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RESEARCH ARTICLE

FLOATING MICROSPHERE AS NOVEL APPROACH DRUG DELIVERY SYSTEM

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ABSTRACT

The present study was carried out to develop Saxagliptin drug delivery System in the form of microsphere dosage form of Saxagliptin by using EC and HPMC and thereafter formulating the formulation. From the study it is observed that formulation act as prolonged dosage form. As the stirring speed increased the size of microsphere decreases and increases the released rate drug. The prepared microsphere of saxagliptin also gave good percent yield, drug entrapment and *Invitro* release. The microspheres of F3 batch were found to be satisfactory in terms of\ percent yield, percent drug entrapment and *In-vitro* release.

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INTRODUCTION

Medication activity can be enhanced by growing new medication conveyance framework, for example, the microsphere sedate conveyance framework. These frameworks stay in close contact with the ingestion tissue, the mucous layer, discharging the medication at the activity site prompting a bioavailability increment and both nearby and foundational impacts (Carvalho *et al.,* 2010). The oral course of medication organization constitutes the most helpful and favored methods for sedate conveyance to foundational dissemination of body. However oral organization of the greater part of the medications in traditional measurements frames has here and now restrictions because of their failure to limit and confine the framework at gastro-intestinal tract. Microspheres constitute an essential piece of these particulate medication conveyance frameworks by uprightness of their little size and productive bearer limit. Microspheres are the bearer connected medication conveyance framework in which molecule estimate is ranges from 1-1000 µm extend in distance across having a center of medication and completely external layers of polymer as covering material. Be that as it may, the accomplishment of these microspheres is restricted because of their short habitation time at site of assimilation. It would, in this way be worthwhile to have implies for giving a private contact of the medication conveyance framework with the engrossing layer.

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Microspheres have focal points like proficient retention and upgraded bioavailability of the medications because of a high surface to volume proportionMicrospheres incorporate microparticles and microcapsules (having a center of medication) of 1-1000µm in distance across and comprising either totally of a floating polymer or having an external covering of it, individually. Microspheres, as a rule, can possibly be utilized for focused and controlled discharge sedate conveyance; however coupling of floating properties to microspheres has extra preferences e.g. effective assimilation and bioavailability of the medications because of high surface to volume proportion, a considerably more personal contact with the mucous layer, particular focusing of medications to the ingestion site.

Types of microspheres

Bio Adhesive microspheres: Adhesion can be defined as sticking of drug to the membrane by using the sticking property of the water soluble polymers. Adhesion of drug delivery device to the mucosal membrane such as buccal, ocular, rectal, nasal etc can be termed as bioadhesion. The term "bioadhesion" describes materials that bind to biological substrates', such as mucosal members. Adhesion of Bioadhesive drug delivery devices to the mucosal tissue offers the possibility of creating an intimate and prolonged contact at the site of administration. This prolonged residence time can result in enhanced absorption and in combination with a controlled release of drug also improved patient compliance by reducing the frequency of administration.

Carrier technology offers an intelligent approach for drug delivery by coupling the drug to a carrier particle such as microspheres, nanospheres, liposomes, nanoparticles, etc., which modulates the release and absorption of the drug. Microspheres constitute an important part of these particulate drug delivery systems by virtue of their small size and efficient carrier capacity (Patel, 2012).

Magnetic microspheres: This kind of delivery system is very much important which localises the drug to the disease site. In this larger amount of freely circulating drug can be replaced by smaller amount of magnetically targeted drug. Magnetic carriers receive magnetic responses to a magnetic field from incorporated materials that are used for magnetic microspheres are chitosan, dextran etc.4 The different type are Therapeutic magnetic microspheres are used to deliver chemotherapeutic agent to liver tumour. Drugs like proteins and peptides can also be targeted through this system (Patel, 2010).

Floating microspheres: In floating types the bulk density is less than the gastric fluid and so remains buoyant in stomach without affecting gastric emptying rate. The drug is released slowly at the desired rate, if the system is floating on gastric content, increases gastric residence and fluctuation in plasma concentration. It also reduces chances of striking and dose dumping and produces prolonged therapeutic effect. Drug (ketoprofen) given through this form (Najmuddin *et al.,* 2012).

Radioactive microspheres: Radio emobilisation therapy microspheres sized 10-30 nm are of larger than capillaries and gets tapped in first capillary bed when they come across. They are injected to the arteries that lead to tumour of interest. So these radioactive microspheres deliver high radiation dose to the targeted areas without damaging the normal surrounding tissues. It differs from drug delivery system, as radio activity is not released from microspheres but acts from within a radioisotope typical distance and the different kinds of radioactive microspheres are α emitters, β emitters, γ emitters (Yadav and Mote, 2008).

Mucoadhesive microspheres: Mucoadhesive microspheres which are of 1-1000mm in diameter and consisting either entirely of a mucoadhesive polymer or having an outer coating of it and coupling of mucoadhesive properties to microspheres has additional advantages, e.g. efficient absorption and enhanced bioavailability of the drugs due to a high surface to volume ratio, a much more intimate contact with the mucus layer, specific targeting of drug to the absorption site achieved by anchoring plant lectins, bacterial adhesions and antibodies, etc. on the surface of the microspheres. Mucoadhesive microspheres can be tailored to adhere to any mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offeringthe possibilities of localized as well as systemic controlled release of drugs (Chowdary *et al.,* 2004).

Points of interest of microspheres drug delivery system

- Because of bond and personal contact, the definition remains longer at the conveyance site enhancing API bioavailability utilizing lower API fixations for infection treatment.
- The utilization of particular bioadhesive atoms takes into account conceivable focusing of specific locales or tissues, for instance the gastrointestinal (GI) tract.
- Increased home time joined with controlled API discharge may prompt lower organization recurrence.
- Offers an incredible course, for the fundamental conveyance of medications with high first-pass digestion, there by offering a more noteworthy bioavailability (Punitha and Girish, 2010).
- Additionally critical cost decreases might be accomplished and measurements related symptoms might be lessened because of API confinement at the sickness site (Gavin *et al.,* 2009). (6) Better patient consistence and comfort because of less incessant medication organization.
- Uniform and wide appropriation of medication all through the gastrointestinal tract which enhances the medication assimilation.
- Prolonged and maintained arrival of medication.
- Maintenance of restorative plasma tranquilize focus.
- Better processability (enhancing dissolvability, dispersibility, flowability).
- Increased wellbeing edge of high strength sedates because of better control of plasma levels.
- Reduction in change in unfaltering state levels and in this way better control of illness condition and decreased power of neighborhood or fundamental symptoms (Ganga, 2007).

Applications of microspheres

A portion of the uses of microspheres are depicted in detail as following:

- Controlled and supported discharge measurement shapes.
- Microsphere can be utilized to plan enteric-covered measurement shapes, with the goal that the medicament will be specifically caught up in the digestive system instead of the stomach.
- It has been utilized to shield drugs from natural dangers, for example, mugginess, light, oxygen or warmth. Microsphere does not yet give an ideal boundary to materials, which debase within the sight of oxygen, dampness or warmth, however an extraordinary level of insurance against these components can be given. For instance, vitamin A and K have been appeared to be shielded from dampness and oxygen through microsphere.
- The partitions of incongruent substances, for instance, pharmaceutical eutectics have been accomplished by exemplification. This is where coordinate contact of materials realizes fluid development. The security improvement of contradictory ibuprofen chlorpheniramine maleate blend is proficient by microencapsulating them two preceding blending.
- Microsphere can be utilized to diminish the instability. A typified unstable substance can be put away for longer circumstances without considerable dissipation.
- Microsphere has additionally been utilized to diminish potential peril of treatment of dangerous or harmful substances. The harmfulness happened because of treatment of fumigants, herbicides bug sprays and pesticides have been beneficially diminished after microencapsulation.
- The hygroscopic properties of numerous center materials might be lessened by microsphere.

- Numerous medications have been microencapsulated to lessen gastric aggravation (Meena *et al.,* 2011; Ali, 2005).
- Microsphere technique has additionally been proposed to get ready intrauterine preventative gadget.
- Helpful attractive microspheres are utilized to convey chemotherapeutic specialist to liver tumor. Medications like proteins and peptides can likewise be focused through this framework. Mucoadhesive microspheres display a drawn out living arrangement time at the site of use and causes hint contact with the assimilation site and delivers better remedial activity.

Floating drug delivery systems: Floating systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuation.

Advantages of Floating Drug Delivery

- **Enhanced Bioavailability:** The bio-availability of some drugs (e.g. riboflavin and levodopa) CR-GRDF is significantly enhanced in comparison to administration of non-GRDF CR polymeric formulations (Mathur and Verma, 2010).
- **Enhanced First-Pass Biotransformation:** When the drug is presented to the metabolic enzymes (cytochrome P-450, in particular CYP-3A4) in a sustained manner, the pre-systemic metabolism of the tested compound may be considerably increased rather than by a bolus input.
- **Sustained drug delivery/reduced frequency of Dosing:** The drugs having short biological half-life, a sustained and slow input from FDDS may result in a flip-flop pharmacokinetics and it reduces the dose frequency. This feature is associated with improved patient compliance and thus improves the therapy.
- **Targeted therapy for local ailments in the upper GIT:** The prolonged and sustained administration of the drug from FDDS to the stomach may be useful for local therapy in the stomach.
- **Reduced fluctuations of Drug concentration:** The fluctuations in plasma drug concentration are minimized, and concentration-dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index that makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.
- **Reduced counter-activity of the Body:** Slow release of the drug into the body minimizes the counter activity leading to higher drug efficiency.
- **Extended time over Critical (effective) concentration:** The sustained mode of administration enables extension of the time
- **Improved Receptor activation selectivity:** FDDS reduces the drug concentration fluctuation over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.
- **Minimized adverse activity at the Colon:** Retention of the drug in GRDF at stomach minimizes the amount of drugs that reaches the colon and hence prevents the degradation of drug that degraded in the colon.
- **Site specific Drug Delivery:** A floating dosage form is a widely accepted approach especially for drugs which have limited absorption sites in upper small intestine (Hardenia *et al.,* 2011; Chandel *et al.,* 2012; Shah *et al.,* 2009).

Diabetes mellitus

Diabetes mellitus is a combination of heterogeneous disorders commonly presenting with episodes of hyperglycaemia and glucose intolerance, as a result of lack of insulin , defective insulin action, or both (Sicree *et al.,* 2006). Such complications arise due to derangements in the regulatory systems for storage and mobilization of metabolic fuels, including the catabolism and anabolism of carbohydrates, lipids and proteins emanating from defective insulin secretion, insulin action, or both (Shillitoe, 1988; Votey and Peters, 2004). Classification of diabetes mellitus is based on its aetiology and clinical presentation. As such, there are four types or classes of diabetes mellitus viz; type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types (Sicree *et al.,* 2006). Type 1 diabetes is said to account for only a minority of the total burden of diabetes in a population although it is the major type of the diabetes in younger age groups at majority of well-to-do countries. The incidence of type 1 diabetes is increasing in both rich and poor countries. Furthermore, a shift towards type 1 diabetes occurring in children at earlier ages is imminent (Sicree *et al.,* 2006). 85 to 95% of all diabetes in high-income countries is of type 2 accounting for an even higher dominance in developing countries. It is intimately associated with improper utilization of insulin by target cells and tissues. It is currently a common and serious health concern globally. According to WHO, (1994), this problem has been aggravated by rapid cultural and social dynamics, ageing populations, increasing urbanization, dietary changes, reduced physical activity and other unhealthy lifestyle and behavioural patterns. Diabetes mellitus and lesser forms of glucose intolerance, particularly impaired glucose tolerance, can now be found in almost every population in the world and epidemiological evidence suggests that, without effective prevention and control programmes, diabetes will likely continue to increase globally (WHO, 1994). In 2010, about 285 million people in the age group 20-79 were envisaged to have diabetes worldwide, about 70% of whom live in developing nations. This estimate is expected to increase to about 438 million, by 2030. Further, by 2030, the number of people with IGT is projected to increase to 472 million, or 8.4% of the adult population (Sicree *et al.,* 2006).

The debilitating effects of diabetes mellitus include various organ failures, progressive metabolic complications such as retinopathy, nephropathy, and/or neuropathy (Piero, 2006). Diabetics are accompanied by risk of cardiovascular, peripheral vascular and cerebrovascular diseases. Several pathogenetic processes are involved in the development of diabetes, including destruction of pancreatic β-cells that lead to lowered sensitivity of insulin action (WHO, 1999; Votey and Peters, 2004).

History of diabetes mellitus: Diabetes mellitus has been known since antiquity, its treatments were known since the middle Ages, and the elucidation of its pathogenesis occurred mainly in the 20th century. Non-progressing Type II diabetics almost went undiagnosed (Patlak, 2002).

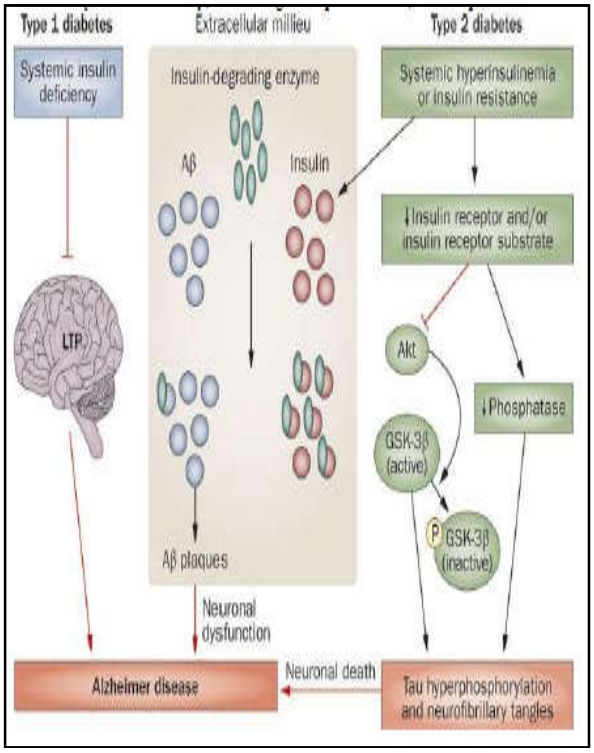

Figure 1.1. Pathophysiology of Type I and Type II diabetes

Table 2.4. Formulations of the floating microspheres prepared

Sr. No	Formulation Code	Saxagliptin (mg)	HPMC (mg)	EC (mg)
1.	F1	50	50	50
2.	F2	50	50	75
3.	F3	50	50	100
4.	F4	50	100	50
5.	F5	50	100	75
6.	F6	50	100	100

Table 2.5. General guideline for stability study

Study	Storage conditions	Minimum time period covered by data at submission
Long term	25±2°C/60±5% RH or 30±2°C/65±5% RH	12 months
Intermediate	30±2°C/65±5% RH	6 months
Accelerated	40±2°C/75±5% RH	6 months

Table 2.6. Sampling Intervals

Storage conditions	Sampling intervals
Real time storage 30°C/75% RH	0, 3, 6, 9, 12, months
Accelerated 40°C/75% RH	0, 3, 6 months

Table 3.1 Percentage Yield for Different Formulation

Formulation	Percentage Yield
F1	82.32±0.51
F2	79.89±0.32
F3	85.45±0.56
F4	82.10±0.41
F5	78.21±0.62
F6	76.65±0.32

The discovery of the role of the pancreas in diabetes was made by Joseph Von Mering and Oskar Minkowski in 1889. They found that upon complete removal of the pancreas from dogs, the dogs exhibited all the signs and symptoms of diabetes and died shortly afterwards. In 1910, Sir Edward Albert Sharpey-Schafer of Edinburgh in Scotland suggested that diabetics lacked a single chemical which was normally produced by the pancreas.

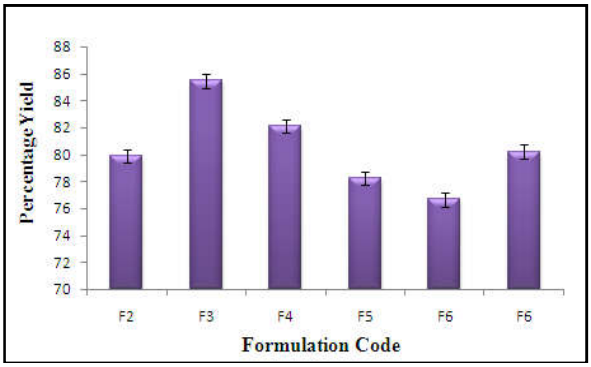

Figure 3.4. Percentage Yield for Different Formulation

Formulation	Drug entrapment (% w/w) of prepared microsphere
F1	65.45±0.45
F2	70.23±0.62
F3	73.21±0.85
F4	69.98±0.65
F5	65.12±0.32
F6	62.78±0.14

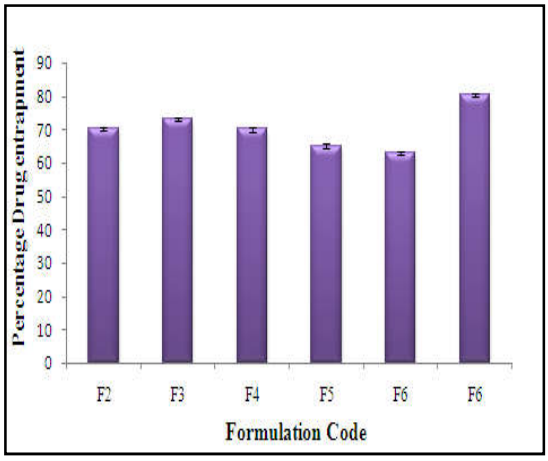

Figure 3.5. Drug Entrapment for Different Formulation

Table 3.3. Percentage Buoyancy and floating lag time of floating microsphere

Formulation	Floating Lag Time	Percentage Buoyancy
F1	45±3	80.23±0.45
F2	62±1	82.85±0.65
F3	35±2	89.45±0.21
F4	69±5	79.95±0.32
F5	42±3	83.14±0.47
F6	46±4	80.14±0.74

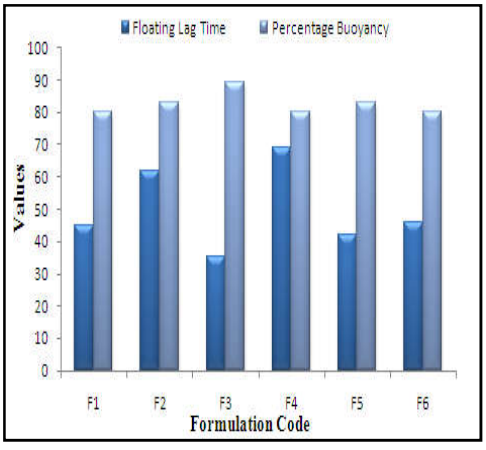

Figure 3.5: Floating Lag Time and Percentage Buoyancy for Different Formulation

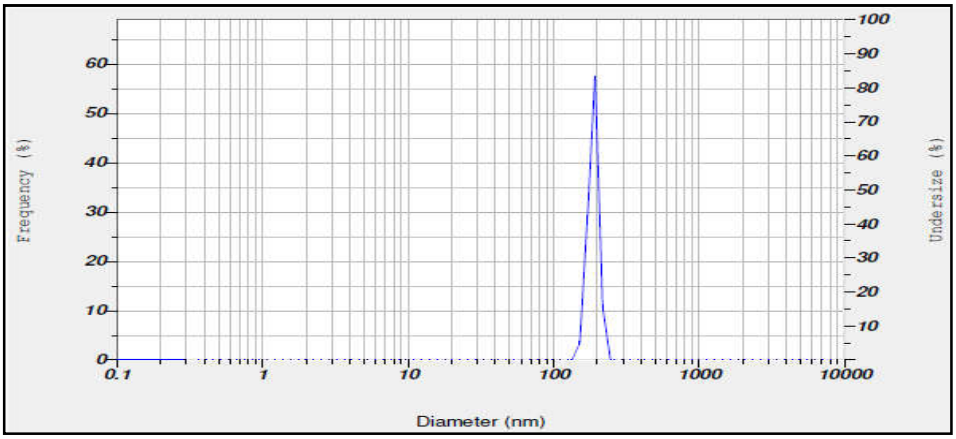

Figure 3.6. Particle size data of optimized microsphere formulation F3

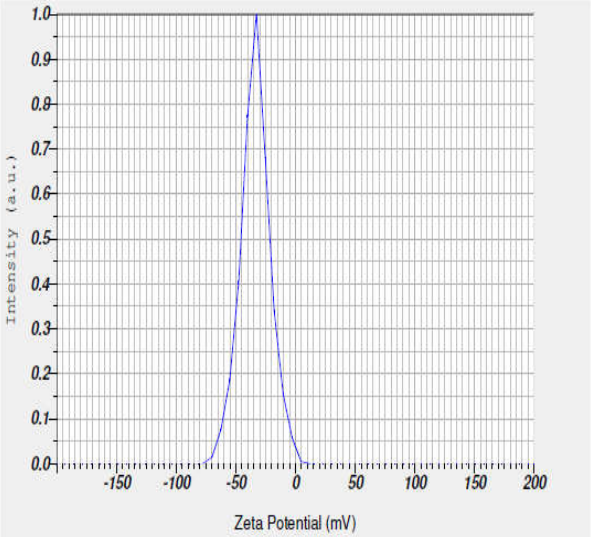

Figure 3.7: Zeta potential data of floating microsphere F3

Table 3.4 . Release Study data of formulation F1-F6

Time	% of Drug Release					
(hr)	F1	F2	F3	F4	F5	F6
0.5	36.45	35.45	26.65	15.65	13.24	13.25

Table 3.4. Release Study data of formulation F1-F6

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	26.65	1.426	73.35	1.865
1	1	0	45.65	1.659	54.35	1.735
2	1.414	0.301	55.32	1.743	44.68	1.650
4	2	0.602	60.36	1.781	39.64	1.598
6	2.449	0.778	68.89	1.838	31.11	1.493
8	2.828	0.903	72.32	1.859	27.68	1.442
10	3.162	1	88.95	1.949	11.05	1.043
12	3.464	1.079	98.89	1.995	1.11	0.045

Table 3.5. Release Kinetics of optimized formulation of microsphere F-3

Time	% of Drug Release					
(hr)	F1	F2	F3	F4	F5	F6
0.5	36.45	35.45	26.65	15.65	13.24	13.25
1	45.65	40.25	45.65	22.12	23.56	20.23
2	69.89	63.12	55.32	31.48	29.89	26.65
4	79.98	74.65	60.36	42.23	40.12	33.65
6	95.65	88.98	68.89	54.45	51.15	45.65
8	-	96.32	72.32	65.85	60.12	56.45
10	-	-	88.95	70.23	68.89	69.98
12	-	-	98.89	78.89	75.45	73.12

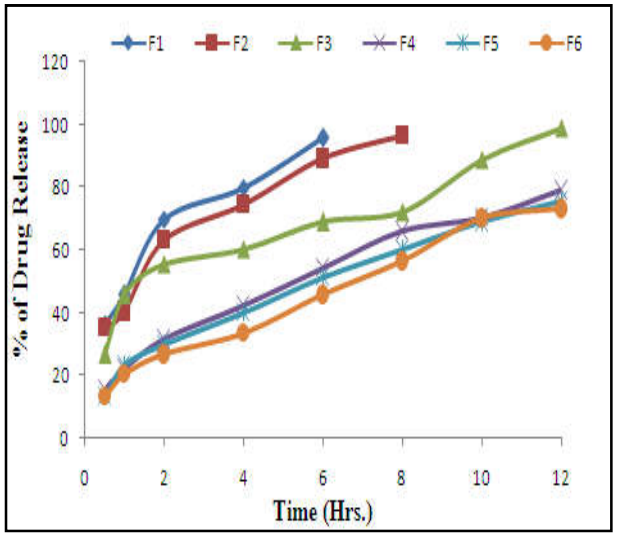

Figure 3.9. Graph of release study of formulation F1-F6

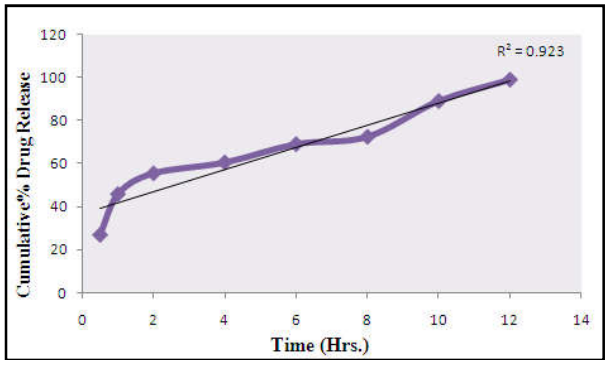

Figure 3.10. Zero order release kinetics graph of optimized formulations

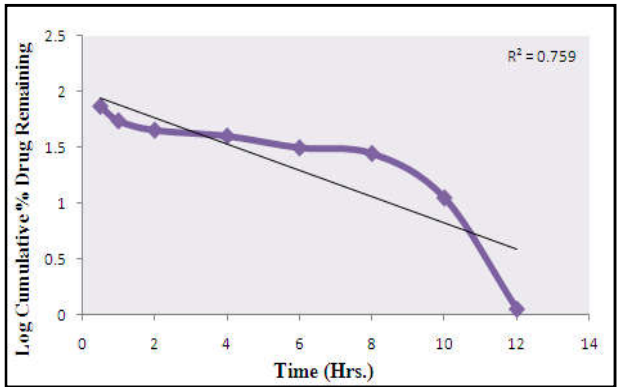

Figure 3.10. First order release kinetics graph of optimized formulations

Table 3.6. Comparative study of regression coefficient for selection of optimized Formulation F-3

Release Kinetics	Zero order	First order
R^2	0.923	0.759

Name of this chemical was later proposed to be insulin (Himsworth, 1936). In 1921, Frederick Grant Banting and Charles Herbert Best repeated the work of Von Mering and Minkowski but went a step further and managed to show that they could reverse the induced diabetes in dogs by giving them an extract from the pancreatic islets of Langerhans of healthy dogs.

This was a step forward in elucidation of the endocrine role of pancreas in metabolism and existence of insulin (Banting *et al.,* 1922). These scientists proceeded on to isolate insulin from bovine pancreases at the University of Toronto in Canada, thereby leading to the availability of aneffective treatment of diabetes mellitus, with the first clinical patient being treated in 1922. The distinction between what is now known as type I and type II diabetes was made by Sir Harold Percival (Harry) Himsworth in 1935 (Himsworth, 1936).

Classification

The Classification of DM Has Undergone the Following Important Changes

- The designations "type 1 diabetes" and "type 2 diabetes," using Arabic numerals, replace the terms "insulin dependent diabetes mellitus" (IDDM) and "non-insulin dependent diabetes mellitus" (NIDDM).
- A new term, "IFG" (impaired fasting glucose), defines glucose values that are greater than or equal to 100 mg/dl and up to 125 mg/dl.
- The revised diagnostic criteria for DM are: A. A1C level ≥ 6.5%. Diagnosis should be confirmed with repeat A1C test unless clinical symptoms and glucose levels ≥ 200 mg/dl are present. (Prior criteria should be used in the absence of A1C testing). (The International Expert Committee, 2009)
- B. Symptoms of hyperglycemia plus casual plasma glucose concentration greater than or equal to 200 mg/dl. "Casual" is defined as any time of the day without regard to time since the last meal. Classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.

Type 1 diabetes mellitus

The American Diabetes Association provides clear definitions of the various types of diabetes and classification, diagnosis, and clinical care of diabetes. Type 1 DM, which results from destruction of beta cells in the pancreas, accounts for approximately 10 percent of all patients with DM in the United States. It leads to absolute insulin deficiency. There are two forms of type 1 DM. One is an immune-mediated disease with autoimmune markers such as islet cell antibodies (ICAs), insulin autoantibodies (IAAs), and autoantibodies to glutamic acid decarboxylase (GAD). As many as 85−90 percent of patients with fasting hyperglycemia are positive for one or more of these markers. Strong human leukocyte antigen (HLA) associations also exist. A second form of type 1 DM, now called idiopathic diabetes, has no known cause. Only a minority of patients fall into this group, which occurs mainly in individuals of African and Asian origin. Idiopathic diabetes is strongly heritable, but it lacks autoimmune markers and is not HLA associated. Although it can occur at any age, type 1 DM is more common in persons less than 30 years of age. The rate of pancreatic destruction is variable and is generally more rapid in infants and children and slower in adults.

Type 2 diabetes mellitus: Type 2 is the most common form of DM worldwide, and its prevalence is increasing. Its underlying defects can vary from predominant insulin resistance with relative insulin deficiency to a predominant insulin secretory defect with insulin resistance.

A great deal of heterogeneity exists, and most patients with type 2 DM do not initially require insulin therapy. Accounting for approximately 90 percent of all cases of DM in the United States, type 2 DM occurs more frequently in adults than in children, and the incidence increases with age, especially after age 40. However, the prevalence of type 2 DM in children is increasing, especially in the high-risk ethnic groups, such as Native Americans, Hispanic Americans, African Americans, and Asian Americans. Most of these children are between 10 and 19 years old, have had symptoms longer, have infrequent or mild diabetic ketoacidosis, are obese, and have a strong family history of diabetes. A characteristic finding is darkening of the skin (acanthosis nigricans) and there is an increased incidence of insulin.

Preparation and characterization

Formulation development

Preparation of Floating microsphere of Saxagliptin: Floating microspheres loaded with Saxagliptin were prepared using solvent diffusion-evaporation method using HPMC and EC in different ratio like 1:1, 1:1.5, 1:2 w/w. 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.

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.

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

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. 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. 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. 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.

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. 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. 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 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 50 rpm. 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 277nm to determine the concentration of drug present in the dissolution medium.

Drug release kinetic data analysis: Several kinetic models have been proposed to describe the release characteristics of a drug from matrix. The following three equations are commonly used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsemeyer-Peppas equation (Plotted as Log cumulative percentage of drug released vs Log time). To study the release kinetics of Saxagliptin from the Floating microspheres the release data was fitted to these three equations

Zero order equation: When a graph of the cumulative percentage of the drug released from the matrix against time is plotted, zero order release is linear in such a plot, indicating that the release rate is independent of concentration.

$$Q_t = k_0.t \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

Where Q_t is the percentage of drug released at time t and k_0 is the release rate constant;

First order equation

$$\text{In } (100\text{-}Q_t) = \text{In } 100\text{- } k_I.t \ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

Where k_I is the release rate constant;

Higuchi's equation

$$Q_t = k_H.t^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots \quad (3)$$

Where K_H is the Higuchi release rate constant

Korsemeyer-Peppas: The curves plotted may have different slopes, and hence it becomes difficult to exactly pin-point which curve follows perfect zero order release kinetics. Therefore, to confirm the kinetics of drug release, data were also analyzed using Korsemeyer's equation.

$$Q_t/Q_\infty = k_{KP}.t^n$$

Where Q_t/ Q_∞ is the fraction of drug released at time t, k_{KP}a constant compromising the structural and geometric characteristics of the device and n is the release exponent. The slope of the linear curve gives the 'n' value. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of 'n' gives an indication of the release mechanism.

When n = 1, the release rate is independent of time (typical zero order release / case II transport); n = 0.5 for Fickian release (diffusion/ case I transport); and when $0.5 < n < 1$, anomalous (non-Fickian or coupled diffusion/ relaxation) are implicated. Lastly, when $n > 1.0$ super case II transport is apparent. 'n' is the slope value of log M_t/M_∞ versus log time curve.

Stability studies for optimized formulation: The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a re-test period for the drug substance or a shelf life for drug product and recommended storage conditions. In general, a drug substance should be evaluated under storage condition (with appropriate tolerances) that test its thermal stability and if applicable, its sensitivity to moisture. Three types of storage conditions are used i.e. long term, Accelerated and where appropriate, Intermediate.

RESULTS AND DISCUSSION

Evaluation of Saxagliptin microspheres

Percentage Yield: Percentage yield of different formulation was determined by weighing the Microspheres after drying. The percentage yield of different formulation was in range of 76.65±0.32–85.45±0.56%. The maximum Percentage Yield was found in formulation F3, 85.45±0.56 as compare to all formulation.

Drug Entrapment: The drug entrapment efficacies of different formulations were in range of 63.23±0.65-76.56±0.65% w/w.

Percentage Buoyancy and floating lag time of floating microsphere: The maximum Percentage Yield, Drug Entrapment, Percentage Buoyancy and floating lag time was found to be formulation F3 in floating microsphere.

The optimized formulation of both batches subjected to further studies.

Particle size analysis: 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. The results of measurement of mean particle size of optimized formulation F3 of floating microsphere was found to be 128.4nm.

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. All the samples were measured in water at 25°C in triplicate. Results of zeta potential of optimized formulation F4 of floating microsphere was found -35.69 mV**.**

***In-Vitro* drug release study**

In vitro drug release study of Saxagliptin loaded Microsphere. Comparative release study of all formulation F1-F6. Graph of release study of formulation F1-F6

Zero order release kinetics graph of optimized formulations

First order release kinetics graph of optimized formulations: The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, in order to determine the mechanism of drug release. When the regression coefficient values were compared, it was observed that an 'r' value of microsphere was maximum zero order i.e 0.923 hence indicating drug releases from formulations was found to follow zero order for floating microsphere.

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