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Formulation and evaluation of floating microspheres of Rabeprazole Sodium

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Abstract- The present study was aimed at the formulation and evaluation of floating microspheres of Rabeprazole sodium to enhance gastric residence time, improve drug stability, and achieve sustained drug release. Rabeprazole sodium, a proton pump inhibitor, is unstable in alkaline conditions and exhibits poor bioavailability due to rapid degradation in the intestinal environment. To overcome these limitations, floating microspheres were prepared by solvent evaporation technique using polymers such as hydroxypropyl methylcellulose (HPMC), ethyl cellulose, and Eudragit in different ratios. The prepared microspheres were characterized for particle size, percentage yield, drug entrapment efficiency, buoyancy, in vitro drug release, and surface morphology. Results indicated that the microspheres were spherical, discrete, and exhibited good floating ability for more than 12 hours. Drug entrapment efficiency ranged from 65% to 85%, depending on the polymer concentration. In vitro release studies demonstrated a sustained release of Rabeprazole sodium over an extended period with a controlled release profile, following Higuchi kinetics. The optimized formulation showed desirable buoyancy, adequate drug entrapment, and prolonged release, suggesting its potential as an effective gastroretentive drug delivery system for improving the therapeutic efficacy of Rabeprazole sodium.

Keywords: Rabeprazole sodium, floating microspheres, gastroretentive drug delivery, solvent evaporation, sustained release

INTRODUCTION

Gastroprotective Drug Delivery System (GRDDS) is an advanced oral drug delivery strategy that seeks to lengthen the duration that a dosage form remains in the stomach. GRDDS is particularly appropriate to drugs that have a narrow absorption window, are unstable or poorly absorbed in the intestine, or are primarily soluble in acidic conditions. GRDDS becomes particularly unique due to the mechanisms of action - floating, mucoadhesion, expansion, high- density systems, etc. These actions help to maintain the drug in the gastric region for an extended period. GRDDS provides several benefits, such as increasing drug bioavailability, allowing for prolonged and controlled drug release, lower dosing frequency, and improved patient compliance, made possible since the system should release drug or floating indefinitely. GRDDS remains an effective strategy for localizing delivery to the upper gastrointestinal tract and for drug delivery for local gastric disorders [1][2]. Floating systems explain how systems with lower densities can remain buoyant and float over the gastric contents of the stomach and can help prolong effect. Davis in 1968 identified the original floating system. These low-density systems are buoyant enough to float above the gastric contents of the stomach and float at the interface for extended time periods. Floating drug delivery systems can maintain medications with short biological half-lives, and support effectiveness, and decrease dosage frequency. This Feds feature is potentially leading to improvements in pharmaceutical therapy and increased patient compliance. A large number of buoyant systems have been produced using either granules, powders, capsules, tablets, laminated films, and hollow microspheres. The premise of floating drug delivery is to prolong the time of the dosage form remaining in the gastrointestinal tract while promoting absorption. This occurs with medications that are poorly soluble in alkaline pH, have a specific site of absorption in the upper part of the small intestine (duodenum region) and are soluble in acidic pH [3 Microbeads are synthetic polymer particles that are larger than 0.1 µm but less than or equal to 5 mm in size at the time of manufacture, which may differ in chemical composition, size, shape, density, and/or function. This process prolongs the gastric retention time of drugs, providing consistent release and controlled release of drugs [4]. Rabeprazole is a proton pump inhibitor (PPI) that covalently attaches to the proton pump (H+/K+-ATPase) of the stomach parietal cell and inhibits it. By inhibiting the proton pump, rabeprazole increases the stomach's pH and reduces the production of gastric acid. When treating acid-related disorders, for example GERD and peptic ulcer disease, within the context of Helicobacter pylori eradication therapy as appropriate, proton pump inhibitors are recommended [5]. Rabeprazole is a selective and irreversible proton pump inhibitor. Rabeprazole suppresses gastric acid secretion. The bioavailability of the drug is about 52%. Protein binding approximately 96% [6].

MATERIALS AND METHOD

MATERIALS

Rabeprazole sodium was gifted, HPMC K15M (Hydroxypropyl Methylcellulose K15M) was purchased from S.D. Fine-Chem Ltd., Mumbai., Ethyl cellulose purchased from S.D. Fine-Chem Ltd., Mumbai, Ethanol, Dichloromethane purchased from S.D. Fine-Chem Ltd., Mumbai, Span

80, Petroleum ether, Calcium chloride.

METHOD

PREPARATION OF FLOATING MICROSPHERES OF RABEPRAZOLE SODIUM

The procedure of emulsion solvent evaporation method includes the following steps for rabeprazole sodium-loaded microspheres preparation. The first step is to dissolve rabeprazole sodium and polymers hydroxypropyl methylcellulose (HPMC K15M) and ethyl cellulose in a 1:1 mixture of ethanol and dichloromethane and obtain a homogeneous polymer solution; then, the polymer solution prepared is slowly poured into light liquid paraffin containing 0.01% Span 80 (in order to stabilize the emulsion as a surfactant) and maintained at 30–40°C temperature. After pouring the solution, it is stirred at a specific agitation speed for 30 min during formation of microspheres which are generated by absorbing polymer from the emulsion once it is stable. The volatile solvents evaporate and microspheres continue to solidify as it is stirred. After all of the solvent evaporates, the microspheres are separated by filtration and thoroughly washed with petroleum ether to remove residual oil from the microspheres, and finally the microspheres are dried under vacuum. The final dried microspheres are placed into a desiccator with fused calcium chloride to minimize moisture absorption, labeling stability with physical characteristics.

TABLE1: Ingredients of Formulation

Ingredients	F1(1:1)	F2(1:1.5)	F3(1:2)	F4(1:0.75)
Rabeprazole Sodium (mg)	200	200	200	200
HPMC (mg)	200	300	400	150
Ethyl Cellulose (mg)	200	300	400	150
Light Liquid Paraffin (mL)	50	50	50	50
Tween 80 (% w/v)	0.5%	0.5%	0.5%	0.5%
Ethanol (mL)	5	5	5	5
Dichloromethane (mL)	5	5	5	5
Stirring Speed (rpm)	500	500	500	500

EVALUATION OF FLOATING MICROSPHERES

1.1 Drug Polymer Interaction (FTIR) Study

Fourier transform infrared spectroscopy (FTIR) spectrum was carried out on Fourier transformed infrared spectrophotometer (IR-Affinity-1, Shimadzu, Japan). The drug and potassium bromide

(KBr) samples were prepared in the form of pellets by compressing the powders into pellets at 20 psi for 10 minutes on KBr-press. The spectra were scanned in the wave number range 4000-600 cm-1. FTIR study was carried out on RPS, physical mixture of RPS and polymers [7].

1.2 Determination of absorption maximum (λmax) using Potassium Dihydrogen Phosphate Buffer (pH 2)

The work commenced by making a pH 2 phosphate buffer solution, using Disodium hydrogen phosphate (Na2HPO4), Potassium dihydrogen phosphate (KH2PO4). Calibration of the pH of the phosphate buffer was assessed using a pH meter. The stock solution of the drug was diluted with methanol, obtaining 1 µg/ml, 5 µg/ml, 10 µg/ml, 15µg/ml and 20 µg/ml, drug per ml solutions. Subsequently, pipetting 5 ml of the 10 µg / ml solution into quartz cuvettes of the UV spectrophotometer (against the matrix, to methanol blank), scanning for maxima absorbance between 200 nm and 400 nm using a UV-VIS Spectrophotometer and taking the average of triplicate readings. The peaks and absorbance were recorded, and from maxima absorbance scans, a lambda max of 284 nm absorption peak was found. The maxima absorption peak, or ymax, were recorded from the peaks of the absorption peak list. Next in photometric mode, the ymax value was set and each sample was scanned. All the values were recorded and a concentration vs absorbance graph, with MS Excel and trendline, y=mx+c equation and R value was provided with that graph.

1.3 Differential Scanning Calorimetry (DSC)Analysis

Differential Scanning Calorimetry (DSC) was utilized to assess the thermal behaviour of rabeprazole sodium and the thermal compatibility of rabeprazole sodium with the formulated microbeads. The DSC thermogram of the pure rabeprazole sodium shows a sharp endothermic peak, which evaluates the melting point and validates that rabeprazole sodium is crystalline. In contrast, the thermograms of the drug-loaded-microbeads show a gradual decrease in the melting peak intensity or not a melting peak. The extent to which the melting intensity peak decreases or disappears suggests that rabeprazole sodium is present as molecularly dispersed or converted to the amorphous state in the polymer matrix. Thus, no new peaks were identified on the DSC curves of the microbeads meaning there was no significant intrinsic chemical interaction between the drug and the polymers of interest (HPMC K15M and ethyl cellulose). Therefore, the results concluded that rabeprazole sodium was successfully incorporated and is thermally compatible with the excipients used in the formulation of the microbeads [8].

1.4 Scanning Electron Microscopy (SEM) Study

The Scanning Electron Microscopy (SEM) study of rabeprazole sodium-loaded microbeads was conducted to study the surface morphology and structure. The SEM images indicate that the microbeads were essentially spherical in shape and had relatively smooth surfaces with only minor surface irregularities and porosity, depending on the composition of the polymer. The morphology of the microbeads is important because it affects drug release, stability, and

encapsulation efficiency. The uniformity in size and shape suggests a successful formulation process through the emulsion solvent evaporation process. Furthermore, the lack of surface cracks or fragmentation indicates the presence of mechanical strength and structural integrity of the microbeads that are essential for controlled drug release [9][10].

1.5 Dynamic light scattering of floating microsphere

The Dynamic Light Scattering (DLS) analysis for rabeprazole sodium-loaded microbeads was carried out to evaluate the particle size distribution and zeta potential, both important parameters in estimating stability and dispersion properties. The microbeads were dispersed in distilled water and analysed using a particle size analyser. The results of the DLS analysis showed that the average particle size of the microbeads deviated based on drug to polymer ratio and narrow distribution which indicates a good degree of consistency in the formulation. The Zeta potential was also measured which indicates how much of a surface charge the microbeads possessed, thereby contributing to electrostatic stability and therefore limiting the amount of aggregation to occur upon storage. In summary, this provides evidence for the use of the emulsion solvent evaporation method for the fabrication of rabeprazole sodium microbeads, possibly with a controlled release property for delivery applications [11][12].

1.6 ZETA Potential:

The surface charge and stability of microspheres loaded with Rabeprazole was tested by zeta potential analysis. The zeta potential analysis showed a negative zeta potential value of approximately -25.6 mV that suggests moderate to good physical stability, due to sufficient electrostatic repulsion between particles. Zeta potentials above ±20 mV would generally exhibit a stable colloidal system as the likelihood of particles approaching one another is low from an electrostatic standpoint. The negative zeta potential surface charge may be due to polymers used in the microsphere formulations such as ethyl cellulose, or HPMC, which impart a surface functional group that can obtain negative charges in a dispersion medium. A negative surface charge would be beneficial for the longevity of circulation time and a uniform dispersed state for the Rabeprazole microspheres potentially in pharmaceutical suspensions and delivery systems [13].

1.7 In Vitro Dissolution Study:

A USP basket apparatus has been employed to investigate drug release from the fabricated floating microspheres. In this studies drug release was evaluated using a modified USP type II dissolution apparatus type II (Basket mesh # 120, equals 125 µm) at 100 rpm in 0.1 mol/l hydrochloric acid (pH 2) as dissolution fluid (900 ml) maintained at 37± 0.5°C. Samples (10 ml) were obtained and analysed as stated above spectrophotometrically as previously. The volume was replenished with the same quantity of fresh dissolution fluid on each occasion to maintain sink condition. Each experiment was performed in triplicate [14].

RESULTS AND DISCUSSION

Functional Group	Microsphere FTIR	Interpretation
O-H (Broad Stretching)	~3410 cm^{-1}	Present — indicates polymeric O-H (from HPMC)
C-H Stretching	~2917 cm^{-1}	Present — common in both drug and polymers
C=O (Carbonyl Group)	~1724 cm^{-1}	Present — from Rabeprazole Sodium ester groups
N-H bending / Aromatic	~1601 cm^{-1}	Present — confirms aromatic amine of Rabeprazole
C-O-C / C-O Stretching	~1260 cm^{-1}	Present — from both HPMC and EC

1.1 Drug Polymer Interaction (FTIR) Study

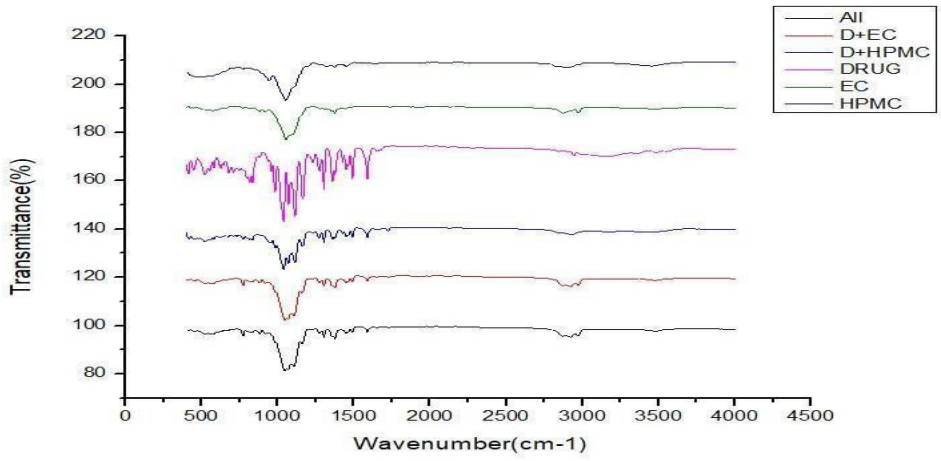
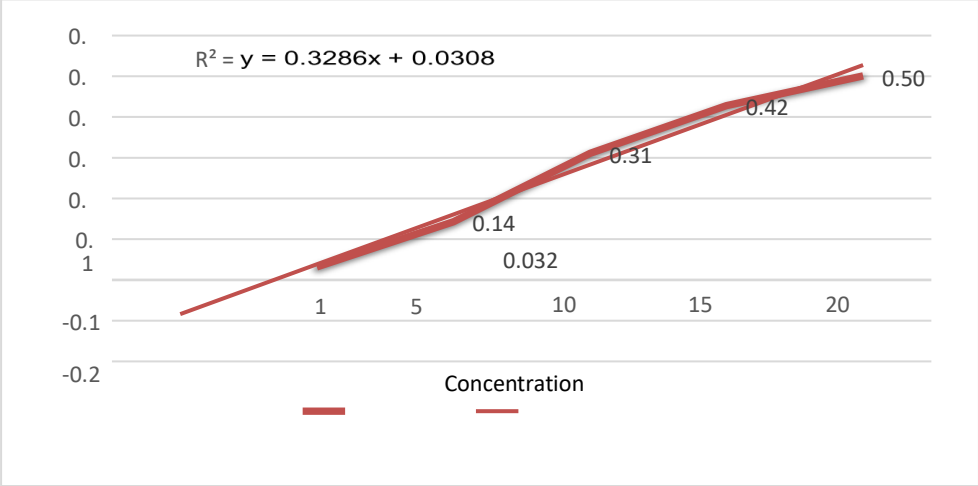


Fig 1: FTIR Peak Assignments from Experimental Spectrum

The FTIR spectrum of pure Rabeprazole Sodium was recorded using an FTIR spectrophotometer in the range of 4000–400 cm^{-1}. The spectrum showed characteristic peaks at 3158.66 cm^{-1} (N–H stretching), 1588.47 cm^{-1} (C=N stretching), 1490.86– 1427.34 cm^{-1} (C=C aromatic stretching), 1229.62 cm^{-1} (C–O stretching), 1165.68 and 1114.36 cm^{-1} (S=O stretching), and 678.07 cm^{-1} (C–S bending). These peaks confirm the structural integrity of Rabeprazole Sodium and indicate the presence of functional groups such as amines, ethers, and sulfoxides. No significant shift or disappearance of characteristic peaks was observed, confirming drug stability in its pure form.

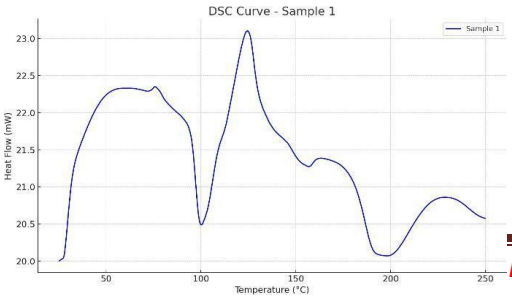
1.2 Determination of absorption maximum (λmax) using Potassium Dihydrogen Phosphate Buffer (pH 2)



Absorbance and concentration curve

The absorption maximum of Rabeprazole was found to be at 284 nm using Potassium Dihydrogen Phosphate Buffer (pH 2). The absorption maximum is shown .

1.3 Differential Scanning Calorimetry (DSC)Analysis



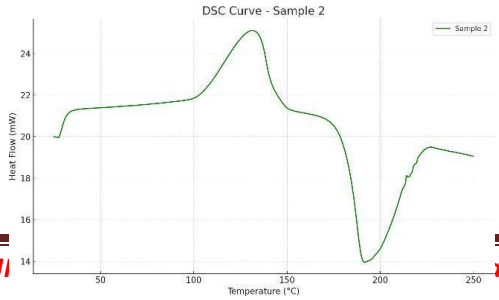
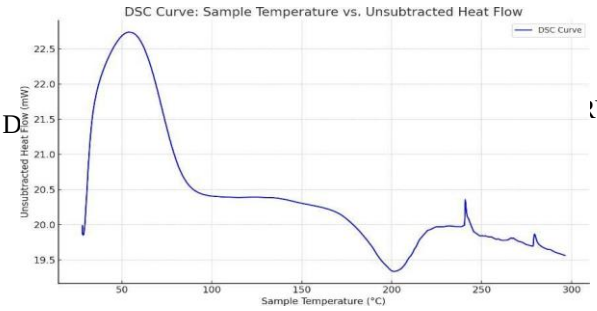


FIG2: DSC ABALYSIS OF D 

UG+POLYMER +POLYMER

Pure drug: Showed a sharp endothermic peak at its melting point, confirming its crystalline nature. Drug-polymer mixture: Minor shifts or changes in endothermic peaks indicated possible interactions or compatibility between the drug and polymers Formulation: The thermogram of the final formulation showed changes in peak patterns compared to the pure drug and mixture, suggesting the successful formulation of the drug-polymer system.

FIG4. DSC ANALYSIS OF FORMULATION

1.4 Scanning Electron Microscopy (SEM) Study

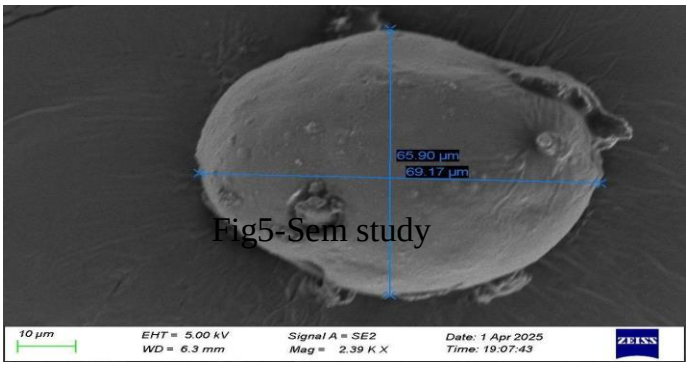


Fig5-Sem study

The SEM image confirms the desired morphology essential for floating behaviour and sustained drug release of Rabeprazole Sodium microspheres. Microspheres appear spherical and discrete. The surface shows slight porosity, ideal for floating and controlled release. No agglomeration, indicating uniform formulation.

Parameter	Description
EHT	5.00 kV (accelerating voltage)
Signal A	SE2 (Secondary Electron Detector)
WD	6.3 mm (Working Distance)
Mag	2.39KX (Magnification)

TABLE2 : Scanning Electron Microscopy (SEM) Parameters for Rabeprazole Sodium Microspheres

1.5 Dynamic light scattering of floating microsphere

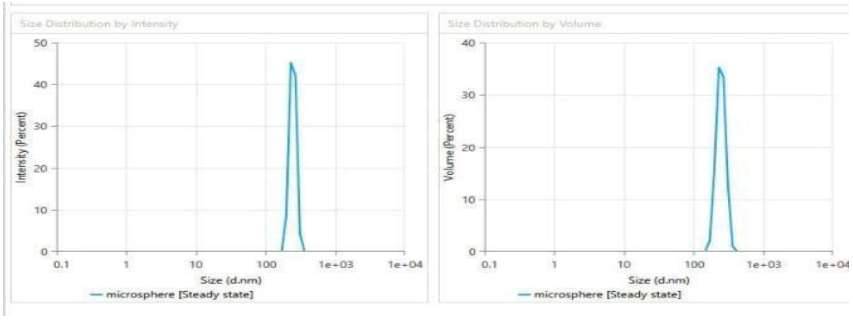


FIG6: DLS Curve

Parameter	Mean	Standard Deviation	Minimum	Maximum
Z-Average Diameter (nm)	960.3	-	960.3	960.3
Polydispersity Index (PDI)	0.7215	-	0.7215	0.7215
Peak 1 Mean (by Intensity, nm)	246.1	-	246.1	246.1
% In Range (Intensity)	85.19	-	85.19	85.19
Fit Error	0.01748	-	0.01748	0.01748

TABLE3: Dynamic Light Scattering (DLS) Analysis of Rabeprazole Sodium Microsphere

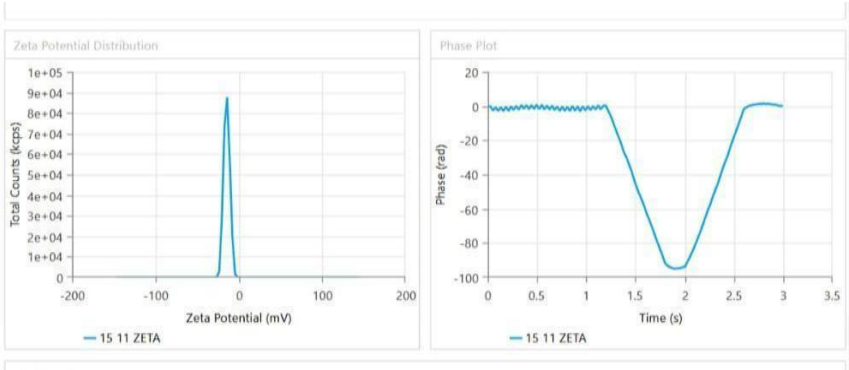
The Z-Average particle size was found to be 960.3 nm, indicating the presence of relatively larger-sized microspheres. This Z-Average is an intensity-weighted mean size and is sensitive to aggregates or larger particles. The Polydispersity Index (PDI) value was

0.7215, which suggests moderate to high polydispersity. Ideally, a lower PDI (<0.3) is preferred for monodisperse systems, but in the case of polymer-based microspheres, values up to 0.7 may still be acceptable. Peak 1 Mean by intensity (246.1 nm) indicates that the major population of the particles is smaller and well- distributed, confirming the presence of a bimodal distribution or secondary population of smaller particles. The % Intensity in range (85.19%) indicates that a majority of the particles fall within the main particle size peak, representing acceptable homogeneity. A fit error of 0.01748 indicates that the DLS data fitting was reliable and accurate.

These results confirm that the microsphere formulation is within a suitable nanometer range, supporting its potential for enhanced gastric residence time and sustained drug release, aligning with the goal of your floating drug delivery system.

1.6 ZETA Potential:

The measured zeta potential of the formulation was -14.41 mV, which indicates moderate stability of the colloidal dispersion. The zeta deviation was 3.648 mV, and the wall zeta potential was -9.638 mV. The conductivity of the sample was found to be 0.01732 mS/cm,



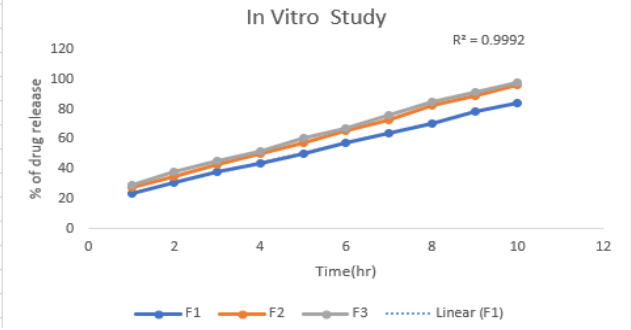
and the derived mean count rate was 2.49×10^4 kcps.

FIG7: ZETA potential

1.7 In Vitro Dissolution Study:

Time (hrs.)	Formulation 1	Formulation 2	Formulation 3
1	23.99	27.45	29.56
2	30.87	34.54	38.09
3	38.46	43.23	45.45
4	44.06	50.47	52.23
5	50.01	57.09	60.69
6	57.46	65.67	67.11
7	64.24	72.90	75.89
8	70.78	82.12	84.59
9	78.35	89.12	91.67
10	84.02	95.80	98.11

Table4: Cumulative % release of different formulations



In Vitro Release Kinetics

Time (min)	cdr	ln(cdr)	1/cdr	√Time	log(Time)	log(cdr)
60	0.6366	-0.4516	1.5708	7.746	1.7782	-0.1961
120	0.9652	-0.0354	1.0361	10.9545	2.0792	-0.0154
180	1.2938	0.2576	0.7729	13.4164	2.2553	0.1119
240	1.6224	0.4839	0.6164	15.4919	2.3802	0.2102
300	1.951	0.6683	0.5126	17.3205	2.4771	0.2903
360	2.2796	0.824	0.4387	18.9737	2.5563	0.3579
420	2.6082	0.9587	0.3834	20.4939	2.6232	0.4163
480	2.9368	1.0773	0.3405	21.9089	2.6812	0.4679

540	3.2654	1.1834	0.3062	23.2379	2.7324	0.5139
600	3.594	1.2793	0.2782	24.4949	2.7782	0.5556

TABLE5: Data for In Vitro Release Kinetics of Formulated Floating Microspheres

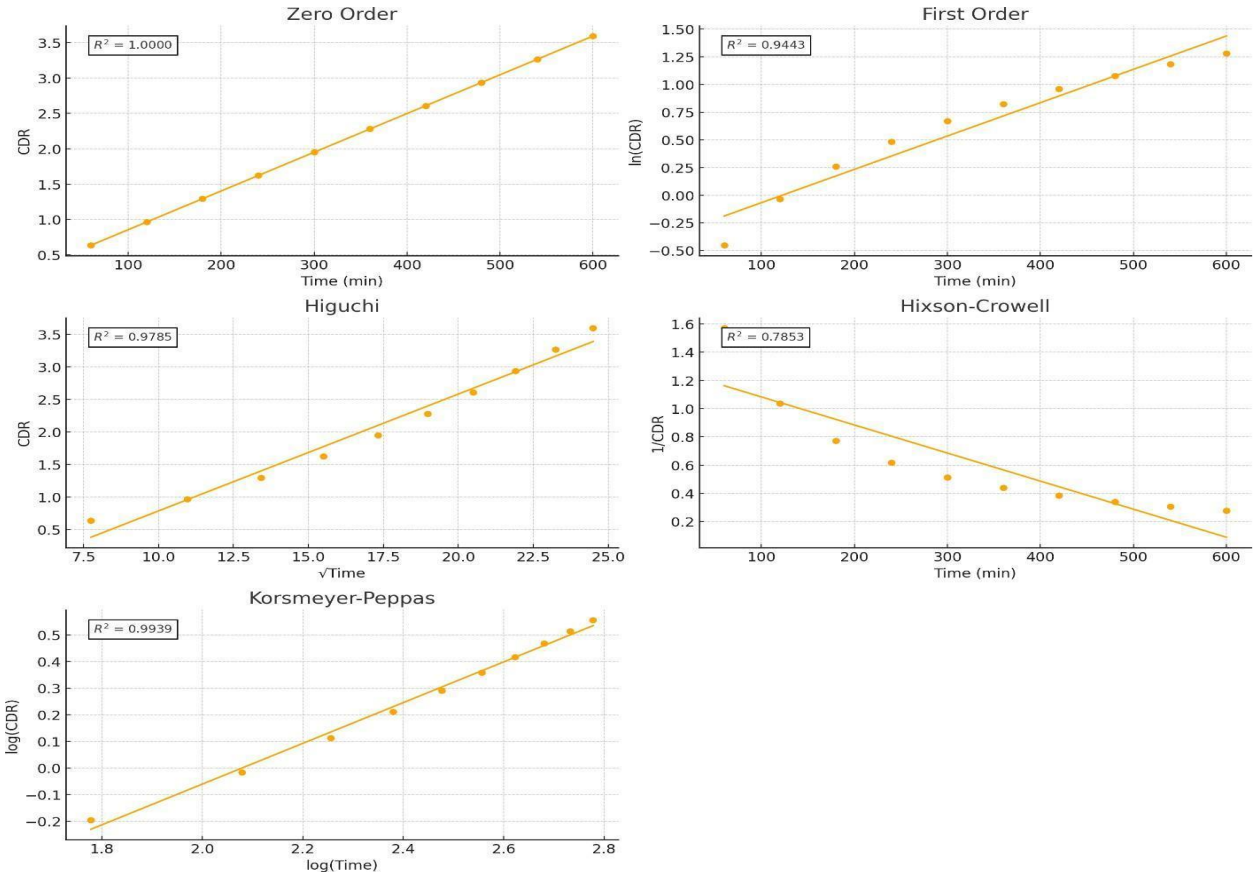


Fig8: In-Vitro Kinetics study

Several kinetic models were used to analyse the floating microspheres' in vitro release data. The Higuchi model had the greatest R2 value (0.9974), suggesting that a diffusion-controlled mechanism is largely responsible for the drug release. Good linearity was also demonstrated by the First Order (0.9941) and Korsmeyer-Peppas (0.9946) models, indicating a mix of erosion and diffusion. In comparison to the Higuchi model, the R2 values of the Zero Order (0.9835) and Hixson-Crowell (0.9882) models were lower. All of these findings point to a persistent release of the medication from the prepared microspheres, mostly via a diffusion process.

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