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Design and Evaluation of Floating Beeds of Diclofenac Sodium by Using Foam Technology

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ABSTRACT:-
The demands of new drug delivery system i.e. floating drug delivery system have ever increasing day by day during the last two/three decade. The objective of this research was to develop an intra gastric floating drug delivery system of Diclofenac Sodium and also effort were made to sustain the release of Diclofenac Sodium. Multiple-unit floating beads of Diclofenac Sodium were prepared from sodium alginate solution containing polaxamer by using foam technology method. These beads were evaluated for entrapment efficiency, drug loading, buoyancy and in vitro drug release. All formulations were the floating lag time below Four Second and shows total floating duration more than 15 hours. It was observed that entrapment efficiency, drug loading and buoyancy was greater with formulation containing sodium alginate 375 mg and 1% calcium chloride solution along with 100 and 150 mg polaxamer. Result of in-vitro dissolution studies reveals that the formulation B1 give sustained release pattern of Diclofenac Sodium upto 15 hrs.

Keywords: Diclofenac Sodium, Sodium alginate, polaxamer, Floating Beads

I. INTRODUCTION:-

The drug bioavailability of pharmaceutical dosage forms is affected by various factors. One of which is gastric residence time (GRT) [1]. The gastric emptying process from the stomach to small intestine commonly ends from a few minutes to 12 h. This changeability leads to an unpredictable bioavailability of an orally administered dosage form.[2] Furthermore, the comparatively short gastric emptying time can result in an incomplete release of drug from dosage form. Floating drug delivery system (FDDS) is one of gastroretentive dosage forms that could prolong GRT to obtain sufficient drug bioavailability [3].

FDDS have a lower density than gastric fluids and thus remain buoyant in the stomach without influenced the gastric emptying rate for a prolonged period of time [4]. Over the years, various approaches have been pursued to increase the retention of an oral dosage form in the stomach. Gastro retentive systems remain in the gastric region for several hours and hence mainly prolong the gastric residence time of drugs [5,6].
These may be

(i) Effervescent system and
(ii)Non effervescent system
Effervescent Floating Dosage Forms: [7,8]

These are matrix types of systems prepared with the help of swellable polymers (methylcellulose and chitosan) and various effervescent compounds (sodium bicarbonate, tartaric acid, and citric acid). They are formulated in such a way that when come in contact with acidic gastric contents, CO2 liberate and gas entrapped in swollen hydrocolloids which provides buoyancy to the dosage forms.

1. Gas-generatingSystems:

These buoyant delivery systems utilize effervescent reactions between carbonate/ bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme.

2. Volatile liquid containing systems:

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber,

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which contains a liquid (like ether, cyclopentane), that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bio-erodible plug made up of PVA, Polyethylene, etc. that gradually dissolves and causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach.

Non-effervescent Floating Dosage Forms: [9,10,11,12]

1. Colloidal gel barrier system:

A system that contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorption sites in the solution form for ready absorption. This system incorporates a high level of one or more gel forming highly swellable cellulose type hydrocolloids.e.g. HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms.

2. Alginate beads:

Multi-unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours.

3. Hollow microspheres / Microballons:

It is prepared by a novel emulsion solvent diffusion method. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug.

4. Intragastric / Microporous compartment system:

The system composed of a drug reservoir encapsulated in a microporous compartment having pores on top and bottom surfaces. The peripheral walls of the reservoir compartment were completely sealed to prevent any physical contact of the undissolved drug with walls of the stomach. Novel levodopa gastro retentive dosage form based on unfolding polymeric membranes which combines extended dimensions with high rigidity. It was folded into a large size gelatin capsules. In vitro studies showed that unfolded form reached within 15 minutes after administration and it was confirmed in vivo in beagle dogs. The unfolded form was maintained for at least 2 hours. It was concluded that this dosage form could improve therapy of different narrow absorption window drugs. However, there are possibilities of the polymeric films to get stuck in the esophagus causing extreme discomfort to the patient or drug related injuries and repeated administration of rigid dosage form may result in gastric obstruction.

II. MATERIAL AND METHOD:-

MATERIAL:-

Diclodfenac Sod. was procured as a gift sample from Oniosome Healthcare Ltd. India. Sodium alginate, Calcium chloride, Poloxamar 188 and Poloxamer 407 were purchased from Thomas baker pvt. Ltd., Signet chemical corporation pvt. Ltd , Ludwigshfen/BASF Company. All reagents used were of analytical reagent grade.

METHOD:-

Sodium alginate was dissolved in distilled water at then poloxamer was then added into the sodium alginate solution and agitated vigorously by using mechanical stirrer at 2600 rpm for 20 min. Then drug was added into the foam solution under vigorous stirring condition continuously. The foam solution was introduced using a 21 gauge syringe into the 1% CaCl2 solution under gentle stirring condition. The distance between the edge of the needle and the surface of the CaCl2 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).

Twelve batches of Diclofenac sod. were evaluated for their entrapment efficiency, % floating, swelling index for the optimization of

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sodium alginate concentration, Calcium chloride % solution and rpm.

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 1 : Batch specifications of different batches of beads prepared using different polymer

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

Table 2: Characterisation of floating beads for optimisation of sodium alginate concentration, Calcium chloride % solution and rpm.

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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

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

Table 3: Composition of final formulations for optimization of final formulation

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 4

S. No.	Formuation 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

Table4: Entrapment efficiency (%) And Drug loading (%)

Percentage Yield: The prepared beads were collected, weighed and % yield was calculated. The data is shown in Table 5

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

Table 5: Percentage yield

Floating Lag time: The time required for the beads to rise to the surface and float was observed and summarized in Table 6

S.No.	Formulation Code	Floating lag time (seconds)
1	B1	2.0
2	B2	3.0
3	B3	4.0
4	B4	3.0

Table 6: Floating Lag Time

Percent Floating : The number of sinking beads was observed visually. The percentage of floating beads was calculated. Results are given in Table 7

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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

Table 7: Percent Floating

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 8

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

Table 8: % Swelling index

Particle Size: The size of beads were determined using optical microscopy method. Approximately 20 beads were counted for size determination. The size of beads of formulations B1-B4 is reported in Table9**.**

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

Table 9: Bead size

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 optimized whose results are shown in Table 10

Parameter	Optimized 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

Table 10: Evaluated parameters of Optimized Formulation

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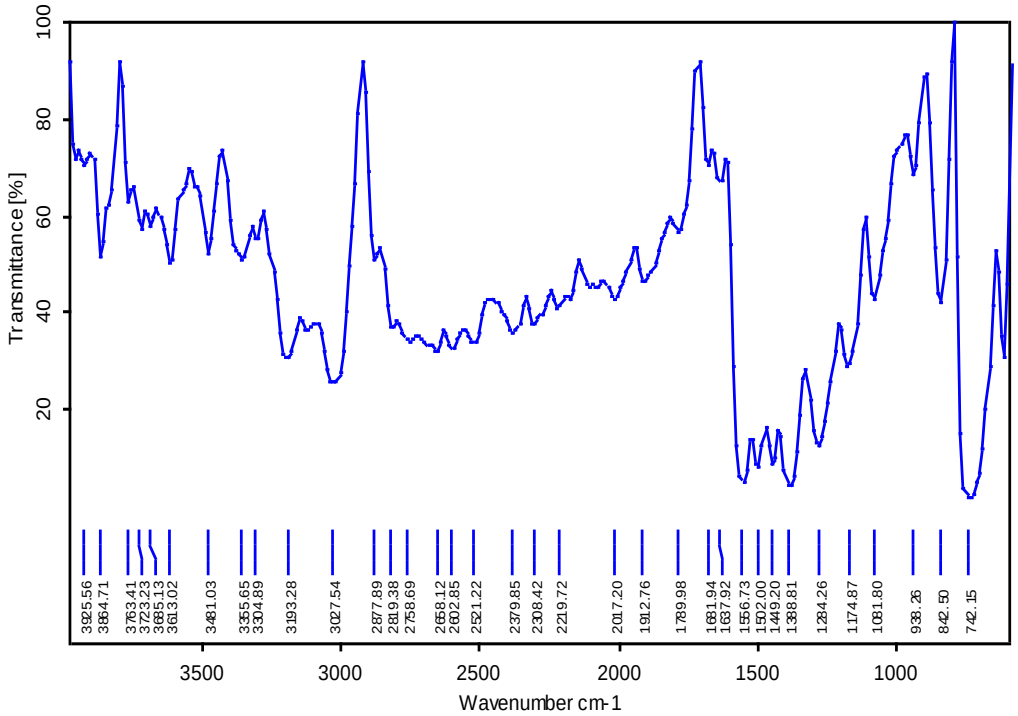
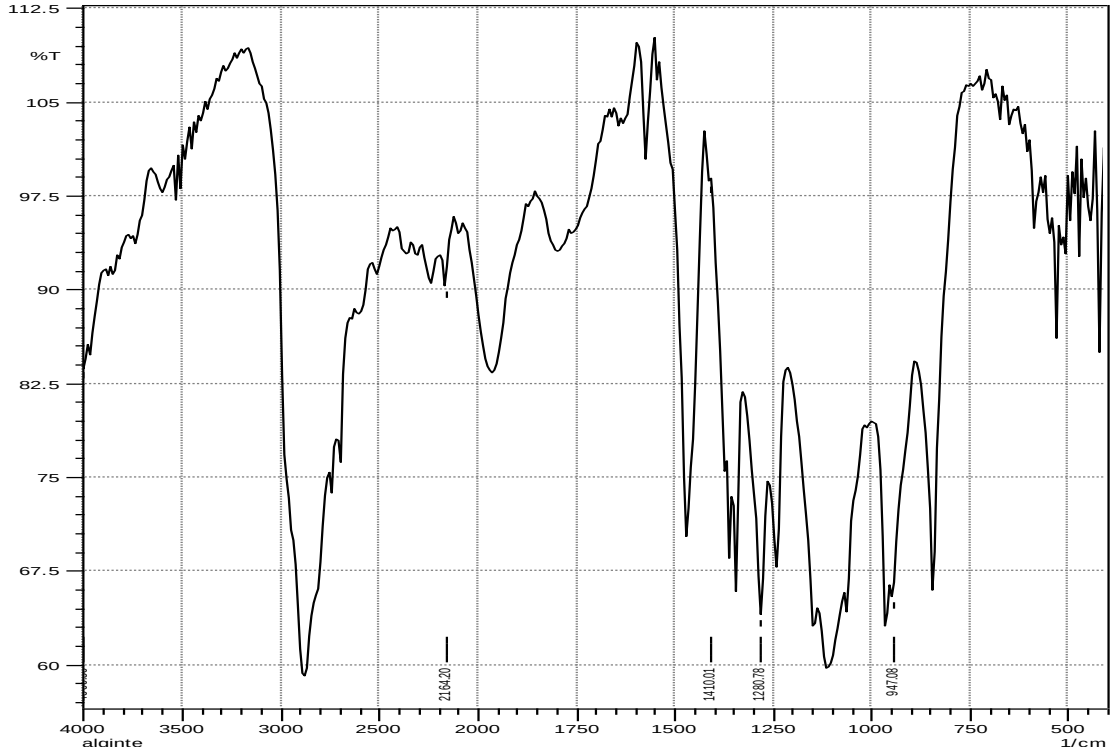


IR spectra of Dicofenac Sodium



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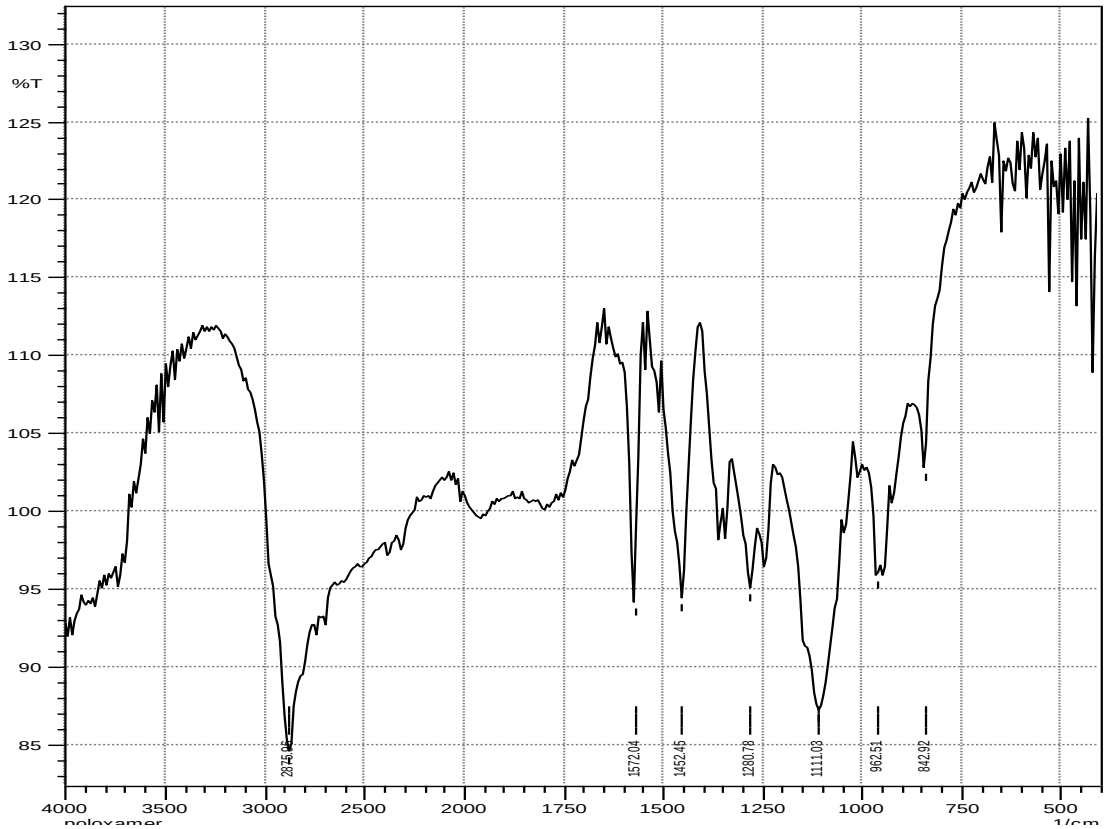
IR spectra of Pure Sodium Alginate



IR spectra of Poloxamer

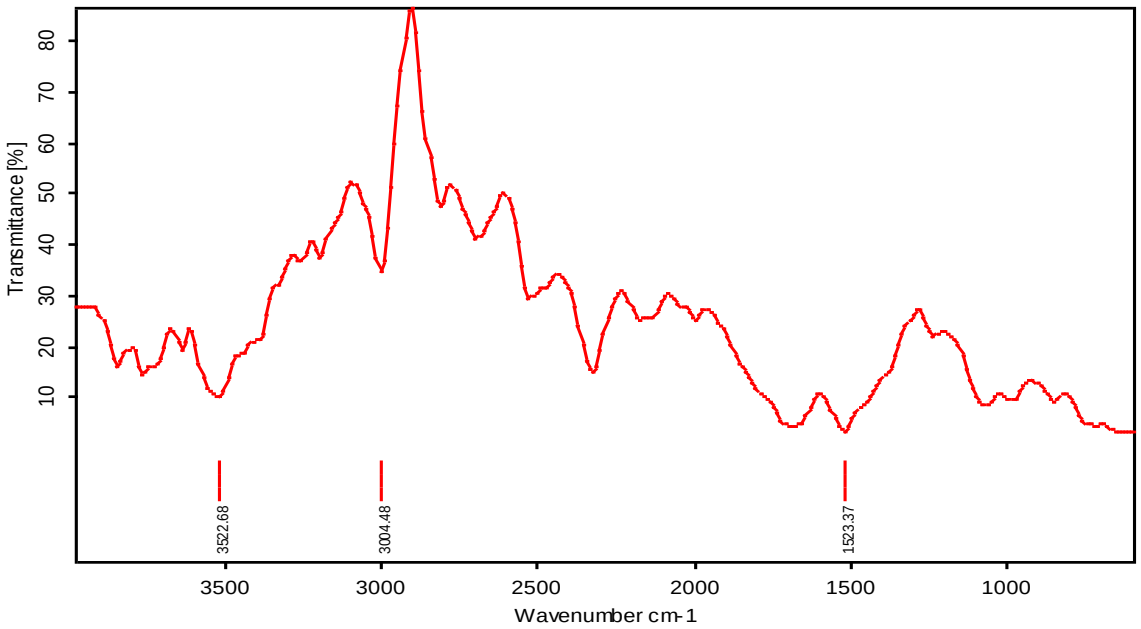


Fig.; FT-IR spectrum of Physical Mixture of Diclofenac sod. With Sodium alginate and Poloxamer 407.

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5.7.2. In-vitro drug release: Beads equivalent to weight 100 mg were taken and in-vitro dissolution study was carried out.

Table 5.19: 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

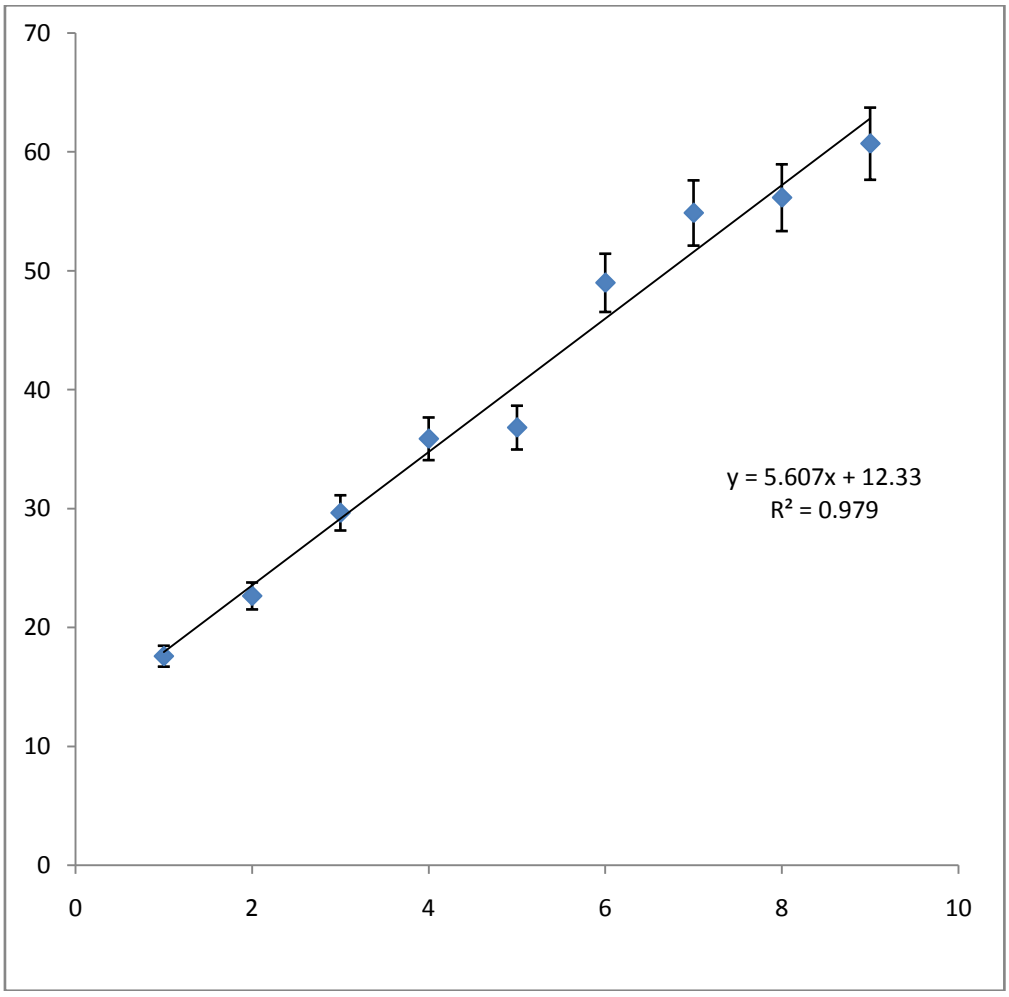

Fig 5.16: Cumulative Percent Drug Release for Optimized Formulation

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.

5.7.3 Drug release kinetic study: Raw data obtained from in–vitro release studies were

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analysed, wherein data were fitted to different equations and kinetics model to calculate the percent drug release and release kinetics of Diclofenac sod. from floating beads.

Table 5.20: Drug Release Kinetic Data of Formulation B1

S.No.	Time (hrs)	Square root of time	Log time	Cumulative Percent Drug Release±SD	Log Cumumlative Percent Drug Release	Cumulative Percent Drug Remaining	Log Cumulative Percent Drug Remaining
1	**0**	**0**	**-**	**0**	**-**	**100**	**2.000**
2	**1**	1	0	**17.59±0.500**	**1.245399**	**82.41**	**1.915**
3	**2**	**1.414**	**0.301**	**22.66±0.438**	**1.355**	**77.34**	**1.888**
4	**3**	**1.732**	**0.477**	**29.64±0.681**	**1.471**	**70.36**	**1.847**
5	**4**	**2.0**	**0.602**	**35.87±1.022**	**1.554**	**64.13**	**1.807**
6	**5**	**2.236**	**0.698**	**36.82±0.520**	**1.566**	**63.18**	**1.800**
7	**6**	**2.449**	**0.778**	**48.99±0.521**	**1.690**	**51.01**	**1.707**
8	**7**	**2.645**	**0.845**	**54.87±0.563**	**1.739**	**45.13**	**1.654**
9	**8**	**2.828**	**0.903**	**56.15±0.691**	**1.749**	**43.85**	**1.641**
10	**9**	**3**	**0.954**	**60.70±0.522**	**1.783**	**39.30**	**1.594**

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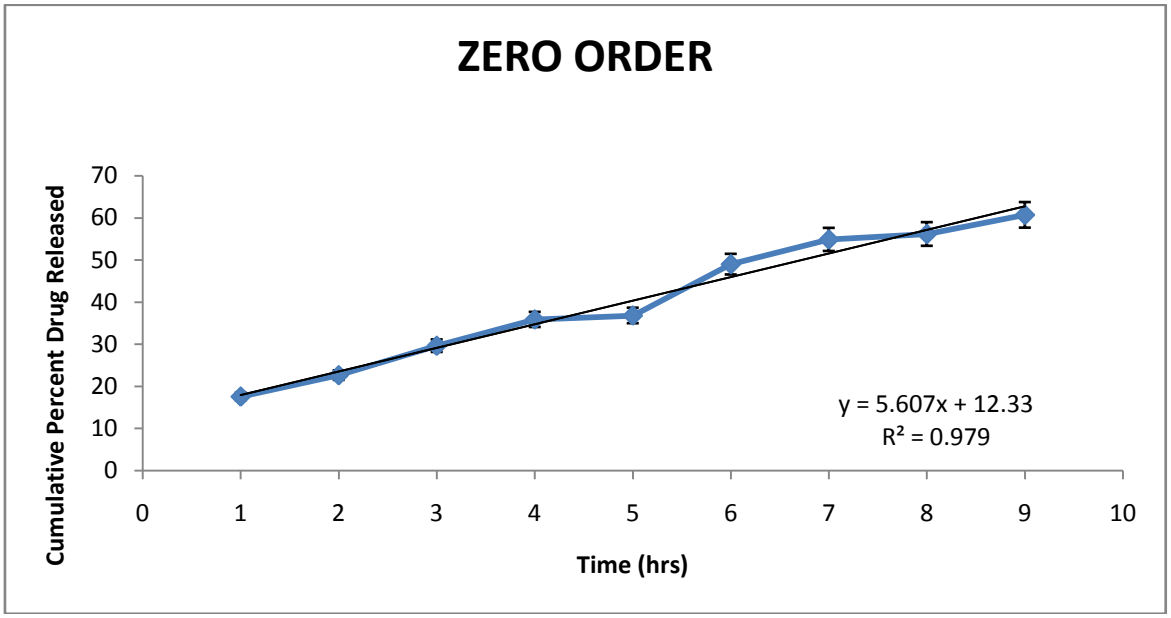

Fig .5.17: Cumulative Percent Drug Released Vs Time Plot (Zero Order)

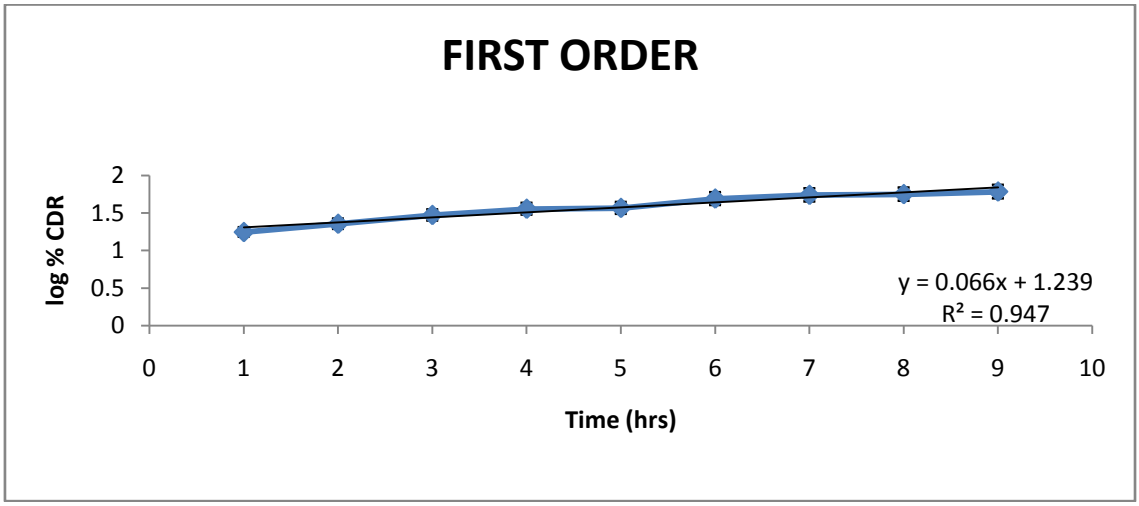

Fig. 5.18: Log Cumulative Percent Drug Remaining Vs Time Plot (First Order)

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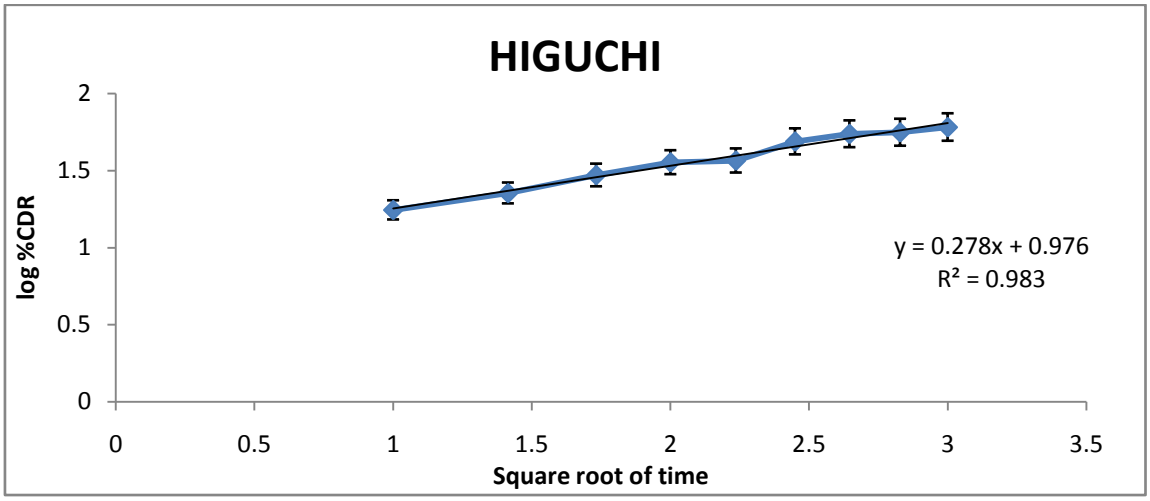

Fig. 5.19: Log cumulative Drug Release Vs Square Root of Time (Higuchi's Plot)

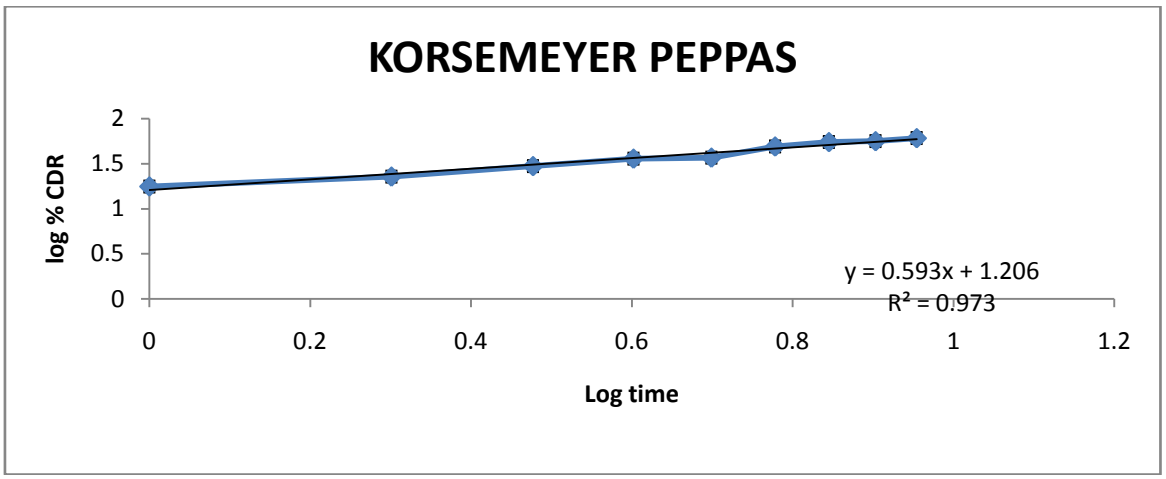

Fig .5.20: Log Cumulative Percent Drug Released Vs Log Time (Peppas Plot)

Linear regression analysis and model fitting shows that formulation B1 follows Higuchi kinetics, which has higher value of correlation coefficient (R^2). The final results are reproduced in Table 5.21

Table 5.21: Regression Coefficient (R^2) Values of Drug Release Data Obtained from various Kinetic Models

Formulation Code	Zero Order (R^2)	Higuchi Model (R^2)	First Order (R^2)	Peppas Model (R^2)
F1	0.979	0.983	0.947	0.9735

Comparison of floating beads of Diclofenac with pure drug and marketed drug

Time	%CDR(BEADS)	%CDR(PURE DRUG)	%CDR(MARKETED)
0	0	0	0
1	17.59	46.66	9.6
2	22.66	53.59	10.15
3	29.64	80.29	14.056
4	35.87	97.12	22.811
5	36.82	97.12	23.95
6	48.99	97.2	27.73
7	54.87	97.2	30.05

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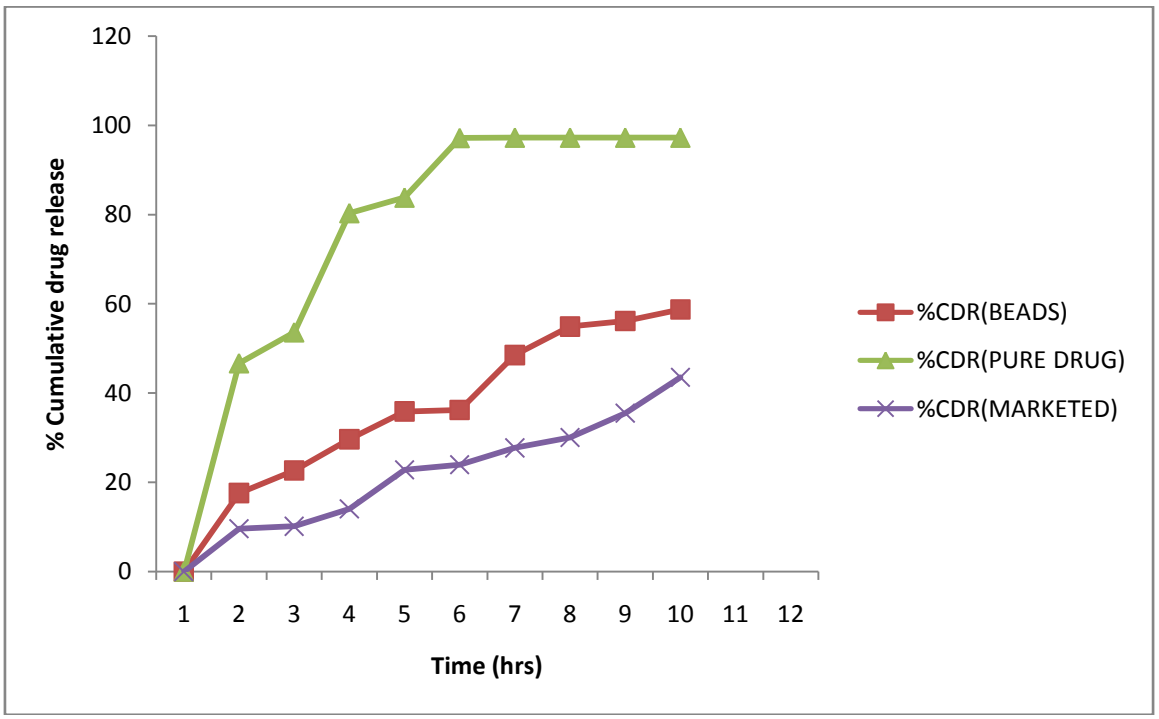
8	**56.15**	**97.2**	**35.166**
9	**60.70**	**97.2**	**43.529**



5.7.5 Accelerated Stability Studies: The optimised formulation was stored at 40±2°C/75±5%RH in HDPE bottles for 6 weeks. Beads were analysed at specified time intervals (0,1,2,4,6 weeks) for entrapment efficiency, % yield, floatation lag time, percent floating and in-vitro dissolution study.

Table 5.22: Effect on various parameters during accelerated stability studies

S.No.	Time intervals (weeks)	Entrapment efficiency (%)	% yield	Floating lag time (sec)	Percent Floating	%CDR
1	**0**	**73.0**	**82.00**	**2 secs**	**79.00**	**60.70**
2	**1**	**72.95**	**81.90**	**2 secs**	**79.14**	**60.45**
3	**2**	**72.40**	**81.79**	**2 secs**	**78.30**	**60.23**
4	**4**	**71.65**	**81.54**	**1 sec**	**77.79**	**60.0**
5	**6**	**70.23**	**78.00**	**1sec**	**75.43**	**58.63**

There are no significant changes in the parameters during accelerated stability condition. Hence, Diclofenac sod. is stable at higher temperature.

III. CONCLUSION:

It concluded from the present study that floating beeds of diclofenac sodium by using foam technology drug can be possible with effective bioavailability. Various polymers can be used as pharmaceutical excipients for oral drug delivery. It was concluded formulation F1 maximum percentage drug release.

Conflict of Interest

No conflict of interest to all authors.

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