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TO PREPARATION AND EVALUATION OF REPAGLINIDE ALGINATE BEADS FOR FLOATING DRUG DELIVERY SYSTEM

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ABSTRACT: The aim of this current work was to formulation and evaluation of alginate beads to increase the sustain release action of repaglinide over the floating drug delivery systems. **Method:** These repaglinide alginate beads were formulated by dripping technique for the multiple division of floating formulation by means of polymeric drug and gas-forming agent. Drug and polymers were subjected for compatibility studies using FTIR. The formulated beads were characterized for particle size, percentage drug entrapment efficiency, scanning electron microscopy, *in-vitro* buoyancy and *in-vitro* drug release. **Results**: Percentage drug entrapment was revealed the range between 59.643±.561 to 86.181±.521. And *in-vitro* drug release was demonstrated to be 53.997±0.297 to 72.819±0.195. From the *in-vitro* drug release, it was indicated the enhancing of the concentration of sodium alginate with the drug that resulted in advance delayed of the drug release. **Conclusions:** The obtained results from the experiment were exhibited the better sustained action of the selected drug for the floating drug delivery in the form of alginate beads. It was also best fitted in Higuchi model.

Key Words: Alginate beads, Sustain, Floating drug delivery, Repaglinide, Dripping Technique.

INTRODUCTION: The successes of gastroretentive are an approach to rest on the considerate of stomach functioning and associated with gastric drain course. This arrangement is advances to the release of prolong GI residence instance along with appropriate drugs which can be nearby dynamic inside the gastric mucosa at stomach site [1]. From the past few years, a numerous gastroretentive drug release systems are created and developed huge concentration system with the intention of preserve drug inside the base of the stomach [2]. This has been marked the some preparation and a number of patents of gastroretentive formulation. It is also correspond to the both floating and non-floating arrangement, but the current advance of this systems help to enlarge the hyfugastric habitation of drug together with bioadhesive systems, low density systems, high density systems, magnetic systems, swelling systems,

unfold able and flexible system [3]. For these types of drug delivery, Thus Multi-unit balanced dosage form had been effectively developed from freeze-dried sodium alginate [4]. The sphere-shaped bead just have about 2.5 mm in diameter which be able to be equipped by dropping method with the solution of sodium alginate in calcium chloride, it can be effective for the precipitation of sodium alginate. The beads are at that time alienated with snap-frozen in fluid nitrogen, and freeze-dried at -40ºC for 24 hrs, primarily to the creation of an absorbent coordination, which could have stay behind a floating force more than 12 hrs [5]. Repaglinide is an antidiabetic drug in the group of medication that is recognized as meglitinides. It acts as oral antihyperglycemic mediator for the type II diabetes. Repaglinide fit in BCS class II medication and it has 56% oral bioavailability over the conventional dosage form [6]. Repaglinide is partly immersed from the GI tract after complete administration with the poorer bioavailability for the reason of the reduced solubility. Consequently, this challenge was completed to enhance the reduce solubility of Repaglinide through formulation of alginate beads [7]. Therefore, it discourages the blood glucose absorption as a result of stimulating the discharge of insulin from pancreatic beta cells. It is made through a perceptive ion channel system [8]. Repaglinide is quickly as well as totally immersed by way of highest plasma absorption by taking place of just about 1 hr following oral way. It possesses short oral bioavailability (56%) owing to hepatic primary metabolism rate later the following administration. which create a regular measured quantity of dosing 0.5 to 4 mg in 2 to 4 period in each day according to required dosing to retain the medicine with curative blood point for extended period [9,10].

METHODOLOGY

MATERIALS AND METHODS

MATERIALS

For the preparation of floating beads, repaglinide was obtained from Pifer pharmaceuticals Pvt. Ltd, Sodium alginate was received from Qualichems Fine Chem. Pvt. Ltd. Vadodara; Calcium carbonate was received from Central Drug House Pvt. Ltd. New Delhi and methanol and ethanol were used the HPLC grade.

Method of Preparation

The dripping technique was selected by decomposing of 0.002 g (2.0 mg) repaglinide by the way of 5 ml distilled water. In this process, the prepared solution was discrete with 30 ml alginate material (3% w/v) included HPMC. Subsequently, a gas-forming compound $CaCO_3$ was considered to use of the solution among to the class as of 0:1 to 1:1 (w/w). For the closing combination of prepared beads was fused underneath vacuum condition. The consequential arrange mixture of beads were put throughout the 26G inject pine needle with the 1% (w/v) Calcium chloride solvent consist of 10% (v/v) Acetic acid. The following arranged beads were enthused by way of magnetic blend for 10 min. The produced beads were assembled and rinsed by methanol as well as distilled water. The arranged beads were air dried at room temperature.

Table 1: Composition of Different Formulation

F. code	Drug (mg)	Alginate:HPMC (9:1)	Calcium carbonate	Sodium bicarbonate	Calcium chloride
F1	2	1%	0	0	1%
F2	2	2%	0	0	1%
F3	2	3%	0	0	1%
F4	2	3%	0.25%	0	1%
F5	2	3%	0.50%	0	1%
F6	2	3%	0.75%	0	1%
F7	2	3%	1%	0	1%
F8	2	3%	0	0.25%	1%
F9	2	3%	0	0.50%	1%
F10	2	3%	0	0.75%	1%

Evaluations of Repaglinide alginate beads

Preformulation Studies

In the preformulation studies Organoleptic properties, Melting point, UV-visible spectra, Solubility Study and Partition coefficient were performed [11].

Physical Appearance

Physical appearance of various formulations of Repaglinide beads by using different carrier in different ratio of the drug and polymers.

Percentage yield of repaglinide alginate beads

The percentage yield of repaglinide alginate beads was calculated by the following formula. [12].

$$\%\text{yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and polymer}} X100$$

Determination of percentage drug entrapment efficiency

The prepared beads of repaglinide (25 mg) were beached and solublized into 100 ml methanol oscillating at 37°C for 24 hrs. By following centrifugation (4000 rpm, 40 min) the drug absorbance was determined with the UV at the wavelength of 237 nm. The encapsulation effectiveness (EE) was determined according to close proximity to the subsequent equations:

$$EE\% = (W1/W2)* 100$$

Where W1 is the sum quantity of drug in the beads and W2 is the total mass of the drug added primarily throughout the preparation [13].

FTIR analysis

FTIR spectrum of developed formulation of repaglinide beads were carried out via FT-IR spectrophotometer (Perkin Elmer). The IR spectra were figured by employing IR spectrophotometer by KBr pellet technique. IR spectra of formulation was recorded in the 4000 - 400 cm-1 region [14].

Morphological study by SEM

Shell and cross sectional morphologies of beads were studied by way of a Scanning Electron Microscope (SEM) (JSM-5310LV Scanning Microscope, Tokyo, Japan). Beads were increase on metal lattice by double-sided strip and covered with gold underneath vacuum condition [15].

***In-vitro* buoyancy**

The floating capability was determined using USP dissolution test equipment II (paddle method). Fifty beads were bring in in the vessels and the paddles were rotated at 50 rpm in 500 ml of simulated gastric fluid (SGF) pH 1.4 and simulated small intestinal fluid (SSIF) pH 6.8, by uphold at 37±0.5 °C for 10 hrs. The floating ability of the beads was pragmatic visually. The preparation was considered to contain buoyancy just when all beads floated on the test solution for the given time phase [16].

***In-vitro* repaglinide alginate beads in release studies**

Drug release from beads was determined in a dissolution tester following the USP paddle method. Beads equivalent to dose (2mg) were used for dissolution study. All tests were conducted in 900 mL of dissolution medium maintained at 37±0.5^{o}C with a paddle rotation speed at 50 rpm. Dissolution study was carried out by using the following: 1. Simulated gastric fluid (SGF) for 2 hrs at pH 1.4, followed by simulated small intestinal fluid (SSIF) for 24 hrs at pH 6.8. Release studies were performed in triplicate. 5ml sample was taken at time intervals (15min, 30min, 1, 2, 3, 4, 6, 8, 10, 12, 24 h) and fresh media was added to replace the sample taken. Concentrations of formulation were determined at 237nm by UV spectrophotometrically [17, 18].

***In-vitro* drug release kinetics**

Data obtained from in vitro drug release studies were fitted to various kinetic models like zero-order, 1st order, and Higuchi and Korsemeyer peppas to predict the drug release mechanism.

RESULT AND DISCUSSION

Organoleptic Properties of drug

Drug Repaglinide was found to be white crystalline powder, odorless and Tasteless. The drug was found to comply with the literature specifications.

Determination of absorption maxima in methanol

Absorption maxima of Repaglinide were found to be at 237 nm similar to literature as shown in **Figure 1.**

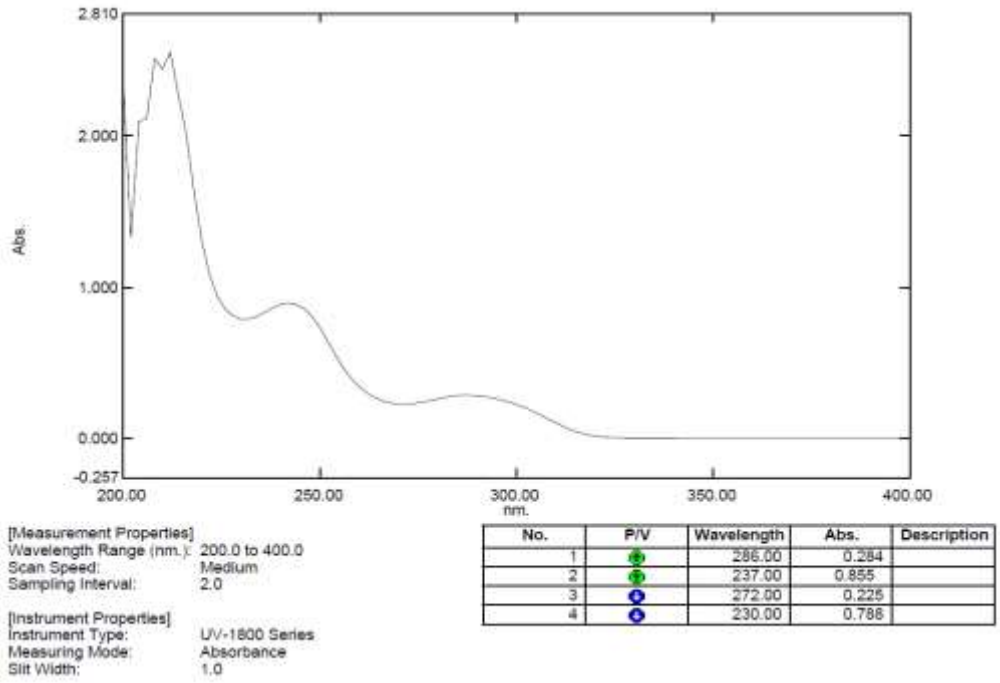

Figure 1: UV spectrum of Repaglinide in methanol

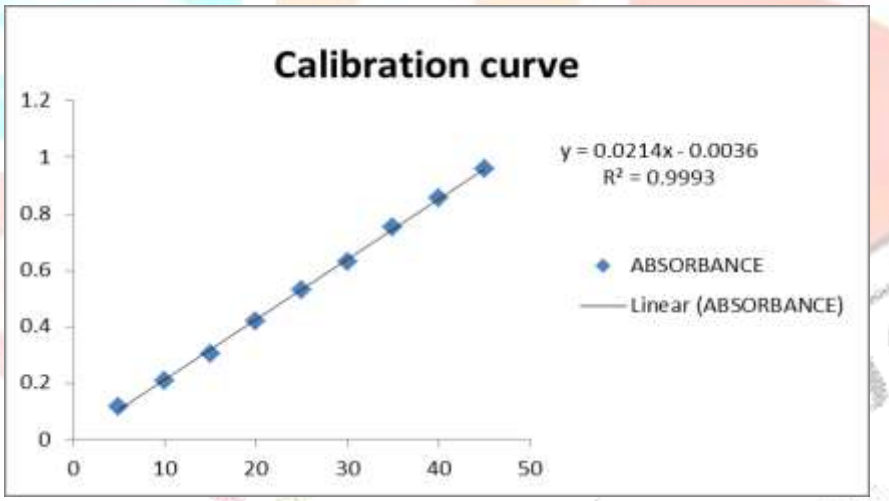

Figure 2: Graph of standard calibration curve of Repaglinide in Methanol

Discussion: - The calibration curve for Repaglinide was obtained by using the5 µg/ml to 45 µg/ml concentration of Repaglinide in methanol. The absorbance was measured at 237 nm. The calibration curve of Repaglinide as shows in graph indicated the regression equation Y= 0.0214x - 0.0036 and R^2 value 0.999, which shows good linearity as shown in **Figure 2.**

FTIR of Repaglinide and Excipients

FTIR of Repaglinide

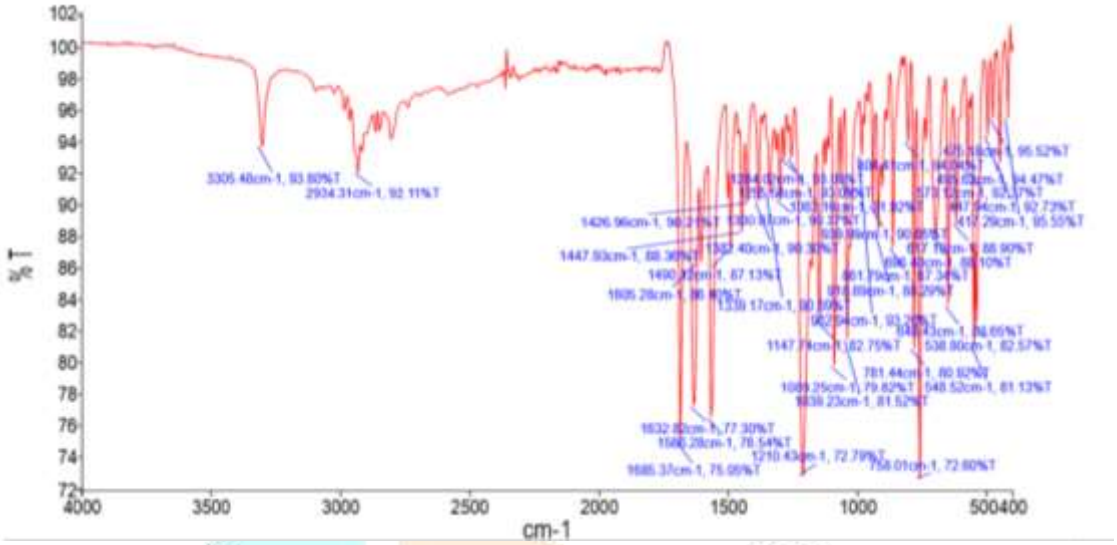

Figure 3: FTIR of repaglinide

The FTIR spectra of repaglinide were shown in the **Figure 3.** The principal IR absorption peaks of repaglinide at 3305.48 cm-1 NH stretching, 2934.31 cm-1 C-H2 Stretching, 1632.82cm-1 N-H bending groups were all observed in the spectra of repaglinide. These observed principal peaks. This observation confirmed the purity and authenticity of the repaglinide. [135]

FTIR of Calcium Carbonate ($CACO_3$)

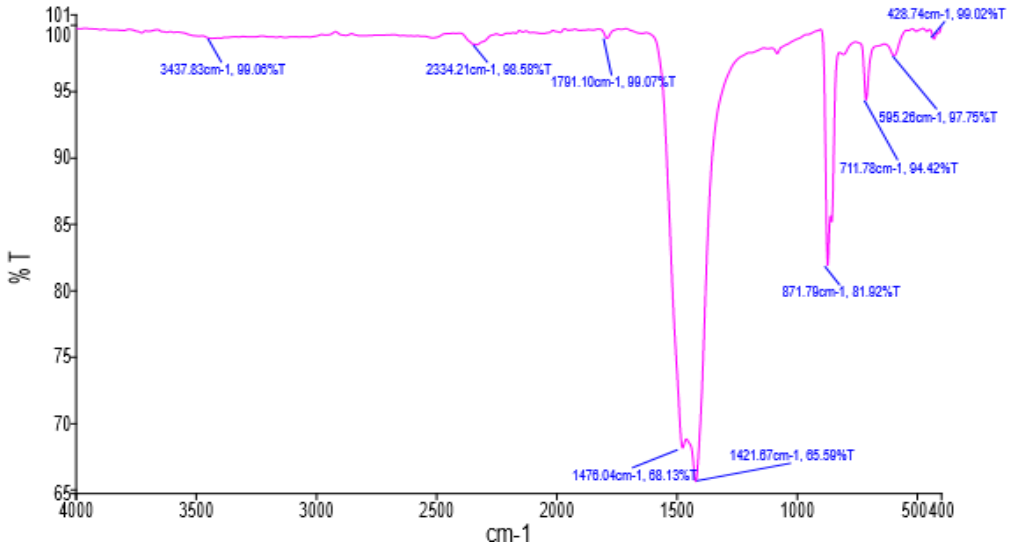

Figure 4: FTIR of calcium carbonate ($CACO_3$)

FTIR of physical mixtures (Repaglinide, Sodium alginate, hydoxypropyle methyl cellulose, Calcium carbonate)

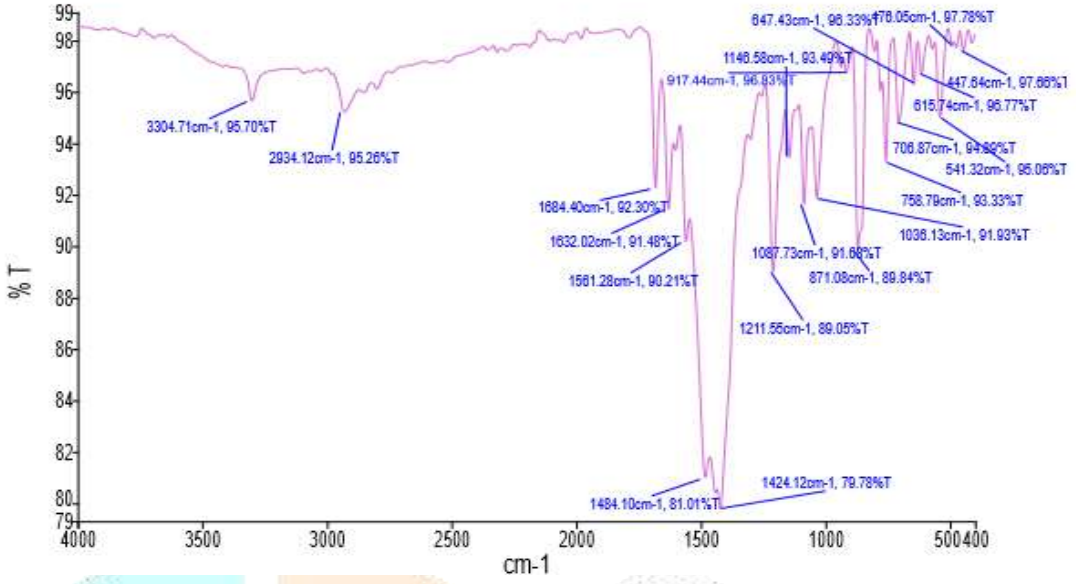

Figure 5: FTIR of physical mixtures (repaglinide, sodium alginate, hydroxyl propyl methyl cellulose, calcium carbonate)

Characterization of Repaglinide alginate beads

Physical Appearance

Figure 6: F-6 Formulation of repaglinide Alginate Beads

Discussion: It shows the good compatibility with drug and after complete formulation. Prepared beads were carried out from F4-F11 along with the incorporation of gas forming agent with successful bead formation.

Particle Size Analysis

Table 2: Average size of different formulations

S.NO	Formulation code	Average size (mm) mean± SD
1	F4	2.801±0.006
2	F5	2.883±0.007
3	F6	2.743±0.005
4	F7	2.923±0.003
5	F8	2.631±0.005
6	F9	2.731±0.006
7	F10	2.801±0.004
8	F11	2.851±0.006

Discussion: Particle size of all bead found in the range from 2.631±0.005 to 2.923±0.003mm. From the result it was found that on increasing gas forming agent concentration particle size increase. The formed beads were sufficiently hard and spherical in shape.

Floating properties

The floating ability of prepared beads was evaluated in simulated gastric fluid and floating property of each formulation was found out as shown on **Table 3.**

Table 3: Floating properties of different formulations

S.NO	Formulation code	%floating
1	F4	0
2	F5	80
3	F6	80
4	F7	70
5	F8	0
6	F9	65
7	F10	60
8	F11	70

Discussion: The results show that all the formulation remain excellent floating ability of beads **(Table 3)**.Formulation F5, F6, F7, F9, F10 and F11 had selected and showed acceptable range of floating property, which indicate the good floating property.

Percentage (%) yield of repaglinide alginate beads

Table 4: Percentage (%) yield of different formulation

S .No	Formulation code	Percentage (%) yield mean±SD
1	F5	88.250±0.021
2	F6	90.240±0.030
3	F7	85.580±0.035
4	F9	79.200±0.034
5	F10	82.24±0.054
6	F11	80.62±0.054

Discussion: From the above **table 4**, **y**ield of repaglinide alginate beads were found to be in the range of 79.200±0.034 – 90.240±0.030.

Drug entrapment efficiency

Table 5: %drug entrapment efficiency of different formulation

S.NO	Formulation code	%EE
1	F5	59.643±.561
2	F6	86.181±.521
3	F7	79.442±0.414
4	F9	61.893±0.434
5	F10	68.288±0.366
6	F11	75.277±0.470

Discussion: It was found that Percentage drug entrapment of all formulation F6 was found to be in a range 59.643±.561-86.181±.521.These results explain that there is a significant effect on percent entrapment efficiency of beads was observed with lipid concentration. Hence, the method adopted for beads formulations was found to be suitable. Formulation F6 is selected for further release study.

FTIR Analysis of formulation F6

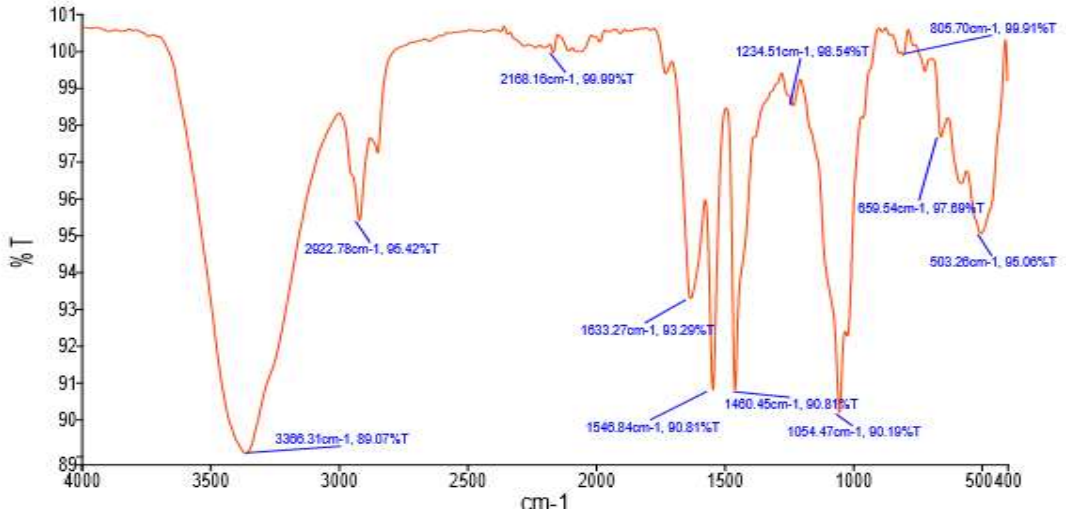

Figure 7: FT-IR spectra of Formulation F6

Discussion: The FTIR spectra of Formulation 6 were shown in the **Figure 7**. The FT-IR spectra of final formulation (F6) at 3366.31cm^{-1}NH stretching,2922.78cm^{-1}C-H_2 Stretching,1633.27cm^{-1} N-H bending,1546.84cm^{-1}. The all characteristic peak that indicate of repaglinide was visible in the repaglinide alginate beads spectrum which indicates that drug was maintained in repaglinide alginate beads.

Morphological Analysis of formulation F6

Figure 8: SEM photographs (cross-sectional morphologies)

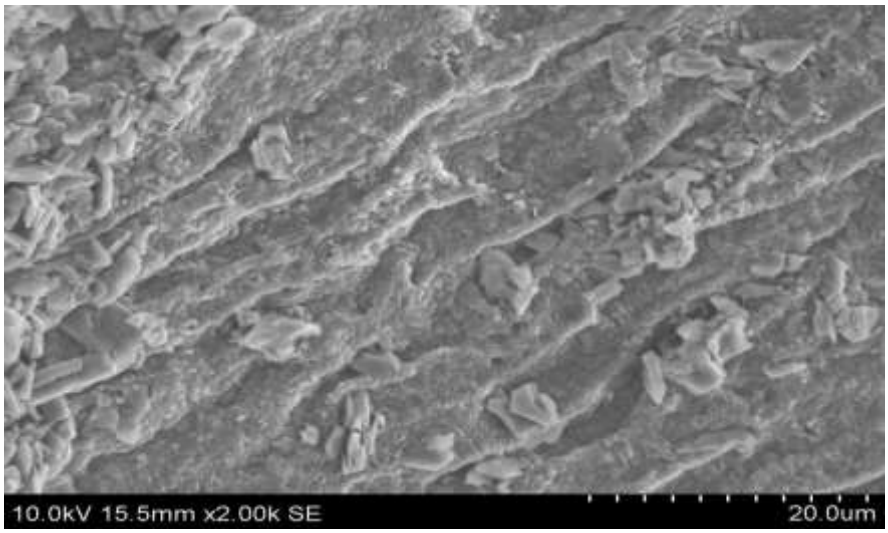

Figure 9: SEM photographs (surface morphologies)

Discussion: It was found that the floating bead of (drug) exhibit spherical morphology. The surfaces of the dried beads of Formulation F6 were rough and porous. Many large hollow pores or multiple small hollow pockets were observed in the alginate matrix. The number of observed pores appears to be directly related to the amount of incorporated gas-forming agent. The precipitated drug crystals can be seen embedded in the matrix. There are shown in above figure.

In-vitro buoyancy

Table 5: Buoyancy of different formulations

S. No	Formulation code	Floating study	Floating time (h)
1	F4	not float	-
2	F5	float	10
3	F6	float	10
4	F7	float	10
5	F8	not float	-
6	F9	float	10
7	F10	float	10
8	F11	float	10

Discussion: The results show that all formulations remain floating up to 10 hrs, reflects excellent floating ability of beads **(Table 5)**. The buoyancy of formulations were maximum floating time of F-5,F-6,F-7,F-9,F-10and F-11.So formulations F-4 and F-8 were discarded from further characterizations.

***In vitro* repaglinide alginate beads in release studies**

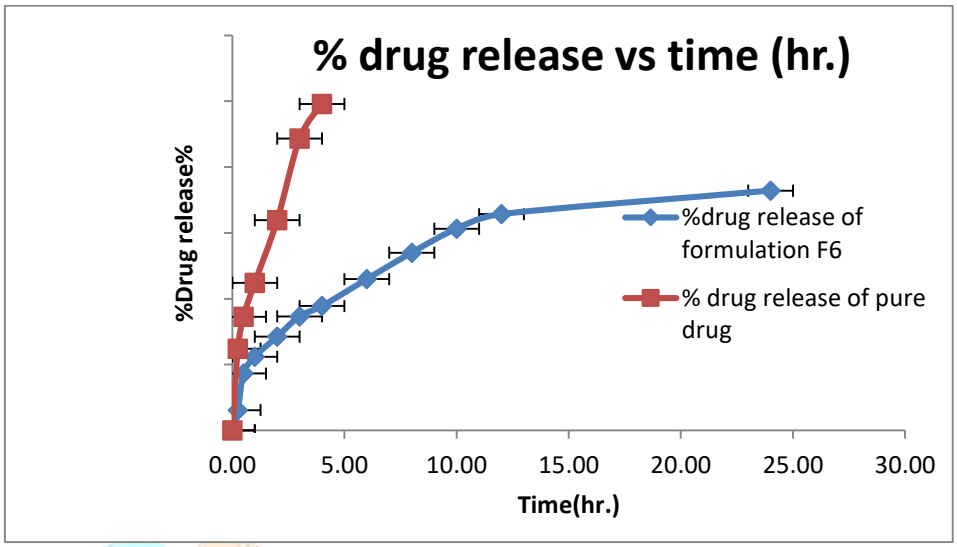

Figure 10: In vitro drug release study of Repaglinide alginate bead

In-vitro drug release kinetic:

In-vitro drug release kinetic study data of F6 Formulation was given below.

Zero-order kinetics:

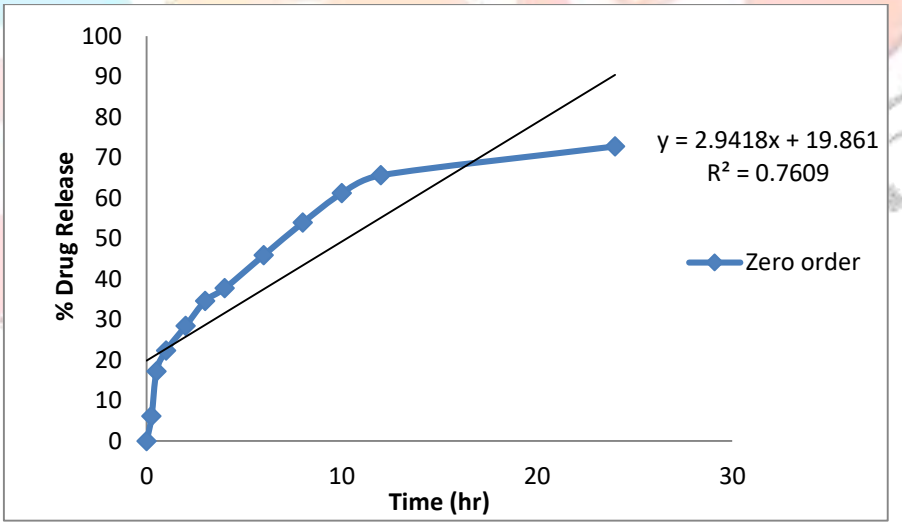

Figure 11: Zero order graph for F6 formulation

First order kinetics:

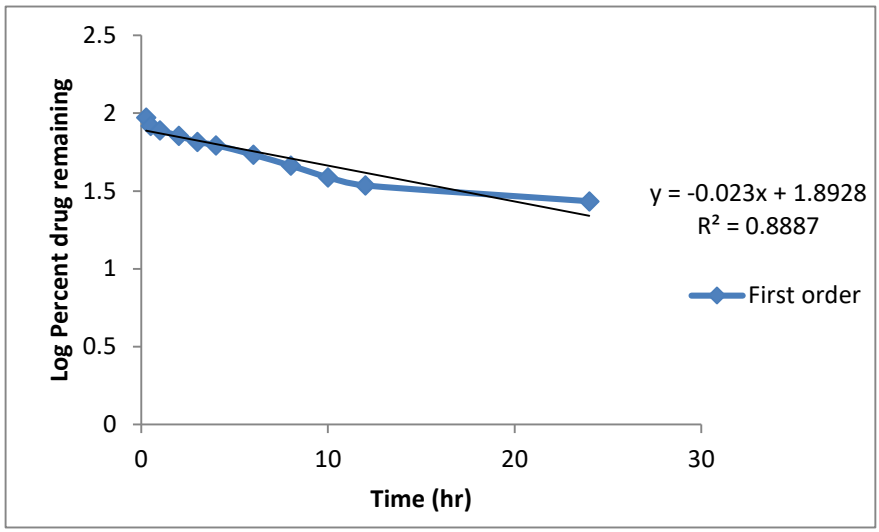

Figure 12: First order graph for F6 formulation

Higuchi's model:

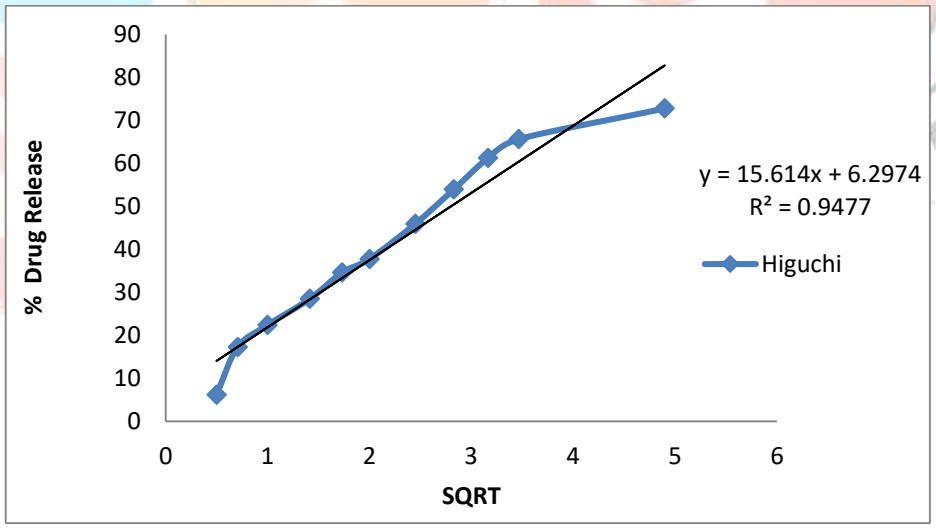

Figure 13: Higuchi order graph for F6 formulation

Korsmeyer-Peppas Model:

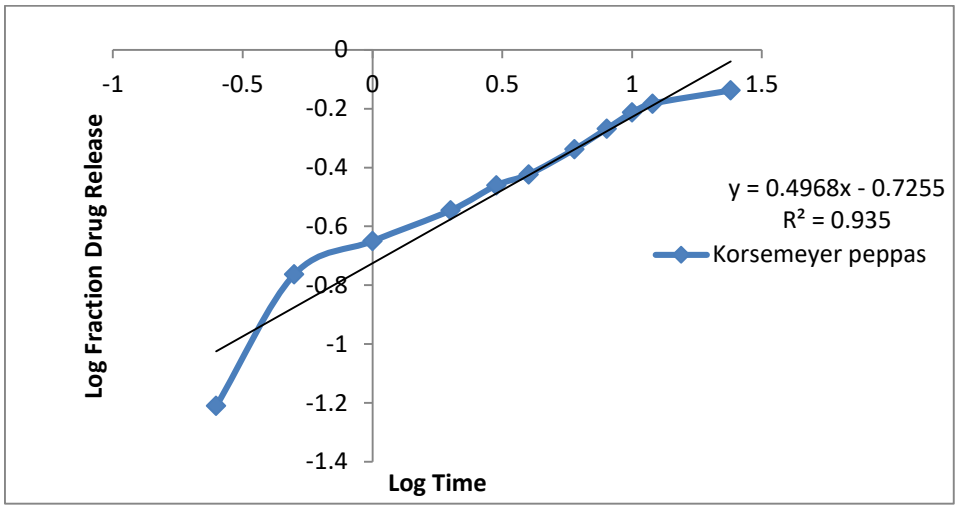

Figure 14: Korsmeyer –Peppas order graph for F6 formulation

Table 6: Kinetic equation parameter of F6 Formulation

Formulation name	Zeroorder		Firstorder		Higuchi		Peppas	
	R^2	K_0	R^2	K_0	R^2	K_0	R^2	K_0
	0.760	2.942	0.888	-0.023	0.947	15.614	0.935	0.496

Discussion: The in-vitro release profiles of repaglinide alginate beads showed sustained release. These behaviours can be explained in terms of release mechanism of the entrapped compound from the lipid beads. The dissolution of the drug particles on the surface of the matrix allows the formation of channels, from which the drug is slowly released. Form the in-vitro drug release study it was found that F6 formulation showed lower drug release as compare to pure drug**.** Mathematical models are commonly used to predict the release mechanism and compare release profile. For the optimized formulation, the % drug release vs time (zero order), log percent drug remaining vs time (first order), log per cent drug release vs square root of time (Higuchi plot), and log of log % drug release vs. log time (Korsmeyer and PeppasExponential Equation) were plotted. In each case, R^2 value was calculated from the graph and reported in **Table 6** And **Figure 10 to Figure 14.** Considering the determination coefficients, Higuchi's model was found (R^2=0.947) to fit the release data best. It could be concluded from the results that the drug was released from repaglinide alginate beads by a Sustained mechanism.

CONCLUSIONS

Floating beads of repaglinide can increase gastric residence instance and thus improve its bioavailability. The developed beads of formulation F6 provide a better-Sustained drug release in evaluation to the new formulations. The solubility outcomes confirm that repaglinide extremely soluble in methanol. The solubility profile of drug in different solvents shows that drug is lipophilic in nature which is further confirmed by the partition coefficient study. The standard curves of repaglinide were prepared methanol and the absorbance data obtained subjected to linear

regression. The correlation coefficients were found to be 0.999 for repaglinide which is closed to one indicated for good linearity. The drug release pattern from the optimized formulations was best fitted to Higuchi's model model. In this analysis drug – excipients compatibility interactions were not observed.

AUTHORS CONTRIBUTIONS

Both authors are equally contributed.

CONFLICTS OF INTERESTS

Authors declare no conflicts of interest.

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