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# FORMULATION AND EVALUATION OF FLOATING MICROSPHERES FOR GASTRORETENTIVE DELIVERY OF ANTIDIABETIC DRUG

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## ABSTRACT

The present study has been performed to microencapsulate alogliptin, an antidiabetic drug (dipeptidyl peptidase-4; DPP-4 inhibitor) for enhancing gastric residence time of drug thereby increasing its bioavailability. The attempt of this study was to formulate the alogliptin loaded floating microspheres by emulsion solvent evaporation technique by varying the ratio of polymers i.e. cellulose acetate butyrate (CAB) and polyethylene oxide (PEO), drug loading and concentration of poly(vinyl alcohol) (PVA) solution. The prepared formulations were studied for entrapment efficiency, particle size, floating behaviour, surface morphology by SEM and *in-vitro* drug release. FTIR spectroscopy was done to confirm the chemical stability of drug after penetration of microspheres. Microspheres formed were spherical with smooth surfaces as revealed by SEM. Formulation F3 composed of CAB: PEO (80: 20 wt%) containing 1.5 wt% PVA solution and drug loading (10 wt%) gave the most advantageous entrapment (87.02±1.06%) and release results after 12 hrs (Q12h=78.19±0.90%) in simulated gastric fluid pH 1.2 as compared to other compositions. The microspheres tend to float over the simulated gastric media for more than 10 h. The % buoyancy of microspheres was found to be up to 89.50±1.53% and showed gastroretentive delivery of the drug. Floating microspheres of alogliptin with good floating ability and gastroretentive release were developed.

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**Keywords:** Floating microspheres, Alogliptin, Emulsion solvent evaporation technique, *In-vitro* drug release.

## INTRODUCTION

To develop oral drug delivery systems, it is necessary to optimize both the residence time of the system within the gastrointestinal tract (GIT) and the release rate of the drug from the system. One of the novel approaches in this area is gastroretentive delivery system (GRDDS) (1-3). Prolonging the gastric retention of a delivery system is sometimes desirable for achieving therapeutic benefit of drugs that are absorbed from the upper part of GIT or that are less soluble in or are degraded by the alkaline pH at the lower part of GIT (4). Gastroretentive delivery systems are thus beneficial for such drugs in improving their bioavailability, therapeutic efficacy, and possible reduction of dose (5, 6). These systems also offer various pharmacokinetic advantages like maintenance of constant therapeutic concentrations of drug over a prolonged period of time and thus, reduce the fluctuation in therapeutic concentrations by minimizing the risk of drug resistance.

Gastric emptying of dosage form is an extremely variable process and the ability of GRDDS to prolong and also to control the emptying time is an important asset for dosage forms. Although extensive studies have been done on the single unit sustained dosage forms, they have a disadvantage of a release, all or nothing emptying process from the stomach, as a result, the absorption of drug shows a high inter-individual variability. To overcome these drawbacks multiple unit systems have been developed. Moreover, the active ingredients are released at a sustained rate and avoid dose dumping (7). Among the various approaches, floating drug delivery systems (FDDS) achieves gastric retention by the mechanism of floatation. These systems have a bulk density less than gastric fluids and hence they remain buoyant in the stomach for a longer period of time without affecting the gastric emptying rate (8). The drug is released slowly when the system floats in the gastric fluid at the desired rate. The residual system is then emptied from the stomach after the drug release. This results in an increased gastric retention time and better control of fluctuations in the plasma drug concentration.

For drugs with relatively short half life, sustained release of the drug into the gastrointestinal tract maintain an effective concentration of drug in the systemic circulation for a long time and result in a flip-flop pharmacokinetics. So, formulating floating microspheres for short half-life drugs shows good therapeutic effect. Alogliptin is a selective DPP-4 inhibitor. DPP-4 inhibitors lower blood glucose by preventing the breakdown of glucagonlike peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, thus prolonging the activity of these peptides (9, 10). Alogliptin has demonstrated high selectivity to DPP-4 relative to other related serine proteases but has a short half-life 1.5 to 2 hours which favours the development of GRDDS.

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Polyethylene oxide (PEO) is a nontoxic and watersoluble polymer, widely used in chemical, cosmetic, and pharmaceutical industries. PEO gels produced in water can be dehydrated and the material so produced is extremely hydrophilic and possesses a good bioadhesive property. Cellulose acetate butyrate (CAB) was chosen as a model hydrophobic polymer, because it has been used frequently in matrices or coating membranes of CR dosage forms (11, 12).

Therefore, in the present investigation efforts were made to formulate and evaluate the CAB and PEO blend microspheres for the gastroretentive floating drug delivery of an antidiabetic drug such as alogliptin by emulsion solvent evaporation technique using different concentrations of polymers inorder to improve the short biological half-life and gastric retention time of drug.

## MATERIALS AND METHODS

### Materials

The alogliptin was kindly received as a gift sample by M/s Active Pharma Labs Pvt. Ltd. (Hyderabad, India). Cellulose acetate butyrate, polyethylene oxide and polyvinyl alcohol was a gift sample procured from Loba Chemie Pvt. Ltd. (Mumbai, India). Analytical reagent grade samples of dichloromethane, methanol, tween 80 and acetone were purchased from S.D Fine chemicals (Mumbai, India). Double distilled water was used throughout the work.

### Preparation of floating micropheres

Floating microspheres of CAB and PEO were prepared by emulsion-solvent evaporation method. CAB, PEO (total quantity of polymer used was 1 g) and different amounts of drug (based on dry weight of CAB–PEO mixture) were all dissolved in 30 mL of dichloromethane (DCM). The solution was then emulsified into 200 mL of PVA solution to form o/w emulsion using a mechanical stirrer (LT400A, Yamoto, Japan) at 600 rpm rotation speed at 30˚C for 4 h. Here, the PVA solution acts as a stabilizer. The microspheres were separated using 0.2 µm membrane filter by applying vacuum. Then, microspheres were washed 2-3 times successively with distilled water to remove the surface adhered PVA and filtered to collect the microspheres. Then, dried for 1 h at room temperature and subsequently stored in desiccators over fused calcium chloride. Different formulations were prepared by varying the amount of CAB, PEO, drug loadings and PVA concentrations. Totally 6 formulations were prepared. Formulation codes and formulation parameters are given in Table 1.

### Evaluation of floating micropheres

### Fourier transform infrared (FTIR) spectral studies

FTIR spectral measurements were performed using FTIR-8400S spectrophotometer, Shimadzu (Japan) to confirm the formation of microspheres and also to find the chemical stability of the drug in the microspheres. FTIR spectra of the drug loaded microspheres were obtained. Samples

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were crushed with KBr to get pellets at 600 kg/cm$^2$ pressure. Spectral scanning was done in the range between 4000–400 cm$^{-1}$ (13).

**Scanning electron microscopy (SEM) analysis**

SEM photographs of the selected floating microspheres were taken at required magnification at room temperature. Microspheres were mounted onto stubs using double sided adhesive tape and vacuum coated with gold film using a sputter coater. The coated surface was observed under SEM (LEO 435VP model, Cambridge, UK) for surface appearance (13).

**Drug entrapment efficiency (%EE)**

Microspheres equivalent to dose of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of simulated gastric fluid (SGF) pH 1.2 repeatedly. The extract was transferred to a 50 ml volumetric flask and the volume was made up using SGF (pH 1.2). The solution was filtered and the absorbance was measured after suitable dilution spectrophotometrically (Systronics 2202, India ) at 236 nm against appropriate blank. Study was done in triplicate and % drug entrapment efficiency can be calculated by using following formula:

$$\text{Entrapment efficiency (\%)} = (\text{actual drug content/theoretical drug content}) \times 100$$

**Particle size measurements**

Particle size of different formulations were observed under an optical microscope (Olympus Model BX 41, Japan) at suitable magnification. The measurements were done in triplicate and volume mean diameter ($V_d$) was recorded (14).

**Floating behavior**

About 100 mg of the floating microspheres were placed in simulated gastric fluid (SGF) (pH 1.2, 100 ml) containing 0.02% (w/v) tween 80 as a dispersing medium. Microspheres were spread over the surface of 500 ml of dispersing medium at 37 ± 0.5$^\circ$C. The mixture was stirred at 100 rpm speed in a magnetic stirrer. After 12 h, the layer of buoyant microspheres was pipetted and separated by filtration. Microspheres in the sinking particulate layer were separated by filtration. Particles of both types were dried in an oven at 40$^\circ$C for 6 h. Both the fractions of microspheres were weighed and the buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking microspheres.

$$\% \text{ Buoyancy} = (W_f / W_f + W_s) \times 100$$

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Where, $W_f$ and $W_s$ are the weights of floating and settled microspheres, respectively. All the determinations were made in triplicate.

***In-vitro* drug release study**

*In-vitro* drug release from different formulations of floating microspheres was investigated in SGF containing 0.02% (w/v) tween 80 as per the procedures reported earlier. These experiments were performed using programmable dissolution tester (Paddle type, Electrolab, model TDT-08L, USP, Mumbai, India). Weighed amount of microspheres equivalent to dose (mg) of the pure drug was filled into a capsule and placed in the basket of dissolution apparatus. Microspheres containing drug were placed in 900 ml of dissolution medium SGF (pH 1.2) with 0.02% tween 80 and stirring rate was 100 rpm. The temperature maintained at 37±0.5°C in dissolution test apparatus. 10 ml of the aliquot was withdrawn at predetermined intervals and filtered. The required dilutions were made with SGF (pH 1.2) and the solution was analyzed by spectrophotometrically (Systronics 2205, India) at 236 nm.

## RESULTS AND DISCUSSION

**Fourier transform infrared (FTIR) spectral studies**

FTIR was used to confirm the formation of the floating microspheres. Figure 1 shows the FTIR spectra of drug loaded microspheres. It was shown that the principle IR peaks of alogliptin at 1023.66 $cm^{-1}$ resulted from C-N stretching and the peak at 3051.99 $cm^{-1}$ resulted from N-H stretching and the peak at 1557.63 $cm^{-1}$ resulted from N-H bending. In the spectra of drug loaded microspheres, the appearance of peaks at 1023.66 $cm^{-1}$ indicates the presence of a C-O-C group. A broad band with less intensity compared to both CAB and PEO matrices is due to the presence of very few uncross-linked hydroxyl groups that are hydrogen bonded to various degrees. It was confirmed by FTIR that the entire principal peaks of alogliptin were present in floating microspheres, which confirm the stability of drug in microparticles.

**Scanning electron microscopy (SEM) analysis**

Scanning electron micrographs of selected alogliptin loaded floating microspheres was shown in Figure 2. It was demonstrated that the microspheres obtained were well identified and present in a nearly perfect sphere like shape with smooth surfaces as demonstrated by SEM images.

**Drug entrapment efficiency (%EE)**

It was indicated that % drug entrapment efficiency (%EE) of the microparticles was in the range between 82.71 ± 1.70% to 87.02 ± 1.06% as shown in Table 2. The % encapsulation efficiency was found to be higher in case of formulations containing 20 wt % PEO as compared to 10 wt % PEO. This could be due to the more hydrophilic nature of PEO, thereby leading to the retention of more of drug particles during the microsphere preparation.

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**Particle size measurements**

It is observed that particle size increased as the PEO content increased. For instance, formulation F3 (20 wt% PEO) has a bigger particle size than F4 (10 wt % PEO). This could be due to the accumulation of more of PEO in the matrix at higher PEO content, leading to the formation of larger particles. Particle size also varies depending upon the drug loading. As the drug loading increased from 10 to 12 wt%, particle size decreased accordingly. Formulation F4 has smaller particle size than F3, whereas F5 exhibits higher particle size than F4. This is due to the retention of less of drug particles at higher drug loadings during the microsphere preparation. The floating microspheres obtained were fell in the size range of 88.20±1.33 µm to 103.02±0.65 µm (Table 2). An increase in size of microspheres was observed with the increase in polymer concentration (1.5 wt% PVA) in the microspheres. This could be due to the fact that at higher amounts of polymer, the viscosity of the polymer solution increased, thus producing bigger droplets during emulsification.

**Floating behavior**

Formulations containing 10 wt% PEO showed less floatability than those containing 20 wt% PEO. This could be due to the fact that as the content of PEO in the matrix increases, there is an increase in the hydrophilicity of the matrix, leading to the dissolution of more PEO from the microspheres. The dissolution of PEO would produce more pores on the surface of the microspheres. Also, buoyancy effect decreased as the drug-loading of the matrix was increased from 10 to 12 wt%. Again, this may be due to an increase in the density of microspheres at higher drug-loadings. These results are shown in Table 2.

***In-vitro* drug release study**

Formulation F5 shows a higher release rate than F3. As the drug loading is increased, there will be accumulation of more of water insoluble drug particles in the polymer matrix, but burst effect was observed in all the formulations. This indicates that release rates vary depending upon the amount of drug present in the matrices that is release is higher in case of formulations containing higher amounts of drug and similarly, release is slower for formulations containing lower amount of drug. The cumulative percentage of drug released after 12 hr from the prepared alogliptin loaded floating microspheres in SGF (pH 1.2) varied from 78.19±0.90% to 99.65±0.81% as shown in Figure 3 and the data are presented in Table 2. The cumulative percentage released is slower in the case of F3 than F6. It was found that with increase in the polymer concentration, the swelling of the matrix decreases which leads to the slower release of drug from the microspheres.

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## CONCLUSION

The present study reports on the development of blend microspheres of CAB and PEO to study the gastroretentive slow release of alogliptin using the solvent evaporation method. The drug loaded microspheres showed encapsulation efficiencies up to 87.02±1.06%. The microspheres also showed good micromeritic properties for their suitability as oral dosage forms. The microspheres having lower densities exhibited good buoyancy effect and hence, these could be retained in the gastric environment for more than 10 h. Thus, the present formulations are helpful in improving the bioavailability of antidiabetic drug such as alogliptin.

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## CONFLICT OF INTEREST

The authors report no conflicts of interest.

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## TABLES AND FIGURES

**Table 1: Composition for floating microspheres.**

| Formulation Code | Drug loading (wt %) | CAB (wt %) | PEO (wt %) | Concentration of PVA solution (wt %) | Amount of DCM (ml) |
|---|---|---|---|---|---|
| **F1** | 10 | 80 | 20 | 1 | 30 |
| **F2** | 10 | 80 | 20 | 1 | 30 |
| **F3** | 10 | 80 | 20 | 1.5 | 30 |
| **F4** | 12 | 90 | 10 | 1.5 | 30 |
| **F5** | 12 | 90 | 10 | 2 | 30 |
| **F6** | 12 | 90 | 10 | 2 | 30 |

**Table 2: Evaluation of drug loaded floating microspheres.**

| Formulation code | % EE (± SD, n=3) | Volume mean diameter (µm) (± SD, n=3) | % Buoyancy (± SD, n=3) | *In-vitro* release (12 h) (± SD, n=3) |
|---|---|---|---|---|
| F1 | 82.71±1.70 | 95.73±0.75 | 83.22±1.55 | 98.71±0.48 |
| F2 | 84.23±1.78 | 98.13±0.65 | 86.72±1.55 | 98.54±0.49 |
| F3 | 87.02±1.06 | 103.02±0.77 | 89.50±1.53 | 78.19±0.90 |
| F4 | 84.72±1.04 | 82.13±0.33 | 84.15±1.85 | 86.04±0.81 |
| F5 | 85.26 ±2.80 | 88.20±0.57 | 87.06±3.21 | 99.65±0.81 |
| F6 | 86.14± 2.04 | 97.13±0.65 | 89.37±2.71 | 79.14±1.31 |

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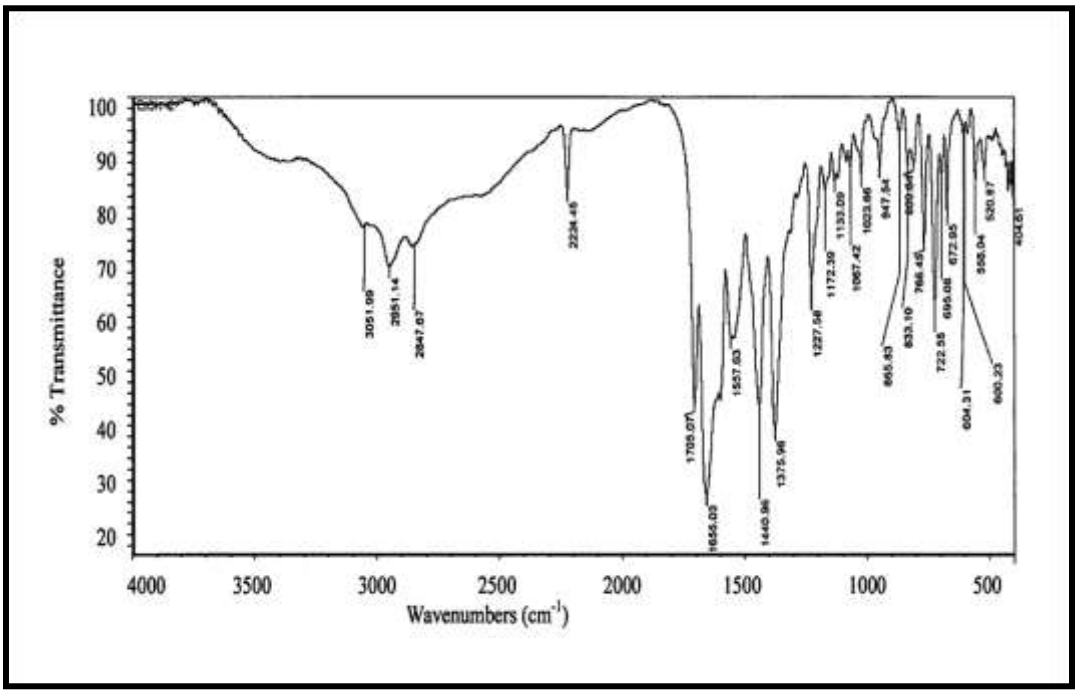


**Figure 1: FTIR spectra of drug loaded floating microsphere.**

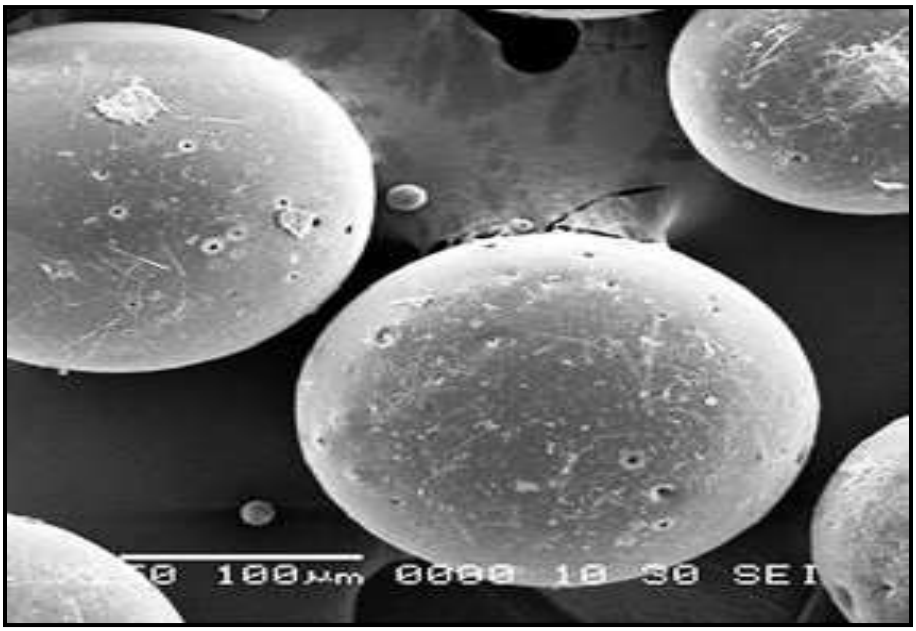


**Figure 2: SEM photograph of selected floating microsphere.**

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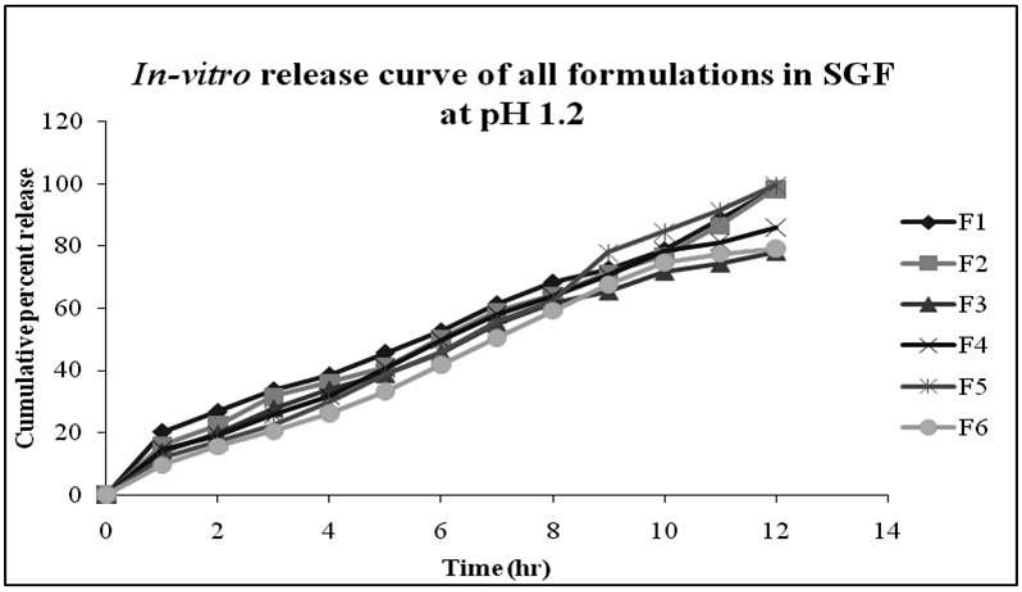


**Figure 3: *In-vitro* drug release profile of different floating microspheres.**