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Formulation and evaluation of gastroretentive microspheres loaded with Repaglinide

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ABSTRACT

Floating microspheres loaded with Repaglinide were prepared using sodium alginate as the natural polymers and guar gum as the release retardant by ionic gelation method. Sodium hydrogen carbonate was utilized as the gas generating agent to render floating property to the microspheres. The formulation of micropsheres was done at various concentrations of the polymers. The drug entrapment efficiencies for the different formulations were in the range of 69.6 to 81.9 % w/w. The floating capacity increased proportionally with the concentration of guar gum. Formulations F4 (83%) and F3 (81%); exhibited the best floating capacity. The percent swelling for all the formulations ranged from 14.5 to 16.9 %. The formulation F2 (15.3%) and F3 (15.8%) exhibited optimal swelling capacities. The cumulative drug release was observed to be 66.363 %, 61.774 %, 63.061 % and 36.035% in formulation F1, F2, F3 and F4 respectively.

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Introduction

Repaglinide is an oral antihyperglycemic agent used for the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Repaglinide lowers blood glucose levels by stimulating the release of insulin from the pancreas. This action is dependent upon functioning beta (β) cells in the pancreatic islets. Insulin release is glucose-dependent and diminishes at low glucose concentrations. It is rapidly and completely absorbed from GI tract and has a very short half life of about 1 hour (drugbank, 2021).

Treatment of disease requires maintenance of uniform concentration of drug in blood for a long period of time. Floating microspheres were envisaged as the most promising drug delivery system owing to their slow dissolution in gastric fluid thereby rendering the capability to prolong the release of drug at the site of absorption. A few attempts have been made to overcome the short half life of repaglinide (Jain et al., 2005; Ahmed et al., 2014; Sharma et al., 2014; Sharma et al., 2015; Sharma et al., 2017).

The objective of this work was the development and investigation of floating drug delivery systems of Repaglinide to modulate its pharmacokinetic profile and increase its half life using guar gum as the release retardant.

Material and Methods

Repaglinide was obtained as gift sample from Torrent Pharmaceuticals Limited, Ahmedabad. Guar gum, sodium alginate and calcium chloride were procured form Oxford Lab fine chemicals.

Preformulation Study

Preformulation studies are an important tool for determination of physical and chemical properties of the drug before incorporating it in formulation development. Organoleptic characters, solubility and melting point of the drug were performed as per reported procedures (Martin, 2003).

Formulation of floating microspheres

Different batches of floating microspheres of Repaglinide were prepared using sodium alginate and varying the concentration of the guar gum (Amin et al., 2016; Achuth Kumar et al., 2018). Method of ionotropic gelation or ionic crosslinking was used to formulate the micropsheres (Table 1).

Sodium alginate was dissolved in deionized water with the aid of gentle heat. Separately, guar gum was dissolved in deionized water and accurately weighed quantity of the drug was added to it and stirred vigorously. To this mixture, the gas forming agent was added to form slurry. The prepared slurry was added slowly to the alginate solution and mixed continoulsy. The crosslinking agent was prepared by dissolving calcium chloride in deionized water to obtain a 5% w/v solution. This solution was enriched with 10% v/v glacial acetic acid. The alginate mixture free from air bubbles was added dropwise through a hypodermic syringe with a 26G needle in to the crosslinking solution under stirring.The formed beads were collected by filtering and air dried for 12 h. These spherical microspheres were stored in air tight containers for further processing.

Evaluation of Formulations (Ramu et al., 2015)

Particle Size

The particle size of the microspheres was determined by using an Olympus microscope, employing the calibrated eye piece and stage micrometer method.

Drug entrapment

The various formulations of the floating microspheres were subjected to drug content analysis. 50 mg of the microspheres of each batch were accurately weighed and crushed. The powdered microspheres were dissolved in 10 mL methanol, in a 100 mL volumetric flask and the volume was made up to the mark with PBS pH 6.8. The solution was filtered through Whatman filter paper No. 44. After filtration 10 mL of this solution was

pipette out and diluted up to 100 mL with PBS pH 6.8. 2 mL of this solution was then diluted up to 10 mL with PBS pH 6.8 and the absorbance was measured at 245 nm against PBS pH 6.8 as blank. The percentage drug entrapment was calculated as per the formula.

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Micromeritic Properties

Angle of repose, Carr's Index, Bulk density, Tapped density and Hausner's ration were determined to assess the flow ability of the prepared microspheres.

Floating Capacity

An *in vitro* floating study was carried out using 0.1M HCl as the dispersion medium. Microspheres were spread over the surface of 400 mL of the dispersing medium at 37±0.5°C. A paddle rotating at 100 rpm was used to agitate the dispersion medium. Each fraction of the microspheres floating on the surface and those settled down were collected at a predetermined time. The collected samples were weighed after complete drying.

Swelling Behavior

The dynamic swelling property of microspheres in the dissolution medium was determined by placing a known weight of microspheres in the dissolution solution for 3 hours and collecting the swollen particles by centrifugation. The particles were blotted on filter paper to remove the absorbed water and then weighing immediately on electronic balance. The percentage swelling of microspheres was calculated

In vitro release

USP type II dissolution apparatus (paddle type) was performed at 50 rpm in 900 mL PBS pH 6.8. 5 mL of the sample was withdrawn at a predetermined interval and the volume of dissolution medium was maintained by adding equal volume of fresh dissolution medium. The absorption of the withdrawn sample was measured spectrophotometrically with suitable dilution and the corresponding concentration was determined from the calibration curve. The temperature was maintained at 37° C throughout the study.

Results and Discussion

Preformulation Characters

The physical characterization of the drug was performed according to the reported procedure and the results obtained were compared with that of the standard specifications (Table 2).

Particle Size analysis and yield

The particle size of various formulations was determined by stage micrometer and eye piece method. If the size of microspheres is less than 500 µm, the release rate of drug will be high and the floating ability will reduce whereas in the microspheres ranging from 500-1000 µm, the floating ability will be more and the drug release rate will be in a sustained manner. The mean particle size of the hollow microspheres was found to be in the range 540-1000 µm (Table 3). The various formulations of the prepared microspheres were also evaluated for the percentage process yield. The percentage yield varied from 65-77% (Table 3).

Entrapment Efficiency

The drug entrapment of various formulations of Repaglinide was carried out as per the procedure and performed in triplicate. The drug entrapment efficiencies of different formulations were in the range of 63.50 to 86.00% (Table 3). Drug entrapment slightly increases with an increase in guar gum concentration.

This may be attributed to the swelling capacity of guar gum in aqueous solutions.

Floating capacity and swelling index

Hollow microspheres were dispersed in 0.1M HCl containing Tween 20 (0.02% w/v). The floating ability of different formulations was found to differ according to the ratio of the guar gum used. The dynamic swelling property of the microcapsules in the dissolution medium was determined and was found to be in the range of 14.5 to 19.9 % (Table 4).

Micromeritic properties

Angle of repose of microspheres was determined by fixed funnel method. The angle of repose was found to be in the range of 21°68' to 29°72'. The apparent bulk density of the formulations was measured with help of measuring cylinder. The bulk density value ranged from 0.341 to 0.444 g/cm^3. The tapped density was determined using tapping method. The tapped density value of various formulations of the microspheres was found to be in the range from 0.378 to 0.487 g/cm^3 The density value of the microspheres was less than the density of gastric fluid (1.004 g/cm^3) thereby the microspheres possessed the ability to be buoyant in the stomach. Carr's Index and Hausner's ratio were calculated using formula (Table 5).

***In vitro* drug release**

The *in vitro* drug release study of the microspheres was evaluated in PBS pH 6.8. The % release, % cumulative release and % log cumulative release was calculated. The *in vitro* release data from different formulations were studied in 0.1M HCl for 12 h using USP-II type dissolution apparatus. From the release data it was observed that the percentage cumulative release and the release rate depended upon the amount of guar gum used. For the formulations F1 to F4 it was found that the release of Repaglinide significantly decreased with increasing the amount of guar gum. This is due to the fact that when higher concentration of polymer is used the density of the polymer matrix is increased thereby increasing the diffusion path length. The cumulative drug release was observed to be 66.363 %, 61.774 %, 63.061 % and 36.035% in formulation F1, F2, F3 and F4 respectively. The formulation F3 exhibited a release of 32.352 % at the first hour which may be due to the burst effect (Figure 1).

For all the formulations, the values of R^2 of zero order, Higuchi and Peppas model were calculated. It was clearly observed that for most of the formulations, the value of resulting regression coefficient is highest for Higuchi model which shows that all the formulations predominantly followed the Higuchi square root kinetics. The corresponding n values of maximum formulations were below 0.5 which indicates that the formulations released drug through Fickian diffusion mechanism .

On the bases of all the evaluation parameters it was found that formulations F2 and F3 were concluded to be the best formulations with good floating characteristics, drug entrapment and drug release profile.

Conclusion

In the present study, gastroretentive microspheres loaded with Repaglinide were prepared by ionic gelation method using sodium alginate as the natural polymer and guar gum as the release retardant. The results obtained showed that this methodology was able to produce reproducible microspheres and for sustained release of drug from the formulations. The microspheres were able to exhibit floating ability in simulated gastric medium. Consequently, it can be concluded that the microspheres produced from sodium alginate by ionic gelation method is an excellent delivery system that has good release behavior for actively releasing drug in the stomach due to its gastro-retentive (floating) ability. Also it was concluded that guar gum was able to provide good release retardant property to the formulation thereby making them suitable for sustained release throughout the day.

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Table 1. Composition of different batches of microspheres

S.No.	Ingredient	Batch Code			
		F1	F2	F3	F4
1	Repaglinide (mg)	10	10	10	10
2	Sodium alginate (% w/v)	3	3	3	3
3	Guar gum (% w/v)	0.25	0.50	0.75	1.0
4	Calcium chloride (% w/v) with 10% v/v glacial acetic acid	5	5	5	5
5	Sodium hydrogen carbonate (% w/v)	2.5	2.5	2.5	2.5
6	Distilled water	q.s	q.s	q.s	q.s

Table 2. Preformulation study of Repaglinide

S No	Parameter	Observation
1	Physical appearance	White to off-white crystalline powder
2	Odour	Odourless
3	Melting Point	240-242°C
4	Solubility	Soluble in water, ethanol, methanol, 0.1N HCl and 0.1N NaOH

Table 3 Yield, particle size and entrapment efficiency of microspheres

Batch Code	Percent Yield (%)	Particle Size (µm)	Drug entrapment (%)
F1	76.34	539	69.6
F2	78.19	812	73.8
F3	73.27	847	77.1
F4	64.16	981	81.9

Table 4 Floating and swelling capacity of microspheres

Batch Code	% Floating Capacity	Floating duration (h)	% Swelling of microspheres
F1	72	7	14.5
F2	76	9.5	15.3
F3	81	11	15.8
F4	83	12.1	16.9

Table 5 Micromeritic properties of microspheres

Batch Code	Angle of repose (°)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index	Hausner's ratio
F1	29.72	0.408	0.469	13.00	1.149
F2	21.68	0.444	0.473	6.13	1.065
F3	28.17	0.416	0.487	14.57	1.170
F4	26.23	0.341	0.378	9.78	1.108

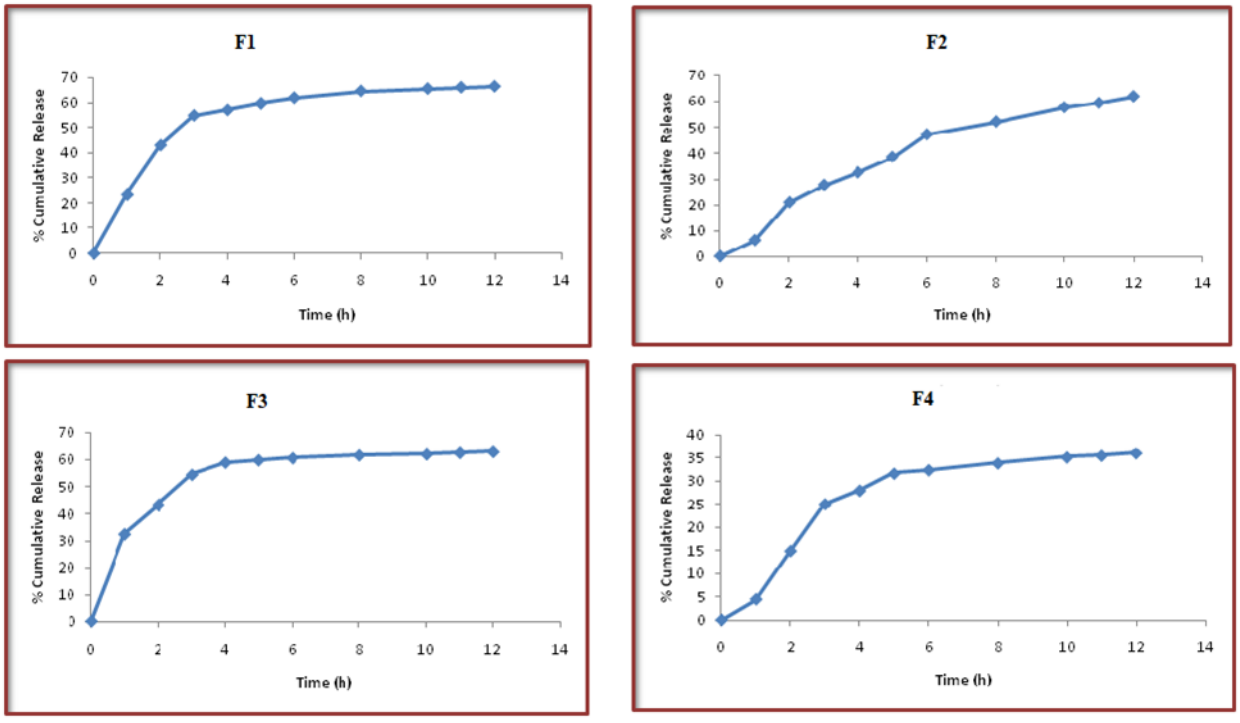

Figure 1. Release of repaglinide from micropsheres

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