Formulation development and Evaluation of Floating tablets containing Alogliptin using different polymers

Rahul Patel*, Suresh Choudhary

Faculty of Pharmacy, Lords University, Alwar, Rajasthan, India

**Correspondence*
Rahul Patel
Research Scholar, Faculty of Pharmacy, Lords University, Alwar, Rajasthan, India
E-mail: royalpatel@gmail.com

Abstract

Formulation F3, comprising of CAB: PEO (80: 20 wt percent) with 1.5 wt percent PVA solution and drug loading (10 wt percent), demonstrated the best entrapment (87.0 and 21.06%) and release (Q12h=78.19 and 0.90%) values in simulated stomach fluid pH 1.2 when compared to other compositions. The microspheres prefer to float over the simulated stomach media for over ten hours. It was discovered that the microspheres' percent buoyancy may reach 89.50 and 1.53%, which suggests that the drug was administered in a gastroretentive way. Stability investigations showed that the particle size distribution and shape of formulation F3 had changed somewhat after one month of storage at 40.2°C and 75% relative humidity. This suggests that formulations were stable under accelerated storage conditions. As a result, efforts were made in the current study to formulate and evaluate CAB and PEO blend microspheres for the gastroretentive floating drug delivery of an antidiabetic drug such as alogliptin using an emulsion solvent evaporation technique with various polymer concentrations in order to improve the drug's short biological half-life and gastric retention time. This study showed that a combination of two hydrophilic and biocompatible polymers, cellulose acetate butyrate (CAB) and polyethylene oxide (PEO), may be used to make floating microspheres for the efficient and successful integration of alogliptin using an emulsion solvent evaporation approach. The production of a blend of this formulation revealed superior floating capabilities than separate polymers, indicating that blend formation is suitable for the preparation of microspheres.

Keywords: cellulose acetate butyrate (CAB), polyethylene oxide (PEO), PVA solution, microspheres, gastroretentive floating drug delivery.

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Introduction

To improve the retention length, several efforts have been complete to recollect the quantity form in the abdominal for a longer amount of time. The floating dosage formulations have proven to be the most popular. Because their bulk density is lower than that of stomach fluids, hydrostatically controlled devices can drift in the abdomen for extended periods of time without impacting the gastric emptying. The pharmaceutical is delivered progressively at the recommended intervals whereas the system is buoyancy on the gastric contents. The stomach's surviving system is drained when the medication is eliminated. GRT improves as a result, and fluctuations in plasma drug concentrations are better regulated. A minimum number of float force (F) is also necessary to maintain the dose form consistently floating on the top of the meals, in additional to a sufficient gastrointestinal system critical for effective realisation of the floating retention concept. The literature has provided a fresh mechanism for studying the dynamics of floating forces.The device works through continually monitoring the amount of effort required to keep the submerged item submerged (as a function of time). The item floats better when F is on the upper brighter note.

This technology aids in the optimization of FDDS in terms of the stability and longevity of the floated forces generated, removing the disadvantages of unexpected intragastric flotation capacity fluctuations.The drug delivery system that a drug is integrated into dictates its fate in vivo. Lipid-based formulations were first commercialised in the 1950s. The introduction of Diazemuls, Diazepam-Lipuro, and Etomidate-Lipuro into the market followed. Initially, parenteral nutrition used intralipid as a safe fat emulsion. Lipid delivery systems are becoming more and more popular, maybe because to the reduced pain and inflammation at the injection site [1]. Designed to maintain drugs in the belly, floating drug delivery devices (FDDS) are especially helpful for prescriptions that have low solubility and stability in digestive fluids. FDDS is used to develop dose forms that are tiny enough to float above the stomach acids. FDDS are hydrodynamically regulated, low-density devices that have enough buoyancy to float over stomach contents and stay floating in the abdomen for a long time without slowing down the rate of gastrointestinal transit [2, 3]. A straightforward and effective method for extending a dose form's stomach residence duration and guaranteeing long-term pharmaceutical release is the floating preparation idea. In some cases, stepping up the therapeutic spreading the abdomen maintenance of a delivery channel to increase the effectiveness of a therapeutic item is beneficial. It has been demonstrated that drugs with limited solubility that degrade at alkaline pH and those with increased concentration at the proximal region of the GIT prolong gastric retention. Additionally, prolong gastric retention of the therapeutic moiety for sustained drug delivery to the stomach and proximal small bowel in the diagnosis of certain circumstances involving peptic ulcers, and offer numerous benefits like improved biodistribution and therapeutic response with dosing frequency sampling rate [4].

Material and Methods

Drug

The alogliptin was kind hearted conventional as a gift sample by M/s Active Pharma Labs Pvt. Ltd. (Hyderabad, India). Cellulose acetate butyrate was procured from Himedia Laboratories Ltd., Mumbai and polyethylene oxide and polyvinyl alcohol was a talent sample procured from Sigma Aldrich Laboratory GMBH (Mumbai, India). S.D Fine chemicals provided analytical reagent grade dichloromethane, methanol, tween 80, and acetone samples (Mumbai, India). Throughout the project, binarypurified water was utilized.

Formulation of floating microspheres

The emulsion-solvent evaporation process was used to make floating microspheres of CAB and PEO. CAB, PEO (whole polymer utilised was 1 g), and various doses of medication were all dissolved in 30 mL of dichloromethane (DCM). By means of a power-drivenagitator (LT400A, Yamoto, Japan) at 600 rpm revolutionrapidity at 30°C for 4 hours, the solution was emulsified into 200 mL of PVA solution to produce an o/w emulsion. The PVA solution functions as a stabiliser in this case. Using a 0.2 m membrane filter and vacuum, the microspheres were separated.The microspheres were then rinsed 2-3 times with distilled water to remove the surface attached PVA and filtered to collect them. The samples were then dried at room temperature for 1 hour before being stored in desiccators over fused calcium chloride. The quantity of CAB, PEO, drug loadings, and PVA amounts were varied to create several formulations. Six formulations were created in all. Table 1 lists the formulation codes as well as the formulations parameters [6].

Table 1: Composition for floating microspheres

Formulation Code	Drug Loading (wt %)	CAB (wt %)	PEO (wt %)	Concertration 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**

Evaluation of micromeritics properties

The final blend will be characterized by evaluating their angle of repose [7], Bulk density and Tapped density [8] and Carr's index [9].

Evaluation of floating microspheres

Evaluating the final prepared floating microspheres on the ground of Particle size analysis [10], calculation of percent yield values [11] and Estimation of drug entrapment efficiency (%EE) [12]

Scanning electron microscope (SEM) analysis

The determination of the SEM education is to collect topographic features of the microspheres, notably their

figure and superficial morphology. SEM pictures of the selected floating microspheres were taken at room temperature at the required brightness. With double-sided sticky tape, microspheres were glued to stubs and vacuum coated with gold film using a sputter coater. A scanning electron microscope (LEO 435VP model, Cambridge, UK) was used to assess the look of the coated surface (13). Aoccupiedcoldness of 26 mm was continued using the secondary electron image (SEI) as a detector120, and an acceleration voltage of 15 kV was used [13].

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

As previously mentioned, in-vitro drug release from different floating microsphere formulations was investigated in SGF containing 0.02 percent (w/v) tween 80. A programmed dissolution tester was used to carry out these experiments. A weighed amount of microspheres was put into a capsule equal to the pure drug's dose (mg) and placed in the dissolving device's basket. The medication-containing microspheres were suspended in 900 ml of SGF (pH 1.2) with 0.02 percent tween 80 and agitated at 100 rpm. The temperature in the dissolving test apparatus was preserved at 37.5°C. 10 ml of the aliquot was obtained and filtered at regular intervals T SGF (pH 1.2) was used to make the required dilutions, and the solution was spectrophotometrically analysed at 236 nm (Systronics 2205, India). To confirm that the tests were repeatable, they were performed in triplicate for each sample. The cumulative percentage medicationannouncement was intended and plotted in contradiction of the purpose of time to examine the design of medicationdischarge [14, 15].

Stability studies

The capacity of a given formulation to adhere to the physical, chemical, therapeutic, and toxicological specifications is known as product stability. The creation of a pharmaceutically acceptable product necessitates the conduct of a stability study. The stability of floating microspheres was tested under accelerated storage conditions for a short period of time. The best microspherical formulation was sealed in amber tinted glass vials and preserved in a stability chamber (MAC® Environmental test chamber, CAT No. MSW-127) for one month at 40°C and 75% percent RH. The microspheres were examined for particle size, percent drug entrapment efficiency, and in-vitro drug release at the conclusion of the storage period [16].

Results and Discussion

Results of micromeritics properties of floating microspheres of alogliptin

The micromeritics propertiesof all microspherical formulations were determined in triplicate and their mean values with standard deviation are shown in Table 2.

Table 2: Micromeritics properties of all formulations (Mean ± SD, n=3)

Formulation Code	Angle of repose (°)	Bulk density (gm/cm^3)	Tapped density (gm/ cm^3)	Carr's index (%)
F1	20.58 ± 1.10	0.5534 ± 0.03	0.6827 ± 0.03	22.94 ± 1.56
F2	19.87 ± 0.35	0.5359 ± 0.01	0.5827 ± 0.03	21.40 ± 3.22
F3	19.11 ± 0.26	0.5432 ± 0.03	0.6353 ± 0.03	20.07± 0.95
F4	19.84 ± 0.48	0.569 ± 0.01	0.6895 ± 0.03	20.36 ± 2.20
F5	20.11 ± 0.51	0.4960 ± 0.03	0.5316 ± 0.04	21.44 ± 1.13
F6	21.61 ± 0.84	0.4822 ± 0.02	0.5133 ± 0.03	21.98 ± 1.13

Particle size analysis

The particle size of all microspherical formulations was strongminded in triplicate and their mean values with SDare exposed in Table 3.

Table 3: Results of particle size analysis of all formulations (Mean ± SD, n=3)

Formulation code	Volume mean diameter (µm) (± SD, n=3)

F1	95.73±0.75
F2	98.13±0.65
F3	103.02±0.77
F4	82.13±0.33
F5	88.20±0.57
F6	97.13±0.65

It was observed that particle size of the microspheres ranges from 82.13±0.33 µm to 103.02±0.77 µm. But, it was found that particle size of F3 was larger i.e. 103.02±0.77 µm as compared to all formulations.

Percent yield values

The percent yield values of all formulations were determined in triplicate and their mean values with standard deviation are shown in Table 4.

Table 4: Percent yield values of all formulations (Mean ± SD, n=3)

Formulation code	**% Yield values (± SD, n=3)**
F1	78.51 ± 3.71
F2	87.85 ± 0.99
F3	95.18 ± 0.94
F4	94.83 ± 6.09
F5	88.08 ± 2.24
F6	90.11 ± 1.90

The percent yield value of alogliptin loaded floating microspheres was improved from 78.51 ± 3.71% to 95.18 ± 0.94%. It was found that percent yield of F3 was higher i.e. 95.18 ± 0.94% as compared to all formulations.

Drug entrapment efficiency (%EE)

The percentage drug entrapment efficiency (%EE) was determined in triplicate and their mean values with standard deviation are shown in Table 5.

Table 5:Drug entrapment efficiency of all formulations (Mean ± SD, n=3)

Formulation code	**% EE (± SD, n=3)**
F1	82.71±1.70
F2	84.23±1.78
F3	87.02±1.06
F4	84.72±1.04
F5	85.26 ±2.80
F6	86.14± 2.04

It was observed that percent drug entrapment efficiency (%EE) was in the range between 82.71±1.70%to 87.02±1.06%. It was found that %EE of F3 was higher i.e.87.02±1.06%as compared to all formulations.

Scanning electron microscopic (SEM) analysis

SEM micrographs of a group of alogliptin loaded floating microspheres of formulation F3 taken at 768 X magnifications are shown in Figure 1.

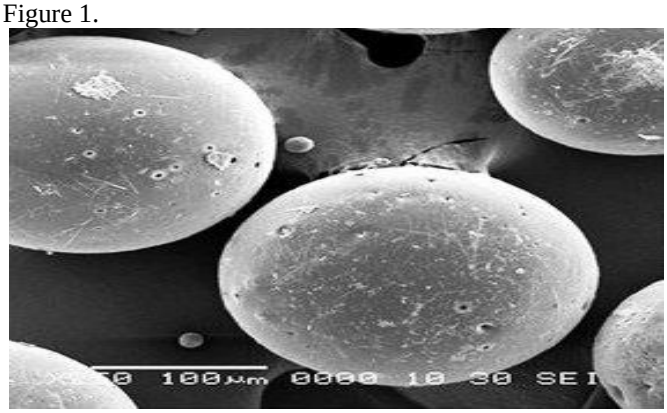

Figure 1: SEM micrograph of a group of alogliptin loaded floating microspheres of formulation F3

Results of *in-vitro* floating behavior

In-vitro floating behaviorfor each formulation was determined in triplicate and their mean values with standard deviation are shown in Table 6.

Table 6: % Buoyancy of all formulations in SGF at pH 1.2 (Mean ± SD, n=3)

Formulation code	% Buoyancy (± SD, n=3)
F1	83.22±1.55
F2	86.72±1.55
F3	89.50±1.53
F4	84.15±1.85
F5	87.06±3.21
F6	89.37±2.71

It was observed that % buoyancy of the microspheres in SGF of pH 1.2 ranges from 83.22±1.55% to 89.50±1.53%. But, it was found that % buoyancy of the formulation F3 was higher i.e. 89.50±1.53% as compared to all formulations.

Conclusion

As a result, efforts were made in the current study to formulate and evaluate CAB and PEO blend microspheres for the gastroretentive floating drug delivery of an antidiabetic drug such as alogliptin using an emulsion solvent evaporation technique with various polymer concentrations in order to improve the drug's short biological half-life and gastric retention time.

The medication's solubility profile in various solvents indicates that it is somewhat hydrophobic in nature, which is supported by n-octanol:water drug partitioning tests, which demonstrate that drug partitioning in n-octanol:water is 0.460.02. A UV spectrophotometer was used to determine the maximum absorbance (max) of alogliptin in SGF (pH 1.2), which was determined to be 236 nm. The existence of all peak values was confirmed by the drug's FTIR spectra. All of these findings backed up the discovery of alogliptin. In-vitro drug estimation was done using a UV spectroscopic technique [17]. The calibration curve was created, and the linear regression equation was calculated. The variable concentration and absorbance has a correlation value of 0.998.Substance matching testing revealed that the drug fits the criteria for identity and purity. FTIR analysis revealed no incompatibility between the medication and the polymer.

The ratio of polymers, cellulose acetate butyrate (CAB) and polyethylene oxide (PEO), drug loading, and concentration of poly(vinyl alcohol) (PVA) solution were varied in order to optimise the process variables on particle size, percent yield, drug entrapment efficiency, surface morphology of the microspheres, floating behaviour, in-vitro drug release rates, and in-vivo drug release rates using the emulsion solvent evaporation technique. After the microspheres were created, Fourier transform infrared spectroscopy was utilised to determine the formation of the mix and the chemical stability of alogliptin (FTIR).The results showed that alogliptin was dispersed amorphously in the polymer matrix. The spherical form of the microspheres generated was verified by scanning electron microscopy (SEM), which revealed smooth surface morphology. When compared to other compositions, Formulation F3, which consisted of CAB: PEO (80: 20 wt percent) containing 1.5 wt percent PVA solution and drug loading (10 wt percent), had the best entrapment (87.021.06%) and release (Q12h=78.190.90%) values in simulated stomach fluid pH 1.2. For more than 10 hours, the microspheres prefer to float above the simulated gastric media. The percent buoyancy of microspheres was found to be up to 89.501.53%, indicating that the medication was delivered in a gastroretentivemanner.After one month of storage at 402°C and 75 percent RH, stability analyses revealed that the particle size distribution and shape of formulation F3 had changed insignificantly, indicating that formulations were stable under accelerated storage circumstances [18, 19].

This work demonstrated that the emulsion solvent evaporation method may be utilised to successfully and efficiently integrate alogliptin by creating floating microspheres made of a combination of two hydrophilic and biocompatible polymers: polyethylene oxide (PEO) and cellulose acetate butyrate (CAB). The creation of a blend using this formulation demonstrated better floating properties than individual polymers, suggesting that blend synthesis is a viable method for microsphere manufacture.

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