RESEARCH PAPER

Development and Characterization of Pioglitazone-Loaded Floating Microspheres for Gastro-Retentive Drug Delivery

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ABSTRACT

Background: Oral drug delivery is the most preferred route of administration due to its convenience, patient compliance, and cost-effectiveness. However, conventional oral dosage forms often suffer from limitations such as rapid gastric emptying and reduced gastrointestinal residence time, which may lead to incomplete drug absorption and suboptimal therapeutic efficacy. The present study aimed to develop and characterize pioglitazone-loaded floating microspheres as a gastro-retentive drug delivery system to enhance gastric retention and provide sustained drug release.

Methods: Floating microspheres were prepared using the emulsion solvent diffusion–evaporation technique employing ethyl cellulose and hydroxypropyl methylcellulose as polymeric carriers. The prepared microspheres were evaluated for percentage yield, particle size, drug entrapment efficiency, buoyancy behaviour, surface morphology, and in vitro drug release profile.

Results: The percentage yield of the formulations ranged from 78.54% to 92.37%, while particle size varied between 220 ± 6.2 µm and 395 ± 9.4 µm. Drug entrapment efficiency was found to be between 67.48% and 89.62%, indicating effective incorporation of the drug within the polymeric matrix. The microspheres demonstrated excellent buoyancy with floating ability up to 95.48%. In vitro drug release studies revealed sustained release of pioglitazone for up to 12 hours, with the optimized formulation following the Higuchi release model, indicating diffusion-controlled drug release.

Conclusion: These findings suggest that floating microspheres represent a promising gastro-retentive system for controlled delivery of pioglitazone.

Keywords: Floating microspheres; Gastro-retentive drug delivery system; Pioglitazone; Sustained drug release; Emulsion solvent evaporation.

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Introduction

Oral drug delivery remains the most widely accepted route of drug administration due to its convenience, non-invasiveness, and high patient compliance. However, conventional oral dosage forms often exhibit limitations such as rapid gastric emptying, short gastrointestinal residence time, and incomplete drug absorption, which may lead to suboptimal therapeutic outcomes. To overcome these challenges, gastro-retentive drug delivery systems (GRDDS) have been developed to prolong the residence time of dosage forms in the stomach, thereby enhancing drug bioavailability and therapeutic effectiveness [1,2].

Floating drug delivery systems (FDDS) are among the most promising approaches within GRDDS. These systems are designed to remain buoyant on the gastric contents due to their lower density compared to gastric fluid, enabling prolonged gastric retention without interfering with normal gastric motility. By maintaining the drug delivery system in the stomach for extended periods, FDDS can provide controlled drug release and improve the absorption of drugs that are primarily absorbed in the upper gastrointestinal tract [3,4].

Floating microspheres, also known as hollow microspheres or micro balloons, represent an important category of multiple-unit floating drug delivery systems. These microspheres are typically spherical particles with sizes ranging from 1 to 1000 µm and are composed of biodegradable or synthetic polymers encapsulating the drug within the matrix. Due to their hollow structure and low density, floating microspheres remain buoyant in gastric fluid for prolonged periods and release the drug in a sustained

manner. Multiple-unit systems offer several advantages over single-unit dosage forms, including reduced risk of dose dumping, improved drug distribution in the gastrointestinal tract, and enhanced reproducibility of drug absorption [5,6].

Various techniques have been employed for the preparation of floating microspheres, including solvent evaporation, solvent diffusion, spray drying, and ionic gelation methods. Among these techniques, the solvent evaporation method is widely used due to its simplicity, reproducibility, and ability to produce microspheres with desirable particle size, high drug entrapment efficiency, and controlled drug release characteristics. The physicochemical properties and performance of the microspheres are influenced by formulation variables such as polymer type, drug-polymer ratio, solvent system, and stirring speed during preparation [7,8].

Pioglitazone, a thiazolidinedione class antidiabetic drug, is commonly used in the management of type 2 diabetes mellitus. It acts by enhancing insulin sensitivity in peripheral tissues and improving glycaemic control. Despite its therapeutic potential, the oral bioavailability of pioglitazone may be affected by limited gastric residence time and variable gastrointestinal absorption. Incorporating pioglitazone into a gastro-retentive floating microsphere system could prolong gastric retention and provide sustained drug release, thereby enhancing therapeutic efficacy and reducing dosing frequency [9].

Therefore, the present study aims to develop and characterize pioglitazone-loaded floating microspheres as a gastro-retentive drug delivery system. The prepared microspheres were evaluated for their physicochemical properties, including particle size, drug entrapment efficiency, buoyancy behaviour, surface morphology, and in vitro drug release profile, to determine their suitability for sustained oral drug delivery [10].

Materials and Methods

Materials

Pioglitazone hydrochloride was obtained as a gift sample from a reputed pharmaceutical company. Ethyl cellulose and hydroxypropyl methylcellulose (HPMC) were used as polymeric carriers for the preparation of floating microspheres. Polyvinyl alcohol (PVA) was used as an emulsifying agent. Dichloromethane and ethanol were employed as organic solvents for polymer dissolution. All other chemicals and reagents used in the study were of analytical grade and used without further purification.

Preparation of Pioglitazone Floating Microspheres

Pioglitazone-loaded floating microspheres were prepared using the emulsion solvent diffusion–evaporation technique, which is widely used for the preparation of hollow microspheres intended for gastro-retentive drug delivery systems [11,12].

In this method, the required quantity of pioglitazone and polymer (ethyl cellulose and HPMC) was dissolved in a mixture of organic solvents consisting of ethanol and dichloromethane to obtain a homogeneous polymeric solution. The prepared solution was slowly introduced into an aqueous phase containing polyvinyl alcohol (0.5–1% w/v) under continuous stirring using a mechanical stirrer to form an oil-in-water emulsion.

During stirring, the organic solvents gradually diffused into the aqueous phase and evaporated, resulting in precipitation of the polymer and formation of hollow microspheres. The diffusion of solvent created an internal cavity within the microspheres, which contributes to their low density and floating ability in gastric fluid [13].

After complete evaporation of the organic solvents, the microspheres were collected by filtration and washed with distilled water to remove residual emulsifier. The microspheres were dried at room temperature for 24 hours and stored in a desiccator until further evaluation.

Evaluation of Floating Microspheres

Percentage Yield

The percentage yield of microspheres was calculated by comparing the practical yield with the theoretical amount of drug and polymer used during formulation [14].

$$\text{Percentage Yield} = \frac{\text{Practical weight of microspheres}}{\text{Total weight of drug and polymer}} \times 100$$

Particle Size Analysis

Particle size of the prepared microspheres was determined using optical microscopy. A small amount of microspheres was dispersed in distilled water and mounted on a glass slide. The diameters of approximately 100 microspheres were measured using a calibrated ocular micrometer, and the mean particle size was calculated [15].

Drug Entrapment Efficiency

Entrapment efficiency was determined by dissolving a known quantity of microspheres in a suitable solvent to extract the drug. The solution was filtered and analyzed spectrophotometrically at the λmax of pioglitazone using a UV–visible spectrophotometer [16].

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

In-Vitro Buoyancy Study

The floating behavior of the prepared microspheres was evaluated using simulated gastric fluid (0.1 N HCl, pH 1.2). A known quantity of microspheres was dispersed in the dissolution medium and agitated using a USP dissolution apparatus. After a specified time, the floating and settled microspheres were separated, dried, and weighed to determine the buoyancy percentage [17].

$$\text{Buoyancy (\%)} = \frac{\text{Weight of floating microspheres}}{\text{Total weight of microspheres}} \times 100$$

Surface Morphology

The surface morphology of the prepared microspheres was examined using scanning electron microscopy (SEM). The dried microspheres were mounted on aluminum stubs and coated with a thin layer of gold before observation under the scanning electron microscope [18].

In-Vitro Drug Release Study

The in-vitro drug release study was performed using a USP dissolution apparatus type II (paddle method). Microspheres equivalent to a specific dose of pioglitazone were placed in 900 mL of simulated gastric fluid (0.1 N HCl, pH 1.2) maintained at 37 ± 0.5°C and stirred at 50 rpm [19].

At predetermined time intervals, samples were withdrawn and replaced with fresh dissolution medium to maintain sink conditions. The samples were filtered and analyzed using a UV-visible spectrophotometer to determine the drug concentration.

Drug Release Kinetics

The drug release data obtained from dissolution studies were fitted into various kinetic models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models to determine the mechanism of drug release from the floating microspheres [20].

Results and Discussion

Physicochemical Properties of Pioglitazone

Before formulation development, the physicochemical characteristics of pioglitazone were evaluated because these properties influence formulation design and drug release behavior.

Table 1 presents the important physicochemical parameters of pioglitazone obtained from literature.

Table 1 Physicochemical properties of Pioglitazone

Parameter	Description
Drug name	Pioglitazone
IUPAC name	5-[[4-[2-(5-ethylpyridin-2-yl)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione
Chemical formula	C19H20N2O3S
Molecular weight	356.4 g/mol
Melting point	193–194 °C
Solubility	Practically insoluble in water
BCS classification	Class II (low solubility, high permeability)

The drug belongs to BCS Class II, indicating low aqueous solubility but high permeability, which justifies the need for modified drug delivery systems to improve its therapeutic performance.

Percentage Yield

The percentage yield of the prepared floating microspheres was determined to evaluate the efficiency of the preparation process.

The percentage yield ranged between 78.54% and 92.37%, indicating that the solvent evaporation method is suitable for preparing floating microspheres with minimal drug loss.

Higher polymer concentration resulted in improved yield due to increased viscosity of the polymeric solution, which reduced diffusion of drug particles into the external aqueous phase.

Table 2 Percentage yield of floating microsphere formulations

Formulation	Percentage Yield (%)
F1	78.54
F2	82.16
F3	85.32
F4	88.45
F5	92.37
F6	89.28

Particle Size Analysis

Particle size plays a crucial role in determining drug release rate, floating behavior, and gastric retention.

The mean particle size of the microspheres ranged from 220 µm to 395 µm. Increasing polymer concentration resulted in larger particle size due to higher viscosity of the polymer solution, which produced larger emulsion droplets during microsphere formation.

Table 3 Particle size of prepared microspheres

Formulation	Particle Size (µm)
F1	220 ± 6.2
F2	248 ± 7.1
F3	280 ± 6.9
F4	315 ± 8.5

F5	350 ± 9.1
F6	395 ± 9.4

Drug Entrapment Efficiency

Entrapment efficiency indicates the ability of the polymer matrix to retain the drug within the microspheres.

The entrapment efficiency ranged between 67.48% and 89.62%. Increasing polymer concentration improved drug entrapment because higher viscosity prevented drug diffusion into the external phase.

Table 4 Drug entrapment efficiency

Formulation	Entrapment Efficiency (%)
F1	67.48
F2	72.16
F3	78.35
F4	82.41
F5	89.62
F6	85.74

In-Vitro Buoyancy Study

Floating ability is a key parameter for gastro-retentive drug delivery systems.

The prepared microspheres showed excellent buoyancy in simulated gastric fluid (0.1 N HCl). The buoyancy percentage ranged from 72.16% to 95.48%, demonstrating their ability to remain afloat for prolonged periods.

Table 5 Buoyancy of floating microspheres

Formulation	Buoyancy (%)
F1	72.16
F2	78.45
F3	84.32
F4	88.57
F5	95.48
F6	91.36

Surface Morphology

The morphology of the microspheres was examined using scanning electron microscopy.

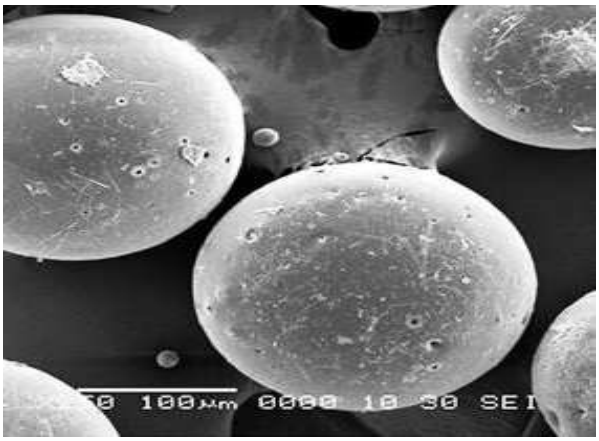


Figure 1 SEM image of floating microspheres

The SEM images revealed that the microspheres were spherical with a smooth surface and hollow internal structure, which is essential for floating behavior.

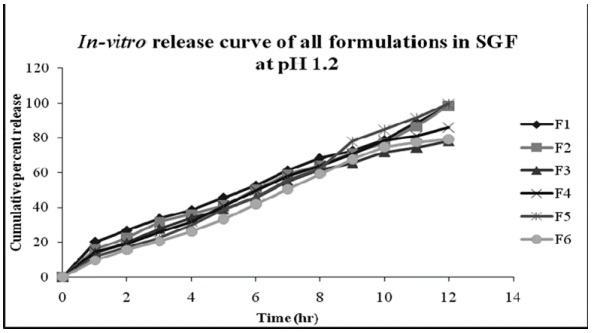
In-Vitro Drug Release Study

The drug release profile of pioglitazone from floating microspheres was evaluated in simulated gastric fluid. The formulations showed sustained drug release for up to 12 hours. The optimized formulation (F5) showed the highest drug release (94.12%) after 12 hours.

Table 6 In-vitro drug release profile

Time (hr)	F1	F2	F3	F4	F5	F6
1	18	16	15	14	12	13
2	28	26	24	22	20	21
4	42	39	37	35	32	34
6	55	52	49	46	44	45
8	68	64	60	57	55	58
10	80	77	74	71	69	70
12	90	88	85	82	94	87

Figure 2 Drug release profile of floating microspheres



The sustained drug release may be attributed to diffusion of the drug through the polymeric matrix of ethyl cellulose and HPMC.

Drug Release Kinetics

The dissolution data were fitted to various kinetic models.

Table 7 Drug release kinetic models

Model	R^2 value

Zero order	0.945
First order	0.962
Higuchi	**0.987**
Korsmeyer-Peppas	0.971

The optimized formulation followed the Higuchi model, indicating diffusion-controlled drug release from the polymeric matrix.

Discussion

Percentage Yield

The percentage yield of the prepared pioglitazone floating microspheres was found to be satisfactory, indicating the effectiveness of the solvent evaporation method in producing polymeric microspheres. The percentage yield of different formulations ranged between 78.54% and 92.37%. The variation in yield among different batches may be attributed to the loss of polymeric material during filtration and washing steps. It was observed that formulations containing higher concentrations of polymer exhibited slightly higher percentage yield due to increased viscosity of the polymeric solution, which facilitated better microsphere formation and minimized drug loss during preparation. Similar observations have been reported for polymeric floating microsphere systems prepared using solvent diffusion techniques [21].

Particle Size Analysis

Particle size is an important parameter influencing drug release behavior and floating ability of microspheres. The mean particle size of the prepared microspheres ranged from 220 ± 6.2 µm to 395 ± 9.4 µm. The results indicated that particle size increased with increasing polymer concentration. This increase can be attributed to the higher viscosity of the polymer solution, which produces larger emulsion droplets during the emulsification process. Larger droplets ultimately result in the formation of microspheres with increased particle size. These findings are consistent with previously reported studies on floating microspheres prepared using hydrophobic polymers such as ethyl cellulose [22].

Drug Entrapment Efficiency

Drug entrapment efficiency is a critical parameter that determines the effectiveness of microspheres in delivering the therapeutic agent. The entrapment efficiency of the prepared formulations was found to range from 67.48% to 89.62%. Higher polymer concentrations significantly improved drug entrapment efficiency. This improvement can be attributed to increased viscosity of the polymeric solution, which reduces the diffusion of the drug into the external aqueous phase during microsphere formation. Consequently, a greater proportion of the drug remains entrapped within the polymeric matrix. Similar trends have been reported in floating microsphere systems prepared using solvent evaporation techniques [23].

In-Vitro Buoyancy Study

The floating ability of microspheres plays a crucial role in achieving prolonged gastric residence time. The in-vitro buoyancy studies revealed that the prepared microspheres exhibited excellent floating behavior in simulated gastric fluid (0.1 N HCl). The buoyancy percentage ranged from 72.16% to 95.48%, indicating that the majority of the microspheres remained afloat for extended periods.

The enhanced buoyancy of the microspheres can be attributed to the formation of hollow internal cavities during solvent evaporation. These cavities reduce the overall density of the microspheres, allowing them to remain buoyant on the gastric fluid surface. The results confirm the suitability of the prepared microspheres as a gastro-retentive drug delivery system for prolonged drug release in the stomach [24].

Surface Morphology

The surface morphology of the prepared microspheres was examined using scanning electron microscopy (SEM). The SEM images revealed that the microspheres were **spherical in shape with a relatively smooth outer surface**. The internal hollow structure responsible for floating behavior was also observed in several microspheres.

The smooth surface of the microspheres indicates uniform polymer distribution during solvent evaporation. The formation of hollow cavities within the microspheres further confirms the successful preparation of floating microspheres using the emulsion solvent diffusion method. These structural characteristics are essential for maintaining buoyancy and sustaining drug release over an extended period [25].

In-Vitro Drug Release Study

The in-vitro drug release profiles of pioglitazone from the prepared floating microspheres were evaluated using simulated gastric fluid (0.1 N HCl, pH 1.2). The results demonstrated sustained drug release over a prolonged period of 12 hours.

Among the different formulations, formulation F5 exhibited the most desirable release profile, showing approximately 94.12% cumulative drug release within 12 hours. The sustained release behavior can be attributed to the diffusion of drug molecules through the polymeric matrix of ethyl cellulose and HPMC. Increasing polymer concentration resulted in slower

drug release due to increased matrix density and longer diffusion pathways.

The sustained release pattern observed in this study indicates that floating microspheres are capable of maintaining therapeutic drug levels over extended periods, which may reduce dosing frequency and improve patient compliance [26].

Drug Release Kinetics

To understand the mechanism of drug release, the dissolution data were fitted to various kinetic models including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models.

The optimized formulation showed the best fit with the Higuchi model (R^2 = 0.987), suggesting that drug release occurred predominantly through diffusion from the polymeric matrix. The Korsmeyer–Peppas model indicated a non-Fickian diffusion mechanism, suggesting that both diffusion and polymer relaxation contributed to drug release from the microspheres.

These results confirm that the prepared floating microspheres provide controlled and sustained drug delivery suitable for gastro-retentive systems [27].

Conclusion

The present study successfully developed pioglitazone-loaded floating microspheres as a gastro-retentive drug delivery system using the emulsion solvent diffusion–evaporation technique. The prepared microspheres exhibited satisfactory physicochemical characteristics including good percentage yield, appropriate particle size distribution, and high drug entrapment efficiency. The in-vitro buoyancy studies demonstrated that the microspheres possessed excellent floating ability, allowing them to remain buoyant in simulated gastric fluid for extended periods, which is essential for prolonged gastric retention.

Surface morphology analysis revealed that the microspheres were spherical with smooth surfaces and hollow internal structures, confirming successful formation of floating microspheres. The in-vitro drug release studies showed sustained release of pioglitazone for up to 12 hours, indicating the capability of the developed system to provide controlled drug delivery. The optimized formulation followed the Higuchi kinetic model, suggesting diffusion-controlled drug release from the polymeric matrix.

Overall, the developed floating microsphere formulation demonstrated promising potential as an effective gastro-retentive drug delivery system for pioglitazone, which may improve drug bioavailability, reduce dosing frequency, and enhance patient compliance in the management of type 2 diabetes mellitus.

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