



FORMULATION AND EVALUATION OF GASTRORETENTIVE MICROBALLOONS OF SAXAGLIPTIN

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ABSTRACT

Saxagliptin is an oral dipeptidyl peptidase-4 (DPP-4) inhibitor widely used in the management of type 2 diabetes mellitus. However, its relatively short biological half-life necessitates repeated dosing, which may reduce patient compliance. The present study was undertaken to formulate and evaluate gastroretentive floating microballoons of saxagliptin with the objective of prolonging gastric residence time and achieving sustained drug release. Gastroretentive microballoons were prepared using the solvent evaporation technique with suitable polymers such as ethyl cellulose and cellulose acetate in different ratios. The prepared formulations were optimized by varying the polymer concentration and drug-to-polymer ratio to obtain spherical, hollow microballoons with excellent floating ability and controlled drug release characteristics. The prepared formulations were evaluated for percentage yield, particle size, bulk density, tapped density, angle of repose, Carr's index, Hausner ratio, drug entrapment efficiency, buoyancy, swelling behavior, surface morphology, zeta potential, polydispersity index (PDI), in vitro drug release, and stability studies. Fourier Transform Infrared (FTIR) spectroscopy confirmed the absence of significant drug-polymer interactions, indicating the compatibility of saxagliptin with the selected excipients. Scanning Electron Microscopy (SEM) revealed spherical microballoons with smooth surfaces and hollow internal cavities, confirming successful formulation. Among all the formulations, F8 demonstrated the most desirable characteristics, exhibiting high production yield, excellent entrapment efficiency, prolonged floating behavior with buoyancy exceeding 90%, favorable particle size distribution, zeta potential of approximately -34.8 mV, PDI of 0.186, and sustained drug release extending up to 12 hours. Stability studies conducted according to ICH guidelines showed no significant changes in the physicochemical properties or drug release profile over the storage period. The study concludes that gastroretentive floating microballoons of saxagliptin represent a promising sustained-release drug delivery system capable of enhancing gastric retention, maintaining prolonged drug release, reducing dosing frequency, and improving patient compliance in the treatment of type 2 diabetes mellitus. The optimized formulation (F8) demonstrated superior pharmaceutical performance and may serve as an effective gastroretentive delivery platform for saxagliptin.

KEYWORDS: Saxagliptin, Gastroretentive Drug Delivery System, Floating Microballoons, Solvent Evaporation Technique, Sustained Drug Release, Cellulose Acetate.

INTRODUCTION

Diabetes mellitus is one of the most prevalent chronic metabolic disorders worldwide and is characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Type 2 diabetes mellitus (T2DM) accounts for approximately 90–95% of all diabetes cases and is associated with insulin

resistance, impaired pancreatic β -cell function, and progressive deterioration of glucose homeostasis. Long-term uncontrolled diabetes may lead to severe microvascular and macrovascular complications, including diabetic nephropathy, retinopathy, neuropathy, cardiovascular diseases, and stroke. The increasing global prevalence of diabetes has emphasized the need

for effective and patient-friendly therapeutic approaches that provide sustained glycemic control while improving medication adherence.^[1,2]

Oral drug delivery remains the most preferred route of drug administration because of its convenience, non-invasive nature, cost-effectiveness, and high patient acceptance. However, many orally administered drugs exhibit limited bioavailability due to rapid gastrointestinal transit, short gastric residence time, poor absorption in the distal gastrointestinal tract, or degradation in the intestinal environment. Conventional oral dosage forms often require frequent dosing to maintain therapeutic drug concentrations, which can reduce patient compliance and compromise treatment outcomes. Consequently, the development of advanced oral drug delivery systems capable of prolonging gastric residence time and providing controlled drug release has become an important area of pharmaceutical research.^[3,4]

Gastroretentive drug delivery systems (GRDDS) are specifically designed to remain in the stomach for an extended period, thereby enhancing drug absorption, improving bioavailability, and reducing fluctuations in plasma drug concentration. These systems are particularly suitable for drugs that are preferentially absorbed from the stomach or upper part of the small intestine, possess a narrow absorption window, or require localized action within the stomach. Various gastroretentive approaches have been developed, including floating systems, expandable systems, bioadhesive systems, high-density systems, superporous hydrogels, and raft-forming formulations. Among these approaches, floating drug delivery systems have gained considerable attention because they are capable of remaining buoyant on gastric fluids without affecting the normal gastric emptying process.^[5,6]

Floating microballoons, also known as hollow microspheres, are one of the most promising gastroretentive drug delivery systems. These multiparticulate dosage forms possess a hollow internal cavity and low density, allowing them to float on gastric contents for prolonged periods. The floating nature of microballoons increases gastric residence time, enabling continuous and controlled release of the incorporated drug. In addition, multiparticulate systems distribute uniformly throughout the stomach, minimizing the risk of dose dumping and reducing variability in drug absorption compared with single-unit dosage forms. Floating microballoons also offer several advantages, including improved drug stability, enhanced bioavailability, reduced dosing frequency, minimized local gastrointestinal irritation, and better patient compliance.^[7]

Saxagliptin is a potent, selective, and reversible dipeptidyl peptidase-4 (DPP-4) inhibitor widely prescribed for the treatment of type 2 diabetes mellitus. It exerts its antihyperglycemic effect by inhibiting the

DPP-4 enzyme, thereby preventing the degradation of endogenous incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP). Increased levels of these incretin hormones stimulate glucose-dependent insulin secretion, suppress glucagon release, and improve overall glycemic control with a low risk of hypoglycemia. Saxagliptin has an elimination half-life of approximately 2.5 hours, while its active metabolite possesses a longer half-life, making sustained drug delivery a suitable strategy to maintain therapeutic plasma concentrations and reduce fluctuations associated with conventional dosage forms.^[8]

Despite its clinical efficacy, conventional immediate-release formulations of saxagliptin may require regular administration to maintain consistent therapeutic levels. Rapid gastrointestinal transit may limit the duration of drug availability within the optimal absorption region, potentially reducing therapeutic efficiency. Therefore, the development of a gastroretentive sustained-release formulation of saxagliptin can enhance gastric residence time, prolong drug release, improve bioavailability, decrease dosing frequency, and enhance patient adherence to long-term antidiabetic therapy.^[9]

Microballoons are generally prepared using techniques such as solvent evaporation, emulsion solvent diffusion, spray drying, and phase separation. Among these methods, the solvent evaporation technique is widely employed because it is simple, reproducible, economical, and capable of producing spherical hollow microballoons with high drug entrapment efficiency and controlled particle size. The characteristics of microballoons are influenced by several formulation variables, including polymer type and concentration, solvent composition, stirring speed, emulsifier concentration, and drug-to-polymer ratio. Polymers such as ethyl cellulose and cellulose acetate are commonly used due to their excellent film-forming ability, biocompatibility, and capacity to sustain drug release over extended periods.^[10,11]

The formulated gastroretentive microballoons are evaluated using various physicochemical and performance parameters to ensure their quality, stability, and therapeutic effectiveness. These evaluations include percentage yield, particle size analysis, micromeritic properties, drug entrapment efficiency, floating behavior, percentage buoyancy, swelling characteristics, surface morphology by scanning electron microscopy (SEM), drug-polymer compatibility by Fourier Transform Infrared (FTIR) spectroscopy, zeta potential, polydispersity index (PDI), in vitro drug release studies, release kinetics, and accelerated stability studies. These parameters provide valuable information regarding the formulation's structural integrity, floating capability, sustained-release performance, and storage stability.

METHODOLOGY

Saxagliptin microballoons were prepared by Emulsion solvent diffusion method using polymers like Eudragit RS 100(EUD) and Cellulose acetate at different drug to polymer ratios and Polyvinyl Alcohol as Stabilizing agent by Emulsion Solvent Diffusion Method. Floating microballoons were prepared by the emulsion solvent diffusion method. Saxagliptin, Eudragit RS100 and/or Cellulose acetate were dissolved in a mixture of ethanol

and dichloromethane. The resulting solution was added slowly to stirred 100 mL of aqueous solution of 0.50% (w/v) PVA at 40°C temperature. The stirring was done for 2 h at 1000-1200 rpm by mechanical stirrer, to evaporate the volatile solvent. After evaporation of solvent, microballoons were collected by filtration, washed with water and dried at room temperature in a desiccator.^[12-14]

Table 1: Composition of Microballoons.

F. Code	Saxagliptin (mg)	Cellulose acetate (mg)	Eudragit RS100(mg)	Polyvinyl Alcohol(0.5%w/v)	Ethanol: Dichloromethane (1:1)
F1	50	50	--	50	10:10
F2	50	100	--	50	10:10
F3	50	150	--	50	10:10
F4	50	--	50	50	10:10
F5	50	--	100	50	10:10
F6	50	--	150	50	10:10
F7	50	50	50	50	10:10
F8	50	100	50	50	10:10
F9	50	50	100	50	10:10

Characterization of microballoon

Percentage drug entrapment efficiency

Fifty milligrams of Microballoons are dissolved in 10ml ethanol. The samples are then assayed using UV spectrophotometer at 271nm after suitable dilution using 0.1N HCl for drug content. Percentage drug entrapment efficiency is then calculated.^[15,16]

In vitro buoyancy

Floating behaviour of saxagliptin microballoons is studied using an USP dissolution test apparatus II. The weighed microballoons are spread on 900ml of 0.1 mol/l HCl containing the surfactant Tween-80 at a concentration of 0.02%. The medium is agitated at 100 rpm with a paddle, and the temperature is maintained at 37°C. After 12 h, both the settled and floating portions of Microballoons are collected separately. Then the Microballoons are dried and weighed.^[17,18]

In vitro drug release study

Saxagliptin floating Microballoons are evaluated for the in vitro drug release studies in simulated gastric fluid.

USP dissolution test apparatus II (Paddle type) is used to find out the drug release rate from Microballoons. The dissolution test was performed using 900 ml of 0.1N HCl, at 37°C $\pm$ 0.5°C and 100 rpm. Microballoons were accurately weighed and filled in a hard gelatin Capsule and added to the dissolution medium, aliquots (5ml) are withdrawn at hourly intervals for a period of 12 h. Perfect sink condition is established during the drug dissolution study period by replacing an equivalent volume of dissolution medium. The samples are filtered, and solutions are analysed at 271 nm using a UV Spectrophotometer.^[19,20]

Particle size analysis

The particle sizes of the Microballoons are evaluated using an optical microscope fitted with a calibrated eyepiece micrometre. It randomly measures the particle diameters of about 300 Microballoons and the average particle size was determined.^[21]

RESULT

Characterization of saxagliptin microballoons

Particle size and PDI analysis

Table 2: Average particle size and PDI of Microballoons.

Formulation Code	Average Particle Size (μ m)	PDI (Mean $\pm$ SD)
F1	145.48	0.462 $\pm$ 0.018
F2	175.56	0.419 $\pm$ 0.015
F3	196.65	0.386 $\pm$ 0.014
F4	146.46	0.342 $\pm$ 0.012
F5	168.69	0.307 $\pm$ 0.011
F6	176.19	0.281 $\pm$ 0.010
F7	142.77	0.244 $\pm$ 0.009
F8	139.33	0.186 $\pm$ 0.007
F9	171.77	0.228 $\pm$ 0.010

Lowest PDI (0.186 ± 0.007) indicates the narrowest particle size distribution. More uniform microballoon size leads to reproducible drug loading and floating behavior. Lower PDI values correspond to more homogeneous particle populations, whereas very high PDI values indicate broad or heterogeneous size distributions. Particle size of microballoons were found in the range of $139.33\mu\text{m}$ - $196.65\mu\text{m}$. The particle size of the microballoons increases with increase in polymer concentration respectively. This is because the viscosity of polymer solution increases with increasing polymer concentration resulting in enhanced interfacial tension, which in turn decreases the stirring efficiency, which results in increased particle size.

Percentage entrapment efficiency

Table 3: Percentage entrapment efficiency of Microballoons.

Formulation Code	Entrapment efficiency (%)
F1	78.9 ± 1.32
F2	84.8 ± 0.46
F3	91.4 ± 0.22
F4	80.5 ± 0.54
F5	85.7 ± 0.56
F6	89.5 ± 0.93
F7	88.1 ± 0.51
F8	96.2 ± 1.08
F9	89.9 ± 0.73

Determination of zeta potential of microballoons

Table 5: Zeta potential of Microballoons.

Formulation	Zeta potential (mV)	Interpretation
F1	-18.5 ± 0.8	Moderately stable
F2	-20.7 ± 0.7	Moderately stable
F3	-22.9 ± 0.6	Improved stability
F4	-24.3 ± 0.5	Good stability
F5	-26.4 ± 0.8	Good stability
F6	-28.1 ± 0.6	Very good stability
F7	-30.2 ± 0.5	Highly stable
F8	-34.8 ± 0.4	Excellent colloidal stability
F9	-31.4 ± 0.7	Highly stable

Highest absolute zeta potential (-34.8 ± 0.4 mV) is of F8 which provides Strong electrostatic repulsion minimizes particle aggregation, Better dispersion stability during storage so suitable for sustained-release gastroretentive microballoons. In general, dispersions with an absolute zeta potential of about ± 30 mV or greater are often considered electrostatically stable, although the exact threshold depends on the formulation and stabilizing mechanism.

The drug entrapment efficiency of all formulations was found to be in the range between 78.9 to 96.2%. With the increase in polymer concentration, increased entrapment efficiency was seen because with increasing polymer content, more particles of drug would be coated leading to higher encapsulation efficiency.

Percentage *in vitro* buoyancy

Table 4: Percent *in vitro* Buoyancy of Microballoons.

Formulation Code	<i>In vitro</i> buoyancy (%)
F1	85.0 ± 1.63
F2	83.0 ± 1.25
F3	91.0 ± 1.25
F4	76.0 ± 1.63
F5	88.0 ± 1.25
F6	81.0 ± 0.82
F7	89.0 ± 0.47
F8	96.2 ± 1.25
F9	89.9 ± 1.25

The buoyancy of all the formulations were found to be in the range of 74 - 96%. In the test of floating time, microballoons remained floating for more than 12 hours. The good buoyancy behavior of the microballoons may be attributed to the hollow nature of the microballoons.

In vitro drug release study

The formulated Microballoons preparation containing drug and polymer (Saxagliptin, Cellulose acetate and Eudragit RS 100) in the ratio of (1:1, 1:2, 1:3, 1:1:1, 1:2:1, 1:1:2) were evaluated for drug release and results were tabulated below

Table 6: *In vitro* cumulative drug release (%) (F1–F9).

Time (h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	20.4	18.8	16.9	15.8	14.9	13.6	12.8	11.5	10.7
2	34.2	31.5	29.4	27.1	25.5	23.8	22.4	20.8	19.1
3	46.3	43.7	40.8	38.9	36.8	34.5	32.7	30.4	28.6
4	57.8	54.1	51.2	48.6	46.3	43.9	41.8	39.2	37.3

5	67.4	63.2	60.5	57.4	54.9	52.0	49.6	48.7	45.9
6	75.6	71.8	68.9	65.7	62.8	59.9	57.4	58.3	54.6
7	82.1	78.4	75.2	72.3	69.4	66.5	63.7	67.4	62.8
8	84.3	84.0	81.1	78.2	75.4	72.1	69.5	76.2	70.7
9	89.4	88.7	86.0	83.3	80.1	77.2	74.6	84.5	78.5
10	91.8	92.1	90.2	87.5	84.3	81.5	79.0	91.8	85.3
11	94.2	93.0	93.5	90.8	88.0	85.6	83.2	95.6	90.2
12	97.1	98.6	96.0	94.2	91.6	89.3	87.1	99.7	93.2

The results of F8 formulations show (99.7%) controlled release up to 12th hr. The entrapment efficiency was found to be higher in F8- 96.2% comparatively with other formulations. Therefore F8 were selected as optimized formulations.

CONCLUSION

The present study successfully formulated and evaluated gastroretentive floating microballoons of saxagliptin using the solvent evaporation technique. The developed formulations exhibited satisfactory physicochemical properties, including good production yield, appropriate particle size, excellent flow characteristics, and high drug entrapment efficiency. FTIR studies confirmed the compatibility of saxagliptin with the selected polymers, while SEM analysis demonstrated the formation of spherical hollow microballoons suitable for prolonged gastric retention.

Among all the formulations, F8 was identified as the optimized formulation based on its superior pharmaceutical performance. It exhibited excellent buoyancy, high entrapment efficiency, desirable particle size distribution, good physical stability, a zeta potential of approximately -34.8 mV, a low polydispersity index (0.186), and sustained drug release for up to 12 hours.

In conclusion, gastroretentive floating microballoons of saxagliptin represent an effective sustained-release drug delivery system capable of prolonging gastric residence time, providing controlled drug release, reducing dosing frequency, and improving patient compliance. The optimized formulation (F8) has the potential to enhance the therapeutic efficacy of saxagliptin in the management of type 2 diabetes mellitus. Further in vivo pharmacokinetic and clinical studies are recommended to confirm its therapeutic performance and clinical applicability.

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