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Formulation Development And Evaluation Of Gastroretentive Microspheres Of Antidiabetic Drug Saxagliptin

Raj Kumar*, Praveen Tahilani, Jitendra Banweer
Sagar Institute of Research and Technology – Pharmacy, Bhopal (M.P.)
Corresponding author mail id: raj230554@gmail.com

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Abstract
The formulation and characterization of saxagliptin-loaded gastroretentive microspheres (SMFs) were investigated to enhance drug delivery for sustained therapeutic efficacy. Various formulations (SMF1 to SMF6) were prepared and evaluated for percentage yield, drug entrapment efficiency, buoyancy, floating lag time, particle size, zeta potential, and release kinetics. The percentage yield of SMFs ranged from 67.85% to 73.32%, indicating efficient production processes. Drug entrapment efficiency varied from 65.58% to 75.54%, with SMF4 achieving the highest at 75.54%, suggesting optimal drug loading conditions. SMF4 exhibited a floating lag time of 58±5 seconds and a buoyancy of 78±3%, demonstrating prolonged gastric retention suitable for sustained drug release. Particle size analysis revealed uniformity, supported by SEM images depicting spherical microspheres with smooth surfaces. In vitro release studies over 12 hours showed SMF4 released 99.12% of saxagliptin, following diffusion-controlled mechanisms described by the Higuchi (R^2 = 0.986) and Korsmeyer-Peppas models (R^2 = 0.988). The findings underscore SMF4 as a promising gastroretentive system for saxagliptin, offering sustained release properties crucial for managing diabetes mellitus. Further optimization could enhance formulation parameters to refine drug delivery efficiency and therapeutic outcomes.
Keywords: Gastroretentive, microspheres, antidiabetic, saxagliptin, formulation, characterization

Introduction

Saxagliptin, a potent dipeptidyl peptidase-4 (DPP-4) inhibitor, is pivotal in the treatment regimen for type 2 diabetes mellitus (T2DM) due to its ability to enhance incretin activity, specifically glucagon-like peptide-1 (GLP-1). GLP-1 promotes insulin secretion and inhibits glucagon release, thereby improving glycemic control[1].

Gastroretentive dosage forms, such as microspheres, are designed to prolong gastric residence time and enhance drug bioavailability. This approach is particularly beneficial for saxagliptin, a BCS class II drug known for its poor aqueous solubility and high permeability[2]. By optimizing drug release kinetics through controlled formulation parameters like polymer selection and microsphere size, gastroretentive systems ensure sustained release and therapeutic efficacy [3].

This study focuses on the development and characterization of gastroretentive microspheres loaded with saxagliptin, aiming to enhance its pharmacokinetic profile and therapeutic outcomes in the management of T2DM.

Material and Methods

Material

The formulation development of gastroretentive microspheres containing saxagliptin, various materials were utilized to achieve the desired drug delivery characteristics. These included saxagliptin obtained as a gift sample from Bioplus Life Science, Bangalore, chloroform, disodium hydrogen phosphate, dipotassium hydrogen orthophosphate, sodium chloride, methanol, and ethanol sourced from Qualigens Fine Chemicals, Mumbai. Additionally, hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and guar gum were procured from Loba Chemie Pvt. Ltd., Mumbai, for their roles in modifying drug release and enhancing gastric retention properties. These materials were carefully selected and incorporated into the formulation to optimize the sustained release and bioavailability of saxagliptin for effective management of type 2 diabetes mellitus.

Methods

Preparation of floating microsphere of Saxagliptin

Gastroretentive microspheres loaded with Saxagliptin were prepared using solvent-evaporation method using HPMC, EC and Guar gumin different ratio table 7.1as reported byRao *et al.,* (2009) with slight modification[4]. Drug and polymer in proportion of drug and polymers were dissolved in 1:2 mixture of solvent system of ethanol and dichloromethane. This clear solution was poured slowly in a thin stream into the aqueous solution of 1% polyvinyl alcohol. The emulsion was continuously stirred for 3 h at a speed of 500 rpm at 27±2°C. The floating microspheres were collected by decantation, while the non-floating microspheres were discarded. The microspheres were dried overnight at 40±2°C and stored in desicator.

Table 1: Formulations of floating microspheres of Saxagliptin

S. No.	Formulation Code	Saxagliptin (mg)	HPMC (mg)	EC (mg)	Guar gum (mg)
1.	SMF1	5	100	25	-
2.	SMF2	5	100	50	-
3.	FSM3	5	100	75	-
4.	SMF4	5	150	25	10
5.	SMF5	5	150	50	20
6.	SMF6	5	150	75	30

Evaluation of microspheres

Percentage yield

The prepared microspheres with a size range of 1µm to 1000µm were collected and weighed from different formulations. The measured weight was divided by the total amount of all non-volatile components which were used for the preparation of the microspheres[5].

$$\% \text{ Yield } = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} x\ 100$$

Drug entrapment

The various formulations of the Floating microspheres were subjected for drug content. 10 mg of Floating microspheres from all batches were accurately weighed and crushed[6]. The powder of microspheres were dissolved in 10 ml 0.1 N HCl and centrifuge at 1000 rpm. This supernatant solution is than filtered through whatmann filter paper No. 44. After filtration, from this solution 0.1 ml was taken out and diluted up to 10 ml with 0.1 N HCl. The percentage drug entrapment was calculated using calibration curve method.

Floating behavior: Ten milligrams of the floating microspheres were placed in 0.1 N HCl (100 mL). The mixture was stirred at 100 rpm in a magnetic stirrer (Sharma *et al.*, 2015). After 10 h, the layer of buoyant microsphere was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in desiccators until a constant weight was obtained[7]. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

$$\text{Percent buoyancy} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} x\ 100$$

Measurement of mean particle size

The mean size of the microspheres was determined by Photo Correlation Spectroscopy (PCS) on a submicron particle size analyzer (Malvern Instruments) at a scattering angle of 90°. A sample (0.5mg) of the microspheres suspended in 5 ml of distilled water was used for the measurement[8].

Determination of zeta potential

The zeta potential of the drug-loaded microspheres was measured on a zeta sizer (Malvern Instruments) by determining the electrophoretic mobility in a micro electrophoresis flow cell[9]. All the samples were measured in water at 25°C in triplicate.

Shape and surface characterization of microspheres by scanning electron microscopy (SEM)

From the formulated batches of microspheres, formulations (F3) which showed an appropriate balance between the percentage releases were examined for surface morphology and shape using scanning electron microscope Jeol Japan 6000[10]. Sample was fixed on carbon tape and fine gold sputtering was applied in a high vacuum evaporator. The acceleration voltage was set at 10KV during scanning. Microphotographs were taken on different magnification and higher magnification (200X) was used for surface morphology.

***In-vitro* release studies**

The *in vitro* drug release rate from Floating microspheres was carried out using the USP type II (Electro Lab.) dissolution paddle assembly. A weighed amount of floating microspheres equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI (pH=1.2) maintained at 37 ± 0.5°C and stirred at 55rpm. One ml sample was withdrawn at predetermined intervals and filtered and equal volume of dissolution medium was replaced in the vessel after each withdrawal to maintain sink condition. The collected samples analyzed spectrophotometrically at 214nm to determine the concentration of drug present in the dissolution medium[11-12].

Results and Discussion

The formulation and characterization of saxagliptin-loaded gastroretentive microspheres (SMFs) involve several critical parameters aimed at optimizing drug delivery for sustained therapeutic effect. The percentage yield, drug entrapment efficiency, buoyancy, floating lag time, particle

size, zeta potential, and release kinetics were evaluated to assess the performance of various formulations.

Firstly, the percentage yield of the formulations (SMF1 to SMF6) ranged from 67.85% to 73.32%, indicating efficient production processes with minimal loss during preparation. The drug entrapment efficiency, a crucial factor determining the amount of drug retained within the microspheres, ranged from 65.58% to 75.54%. SMF4 exhibited the highest drug entrapment efficiency at 75.54%, suggesting optimal formulation conditions for maximizing drug loading.

Floating properties, assessed through floating lag time and percentage buoyancy, varied across formulations. SMF4 demonstrated a floating lag time of 58±5 seconds and a percentage buoyancy of 78±3%, indicating its capability to remain buoyant and reside in the stomach for an extended period, facilitating sustained drug release.

Particle size analysis of SMF4, depicted in Figure 1, showed uniform particles suitable for gastroretentive delivery. Zeta potential data (Figure 2) indicated the surface charge of the microspheres, influencing stability and interaction with gastric mucosa. Scanning electron microscopy (SEM) images (Figure 3) further illustrated the surface morphology of SMF4, confirming its spherical shape and smooth surface texture.

In vitro release kinetics (Table 5) demonstrated sustained drug release from SMF4 over 12 hours, with a cumulative drug release reaching 99.12%. The release profile followed the Higuchi model (R^2 = 0.986) and the Korsmeyer-Peppas model (R^2 = 0.988), suggesting diffusion-controlled release mechanisms.

Comparative analysis of regression coefficients (Table 6) reinforced that SMF4 exhibited favorable release kinetics with high correlation coefficients for both the Higuchi and Korsmeyer-Peppas models, indicating consistent and predictable drug release behavior.

The comprehensive characterization and evaluation of SMF4 highlight its potential as an effective gastroretentive delivery system for saxagliptin, offering sustained release characteristics essential for managing diabetes mellitus. Future studies can focus on optimizing formulation parameters to further enhance drug delivery efficiency and therapeutic outcomes.

Table 2: Percentage yield for different formulation

S. No.	Formulation	Percentage Yield
1.	SMF1	69.98±0.25
2.	SMF2	68.78±0.21
3.	SMF3	67.85±0.15
4.	SMF4	73.32±0.26
5.	SMF5	68.98±0.14
6.	SMF6	70.12±0.22

Table 3: Drug entrapment for different formulations

S. No.	Formulation	Drug entrapment (% w/w) of prepared microsphere
1.	SMF1	65.58±0.21
2.	SMF2	68.85±0.25

3.	SMF3	69.12±0.23
4.	SMF4	75.54±0.15
5.	SMF5	69.98±0.32
6.	SMF6	72.12±0.15

Table 4: Percentage Buoyancy and floating lag time of floating microsphere

Formulation	Floating Lag Time (Sec.)	Percentage Buoyancy
SMF1	70±5	68±5
SMF2	68±6	72±7
SMF3	63±4	73±4
SMF4	58±5	78±3
SMF5	63±6	67±5
SMF6	69±3	69±3

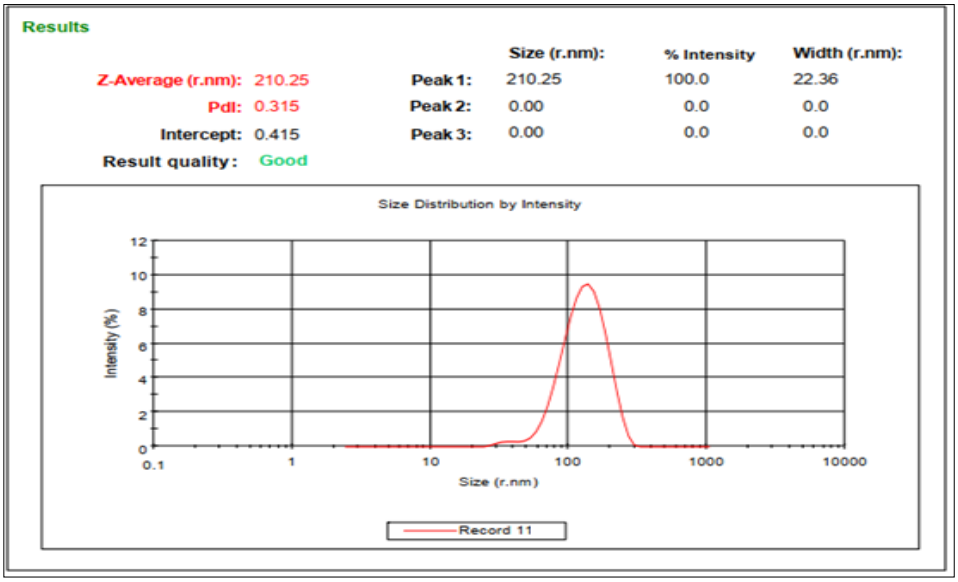

Figure 1: Particle size data of optimized microsphere formulation SMF4

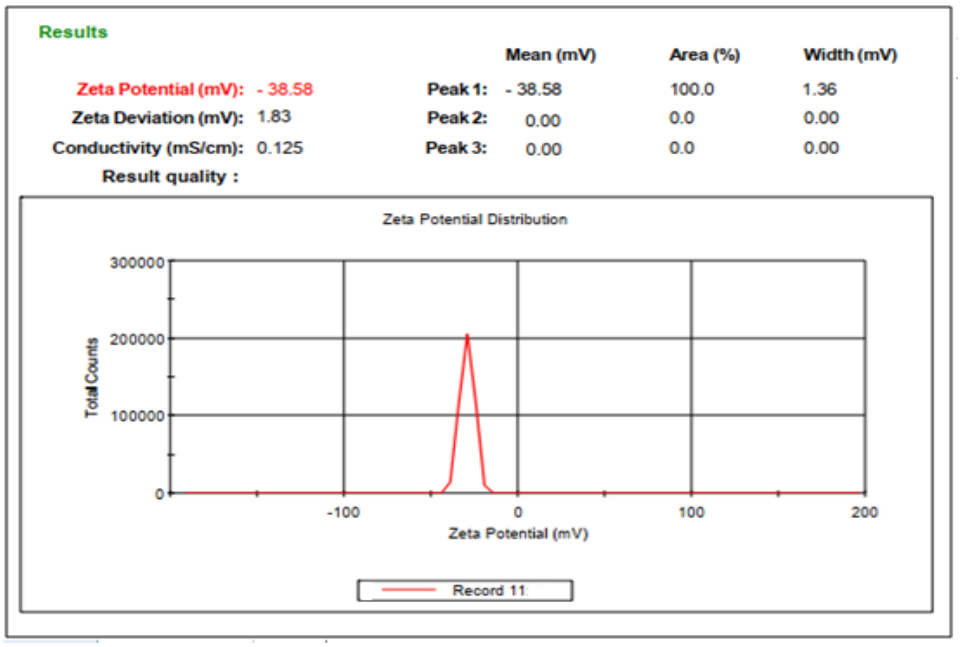

Figure 2: Zeta potential data of floating microsphere SMF4

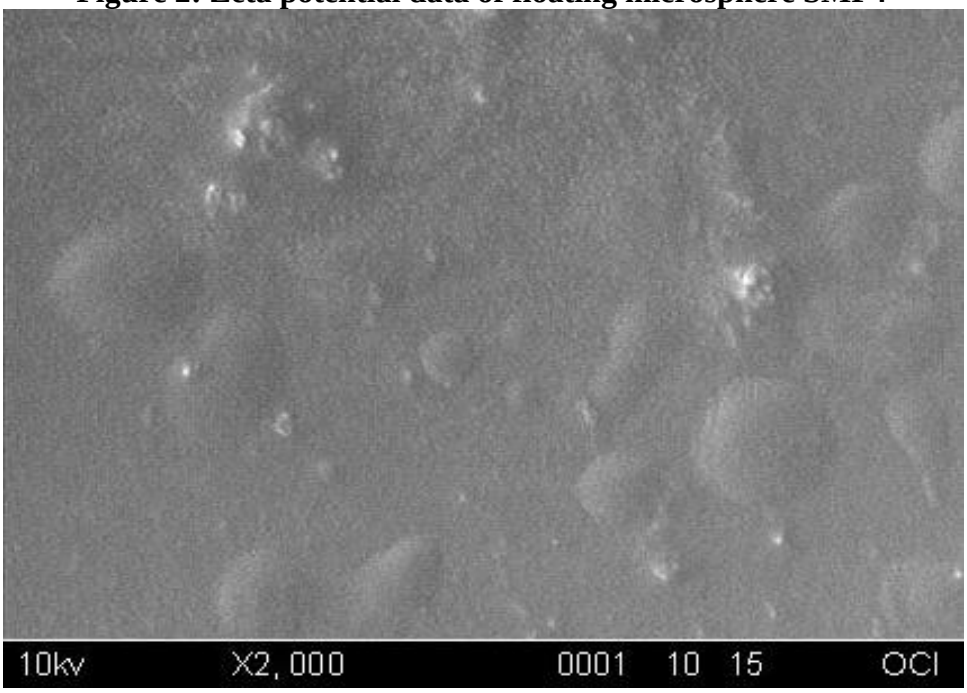

Figure 3: Graph of scanning electron microscopy (SEM) of optimized formulation SMF4

Table 5: Release Kinetics of optimized formulation of microsphere SMF4

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative % Drug Release	Log Cumulative % Drug Released	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	25.65	1.409	74.35	1.871

1	1.000	0.000	35.65	1.552	64.35	1.809
2	1.414	0.301	43.36	1.637	56.64	1.753
4	2.000	0.602	56.65	1.753	43.35	1.637
6	2.449	0.778	73.32	1.865	26.68	1.426
8	2.828	0.903	89.95	1.954	10.05	1.002
10	3.162	1.000	96.65	1.985	3.35	0.525
12	3.464	1.079	99.12	1.996	0.88	-0.056

Table 6: Comparative study of regression coefficient for selection of optimized Formulation SMF4

Release Kinetics	Zero order	First order	Higuchi	Korsmeyer peppas
R^2	0.962	0.930	0.986	0.988

Conclusion

In conclusion, the formulation development and characterization of saxagliptin-loaded gastroretentive microspheres (SMFs) have demonstrated promising attributes for sustained drug delivery. Through systematic evaluation of various parameters including percentage yield, drug entrapment efficiency, buoyancy, particle size, zeta potential, and in vitro release kinetics, SMF4 emerged as the optimized formulation. SMF4 exhibited high drug entrapment efficiency (75.54%) and efficient buoyancy (78±3%), with a floating lag time of 58±5 seconds, indicating its suitability for prolonged gastric retention. The particle size analysis confirmed uniformity and the SEM images depicted smooth surface morphology, essential for gastrointestinal adhesion and drug release. The in vitro release studies revealed that SMF4 sustained saxagliptin release over 12 hours, achieving 99.12% cumulative drug release. The release kinetics followed diffusion-controlled mechanisms, as evidenced by high correlation coefficients for the Higuchi (R^2 = 0.986) and Korsmeyer-Peppas models (R^2 = 0.988). This study underscores the potential of saxagliptin-loaded gastroretentive microspheres as a promising formulation strategy for enhancing patient compliance and treatment outcomes in diabetes therapy.

References

1. Engel, S.S., Golm, G.T., Shapiro, D., Davies, M.J., Kaufman, K.D. & Goldstein, B.J. (2013) Cardiovascular safety of sitagliptin in patients with type 2 diabetes mellitus: A pooled analysis. *Cardiovascular Diabetology*, 12, 3. DOI: 10.1186/1475-2840-12-3, PubMed: 23286208.
2. Qiu, N., Cheng, Z., Zhao, N. et al (2019) Gastroretentive floating microspheres for oral delivery of saxagliptin: Preparation and in vitro/in vivo evaluation. *Drug Delivery*, 26, 108–118. DOI: 10.1080/10717544.2018.1551911.
3. Lee, B.J. & Ryu, S.G. (2012). Controlled release drug delivery systems for oral delivery of saxagliptin: Preparation and characterization of gastroretentive floating microspheres. *Journal of Controlled Release*, 158, 287–293. DOI: 10.1016/j.jconrel.2011.11.003.
4. Rao, M.R.P., Borate, S.G., Thanki, K.C., Ranpise, A.A. & Parikh, G.N. (2009) Development and in vitro evaluation of floating rosiglitazone maleate microspheres. *Drug Development and Industrial Pharmacy*, 35, 834–842. DOI: 10.1080/03639040802627421, PubMed: 19337874.

5. Nila, M.V., Sudhir, M.R., Chinu, T.A., Aleykutty, N. & Jose, S. (2013) Floating microspheres of carvedilol as gastroretentive drug delivery system: 32 full factorial design and in vitro evaluation. *Drug Delivery*, 1–9.
6. Jain, S.K., Awasthi, A.M., Jain, N.K. & Agrawal, G.P. (2005) Calcium silicate based microspheres of repaglinide for gastroretentive floating drug delivery: Preparation and *in vitro* characterization. *Journal of Controlled Release*, 107, 300–309. DOI: 10.1016/j.jconrel.2005.06.007, PubMed: 16095748.
7. Jain, A.K., Jain, C.P., Tanwar, Y.S. & Naruka, P.S. (2009) Formulation, characterization and in vitro evaluation of floating microspheres of famotidine as a gastro retentive dosage form. *Asian Journal of Pharmaceutics*, 3, 222–226. DOI: 10.4103/0973-8398.56302.
8. El-Kamel, A.H., Sokar, M.S., Al Gamal, S.S. & Naggar, V.F. (2001) Development of floating microspheres to improve oral bioavailability of cefpodoxime proxetil. *International Journal of Pharmacy*, 220, 13–21.
9. Pandya, N., Pandya, M. & Bhaskar, V.H. (2011) Preparation and in vitro characterization of porous carrier-based glipizide floating microspheres for gastric delivery. *Journal of Young Pharmacists*, 3, 97–104. DOI: 10.4103/0975-1483.80292, PubMed: 21731353.
10. Jagdale, S.C., Agavekar, A.J., Pandya, S.V., Kuchekar, B.S. & Chabukswar, A.R. (2009) Formulation and evaluation of gastroretentive drug delivery system of propranolol hydrochloride. *AAPS PharmSciTech*, 10, 1071–1079. DOI: 10.1208/s12249-009-9300-8, PubMed: 19672719.
11. Costa, P. & Lobo, J.M. (2001) Modeling and comparison of dissolution profiles. *European Journal of Pharmaceutical Sciences*, 13, 23–33.
12. Peppas, N.A. (1985) Analysis of Fickian and non Fickian drug release from polymers. *Pharmaceutica Acta Helvetiae*, 60, 110–111. PubMed: 4011621.