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Formulations and evaluations of repaglinide microspheres by ionotropic gelation technique

B Archana*[1], Balla Vaishnavi[2], kannayyagari Sindhu[2], Keesari Meena Goud[2], D. Sai poojitha[2].

[1]Assistant professor, Department of Pharmacology, Bojjam Narasimhulu Pharmacy College for women, 17-1-383, Vinay Nagar campus, saidabad, Hyderabad, 500059, Telangana, India.

[2]Bojjam Narasimhulu Pharmacy College for women, 17-1-383, Vinay Nagar campus, saidabad, Hyderabad, 500059, Telangana, India.

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Abstract

The current study aimed to formulate and evaluate Repaglinide microspheres utilizing the ionotropic gelation process, with sodium alginate, HPMC, and Carbopol as polymers and Cacl2 as a cross-linking agent. Because of its high biocompatibility and lack of toxicity, sodium alginate is a biodegradable natural polymer with considerable promise for therapeutic uses. Repaglinide microspheres offer desirable qualities. The ionotropic gelation approach allows for high medication integration in microspheres without harmful agents that have adverse side effects. The microspheres are tested for percentage yield, entrapment efficiency, micromimetic properties, in-vitro drug release, etc. Extensive in-vitro testing revealed that more than 102% of the medication is released after 11-12 hours; however, in this formulation, drug release is maintained for up to 12 hours. The percentage entrapment efficiency is 102%. The microspheres had a percentage yield of 96%. Using essential equipment, ionotropic gelation can also be carried out under relatively mild situations. Managing numerous manufacturing parameters is critical in producing microspheres with superior sphericity, high yield, and exceptional drug encapsulation.

*Corresponding Author

Name: B Archana
Email: archanabiradar07.abab@gmail.com

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INTRODUCTION

Oral administration is the most convenient way of drug delivery and is associated with higher patient compliance when compared to other methods of drug consumption. However, oral administration is only helpful for significant medications from many pharmacological categories with low oral bioavailability due to insufficient absorption and/or degradation in the GIT. Oral medication delivery systems account for approximately 50% of the market and offer benefits such as patient acceptance and ease of administration. Short GRT,

or the time it takes for stomach contents to enter the small intestine, often limits oral medicine absorption. Microspheres are small, spherical particles with dimensions ranging from 1 to 1000 µm [1]. A well-designed controlled drug delivery system can solve some of the challenges of conventional therapy while also increasing the therapeutic efficacy of a specific drug. To achieve maximal therapeutic efficacy, the drug must be delivered to the target area appropriately and with low toxicity and adverse effects. Repaglinide decreases blood glucose levels by increasing insulin secretion from the pancreas' beta islet cells. This is accomplished by closing ATP-dependent potassium channels in the membrane of beta cells. Repaglinide has a protein binding affinity for albumin that exceeds 98%. The liver largely metabolizes repaglinide, specifically CYP450 2C8 and 3A4, and, to a lesser amount, glucuronidation. Repaglinide's metabolites are inert and have no glucose-lowering effects; 90% is eliminated in the feces and 8% in the urine. 0.1% is excreted unaltered in urine [2].

MATERIALS AND METHODS

MATERIAL USED

Repaglinide, HPMC E15 was a gift sample from Rakshit Drug Pvt Ltd., Hyderabad; Carbopol 934 was a gift sample; and sodium alginate and calcium chloride were purchased from Merck Specialities Pvt Ltd, Mumbai, India.

PREPARATION OF MICROSPHERES OF REPAGLINIDE

The microspheres were made using the Ionotropic gelation process.

↓Stirr at 300 RPM

The resultant solution was sonicated for 30 minutes to get rid of any air bubbles. The dispersion was added dropwise from a 22 G needle at a height of around 5 cm into 100 ml of calcium chloride (CaCl2) solution to create microspheres.

↓Continuous Stirring

For 30 minutes, the additional droplet was kept in the calcium chloride solution to finish the curing process and create spherically rigid microspheres.

↓

The Whatman filter paper was then used to filter the solution that contained the microspheres that had formed.

↓

The microspheres obtained were kept in a tightly sealed container after being allowed to dry at 400 c for six hours.

Drug-Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy:

Studies of drug-excipient interactions are essential for effectively formulating all dosage forms. Physicochemical compatibility and interactions were evaluated using Fourier Transform Infrared (FTIR) spectroscopy investigations to predict how medicine will interact with other excipients. Physical mixtures used for compatibility study analysis were prepared in the current investigation using a 1:1 ratio. FT-IR investigations were conducted utilizing the direct sample approach at a Bruker ATR FTIR facility [3].

SEM (Scanning Electron Microscope) studies:

The SEM was used to analyze the layered sample's surface morphology. Using a POLARON-E 3000

Table 1 Composition of Microspheres

Formulation	Drug Repaglinide	HPMC E15	Carbopol	Sodium Alginate	CaCl2
F1	2.0	0.245	0.800	2	5
F2	2.0	0.495	0.550	2.4	5
F3	2.0	0.395	0.650	4	5
F4	2.0	0.295	0.700	4.5	5
F5	2.0	0.345	0.750	6	5
F6	2.0	0.395	0.600	8	5
F7	2.0	0.445	0.500	7	5
F8	2.0	0.345	0.650	6	5

sputter coater, a thin coating (300A) of gold was applied on aluminum stubs with a carbon tab, and a little powder was manually spread onto it. With direct data collection of the images onto a computer, the samples were analyzed using SEM [4].

EVALUATIONS OF MICROSPHERES

1. Percentage Yield:

Weighing the developed microspheres from each batch was done precisely. The measured weight of the manufactured microspheres was divided by the total amount of each drug and excipient used in their production to get the overall percentage yield of microspheres. This equation was used to calculate it [5]:

$$\% \text{ Yield} = \frac{Weight\ of\ Product}{Drug\ and\ Excipients\ total\ weight}\ X\ 100$$

Particle size and shape:

The size, shape, and external structure of the microspheres can be ascertained using light and scanning electron microscopy [6].

2. Micromeritic Studies:

The size, shape, and external structure of the microspheres can be ascertained using light and scanning electron microscopy [7].

Bulk density ([8], [9])

$$Bulk\ Density = \frac{Microspheres\ Weight\ (W)}{Volume\ acquired\ Initially}$$

Tapped density

$$\text{Tapped Density} = \frac{Microspheres\ Weight}{Final\ \ Volume}$$

Carr's compressibility index

$$Carr's\ index = \frac{\boldsymbol{Tapped\ Density - Bulk\ Density}}{\boldsymbol{Tapped\ Density}} \text{X } 100$$

Hausner's ratio

$$\text{Hausner's Ratio} = \frac{Tapped\ Density}{Bulk\ Density}$$

The angle of repose

$\tan \omega = h/r$

$\omega = \tan^{-1} h/r$

Drug loading and Drug Entrapment [10]

For examination, 50 mg of the drug was placed in microspheres. The microspheres were ground up and repeatedly extracted using aliquots of 0.1MHCL to quantify the entrapped amount. 0.1MHCL was used to make up the volume after the extract was moved to a 100-millilitre volumetric flask. After the solution was filtered and diluted appropriately, the absorbance was measured using Systronic (2201) spectrophotometry at 237 nm compared to a suitable blank. Using the following formulas, the amount of drug loaded and trapped in the microspheres was determined:

Drug loading percentage is calculated by dividing the weight of the drug loaded in the microspheres (DC) by the total weight of the microspheres.

To calculate the percentage of drug entrapment, divide the amount of drug present (DC) by the theoretical drug load expected X 100 [10].

In- vitro Release study

According to the monograph, the in-vitro release profile in the dissolving media, which is the same as the fluid at the absorption site, is evaluated using standard IP/BP/USP dissolution equipment [11].

Kinetic study

Zero-order kinetics

The following formula can represent drug dissolution from pharmaceutical dosage forms that do not break down and release the drug gradually as long as the area stays constant and no equilibrium requirements are achieved [12].

$$Q_t = Q_o\ +\ K_o\ \text{t}$$

First order kinetics

First-order release kinetics was examined by fitting the following equation into the release rate data.

$$\text{Log } Q_t = \log Q_o\ +\ \frac{K_t}{2.303}$$

Higuchi model

Higuchi developed several theoretical models to study the release of drugs integrated into solid

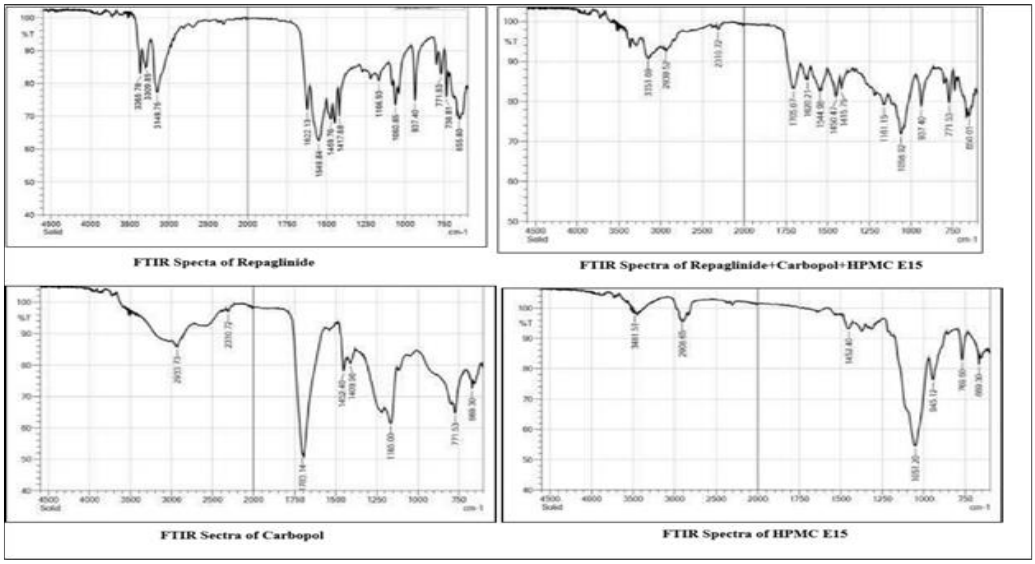

Figure 1 FTIR Spectrums of drug and polymer mixtures

matrices or either low-soluble or water-soluble semisolids. Mathematical formulas were developed for drug particles dispersed in a homogeneous matrix serving as the diffusion media; the equation is

$$Q_t = K_H . t_{\frac{1}{2}}$$

Korsemeyer and Peppas Release model

The release rate data is fitted to the following equation for analysis of this model.

$$\mathrm{F} = \frac{M_t}{M} = K . t_n$$

RESULTS AND DISCUSSION:

Qualitative Analysis by FTIR:

Fourier-transform infrared spectroscopy (FTIR) was used to qualitatively analyze the drug's purity in dose form.

Analysis by Scanning electron microscope (SEM):

Atoms at different depths within the sample interact with the beam of electrons to produce the signals that a scanning electron microscope uses to create an image.

Evaluation of Microspheres:

Percentage Yield:

Table 2 lists the percentage yield of various batches of Repaglinide microspheres. The range is 59.11 percent to 97.02%. Batch 6 produced the highest percentage yield, which contained 1.5% medication, 1.0% polymer, and 5% Cacl2 prepared at 300 rpm for 30 minutes. As the polymer and medication concentrations grow, the percentage yield falls. As the concentration of Cacl2 decreases, the percentage yield rises.

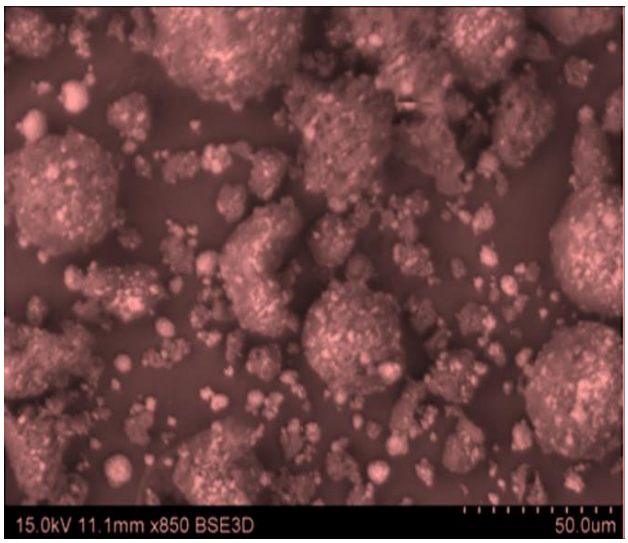

Figure 2 SEM of Repaglinide Microspheres

Entrapment Efficiency:

Table 3 lists the entrapment efficiency of the different batches of Repaglinide microspheres. The drug obtained from Repaglinide microspheres had an entrapment efficiency ranging from 58.02% to 103%. The amount of the total amount of drug that is available is the entrapment efficiency of the drug. As the drug concentration rises, so does the entrapment

Table 2 Percentage yield of Repaglinide microspheres

Formulation	Theoretical weight (mg)	Practical yield (mg)	Percentage yield %
F1	2222	1299	59.11%
F2	2183	1395	64.95%
F3	2012	1658	78.01%
F4	2001	1754	88.7%
F5	2346	1836	79.24%
F6	1958	1891	97.02%
F7	2217	1876	93.03%
F8	2331	1873	88.14%

Micromimetics Property:

Table 3 Micromimetics property

Formulation	Bulk density (g/cm3)	Tapped density (g/cm3)	Compressibility Index (%)	Hausner's Ratio	Angle Of Repose (ω)
F1	0.222	0.271	18.13	1.214	25.95
F2	0.308	0.352	13.29	1.188	24.76
F3	0.372	0.376	19.14	1.014	26.76
F4	0.347	0.368	7.73	1.604	27.78
F5	0.318	0.392	19.98	1.24	31.61
F6	0.302	0.332	8.37	1.105	34.73
F7	0.314	0.336	15.06	1.019	27.72
F8	0.316	0.364	8.44	1.102	29.64

Table 4 Drug loading and Repaglinide microsphere drug entrapment

Formulation	Actual drug content	Theoretical drug content	Total weight of microspheres	% drug loading	% drug entrapment
F1	1.288	9.6	50	17.67%	58.03%
F2	0.769	11	50	16.79%	64.38%
F3	1.323	11.4	50	15.71%	79.24%
F4	0.997	11.8	50	14.64%	88.31%
F5	0.568	12.1	50	14.7%	89.0%
F6	0.246	12.2	50	12.6%	103%
F7	0.544	11.9	50	15.63%	88.02%
F8	1.295	11.7	50	15.76%	102%

efficiency. As the Cacl2 concentration, stirring time, and stirring speed increase, the entrapment efficiency falls. The drug's high solubility could be the cause of the low entrapment efficiency.

Because the polymer's increased viscosity alters the drug's diffusion coefficient, the drug entrapment efficiency likewise drops as the concentration of the polymer rises.

Particle size:

The average particle size of Repaglinide microspheres is 100µm for Formulation F1.

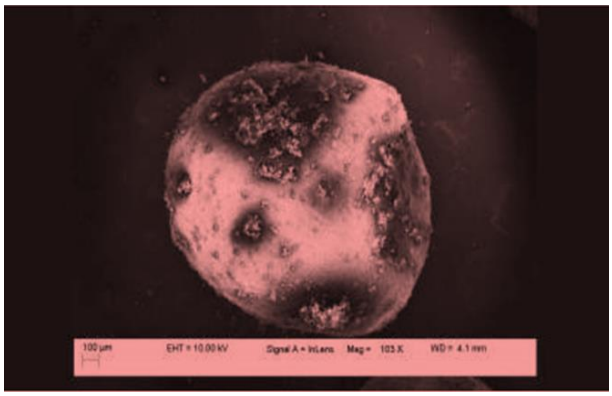

Figure 3 Average particle size of Repaglinide microspheres

In vitro dissolution studies

Table 5 In vitro dissolution studies of Repaglinide microspheres

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	7.878556	11.68	12.63322	12.4734	13.2074	14.7414	14.2085	14.7515
2	14.24256	17.20016	16.37	16.28856	18.41422	19.05732	19.41533	19.05633
3	22.83326	24.62072	25.594	27.827	26.466	30.64456	27.456	30.65467
4	31.26	31.62822	33.52326	35.72826	33.65456	38.607	34.66567	38.606
5	36.32272	42.5864	43.37456	45.414	41.96026	48.42044	42.97017	48.41033
6	45.1644	51.582	57.7844	56.46426	52.44356	56.00416	50.44467	56.00517
7	55.04022	58.1834	64.78222	62.93344	62.48756	60.72334	61.48867	60.71433
8	63.2684	71.47665	75.18556	67.93422	71.82244	70.78622	70.81233	70.78733
9	72.67656	81.35326	83.72272	73.80746	82.7734	75.87522	81.7845	75.87633
10	78.36616	91.60084	92.5864	81.95372	93.46216	83.9274	92.45317	83.9175
11	83.9324	94.27256	95.46322	94.28556	95.25	96.24422	96.24	96.25433
12	93.52822	96.62356	94.87526	96.63756	97.596	102.2514	98.597	102.2615

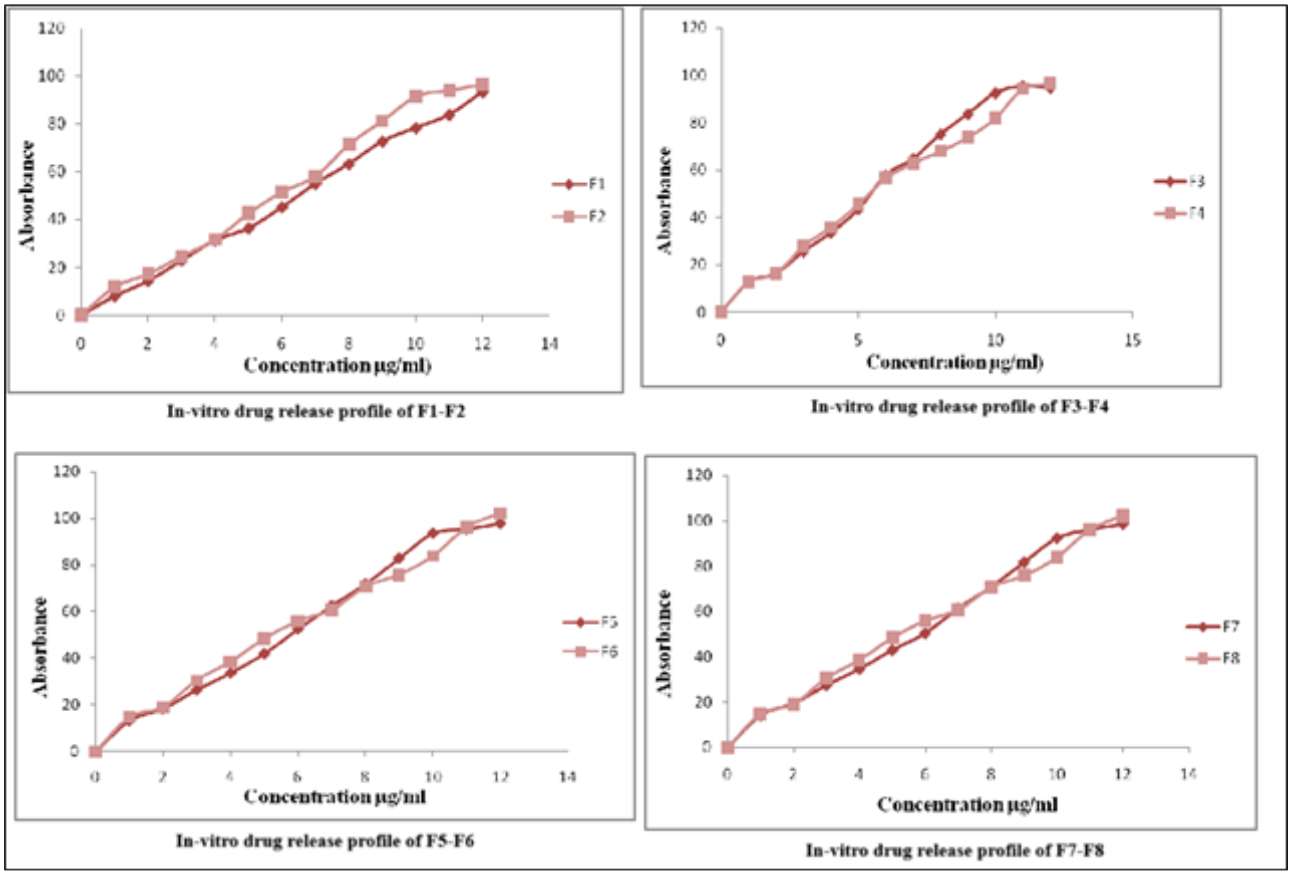

Figure 4 In-vitro drug release profile of F1-F8

Table 6 Kinetics of drug release in vitro Data on the diffusion exponent and correlation coefficient for the F1–F8 formulas

Formulation code	Correlation Coefficient values (R^2)				Diffusion Exponent value (n)
	Zero-order	First order	Higuchi	Korsmeyer-Peppas	
F6	0.9883	0.7922	0.9858	0.9968	0.7380

The correlation coefficient R2 was 0.9781, 0.9881, 0.9910, 0.9763, 0.9885, 0.9892, 0.9916, and 0.9768, in that sequence, based on the Korsemeyer-Peppas formulas for F1, F2, F3, F5, F6, F7, and F8. Both the Zero order and Korsemeyer-Peppas models are supported by the F6 formulation, which displays a diffusion release mechanism followed by non-fiction transport.

CONCLUSION:

Repaglinide microspheres have demonstrated potential as drug delivery vehicles due to their numerous benefits. First, sodium alginate is a naturally occurring polymer with biocompatible and biodegradable qualities, so it is considered a safe substance. Second, it is a water-soluble polymer, making it a perfect drug carrier.

As a result, moderate and easy preparation techniques can be used. This makes sodium alginate microspheres a viable drug delivery vehicle for various drugs, including labile and macromolecules. Out of all the batches that were examined, Based on in vitro drug release, encapsulation effectiveness, particle size, and percentage yield, batch 6 made with 1.5% drug, 1% polymer, 5% Cacl2 concentration, 30 minutes of stirring duration, and 300 rpm of stirring speed was determined to be the best.

Ultimately, it can be said that the ionotropic gelation approach can be applied widely to encapsulate a variety of pharmaceuticals to provide regulated drug delivery.

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Author Contribution

All authors made substantial contributions to the conception, design, acquisition, analysis, or interpretation of data for the work. They were involved in drafting the manuscript or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work, ensuring its accuracy and integrity.

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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