ISSN: 2320-2831

International Journal of Pharmacy and Analytical Research (IJPAR)

IJPAR |Vol.13 | Issue 1 | Jan - Mar -2024

www.ijpar.com

DOI : https://doi.org/10.61096/ijpar.v13.iss1.2024.58-68

Research

Formulation And Evaluation Of Floating Microspheres Of Repaglinide By Ionic Gelation Method

Sirsinigandla Bindu Sri[1*], D. Venkata Ramana, K. Sai Kiran, J.Pravalika

[1]Department of Pharmaceutics, Holy Mary Institute of Technology & Science (College of Pharmacy), Bogaram Village, Keesara Mandal, Hyderabad, Telangana, India

[*]Author for Correspondence: Sirsinigandla Bindu Sri
Email: bindusiri.s@gmail.com

Published on: 22 Feb 2024

Published by:
DrSriram Publications

Abstract

The objective of the present study was to Prepare the alginate microspheres of Repaglinide (model drug) using calcium chloride as a crosslinking 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. Among all formulations of floating microspheres F7 was considered as optimised for floating microspheres. From the release kinetics data, it was evident that floating optimised formulation follows Peppas release kinetics.

Keywords: Repaglinide, Floating microspheres, Sodium alginate, HPMC, Ethyl cellulose, Carbopol 934P.

INTRODUCTION

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. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. The development of new delivery systems for the controlled release of drugs is one of the most interesting fields of research in pharmaceutical sciences.[1] 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. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. The process of targeting and site specific delivery with absolute accuracy can be achieved by attaching bioactive molecule to liposome, bio erodible polymer, implants,

monoclonal antibodies and various particulate. One such approach is using microspheres as carriers for drugs. Microsphere can be used for the controlled release of drugs, vaccines, antibiotics, and hormones.

For example, by taking advantage of the characteristics of microspheres, beyond the basic benefits, the microspheres could provide a larger surface area and possess an easier estimation of diffusion and mass transfer behavior. Microspheres are defined as "Monolithic sphere or therapeutic agent distributed throughout the matrix either as a molecular dispersion of particles" (or) can be defined as structure made up of continuous phase of one or more miscible polymers in which drug particles are dispersed at the molecular or macroscopic level. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as micro particles. Biodegradable synthetic polymers and modified natural products such as starches, gums, proteins, fats and waxes. The natural polymers include albumin and gelatin, the synthetic polymer include poly lactic acid and polyglycolic acid. The solvents used to dissolve the polymeric materials chosen according to the polymer and drug solubility and stabilities, process safety and economic considerations. Microspheres for oral use have been employed to sustain the drug release, and to reduce or eliminate gastrointestinal tract irritation. 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 forms such as no disintegrating, polymeric matrix tablets. Unwanted intestinal retention of the polymeric material, which may occur with matrix tablets on chronic dosing, can also be avoided. Microencapsulation is used to modify and retard drug release. Due to its small particle size, are widely distributed throughout the gastrointestinal tract which improves drug absorption and reduces side effects due to localized build-up of irritating drugs against the gastrointestinal mucosa.

The oral route is considered as the most promising route of drug delivery. Conventional drug delivery system achieves as well as maintains the drug concentration within the therapeutically effective range only when taken several times a day depending upon the dosage regimen. This result shows significant fluctuation in drug level. An approach overcome such fluctuations onventional led to the development of several novel drug delivery systems (NDDS) that could revolutionize methods of formulation and provide a number of therapeutic benefits. The main objectives of these new drug delivery systems are:

1) It would be single dose which releases the active ingredient over an extended period of time.
2) It should deliver the active entity directly to the site of action thus minimizing or eliminating the side effects.

Recent advances in novel drug delivery system to enhance the safety and efficacy of the drug molecule by formulating a dosage form being convenient for administration. The high level of patient compliance has been observed in taking oral dosage forms is due to the ease of administration and handling of these forms. There are lot of advancements have been seen in oral controlled drug delivery system in the last few decades, this system has been of limited success in case of drugs with a poor absorption window throughout the GIT (Gastro Intestinal Tract). To modify the GIT time is one of the main challenge in the development of oral controlled drug delivery system. Gastric emptying of dosage form is extremely variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than conventional dosage forms. Several difficulties are faced in designing controlled released systems for better absorption and enhanced the bioavailability.

MATERIALS AND METHODS

Repaglinide Procured from SURA LABS, HPMC from Merck Specialities Pvt Ltd, Mumbai, India, Ethyl cellulose from Merck Specialities Pvt Ltd, Mumbai, India, Carbopol 934P from Merck Specialities Pvt Ltd, Mumbai, India, Sodium Alginate from Merck Specialities Pvt Ltd, Mumbai, India, Sodium bicarbonate from Merck Specialities Pvt Ltd, Mumbai, India, Calcium chloride from Merck Specialities Pvt Ltd, Mumbai, India, Acetic acid from Merck Specialities Pvt Ltd, Mumbai, India, Glutaraldehyde from Merck Specialities Pvt Ltd, Mumbai, India

Analytical method development

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

100mg of Repaglinide pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCL(stock solution-2 i.e 100µg/ml). From this take 0.2, 0.4, 0.6, 0.8 and 1.0 ml of solution and make up to 10ml with 0.1N 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 (R^2) 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& figure.

Preparation of microspheres

Floating Microspheres are matrix systems that contains drug throughout their structure and are potential candidates for oral controlled release. Microspheres can be defined as solid spherical particles ranging from 1 to 1000µm in size. The choice of methods for the preparation of microspheres depends on many factors such as the drug solubility, partition co efficient, Polymer composition, molecular weight etc.

The Floating microspheres was prepared by Ionic gelation technique using Table. 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 hr and dried at 60 degrees -2 hours 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

All the quantities were in mg

RESULT 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.

Analytical Method

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.

Table 2: Standard curve of Repaglinide in 0.1N HCL

S.NO	Concentration µg /ml	Absorbance
1	0	0
2	2	0.115
3	4	0.229
4	6	0.339
5	8	0.449
6	10	0.561

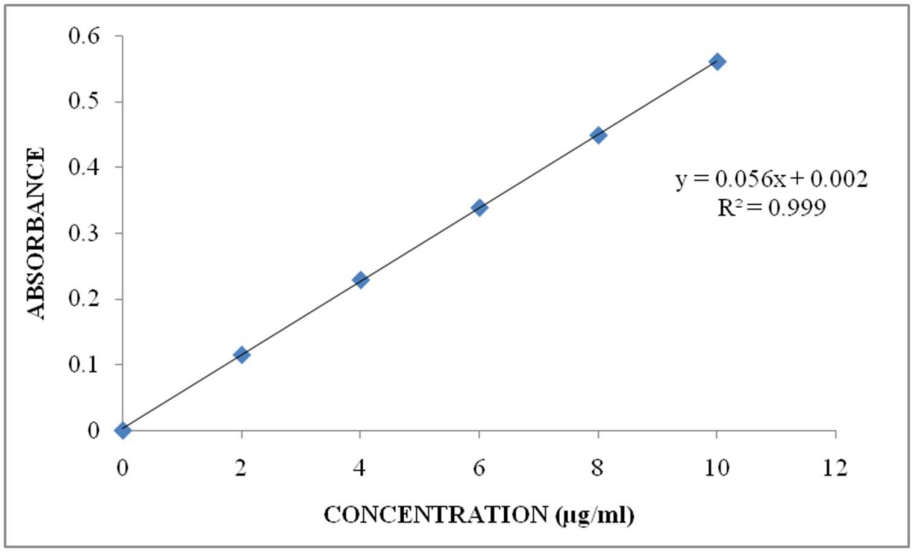

Fig 1: Calibration curve of Repaglinide in 0.1 N HCL at 241 nm

EVALUATION PARAMETERS

Table 3: 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 (θ)
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	481.80	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'

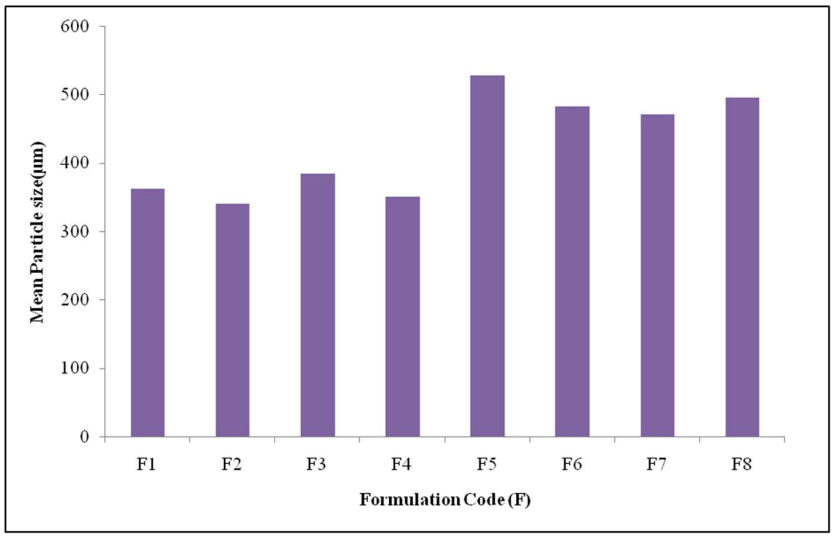

Fig 2: Comparison of Mean Particle Size of floating microspheres of Repaglinide

Micromeritic properties of Microspheres

Table 4: 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	55.30	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

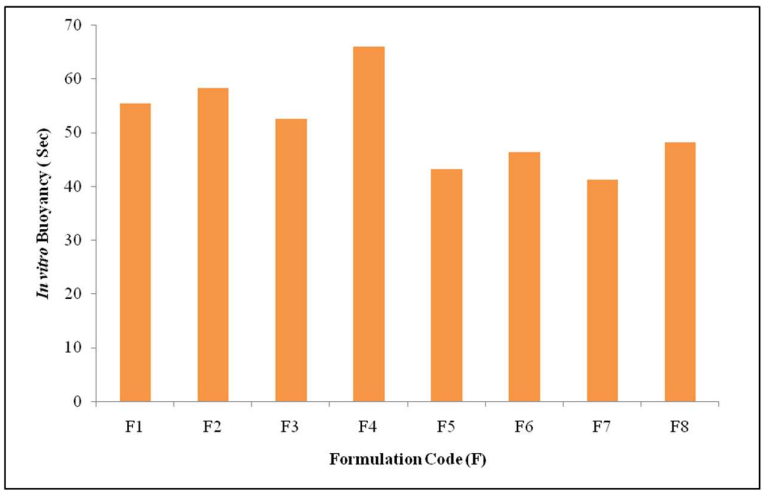

Fig 3: Comparison of *In vitro* Buoyancy of floating microspheres of Repaglinide

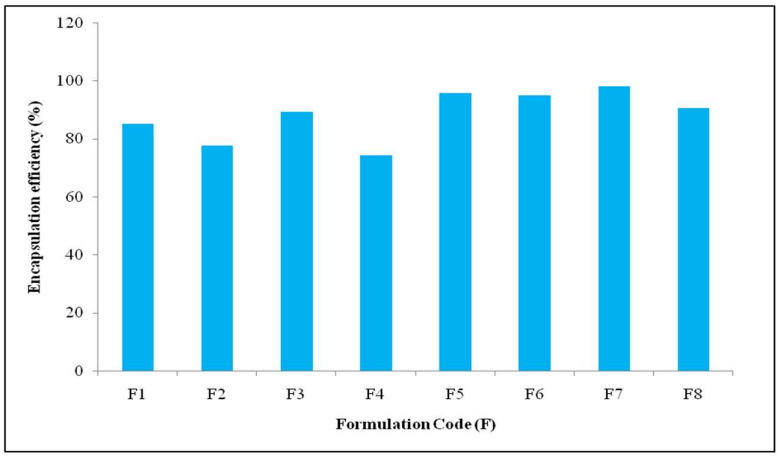

Fig 4: Comparison of Encapsulation efficiency of floating microspheres of Repaglinide

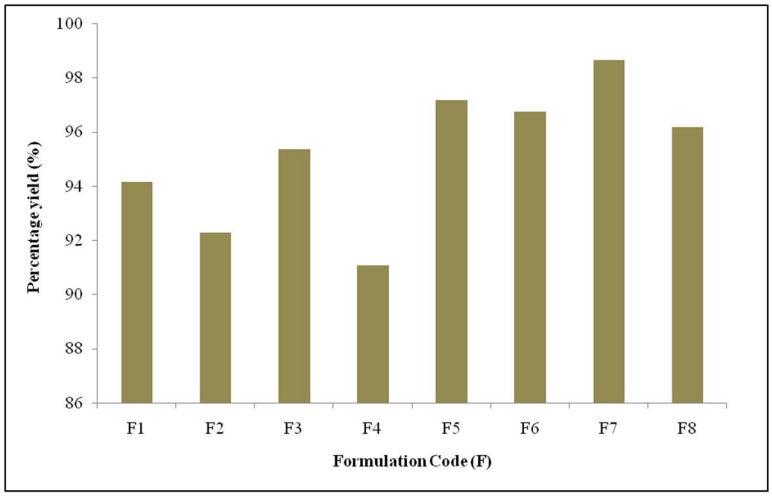

Fig 5: Comparison of Percentage Yield of floating microspheres of Repaglinide

***In-Vitro* Drug release studies**

Table 5: *In vitro* drug release of containing Repaglinide F1 to F4 formulations

TIME (hr)	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	85.10	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

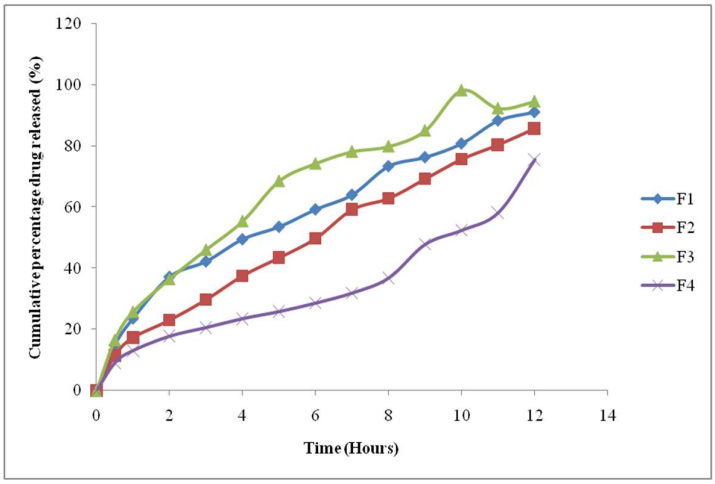

Fig 6: Dissolution study of Repaglinide Floating Microspheres (F1 to F4)

Table 6: *In vitro* drug release of Repaglinide F5 to F8 formulations

TIME	CUMULATIVE PERCENT DRUG RELEASED			
(hr)	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	85.80	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

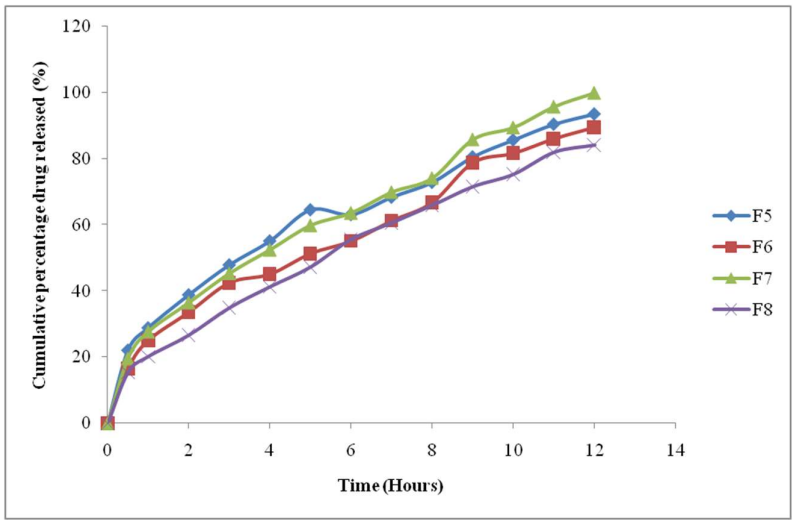

Fig 7: Dissolution study of Floating Microspheres (F5 to F8)

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 hours. 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 hours.

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 optimised formulation.

Application of Release Rate Kinetics to Dissolution Data

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 and the results were shown in below table.

Table 7: Release kinetics data for optimized formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS 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

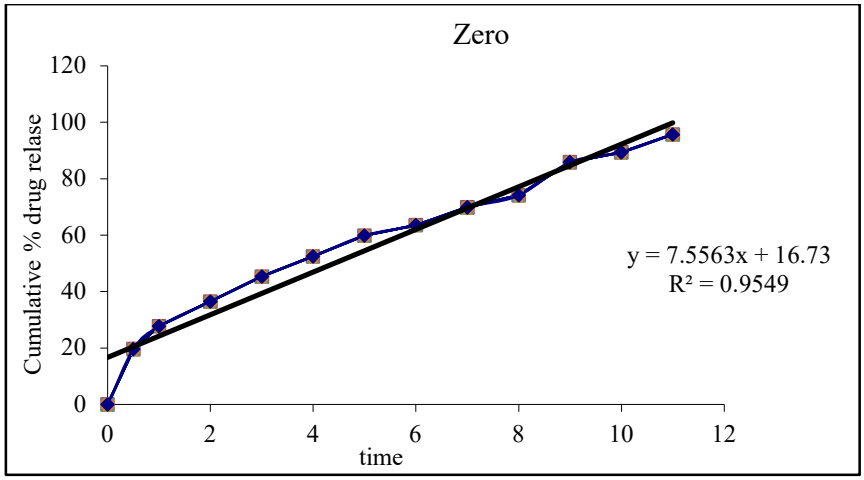

Fig 8: Graph of Zero Order kinetics

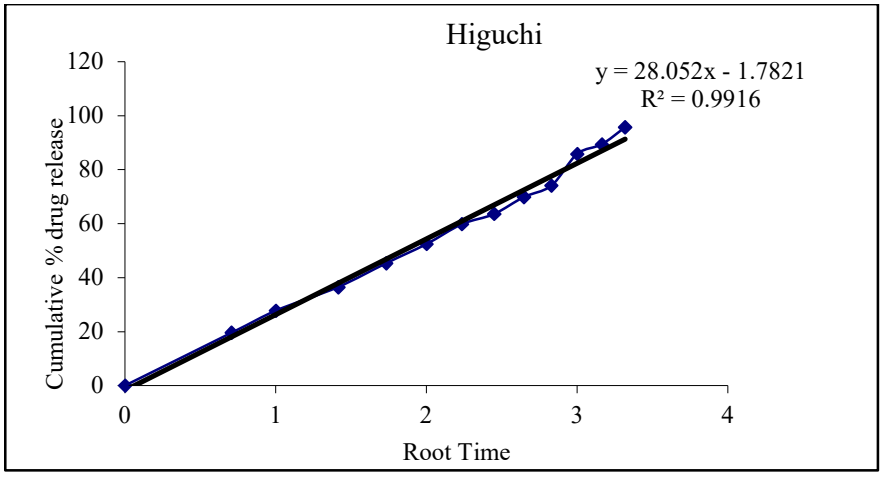

Fig 9: Graph of Higuchi Release kinetics

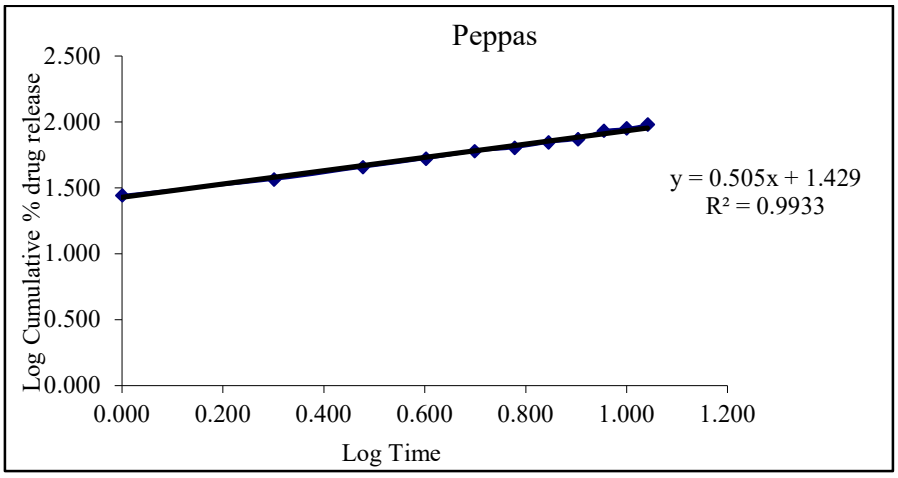

Fig 10: Graph of Peppas Release kinetics

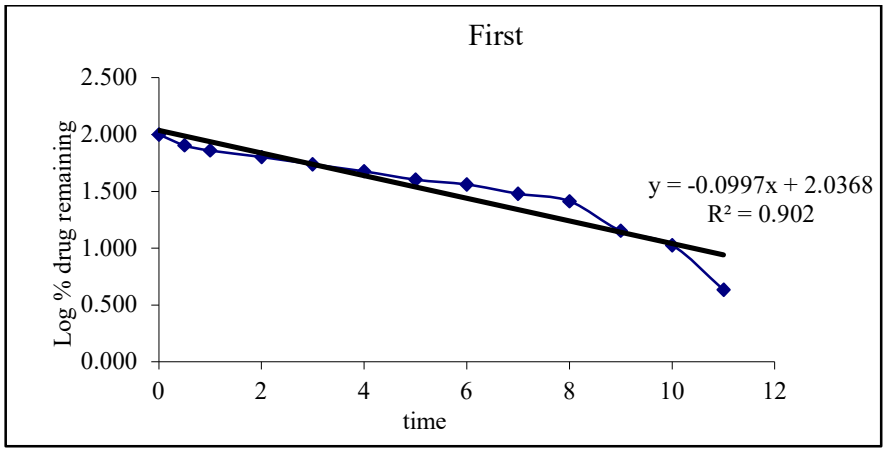

Fig 11 : graph of First Order release kinetics

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

Drug – Excipient compatibility studies
FTIR

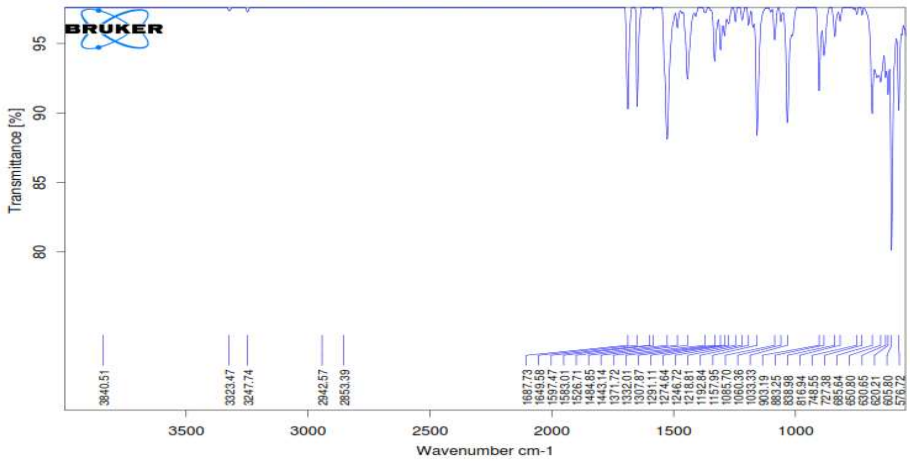

Fig 12: FTIR of Repaglinide pure drug

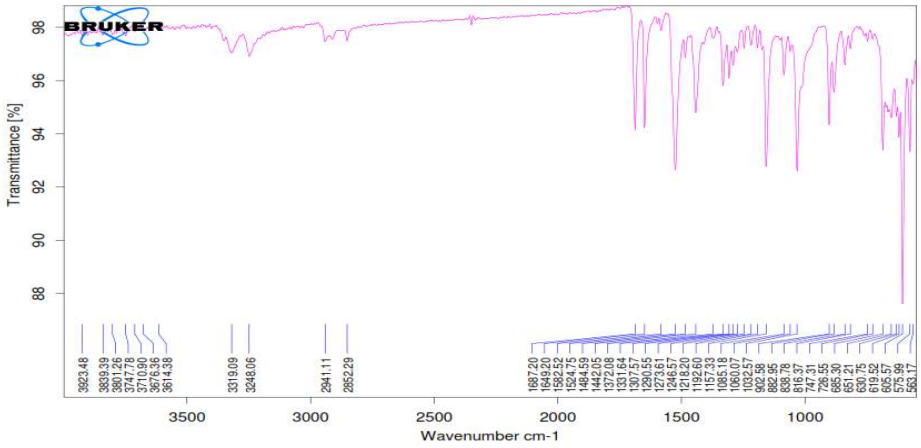

Fig 13: FTIR of Repaglinide Optimised formulation

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

SEM

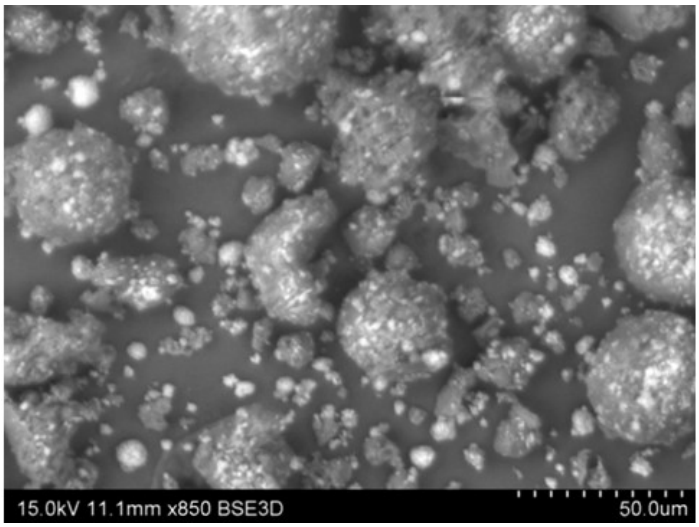

Fig 14: SEM of Repaglinide Floating Microspheres optimised formulation

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 hrs. 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 optimised formulation. The optimized formulation followed Peppas release kinetics.

REFERENCES

1. Jain NK, editor. Controlled and novel drug delivery. New Delhi: CBS publishers & distributors; 1997. 04 Edition, 21, 236-237. Available from: https://www.cbspd.co.in/toc/9789354666957.pdf
2. Chein YW. Oral Drug Delivery Systems: In Novel drug delivery systems.Marcel Dekker, Inc., New York. 1992; 50:139-177.
3. Sam MT, Gayathri DS, Prasanth V, Vinod B. NSAIDs as microspheres. Internet J Pharmacol. 2008;6(1):1-8.
4. Li SP, Kowarski CR, Feld KM, Grim WM. Recent advances in microencapsulation technology and equipment. Drug Development and Industrial Pharmacy. 1988 Jan 1;14(2-3):353-76. https://www.tandfonline.com/doi/pdf/10.3109/03639048809151975
5. NASA P, MAHANT S, SHARMA D. International Journal of Pharmacy and Pharmaceutical Sciences. Int J Pharmacy and Pharm Sci. 2010; 2(3):2-7. https://scholar.archive.org/work/qn5syaq7hzednbkub326nesi4e/access/wayback/http://ijppsjournal.com/Vol2Suppl3/557.pdf
6. Gayathridevi M , J. Adlin Jino Nesalin and T. Tamizh Mani. Floating Microsphere: A Review. IJRPC 2016, 6(3), 501-510. http://www.ijrpc.com/files/01-07-16/15-670.pdf
7. Mali AD, Bathe RS, Patil MK. Floating microspheres: a novel approach in drug delivery system. Science and Technology. 2015;1(5):134-53.
8. Griffith GH, Owen GM, Kirkman S, Shields R. Measurement of rate of gastric emptying using chromium-51. Lancet. 1966;1:1244-5. https://www.gastrojournal.org/article/S0016-5085(76)80095-9/pdf
9. Wilding IR, Coupe AJ, Davis SS. The role of γ-scintigraphy in oral drug delivery. Advanced drug delivery reviews. 2001 Mar 1;46(1-3):103-24. https://www.sciencedirect.com/science/article/pii/S0169409X00001356
10. Hafeez A, Maurya A, Singh J, Mittal A, Rana L. An overview on floating microsphere: Gastro Retention Floating drug delivery system (FDDS). The Journal of Phytopharmacology.2013;2(3):1-2. https://phytopharmajournal.com/assets/pdf_files/V2issue3012.pdf
11. Kavitha K, Yadav SK, Tamizh MT. The need of floating drug delivery system: A review. RJBPS. 2010 Apr;1(2):396-405.
12. Shaha SH, Patel JK, Pundarikakshudu K, Patel NV. An overview of a gastro-retentive floating drug delivery system. Asian journal of pharmaceutical sciences. 2009 Jan;4(1):65-80.
13. Zate SU, Kothawade PI, Mahale GH, Kapse KP, Anantwar SP. Gastro retentive bioadhesive drug delivery system: A review. Int J Pharm Res. 2010 Jun;2:1227-35.
14. Chawla G, Bansal A. A means to address regional variability in intestinal drug absorption. Pharm tech. 2003 Jul;27(2):50-68.
15. Sangekar S, Vadino WA, Chaudry I, Parr A, Beihn R, Digenis G. Evaluation of the effect of food and specific gravity of tablets on gastric retention time. International Journal of Pharmaceutics. 1987 Mar 1;35(3):187-91. https://www.sciencedirect.com/science/article/pii/0378517387901293