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FORMULATION AND EVALUATION OF SITAGLIPTIN MUCCOADHESIVE MICROSPHERES USING DIFFERENT POLYMERS BY HEAT STABILIZATION METHOD

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ABSTRACT

Emulsion cross linking method can be successfully employed to fabricate Sitagliptin microspheres by heat stabilization method. The technique provides characteristic advantage over conventional microsphere method, which involves an "all-aqueous" system, avoids residual solvents in microspheres. Other methods utilize larger volume of polymer, uneasy in dropping through syringe , air pollution, toxicity and difficult to remove traces during filtration .FT-IR spectra of the physical mixture revealed that the drug is compatible with the polymers and copolymer used. Micromeritic studies revealed that the mean particle size of the prepared microspheres was in the size range 664-903µm for ionotropic gelation method and 511- 826 µm for emulsion cross linking method,size of ionotropic gelation have high mean partice size than emulsion cross link method and are suitable for bioadhesive microspheres for oral administration.Increase in the polymer concentration led to increase in % Yield, % Drug entrapment efficiency, Particle size, % swelling and % Mucoadhesion.The *in-vitro* mucoadhesive study demonstrated that microspheres of Sitagliptin using chitosan as polymer and glutaraldehyde as cross linking agent adhered to the mucus to a greater extent than sodium alginate along with Carbopol934.The *invitro* drug release decreased with increase in the polymer and copolymer concentration.The invitro drug release shows almost same result for T3 and T7 but T7 of emulsion cross linking method was optimized based on optimum swelling index, percentage mucoadhesion , drug entrapment and drug relaese.

Key Words: Sitagliptin, microspheres, Ionotropic gelation method, Carbopol

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INTRODUCTION

For many decades, medication of an acute disease or a chronic disease has been accomplished by delivering drugs to the patients via various pharmaceutical dosage forms like tablets, capsules, pills, creams, ointments, liquids, aerosols, injectables and suppositories as carriers. To achieve and then to maintain the concentration of drug administered within the therapeutically effective range needed for medication, it is often necessary to take this type of drug delivery systems several times in a day. This results in a fluctuated drug level and consequently

undesirable toxicity and poor efficiency. This factor as well as other factors such as repetitive dosing and unpredictable absorption leads to the concept of controlled drug delivery systems. The word new or novel in the relation to drug delivery system is a search for something out of necessity. An appropriately designed sustained or controlled release drug delivery system can be major advance toward solving the problem associated with the existing drug delivery system. The objective of controlled release drug delivery includes two important aspects namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to a specific organ or tissue, while Temporal delivery refers to controlling the rate of drug delivery to the target tissue. Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation. However, this approach is be dilled with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable motility and relatively brief gastric emptying time (GET) in humans which normally averages 2-3 hr through the major absorption zone, i.e., stomach and upper part of the intestine can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose. The objective in designing a controlled release system is to deliver the drug at a rate necessary to achieve and maintain a constant drug blood level. This rate should be similar to that achieved by continuous intravenous infusion where a drug is provided to the patient at a rate just equal to its rate of elimination. This implies that the rate of delivery must be independent of the amount of drug remaining in the dosage form and constant over time, i.e release from the dosage form should follow zero-order kinetics.

Microencapsulation has also been used medically for the encapsulation of live cells and vaccines. Biocompatibility can be improved by the encapsulation of artificial cells and biomolecules such as peptides, proteins, and hormones, which can prevent unwanted immunological reactions that would lead to inactivation or rejection. Microspheres are used for isolating materials until their activity is needed. The biotechnology industry employs microspheres to contain organisms and their recombinant products to aid in the isolation of these products. Microsphere carrier systems made from the naturally occurring biodegradable polymers have attracted considerable attention for several years in sustained drug delivery. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of novel drug delivery systems. Microspheres form an important part of such novel drug delivery systems. Microspheres have varied applications and are prepared using assorted polymers. However; the success of these microspheres is limited owing to their short residence time at the site of absorption. So, various attempt have been made to increase the bioavailability as well as prolong the gastric residence time of dosage form in the stomach resulted in development of bio adhesive drug delivery system which will provide an intimate contact of the drug delivery system with the absorbing membranes. This can be achieved by coupling mucoadhesion characteristics to microspheres and developing mucoadhesive microspheres. Mucoadhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio, a much more intimate contact with the mucus layer, and specific targeting of drugs to the absorption site. Gastric mucoadhesive drug delivery offers a number of applications for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability (1-6).

Aim of the study is to formulate sitagliptin muccoadhesive microspheres using different polymers by heat stabilization method.

MATERIALS AND METHODS

Heat stabilization technique (5-11)

Drug is dispersed in mixture of 5ml of 1%w/v albumin solution, 5ml of 2%w/v chitosan in 2% acetic acid and pour into 5ml of 15% w/v gelatin solution (water) containing 1.5% w/v $CaCO_3$ and syringe in to 25ml of liquid paraffin containing 0.5% w/v span 80 gently stirred for 10min at 60-70^{0}c and 1000rpm (w/o emulsion is formed) then it is cooled at 50 ^{0}c for 30min , washed with petroleum ether and dried at 45^0 c (Table-1).

Table-1 Prepared formulation of Floating Beads

S.no.	Formulation code	Drug:Polymer ratio	Polymer ratio (albumin: chitosan)
1	F_1	1:1	1:1
2	F_2	1:1.5	1:2
3	F_3	1:2	1:3
4	F_4	1:1.5	2:1
5	F_5	1:2	1:1
6	F_6	1:2.5	2:3
7	F_7	1:2	3:1
8	F_8	1:2.5	3:2
9	F_9	1:3	1:1

Characterization of microspheres (6-11)

Percentage yield

The percentage of production yield was calculated from the weight of dried microspheres recovered from each batch and the sum of the initial weight of starting materials.

Drug entrapment efficiency

Microspheres equivalent to 100mg of the drug sitagliptin were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres. The powder was transferred to a 100 ml volumetric flask and dissolved in 10ml of methanol and the volume was made up using 0.1N HCl. After 24 hours the solution was filtered through Whatmann filter paper and the absorbance was measured after suitable dilution spectrophotometrically at 288 nm. The amount of drug entrapped in the microspheres was calculated.

Particle size analysis

Samples of the microparticles were analyzed for particle size by optical microscope. The instrument was calibrated and found that 1unit of eyepiece micrometer was equal to 12.5µm. Nearly about 100 Microparticles sizes were calculated under 45 x magnifications.

Swelling study

Swelling ratio of different dried microspheres were determined gravimetrically in 0.1N HCl at 12th hr.The microspheres were removed periodically from the solution, blotted to remove excess surface liquid and weighed on balance. Swelling ratio (% w/v) was determined.

Evaluation of mucoadhesive property

The mucoadhesive property of microspheres was evaluated by an in vitro adhesion testing method known as wash-off method. Freshly excised pieces of goat stomach mucous were mounted on to glass slides with cotton thread. About 20 microspheres were spread on to each prepared glass slide and immediately thereafter the slides were hung to USP II tablet disintegration test, when the test apparatus was operated, the sample is subjected to slow up and down movement in 0.1N HCl at 37^{0}C contained in a 1-litre vessel of the apparatus. At a time point of 12th hour the machine is stopped and number of microspheres still adhering to mucosal surface was counted.

***In vitro* drug release study**

The dissolution studies were performed in a fully calibrated eight station dissolution test apparatus (37 ± 0.5^{0}C, 100 rpm) using the USP type – I rotating basket method in 0.1N HCl (900ml). A quantity of accurately weighed microspheres equivalent to 100 mg sitagliptin each formulation was employed in all dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 288nm. At the same time the volume withdrawn at each time intervals were replenished immediately with the same volume of fresh pre-warmed 0.1N HCl maintaining sink conditions throughout the experiment.

RESULTS AND DISCUSSION

It was observed that as the polymer ratio in the formulation increases, the product yield also increases. The low percentage yield in some formulations may be due to blocking of needle andwastage of the drug- polymer solution, adhesion ofpolymer solution tothe magnetic bead andbeads lost during the washing process. The percentage yield was found to be in the range of80 to 88% for microspheres containing albumin and chitosan . The percentage yield of the prepared microspheresis recordedin Table-2. Percentage Drug entrapment efficiency of Sitagliptinranged from 62.66 to 88.66% for microspheres containing albumin and chitosan. The drug entrapment efficiency of the prepared beads increased progressively with an increase in proportion of the respective polymers. Increase in the polymer concentration increases the viscosity of the dispersed phase. The particle size increases exponentially with viscosity. The higher viscosity of the polymer solution at the highest polymer concentration would be expected to decrease the diffusion of the drug into the external phase which would result in higher entrapment efficiency. The % drug entrapment efficiency of the prepared beads is displayed in Table-2.

Table-2 Percentage yield and percentage drug entrapment efficiency of the prepared Microspheres

S.No.	Formulation code	% yield	Drug Content (mg)	% Drug entrapment efficiency
1	F_1	80	79.40	62.66
2	F_2	83.33	78.66	64.4
3	F_3	85	78.70	66.66
4	F_4	86	79.5	70
5	F_5	82.22	71.07	73.2
6	F_6	80	72.25	75
7	F_7	88	85.29	88.66
8	F_8	87	83.5	86.66
9	F_9	80	83.01	83.73

Swelling index was found to range from 30% to 45% within two hours time period, which shows that the formulations swell to a certain degree after coming in contact with the simulated gastric medium (Table-3).

Formulation Code	Swelling index (%)
F1	30.32
F2	33.66
F3	39.91
F4	42.33
F5	33.11
F6	35.18
F7	43.55
F8	48.65
F9	42.75

Table-3 Swelling index of Formulation

Among all the formulations F7 shows more susutainity after 9 hourwhere as all other shows optimum sustainity like F7 but F7 shows highest drug release at 12Hr where as remaining all other shows less percent of drug release so F7 was optimized as best formulation (Fig-1-3).

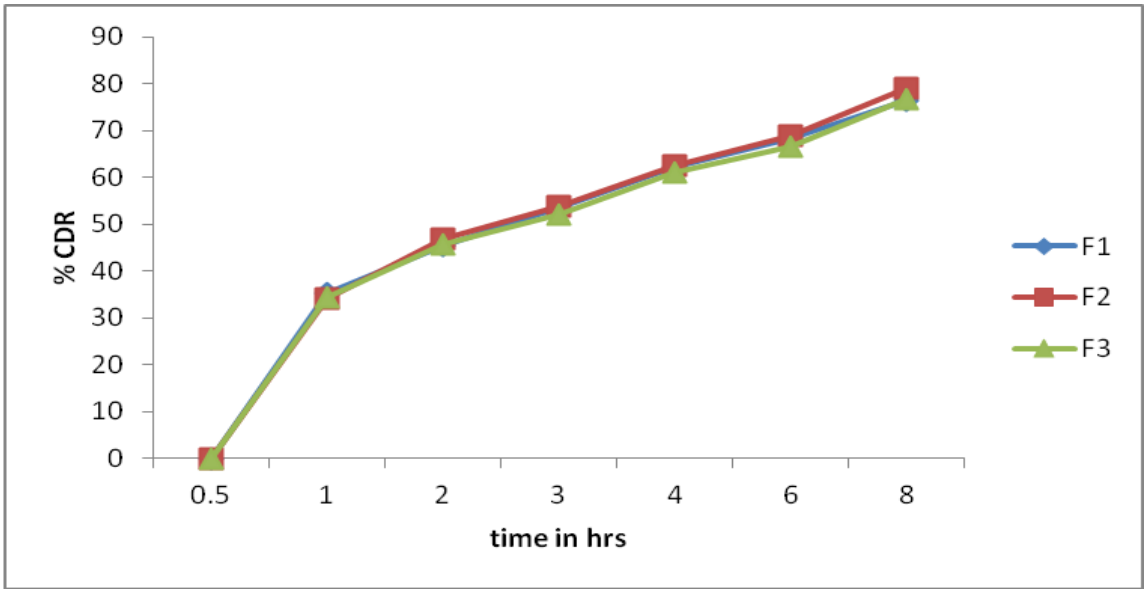

Fig-1 Dissolution profile of Sitagliptin Microspheres (F1, F2, F3) formulations.

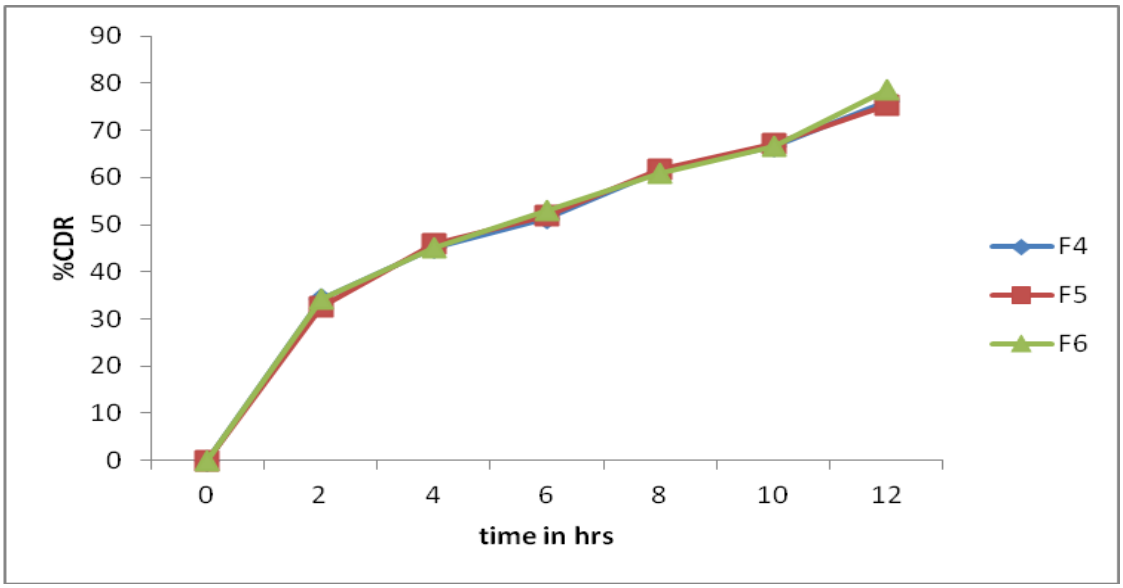

Fig-2 Dissolution profile of Sitagliptin Microspheres (F4, F5, F6) formulations.

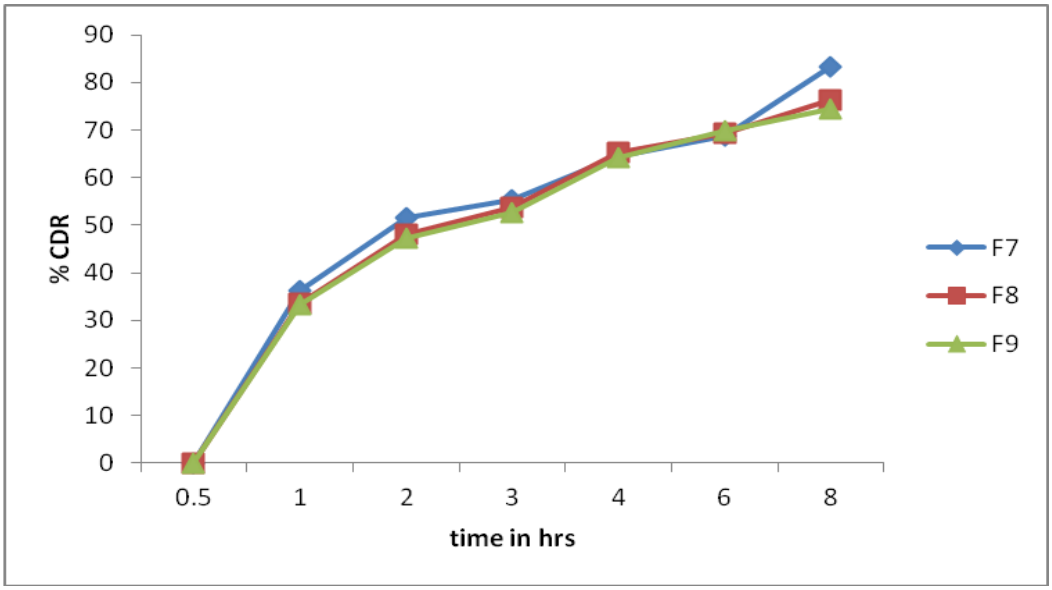

Fig-3 Dissolution profile of Sitagliptin Microspheres (F7, F8, F9) formulations

The F7 formulation follows first order kinetics with R^2 value of 0.9317 and also follows Higuchi model with an R^2 value of 0.9844 and also follows non fickanian model of drug release (Table-4).

Table-4 Regression coefficient values for kinetic models

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	5.889464286	-0.05603176	22.65506214	1.450970956
Intercept	16.17607143	1.963053391	1.935458668	0.545848097
Correlation	0.937478829	-0.96822924	0.992152896	0.845158123
R 2	0.878866555	0.937467862	0.98436737	0.714292252

CONCLUSION

The present study has been a satisfactory attempt to formulate microspheres of Sitagliptin, a new anti diabetic drug giving a controlled release of the drug. From the experimental results it can be concluded that, FT-IR study shows no significant shifting of the peaks therefore it confirms the short term stability of the drug in the beads. Biocompatible polymers like can be chitosan and albumin used to formulate microspheres. Good percentage drug entrapment and practical yields were obtained with both the polymers. The flow properties of all formulations were within the acceptable range and therefore they could be easily filled into capsules. Cumulative percentage drug release significantly decreased with increase in polymer concentration. The overall curve fitting into various mathematical models was found to be on an average. The formulations F 7 best fitted into First order kinetic model and Higuchi model. Thus, the formulated microspheres seem to be a potential candidate as an oral controlled drug delivery system in prolonging the drug release and increasing the bioavailability of drug.

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