1, 1.2, 1.4, and 1.6 ml were taken in 10 ml volumetric flask made up the volume by in 0.1 N HCl to prepare 2, 4, 6, 8, 10, 12, 14, and 16 µg/ml, respectively. The absorbance was measured at 237 nm using the UV spectrophotometer. A plot of concentrations of drug versus absorbance was plotted [Figure 1].

### Determination of weight variation test and assay

#### *Weight variation test*

Weigh an intact capsule. Open the capsule without losing any part of the shell and remove the contents as completely as possible. Weigh the shell. The weight of the contents is the difference between the weighing. Repeat the procedure with a further 19 capsules.[13-15] Determine the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation shown in Table 3.

#### *Assay*

Accurately weighed SSM capsule contents equivalent to 90 mg drug were taken in a beaker having 100 ml of, 0.1 N hydrochloric acid heated to 60°C–70°C and allowed to cool to room temperature. The lipid was solidified and the drug solution was filtered through Whatman filter paper.[16] The sample was analyzed for drug content by UV spectrophotometer at 237 nm after suitable dilutions. Determinations were performed in triplicate. Percentage yield of each formulation was calculated [Table 3].

### *In vitro* dissolution studies

The release of diltiazem from the SSM capsule was studied up to 12 h in 900 mL of 0.1 N HCl as dissolution medium using a

**Table 1:** Formulations of sustained release semisolid matrix capsules

| Formulation code | Drug: carrier ratio | Drug (mg) | Gelucire 43/01 (mg) | Gelucire 50/02 (mg) | Gelucire 50/13 (mg) |
|---|---|---|---|---|---|
| F1 | 1:1 | 90 | 90 | - | - |
| F2 | 1:1.5 | 90 | 135 | - | - |
| F3 | 1:2 | 90 | 180 | - | - |
| F4 | 1:1 | 90 | - | 90 | - |
| F5 | 1:1.5 | 90 | - | 135 | - |
| F6 | 1:2 | 90 | - | 180 | |
| F7 | 1:1 | 90 | - | - | 90 |
| F8 | 1:1.5 | 90 | - | - | 135 |
| F9 | 1:2 | 90 | - | - | 180 |
| F10 | 1:1:0.25 | 90 | 90 | - | 22.5 |
| F11 | 1:1:0.5 | 90 | 90 | - | 45 |
| F12 | 1:1:0.75 | 90 | 90 | - | 67.5 |
| F13 | 1:1:0.25 | 90 | - | 90 | 22.5 |
| F14 | 1:1:0.5 | 90 | - | 90 | 45 |
| F15 | 1:1:0.75 | 90 | - | 90 | 67.5 |

USP dissolution basket assembly at 100 rpm and 37 ± 0.5°C. An aliquot (5 mL) was withdrawn at specific time intervals and drug content was determined by UV-visible spectrophotometer at 237 nm.[17] An equal volume of fresh dissolution medium was replaced to maintain the dissolution volume. Dissolution studies were performed 3 times for a period of 12 h and the mean value was taken. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

## RESULTS AND DISCUSSION

### Standard graph of diltiazem hydrochloride

Standard graph of diltiazem hydrochloride was constructed using 0.1 N HCl and 6.8 pH phosphate buffer. Various concentrations of 2–16 µg/ml were prepared. The absorbance of prepared concentrations was measured at 237 nm by adjusting to zero with blank sample. A graph was plotted by taking concentration on x-axis and absorbance on y-axis and the best fit line was drawn, and regression value and equation were calculated.

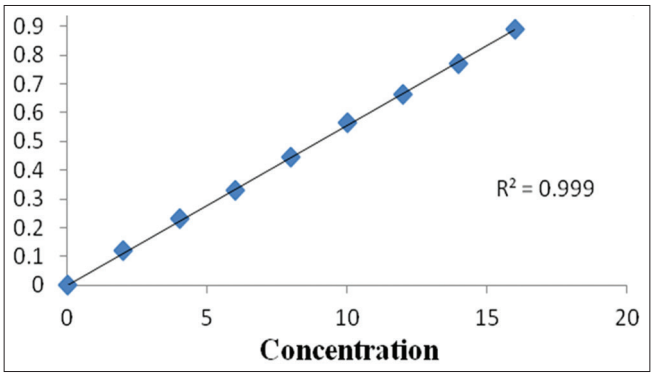


**Figure 1:** Standard graph of diltiazem hydrochloride in 0.1 N HCl

### Drug-excipients compatibility studies by FT-IR analysis

The stretching frequency obtained in the spectrum of formulation (F10) correlates with the stretching frequency of drug spectrum. This indicates that the drug was compatible with the formulation components [Table 2 and Figures 2 and 3].

**Table 2:** Values of FT-IR spectra of different functional groups

| IR spectra | Stretching frequency of functional groups (wavelength cm$^{-1}$) | | | |
|---|---|---|---|---|
| | C=O Ester | C-O Acid | C-N Aliphatic | C=C Aromatic |
| Diltiazem HCl | 1741 | 1215 | 1025 | 1606 |
| F10 | 1740 | 1172 | 1025 | 1607 |

FT-IR: Fourier transform infrared

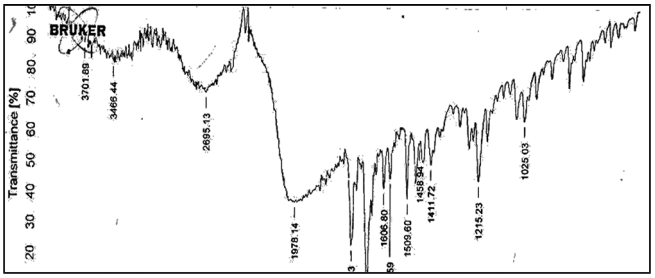


**Figure 2:** Fourier transform infrared analysis of pure drug (diltiazem hydrochloride)

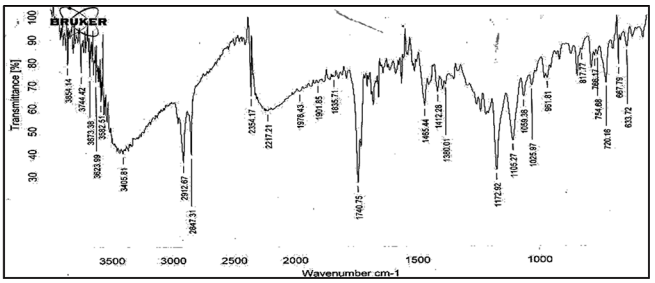


**Figure 3:** Fourier transform infrared analysis of optimized formulation (F10)

### DSC

In formulation F10, endothermic peak at 215.17°C was observed near the melting point of drug along with polymers endothermic peak. The analysis of thermograms revealed no physical interaction between the lipid and the drug in the formulation F10 [Figures 4 and 5].

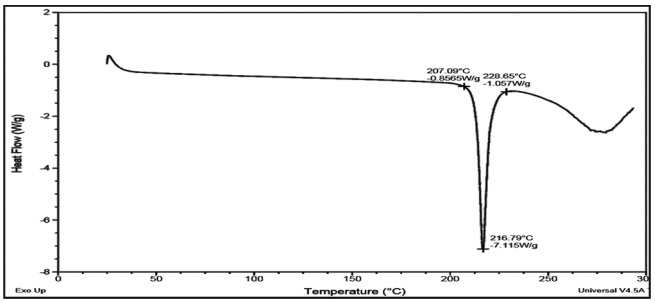


**Figure 4:** Differential scanning calorimetry thermograms of pure drug (diltiazem hydrochloride)

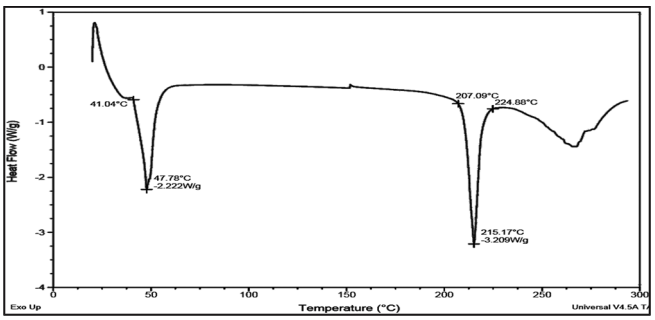


**Figure 5:** Differential scanning calorimetry thermograms of formulation F10

## Weight variation and assay studies

### *Weight variation*

The results of assay and weight variation of the capsules are given in Table 3. All the capsules of different batches compiled with official requirements 10% of weight variation pass the limits [Table 3].

### *Assay*

All the formulations satisfied the content of the drug as they contained 90–110% of diltiazem hydrochloride, a good uniformity in drug was observed. Thus, all parameters were found to be practically with in control [Table 3].

**Table 3:** Weight variation and assay of diltiazem hydrochloride capsules

| Formulations code | [a]Assay (% drug content) | [b]Weight variation |
|---|---|---|
| F1 | 96.65±1.71 | 177.66±2.51 |
| F2 | 97.14±1.99 | 225.53±1.50 |
| F3 | 98.27±1.05 | 268.83±1.87 |
| F4 | 95.66±0.98 | 179.73±1.75 |
| F5 | 97.21±1.77 | 225.33±1.26 |
| F6 | 96.51±1.70 | 269.80±1.08 |
| F7 | 97.65±0.78 | 180.66±2.28 |
| F8 | 97.26±1.28 | 224.96±1.45 |
| F9 | 96.46±1.91 | 270.46±1.96 |
| F10 | 97.32±1.81 | 202.93±2.10 |
| F11 | 98.08±0.94 | 225.66±2.30 |
| F12 | 100.90±2.7 | 247.75±1.74 |
| F13 | 98.16±1.04 | 202.03±1.51 |
| F14 | 100.60±1.52 | 225.50±1.35 |
| F15 | 98.50±1.32 | 247.39±1.54 |

*All values are mean±SD, [a]*n*=3, [b]*n*=20

## *In vitro* dissolution studies

*In vitro* dissolution study was carried out in 0.1 N HCl and using USP type I dissolution apparatus, dissolution was carried out up to 12 h by withdrawing samples every 1 h up to 12 h (all dissolution values are mean ± SD, $n = 6$).

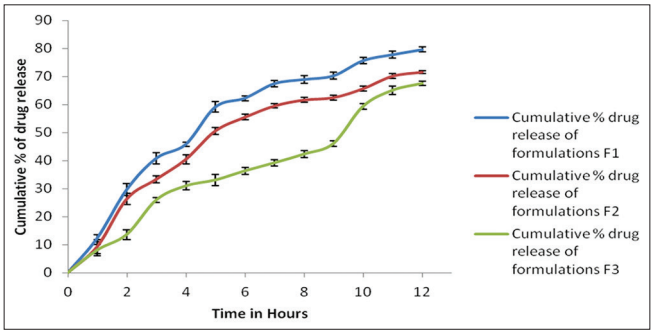


**Figure 6:** Graphical representation of *in vitro* drug release from formulations F1, F2, and F3

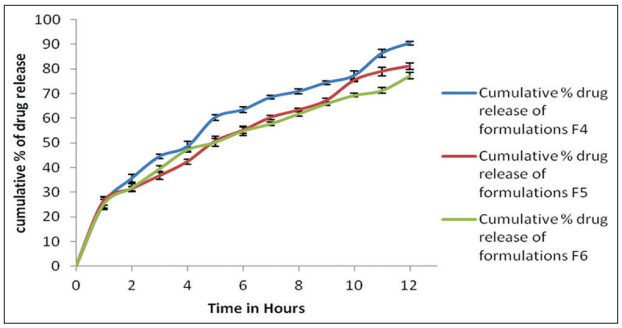


**Figure 7:** Graphical representation of *in vitro* drug release from formulations F4, F5, and F6

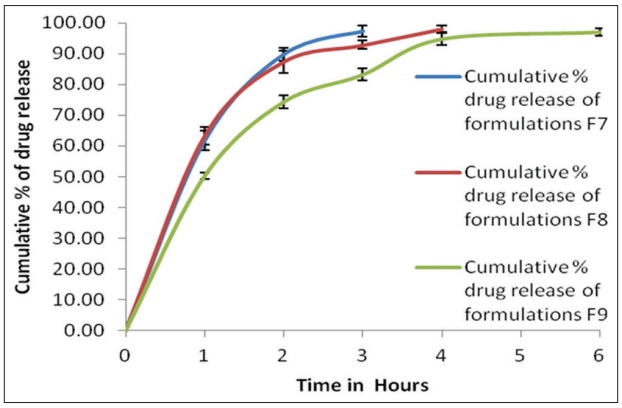


**Figure 8:** Graphical representation of *in vitro* drug release from formulations F7, F8, and F9

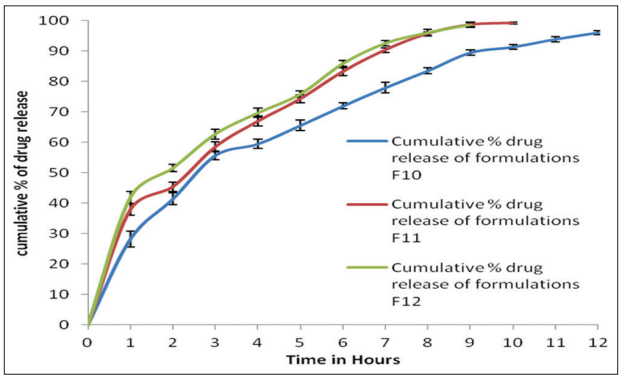


**Figure 9:** Graphical representation of *in vitro* drug release from formulations F10, F11,and F12

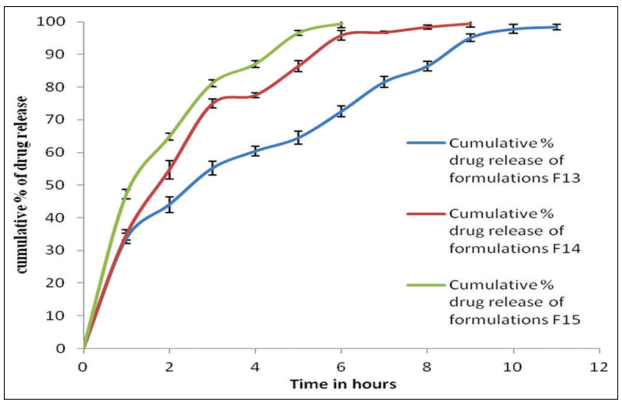


**Figure 10:** Graphical representation of *in vitro* drug release from formulations F10, F11, and F12

Formulations were prepared with drug and Gelucire 43/01 in 1:1, 1:1.5, and 1:2 (F1–F3) failed to release the drug within 12 h.

- Formulations were prepared with drug and Gelucire 50/02 in 1:1, 1:1.5, and 1:2 (F4–F6) failed to release the drug within 12 h.
- Formulations were prepared with drug and Gelucire 50/13 in 1:1, 1:1.5, and 1:2 (F7–F9) failed to retard the drug release up to 12 h.
- Formulations were prepared with drug Gelucire 43/01 and Gelucire 50/13 in 1:1:0.25, 1:1:0.5, and 1:1:0.75 (F10–F12). F10 is able to retard drug release up to 12 h. F10 formulation was able to release 96.03% of drug at the end of 12$^{th}$ h. F11 and F12 were unable to retard drug release up to 12 h.
- Formulations were prepared with drug Gelucire 50/02 and Gelucire 50/13 in 1:1:0.25, 1:1:0.5, and 1:1:0.75 (F13–F15) unable to retard drug release up to 12 h.
- Among the all formulations, F10 was optimized formulation containing the drug, Gelucire 43/01 and Gelucire 50/13 in the ratio 1:1:0.25, respectively.

### Radiographic studies in fasting condition

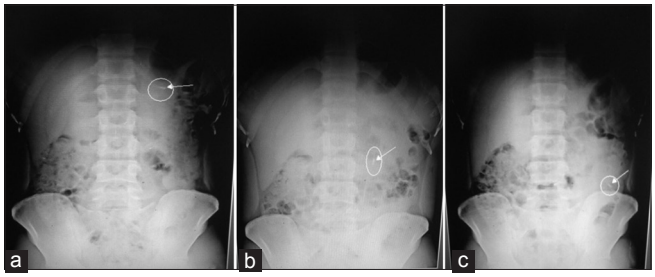


**Figure 11:** Radiographic images showing the presence of $BaSO_4$-loaded floating capsules in the GIT and images (c) show the displacement of tablet from stomach due to housekeeper waves in fasting condition. Images were taken after (a) 1 h, (b) 1 h 30 min, and (c) 2$^{nd}$ h after tablet administration ($n$ = 3 subjects)

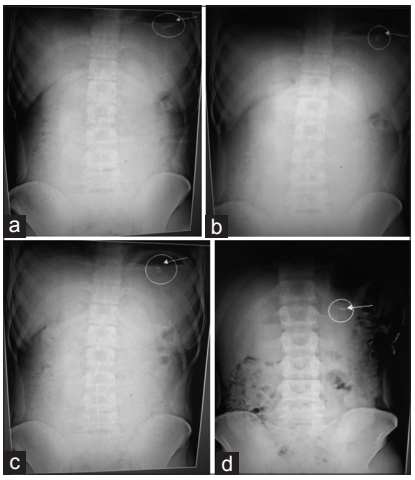


**Figure 12:** Radiographic images showing the presence of $BaSO_4$-loaded floating capsules in the GIT at different time periods in fed condition. The capsules have not altered its position in the stomach even after 6 h of capsule administered to volunteer. Images were taken at (a) 1 h, (b) 2 h, (c) 4 h, (d) 6 h after capsule administration ($n$ = 3 subjects)

## CONCLUSION

In the present study, an attempt was made to formulate a sustained release floating formulation of diltiazem hydrochloride using different grades of Gelucires. When lipophilicity Gelucire grade used alone drug release was highly retarded. Gelucire grades having hydrophilicity could enhance dissolution rate. The combination of both lipophilic and hydrophilic grades used for the successful development of sustained release matrix capsules of diltiazem hydrochloride. Radiographic images showing the presence of BaSO4-loaded floating capsules in GIT, Figure 11 shows the displacement of the tablet from the stomach to intestine after 2 h of capsule administered to volunteer due to housekeeper waves in fasting condition (i.e., when volunteer was administered with optimized formulation in fasting condition), Figure 12. Radiographic images show the presence of $BaSO_4$-loaded floating capsules in GIT at different time periods in fed condition. The capsules have not altered its position in the stomach even after 6 h of capsule administered to volunteer.

The study was conducted in human volunteers with permission from the Institutional Human Ethics Committee and their Approval no: REF. NO: ICE/RVSIMS/2017/09.

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