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Research Article

FORMULATION AND OPTIMIZATION OF BACLOFEN FLOATING MICROSPHERES: A GASTRORETENTIVE DRUG DELIVERY APPROACH

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ABSTRACT

The aim of the present study was to develop and evaluate Baclofen floating microspheres to prolong the gastric residence time of Baclofen, a drug with an absorption window in the upper gastrointestinal tract. The microspheres were prepared using the solvent evaporation technique. The dependent variables studied were particle size (Y1), percentage drug entrapment efficiency (Y2), percentage buoyancy (Y3), in-vitro drug release at 1 hour (Y4), and in-vitro drug release at 6 hours (Y5). A 3^2 full factorial design was employed to assess the combined effect of two independent variables Eudragit RL100 (X1) and Eudragit RS100 (X2), on the aforementioned responses. Multiple regression analysis revealed that increasing concentrations of Eudragit RL100 and Eudragit RS100 led to a reduction in in-vitro drug release, while enhancing particle size, drug entrapment efficiency, and buoyancy. The optimized formulation consisted of microspheres with an average particle size of 115.96 µm, drug entrapment efficiency of 90.06%, and buoyancy of 90.76%. In-vitro studies demonstrated sustained drug release for up to 24 hours. The floating microspheres were free-flowing, porous, and nearly spherical in shape. Drug release followed Fickian diffusion and best fitted the Higuchi model, as determined by drug release kinetics studies.

Key Words: Baclofen, Floating microspheres, Gastric retention, Solvent evaporation, Eudragit RL100, Eudragit RS100, Drug release kinetics

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INTRODUCTION

Drugs that are easily absorbed from alimentary canal (GIT) and have short half- lives are eliminated quickly from the circulation. Frequent dosing of those drugs is required to realize suitable therapeutic activity. To avoid this limitation, the event of oral sustained-controlled release formulations is an effort to release the drug slowly into the alimentary canal (GIT) and maintain an efficient drug concentration in the systemic circulation for a long time (Sowmya B *et al*., 2019). Gastro-retentive delivery systems are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enabling sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract (Gupta R *et al*., 2018; Juthi AZ and Bithi TZ, 2018). Gastro retentive delivery system can be classified as follows.

- Bio adhesive Drug Delivery System
- Expandable Drug delivery System
- Floating Drug Delivery System
- High-Density Systems.

Among these systems, FDDS have been most commonly used. Floating drug delivery systems is one of the important approaches to achieve gastric retention to obtain sufficient drug bioavailability (Patel B *et al*., 2019). Floating systems are low density systems that have maximum buoyancy to float on the gastric material and remain in the stomach for longer period of time. Due to these parameters, the drug is released in a sustained manner with desired rate, and minimizes fluctuation also (Baviskar P *et al*., 2019). A low amount of gastric content is required to permit the right achievement of the buoyancy retention principle, a minimal level of floating force (F) is required to stay the dosage form buoyant on the surface of the gastric content. A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug (Kandukoori NR *et al*., 2017).

Drugs that have poor bioavailability due to site specific absorption from the upper part of the GIT are potential candidates to be formulated as floating drug delivery systems thereby increasing their absorption. Floating microspheres are gastro- retentive drug delivery systems supported non- effervescent approach (Purohit K *et al*., 2019; Patil P *et al*., 2018). Hollow microspheres are considered as one of the most promising buoyancy systems, as they possess the unique advantages of multiple unit systems as well as the better floating properties, because of the central hollow space inside the microspheres. These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 µm (Saroja SP *et al*., 2019; Ghule PN *et al*., 2014).

Baclofen isa gamma-aminobutyric acid(GABA) agonist used as skeletal muscle relaxant used for there lief of painful and uncomfortable muscle spasms caused by a variety of conditions (Keservani R *et al*., 2020). It is known to be particularly useful in treating muscle spasticity associated with spinal cord injury. Baclofen is administered for the relief of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and associated pain and clonus, in addition to muscular rigidity. Baclofen has a bioavailability of 70% to85%and is therefore rapidly absorbed through the gastrointestinal tract following oral administration. Peak plasma concentrations are generally observed 2 to 3 h after ingestion. The absorption is dose-dependent and increases with higher doses. Baclofen is rapidly and extensively absorbed and eliminated. The half-life of the drug is2.5to4hin plasma. Baclofen has absorption window in upper Gastrointestinal (G.I.) tract. Baclofen is difficult to formulate in to sustained release dosage forms because on arrival to colon its absorption is diminished or non-existent. In the present investigation efforts were made to formulate floating microspheres of Baclofen to improve theabsorption of Baclofen in stomach, to prepare spherical floating microspheres, to study sustained effect of floating microspheres, to study the effect of different polymers on buoyancy and % drug release and Statistical optimization of factorial design formulation (Dasari N *et al*., 2016; Thakar K *et al*., 2013).

MATERIALS AND METHOD

Materials Used

Baclofen (Astron PVT. LTD. Ahmedabad),Eudragit RS100 and Eudragit RL100 (Yarrow Chemicals Mumbai), HPMC K4M and Magnesium stearate (Central Drug House LTD. Mumbai), Acetone (Rankem Delhi) and Light liquid paraffin and Heavy liquid paraffin (Astron chemicals India).

METHODS

Drug Excipients Compatibility Study by Differential Scanning Calorimetry (DSC)

Drug- excipients interactions play a vital role in the release of drug from formulation. The physiochemical compatibilities of the optimized formulations were tested by differential scanning calorimetric (DSC) analysis (Sundar V D *et al*., 2018). Differential Scanning Calorimetry (DSC) spectra of (i) Baclofen (ii) polymer mixture (Eudragit RS100, Eudragit RL100) (iii) Baclofen and polymer mixture (Eudragit RS100, Eudragit RL100) of all these were recorded using DSC (DCS-60, Shimadzu Corporation, Japan). Their baclofen spectra and mixture of baclofen and polymers spectra is shown in result and discussion section (Jagtap YM *et al*., 2012; Singh V *et al*., 2011).

Preparation of Baclofen Floating Microspheres

Floating microspheres loaded with baclofen were prepared by solvent evaporation technique. Firstly polymers (Eudragit RS 100, Eudragit RL100 and Hydroxy Propyl Methyl Cellulose) were dissolved in organic solvent (acetone), then drug was dispersed in polymer solution. Drug polymer solution was added drop wise using hypodermic needle in continuous phase (light liquid paraffin + heavy liquid paraffin). Organic solvent was evaporated due to continuous stirring using propeller mixer. After 2 h floating microspheres were washed with hexane several times and filtered and dried at room temperature.

Evaluation of Baclofen Floating Microspheres

Particle Size Analysis

Particle size analysis of drug-loaded Eudragit microspheres was performed by optical microscopy using a compound microscope. The slide containing Eudragit microspheres was mounted on the stage of the microscope and diameter of at least 300 particles was measured using a calibrated ocular micrometre. The average particle size of microspheres was determined by the total size of the

microspheres divided by the number of microspheres (Sagar B *et al.,* 2017; Abdul Khaleq, N. M *et al., 2023*).

Percentage Yield

The prepared microspheres were collected and weighed. The measured weight was divided by the total amount of drug and polymers which were used for the preparation of the microspheres to obtained percentage yield. Results of percentage Yield was calculated using following equation (Mishra A *et al.,* 2018).

%Yield=Practical yield/Theoreticalyield×100

Percentage Drug Entrapment Efficiency

To determine the incorporation efficiency, 25 mg microspheres were crushed and dispersed in 100ml0.1 N HCl and sonicated for 10-15 min. The dispersion was stirred on a magnetic stirrer for 24 h. The dispersion was filtered, and Drug content was analysed spectrophotometrically at 220 nm. The percentage drug entrapment efficiency was calculated using the following equation (Meghana KJ *et al.,* 2019; Khan R *et al.,* 2018).

%DEE=Actual drug content /Theoreticaldrugcontent×100

Percentage Buoyancy Study

100 mg of floating microspheres were spread over the surface of a type II USP dissolution apparatus filled with 900 ml of 0.1 N HCl. The medium was agitated with a paddle rotating at 100rpm for 8h. After 8h, the layer of buoyant microparticles was pipetted and separated by filtration. The particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator and weighed. The percentage buoyancy was calculated from the weight of floating particles to the sum of floating and sinking particles (Joselin J *et al.,* 2015).

%Buoyancy=Initialweightofmicrospheres/Weightofflo atingmicrospheres×100

***In-Vitro* Drug Release**

Percentage cumulative drug release studies were carried out for all formulations taking 20 mg drug equivalent microspheres in USP type II dissolution test apparatus containing 900ml of 0.1 N Hydrochloric acid (HCl) (pH 1.2) maintained at 37 ± 0.20 ℃ at a rotation speed of 100 rpm. The amount of the drug was determined first- derivative (D1) spectrophotometrically at 220 nm adopting the peak height method (Gande S *et al.,*2011; Kumar KR *et al.,*2017; Nath B *et al.,*2011).

Residual Solvent Analysis

Residual solvent analysis was done through Gas Chromatography.

Surface Morphology Study

The surface morphology of microspheres was determined by Scanning Electron Microscopy. Dry microspheres were placed in a scanning electron microscope brass stub and coated with gold in an ion sputter. Picture of microspheres was taken by random scanning of the stub (Kanteepan P *et al.,* 2018; Subbarao K *et al.,* 2018).

Statistical Analysis

A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses (Khairnar G *et al.,* 2017; Kumar P *et al.,* 2023). Mathematical modelling, evaluation of the ability to fit to the model and response surface modelling were performed by employing Design-Expert software.

$$Yi=b0+b1\times1+b2\times2+b12\times1\times2+b11\times12+b22\times22$$

Where Yi is the dependent variable, b0 is the intercept (arithmetic mean response of 9 runs), b1 to b22 are regression coefficients, X1, X2, are the independent variables. Here the dependent variables are particle size (Y1),% yield(Y2),%drug entrapment efficiency (Y3),%buoyancy (Y4),in-vitro drug release at 1 hour(Y5), in-vitro drug release at 6 hour (Y6) and independent variables are concentration of EudragitRL100 (X1) and concentration of Eudragit RS100 (X2).

Stability Study

Stability study was carried out on formulated microspheres after storing at 40 ℃ and 75% relative humidity for one month according to ICH guidelines (Ibrahim M *et al.,* 2020; Wavhule P *et al.,* 2021).

Table 1: Composition of Formulation batches

Batches	Particle Size (µm)	%Yield (%)	DEE (%)	% Buoyancy (%)
E_1	68.20±2.32	52.12±1.96	71.25±1.2	80.60±1.2
E_2	81.30±2.23	57.23±2.24	75.12±2.3	83.66±1.7
E_3	95.41±1.52	65.06±2.45	83.32±3.2	85.12±1.2
E_4	85.12±1.61	59.02±2.47	80.21±1.5	85.21±1.8
E_5	98.15±1.29	67.51±2.21	78.12±3.5	82.16±1.5
E_6	105.13±2.18	74.22±2.52	85.28±3.5	88.01±2.1
E_7	100.01±1.56	67.89±2.50	87.41±2.3	87.50±1.6
E_8	112.03±1.94	77.91±2.55	89.42±2.8	90.12±1.9
E_9	119.05±2.45	85.11±3.16	92.06±3.8	92.21±2.5

Table 2: Particle size, %yield, % Drug entrapment efficiency, % Buoyancy

Batches	Particle Size (µm)	%Yield (%)	DEE (%)	% Buoyancy (%)
E_1	68.20±2.32	52.12±1.96	71.25±1.2	80.60±1.2
E_2	81.30±2.23	57.23±2.24	75.12±2.3	83.66±1.7
E_3	95.41±1.52	65.06±2.45	83.32±3.2	85.12±1.2
E_4	85.12±1.61	59.02±2.47	80.21±1.5	85.21±1.8
E_5	98.15±1.29	67.51±2.21	78.12±3.5	82.16±1.5
E_6	105.13±2.18	74.22±2.52	85.28±3.5	88.01±2.1
E_7	100.01±1.56	67.89±2.50	87.41±2.3	87.50±1.6
E_8	112.03±1.94	77.91±2.55	89.42±2.8	90.12±1.9
E_9	119.05±2.45	85.11±3.16	92.06±3.8	92.21±2.5

DEE – Drug entrapment efficiency

Table 3: In-Vitro drug release study

Time (h)	Batches								
	E1	**E2**	**E3**	**E4**	**E5**	**E6**	**E7**	**E8**	**E9**
1	42.32±1.81	44.41±1.15	39.56±1.77	32.15±1.72	31.21±1.04	33.56±1.99	27.31±1.8	26.37±1.85	25.35±1.16
2	52.35±1.05	55.76±1.64	45.23±1.09	40.28±1.71	41.28±1.96	42.53±1.05	34.23±1.90	31.9±1.13	31.12±1.08
3	65.67±1.48	68.40±1.93	54.36±1.76	55.16±1.89	56.12±1.19	49.25±1.63	47.42±1.38	4535±1.65	38.25±1.90
4	83.33±1.17	79.29±1.77	63.26±1.45	64.23±1.19	64.56±1.16	57.63±1.95	54.82±1.04	52.33±1.92	43.21±1.19
5	91.57±1.84	89.49±1.01	74.36±1.78	72.15±1.69	71.1±1.85	69.12±1.83	63.15±1.14	58.91±1.95	50.35±1.05
6	99.42±1.55	96.20±1.01	79.56±1.59	79.20±1.95	77.27±1.06	75.69±1.83	69.56±1.44	66.53±1.56	64.56±1.13
7	-	100.01±1.09	87.26±1.14	85.5±1.29	82.26±1.99	81.23±1.05	73.21±1.02	70.1±1.98	73.45±1.10
8	-	-	93.5±1.89	92.21±1.94	88.15±1.69	84.56±1.45	85.56±1.45	77.21±1.02	75.21±1.12
9	-	-	96.33±1.17	99.13±1.24	93.6±1.62	90.11±1.78	93.42±1.64	81.62±1.16	79.85±1.92
10	-	-	102.9±1.26	100.3±1.02	99.08±1.09	95.1±1.32	99.56±1.94	85.62±1.70	82.56±1.14
12	-	-	-	-	-	99.32±1.28	100.03±1.39	92.93±1.97	85.33±1.84
14	-	-	-	-	-	-	-	98.63±1.26	88.27±1.56
16	-	-	-	-	-	-	-	-	92.56±1.02
18	-	-	-	-	-	-	-	-	97.02±1.59
20	-	-	-	-	-	-	-	-	98.12±1.02

Table 4: Regression analysis for effect of X1 (EudragitRL100) and X2(EudragitRS100)

Parameters	R Square	Adjusted RS quare	Observations	Source	Sum of Squares	P- Values
				Model	2003.21	<0.0001
				X_1	731.51	<0.0001
Average particle size (Y_1)	0.9955	0.9955	0.9955	$X_2X12X_1^2X$	1238.12 16.65	<0.0001 0.0089

				2^2	11.58 0.71	0.0202 0.4825
	Full model equation: Y_1=+97.87+11.04X_1+14.37X_2-2.04X_1X_2-2.05X_1^2-0.51X_2^2					
	Reduced model equation: Y_1=+97.87+11.04X_1+14.37X_2-2.04X_1X_2-2.05X_1^2					
				Model	416.88	<0.0001
				X_1	79.13	0.0003
% Drug entrapment efficiency (Y_2)	0.9705	0.9705	0.9705	X_2 X_1X_2 X_1^2 X_2^2	256.11 13.76 24.71 17.48	<0.0001 0.0281 0.0077 0.0171
						2
	Full model equation: Y_2=+78.59+3.63X_1+653X_2-1.85X_1X_2+2.99X_1^2+2.52X_2					
						2
	Reduced model equation: Y_2=+78.59+3.63X_1+6.53X_2-1.85X_1X_2+2.99X_1^2+2.52X_2					
				Model	136.50	0.0038
				X_1	24.12	0.0189
	0.8817	0.8817	0.8817	X_2 X_1X_2	69.70 9.02	0.0013 0.9548
% Buoyancy (Y_3)				X_1^2	11.55	0.0738
				X_2^2	14.93	0.0483
						2 2
	Full model equation: Y_3=+82.25+2.00X_1+3.41X_2+0.048X_1X_2+2.04X_1+2.32X_2					
	Reduced model equation: Y_3=+82.25+2.00X_1+3.41X_2+2.32X_2^2					
% Cumulative drugreleaseatQ_1 (*in-vitro* drug release at 1 h) (Y_4)	0.9086	0.9086	0.9086	Model X_1 X_2	374.08 1.83 372.25	<0.0001 0.5020 <0.0001
	Full model equation: Y_4=+32.85-0.55X_1-7.88X_2					
	Reduced model equation: Y_4=+32.85-7.88X_2					
% Cumulative drug release at Q_6 (*in-vitro* drug releaseat6h) (Y_5)	0.9271	0.9271	0.9271	Model X_1 X_2	1046.33 205.22 841.11	<0.0001 0.0005 <0.0001
	Full model equation: Y_5=+70.21-5.85X_1-11.84X_2					
	Reduced model equation: Y_5=+70.21-5.85X_1-11.84X_2					

Table 5: Formulation of check point batch

Ingredients	Batches	
	C_1	C_2
Baclofen (mg)	100	100
EudragitRL100 (mg)	285.31	174.49
EudragitRS100 (mg)	285.17	114.60
HPMCK4M (mg)	50	50
Magnesium stearate (mg)	5	5
Acetone (ml)	10	10

Table 6: Predicted response and actual response of checkpoint batch

Evaluation Parameters	Batch–C_1			Batch–C_2		
	Predicted value	Actual value	%Error	Predicted value	Actual value	%Error
Particle size (µm)	116.81	112.21	4.09	81.83	83.56	2.07
% Drug Entrapment	89.90	86.50	3.93	73.70	75.56	2.46
%Buoyancy	90.66	93.21	2.73	81.26	79.23	2.56
%CDRatQ_1	25.67	26.96	4.78	39.72	41.26	3.73
%CDRatQ_6	55.13	53.12	3.78	81.81	84.50	3.18

Table7: Optimized batch

Ingredients	Quantity
Baclofen	100mg
EudragitRL100	297.56 mg
EudragitRS100	278.78 mg
HPMCK4M	50mg
Magnesium stearate	5mg
Acetone	10ml

Table 8: Dissolution profile for optimized batch

TIME (h)	%CDR
1	25.50
2	32.23
3	38.59
4	42.26
5	56.26
6	64.35
7	72.21
8	77.27
9	81.15
10	85.91
12	91.10
14	96.01
16	98.23
18	100.05
20	100.15

Table 9: Evaluation parameters of optimized batch

Evaluation Parameters	Observations
Particle size	115.96µm
% Drug entrapment	90.06%
%Buoyancy	90.76%

Table 10: Kinetic model for drug release of optimized batch

Batch	Zero- Order	First- Order	Higuchi Model	Korsmeyer- Peppa's Model	
	R^2	R^2	R^2	R^2	N
Optimized batch	0.8783	0.7715	0.9793	0.978	0.4857

Table 11: Evaluation of optimized batch for stability study.

Parameters	Time (Months)	Observations	
		Initial	After stability
Particle size	1	115.96µm	114.56µm
% Drug entrapment	1	90.06%	90.01%

% Buoyancy	1	90.76%	90.56%
%CDRatQ_1	1	25.50%	26.01%
%CDRatQ_6	1	56.26%	56.01%

Figure 1: Differential scanning calorimetry spectra of Baclofen

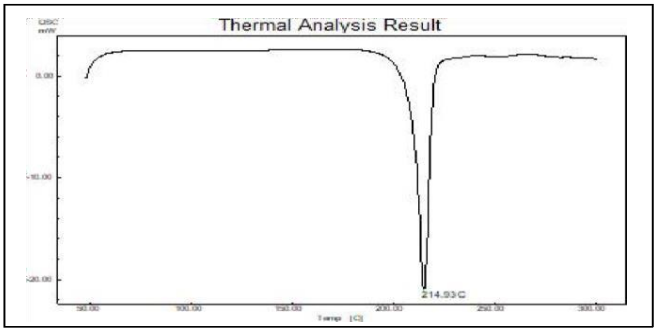


Figure 2: Differential scanning calorimetry spectra of mixture (Eudragit RL100 + Eudragit RS100)

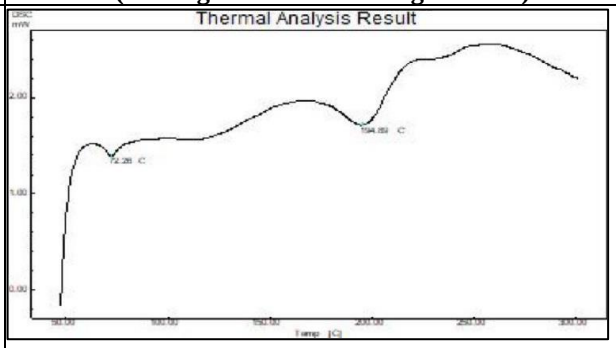


Figure 3: Differential scanning calorimetry spectra of polymer Baclofen and polymer mixture (Eudragit RL100 + Eudragit RS100)

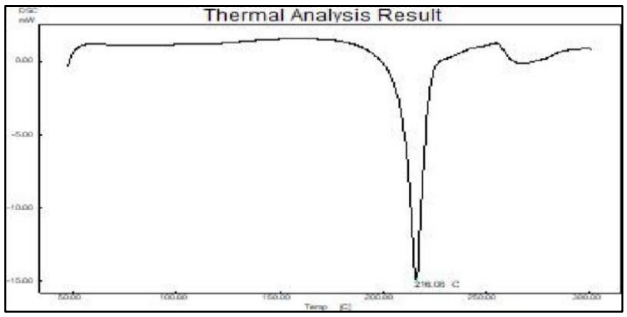


Figure 4: Baclofen floating microspheres (microspheres floating over the surface in 0.1N HCl)

Figure 5: In-Vitro drug release profile

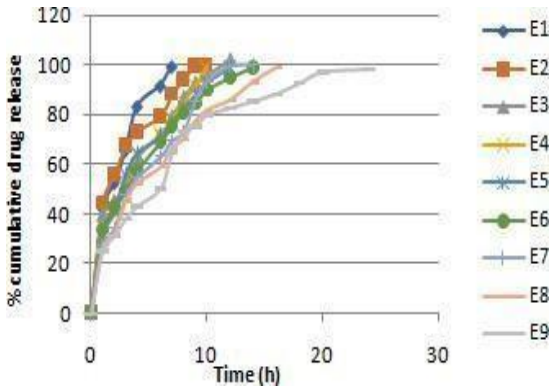


Figure 6: Gas chromatography of acetone

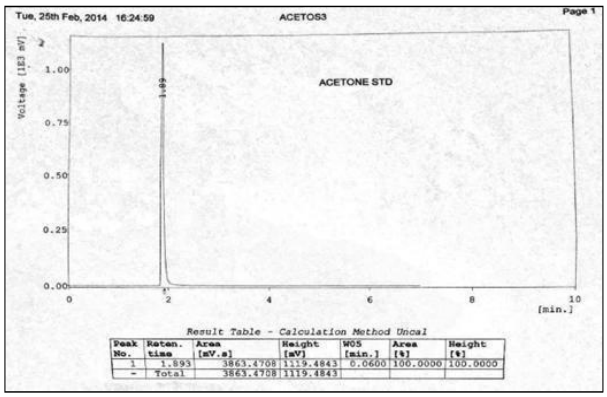
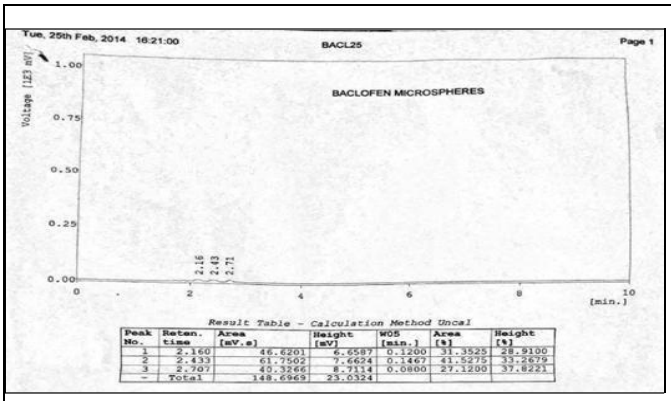


Figure 7: Gaschromatography of floating microspheres of Baclofen

Figure 8: Scanning electron microscopy images:
a) Spherical floating microspheres of Baclofen,
b) Zoomed view of spherical floating microspheres of Baclofen,
c) Porous surface of floating microsphere of Baclofen



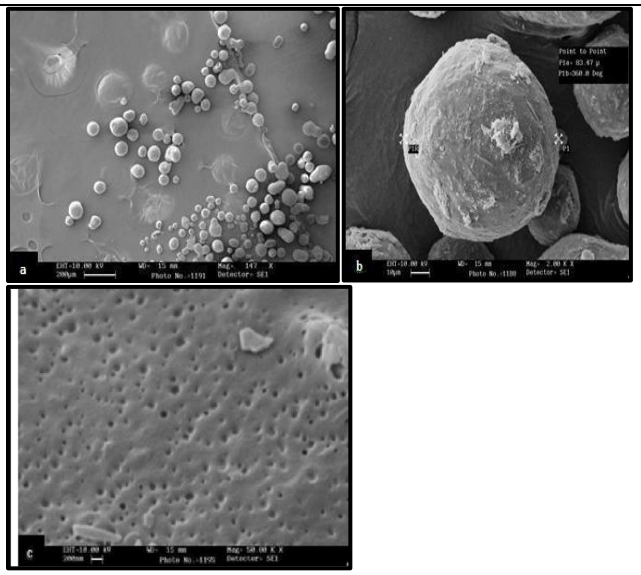
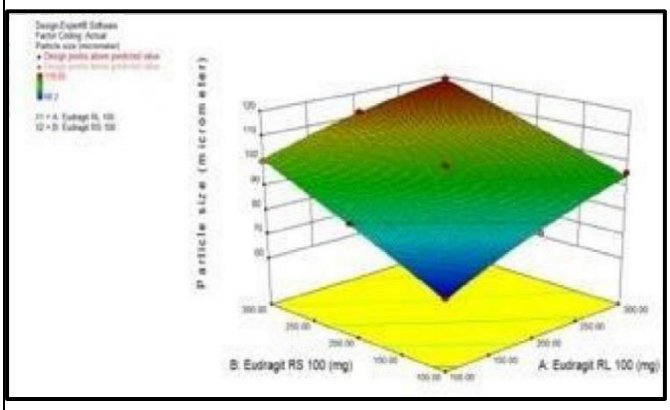


Figure 9: 3Dresponse surface graph for particle size

Figure 10: D response surface graph for drug entrapment



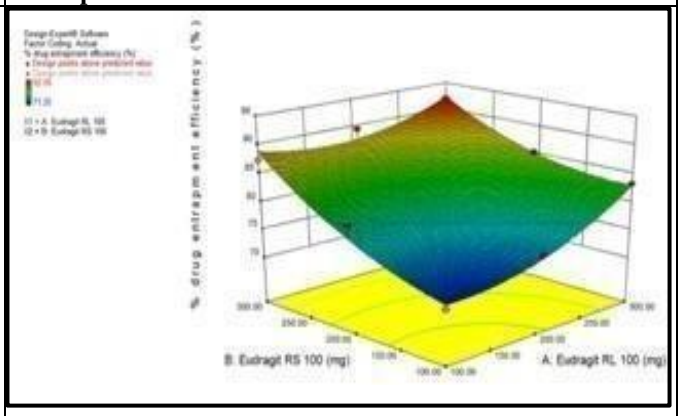
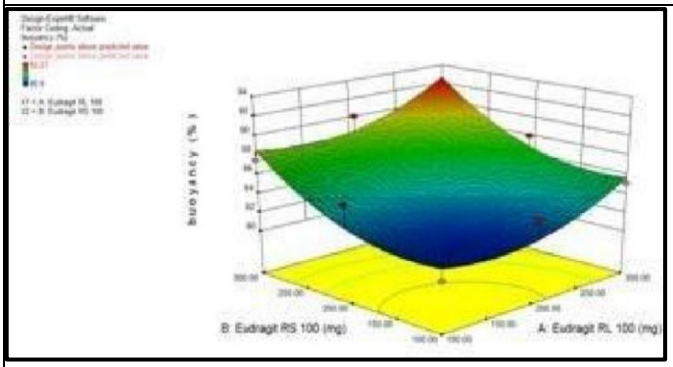


Figure 11: 3D response surface graph for % buoyancy

Figure 12: 3D response surface graph for % cumulative drug release (CDR) at 1 hr



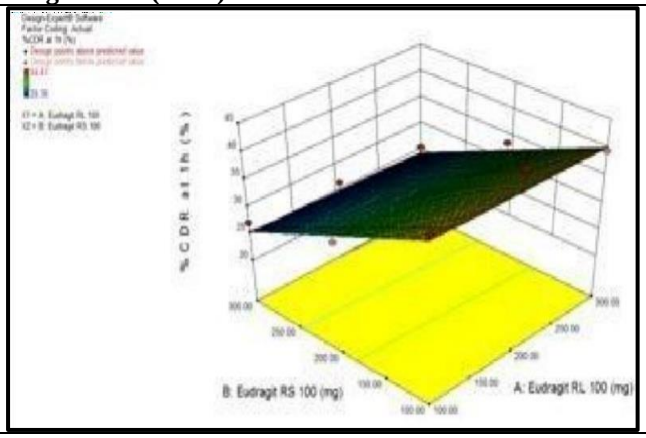


Figure 13: 3D response surface graph for % cumulative drug release (CDR) at 6 hr

Figure 14: Overlay plot of response variable

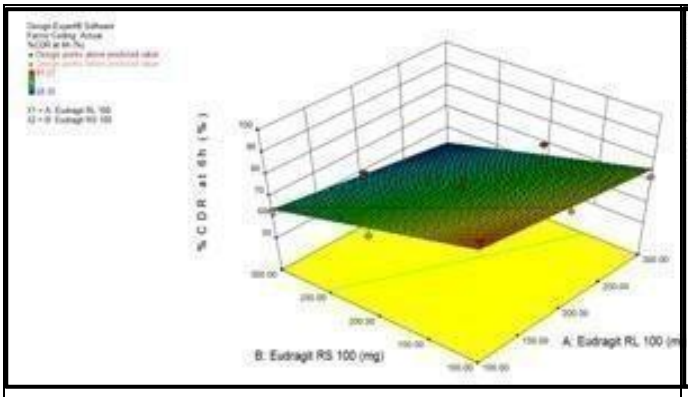


Figure 15: Optimized batch from overlay plot

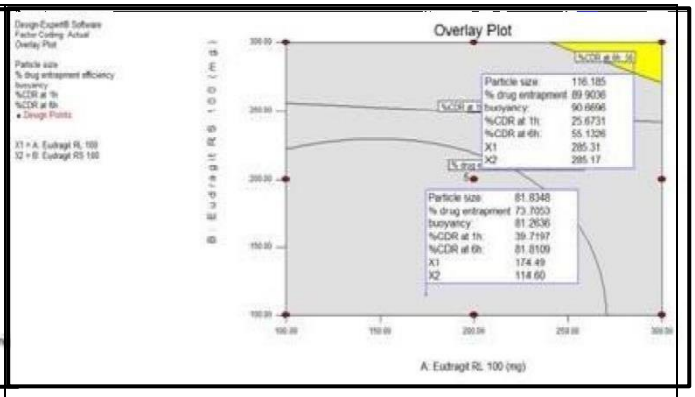


Figure16: Zero-order plot of optimized batch

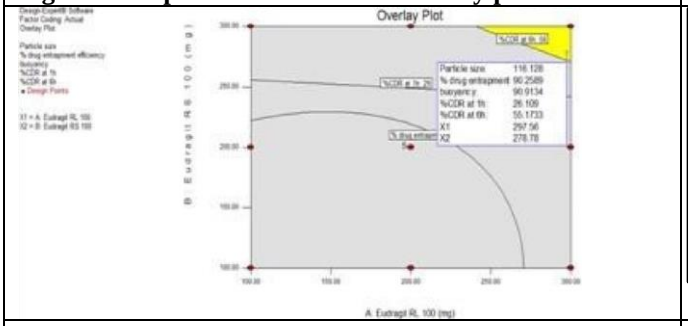


Figure17: First orderplot of optimized batch

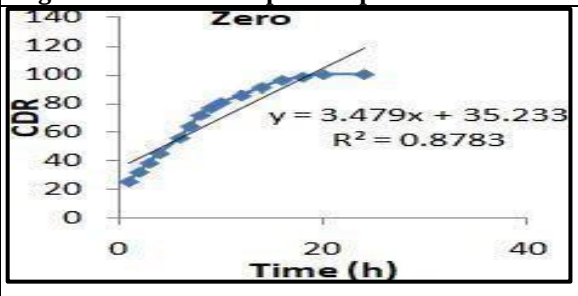
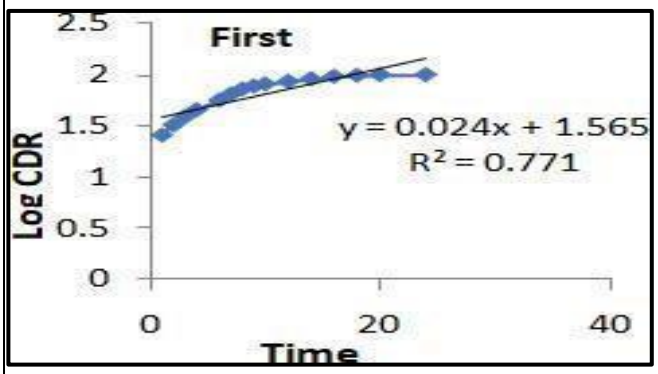


Figure 18: Higuchi plot of optimized batch



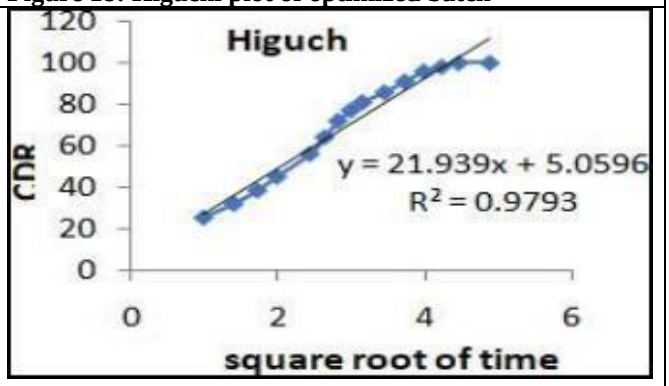
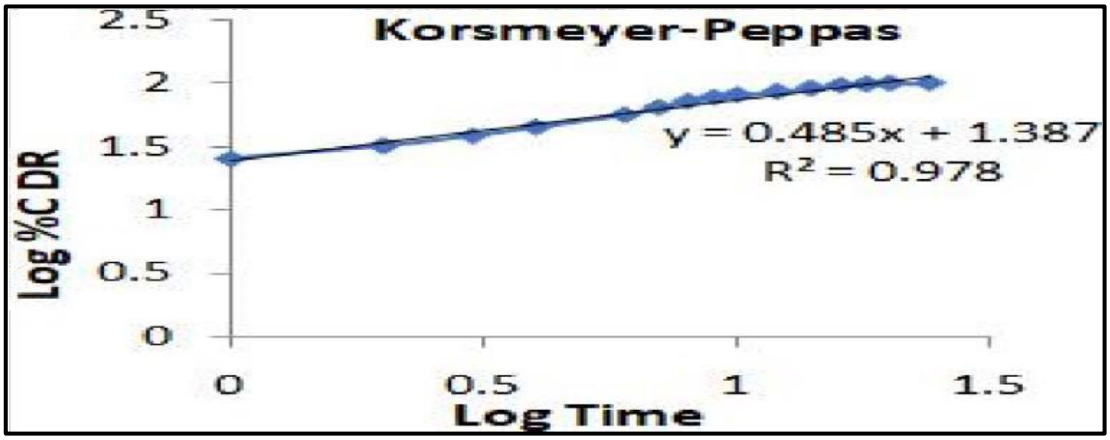


Figure 19: Korsmeyer-Peppa's plot of optimized batch



RESULTS AND DISCUSSION

Drug Excipients Compatibility Study by Differential Scanning Calorimetry (DSC): In Differential Scanning Calorimetry of drug and physical mixture of drug and polymer. All peaks were not much shifted in spectra so there was no in compatibility between baclofen and polymers. It is shown in following Figure1, 2 and 3.

Results of Batches of Baclofen Floating Microspheres

Floating microspheres of baclofen were prepared by solvent evaporation technique using polymers. Results of baclofen floating microspheres are shown in Table 2. Floating microspheres of baclofen are showed in Figure 4.

Particle Size Analysis

Floating microspheres containing baclofen was successfully prepared by solvent evaporation method. The average particle size Table 2 of the prepared floating microspheres was lowest for the E_1 formulation (68.2 µm) and was highest for E_9 formulation (119.05 µm). From the results of the particle size measurement it was concluded that as the core to coat ratio (drug to polymer ratio) increased there was an increase of the particle size. This may be attributed to the increase in the viscosity of the solution containing drug and polymer mixture, as constant amounts of the solvents were used for their solubilisation. Here Eudragit RS100 has more effect on particle size than Eudragit RL100. %Yield From Table 2,it shows that as drug: polymer ratio was increased; the %yield was increased.

Percentage Drug Entrapment Efficiency

The drug entrapment efficiency Table 2 was higher in E_9 batch (92.06%). The results obtained clearly indicated that the drug entrapment efficiency increased as the drug to polymer(core to coat) ratio increased. This may be attributed to the availability of more coat material per core molecule. The entrapment efficiency was also higher because the drug was present in a non-aqueous media (light liquid paraffin +heavy liquid paraffin) in which the solubility of the drug is very low, thereby preventing the loss of the drug into the dispersion medium during the formulation of microspheres.

Percentage Buoyancy

The floating ability (Table 2) of E_1 formulation was lowest, amounting to 80.6% and it was highest for E_9 formulation (92.21%).The formulations prepared from more ratio of Eudragit RS100+EudragitRL100 polymer were found to have good floating ability than those formulated from less ratio of Eudragit RS100+ Eudragit RL100 polymer. The lower floating ability of the prepared floating microspheres maybe ascribed to their small size. Here Eudragit RS100 has better floating ability as compared to Eudragit RL100 because of its low bulk Optimized batch from overlay plot Eudragit RL100. As the size was small, the mass/ volume ratio (density) may be more, leading to an early settling of the microspheres.

In-Vitro Drug Release Study

From the Figure 5 and Table 3, it can be seen that increased in drug: polymer ratio decreased the release rate. It was due to as increased in polymer concentration the matrix wall of micro sphere became thicker with less no of pores. Here drug release pattern was initially bursting and then sustained. It was due to drug crystal might be present on surface of microspheres. It was also observed that the release rate of drug from (1: 2) ratio of drug (baclofen) + polymer mixture (Eudragit RL100, Eudragit RS 100) microspheres was a higher than that of (1:6) ratio of drug (baclofen) + polymer mixture (Eudragit RL100, Eudragit RS 100) microspheres. The thick polymeric barrier slows the entry of surrounding dissolution medium in to the microspheres and hence less quantity of drug leaches out from the polymer matrices of the microspheres exhibiting slow release.

Fromtheresidualsolventanalysisreportitwasconcludedthat acetoneisabsentinpreparedfloating microspheres as peak of acetone is not visible in GC of microspheres as shown in Figure 6 and 7.

Surface Morphology Study

From scanning electron microscopy study, it is concluded that microspheres were fairly smooth and spherical in shape having porous structure. The surface of microspheres consists of crystals of remaining drug which is responsible for initial bursting effect as shown in Figure 8.

Statistical Analysis

Average particle size was varying from 68. 2-119.05 µm (Table2) and showed correlation 0.9955 (Table4). The p values lower than 0.05 so X_1 and X_2 have a significant effect. X_1 (Eudragit RL100) and X_2 (Eudragit RS100) both had a positive effect. It indicates that as the drug to polymer ratio increases the particle size increases. So, both $X_1$and X_2 significantly affect the particle size. Here X_2 has more significant effect as compared to X_1.

Percentage drug entrapment efficiency was varying from 71.25 - 92.06% Table 2 and showed correlation 0.9705 Table 8.4. The p values lower than 0.05so $X_1$and X_2have a significant effect.X_1(Eudragit RL 100) and X_2(Eudragit RS100) both had a positive effect. It indicates that as the drug to polymer ratio increases, drug entrapment efficiency increases. So, both $X_1$and

X_2significantly affect entrapment efficiency. Here X_2 has a more significant effect as compared to X_1.

Percentage buoyancy was varying from 80.6-92.21% as shown in Table 2 and showed correlation 0.8817 in Table4.Thep values lower than 0.05so $X_1$and X_2have significant effect. X_1(Eudragit RL 100) and X_2(Eudragit RS 100) both had positive effect. It indicates that as the drug to polymer ratio increases buoyancy increases. So, both $X_1$and X_2significant affect the buoyancy. Here X_2has more significant effect as compared to X_1.

In-vitro drug release at 1 h was varying from 42.32- 25.35% as shown in Table 3 of E_1 to E_9 batch and showed correlation 0.9086 in Table 4. The p values lower than 0.05 so $X_1$and X_2have significant effect. X_1 (Eudragit RL100)and X_2(Eudragit RS100) both had negative effect. It indicates that as the drug to polymer ratio increases, it decreases the drug release. So, both $X_1$and X_2significant affect the drug release. Here X_2has more significant effect as compared to X_1. The p value of $X_1$was more than 0.05 so it was insignificant and do not affect % cumulative drug release (CDR) at 1h.

In-vitro drugreleaseat6h was varying from 99.42-64.56%as shown in Table 3 ofE_1 toE_9 batch and showed correlation 0.9271 in Table 4. The p value slower than 0.05 so they are significant effect. X_1(Eudragit RL 100) and X_2(Eudragit RS 100) both had negative effect. It indicates that as the drug to polymer ratio increases it decreases the drug release. So, bothX_1 and X_2significant affect the dissolution. Here X_2has more negative effect as compared toX_1. The p value of both $X_1$and $X_2$was less than 0.05 therefore they both have significant effect.

Preparation of Check Point Batch from Overlay Plot

Checkpoint batch $C_1$and C_2were selected from the overlay plot of responses. The amount of Eudragit RL100 and Eudragit RS100 and according to their amounts, the predicted responses were given in the Overlay plot flag or in the solution of overlay data. From that, any two batches $C_1$and C_2were selected for the verification of the model. Following Table 5 is showing the formula for $C_1$and C_2batches.

Verification of Model by Comparing Predicted Response to Actual Response

The actual response of the C_1 and C_2 batch was measured and compared with the predicted response of the checkpoint batch, Table 6. An error was found to be less than 5 of all the responses. Hence, this model was valid, and an optimized batch Table 7 can be selected from the overlay plot of this model.

Kinetic Modelling and Mechanism of Drug Release of Optimized Batch

Dissolution profile of optimized batch was fitted to various models, and release data was analyzed on the basis of Korsmeyer- Peppa's equation, Zero-order, first- order, and Higuchi kinetics (Table 10).

The best fit model was selected on the basis of relatively high correlation coefficient values.

Stability Study of Optimized Batch

A stability study was done to detect the effect of temperature and humidity (40 °C, 75% RH) on floating microspheres during the storage time. Floating microspheres were evaluated periodically (0 and 1 months) for particle size, % drug entrapment, % buoyancy, and in vitro drug release (% CDR) Table 11**.**

CONCLUSION

In conclusion, the present study underlines the importance of formulation and evaluation of floating microspheres of Baclofen. Baclofen-loaded floating microspheres were successfully prepared by solvent evaporation technique with having good particle size, yield, entrapment efficiency, buoyancy, and *in-vitro* drug release. The Baclofen loaded floating microspheres sustained drug release up to 24 h; thereby, it could be capable of reducing the frequency of administration and the dose-dependent side effects with the repeated administration of conventional baclofen tablets. This type of sustained formulation will be better suitable for spasticity patients. No drug-polymer interaction was found, and formulations remained stable over a long period of time.

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REFERENCES

1. Abdul Khaleq NM, Ghareeb MM. 3D printing of baclofen gastro-floating drug delivery systems: a comparison study with in vitro and in vivo evaluation. *Res J Pharm Technol*. 2023;16(1):363-372.
2. Baviskar P, Patil P, Saudagar RB. Floating drug delivery system: a comprehensive review. *J Drug Deliv Ther*. 2019;9(3-s):839-846.
3. Dasari N, Enjamuri A, Sudhakar M. Formulation and evaluation of baclofen floating tablets. *Asian J Res Pharm Sci*. 2016;6(4):255-260.
4. Gande S, Rao YM. Sustained-release effervescent floating matrix tablets of baclofen: development, optimization and in vitro-in vivo evaluation in healthy human volunteers. *DARU J Pharm Sci*. 2011;19(3):202-209.

5. Ghule PN, Deshmukh AS, Mahajan VR. Floating drug delivery system (FDDS): an overview. *Res J Pharm Dosage Forms Technol*. 2014;6(3):174-182.
6. Gupta R, Tripathi P, Bhardwaj P, Mahor A. Recent advances in gastro retentive drug delivery systems and its application on treatment of H. pylori infections. *J Anal Pharm Res*. 2018;7(4):404-410.
7. Ibrahim M, Sarhan HA, Naguib YW, Abdelkader H. Design, characterization and in vivo evaluation of modified release baclofen floating coated beads. *Int J Pharm*. 2020;582:119344.
8. Jagtap YM, Bhujbal RK, Ranade AN, Ranpise NS. Effect of various polymers concentrations on physico-chemical properties of floating microspheres. *Indian J Pharm Sci*. 2012;74(6):512-520.
9. Joselin J, Daisy PA, Boby JG, Praveenraj R, Thomas N, Carla B. Formulation and evaluation of floating microspheres of pantoprazole sodium. *Int J Pharm Pharm Res*. 2015;4(4):136-147.
10. Juthi AZ, Bithi TZ. Gastroretentive drug delivery technologies: review. *World J Pharm Med Res*. 2018;4(2):11-15.
11. Kandukoori NR, Shanthi MS, Sushma J, Ramya C, Swapna M, Madhu G, et al. A review on floating drug delivery system. *World J Pharm Res*. 2017;6(5):553-568.
12. Kanteepan P, Bhikshapathi DVRN. Formulation development and evaluation of pirenzepine floating microspheres. *Int J Pharm Anal Res*. 2018;7(1):64-74.
13. Keservani R, Gautam S. Formulation and evaluation of baclofen liposome vesicles using lecithin. *Ars Pharm*. 2020;61(3):175-180.
14. Khairnar G, Naik J, Mokale V. A statistical study on the development of micro particulate sustained drug delivery system for Losartan potassium by 3^2 factorial design approach. *Bull Fac Pharm Cairo Univ*. 2017;55:9-29.
15. Khan R, Arora R, Ojha A, Chopra H, Upadhayaya K. Formulation and evaluation of floating microspheres of levofloxacin. *Int Res J Pharm*. 2018;9(7):186-191.
16. Kumar KR, Bhikshapathi DVRN, Haarika B. Design & in-vitro evaluation of floating microspheres using misoprostol. *Int J Pharm Anal Res*. 2017;6(1):108-117.
17. Kumar P, Kumar K, Joshi A, Rajput V. Development and evaluation of floating beads of baclofen as a gastroretentive dosage form. *Int J Indig Herbs Drugs*. 2023;:33-39.
18. Meghana KJ, Ashok KP, Suresh VK, Manjunath K. Formulation and in-vitro evaluation of floating microspheres of anti-diabetic drug. *Int J Pharm Res Health Sci*. 2019;7(3):3007-3012.
19. Mishra A, Rathore S, Marothia D, Chauhan CS. Formulation and evaluation of floating microspheres of an antidiabetic agent. *Int J Drug Dev Res*. 2018;10(2):7-11.
20. Nath B, Nath KL, Kumar P. Preparation and in vitro dissolution profile of Zidovudine loaded microspheres made of Eudragit RS 100, RL 100 and their combinations. *Acta Pol Pharm*. 2011;68(3):409-415.
21. Patel B, Kushwaha RS, Jain S. Formulation, development and evaluation of floating microsphere of losartan potassium using natural polymer. *J Drug Deliv Ther*. 2019;9(3-s):223-228.
22. Patil P, Singh S, Sarvanan J. Preparation and evaluation of microspheres of flurbiprofen. *Int J Pharm Sci Res*. 2018;9(12):5388-5393.
23. Purohit K, Garud N. Formulation and evaluation of floating microspheres of losartan potassium using sodium alginate and HPMC by solvent evaporation method. *J Drug Deliv Ther*. 2019;9(1-s):60-66.
24. Sagar B, Singh SK, Jalwal P. Formulation and evaluation of gastro-retentive floating microspheres bearing metformin HCl for treatment of diabetes mellitus. *Pharma Innov J*. 2017;6(10):173-180.
25. Saroja SP, Sudheer P. Formulation and evaluation of aceclofenac mucoadhesive microspheres for oral controlled drug delivery. *Asian J Pharm Clin Res*. 2019;12(9):184-190.
26. Singh V, Chaudhary A. Preparation of Eudragit E100 microspheres by modified solvent evaporation method. *Acta Pol Pharm*. 2011;68(6):975-980.
27. Sowmya B, Arvapalli S, Gupta AVSSS. A review on gastroretentive drug delivery system. *World J Pharm Life Sci*. 2019;5(4):101-110.
28. Subbarao K, Suresh G. Development and evaluation of sustained release floating microspheres containing Ropinirole HCl. *Int J Pharm Sci Drug Res*. 2018;10(3):158-164.
29. Sundar VD, Divya P, Suneendra G, Dhanaraju MD. Design development and evaluation of gastro retentive floating microspheres of atazanavir sulfate. *Int J Pharm Sci Res*. 2018;9(11):4642-4650.
30. Thakar K, Joshi G, Sawant KK. Bioavailability enhancement of baclofen by gastroretentive floating formulation: statistical optimization, in vitro and in vivo pharmacokinetic studies. *Drug Dev Ind Pharm*. 2013;39(6):880-888.
31. Wavhule P, Devarajan PV. Development and optimization of microballoons assisted floating tablets of Baclofen. *AAPS PharmSciTech*. 2021;22:1-15.

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