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FORMULATION AND EVALUATION OF FLOATING MICROSPHERES OF BACLOFEN

Hinal Prajapati [*1], Keyur Patel [2] and Arun Kumar Gupta [1]

Chameli Devi Institute of Pharmacy [1], Indore - 452020, Madhya Pradesh, India.
Kalol Institute of Pharmacy [2], Kalol, Gandhinagar - 382721, Gujarat, India.

Keywords:

Baclofen, Floating Microspheres, Eudragit RL100, Eudragit RS100, Sustained drug delivery

Correspondence to Author:
Hinal Prajapati

Chameli Devi Institute of Pharmacy, Village Umrikheda, Khandwa Road, Indore - 452020, Madhya Pradesh, India.

E-mail: hinaldcruz@gmail.com

ABSTRACT: The present study was aimed to formulate and evaluate floating microspheres of Baclofen. The research work's objective was to retain Baclofen in the stomach for a prolonged period of time, which has absorption window in the upper gastrointestinal tract. The microspheres were prepared by solvent evaporation technique. A 3^2 full factorial was applied to investigate the combined effect of the two independent variables, *i.e.*, the concentration of Eudragit RL100 (X1) and concentration of Eudragit RS 100 (X2) on the dependent variables particle size (Y_1), percentage drug entrapment efficiency (Y_2), percentage buoyancy (Y3), *in-vitro* drug release at 1 h (Y4), *in-vitro* drug release at 6 h (Y_5). Results of the multiple regression analysis revealed that *in-vitro* drug release decreased and particle size, percentage drug entrapment efficiency, percentage buoyancy was increased with increasing the concentration of Eudragit RL100 and Eudragit RS100. The optimized formulation has a particle size of 115.96 µm, percentage drug entrapment of 90.06%, and buoyancy of 90.76%. *In-vitro* drug release of Baclofen floating microspheres showed a sustained release up to 24 h. The floating microspheres were free-flowing, porous, and almost spherical in shape. The *in-vitro* drug release kinetics studies revealed that the Higuchi model was followed by the formulation and drug release by fickian diffusion mechanism.

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 [1].

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Gastro retentive delivery systems are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal (GI) tract. Gastro retentive delivery system can be classified as follows.

- Bioadhesive Drug Delivery System
- Expandable Drug Delivery System
- Floating Drug Delivery System and
- 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 [3].

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. During the system hangover the gastric contents, the drug is released sustain with desired rate, which results in elevated gastric retention time and minimizes fluctuation also [4]. 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 [5].

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. 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.[6]These microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers, ideally having a size less than 200 micrometre.

Baclofen is a gamma-aminobutyric acid (GABA) agonist used as a skeletal muscle relaxant used for the relief of painful and uncomfortable muscle spasms caused by a variety of conditions. 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% to 85% and is therefore rapidly absorbed through the gastrointestinal tract following oral administration. Peak plasma concentrations are generally observed 2 to 3 hours 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 is ~2.5 to 4 hrs in 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 [7, 8]. In the present investigation efforts were made to formulate floating microspheres of Baclofen to improve the absorption 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.

MATERIALS AND METHODS:

Materials Used: Baclofen (Astron PVT. LTD. Ahmedabad), Eudragit RS 100 and Eudragit RL 100 (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).

Method:

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 [9]. 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.

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 [10].

TABLE 1: COMPOSITION OF FORMULATION BATCHES

Ingredients	Baclofen	Eudragit RL100	Eudragit RS100	HPMC K4M	Mg stearate	Solvent (Acetone) (ml)
Batches	Quantity taken (mg)					
E1	100	100	100	50	5	10
E2	100	200	100	50	5	10
E3	100	300	100	50	5	10
E4	100	100	200	50	5	10
E5	100	200	200	50	5	10
E6	100	300	200	50	5	10
E7	100	100	300	50	5	10
E8	100	200	300	50	5	10
E9	100	300	300	50	5	10

HPMC K4M: Hydroxymethyl Ethylcellulose

Evaluation of Baclofen Floating Microspheres:

Particle Size Analysis: Particle size analysis of drug-loaded Eudragit microspheres was performed by optical microscopy using a compound micro-scope. 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 [11].

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 [12]. Results of percentage Yield was calculated using following equation.

% Yield = Practical yield / Theoretical yield × 100

Percentage Drug Entrapment Efficiency: To determine the incorporation efficiency, 25 mg microspheres were crushed and dispersed in 100 ml 0.1 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 analyzed Spectrophotometrically at 226.5 nm. The percentage drug entrapment efficiency was calculated using the following equation [13].

% DEE = Actual drug content / Theoretical drug content × 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 100 rpm for 8 h. After 8 h, 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 [14]. The percentage buoyancy was calculated from the weight of floating particles to the sum of floating and sinking particles.

% Buoyancy = Initial weight of microspheres / Weight of floating microspheres × 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 900 ml of 0.1 N Hydrochloric acid (HCl) (PH 1.2) maintained at 37 ± 0.20 C at a rotation speed of 100 rpm. The amount of the drug was determined first-derivative (D1) Spectrophotometrically at 226.5 nm adopting the peak height method [16].

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 [17]. 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.

Statistical Analysis: A statistical model incorporating interactive and polynomial terms was utilized to evaluate the responses. Mathematical modelling, evaluation of the ability to fit to the

model and response surface modelling were performed by employing Design-Expert software [18].

$$Yi = b_0 + b_1 \times_1 + b_2 \times_2 + b_{12} \times_1 \times_2 + b_{11} \times_{12} + b_{22} \times_{22}$$

Where Y_i is the dependent variable, b_0 is the intercept (arithmetic mean response of 9 runs), b_1 to b_{22} are regression coefficients, X_1, X_2, are the independent variables. Here the dependent variables are particle size (Y_1), % yield (Y_2), %drug entrapment efficiency (Y_3), %buoyancy (Y_4), in-vitro drug release at 1 hour (Y_5), *in-vitro* drug release at 6 hour (Y_6) and independent variables are concentration of Eudragit RL100 (X_1) and concentration of Eudragit RS100 (X_2)

Stability Study: Stability study was carried out on formulated microspheres after storing at 40 °C and 75% relative humidity for one month according to ICH guidelines [19].

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 incompatibility between baclofen and polymers. It is shown in following **Fig. 1, 2** and **3**.

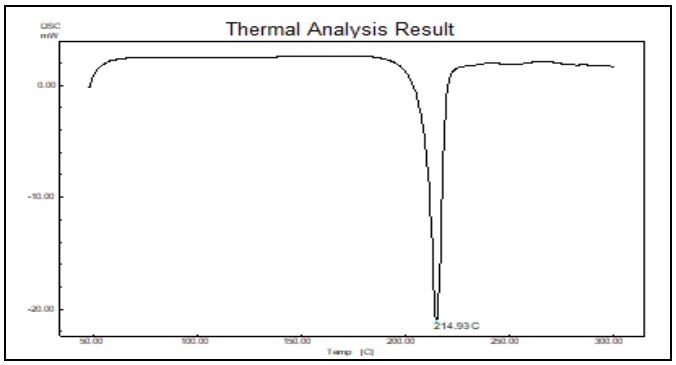


FIG. 1: DIFFERENTIAL SCANNING CALORIMETRY SPECTRA OF BACLOFEN

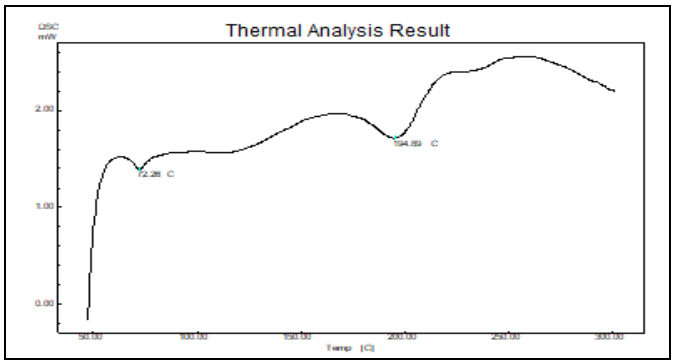


FIG. 2: DIFFERENTIAL SCANNING CALORIMETRY SPECTRA OF POLYMER MIXTURE (EUDRAGITRL100+EUDRAGIT RS100)

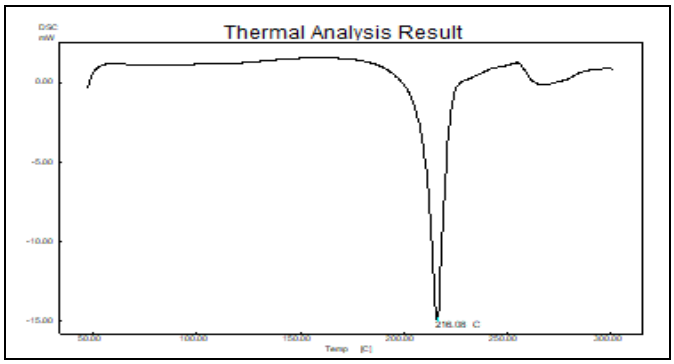


FIG. 3: DIFFERENTIAL SCANNING CALORIMETRY SPECTRA OF BACLOFEN AND POLYMER MIXTURE EUDRAGIT RL100+EUDRAGIT RS100)

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 **Fig. 4**.

FIG. 4: BACLOFEN FLOATING MICROSPHERES (MICROSPHERES FLOATING OVER THE SURFACE IN 0.1N HCl)

TABLE 2: PARTICLE SIZE, % YIELD, % DRUG ENTRAPMENT EFFICIENCY, % BUOYANCY

Batch	Particle size (µm)	Percentage yield (%)	DEE (%)	Percentage Buoyancy (%)
E1	68.20±2.32	52.12±1.96	71.25±1.2	80.60±1.2
E2	81.30±2.23	57.23±2.24	75.12±2.3	83.66±1.7
E3	95.41±1.52	65.06±2.45	83.32±3.2	85.12±1.2
E4	85.12±1.61	59.02±2.47	80.21±1.5	85.21±1.8
E5	98.15±1.29	67.51±2.21	78.12±2.5	82.16±1.5
E6	105.13±2.18	74.22±2.52	85.28±3.5	88.01±2.1
E7	100.01±1.56	67.89±2.50	87.41±2.3	87.50±1.6
E8	112.03±1.94	77.91±2.55	89.42±2.8	90.12±1.9
E9	119.05±2.45	85.11±3.16	92.06±3.8	92.21±2.5

Dee: drug entrapment efficiency

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 E1 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.[10]

%Yield: From **Table 2**, it shows that as drug: polymer ratio was increased; the %yield was increased [10].

Percentage Drug Entrapment Efficiency: The drug entrapment efficiency **Table 2** was higher in E9 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 [20].

Percentage Buoyancy: The floating ability **Table 2** of E1 formulation was lowest, amounting to 80.6% and it was highest for E9 formulation (92.21 %). The formulations prepared from more ratio of Eudragit RS100+ Eudragit RL100 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 may be ascribed to their small size. Here Eudragit RS100 has better floating ability as compared to Eudragit RL100 because of its low bulk density and low permeability than 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:**

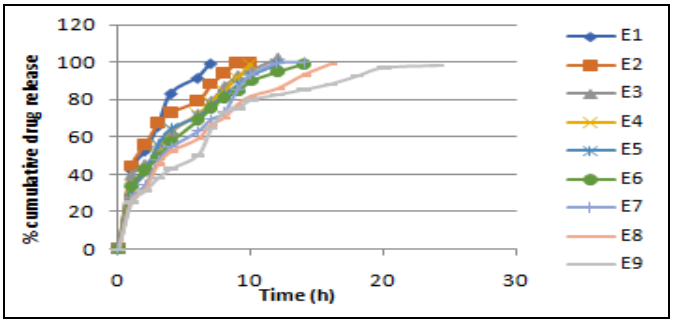


FIG. 5: *IN-VITRO* DRUG RELEASE PROFILE

TABLE 3: *IN-VITRO* DRUG RELEASE STUDY

TIME (hour)	Batch code								
	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± 1.82	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	45.35± 1.65	38.25± 1.90
4	83.33±	79.29±	63.26±	64.23±	64.56±	57.63±	54.82±	52.33±	43.21±

	1.17	1.77	1.45	1.19	1.16	1.95	1.04	1.92	1.19
6	91.57±	89.49±	74.36±	72.15±	71.1±	69.12 ±	63.15±	58.91±	50.35±
	1.84	1.01	1.78	1.69	1.85	1.83	1.14	1.95	1.05
7	99.42±	96.20±	79.56±	79.20±	77.27±	75.69±	69.56±	66.53±	64.56±
	1.55	1.01	1.59	1.95	1.06	1.83	1.44	1.56	1.13
8		100.01	87.26±	85.5±	82.26±	81.23±	73.21±	70.1±	73.45±
		±1.09	1.14	1.29	1.99	1.05	1.02	1.98	1.10
9			93.5±	92.21±	88.15±	84.56±	85.56±	77.21±	75.21±
			1.89	1.94	1.69	1.45	1.45	1.02	1.12
10			96.33±	99.13±	93.6±	90.11±	93.42±	81.62±	79.85±
			1.17	1.24	1.62	1.78	1.64	1.16	1.92
12			102.9±		99.08±	95.1±	99.56±	85.62±	82.56±
			1.26		1.09	1.32	1.94	1.70	1.14
14						99.32±	100.03	92.93±	85.33±
						1.28	±1.39	1.97	1.84
16								98.63±	88.27±
								1.26	1.56
18									92.56±
									1.02
20									97.02±
									1.59
24									98.12±
									1.02

*Values are expressed as mean ± SD (n=3)

From the **Fig. 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 microspheres 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 [21].

Residual Solvent Analysis:

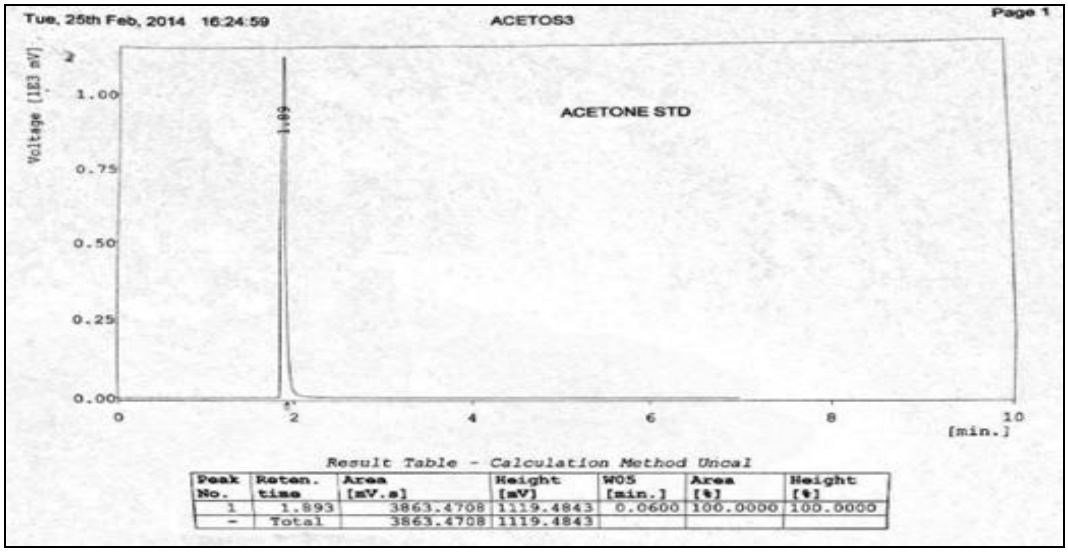
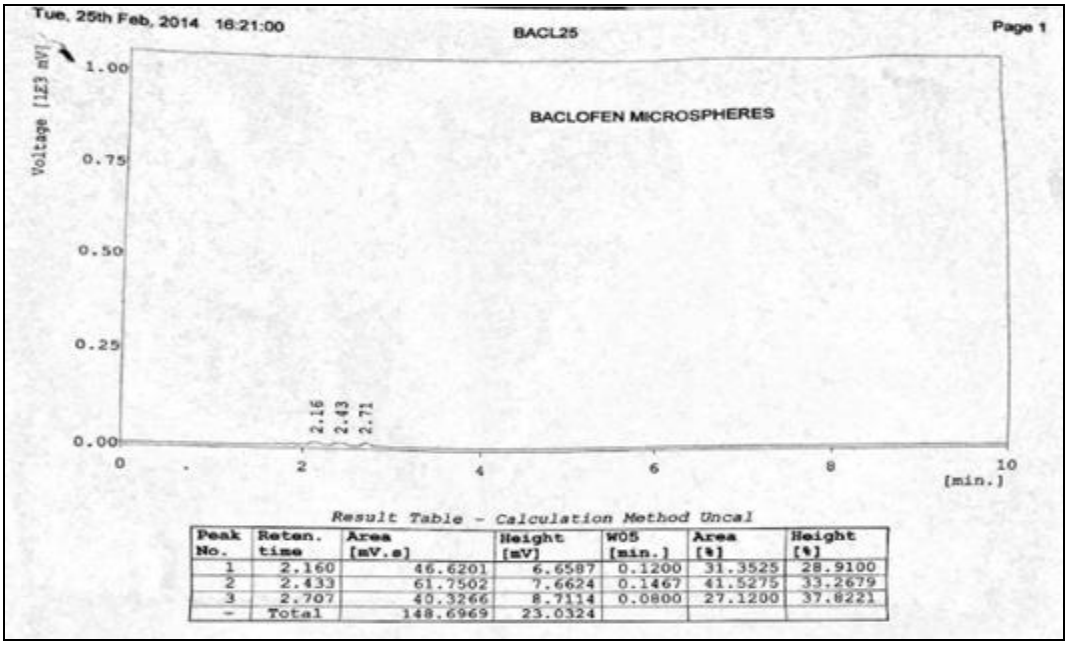


FIG. 6: GAS CHROMATOGRAPHY OF ACETONE



Result Table - Calculation Method Uncal

Peak No.	Reten. time	Area [mV.s]	Height [mV]	W05 [min.]	Area [%]	Height [%]
1	2.160	46.6201	6.6587	0.1200	31.3525	28.9100
2	2.433	61.7502	7.6624	0.1467	41.5275	33.2679
3	2.707	40.3266	8.7114	0.0800	27.1200	37.8221
-	Total	148.6969	23.0324			

FIG. 7: GAS CHROMATOGRAPHY OF FLOATINGMICROSPHERES OF BACLOFEN

From the residual solvent analysis report it was concluded that acetone is absent in prepared floating microspheres as peak of acetone is not visible in GC of microspheres as shown in **Fig. 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 **Fig. 8**.[10, 20]

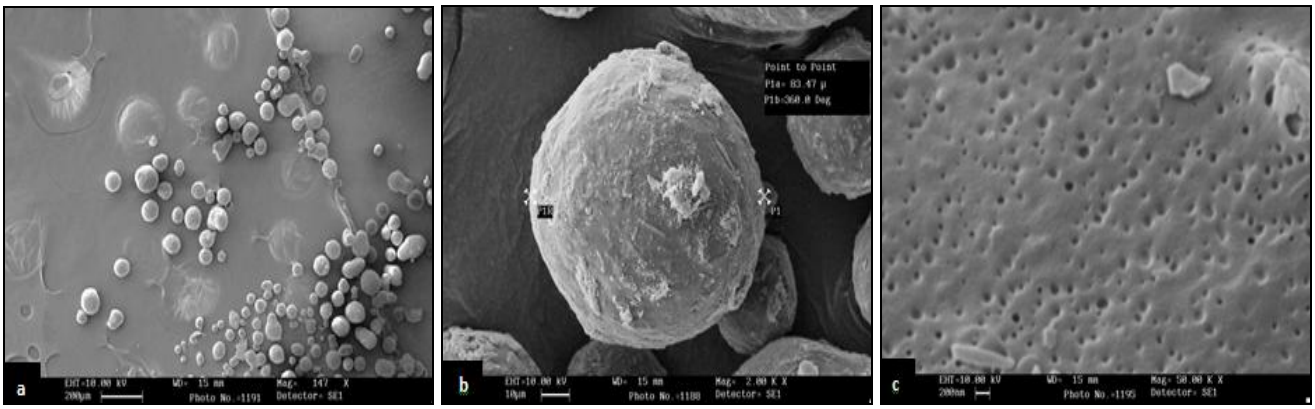


FIG. 8: SCANNING ELECTRON MICROSCOPY IMAGES: A) SPHERICAL FLOATING MICROSPHERES OF BACLOFEN B) ZOOMED VIEW OF SPHERICAL FLOATING MICROSPHERE OF BACLOFEN C) POROUS SURFACE OF FLOATING MICROSPHERE OF BACLOFEN

Statistical Analysis: Average particle size was varying from 68. 2-119.05 µm **Table 2** and showed correlation 0.9955 **Table 4**. The p values lower than 0.05 so ×1 and × 2 have a significant effect. × 1 (Eudrgit RL100) and × 2 (Eudragit RS100) both had a positive effect. It indicates that as the drug to polymer ratio increases the particle size increases. So, both × 1 and × 2 significantly affect the particle size. Here × 2 has more significant effect as compared to × 1.

Percentage drug entrapment efficiency was varying from 71.25 - 92.06% **Table 2** and showed correlation 0.9705 **Table 4**. The p values lower than 0.05so X_1 and X_2 have a significant effect. X_1 (Eudrgit 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_2 significantly 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 **Table 4**. The p values lower than 0.05so X_1 and X_2 have significant effect. X_1 (Eudrgit 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_1andX_2 significant affect the buoyancy. Here X_2 has more significant effect as compared toX_1.

In-vitro drug release at 1 h was varying from 42.32-25.35% as shown in **Table 3** of E1 to E9 batch and showed correlation 0.9086 in **Table 4**. The p values lower than 0.05 so X_1 and X_2 have significant effect. X_1 (Eudrgit RL100) 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, both X_1andX_2 significant affect the drug release. Here X_2 has 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 drug release at 6 h was varying from 91.57-50.35% as shown in **Table 3** of E1 to E9 batch and showed correlation 0.9271 in **Table 4**. The p values lower than 0.05 so they are significant effect. X_1 (Eudrgit 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, both X_1 and X_2 significant affect the dissolution. Here X_2 has 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.

TABLE 4: REGRESSION ANALYSIS FOR EFFECT OF X1(EUDRAGIT RL100) & X2(EUDRAGIT RS100)

Parameter	R Square	Adjusted R square	Observations	Source	Sum of squares	P-value
Average particle size (Y_1)	0.9955	0.9955	0.9955	Model	2003.21	<0.0001
				X_1	731.51	<0.0001
				X_2	1238.12	<0.0001
				X_{12}	16.65	0.0089
				X_1^2	11.58	0.0202
				X_2^2	0.71	0.4825
			Full model equation: $\mathbf{Y_1 = +97.87+11.04X_1+14.37X_2-2.04X_1X_2-2.05X_1^2-0.51X_2^2}$			
			Reduced model equation: $\mathbf{Y_1=+97.87+11.04X_1+14.37X_2-2.04X_1X_2-2.05X_1^2}$			
% drug entrapment efficiency (Y_2)	0.9705	0.9705	0.9705	Model	416.88	<0.0001
				X_1	79.13	0.0003
				X_2	256.11	<0.0001
				X_{12}	13.76	0.0281
				X_1^2	24.71	0.0077
				X_2^2	17.48	0.0171
			Full model equation: $\mathbf{Y_2 = +78.59+3.63X_1+6.53X_2-1.85X_1X_2+2.99X_1^2+2.52X_2^2}$			
			Reduced model equation: $\mathbf{Y_2= +78.59+3.63X_1+6.53X_2-1.85X_1X_2+2.99X_1^2+2.52X_2^2}$			
% buoyancy (Y_3)	0.8817	0.8817	0.8817	Model	136.50	0.0038
				X_1	24.12	0.0189
				X_2	69.70	0.0013
				X_{12}	9.025E-003	0.9548
				X_1^2	11.55	0.0738
				X_2^2	14.93	0.0483
			Full model equation: $\mathbf{Y_3 = +82.25+2.00X_1+3.41X_2+0.048X_1X_2+2.04X_1^2+2.32X_2^2}$			
			Reduced model equation: $\mathbf{Y_3=+82.25+2.00X_1+3.41X_2+2.32X_2^2}$			
%cumulative drug release at Q_1 (*in-vitro* drug release at 1h) (Y_4)	0.9086	0.9086	0.9086	Model	374.08	<0.0001
				X_1	1.83	0.5020
				X_2	372.25	<0.0001
			Full model equation: $\mathbf{Y_4= +32.85-0.55X_1-7.88X_2}$			
			Reduced model equation: $\mathbf{Y_4= +32.85-7.88X_2}$			
%cumulative drug release at Q_6 (*in-vitro* drug release at 6h) (Y_5)	0.9271	0.9271	0.9271	Model	1046.33	<0.0001
				X_1	205.22	0.0005
				X_2	841.11	<0.0001
			Full model equation $\mathbf{Y_5= +70.21-5.85X_1-11.84X_2}$			
			Reduced model equation $\mathbf{Y_5= +70.21-5.85X_1-11.84X_2}$			

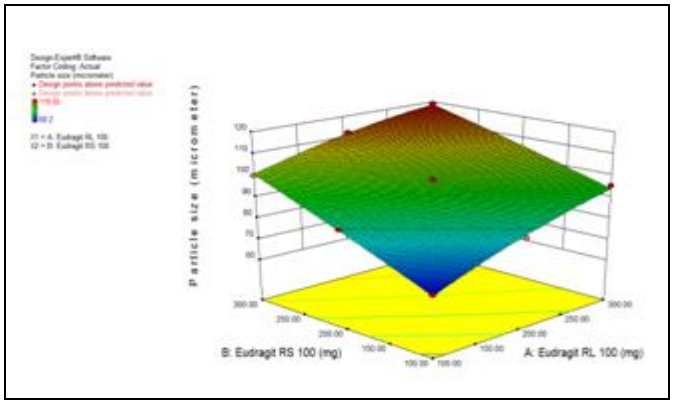


FIG. 9: 3D RESPONSE SURFACE GRAPH FOR PARTICLE SIZE

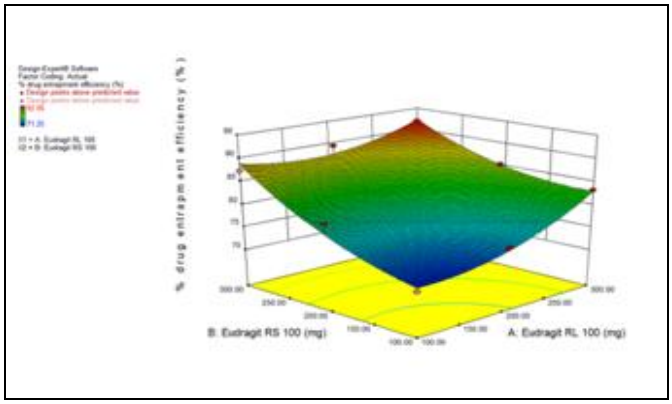


FIG 10: 3D RESPONSE SURFACE GRAPH FOR DRUG ENTRAPMENT

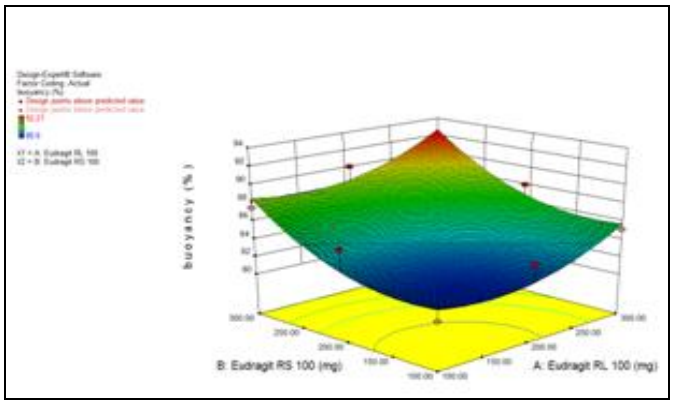


FIG. 11: 3D RESPONSE SURFACE GRAPH FOR %BUOYANCY

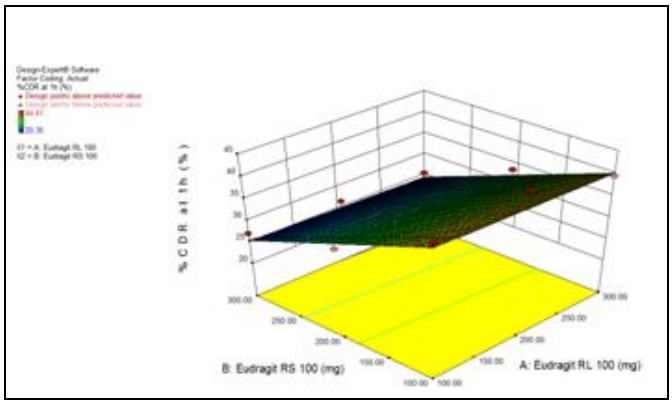


FIG. 12: 3D RESPONSE SURFACE GRAPH FOR %CUMULATIVE DRUG RELEASE (CDR) AT 1h

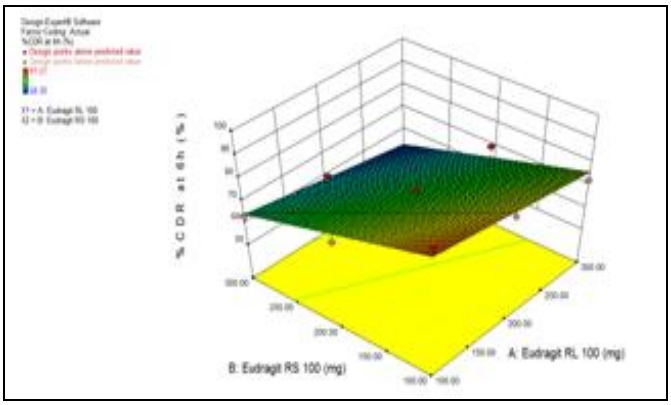


FIG. 13: 3D SURFACE RESPONSE GRAPH FOR %CUMULATIVE DRUG RELEASE (CDR) AT 6 h

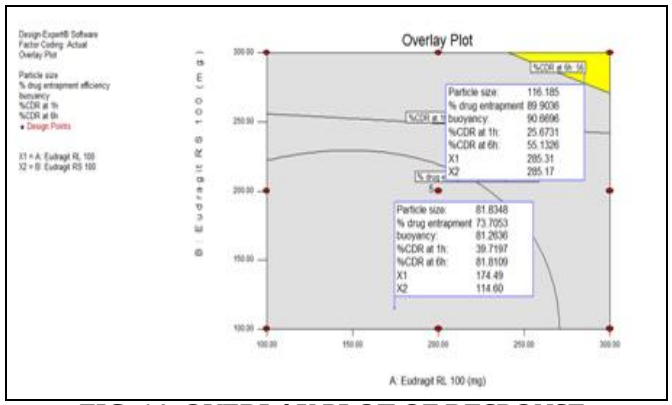


FIG. 14: OVERLAY PLOT OF RESPONSE VARIABLE

Preparation of Check Point Batch from Overlay Plot: Checkpoint batch C_1 and C_2 were 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_2 were selected for the verification of the model.

Following **Table 5** is showing the formula for C_1 and C_2 batches:

TABLE 5: FORMULATION OF CHECKPOINT BATCH

Ingredients	Batch C1	Batch C2
	Quantity taken (mg)	
Baclofen	100	100
Eudragit RL100	285.31	174.49
Eudragit RS100	285.17	114.60
HPMC K4M	50	50
Mg-stearate	5	5
Acetone	10ml	10ml

HPMC K4m: Hydroxy Propyl Methyl Cellulose

Verification of Model by Comparing Predicted Response to Actual Response: Table 6 showing the comparison of the predicted and actual response of checkpoint batches.

TABLE 6: PREDICTED RESPONSE AND ACTUAL RESPONSE OF CHECKPOINT BATCH

Evaluation Parameters	Batch C1			Batch C2		
	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
% CDR at Q_1 (h)	25.67	26.96	4.78	39.72	41.26	3.73
% CDR at Q_6(h)	55.13	53.12	3.78	81.81	84.5	3.18

CDR: Cumulative Drug Release

The actual response of the C1 and C2 batch was measured and compared with the predicted response of the checkpoint batch. 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.

TABLE 7: OPTIMIZED BATCH

Ingredients	Quantity(mg)
Baclofen	100
Eudragit RL100	297.56
Eudragit RS100	278.78
HPMC K4M	50
Magnesium stearate	5
Acetone	10ml

HPMC K4M: Hydroxy Propyl Methyl Cellulose

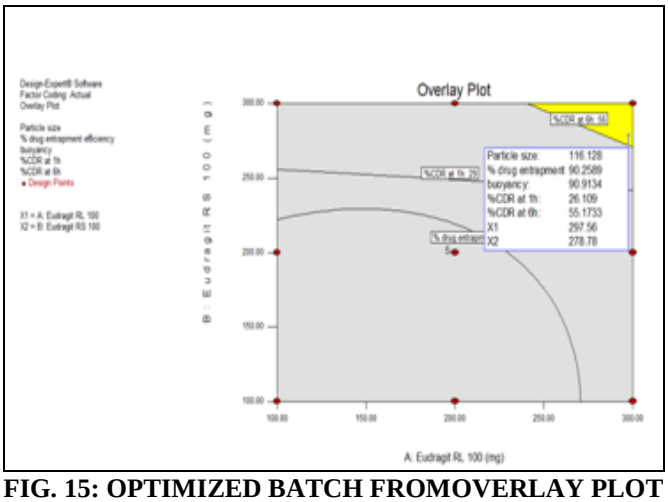


FIG. 15: OPTIMIZED BATCH FROMOVERLAY PLOT

TABLE 8: DISSOLUTION PROFILE OF OPTIMIZED BATCH

Time (hr)	% CDR
1	25.5
2	32.23
3	38.59
4	42.26
6	56.26
7	64.35
8	72.21
9	77.27
10	81.15
12	85.91
14	91.1
16	96.01
18	98.23
20	100.05
24	100.15

%CDR: Cumulative Drug Release

Evaluation of Optimized Batch:

TABLE 9: PARTICLE SIZE, % DRUG ENTRAPMENT AND % BUOYANCY OF OPTIMIZED BATCH

Particle size	115.96 µm
% Drug entrapment	90.06%
% Buoyancy	90.76%

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 [15] **Table 10**.

TABLE10: KINETIC MODEL FOR DRUG RELEASE OF OPTIMIZED BATCH

Batch	Zero-order	First-order	Higuchi	Korsmeyer-Peppa's model	
	R^2	R^2	R^2	R^2	N
Optimized batch	0.8783	0.7715	0.9793	0.9785	0.4857

The best fit model was selected on the basis of relatively high correlation coefficient values. Thus, it may be concluded that from the above data Higuchi model was followed by formulation. The drug release path was fickian diffusion.

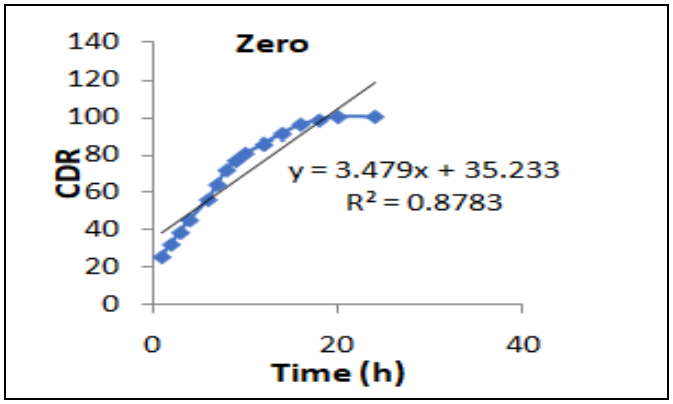


FIG. 16: ZERO ORDER PLOT OF OPTIMIZED BATCHFIG

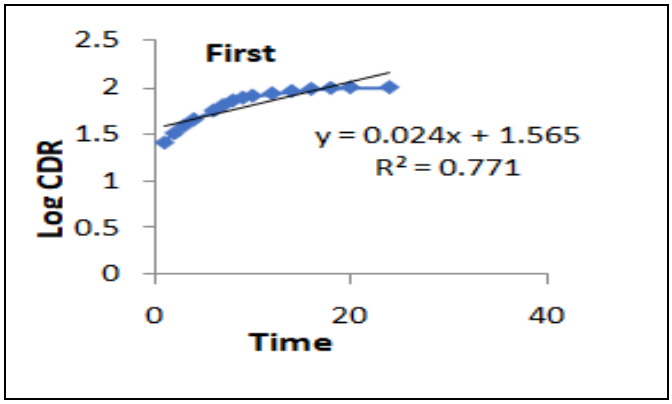


FIG. 17: FIRST ORDER PLOT OF OPTIMIZED BATCH

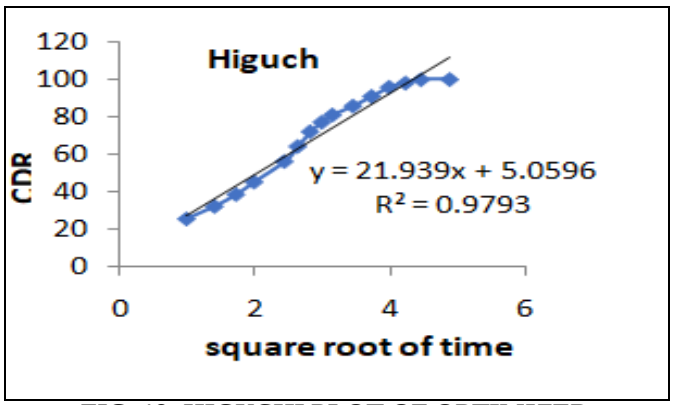


FIG. 18: HIGUCHI PLOT OF OPTIMIZED BATCHFIG

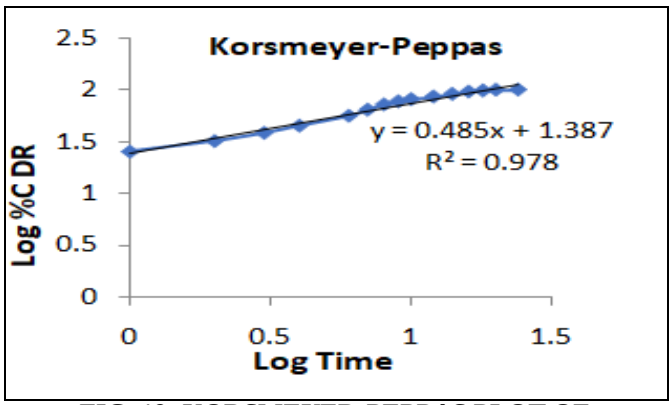


FIG. 19: KORSMEYER-PEPPAS PLOT OF OPTIMIZED BATCH

Stability Study of Optimized Batch: A stability study was done to e eth the effect of temperature and humidity (400 °C, 75% RH) on floating microspheres during the storage time. Floating microspheres were evaluated periodically (0 and1months) for particle size, % drug entrapment, % buoyancy, and in vitro drug release (% CDR) **Table 11**.

TABLE 11: EVALUATION OF OPTIMIZED BATCH FOR STABILITY

Parameter	Time	Initial	After Stability
Particle size	1 month	115.96 µm	114.56 µm
% Drug entrapment	1 month	90.06%	90.01%
% Buoyancy	1 month	90.76%	90.56%
%CDR at Q_1	1 month	25.5%	26.01%
%CDR at Q_6	1 month	56.26%	56.01%

%CDR: cumulative drug release

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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