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DEVELOPMENT AND EVALUATION OF FLOATING BILAYER TABLET OF BACLOFEN

Ritul B. Gabani*, Dr. H. M. Tank and Nikunj Gabani

Department of Pharmaceutics, Manavar College of Pharmacy, Dumiyani, Rajkot, Gujarat.

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***Corresponding Author**
Ritul B. Gabani
Department of Pharmaceutics, Manavar College of Pharmacy, Dumiyani, Rajkot, Gujarat.

ABSTRACT

The objective of this present study to develop and evaluate bilayer tablet of baclofen. Tablet comprised in two layer i.e. immediate release layer and sustain release layer and in sustain layer gas generating agent add like sodium bicarbonate and citric acid used for floating of tablet in stomach. For immediate release of drug use superdisintegrant like sodium starch glycolate, crospovidone, croscarmellose sodium and for sustain release of drug use hydrophilic natural polymer like guar gum, pectin and xanthan gum. First sustain layer was compressed with low hardness and then final immediate layer was compressed by direct compression method. In Preformulation study FTIR, calibration curve, melting point is done. Results in xanthan gum shows better sustain release up to 24 hours and release maximum drug like 99.10 % than the guar gum (95.30) and pectin (93.50). And in immediate release layer crospovidone release the drug in 15.10 min where SSG and croscarmellose sodium take more time for drug release. 3^2 factorial design applied and also done dissolution study of all batch and then batch F5 was optimized from result.

KEYWORDS: Tablet, Baclofen, Xanthan Gum, Crospovidone, Dissolution Study.

INTRODUCTION

Rationale

- Short half-life of baclofen suggest that it is a rationale drug for sustain release drug delivery system.
- Bioavailability of baclofen administered with tablet formulation relative to intravenous infusion is about 60%.
- Baclofen is stable and well absorbed in pH range 1 – 4.

- Currently, the most commonly used dosage form of baclofen is immediate release tablet formulation with dose range 5 – 20mg and generally it is prescribed in T.I.D so, fluctuation and patient noncompliance is also suggest that it is rationale drug for this type of formulation. Patient noncompliance because of side effect of baclofen like drowsiness, dizziness.
- Baclofen's high solubility, enzymatic and chemical stability and absorption profile in acidic pH suggest make gastro retentive dosage form.

AIM

- Development and evaluation of floating bilayer tablet of baclofen.

Objective

- The research work is give sustained release as well as immediate release of drug.
- One layer is an immediate release layer which release baclofen drug that achieve effective plasma concentration.
- And other layer is a sustained release layer which release baclofen drug over several hours with gastro retentive system.
- Formulate tablet using natural polymer and disintegrating agent to make gastro- retentive floating system.
- In – Vitro Dissolution.

EXPERIMENTAL

List of Materials

Table no. 1. List of materials used in preparation

Sr. No.	Materials	Manufacturer
1	Baclofen	Glow Derma, Mumbai
2	Crospovidone	Maruti chemical
3	Croscarmellose sodium	Sama lab.
4	Sodium starch glycolate	Rinse chemical
5	MCC	Fine chem, Mumbai
6	Xanthan Gum	National chemical
7	$NaHCO_3$	Purple remidies
8	Citric acid	Maruti chemical
9	Lactose	Fine chemical
10	Magnesium Stearate	S. D. chemical
11	Colour	S. D. chemical

List of Equipments

Table no. 2. List of equipments used in preparation

Sr. No.	Equipments	Company
1.	UV Visible Spectrophotometer	Labtronics – LT-2900
2.	FTIR Spectrometer	Simsdzu – 8400S with DRS
3.	Electronic Balance	Shimazu Corporation-BL-220H
4	Monsanto Hardness tester	Dolphin
5	Friability tester	FTA - 023
6	Vernier callipers	Systronic
6	Dissolution Apparatus	Veego
7	Tableting Machine	Rimek-Karanavati
8	Sieve shaker	Dolphin
9	Disintegration apparatus	Veego
10	Thiele tube	Piramal glass

- **Analysis of drug Description of drug**[34]

Colour, Odour and Appearance study of Baclofen sample.

Melting point of drug[34]

Melting point was find by open capillary method using thiele tube. The Thiele tube is a glass tube designed to contain heating oil and a thermometer to which a capillary tube containing the sample is attached.

Solubility Study[35]

Determination of λ max[35]

The UV spectrum was recorded in the range of 200-400 nm on UV Visible Spectrophotometer.

Standard curve of baclofen[35]

- **Priliminary trial batches: Selection of polymer**

Table no. 3. Preliminary formulation contain different polymer

Ingredient	X1(Guar gum)	X2(pectin)	X3(xanthan gum)
Baclofen	21	21	21
Polymer	60	60	60
NaHCO3	30	30	30
Citric acid	20	20	20
Lactose	38	38	38
Magnesium stearate	1	1	1
Total (mg)	195	195	195

For selection of superdisintegrant

Table no. 4. Preliminary formulation contain different superdisintegrant

Ingredient	X4 (SSG)	X5 (crospovidone)	X6 (croscarmellose sodium)
Immediate release layer			
Baclofen	5	5	5
Superdisintegrant	15	14	20
MCC	44	40	36
Mg. stearate	0.5	0.5	0.5
Colour	0.5	0.5	0.5
Total (mg)	60	60	60
Sustained release layer			
Baclofen	21	21	21
Xanthan gum	60	60	80
NaHCO3	30	30	30
Citric acid	20	20	20
Lactose	38	38	38
Mg. stearate	1	1	1
Total (mg)	195	195	195
Final total (mg)	255	255	255

- **Evaluation of preliminary trial batches: Buoyancy time**[36]

Buoyancy time is the total time for which the tablets float in dissolution medium before getting disintegrated or settling down and here 0.1 N HCL was used as a dissolution medium.

% Friability[35,36]

Friability is the measure of tablet strength. Roche type friabilator was used for testing the friability using the following procedure.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets - Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100 \ldots\ldots\ldots\ldots 1$$

Bulk density[37]

It is measured by pouring the weighed amount of powder into a measuring cylinder and then the initial volume is noted.

This initial volume is called bulk volume. It is calculated by below formula.

$$BD = m/v0 \ldots\ldots\ldots\ldots\ldots\ldots 2$$

Where,

M = mass of powder,

V_0 = bulk volume of powder

Tapped density[37]

It is measured by tapping the powder for standard time and then note volume it called tapped volume.and density calculated by below formula.

$$TD = m/vt \ldots\ldots\ldots\ldots\ldots\ldots 3$$

Where,

M = mass of powder,

Vt = tapped volume of powder

Carr's index[37]

It is calculated by the below formula and expressed as percentage (%)

$$\%CI = \text{tapped density} - \text{bulk density} / \text{tapped density} * 100 \ldots\ldots\ldots 4$$

Angle of repose[37]

Flow properties of first three batches X1, X2, X3. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The angle of repose of powder is determined by using funnel method.

$$\theta = \tan^{-1}(h/r) \ldots\ldots\ldots\ldots\ldots\ldots 5$$

Where,

θ = Angle of repose, h = Height of heap,

r = Redius of heap

Hausner's ratio[37]

It is measurement of frictional resistance of the drug. The ideal range should be 1.2-1.5 and determined by dividing tapped density to bulk density.

In vitro dissolution study[35]

In vitro dissolution study on batch X1, X2, X3 by USP dissolution apparatus II.

In vitro disintegration time[35]

The disintegration time for immediate release layer of batches X4, X5, X6 was carried out using tablet disintegration test apparatus.

The medium was maintained at a temperature 37±2 ºC and time taken for the immediate layer of tablet disintegrate completely was noted.

Application of 3^2 full factorial design

Effect of increase in concentration of hydrophilic swellable polymer (Xanthan gum) and sodium bicarbonate on floating time and percent drug release.

A 3^2 randomized full factorial design was used in development of the dosage form. In this design, 2 factors were evaluated each at 3 levels and experimental trials were performed using all possible 9 combinations.

In the present study, the amount of Xanthan gum (X1) and content of sodium bicarbonate (X2) were selected as independent variables. The total floating time (TFT) and % drug release at 24 hours (t_{24}) were selected as dependent variables.

The formulations designed according to experimental design are shown in table no. 5

Table no. 5. Experimental Design

Variable	Level		
	-1	0	1
X1 = Xanthan gum (in mg)	40	60	80
X2 = Sodium bicarbonate (in mg)	25	30	35

Formulation task

Table no. 6. Design batches formulation

Formulation No.	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredient	Formulation of Immediate release layer								
Baclofen	5	5	5	5	5	5	5	5	5
crospovidone	14	14	14	14	14	14	14	14	14
MCC	40	40	40	40	40	40	40	40	40
Mg. stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Colour	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total (mg)	60	60	60	60	60	60	60	60	60
	Formulation of sustained release layer								
Baclofen	21	21	21	21	21	21	21	21	21
Xanthan gum	40	40	40	60	60	60	80	80	80
NaHCO3	25	30	35	25	30	35	25	30	35
Citric acid	20	20	20	20	20	20	20	20	20
Lactose	88	83	78	68	63	58	48	43	38
Mg. stearate	1	1	1	1	1	1	1	1	1
Total (mg)	195	195	195	195	195	195	195	195	195
Final total (mg)	255	255	255	255	255	255	255	255	255

Preparation method

i) Preparation of Immediate Release layer

Baclofen, Crospovidone and MCC were passed from sieve # 40. Magnesium stearate was then passed through sieve # 60 and added to the above mixture and also add Colour to the above mixture.

ii) Preparation of the Sustained Release layer

Baclofen, xanthan gum and lactose were passed from sieve # 40 and mixed for 10 min. NaHCO3 and citric acid was then passed through sieve # 60 and added to the above mixture.

iii) COMPRESSION OF THE BILAYER TABLET

The bilayer tablet was compressed on a Tableting compression machine on 8 mm concave shaped punch. The hardness was maintained at 7-8 kg/cm^2.

The final compression was done only after both the powders occupied the die cavity one on top of the other. Both the layers were identified on the basis of color.

Evaluation of Experimental design batches

i. Tablet thickness and Diameter

ii. Tablet hardness

iii. % Friability

iv. Weight variation

Twenty tablets were selected at random and the average weight was calculated. Weight variation was calculated and was compared with I. P. standards.

v. Uniformity of content

Twenty tablets were crushed and powder equivalent to weight of tablet dissolved in 0.1 N HCl. Then suitable dilutions were made and absorbance at 266 nm wavelength was taken by using a UV visible spectrophotometer.

Drug content was calculated by using absorbance at wavelength 266 nm. The results obtained were compared with I. P. standards.

vi. Buoyancy lag time vii. Buoyancy time

vii. *In vitro* dissolution studies

RESULTS AND DISCUSSION

Description of drug

The sample of baclofen was found to be a light white crystalline powder.

Melting point

The melting point of baclofen was found to be in the range of 207-209°C.

Determination of solubility

The solubility of baclofen as observed in 0.1 N HCl and buffers of various pH values 4.5 and 6.8 are presented in below Table.

Baclofen exhibited a pH dependent solubility phenomenon in various aqueous buffers. Very high solubility of baclofen was observed in acidic pH values, while the solubility dropped rapidly as the pH increased.

Table no. 7. Solubility data

Solvent	Solubility (mg/ml)
0.1 N HCL	20
pH 1.2	15
pH 4.5	8
pH 6.8	5

Determination of λmax

Wavelength of maximum absorbance (λ_{max}) of baclofen was found to be 220 nm in 0.1 N HCl.

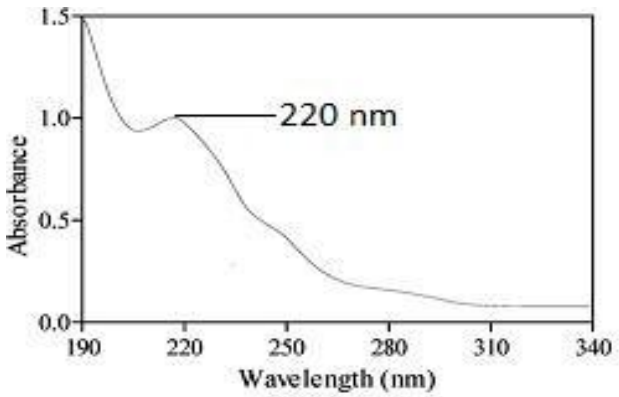

Figure: 1. UV spectrum of Baclofen

Calibration curve for baclofen

The calibration curve for baclofen in 0.1 N HCl is shown in Figure. The graph of absorbance vs. concentration for baclofen was found to be linear in the concentration range of 4-24 µg/ml at 220 nm. The $r^2$of the calibration curve was found to be 0.9998.

Table no. 8. Calibration data of Baclofen

Sr. no.	Concentration (µg/ml)	Absorbance at 220 nm*(n=3, Mean ± SD)
1	0	0.000 ± 0.00
2	4	0.1355 ± 0.07
3	8	0.2615 ± 0.20
4	12	0.3935 ± 0.03
5	16	0.5145 ± 0.45
6	20	0.6393 ± 0.10
7	24	0.7693 ± 0.71

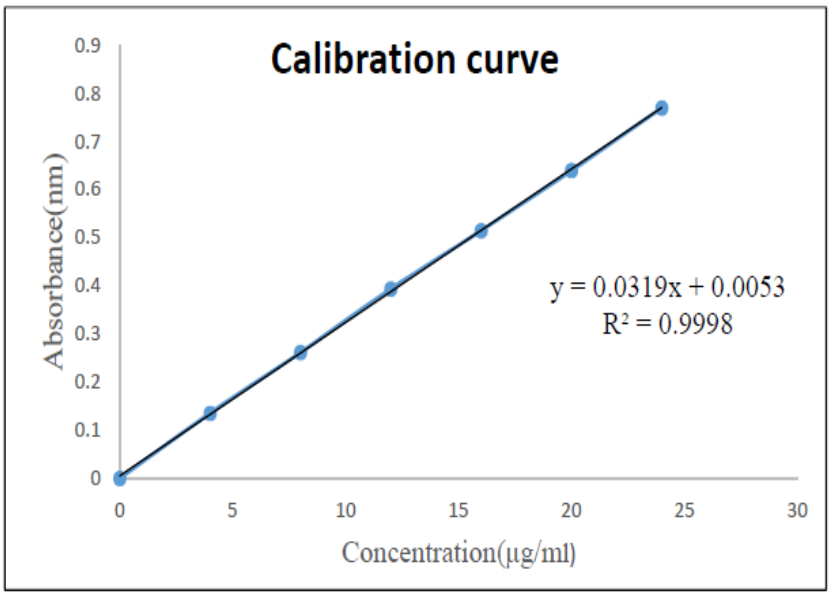

Figure: 2. Calibration curve of Baclofen

Evaluation of Preliminary trial batches

Buoyancy time and % Friability

Table no. 9. Data of TFT and % friability

Formulation	Total floating time (hours)	% Friability
X1	20	0.82 ± 0.08
X2	18	0.88 ± 0.05
X3	24	0.71 ± 0.03

Pre compression parameter

Table no. 10. Obtained data of Bulk and Tapped density and Angle of repose

Formulation	Bulk density	Tapped density	Carr's index	Hausner ratio	Angle of repose
X1	0.301	0.350	14.1	1.16	29.5º
X2	0.304	0.361	15.5	1.18	31.5º
X3	0.306	0.341	11.7	1.11	25.7º

In vitro Dissolution study of batch X1,X2,X3

Table no. 11. % CDR data of preliminary batches X1, X2 and X3

Time (min)	% Cumulative drug release		
	X1	X2	X3
0	0	0	0
30	30.55	22.25	17.2
60	38.45	28.45	22.1
120	45.75	40.75	29.9
240	62.2	49.5	45.5
480	80.95	78.4	67.9
960	95.3	87.3	85.4
1440		93.95	99.1

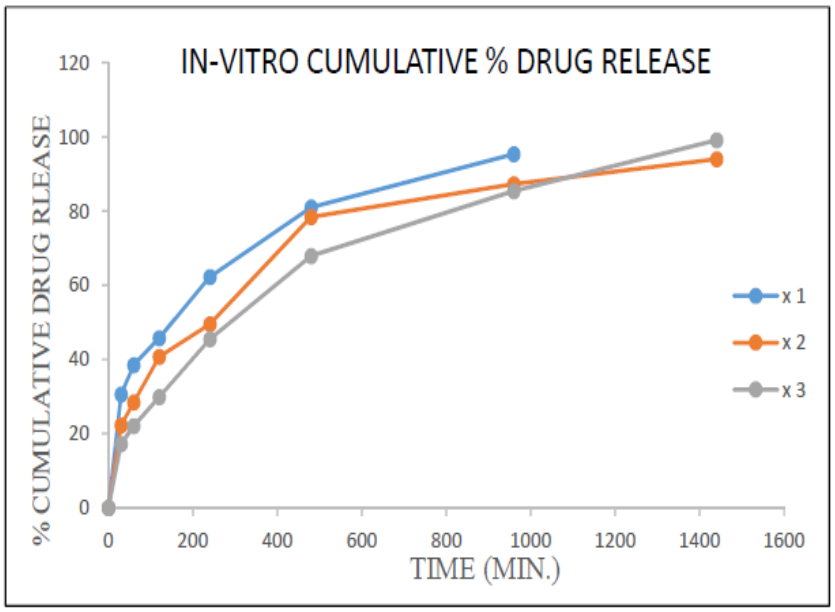

Figure: 3. Graph of % CDR of Preliminary batches X1, X2 and X3

From table no. 9, 10, 11 and figure no. 3 show preliminary batch X3 contain xanthan gum show good flow properties and more than 24 hours floating and % friability 0.71 with % cumulative drug release is high 99.10 at 24 hours. This all parameter of batch X3 show better result than the batch X1, X2.

In vitro Disintegration Time

In vitro disintegration time for immediate release layer of batches X4, X5, and X6 and calculate % drug release after disintegration.

Table no. 12 Data of Disintegration of Preliminary batch X4, X5 and X6

Formulation	Disintegration time (min.)
X4	18.30
X5	15.10
X6	22.20

From table no. 12 batch X5 show less disintegration time than the batch X4, X6.

Evaluation of Experiment Design Batches

Hardness, Thickness, % Friability and Diameter of Formulation

Table no. 13. Data of physical parameter of batches F1–F9

Formulation	Hardness (kg/cm^2)	Thickness (mm)	% friability
F1	7.2±0.5	4.15±0.02	0.72±0.02
F2	7.3±0.6	4.10±0.03	0.70±0.01
F3	7.2±0.1	4.11±0.03	0.71±0.03
F4	7.4±0.3	4.10±0.02	0.69±0.02
F5	7.3±0.4	4.14±0.05	0.70±0.03
F6	7.4±0.3	4.10±0.03	0.68±0.01
F7	7.1±0.2	4.00±0.05	0.73±0.03
F8	7.3±0.5	4.10±0.03	0.72±0.04
F9	7.2±0.3	4.15±0.02	0.71±0.01

n = 3, mean ± SD

Diameter of tablets for all batches is 8 ± 0.05 mm.

Weight variation, Content uniformity, Buoyancy time and Buoyancy lag time

Table no. 14. Data of content uniformity and buoyancy time for batches F1-F9

Formulation	Weight variation (mg)	Content uniformity (%)	Buoyancy time (hr.)	Buoyancy lag time (sec.)
F1	254±0.9	101.35±0.15	20.45	67
F2	255±0.4	100.1±0.25	23.40	58
F3	256±0.1	99.87±0.90	23	62
F4	255±0.2	98.90±0.84	21.50	61
F5	254±0.8	99.23±1.02	24	54
F6	255±0.3	98.27±063	23.10	62
F7	254±0.4	101.58±1.42	21	68
F8	254±0.5	98.44±2.27	24	59
F9	256±0.4	99.13±.48	23	65

From table no. 14 show increase in concentration of polymer and gas generating agent total floating time is rise and buoyancy lag time is decrease and in all formulation weight variation and content uniformity was in standard limit.

In-vitro dissolution of tablets

Table no. 15. In-vitro dissolution data of batches F1 – F9

Time (min.)	% Cumulative drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	30.35	24.90	25.90	22.15	19.90	21.60	15.23	18.90	19.20
10	33.28	30.58	27.90	24.89	23.10	25.74	18.64	21.90	22.10
15	36.59	34.79	31.20	27.43	25.95	28.80	25.78	25.30	24.25
30	40.45	42.12	34.65	31.20	30.35	30.45	35.12	31.45	30.95
60	51.63	47.35	43.95	37.59	35.85	36.50	40.29	34.85	33.85
120	63.89	60.48	52.90	40.75	42.10	45.56	47.63	40.25	42.50
240	75.81	72.63	70.45	56.61	54.10	55.95	52.85	55.78	52.90
480	88.12	78.26	82.64	69.28	66.95	63.27	60.10	70.71	65.10
960	95.10	88.35	89.95	82.77	80.90	84.69	73.47	80.90	79.90
1440		96.10	96.90	97.70	98.90	97.10	90.10	94.24	95.90

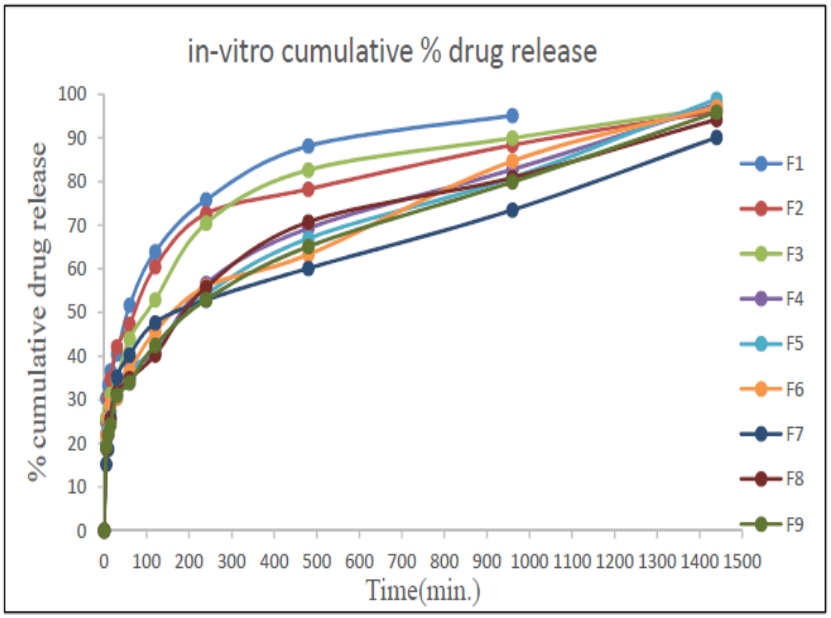

Figure: 4. Graphical presentation of in-vitro dissolution of design batches

Table no. 15 and figure no. 4 shows at low concentration (40 mg) of xanthan gum give more release and also with high concentration (80mg) of xanthan gum shows decrease release of drug because more matrix layer is form so, drug is not come out from tablet.

But the concentration (60mg) of xanthan gum shows sustain release of drug for 24 hours.

Evaluation of factorial design

Present investigation, the effect of xanthan gum and sodium bicarbonate was studied using 3^2 full factorial design. The responses studied total floating time and % CDR at 24 hrs. For the designed 9 formulations shown in Table no. 18.

Table no. 16. Data of TFT and %CDR for F1 – F9 batches

BATCH	XANTHAN GUM (X1)	NaHCO3 (X2)	TFT	% CDR
F1	-1	-1	20.45	95.10
F2	-1	0	23.40	96.10
F3	-1	1	23	96.90
F4	0	-1	21.50	97.70
F5	0	0	24	98.90
F6	0	1	23.10	97.10
F7	1	-1	21	90.10
F8	1	0	24	94.24
F9	1	1	23	95.90

SUMMARY AND CONCLUSION

Baclofen drug is related to GABA (gamma-amino butyric acid), which blocks the action of nerves within the part of the brain that controls the contraction and relaxation of skeletal muscles.

In the present work baclofen floating tablet prepared using hydrophilic polymer and super disintegrant. In case of hydrophilic polymer use natural polymer like guar gum, pectin and xanthan gum and croscarmellose sodium, crospovidone and sodium starch glycolate as sa super disintegrant. Here, first preliminary batches prepared and then finalised final formulation as per results.

And evaluation of preliminary batches like disintegration time, angle of repose, in-vitro dissolution and buoyancy time.

And results of preliminary batches, contain xanthan gum show better drug release profile like 99.1% with good flow properties and crospovidone show better disintegration time 15.10 min. so, from above results we can conclude that xanthan gum and crospovidone use as a polymer and super disintegrant for further final formulation.

In preformulation study like appearance, melting point, standard curve, calibration curve and solubility is done.

Finalised formulation in 3^2 factorial design is applied and prepare 9 formulations according to design, evaluate all batches like buoyancy time, buoyancy lag time, content uniformity, physical properties and in-vitro dissolution.

From the results of design batches we can concluded that batch F5 is better because batch F5 having % CDR 98.90 and total floating time 24 hours.

Conclusion of present work is batch F5 show better results on buoyancy time, drug content, in-vitro dissolution and in-vitro disintegration and also after stability study no any changes observed.

Conclusively, the present study attained the successful design, preparation and evaluation of floating bilayer sustained release formulation of a slightly soluble drug baclofen by gastroretentive drug delivery system and in tablet immediate release layer and sustained release layer achieved one third drug release and sustain for 24 hours with gastric retention for the desired period of time by gas generating agent.

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