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FORMULATION DESIGN AND EVALUATION OF SAXAGLIPTIN SUSTAINED RELEASE MICROSPHERES

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Abstract:

Sustained release oral product namely microspheres for Saxagliptin prepared by Ionotropic gelation technique to overcome the drug-related adverse effects like gastric irritation, improve its bioavailability in different gastrointestinal pH conditions. Total nine formulation batches (F1-F6) were formulated using sodium alginate as drug release modifiers in various proportions and investigate for physicochemical properties and drug release potential. All investigated properties showed satisfactory results. While increase in the concentration of sodium alginate dispersions increased sphericity, size distribution, flow properties and mean diameter of the Microspheres. The drug entrapment efficiency obtained in the range 78.4% to 95.42%. Increase in the concentration of calcium chloride was significantly affects the mean diameter but no appreciable change in morphology and drug release behavior. In-vitro study proves that drug release slowly increases as the p^H of the medium is increased. The drug release in batch F1, F2, F3 F4, F5 and F6 containing sodium alginate. The mechanism drug release from Microspheres was found to be following Higuchi model graph. From the study it was concluded that controlled release Saxagliptin Microspheres can be developed successfully by using ionotropic gelation technique.

Key words: *Microencapsulation; Ionotropic gelation, Microspheres, Sodium alginate, pH dependent.*

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INTRODUCTION:

Microencapsulation is well known method to delay and modify drug release characteristics. For oral use, it has been employed to sustain the drug release and to reduce or eliminate gastrointestinal tract irritation[1]. It is a process of enclosing micron size particles of solid or liquid or gases in an inert shell resulting in the formation of microparticles or microcapsules or microspheres [2]. As multiparticulate drug delivery lead to wide and uniform distribution throughout GIT, a localized high concentration at a specific point may be avoided. In addition, multiparticulate delivery systems spread out more uniformly in the gastrointestinal tract. This results in more reproducible drug absorption and reduces local irritation when compared to single unit dosage form such as non disintegrating polymeric matrix tablets [3,4]. Sodium alginate, a natural polysaccharide which is a mixture of polyuronic acids composed of residues of d-mannuronic acid and l-guluronic acid [5]. Alginates have the ability to form gels by reaction with divalent cations (Ca^{2+}). The gelation and crosslinking of the polymers are mainly achieved by exchange of sodium ions from the guluronic acids with divalent cations, and the stacking of these guluronic groups to form the characteristic egg-box structure. The divalent cations bind to the α-L-guluronic acid blocks in the highly cooperative manner and the size of the cooperative unit is more than 20 monomers. Each alginate chain dimerizes to form junctions with many other chains and as the result gel network are formed [6]. Alginate shrinks at the low pH and the encapsulated drugs are not released. In gastric fluid, the hydrated sodium alginate is converted into porous, insoluble so-called alginic acid skin. Once passed into higher pH of the intestinal tract, the alginic skin is converted to soluble viscous layer. This pH dependent behavior of alginate can be exploited to customize release profiles [6,7.] To design a new formulation in the field of pharmaceutical dosage forms, it is very important to identify the parameters and variables in the method of preparation that may affect the properties of the new dosage form. Statistical design can be used for analyzing the influence of different factors on the properties of the system being studied [8].

The objective of the present study was to develop microspheres of Saxagliptin by Ionotropic Gelation Technique using hydrophilic carrier to sustain the release so as to reduce the frequency of dosing and to improve patient compliance.

MATERIALS AND METHODS:

Saxagliptin From Spectrum lab Hyderabad, Sodium alginate and Calcium Chloride from Sd.Fine Chem. Ltd., Mumbai

Methods

Preformulation Study:

Prior to the development of any dosage form, to optimize the performance of drug products it is necessary to have a complete understanding of the physical and chemical properties of drug substance by the study of preformulation data.

The development of a new drug substance, as a dosage forms such as tablet, capsule, suspensions, etc. we must record some Preformulation data such as organoleptic characteristics, particle size, crystallization characteristics, compatibility with excipient, and also certain techniques like I.R. analysis, thin layer chromatography, spectrophotometry, sieving analysis, etc.

Standard Plot for Saxagliptin:

Acid buffer (pH 1.2)

Accurately weighed 200mg of saxagliptin was dissolved in 10ml of methanol in a 100ml of volumetric flask and make up the volume with pH 1.2 buffer solution. Take 10ml of this solution in a 100ml of volumetric flask and make up the volume with pH 1.2 buffer solution to get working stock solution having concentration 100µg/ml. From this stock solution aliquots 1ml, 2ml, 3ml, 4ml and 5ml were pipetted out into a series of 50ml volumetric flasks and make up to mark with pH 1.2 buffer solution in order to get a concentration within the Beer's range from 2-10µg/ml. The absorbance of the resulting solution was then measured at 243nm using

UV spectrophotometer against respective parent solvent as a blank. The standard curve was obtained by plotting absorbance V/s concentration in µg/ml.

Phosphate Buffer (pH 6.8):

Accurately weighed 200mg saxgliptin was dissolved in 100ml of pH 6.8 phosphate buffer solution. Take 10ml of this solution in a 100ml of volumetric flask and make up the volume with phosphate buffer (pH 6.8) solution to get working stock-solution having concentration 100µg/ml.

From this stock-solution aliquots of 1ml, 2ml, 3ml, 4ml and 5ml were pipetted out into a series of 50ml volumetric flasks and make up to mark with pH 6.8 phosphate buffer solution in order to get a concentration within the Beer's range from 2-10 µg/ml.

The absorbance of the resulting solution was then measured at 210nm using UV Spectrophotometer against respective parent solvent as a blank (i.e. pH 6.8 buffer solution). The standard curve was obtained by plotting absorbance V/s concentration in µg/ml.

Table 1: Formulation design of microspheres

Formulation	Saxagliptin (mg)	Sodium alginate(w/v)	$CaCl_2$ (w/v)
F1	200	1%	3%
F2	200	1.5%	5%
F3	200	2%	7%
F4	200	0.5%	5%
F5	200	0.75%	5%
F6	200	1.0%	5%

Preparation of Microspheres

Microspheres of saxagliptin were prepared by Ionotropic gelation technique. In the present work four sets Microspheres were prepared by using sodium alginate and Calcium chloride as counter ion. The detailed composition of the various formulations prepared is as mentioned in table no.1

Preparation of Sodium alginate Microspheres

In the first set three batches of drug-loaded Microspheres were prepared (F1, F2, F3). A solution of sodium alginate (2-4% w/v) was prepared in 100ml of de ionized water. In 50ml of sodium alginate solution, weighed quantity (200mg) of saxglipton was dispersed uniformly. Bubble free dispersion was dropped through a syringe into 100ml aqueous calcium chloride solution and stirred at 100rpm. After stirring for 10minutes, the gelled beads filtration, washed with distilled water, air dried and finely dried at 60^0C for 6 h in a oven.

In second set microspheres were prepared (F4,F5, F6) using sodium alginate and Calcium chloride as a polymer. These Microspheres were prepared as described above same as alginate-ethyl cellulose Microspheres, with a slight modification. In this pectin was mixed along with weighed quantity (200mg) saxagliptin and dispersed in 50ml sodium alginate solution.

Evaluation parameters of microspheres:

Measurement of Micromeritic Properties of Microspheres:

Granulometric Study

The particle size has very significant effect on the release profile of Microspheres. Granulometric study was conducted to determine the particle size distribution pattern. For this study sieve analysis was carried out on mechanical sieve shaker, using different meshes (#12, #16, #22, #30) of American Society of Testing Materials (ASTM). The size distribution of Microspheres is reported in table no.3.

Flow Property

The flow properties were investigated by measuring the angle of repose of drug-loaded Microspheres using fixed-base cone method to assess the flowability.

The fixed-base cone method, a funnel was secured with its tip at a 1cm height (H) above the graph paper that was placed on a flat horizontal surface. Microspheres were carefully poured through the funnel until the apex of the conical pile just touched the tip of the funnel. Measure the height of he pile (h) and the radius of the base (r) with

ruler. The angle of repose was determined by using the equation, and reported in table no.4.

$$\tan\theta = H/R \quad \text{or} \quad \theta = \tan^{-1} H/R$$

Where θ = angle of repose,

R = radius of the base of pile

H = height of pile.

Bulk and tapped density

The bulk and tapped densities were measured in a 10ml graduated measuring cylinder to measure packability of the Microspheres. The sample contained in the measuring cylinder was tapped mechanically by means of constant velocity rotating cam with change in its initial bulk density to a final tapped density when it has attained its most stable form. Each experiment was carried out in triplicate. The bulk and tapped density can be determined and reported in table no.4.

Particle size analysis

Particle size analysis of drug-loaded Microspheres was performed by optical microscopy (Olympus Model Szx-12). A small amount of microspheres was suspended in purified water (10ml). Mount the sample on a clean glass slide and placed it on mechanical stage of the microscope. The eye piece of microscope fitted with a micrometer by which the size of the beads could be determined. The process was repeated for each batch of prepared Microspheres and mean particle size can be reported in table no.4.

Surface study

The surface morphological details of the Microspheres were determined by using a scanning electron microscope (SEM) model JSM, 35CF JEOL, Japan.The samples were dried thoroughly in vacuum desicator before mounting on brass specimen studies. The samples were mounted on a specimen studies using double sided adhesive tape, and gold-palladium alloy of 120Å

Kness was coated on the sample using spatter coating unit (Model E5100 Polar on, UK) in an argon ambient of 8-10 pascal with plasma voltage about 2Kv and discharge current about 20mA. The sputtering was done for nearly 3minutes to obtain uniform coating on the samples to enable good quality SEM images. The SEM operated at low accelerating voltage of about 15Kv with load current of about 80mA The condenser lens position was maintained bet ween 4.4 – 5.1. The objective lens aperture has a diameter of 240 microns and the working distance WD = 39mm.

Loose-Surface Crystal Study

In this study accurately weighed 25mg of Microspheres (#16) was suspended in the phosphate buffer pH 6.8 and was shaken vigorously for 5min. The drug leached out from the surface of the micro pellets was analyzed at 243nm wavelength spectrophotometrically.

Swelling Properties

The swelling properties of prepared Microspheres were determined in acidic buffer pH 1.2. Thirty dried beads were placed in a beaker to which 200ml of buffer solution and then stirred with a magnetic stirrer at a speed 50 rpm. After 1hr interval, the equilibrium swollen beads were observed and measured under optical microscope. The magnitude of swelling was presented by the ratio of the mean diameter of swollen beads to the mean diameter of the dried beads before the test swown in table 6.

Drug Entrapment Efficiency (DEE)

Drug entrapment efficiency of Microspheres was performed by accurately weighed 50mg of Microspheres were suspended 100ml of phosphate buffer pH 6.8±0.1. The resulting solution was kept for 24 hours. Next day it was stirred for 15 min and subjected for filtration. After suitable dilution, saxagliptin content in the filtrate was analyzed spectrophotometrically at 210nm using Shimadzu 1201 UV-visible spectrophotometer. The obtained absorbance was plotted on the standard curve to get the exact concentration of the entrapped drug. Calculating this concentration with dilution factor we get the percentage of actual drug encapsulated in Microspheres.

The drug entrapment efficiency was determined using following relationship:-

$$\%DEE = \frac{\text{Actual Drug Content}}{\text{Theoretical Drug Content}} \times 100$$

The results of DEE (Drug Entrapment Efficiency) are reported in table no.5.

***In-vitro* Dissolution Studies:**

The physicochemical property of most drugs that has greatest influence on their absorption characteristics from the GIT is dissolution rate. "The drug is expected to release from the solid dosage forms (granules, tablets, capsules etc) and immediately go into molecular solution. This process is called as dissolution".

Drug Release Studies

The method is specified in USP for drug release study was followed:

Apparatus:- USP II dissolution rate test apparatus employing the round bottom dissolution vessel and rotating paddle assembly.

Acid Stage:- 900ml of simulated gastric fluid TS (acid buffer pH 1.2±0.05 without enzymes.

Buffer stage:- 900ml of pH 6.8 (duodenal fluid) and simulated intestinal fluid TS (phosphate buffer pH 7.4±0.05 without enzymes.

Procedure:- Microspheres equivalent to 100mg of Saxagliptin and were evaluated for in-vitro dissolution studies. The study was carried out in a USP II rotating paddle apparatus. Dissolution fluid consists of 900ml of simulated gastrointestinal fluids of increasing pH namely pH 1.2 (-2 hr), pH 6.8 (1hr) and pH 7.4 (up to 10 hrs) maintained temperature at $37^0C \pm 0.5^0C$ and the basket was rotated at a constant speed of 50rpm.

Aliquots of samples were withdrawn after predetermined periods of time and the same volume of fresh medium was added immediately to the test medium. The withdrawal samples were filtered through a 0.45µm membrane filter. The drug content was determined in the filtrate after appropriate dilution and analyzed at 210 nm spectrophotometrically using Shimadzu 1201 UV-visible spectrophotometer. Corresponding concentrations in the samples were calculated from standard plot and calculate cumulative percentage of drug release from each formulation.

Kinetic study:

The data obtained from *the in-vitro* dissolution studies subjected for kinetic treatment to obtain the order of release and best fit model for the formulations by using PCP-Disso-V2 software.

RESULTS AND DISCUSSION:

In the present work Saxagliptin microspheres were prepared by ionotropic gelation technique using sodium alginate and also with three different coating polymers. Total nine batches of microspheres (F1-F6) were prepared and investigated the physico-chemical properties like granulometric study, flow properties, particle size, drug-entrapment efficiency, swelling properties, scanning electron microscopy, loose-surface crystal study and *in-vitro* drug release behaviors.

Preformulation studies:

Calibration development for Saxagliptin adopting

spectro photometric technology. The λ_{max} of Saxagliptin at 210nm were identified using UV-Visible spectrophotometry. A standard curve from the stock solution was obtained in the range of 2-12 µg/ml concentrations using p H 1.2 (acid buffer), pH 6.8 (phosphate buffer) by measuring absorbance at 210 nm.

The absorbance values are given in table 2 and the λ_{max}, standard plots of Saxagliptin are shown in figures 1,2 and 3.

The IR spectra of drug-sodium alginate did not show much change. The possibility of interaction was ruled out as there was no major shift in absorption bands of the drug and physical mixtures shows that there is no appearance or disappearance of peaks. It is, therefore, expected the drug and polymer are compatible and free from chemical interactions.

Table 2: standard calibration curve for Saxagliptin

S.No.	Concentration (µg/ml)	Absorbance at 210 nm	
1	2	0.026	0.032
2	4	0.048	0.062
3	6	0.075	0.090
4	8	0.098	0.119
5	10	0.122	0.148
6	12	0.144	0.178

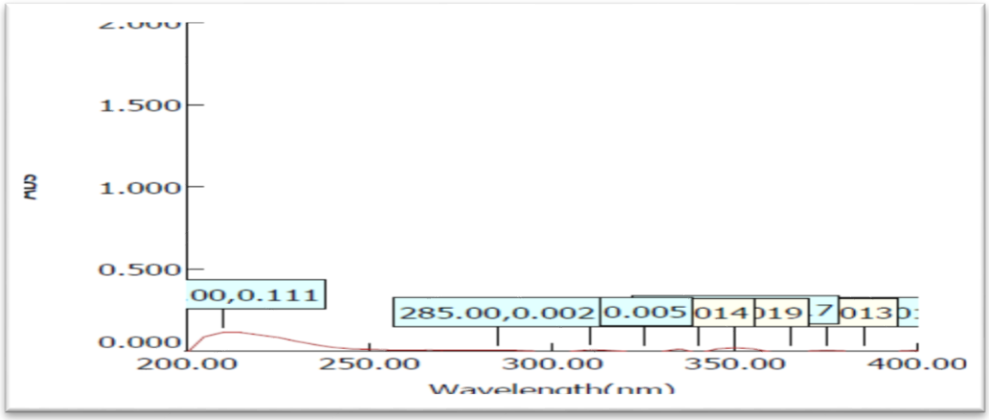

Fig 1: Spectrum of Saxagliptin 210nm

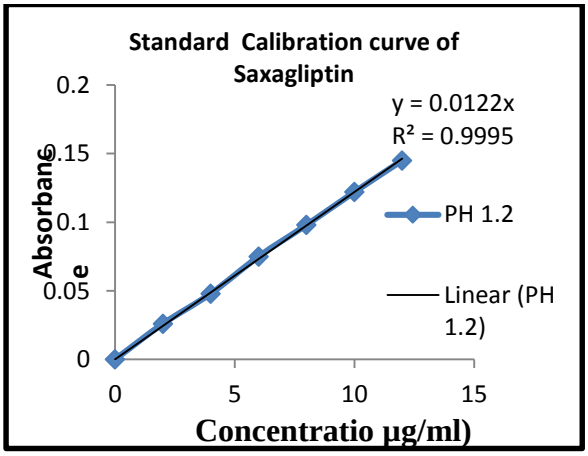

Fig 2: standard calibration curve of Saxagliptin at pH 1.2

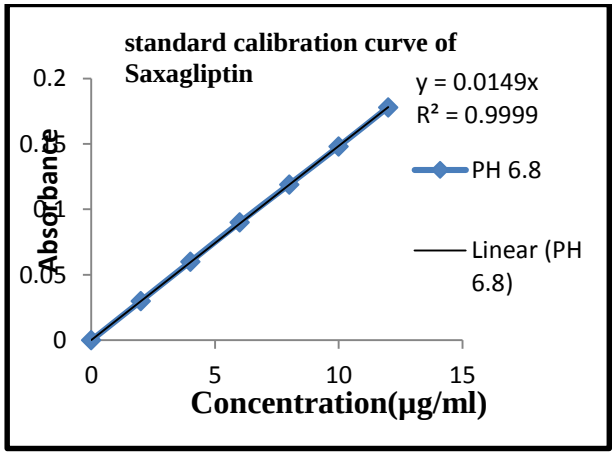

Fig 3: standard calibration curve of Saxagliptin at pH 6.8

Granulometric Study

In the granulometric study, the size distribution of the microspheres in different sieves were observed table no.3, and found that 42.46% to 79.50% of microspheres were retained in #20 sieve, which proves the uniformity size of microspheres. On other hand with increase in the concentration of coating polymers in the formulated microspheres of batch F1, F2, F3(Sodium alginate) F4, F5, F6 (Pectin), F7, F8, F9 (Sodium CMC) and observed that the distribution of the particle size slightly shifts to the lower pore size due to increase in the physical behaviors of the microspheres.

concentration of sodium alginate by increase in the diameter of the particles. The mean diameter of the microspheres is reported in table no4.

Flow Property

The flow properties of the prepared formulations were determined by measuring the angle of repose, using fixed-base cone method. All the formulations showed an acceptable range of angle of repose. The determined range of the formulations as reported in table no.4.

Particle Size

Particle size of drug-loaded microspheres was measured by optical microscopy. The size of the spheres was obtained in the range 1 to1000 µm. The mean diameter of the particles was found to decrease by increasing in the concentration of calcium chloride solution and also increasing in the

Scanning Electron Microscopy:

The physical parameters like shape and particle size were analyzed by scanning electron microscopes62, which was presented for determining the surface and size. The SEM's of the formulation showed that the spheres are having the size-range within the standard limits.

From the photo micrographic observation it can be stated that bridging and dense nature of the formulation batches F3 were significantly prolong the drug release compared with other formulation batches.

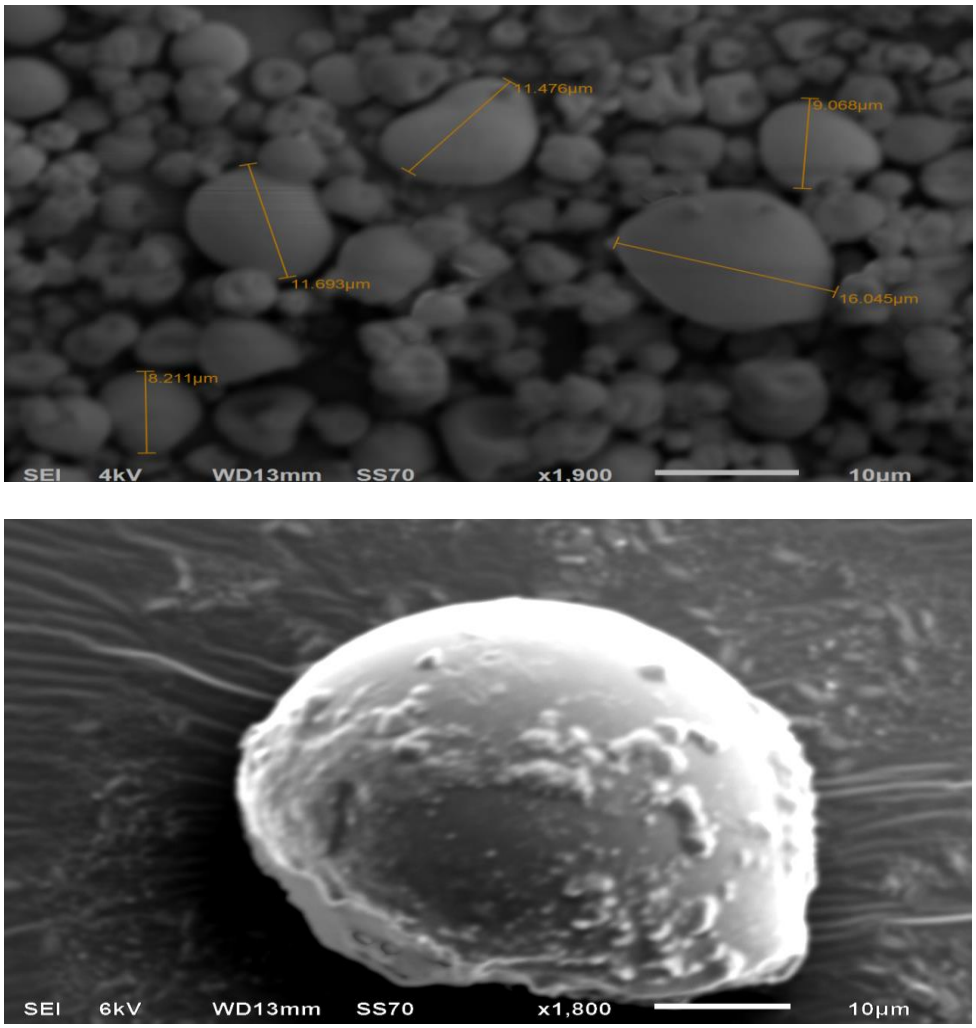

Fig 4: SEM analysis for Saxagliptin + sodium alginate

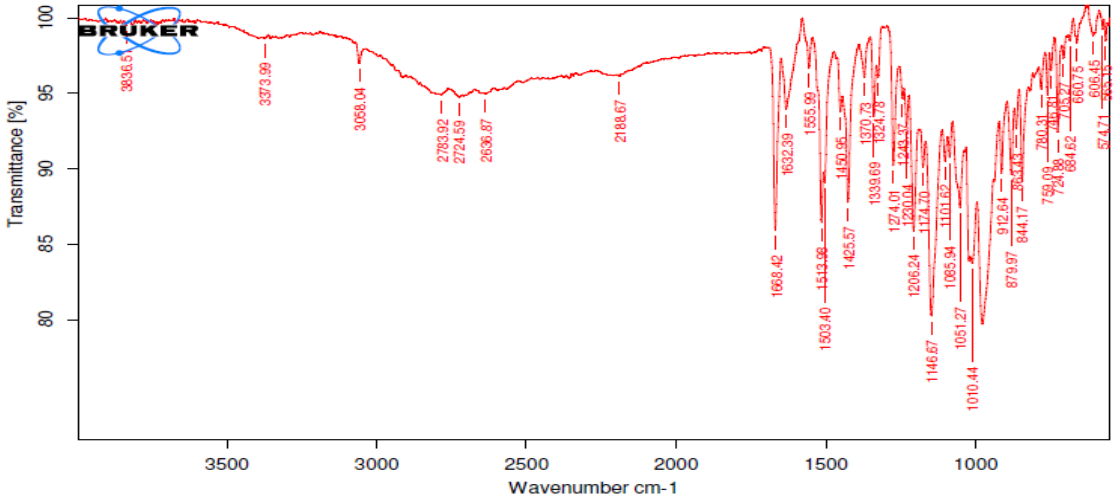

Fig 5: FTIR Spectra of Saxagliptin

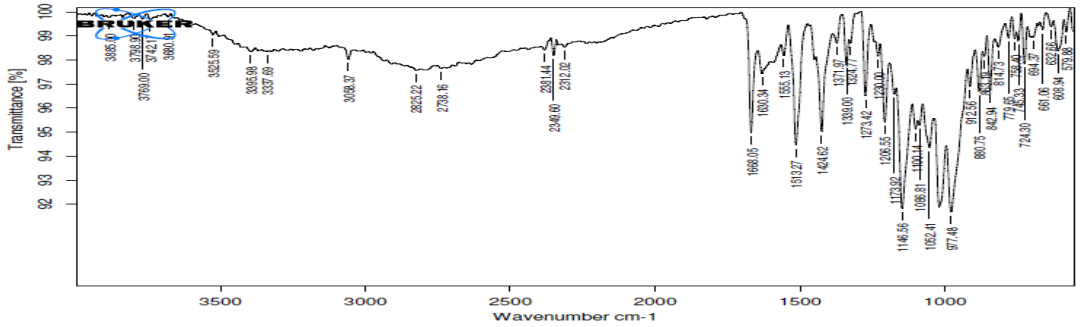

Fig 6: FTIR Spectra of Saxagliptin + sodium alginate

Drug entrapment efficiency:

The drug entrapment efficiency of all the batches are shown in table 5. The batches F1, F2 and F3 shows the drug entrapment efficiency values of 70.4%,77.2% and 85.3% respectively. Drug entrapment efficiency of microspheres increase with increasing in the percentage of sodium alginate as well as by concentration of coating polymers like ethyl cellulose and pectin. The observations are still further depicts the drug entrapment efficiency of batch F4 and F5,F6 were 89.9% and 90.7% respectively. These may be due to drug adhering property of the polymers and also reduced the loss of drug in the curing medium and formation of dense matrix structure shows increase in the drug entrapment efficiency of the Microspheres. The amount of calcium chloride has probably no significant effect on the drug entrapment efficiency.

Table 3: percentage of weight remained on various sieves

Batch no.	#12 (1.68mm) 1190-1680µm	#16 (1.19mm) 840-1190µm	#20 (0.84mm) 590-840µm	#30 (0.59mm) 297-590µm
F1	8.40	7.50	79.50	4.60
F2	5.15	22.83	68.40	3.62
F3	4.78	27.13	63.62	4.47
F4	5.97	34.35	57.82	1.86
F5	8.67	38.92	51.40	1.01
F6	5.86	49.96	42.46	1.72

Table 4: Micromeritic properties of drug loaded microspheres

Batch no.	Angle of Repose (°)	Bulk Density (g/ml)	Tapped Density (g/ml)	Mean diameter (µm)
F1	32°.25	0.485	0.693	822.15
F2	30°.15	0.695	0.755	794.25
F3	28°.20'	0.785	0.862	778.50
F4	26°.20'	0.735	0.806	860.15
F5	25°.30'	0.764	0.810	890.55
F6	25°.40'	0.725	0.835	970.60

Table 5: Drug entrapment efficiency of microspheres

S. No.	Theoretical Drug Content (%)	ActualDrug Content (%)	Drug Entrapment efficiency (%)
F1	82.38	58	70.405
F2	80.26	62	77.248
F3	8.53	67	85.317
F4	74.77	68	90.945
F5	72.86	69	94.702
F6	80.17	72	89.921

Table 6: swelling properties of drug loaded microspheres in different time periods at pH 1.2

Formulation Code	Mean diameters of microspheres (µm)		
	0 hr	1 hr	2 hr
F1	522.15	638.60	662.30
F2	494.25	606.15	623.40
F3	478.50	587.50	603.20
F4	560.15	684.05	610.40
F5	590.55	605.65	631.30
F6	670.60	696.40	729.10

Swelling Properties:

The *"Swelling-dissolution-erosion"* process is highly complex. In systems based on sodium alginate cross-linked with calcium chloride, the osmotic pressure gradient that exists between the alginate gel and the environment comprises an important factor in the swelling process. Under acidic conditions swelling of calcium alginate spheres scarcely occurs.

The observations of swelling properties of the microspheres in pH 1.2 were reported in table 6.The swelling behavior of the prepared Microspheres was studied in pH 1.2 up to 2 hrs. Increasing concentration of calcium chloride in the counter ion solution produces spears with higher levels of Ca2+ ions will reduces the swelling of the spears, consequently increasing the concentration cross-linking polymers also decreasing of the swelling properties of the spears in acidic medium. Due to increased dissolution behavior of the Microspheres in the pH 6.8 the swelling behavior study was not disintegration and dissolution of carried out in those phosphate buffers.

***In-vitro* Dissolution Studies:**

The dissolution studies were conducted by using three different dissolution mediums simultaneously in pH 1.2 for 2 hrs, then the spears shifted at pH 6.8 determined studied up to 09 hrs. The results of the *in-vitro* dissolution studies of formulations F1 to F6 as shown in table 7. The plots of cumulative percentage drug release V/s time as shown in figure 7.

The *in-vitro* release data shows the % cumulative drug release at 14 hours for batch F3 in range 95.54 w/w. Whereas % cumulative drug release at batch F4 ,F5and F6 were 85 to92% w/w. The formulated Microspheres showed increase in drug at pH 1.2 and trend is continued in pH 6.8 because due to cross-linking takes place only between carboxylate residue of GG-blocks and Ca2+ ions forms a tight-gel network structure. The toughness of the network structure and subsequent

alginate particles taking place through ion- exchange between the bound Ca^{+2} ions and Na^{+} ions present in some extent. Thus the release of Saxagliptin from the microspheres appears to be significantly with increase in initial alginate concentration but not with calcium ions.

The kinetic data of *in-vitro* release proves that the aim of the research to formulate sustained release drug formulations for Saxagliptin using sodium alginate and different coating polymers.

The estimated physicochemical and *in-vitro* release data proves that the formulated Saxagliptin Microspheres having the characteristics that required for the formulation of sustained release dosage forms.

However, it can be proved the release drug may be retarded and produce proper sustained effect in the formulation F3 was showing better sustained release pattern when compared to the other batches.

Further, all the formulations were subjected for dissolution medium leading to extended release to mathematical treatment to check whether the release is following first-order or zero-order kinetics.

The drug diffusion coefficient and correlation coefficient were assessed using various mathematical models using PCP Dissco-V2 software and reported in table 8.

The values of coefficient of correlation (r) were calculated and was found to be more linear for zero order release as compared to first-order. It was concluded that release of drug from formulation batches F1 to F6 followed Zero order kinetics.

The kinetic data was best fitted to Korsmeyer-Peppas model. The values of diffusion coefficient (n) for formulation F3 shows to be 0.8674, diffusion following non-Fickian transport mechanism.

Table 7: *In-vitro* release kinetic data of drug loaded microspheres containing sodium alginate

Time in Hours	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
2	14.85±0.45	19.82±1.33	18.14± 1.76	13.23± 1.43	12.28±1.32	12.21± 1.44
4	26.71±0.99	32.14±1.65	29.25± 1.78	25.23± 1.66	22.12±0.87	23.18±1.44
6	38.82±1.23	46.52±1.83	42.45±1.61	36.48± 1.99	36.54± 0.78	34.63±0.89
8	52.14±1.12	59.61±1.61	58.62±1.43	51.71±1.39	49.82±1.27	45.44±1.23
10	65.61±1.18	72.23±1.77	69.23±1.5	66.85±1.44	60.14±0.37	57.23±0.99
12	78.23±1.87	85.45±1.22	81.45±1.72	79.33±1.37	74.83±0.83	72.45±1.19
14	88.23±1.45	91.33±1.83	95.54±1.85	92.41±1.29	89.80±1.41	85.22±1.17

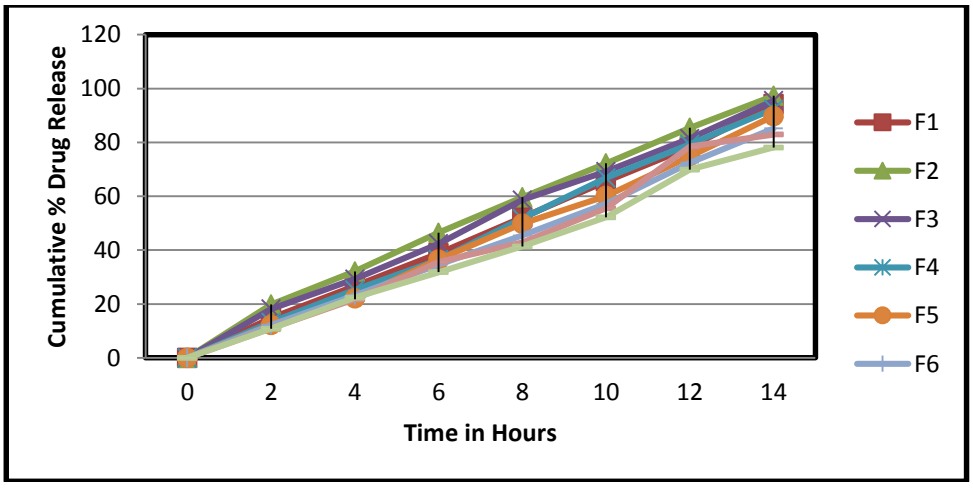

Fig 7: *In vitro* Cumulative percentage Drug Release of Formulations F1, F2, F3, F4 F5 & F6

Table 8: Model fitting data of the release profile for saxaglptin using five different models (r-values)

Formulation Code	Mathematical Models (Kinetics)					
	Zero Order	First Order	Higuchi Matrix	Krosmeyer –Peppas	Hexan crowell	'n' values
F3	0.953	0.879	0.960	0.613	0.932	0.8674

CONCLUSION:

Sustained release formulation of Saxagliptin was successfully prepared using sodium alginate by Ionotropic Gelation Technique. The in vitro dissolution data showed sustained release of the formulation up to 10 hours. The microspheres were prepared without the use of organic solvents. Microspheres of Saxagliptin decrease the incidence of side effects and also improve patient compliance by reducing the number of dosings and by reducing the fluctuations of drug in the blood.

In the present study six formulations were formulated by using sodium alginate as drug release modifiers in various proportions, and evaluate their physicochemical properties and in-vitro drug release potential. Results of preformulation study, granulometric study, bulk and tapped density, mean particle size, angle of repose, drug- entrapment efficiency, *in-vitro* dissolution study, *In-vitro* release study of formulations F1, F2, F4, F5 and F6 showed a release slowly to some extent with increased percentage of sodium alginate.

The Microspheres were further subjected to surface and particle size determination by scanning electron microscopy wherein formulations F3 containing sodium alginate as polymers showed bridging which indicated for dense nature, low porosity of the coating materials and larger particle size.

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