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Formulation and Evaluation of Gastro-retentive Microsphere of Saxagliptin Antidiabetic Agent

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ABSTRACT

The objective of this study was to develop a gastro-retentive microsphere of Saxagliptin. Saxagliptin is an orally active hypoglycemic drug of the new dipeptidylpeptidase-4(DPP4) inhibitor class of drug. Nine formulations of Saxagliptin microsphere are prepared by Emulsion solvent diffusion method using polymers like Eudragit RS 100 and Ethyl cellulose at different drug to polymer ratios and Polyvinyl Alcohol as Stabilizing agent by Emulsion Solvent Diffusion Method. The formulations were optimized on the basis of percent buoyancy and in vitro drug release. The prepared microspheres were evaluated for physicochemical parameters and found to be within range.

Key words: Gastro retentive, Saxagliptin, Ethyl cellulose, Floating microsphere, Eudragit RS 100, Polyvinyl alcohol.

1. INTRODUCTION

Oral ingestion has long been the most convenient and commonly employed route of drug delivery. Indeed, for controlled release systems the oral route of administration has received attention with respect to research on physiological and drug constraints as well as design and testing of product. Drug delivery technologies are the formulation technologies that modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. Most of the oral controlled drug delivery systems rely on diffusion, dissolution or combination of both mechanisms, to release the drug in a controlled manner to the Gastrointestinal Tract. Novel oral drug delivery systems are broadly classified in to two categories as they may controlled release dosage forms as well as targeting dosage forms. General controlled manner in the GIT for systemic uptake and no particular area of GIT specified. In contrast, targeted preparations are releasing the drug in a specified area or tissue of the GIT (e.g. colon specific drug delivery systems).^{1,2}

2. GASTRO-RETENTIVE DRUG DELIVERY SYSTEM (GRDDS)

The extent of GIT drug absorption is related to contact time with the small intestinal mucosa.³ Conventional drug delivery system maintains the drug concentration within the therapeutically effective range needed for treatment, only when taken several times a day.⁴ Success of oral drug delivery system depends on its degree of absorption through GIT. Thus, the idea of enhancing drug absorption pioneered the idea of development of Gastro-retentive drug delivery system. On the basis of the mechanism of mucoadhesion, floatation, sedimentation or by the simultaneous administration of pharmacological agents, the controlled gastric retention of solid dosage forms may be achieved, which delay gastric emptying.⁵

2.1 Suitable Drug Candidate for Gastro-Retentive Drug Delivery

Sustained release in the stomach is an issue for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited. Under normal or average conditions, for example, material passes through the small intestine in as little as 1-3h. For the floating system the drug candidates should have the appropriate properties like poor absorption in the colonic region but are characterized by better absorption in the upper part of GI tract. So, the ideal drug candidates should have the following criteria:

- a) Primarily absorbed from stomach and upper part of GI tract, e.g., calcium supplement, cinnarizine.
- b) Narrow absorption window in GI tract, e.g., riboflavin and levodopa.
- c) Drugs that degrade in the colon, e.g., ranitidine HCl, metronidazole.
- d) Drugs that act locally in the stomach, e.g., antacids and misoprostol.
- e) Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate
- f) Drugs are locally active in the stomach, e.g., drugs used in the eradication of helicobacter pylori, which is now believed to be the causative bacterium for chronic gastritis and peptic ulcer (tetracycline).

2.2 Approaches to Design Gastro-retentive Dosage Forms

Various approaches have been pursued to increase the retention of an oral dosage form in the stomach. These systems include

- Floating systems
- Bioadhesive systems
- Raft forming systems
- Swelling and expanding systems
- Superporous Hydrogels
- Magnetic systems
- High density systems⁷

2.2.1 Hollow Microspheres

Microspheres are gastro retentive drug-delivery systems with a non-effervescent approach. A hollow microsphere is, in strict sense, an empty particle of spherical shape without a core. These microspheres are characteristically free flowing powders comprising proteins or synthetic polymers, ideally having a size less than 200 micrometers.

Microspheres are considered as one of the most favorable buoyant systems with the unique advantages of multiple unit systems as well as better floating properties, because of the central hollow space inside the microsphere. The novel techniques involved in their preparation include simple solvent evaporation method, emulsion-solvent diffusion method, single emulsion technique, double emulsion technique, phase separation coacervation technique, polymerization technique, spray drying and spray congealing method and hot melt encapsulation method. The slow release of drug at a desired rate and better floating properties mainly depend on the type of polymer, plasticizer and the solvents employed for the preparation. Polymers such as polylactic acid, Eudragit® S and hydroxypropyl methyl cellulose. Cellulose acetate is used in the formulation of hollow microspheres, and the release of drug can be modulated by optimizing polymer concentration and the polymer-plasticizer ratio.⁸

2.2.2 Mechanisms of Microsphere

The mechanism of drug release from multi-particulates can occur in the following ways:

Diffusion: On contact with aqueous fluids in the gastrointestinal tract, water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

Erosion: Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle.

Osmosis: In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating.⁹

2.2.3 Methods of Preparation of Microspheres

- Solvent Evaporation Method
- Emulsion solvent diffusion method
- Solvent diffusion-evaporation technique

2.2.4 Methods and Materials in Formulation

The saxagliptin and ethyl cellulose were obtained from Spectrum laboratories Hyderabad.

Other excipients were obtained from Hi media laboratories Pvt. Ltd,

2.3 Pre-Formulation Studies

Preparation of standard curve of saxagliptin

- Standard curve Method

100mg of Saxagliptin was weighed and poured into 100ml volumetric flask. It was dissolved and volume made up with 0.1N HCl to give 1000µg/mlsol.¹⁰

- Procedure

The standard stock solution was then serially diluted with 0.1N HCl to get 1 to 20µg/ml of Saxagliptin. The absorbance of the solution was determined against 0.1N HCl as blank at 271 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.¹¹⁻¹³

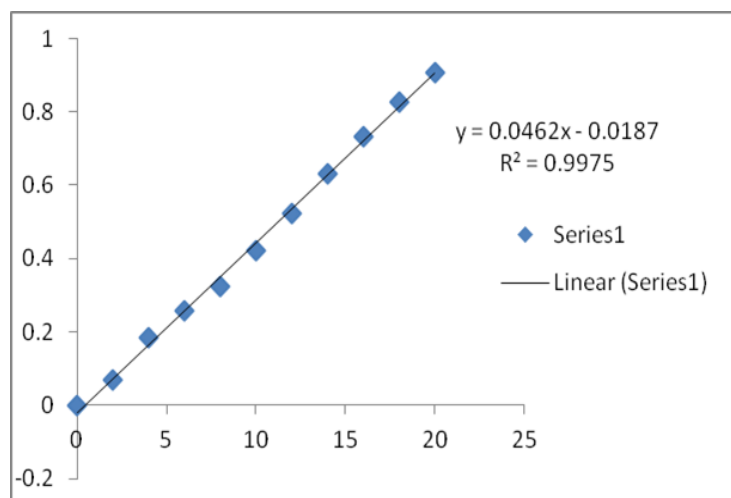


Figure 1: Calibration curve of drug in 0.1 NHCl

2.4 Formulation Development

2.4.1 Formulation of Gastro-Retentive Saxagliptin Hydrochloride Microsphere

Saxagliptin hydrochloride Microsphere were prepared by Emulsion solvent diffusion method using polymers like Eudragit RS 100 (EUD) and Ethyl cellulose (EC) at different drug to polymer ratios and Polyvinyl Alcohol as Stabilizing agent by Emulsion Solvent Diffusion Method.¹⁴⁻¹⁶

2.4.2 Emulsion Solvent Diffusion Method

Floating microspheres were prepared by the emulsion solvent diffusion method. Saxagliptin Hydrochloride, Eudragit RS100 and/or Ethyl Cellulose 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, microsphere was collected by filtration, washed with water and dried at room temperature in a desiccator for 24 h.

2.4.3 Composition of Saxagliptin Hydrochloride Microsphere

Table 1: Composition of Saxagliptin Hydrochloride

F. Code	Saxagliptin Hydrochloride (mg)	Ethyl Cellulose (mg)	Eudragit RS100 (mg)	Polyvinyl Alcohol (0.5%w/v) (ml)	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

2.5 Pre-Formulation Study of Optimized Microsphere

2.5.1 Flow Property Measurements¹⁷

The flow properties are critical for an efficient tableting and capsule filling operation. A good flow of the powder or granules is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets and capsules. The flow property measurements include bulk density, tapped density,

angle of repose, compressibility index and Hausner's ratio. The flow property measurements of saxagliptin Hydrochloride Microspheres are determined.

2.5.2 Bulk Density (ρ_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. From this the bulk density was calculated according to the formula mentioned below. It is expressed in g/ml and is given by,

$$\rho_b = M/V_b$$

Where, M and V_b are mass of powder and bulk volume of the powder respectively.

2.5.3 Tapped Density (ρ_t)

It is the ratio of weight of the powder to the tapped volume of powder. The powder was introduced into a measuring cylinder with the aid of funnel and tapped for 300 times on a wooden surface at a 2 sec interval and the volume attained is the tapped volume.

$$\rho_t = m/V_t$$

2.5.4 Angle of Repose (θ)

The flow properties were characterized in terms of angle of repose, Carr's index and Hausner's ratio. For determination of angle of repose, the drug and the blend were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above hard surface. The drug or the blends were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. Angle of repose was calculated using following equation.

$$\Theta = \tan^{-1}(h/r)$$

Where h=height of pile in cm; r=radius of pile in cm.

2.5.6 Carr's Index or % Compressibility

It indicates powder flow properties. It is measured for determining the relative importance of inter particulate interactions. It is expressed in percentage.

2.5.7 Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula.

$$HR = \rho_t / \rho_b$$

Where, ρ_t and ρ_b are tapped density and bulk density respectively.

Table 2: Calculation of parameters

F. code	Bulk density (g/ml) *	Tapped density (g/ml) *	Carr's Index (%) *	Hausner's ratio	Angle of repose (θ)
F8	0.49±0.01	0.54±0.01	10.20±0.02	1.10	33°50'

2.5.8 Surface Morphology Analysis

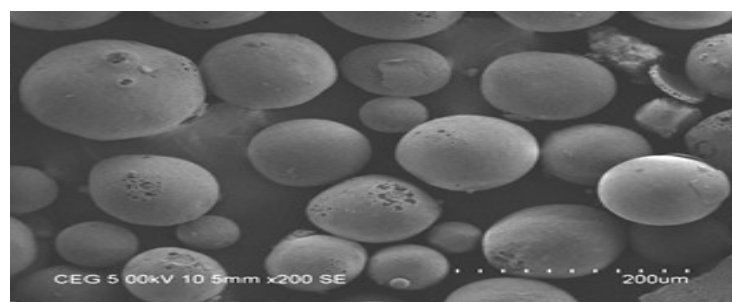


Figure 2: SEM image of optimized formulation

The shape and surface morphology of optimized formulations F8 were observed in scanning electron microscope. It shows spherical and circular shape with smooth surface.

2.5.9 Percentage Yield

Table 3: Percentage yield of Saxagliptin Hydrochloride Microsphere

Formulation Code	Theoretical Yield (g)	Practical Yield (g)	Percentage yield (%)
F1	2.0	1.38	68.00
F2	3.0	2.32	76.3
F3	4.0	3.27	81.65
F4	2.0	1.41	48.99
F5	3.0	1.45	48.34
F6	4.0	2.82	69.99
F7	3.0	1.86	62.01
F8	4.0	3.45	86.25
F9	4.0	3.12	77.90

2.5.10 Percentage Entrapment Efficiency

Table 4: Percentage entrapment efficiency of saxagliptin Microspheres

Formulation Code	Entrapment efficiency (%) *
F1	79.9±1.33
F2	84.8±0.45
F3	91.4±0.21
F4	80.5±0.52
F5	85.7±0.57
F6	89.5±0.94
F7	88.1±0.52
F8	93.2±1.07
F9	89.9±0.78

The drug entrapment efficiency of all formulations was found to be in the range between 79.9 to 93.2%. 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.

2.5.11 Percentage *in vitro* Buoyancy

2.5.11.1 *In vitro* Buoyancy

Floating behavior of saxagliptin hydrochloride microspheres is studied using an USP dissolution test apparatus II. The weighed microspheres are spread on 900ml of 0.1 mol/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 Microspheres are collected separately. Then the Microspheres are dried and weighed. The percentage of microspheres are calculated.

Table 5: Percent *in vitro* Buoyancy of Saxagliptin Microsphere

Formulation Code	<i>In vitro</i> buoyancy (%)
F1	85.0±1.63
F2	83.0±1.25
F3	91.0±1.25
F4	77.0±1.63
F5	88.0±1.25
F6	81.0±0.82
F7	89.0±0.47
F8	94.0±1.25
F9	89.9±1.25

The buoyancy of all the formulations were found to be in the range of 77- 94%. In the test of floating time, microspheres remained floating for more than 12hours. The good buoyancy behavior of the microspheres may be attributed to the hollow nature of the microspheres. As the concentration of polymers increases, buoyancy also increases.

2.5.11.2 *In vitro* Drug Release Study

Saxagliptin Hydrochloride floating Microspheres 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 Microspheres. The dissolution test was performed using 900 ml of 0.1N HCl, at 37°C ±0.5°C and 100 rpm. Microspheres 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 analyzed at 271 nm using a UV Spectrophotometer.

3. CONCLUSION

The purpose of this research was to formulate Microsphere of Saxagliptin Hydrochloride for controlled release of drug and to improve bioavailability. Saxagliptin Hydrochloride is a sparingly water-soluble drug with low bioavailability thus selected as a drug for GRDDS to overcome the problem and to release the drug in a controlled manner. Saxagliptin Hydrochloride is formulated as Microsphere by Emulsion Solvent Diffusion method using Eudragit RS 100 and Ethyl Cellulose as polymers, Polyvinyl alcohol as stabilizing agent. The observed results showed the optimized and best formulation is F8. The foregoing results attempt to suggest that saxagliptin Hydrochloride Microspheres can be considered as an alternative to conventional drug delivery for better management of disease.

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Table 6: *In vitro* drug release for all formulations

Time (hrs)	PERCENTAGE DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	2.55	2.25	1.8	2.16	0.7	1.51	0.36	1.62	1.98
1	15.54	9.38	9.38	6.5	10.71	3.88	1.44	10.54	9.02
1.5	29.48	16.68	16.68	20.16	16.86	10.76	23.49	13.27	10.38
2	38.38	32.08	21.18	28.8	25.24	16.55	34.28	22.6	20.93
3	47.59	36.84	34.83	45.63	35.6	27.9	37.27	24.01	24.76
4	59.21	45.79	42.05	49.28	53.35	40.35	51	35.35	46.09
5	61.59	52.77	56.45	70.33	61.05	47.81	60.92	37.44	59.38
6	91.54	66.75	64.8	75.87	71.61	70.29	72.1	47.83	68.7
7	94.38	73.77	69.37	86.78	75.08	83.83	80.98	50.06	80.62
8	95.9	84.64	81.44	95.86	81.19	-	94.44	57.43	86.16
9	-	87.52	85.55	-	85.65	-	-	62.81	90.86
10	-	96.8	87.89	-	90.42	-	-	73.73	93.8
11	-	-	93.21	-	-	-	-	87.83	94.94
12	-	-	98.04	-	-	-	-	99.2	95.25

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