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Formulation & Evaluation of Floating Beads of Non-Steroidal anti-inflammatory agent by using Foam Technology

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ABSTRACT:

Floating Drug delivery systems are designed to prolong the gastric residence time after oral administration. Diclofenac sodium is the non-steroidal anti-inflammatory drugs. Diclofenac Sodium is one of a series of phenylacetic acids that has demonstrated anti-inflammatory and analgesic properties in pharmacological studies. It is thought to inhibit the enzyme cyclooxygenase, which is essential in the biosynthesis of prostaglandins. The objective of the present study was to formulate a floating (GR) drug delivery system of drug Diclofenac sodium

Floating beads containing highly water-soluble Diclofenac sod. were prepared by dripping method using poloxamer 188 as foaming agent and sodium alginate as foam stabilizer.

KEYWORDS: Floating Drug Delivery, Beads, Polymer.

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INTRODUCTION:

The oral route is increasingly being used for the delivery of therapeutic agents because the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems[1]. Controlled-release drug delivery systems (CRDDS) provide drug release at a predetermined, predictable, and controlled rate. Controlled-release drug delivery system is capable of achieving the benefits like maintenance of optimum therapeutic drug concentration in blood with predictable and reproducible release rates for extended time period. GRDFs means which remain in stomach for prolonged period of time[2]. GRDFs increase the gastric retention time (GRT) which ultimately increases the duration of drug release, reduce drug waste, and improves the drug solubility of that drug which is less soluble in high pH environment. Prolonged GRT in the stomach could be advantageous for local action in the upper part of small intestine e.g., treatment of peptic ulcer[3].

MATERIAL AND METHOD:

Diclofenac sodium was a gift sample from Oniosome healthcare pvt. Ltd., Mohali. Sodium alginate was obtained from Thomas Baker Pvt. Ltd., Mumbai. Poloxamer 188 obtained from Signet Chemical Corp. Pvt. Ltd., Mumbai. Poloxamer 407 obtained from BASF The Chemical Company, Germany. All other chemicals and reagents used were of analytical grade.

DRUG EXCIPIENT COMPATIBILITY STUDY

Successful formulation of a stable and effective solid dosage form depends on the useful selection of excipients which are added to facilitate administration, promote the consistent release and bioavailability of drug and protest it from degradation. FT-IR analysis of polymers and drug-polymer mixture were carried out in order to access drug polymer interaction. For this, the FT-IR of drug and polymers were carried out separately as well as in mixture of drug-polymer in the ratio 1:1.

DEVELOPMENT OF CALIBRATION CURVE

Accurately weighed 100mg Diclofenac sod. and dissolved in 100ml of phosphate buffer to get a solution containing 100mcg/ml. Aliquots of (0.1-1.0 ml) standard solution was pipette out into 10ml volumetric flasks. The volume was made up to the mark with buffer to produce the concentration ranging from 1-10 mcg/ml. the absorbance of each prepared solution was measured at 276 nm in Shimadzu UV-1800 spectrophotometer against an appropriate blank. All the absorbance were conducted in triplicate (n=3)

PREPARATION OF FOAM SOLUTION USING DIFFERENT FOAMING AGENTS[4]

Sodium alginate was dissolved in distilled water at a concentration of 1.5% w/v. Different foaming agents in varied amount was then added into sodium alginate solution and agitated vigorously for 20min at 2600pm. Foams were immediately transferred into a graduated cylinder for continued observation.

PREPARATION OF ALGINATE/POLOXAMER FLOATING BEADS DRIPPING METHOD[5,6]

Floating beads containing highly water-soluble Diclofenac sod. were prepared by dripping method using poloxamer 188 as foaming agent and sodium alginate as foam stabilizer. Sodium Alginate was dissolved in double distilled water at a concentration of 1.5% (w/v), poloxamer 188 was then added into sodium alginate solution while stirring at 2600 rpm held by mechanical stirrer (REMI Mumbai) equipped with three blade propellers, at room temperature. The whole system was stirred for 20 minutes to completely form the foam solution. Diclofenac sod. (100 mg) was added into foam solution under vigorous stirring condition continuously. The foam solution was pumped using a syringe of 5c into 1 % $CaCl_2$ (100 ml). The distance between the edge of the needle and the surface of the $CaCl_2$ medium was about 10 cm. The beads formed were left in the solution with gentle stirring for 10 min at room temperature to be cured. The beads were collected, washed with distilled water twice and oven-dried subsequently (40°C).

Table 1: Composition of different formulation

S. No.	Formulation Code	Drug (mg)	Sodium alginate (mg)	Poloxamer 188	Poloxamer 407	Calcium Chloride (1%)
1.	B1	100	375	150	-	1
2.	B2	100	375	100	-	1
3.	B3	100	375	-	150	1
4.	B4	100	375	-	100	1

EVALUATION OF FLOATING BEADS OF DICLOFENAC SODIUM.

PERCENTAGE ENTRAPMENT EFFICIENCY (EE %) AND DRUG LOADING (%)[7]

20 mg of floating beads were weighed and was dissolved in 10 ml of buffer with agitating at room temperature for 12 hours. Then it was filtered through wattmann's filter paper. The filtrate was assayed by spectrophotometrically at 276nm. The drug loading (%) and entrapment efficiency (%) was calculated according to following relationship.

% Drug Loading = Weight of drug loaded in beads in gms / Weight of quantity of beads in gms

$$\textbf{EE (\%)} = W_A/Wr$$

Where :

W_A = Actual drug content

Wr = theoretical drug content

PERCENTAGE (%) YIELD[8]

The prepared floating beads were collected and weighed. The measured weight was divided by the total weight of all the excipients and drug. The % yield was calculated using following formula

% yield = Total bead weight/Total weight of all excipients

FLOATATION LAG TIME[9]

The beads were placed in 100ml beaker containing 0.1 N HCl. The time required for the beads to rise to surface and float was determined as Floating Lag time (FLT).

PERCENT FLOATING[10]

Beads 100 of each batch were placed in 100 ml of 0.1 N HCl, agitated at 100 rpm and temperature was maintained at 37±2°C. The number of sinking beads was observed visually after 24 hours. The percentage of floating beads was calculated according to the following equation:

$$\textbf{F (\%)} = N_F/N_T \times 100$$

Where: F= Floating percent

N_F = Number of floating beads

N_T = Total number of beads

SWELLING STUDY[11]

The swelling behaviour of the floating beads was studied in 0.1 N HCl. Previously weighed (W_1) beads were immersed in media. The weight (W_2) of beads was determined for 8 hours i.e. every 30 min for the first 2 hours and then every hour after that. The swelling index of each batch was calculated using the following equation:

$$\mathbf{SI\ (\%) = (W_2 - W_1)/\ W_1 \times 100}$$

Where: SI = Swelling Index

W_1= Weight of dried beads

W_2= Weight of swollen beads

BEAD SIZE

The size of beads was determined using a microscope fitted with an ocular micrometer and stage micrometer. The particle size was measured by taking 20-25 particles on the glass slide under polarized light. The mean diameter was calculated by measuring the number of divisions of the ocular micrometer covering the beads. The stage micrometer was previously used to standardize ocular micrometer.

SELECTION OF OPTIMIZED FORMULATION

Formulation was optimized on the basis of % entrapment efficiency, % yield, floating lag time, percent floating, swelling study and bead size measurement.

EVALUATION OF OPTIMISED FORMULATION

SHAPE AND MORPHOLOGY STUDY

The shape and morphology study of optimized formulation was performed by Scanning Electron Microscopy (SEM). The samples for SEM were prepared by lightly sprinkling on a double adhesive tape stuck to an aluminium stub. The stubs were then coated with platinum to a thickness under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The stub containing the coated samples was placed in SEM chamber. The samples were then randomly scanned, and photomicrographs were taken at acceleration voltage of 10 kV.

IN-VITRO DISSOLUTION STUDIES[12]

The beads equivalents to weight containing 100mg of Diclofenac sod. were immersed in dissolution medium. To assure the release of drug in solution at appropriate rate, dissolution test has

been performed for optimized formulation in triplicate. The in-vitro release of Diclofenac sod. from the beads was examined using USP Type II dissolution apparatus. 6.8 phosphate buffer (900 ml) was used as the dissolution medium and maintained at 37±0.5°C at a rotation speed of 100 rpm. An aliquot of 5 ml of the solution was withdrawn at predetermined time intervals and replaced by 5 ml of fresh dissolution medium. Samples were assayed spectrophotometrically at 276 nm after filtration through a 0.45 µm membrane filter (Millipore) against 6.8 phosphate buffer as blank.

RESULT & DISCUSSION:

DRUG-EXCIPIENT COMPATIBILITY STUDY

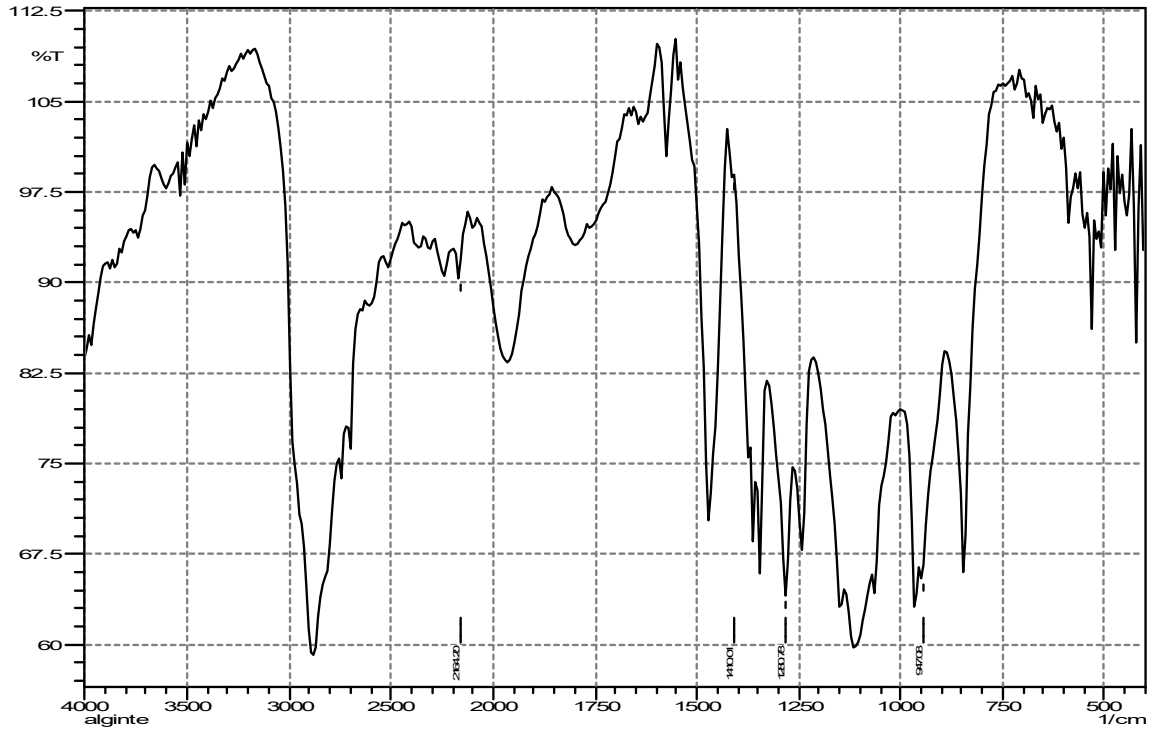

Figure 1: Drug -Excipient Compatibility Study

ESTABLISHMENT OF CALIBRATION CURVE IN 6.8 PHOSPHATE BUFFER:

Absorbance data for standard calibration curve is given in the Table 5.6. Using the absorbance of Diclofenac sod. at varied concentrations, calibration curve was constructed. The calibration equation for straight line was observed to be y=0.0641x+0.0343 with correlation coefficient of 0.9903 this was used for the determination of concentration of unknown samples.

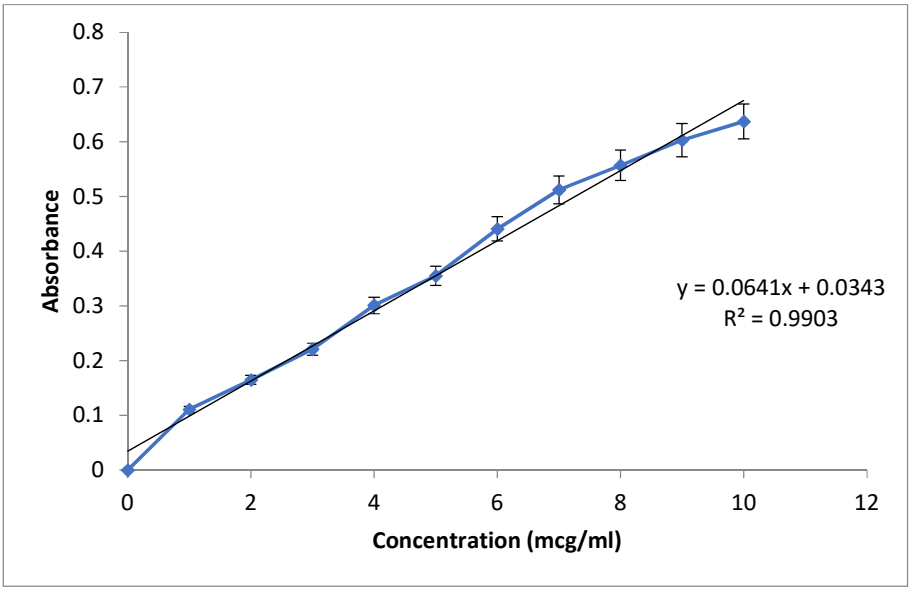

Figure 2: Calibration curve in 6.8 phosphate buffer

CHARACTERISATION OF FOAM SOLUTION BASED ON FOAMBILITY AND FOAM STABILITY

The data of foamability and foam stability is shown in Table 1.1

Table 2: Foambility and Foam Stability

Poloxamer 188						
Amount (mg)	50	100	150	200	250	500
Foambility (%)	1.44±0.11	1.76±0.88	2.0±0.14	1.48±0.21	1.92±0.025	3.2±0.21
Foam stability (min)	10.0±4.0	22±3.0	32±2.0	50±3.0	60±3.0	75±2.0
Poloxamer 407						
Amount (mg)	50	100	150	200	250	500
Foambility (%)	2.04±0.08	2.08±0.14	2.28±0.21	1.8±0.11	1.64±0.21	2.16±0.14
Foam stability (min)	45±2.0	52±3.0	44±2.0	59±4.0	60±3.0	84±2.0

Foam is defined as a dispersion of gas in a liquid or a solid. The presence of a foaming agent is essential for foam generation and stabilisation. Foaming agents are amphiphilic substances; the hydrophilic part of a molecule is responsible for its solubility in water. When a foaming agent is added in water, the hydrophobic part arranges themselves in a way to minimise the area of contact with water. This leads to their orientation at the air-water interface and formation of micelle in the bulk of liquid phase. When the foaming agent is adsorbed into the air-water interface, the surface tension of water is lowered and surface pressure is increased. The rate of foaming agent adsorption depends on its diffusion rate, concentration and agitation in the bulk of liquid. Addition of some polymers leads to the formation of surface-polymer

complex through interactions between polymer and surfactant, which contributes foam stability to foamable formulations. In some homologous series of foaming agents, the maximum foaming stability is observed at a concentration equal to. or near to the critical micelle concentration.

PREPARATION OF FLOATING BEADS

A simple and rapid method was developed to prepare a novel kind of inner-porous floating beads. The beads were prepared by dripping method with foam solution using poloxamer grade as foaming agents and sodium alginate as foaming stabilizer. Poloxamer is an effective amphiphilic surfactant and can lower the water surface tension significantly. Foam solution can be formed by stirring in the presence of poloxamer, the alginate can winding in microbubbles and stabilised the foam solution. Then the foam solution was dripped into $CaCl_2$ solution through a syringe, the porous beads were formed is shown in Fig.3

Figure 3: Image of Beads.

EVALUATION OF FLOATING BEADS OF DICLOFENAC SODIUM:

Twelve batches of Diclofenac sod. were evaluated for their entrapment efficiency, % floating, swelling index for the optimization of sodium alginate concentration, Calcium chloride % solution and rpm.

Table 3 Batch specifications of different batches of beads prepared using different polymer Ratios

Batch No.	Sodium Alginate	Poloxamer 188	Drug	%$CaCl_2$ Solution	rpm
F1	0.125g	0.15g	0.1g	1%	2600
F2	0.25g	0.15g	0.1g	1%	2600
F3	0.375g	0.15g	0.1g	1%	2600
F4	0.5g	0.15g	0.1g	1%	2600
F5	0.625g	0.15g	0.1g	1%	2600
F6	0.375g	0.15g	0.1g	0.5%	2600
F7	0.375g	0.15g	0.1g	2%	2600
F8	0.375g	0.15g	0.1g	2.5%	2600
F9	0.375g	0.15g	0.1g	1%	500
F10	0.375g	0.15g	0.1g	1%	1500
F11	0.375g	0.15g	0.1g	1%	2000
F12	0.375g	0.15g	0.1g	1%	3000

Table 4 Characterisation of floating beads for optimisation of sodium alginate concentration, Calcium chloride % solution and rpm.

Parameters ⇨ / Batch no. ⇩	% Entrapment Efficiency	% Floating	%Swelling Index
F1	Not formed	-	-
F2	Not formed	-	-
F3	73.0±0.78	91.0±1.0	175.0±0.65
F4	12.5±0.83	57.0±0.65	105.0±3.65
F5	12.1±0.55	68.7±0.66	125.0±1.02
F6	67.2±1.67	30.0±0.56	133.0±0.35
F7	36.0±1.0	79.3±0.38	141.0±0.85
F8	23.5±0.56	55.6±0.63	113.0±0.69
F9	13.0±0.66	83.0±0.85	120.0±0.45
F10	18.5±0.46	44.3±0.66	89.0±0.35
F11	11.12±0.36	65.6±0.65	64.0±0.62
F12	38.8±0.61	79.23±0.68	55.0±0.86

From the above table, we can conclude that F3 formulation had the best %EE, %floating and %Swelling index.

Therefore, we use the **Sodium Alginate concentration = 0.375mg**

Drug = 100mg

Calcium Chloride (%) = 1% Solution

Rpm = 2600 rpm

Above values are concerned as standard for further formulations B1, B2, B3, B4

Table 5 Composition of final formulations for optimization of final formulation

S. No.	Formulation Code	Drug (mg)	Sodium alginate (mg)	Poloxamer 188	Poloxamer 407	Calcium Chloride (1%)
1.	B1	100	375	150	-	1
2.	B2	100	375	100	-	1
3.	B3	100	375	-	150	1
4.	B4	100	375	-	100	1

EVALUATION OF FLOATING BEADS OF DICLOFENAC SODIUM

Above four formulations of Diclofenac sod. prepared were evaluated for their entrapment efficiency, % yield, floatation lag time, percent floating, swelling index and bead size.

ENTRAPMENT EFFICIENCY AND DRUG LOADING (%):

The % entrapment efficiency for formulations B1-B4 was determined using 0.1N HCl, The data is summarized in Table 6.

Table 6: Entrapment efficiency (%) And Drug loading (%)

S. No.	Formulation Code	% Entrapment Efficiency	%Maximum drug loading
1	B1	73.0±0.41	3.95±0.31
2	B2	55.0±0.36	3.25±0.28
3	B3	35.0±0.34	1.92±0.32
4	B4	61.6±0.28	3.64±0.23

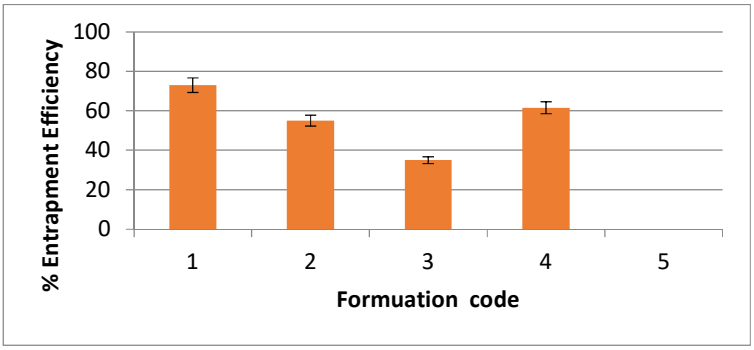

Fig.4: Percent Entrapment efficiency

From the table, we can conclude that increase in poloxamer 188 ratio can improve the maximum loading capacity and its corresponding %EE. Formulation containing 150 mg of Pol 188 (B1) shows high %EE. But with Poloxamer 407 low %EE may be due to high porous nature of alginate matrix, due to which drug diffuses back into the cross linking solution from the bead matrix during cross linking period i.e. Diclofenac sod. molecules orientate themselves at the surface of foaming solution, cause an increase in surface pressure and reduction of elasticity of surface film, leading to rupture of foam.

PERCENTAGE YIELD: The prepared beads were collected, weighed and % yield was calculated. The data is shown in Table 7

Table 7: Percentage yield

S. No.	Formulation Code	% Yield
1	B1	82.0±0.56
2	B2	79.52±0.38
3	B3	81.49±0.74
4	B4	80.91±0.39

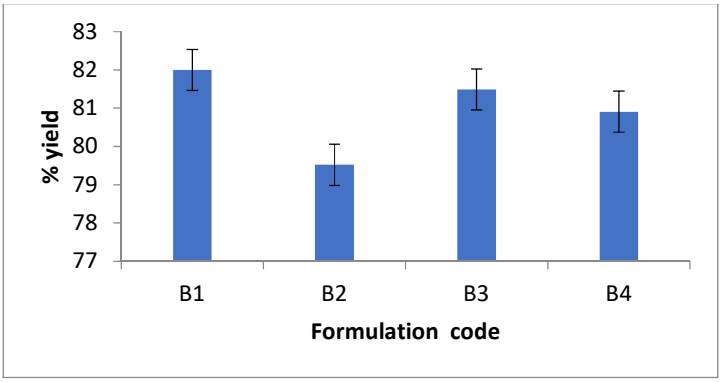

Fig. 5: Percentage Yield

The result obtained show no significant change among all the formulations but much better yield in formulation containing Pol 188 (B1).

PERCENT FLOATING: The number of sinking beads was observed visually. The percentage of floating beads was calculated. Results are given in Table 8

Table 8: Percent Floating

S.No.	Formulation Code ⇩	Time (hrs) ⇨	Percent Floating (%)							
			0	0.5	1	2	4	6	8	10
1	B1		100	100	100	100	100	94	86	79
2	B2		100	100	100	100	100	95	89	75
3	B3		100	100	96	81	78	73	70	64
4	B4		100	100	98	95	93	91	88	85

B2 and B3 formulations show less % floating, presumably due to high water uptake by polymer that would directly increase bead density. B1 already showed good buoyancy, therefore, high percent floating i.e. floating ability of beads is directly affected by Foambility and foam stability of foam solution.

SWELLING STUDY: The swelling behaviour of floating beads was studied in 0.1N HCl and swelling index was calculated and results are shown in Table 9

Table 9: % Swelling index

S.No.	Formulation Code	Swelling Index (%)
1	B1	175.0±0.65
2	B2	133.0±0.035
3	B3	120.0±0.65
4	B4	141.0±0.85

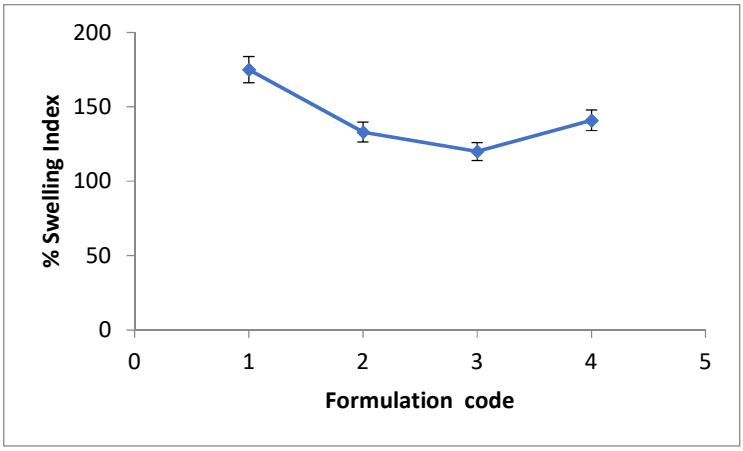

Fig.6: Swelling index

Swelling index was maximum in B1 with a value of 175% might be due to higher water uptake by polymer i.e. degree of swelling is proportional to ratio of drug to polymer and it effects the property of drug release from polymer.

PARTICLE SIZE: The size of beads was determined using optical microscopy method. Approximately 20 beads were counted for size determination. The size of beads of formulations B1-B4 is reported in Table 10**.**

Table 10: Bead size

S.No.	Formulation Code	Bead size (mm)
1	B1	1.81±0.08
2	B2	1.09±0.06
3	B3	1.62±0.08
4	B4	0.52±0.09

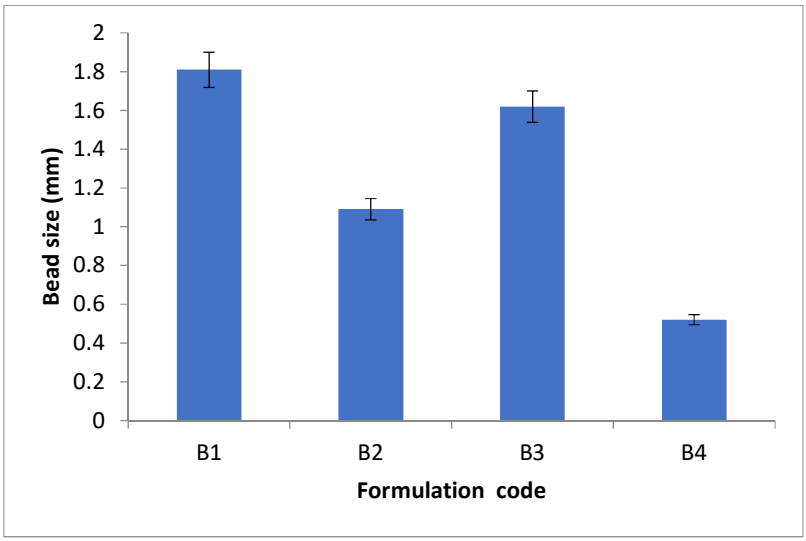

Fig 7: Bead Size

The mean partical size of four formulations was between 1.52-1.81. It was observed that increase in proportion of Pol 188 lead to an increase in size of beads.

SELECTION OF OPTIMIZED FORMULATION:

The best formulation is optimized in the basis of % entrapment efficiency, % yield, floating lag time and percent floating, swelling index and particle size. The formulation B1 is optimised whose results are shown in Table 11

Table 11: Evaluated parameters of Optimised Formulation

Parameter	Optimised Value
% Entrapment Efficiency	73.0±0.41
% Yield	82.0±0.56
Floating lag time	2 secs
Percent Floating	79%
Swelling Index	175.0±0.65
Particle size	1.81±0.08

EVALUATION OF OPTIMISED FORMULATION

SHAPE AND SURFACE MORPHOLOGY:

The prepared beads of formulation B1 was subjected to Scanning Electron Microscopy (SEM) and image is shown in Fig.8

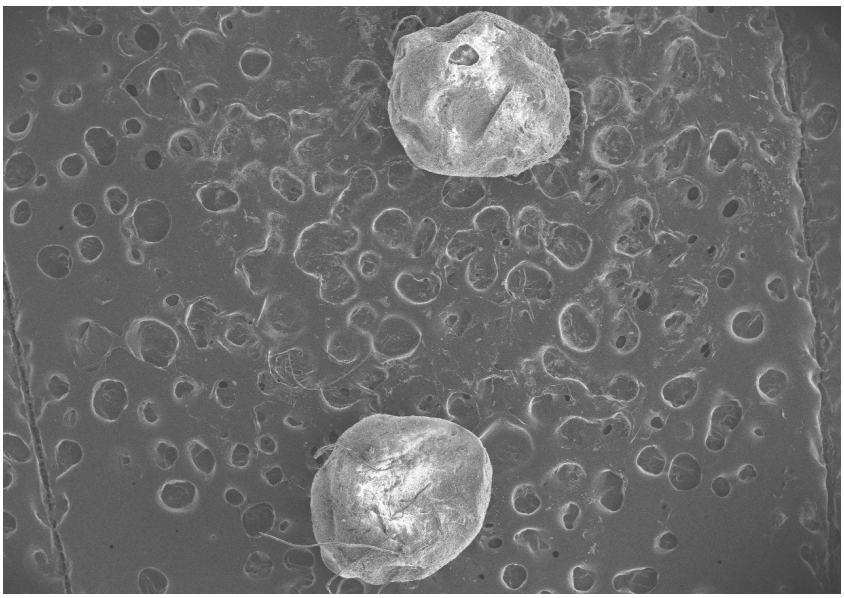

Fig.8. SEM image of floating beads.

SEM image of beads shows that beads are spherical and highly porous with uniform distribution of drug throughout the bead. The surface of bead seems to be rough.

IN-VITRO **DRUG RELEASE:** Beads equivalent to weight 100 mg were taken and *in-vitro* dissolution study was carried out.

Table 10: Cumulative Percent Drug Release for Optimized formulation

Time (hrs)	Absorbance	%CDR (mean±SD)
1	0.31	17.59±0.500
2	0.389	22.66±0.438
3	0.498	29.64±0.681
4	0.595	35.87±1.022
5	0.609	36.82±0.520
6	0.799	48.99±0.521
7	0.89	54.87±0.563
8	0.909	56.15±0.691
9	0.979	60.70±0.522

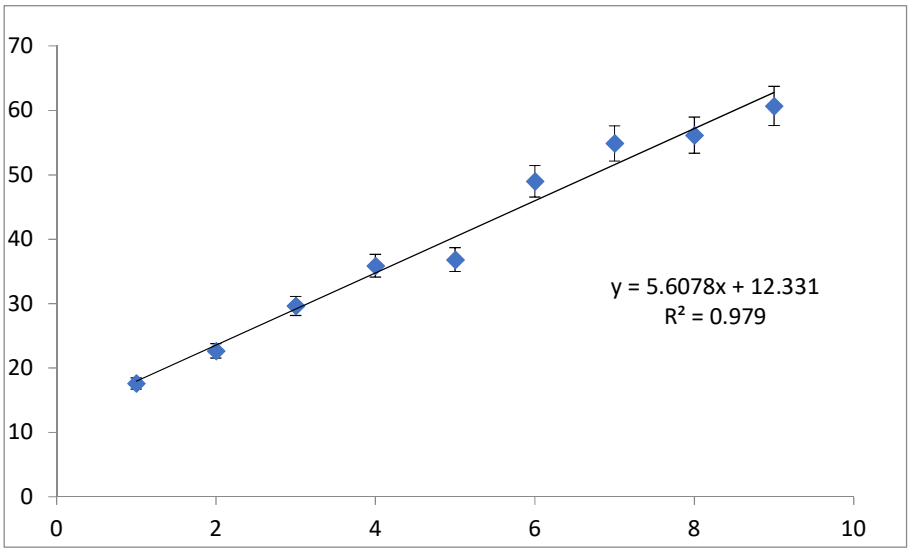

Fig 9: Cumulative Percent Drug Release for Optimized Formulation

B1 formulation made with Pol 188 (150mg) containing 100 mg Diclofenac sod. shows 60% release in 9 hours. This was because beads which were composed of hydrophilic polymeric matrix, on contact with water build a gel layer around the bead core which governed the drug release. Sodium alginate helps to sustain the drug release.

CONCLUSION

In the present study, a simple and rapid method was developed to prepare a novel kind of inner-porous floating beads. The beads were prepared using foam solution consisting numerous of microbubbles with poloxamer 188 as foaming agents, sodium alginate as foaming stabilizer. Foamability and foam stability of the foam were investigated. The addition of non-ionic surfactants

poloxamer 188 & 407 could lead to the formation of a surfactant–polymer complex through interactions between polymer and surfactant, which contributes to foamability and foam stability. The higher concentration of the poloxamer 188 can increase the foamability and foam stability of the mixed solution.

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