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Formulation and Evaluation of Floating Microspheres of Repaglinide by Ionic Gelation Method

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ABSTRACT

Repaglinide is an antidiabetic drug in the class of medications known as meglitinides, and was invented in 1983. Repaglinide is an oral medication used in addition to diet and exercise for blood sugar control in type 2 diabetes mellitus. The mechanism of action of repaglinide involves promoting insulin release from β-islet cells of the pancreas; like other antidiabetic drugs. The present investigation involved the formulation of the alginate microspheres of Repaglinide (model drug) using calcium chloride as a cross linking agent by inotropic gelation method. Microspheres were prepared by using 2%, 2.2% sodium alginate concentrations. Polymers (HPMC, Ethyl cellulose, Carbopol 934P) were used in combination concentration to prepare Microspheres. Microspheres were evaluated for micromeritic properties like angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio and for drug content. The in vitro drug release study was done for microspheres All formulations. The mean particle size, In vitro Buoyancy, Encapsulation efficiency%, Percentage yield (%) were within limits. Floating Microspheres of Repaglinide improves patient compliance by decreasing dosing frequency. Gastric retention time is increased because of buoyancy. Enhanced absorption of drugs which solubilise only in stomach. Drug releases in controlled manner for prolonged period, site-specific drug delivery.

Keywords: Repaglinide, Antidiabetic, Floating microspheres, Inotropic gelation method, Sodium alginate, Carbopol 934P, HPMC, Ethyl cellulose

INTRODUCTION

A well-designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects [1,2].

Repaglinide lowers blood glucose by stimulating the release of insulin from the beta islet cells of the pancreas. It achieves this by closing ATP-dependent potassium channels in the membrane of the beta cells. This depolarizes the beta cells, opening the cells' calcium channels, and the resulting calcium influx induces insulin secretion [3]. Repaglinide has a 56% bioavailability when absorbed from the gastrointestinal tract. Bioavailability is reduced when taken with food; the maximum concentration decreases by 20%. The protein binding of repalglinide to albumin is greater than 98%. repaglinide is primarily metabolized by the liver - specifically CYP450 2C8 and 3A4 - and to a lesser extent via glucuronidation. Metabolites of repaglinide are inactive and do not display glucose-lowering effects and it is 90% excreted in the feces and 8% in the urine. 0.1% is cleared unchanged in the urine [4].

The word new or novel in the relation to drug delivery system is a search for something out of necessity [5]. 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 aim of any drug delivery system is to afford a therapeutic amount of drug to the proper site in the body to attain promptly, and then maintain the desired drug concentration [6]. Oral drug delivery has been known for decades as the most widely used route of administration among all the routes that have been explored for the

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systemic delivery [7]. All controlled release systems have limited applications if the systems cannot remain in the vicinity of the absorption site. Floating drug delivery systems were first described by Davis in 1968. It is possible to prolong the gastric residence time of drugs using these systems [1]. Several techniques are used to design gastro retentive dosage forms. These include floating, swelling, inflation, adhesion, high-density systems and low-density systems that increase the gastric residence time [7]. Gastric retention is useful for drugs which (i) act locally; (ii) have a narrow absorption window in the small intestinal region; (iii) unstable in the intestinal environment; (iv) low solubility at high pH environment [8].

MATERIALS AND METHODS

Materials

Repaglinide from Rakshit Drug PVT LTD., Hyderabad, HPMC, Ethyl cellulose, Carbopol 934P, Sodium Alginate, Sodium bicarbonate, Calcium chloride, Acetic acid, Glutaraldehyde, Merck Specialities Pvt Ltd, Mumbai, India.

Equipments

Weighing Balance, Automatic dissolution test apparatus,Brookfield digital viscometer, Sartorious digital IR balance, Scanning electron microscope, Magnetic stirrer, DissolutionApparatus, UV-Visible Spectrophotometer, pH meter, FT-IR Spectrophotometer.

METHODOLOGY

Preparation of 0.1n Hcl (Ph 1.2)

Take 8.6ml of HCL in a 1000ml volumetric flask and make up the volume with distilled water.

Preparation calibration curve

100 mg of Repaglinide pure drug was dissolved in 15 ml of Methanol and volume make up to 100 ml with 0.1N HCL (stock solution-1). 10 ml of above solution was taken and make up with 100 ml by using 0.1 N HCL(stock solution-2 i.e. 100 µg/ml). From this take 0.2, 0.4, 0.6, 0.8 and 1.0 ml of solution and make up to 10ml with 0.1 N HCL to obtain 2, 4, 6 ,8, and 10 µg/ml of Repaglinide solution. The absorbance of the above dilutions was measured at 241 nm by using UV-Spectrophotometer taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight-line Linearity of standard curve was assessed from the square of correlation coefficient (R2) which determined by least-square linear regression analysis. The experiment was performed in triplicate and based on average absorbance; the equation for the best line was generated. The results of standard curve preparation are shown in **Table 1 and Figure 1.**

Preparation of microspheres

The floating microspheres were prepared by Ionic gelation technique using the formulation showed in **Table 1**. A solution of sodium alginate is prepared. The gelation medium was prepared by dissolving calcium chloride in 2% glacial acetic acid and was added to solution. In this method cross-linking agent & polymer in combination were dispersed in the purified water to form a homogeneous polymer mixture. Resultant solution was extruded drop wise with the help of syringe and needle into aqueous calcium chloride solution and stirred at 100 rpm. The drug was added to the polymer dispersion and mixed thoroughly on a magnetic stirrer to form a homogeneous dispersion. The homogenous alginate solution was extruded using syringe needle into the gelation medium. Then, microsphere was collected and washed with distilled water twice, dried at room temperature for 24 h and dried at 60°C for 2 h in a hot air oven and stored in dessicator.

Table 1. Composition of floating microspheres.

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Repaglinide (gm)	500gm	500 gm	500 gm	500 gm	500 gm	500 gm	500 gm	500 gm
HPMC	166.6	250	125	125	166.6	250	125	125
Ethyl cellulose	166.6	125	250	125	166.6	125	250	125
Carbopol 934P	166.6	125	125	250	166.6	125	125	250
Sodium Alginate(%)	2	2	2	2	2.2	2.2	2.2	2.2
Sodium bicarbonate (% w/w	10	10	10	10	10	10	10	10
Calcium chloride(% w/v	12	12	12	12	12	12	12	12
Acetic acid (%v/v)	2	2	2	2	2	2	2	2
Glutaraldehyde %	5	5	5	5	5	5	5	5

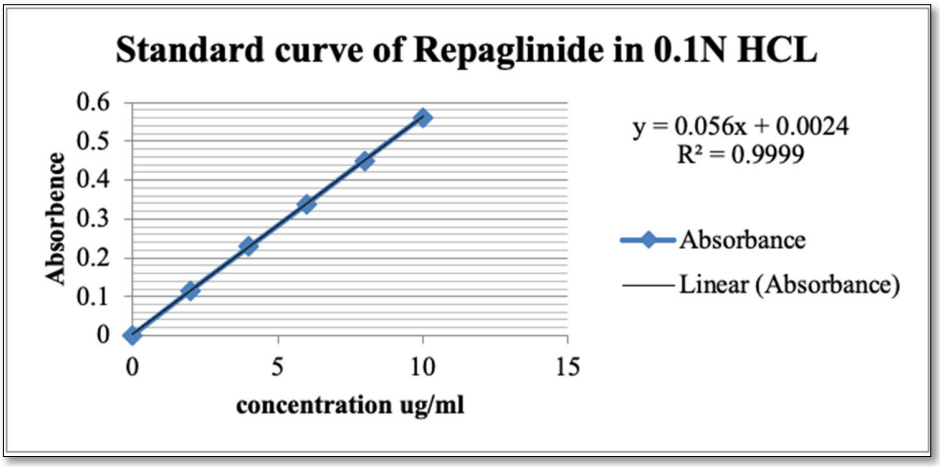

Figure 1. Calibration curve of Repaglinide in 0.1 N HCL at 241 nm.

Micromeritic properties of microspheres

The microspheres are characterized by their micromeritic properties, such as particle size, tapped density, compressibility index, true density, and flow property [9]. The tapping method was used to calculate tapped densities and percentage compressibility index. Tapped densities and percentage compressibility index can be calculated using following equation:

Tapped density:

$$D_t = \frac{M}{V_t} \quad (1)$$

Where, M = mass of the powder

V_t = tapped volume of powder

Carr's compressibility index

$$I = \frac{tapped\ density - bulk\ density}{tapped\ density} \times 100$$

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where, D_t = Tapped density of the powder (g)

D_b = Bulk density of the powder (mL)

The angle of repose (ϕ) of the microspheres, which measures the resistance to particle flow, was measured using fixed funnel method and calculated as per following equation:2

$$\theta = tan^{-1}h/r \quad (2)$$

Where, θ= angle of repose

h = height (cm)

r = radius (cm)

Results of micromeritic properties like Angle of Repose, Compressibility Index

Determination of mean particle size: The particle size was measured using an optical microscope and the mean particle size was calculated by measuring 200 particles with the help of a calibrated ocular micrometer. A small amount of dry microspheres was suspended in purified water (10 ml). A small drop of suspension thus obtained was placed on a clean glass slide. The slide containing microspheres was mounted on the stage of the microscope and diameter of at least 100 particles was measured using a calibrated optical micrometer.

Incorporation efficiency (IE): To determine the incorporation efficiency, 10 mg microspheres were thoroughly triturated and dissolved in minimum amount of ethanol. The resulting solution was made up to 100 ml with 0.1 N HCL and filtered. Drug content was analyzed spectrophotometrically at 320 nm. Calculation was done as per equation 3:

$$\%\ Incorporation\ efficiency = \frac{Actual\ drug\ content}{Theoretical\ content} \times 100 \quad (3)$$

Percentage buoyancy: The floating test was carried out to investigate the floatability of the prepared microspheres. To assess the floating properties, the microspheres were placed in 0.1 N HCL containing 0.02% v/v Tween 20 surfactant (pH 2.0, 100 ml) to simulate gastric conditions. The use of 0.02% Tween 20 was to account for the wetting effect of the natural surface-active agents, such as phospholipids in the GIT. The mixture was stirred at 100 rpm in a magnetic stirrer. After 12 h, the layer of buoyant microparticles was pipetted and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in an oven at 65°C until constant weight. Both the fractions of microspheres were weighed, and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles. Despite

the solution being stirred for 12 h, the microspheres still floated, indicating that the microspheres exhibit an excellent buoyancy effect. Density values of the microspheres (<1.000 g/cm^3) were less than that of the gastric fluid (1.004 g/cm^3), further supporting the floating nature. The *in vitro* floating test was conducted on the drug-loaded microspheres. Results of percentage buoyancy calculated using equation 4:

$$\% \, Buoyancy = \frac{Weight \, of \, floating \, microspheres}{Initial \, weight \, of \, microspheres} \times 100 \quad (4)$$

Yield: Production yield of microspheres containing a drug was determined by the weight ratio of the dried microspheres to the loading amount of the drug and Polymer. Production yield was calculated using equation 5:

$$\% \, Production \, yield = \frac{Total \, weight \, of \, the \, microsphere}{Total \, weight \, of \, drug \, and \, polymer} \times 100 \quad (5)$$

***In vitro* drug release study:** The release rate of Repaglinide from microspheres was determined using USP dissolution testing apparatus I (Basket type). The dissolution test was performed using 900 ml of 0.1 N HCL, at 37 ± 0.5°C and 100 rpm [8]. Microspheres equivalent to 25 mg were used for the test. Aliquots (5 ml) were withdrawn at hourly intervals for 12 h. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through Whatman filter paper and solutions were analyzed using UV spectrophotometer (Shimadzu 1700 UV/V is double beam Spectrophotometer Kyoto, Japan).

***In vitro* drug release studies:**

Apparatus	--	USP-I, Basket Method
Dissolution Medium	--	p H 0.1N HCL
RPM	--	100
Sampling intervals (hrs).	--	1, 2, 3, 4, 5, 6, 8, 10 & 12.
Temperature	--	37°c ± 0.5°C

Where, Mt is the amount of drug released at time t, M ∞ is the amount of drug released after infinite time, Kt is a kinetic constant and n is the diffusional exponent indicative of the drug release mechanism. Calculated from the slope of the plot of log of fraction of drug released.

Drug-Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy: Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a Bruker, ATR FTIR facility using direct sample technique [10].

SEM (Scanning Electron Microscope) studies: The surface morphology of the layered sample was examined by using SEM (JEOL Ltd., Japan). The small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stubs were coated with a thin layer (300A) of gold by employing POLARON - E 3000 sputter coater [11]. The samples were examined by SEM with direct data capture of the images onto a computer.

RESULTS AND DISCUSSION

The present work was designed to developing Floating Microspheres of Repaglinide using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Standard graph of Repaglinide in 0.1N HCL: The scanning of the 10µg/ml solution of Repaglinide in the ultraviolet range (200-400 nm) against 0.1 N HCL the maximum peak observed at λ_{max} as 241 nm. The standard concentrations of Repaglinide (2-10 µg/ml) was prepared in 0.1N HCL showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Evaluation Parameters (Tables 2 & 3, Figures 2-5)

The floating property of the microspheres was calculated from the fractional amount of drug and polymer density of the microspheres. As shown in **Table 2**, the Floating efficiency of the microspheres. As the concentration of HPMC increases in formulation the floating lag time decreases and % drug release is retard as the concentration. Ethyl cellulose acts as floating enhancer.

The high levels of sodium alginate lead to increased encapsulation efficiency. The percentage yield (%) is more for F5-F8 Formulations.

Table 2. Evaluation of floating microspheres.

Batch No	Mean Particle size(µm)	Bulk Density (gm/ml)	Tapped density (gm/ml)	Carr's Index	Hausner's ratio	Angle of repose
F1	361.66	0.771±0.054	0.434±0.016	17.62 ±1.98	40.58 ±1.76	35°55'±0.85'
F2	340.48	0.786±0.064	0.443±0.023	17.82 ±1.57	38.76± 1.76	33°56'±1.82'
F3	384.64	0.729±0.034	0.418±0.009	17.34±1.45	45.43±1.54	40°07'±0.53'
F4	350.75	0.738±0.024	0.420±0.006	18.34 ±2.32	43.45±1.54	38°46'±0.82'
F5	527.85	0.744±0.023	0.425±0.005	16.48 ±2.12	42.4.±1.43	34°65'±0.59'
F6	481.8	0.748±0.017	0.439 ±0.01	17.32 ±1.23	39.38±1.52	32°21'±1.82'
F7	470.47	0.743±0.026	0.432±0.006	16.62 ±1.67	39.68±1.73	33°45'±0.92'
F8	495.75	0.723±0.016	0.422±0.011	15.34 ±1.89	41.43±1.78	31°54'±0.65'

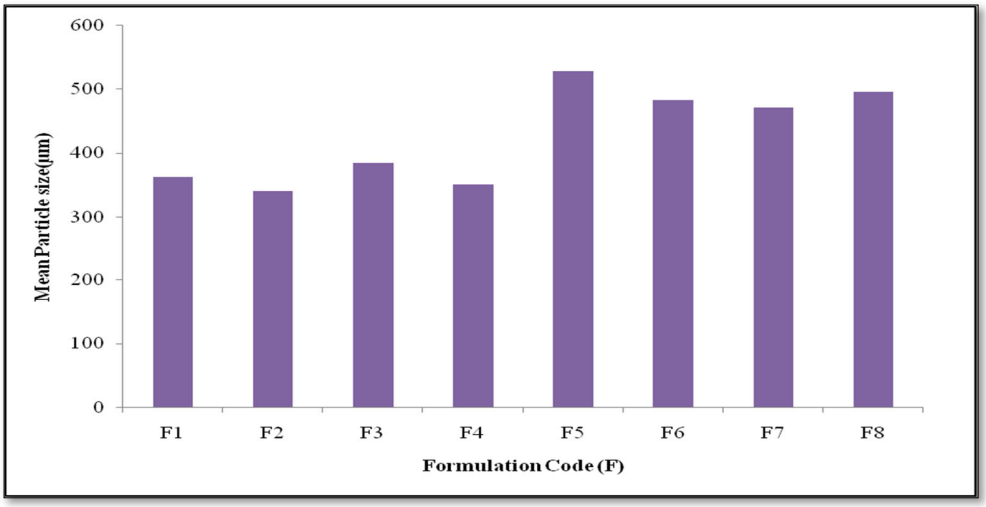

Figure 2. Comparison of Mean Particle Size of floating microspheres of Repaglinide.

Table 3. Result of mean particle size, *in vitro* buoyancy and encapsulation efficiency %, percentage yield.

Batch No:	*In vitro* Buoyancy (in sec)	Encapsulation efficiency%	Percentage yield(%)
F1	55.3	85.16	94.14
F2	58.26	77.48	92.29
F3	52.52	89.33	95.35
F4	65.87	74.34	91.08
F5	43.15	95.65	97.17
F6	46.24	94.84	96.74
F7	41.12	98.03	98.64
F8	48.09	90.58	96.17

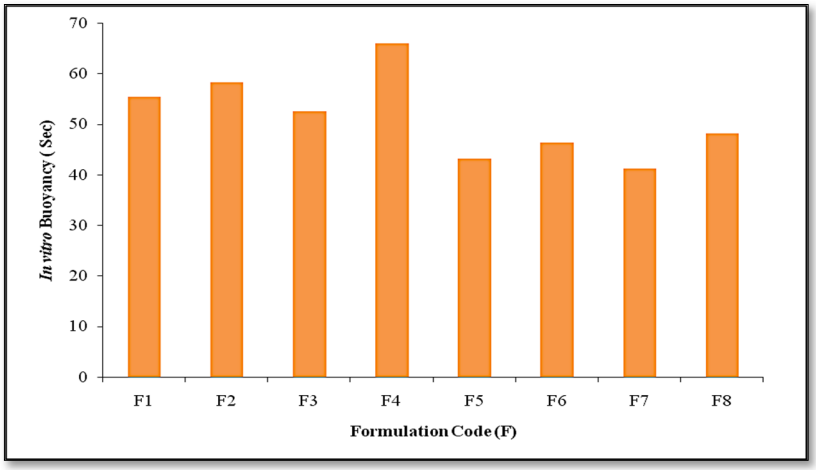

Figure 3. Comparison of *in vitro* buoyancy of floating microspheres of Repaglinide.

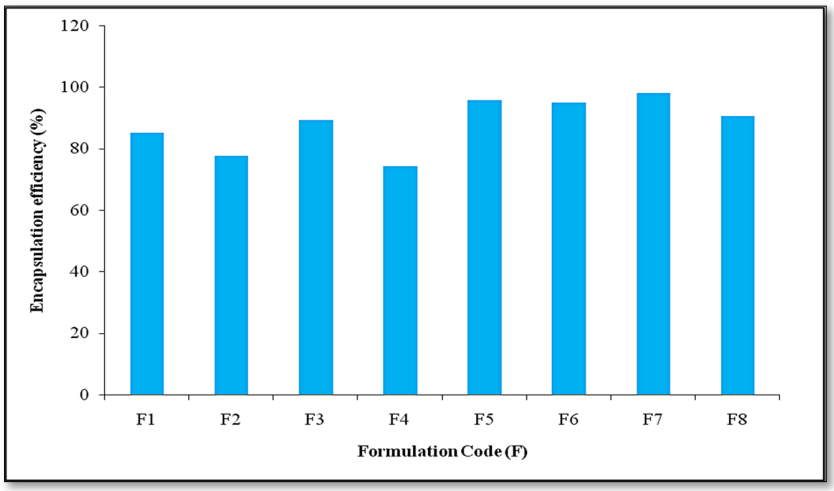

Figure 4. Comparison of encapsulation efficiency of floating microspheres of Repaglinide.

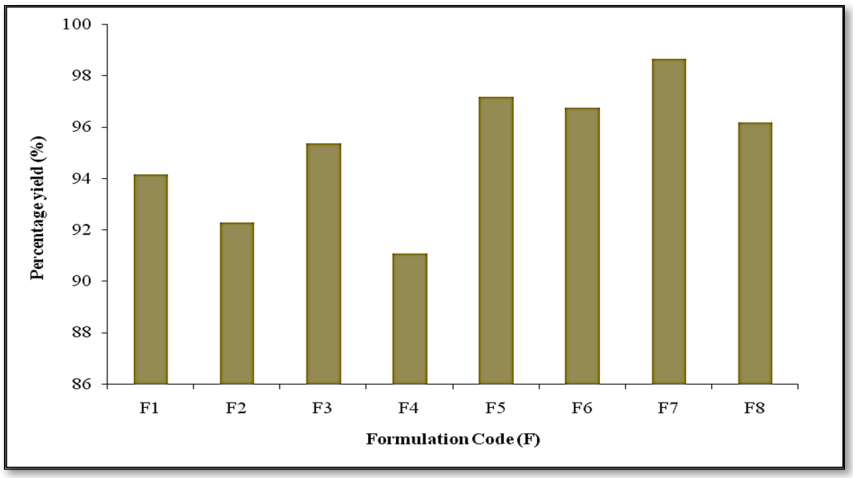

Figure 5. Comparison of percentage yield of floating microspheres of Repaglinide.

***In vitro* drug release study**

Table 4. *In vitro* drug release of containing Repaglinide F1 to F4 formulations.

TIME (h)	CUMULATIVE PERCENT DRUG RELEASED			
	F1	F2	F3	F4
0	0	0	0	0
0.5	14.94	11.57	16.65	9.14
1	23.67	17.39	25.85	13.15
2	37.28	23.12	36.55	17.84
3	42.31	29.82	46.14	20.65
4	49.57	37.65	55.48	23.58
5	53.64	43.55	68.62	25.87
6	59.32	49.87	74.32	28.67
7	64.12	59.31	78.21	31.95
8	73.45	62.99	79.92	36.87
9	76.38	69.39	85.1	47.88
10	80.87	75.84	98.26	52.45
11	88.39	80.55	92.36	58.22
12	91.14	85.88	94.61	75.57

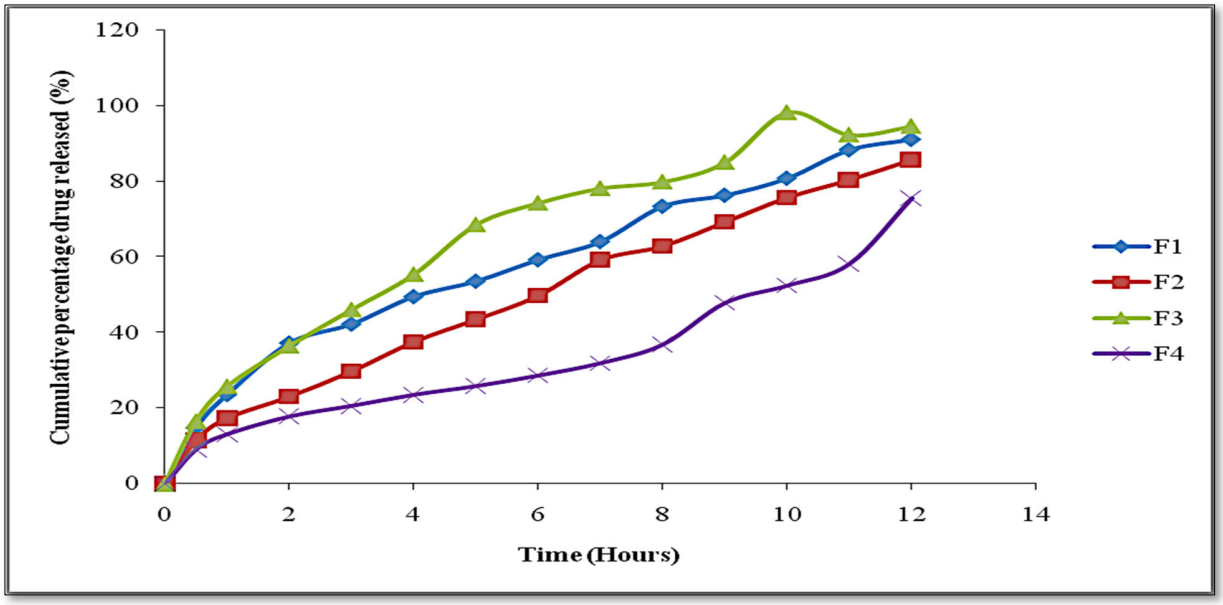

Figure 6. Dissolution study of Repaglinide Floating Microspheres (F1 to F4).

Table 5. *In vitro* drug release of Repaglinide F5 to F8 formulations.

TIME (h)	CUMULATIVE percent drug released			
	F5	F6	F7	F8
0	0	0	0	0
0.5	22.15	16.59	19.61	15.41
1	28.91	25.11	27.74	20.22
2	38.87	33.65	36.51	26.69
3	47.91	42.54	45.35	34.95
4	55.14	45.16	52.47	41.32
5	64.56	51.39	59.84	47.29
6	63.11	55.16	63.61	55.64
7	68.38	61.31	69.87	60.65
8	72.87	66.87	74.11	65.96
9	80.54	78.91	85.8	71.58
10	85.64	81.74	89.39	75.32
11	90.39	86.12	95.68	81.99
12	93.49	89.58	99.87	84.15

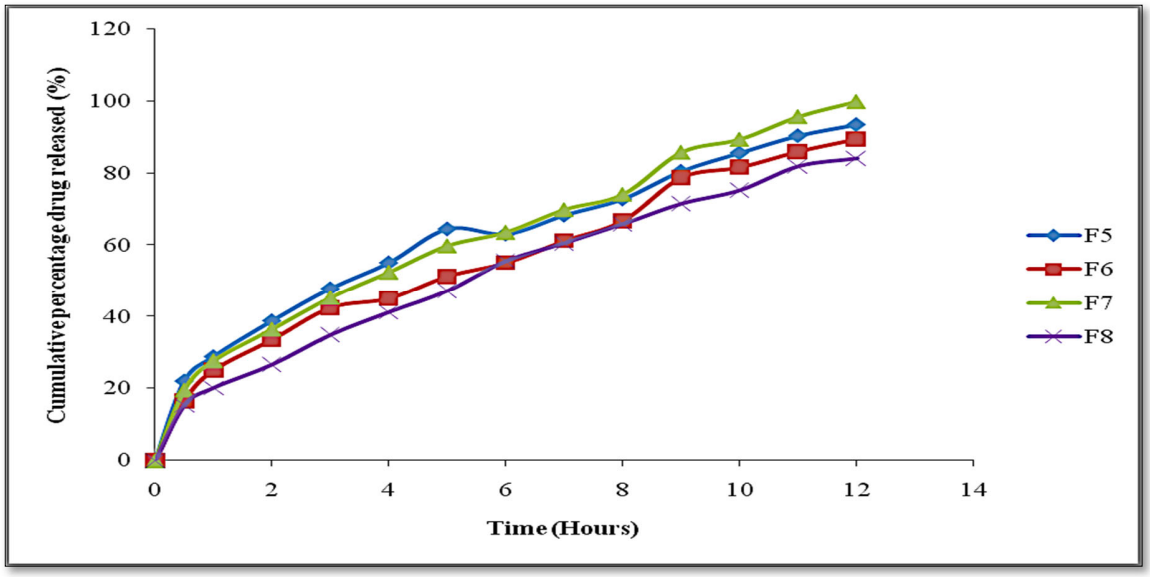

Figure 7. Dissolution study of Floating Microspheres (F5 to F8).

The % drug release of formulations (F5 to F8) containing HPMC, Ethyl Cellulose, Carbopol depends on the concentration of Sodium Alginate (2.2%). In that F7 formulation was maximum drug release (99.87%) was showed at 12 h **(Table 6)**.

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Repaglinide release. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyer peppas mechanisms **(Figures 8-11)**.

Table 6. Release kinetics study for optimized formulation.

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG (%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE/t)	1/CUM % RELEASE	PEPASS log Q/100	% Drug remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
19.61	0.5	0.707	1.292	-0.301	1.905	39.220	0.0510	-0.708	80.39	4.642	4.316	0.326
27.74	1	1.000	1.443	0.000	1.859	27.740	0.0360	-0.557	72.26	4.642	4.165	0.476
36.51	2	1.414	1.562	0.301	1.803	18.255	0.0274	-0.438	63.49	4.642	3.989	0.652
45.35	3	1.732	1.657	0.477	1.738	15.117	0.0221	-0.343	54.65	4.642	3.795	0.847
52.47	4	2.000	1.720	0.602	1.677	13.118	0.0191	-0.280	47.53	4.642	3.622	1.019
59.84	5	2.236	1.777	0.699	1.604	11.968	0.0167	-0.223	40.16	4.642	3.425	1.217
63.61	6	2.449	1.804	0.778	1.561	10.602	0.0157	-0.196	36.39	4.642	3.314	1.328
69.87	7	2.646	1.844	0.845	1.479	9.981	0.0143	-0.156	30.13	4.642	3.112	1.530
74.11	8	2.828	1.870	0.903	1.413	9.264	0.0135	-0.130	25.89	4.642	2.958	1.683
85.8	9	3.000	1.933	0.954	1.152	9.533	0.0117	-0.067	14.2	4.642	2.422	2.220
89.39	10	3.162	1.951	1.000	1.026	8.939	0.0112	-0.049	10.61	4.642	2.197	2.444
95.68	11	3.317	1.981	1.041	0.635	8.698	0.0105	-0.019	4.32	4.642	1.629	3.013
99.87	12	3.464	1.999	1.079	-0.886	8.323	0.0100	-0.001	0.13	4.642	0.507	4.135

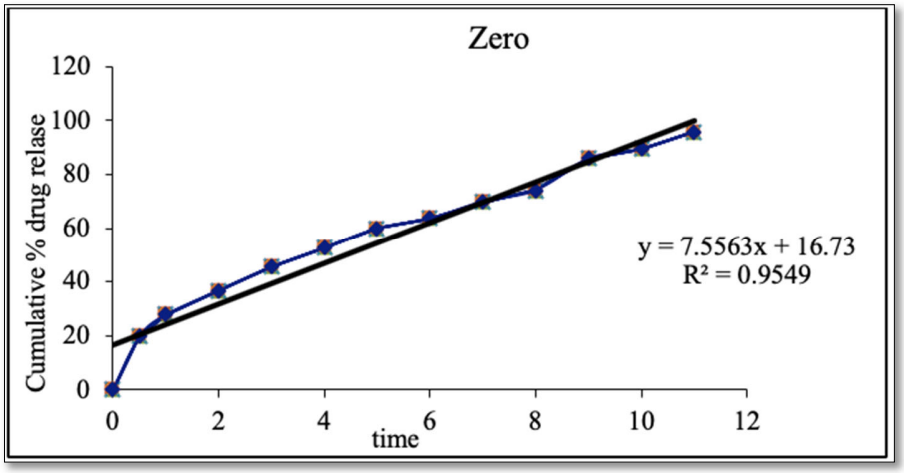

Figure 8. Graph of Zero Order kinetics.

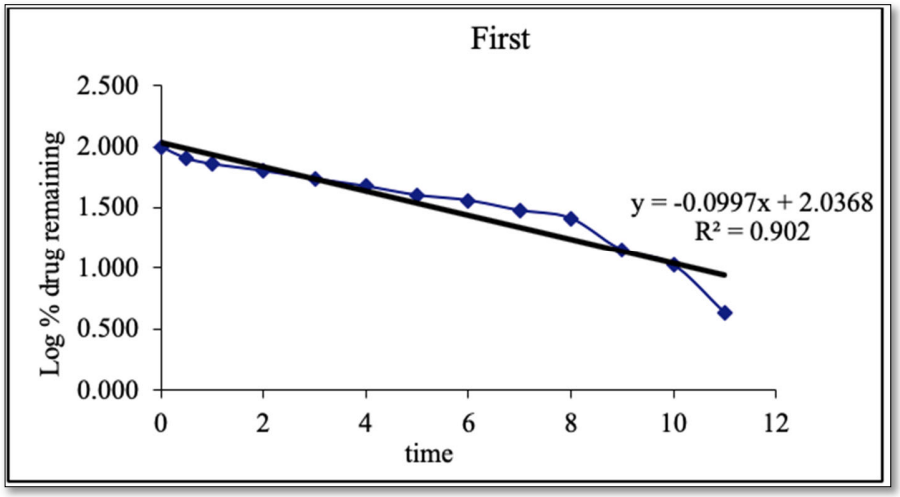

Figure 9. Graph of First Order release kinetics.

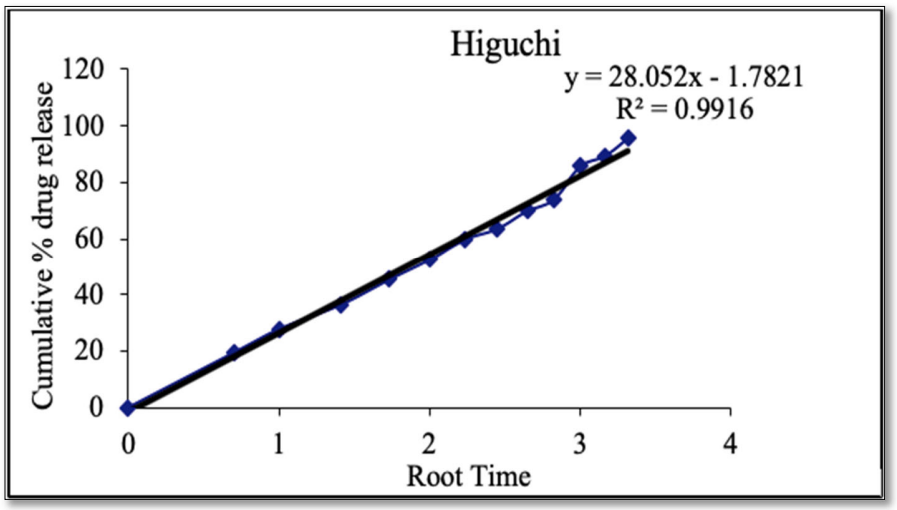

Figure 10. Graph of Higuchi Release kinetics.

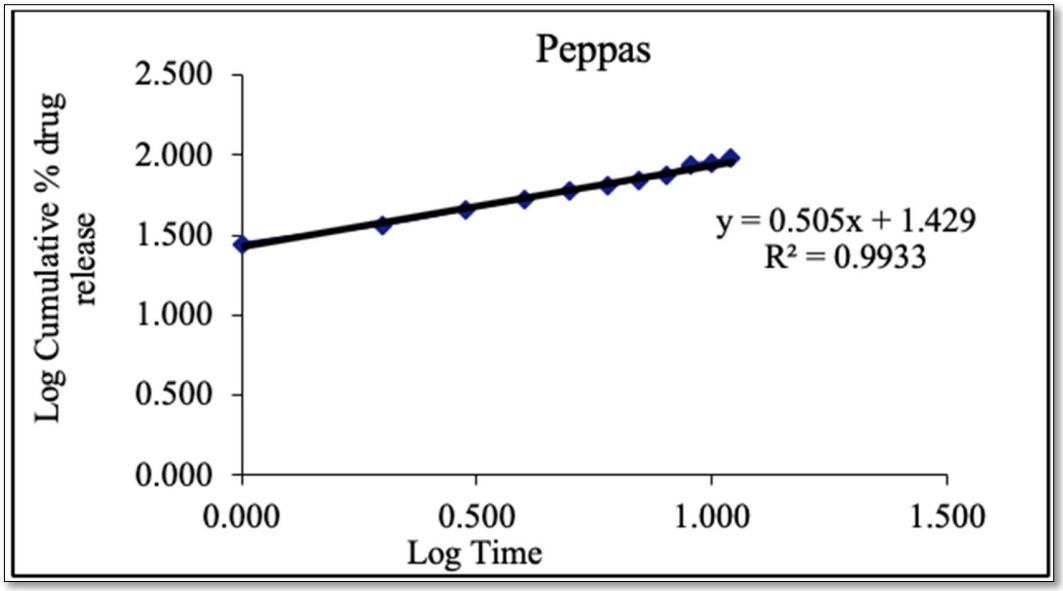

Figure 11. Graph of Peppas Release kinetics.

Based on the data above results of regression analysis R^2 value for Zero **order kinetics** was shown 0.954, **first order kinetics** 0.905, Higuchi 0.9916 and Peppas model was shown 0.9933.

Qualitative Analysis by FTIR

Qualitative identification for purity of the drug in dosage form was analyzed by **Fourier-transform infrared spectroscopy (FTIR) (Figures 12 and 13)**.

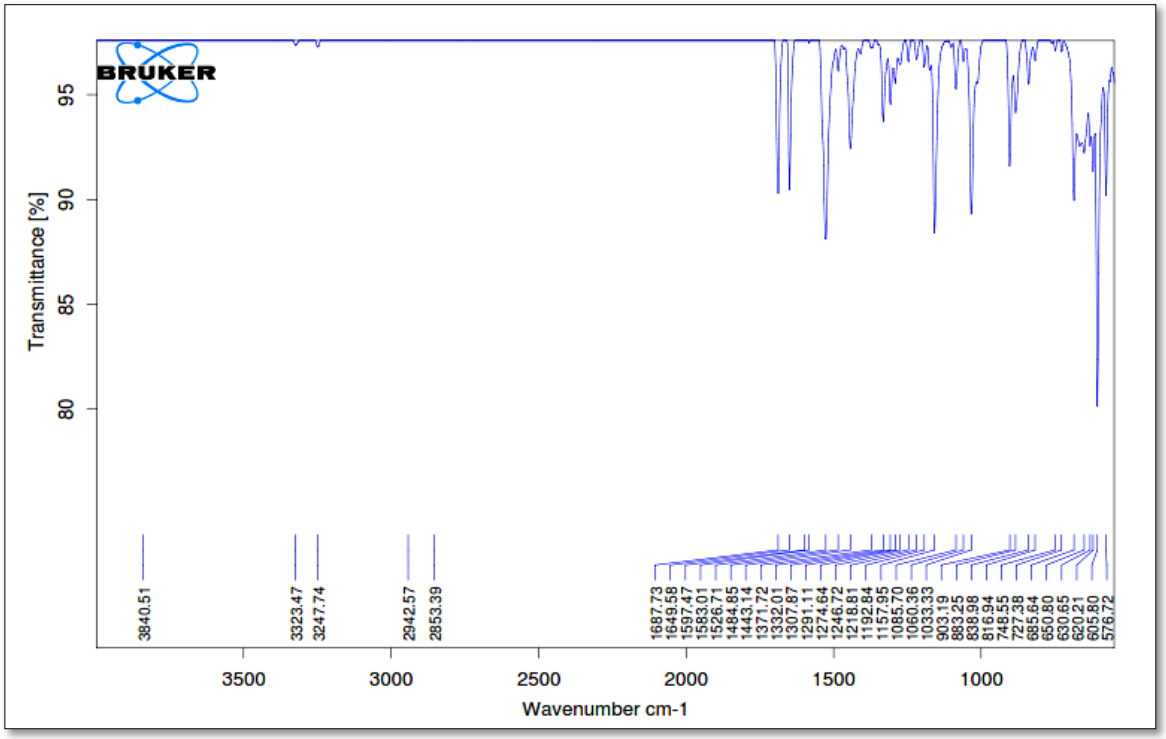

Figure 12. FTIR of Repaglinide pure drug.

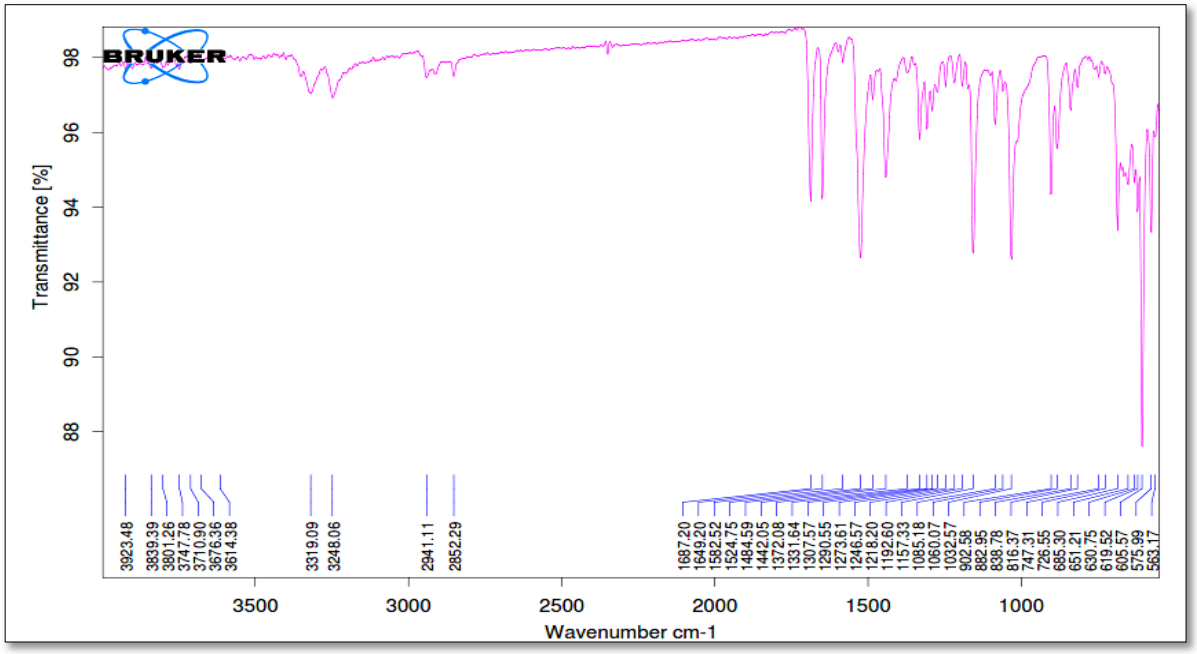

Figure 13. FTIR of Repaglinide Optimized formulation.

Pure drug and the optimized formulation both were showing transmittance signal at very narrow wavelength. This results in a spectrum with points separated by equal frequency intervals.

Analysis by Scanning electron microscope (SEM)

The signals used by a scanning electron microscope to produce an image result from interactions of the electron beam with atoms at various depths within the sample **(Figure 14)**.

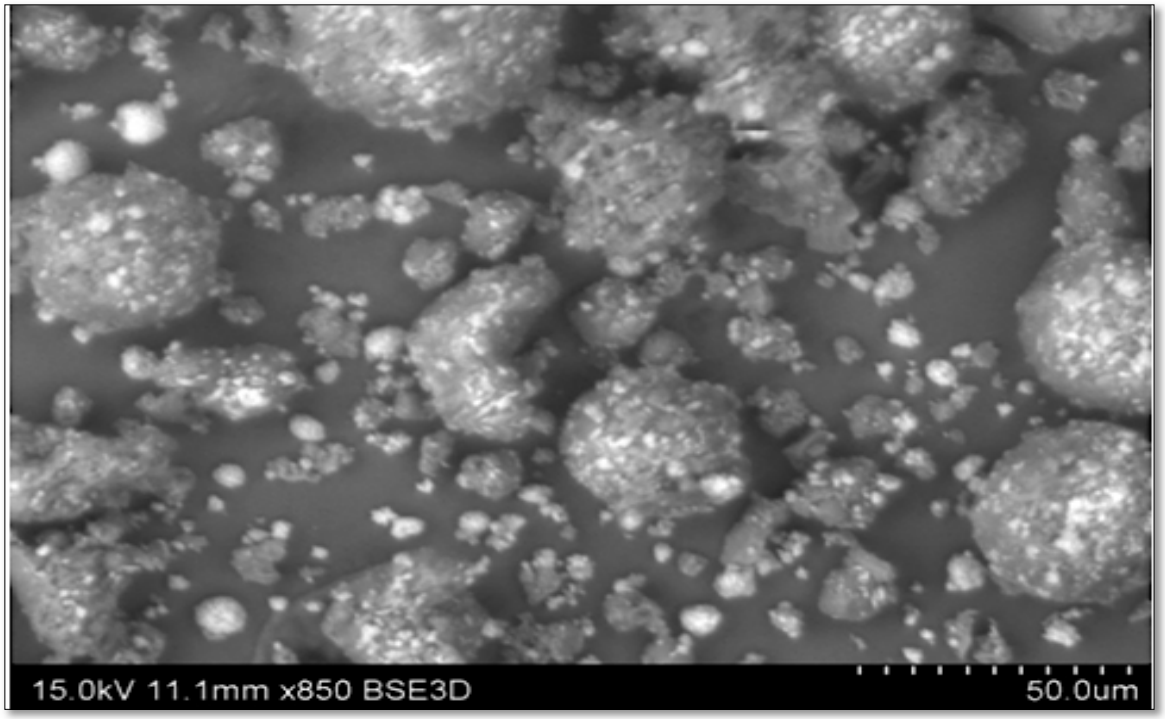

Figure 14. SEM of Repaglinide Floating Microspheres optimized formulation.

SUMMARY

The standard concentrations of Repaglinide (2-10 µg/ml) was prepared in 0.1N HCL showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law. The Micromeritic properties of different batch are shown in **Table 6**. The mean diameter of the Repaglinide-loaded HPMC, Ethyl cellulose, Carbopol 934P microspheres, the mean diameter of batch 1 to 8 ranges between 350.75 and 527.85 µm. The results indicated the proportional increase in the mean particle size of the microspheres with increasing amount of sodium alginate in the formulations. This could be attributed to an increase in the relative viscosity at higher concentration of sodium alginate and formation of large droplets during addition of the polymer solution to the cross linking agents.

The average size of the microspheres increased slightly as the amount of polymer concentration increased. The hardening agent caused a decrease in bead size as it promoted the formation of cross-links between the alginate molecules. The tapped density of beads of different batch 1-8 ranges between 0.406 ± 0.012 - 0.439 ± 0.01 g/ml respectively. The Compressibility Index ranges between 14.43-18.34 g/ml, shows that all the formulation preparations were good flowability. The Hausner's ratio of different batch ranges between 38.76-45.43. The Hausner's ratio result shows that all the preparations were good flowability.

The high levels of sodium alginate lead to increased encapsulation efficiency. The percentage yield (%) is more for F5-F8 Formulations.

The % drug release of formulations (F1 to F4) containing HPMC, Ethyl Cellulose, Carbopol depends on the concentration of Sodium Alginate (2%). The concentration of HPMC was able to retard the drug release up to desired time. As the concentration of HPMC increases in formulation the % drug release is retard as the concentration. In F3 formulation was maximum drug release was showed at 12 h. The order of drug release is F3>F1>F2>F4.

The % drug release of formulations (F5 to F8) containing HPMC, Ethyl Cellulose, Carbopol depends on the concentration of Sodium Alginate (2.2%). In that F7 formulation was maximum drug release (99.87%) was showed at 12 h.

Hence based on dissolution data of 8 formulations, F1, F2, F3, F4,F5,F6, F7,F8 formulations showed better release up to 12 hours. Among these formulations F7 formulation showed the drug release (99.87%) within the specified limits. So F7 formulation is Considered as optimized formulation.

Based on the data above results the optimized formulation followed Peppas release kinetics.

From the FTIR studies, those studies were revealed that good compatibility between drug and excipients.

CONCLUSION

Microspheres are one of the microparticulate systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance.

The purpose of present work was to develop floating microspheres of Repaglinide for sustained drug delivery. From the results it seem that formulation F7 was found to be satisfactory in terms of excellent micromeritic properties, yield of microsphere, encapsulation efficiency, *in vitro* buoyancy and highest *in vitro* drug release of 98.64 %, 98.03 %, 41.12 sec and 99.87 % in a sustained manner with constant fashion over extended period of time for 12 h. Hence the prepared floating microspheres of Repaglinide may prove to be potential candidate for safe and effective sustained drug delivery. Among these formulations F7 formulation showed the drug release (99.87%) within the specified limits. So F7 formulation is optimized formulation. The optimized formulation followed Peppas release kinetics.

CONFLICT OF INTERESTS

This article has not published before and it is not under consideration for publication in any other journal.

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