Original Research

FORMULATION DEVELOPMENT AND CHARACTERIZATION OF FLOATING TABLETS OF CELECOXIB

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ABSTRACT:
In the present work an attempt has been made to prepare floating tablets of celecoxib, a NSAID drug used for the treatment of osteoarthritis, rheumatoid arthritis and acute pain. This drug has low bioavailability and has good absorption in the acidic part of the stomach, therefore the formulations are developed which can retain in the stomach for longer periods of time without being effected by gastric emptying. Different formulations have been developed by using sodium bicarbonate as the gas generating agent and the polymers like HPMC, guar gum and xanthan gum were used to entrap the gas bubbles produced by sodium carbonate and make the tablets float. The powder blends of the formulations were evaluated for their flow properties and were having good flow properties. The prepared tablets are evaluated for in-process quality control tests and were within the specified limits. The buoyancy lag time of all the developed formulations was less than 20secs and exhibited good floating nature. In-vitro dissolution studies were performed and found that combination of polymers were more efficient in obtaining the desired release from the formulations. Of all the formulations developed formulation F8 is considered as the best formulation as it has a low buoyancy lag time along with controlled drug release for 12hours with a maximum drug release of 96.41% with zero–order release kinetics and diffusion mechanism of drug release.

KEYWORDS: Floating tablets, Celecoxib, Osteoarthritis, Buoyancy lag time, zero–order release kinetics.

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INTRODUCTION:

It is evident from the recent scientific and patient literature that an increased interest in dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. Conventional oral controlled dosage forms suffer from mainly two adversities[1]. The short gastric retention time (GRT) and unpredictable gastric emptying time (GET). A relatively brief GI transit time of most drug products impedes the formulation of single daily dosage forms. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the GI tract is to control the gastric residence time (GRT), i.e. gastro retentive dosage form (GRDFs or GRDS)[2]. GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals, but also increase patient compliance beyond the level of existing controlled release dosage form. Dosage form with prolonged GRT, i.e. gastro retentive dosage forms (GRDF), will bring about new and important therapeutic option for drugs that are locally active in stomach, that have an absorption window in the stomach or in the upper small intestine, that are unstable in the intestinal or colonic environment[3,4].

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms and to reduce numbers of colon and rectum polyps in patients with familial adenomatous polyposis[5]. It has an oral bioavailability of 40% with low aqueous solubility[6]. It has maximum solubility and absorption in the stomach, there by formulating a gastroretentive dosage form can increase its residence time in stomach and enhances the bioavailability of Celecoxib. Thus the present research work is aimed to formulate floating tablets of Celecoxib by employing sodium bicarbonate as a gas generating agent and polymers such as HPMC, xanthan gum and guar gum to control the release of drug.

MATERIALS AND METHODS:

Celecoxib was obtained as a gift sample from Chandra labs, Hyderabad. HPMC was purchased from Sisco research laboratories Pvt. Ltd Mumbai. Xanthan gum and guar gum were purchased from MYL Chem Mumbai. Sodium bicarbonate, micro crystalline cellulose, magnesium stearate and Talc were purchased from S.D Fine chem. LTD Mumbai.

Methods:

Formulation of floating tablets of Celecoxib by direct compression:

The tablets were prepared by using direct compression method. First the drug, polymer and other excipients selected were passed through 40 mesh sieve. Required quantity of drug, polymer and excipients were weighed properly as mentioned in the table-1 and transferred into polyethylene bag and the blend was mixed for at least 15mins to have uniform distribution of drug in the formulation. The blend obtained was then lubricated by adding 1% magnesium stearate and again mixed for another 5mins to ensure good lubrication. About 400 mg of the powder mix was weighed accurately and fed into the die of single punch machinery and compressed to get the tablets.

Table.1: Formulae for preparing the floating tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Celecoxib	200	200	200	200	200	200	200	200	200
Guar gum	80	-	-	100	-	-	60	80	40
Xanthan gum	-	80	-	-	-	40	-	-	-
HPMC K4M	-	-	80	-	100	80	60	40	80
Sodium bicarbonate	25	25	25	25	25	25	25	25	25
Tartaric acid	35	35	35	35	35	35	35	35	35
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Talc	8	8	8	8	8	8	8	8	8
Magnesium stearate	8	8	8	8	8	8	8	8	8
Total weight(mg)	400	400	400	400	400	400	400	400	400

EVALUATION:

Evaluation of pre compression parameters[7]

Bulk density

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring powder blend into a graduated cylinder via a large funnel and measure the volume and weight.

$$\textit{Bulk density}(BD) = \frac{\textit{weight of powder}}{\textit{Bulk volume of powder}}$$

Bulk density was expressed in g/cc.

Tapped density:

Tapped density is determined by placing a graduated cylinder containing a known mass of powder blend in mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the tapped density may be computed.

$$\textit{Tapped density}(TD) = \frac{\textit{weight of powder}}{\textit{Tapped volume of powder}}$$

Carr's Index (CI):

Carr's index is measured using the values of bulk density and tapped density. The following equation is used to find the Carr's index.

$$CI = \frac{(TD - BD)}{TD} \times 100$$

Table.2: Flow properties and corresponding Carr's Index values

Excellent	<10
Good	11 – 15
Fair	16 – 20
Possible	21 – 25
Poor	26 – 31
Very poor	32 – 37
Very very poor	>38

Hausner's Ratio:

It indicates the flow properties of the powder and ratio of Tapped density to the Bulk density of the powder or granules.

$$\textit{Hausner's Ratio} = \frac{\textit{Tapped density}}{\textit{Bulk density}}$$

Table.3: Flow Properties and Corresponding Hausner's ratio

Less than 1.25	Good flow
Greater than 1.25	Poor flow
Between 1.25-1.5	Added glidant normally improves the flow

Angle of repose:

The manner in which stresses are transmitted through a powder bed and the beds response to applied stress are reflected in the various angles of friction and response. The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

$$\theta = Tan^{-1} (h/r)$$

Where, h= height of the heap, r= Radius of the heap.

Table.4:Flow Properties and Corresponding Angle of Repose

Angle of Repose	Powder Flow
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very poor

Post compression evaluation of tablets:

The formulated tablets were evaluated for the following physicochemical characteristics:

General appearance:

The formulated tablets were assessed for its general appearance and observations were made for shape, color, texture and odor.

Hardness:

Hardness of the tablet was determined by using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the

barrel to indicate the force. It is expressed in kg/cm^2.

Weight Variation[7]:

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within the permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for >300 mg tablets and none by more than double that percentage.

Friability test[7]:

The friability of the tablets was determined using Roche friabilator. It is expressed in percentage. 20 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 min. After four minutes the tablets were weighed again. The % friability was then calculated using the formula,

$$\textbf{Friability}\ [\%] = \frac{\textbf{Initial weight} - \textbf{Final weight}}{\textbf{initial weight}} \times 100$$

Drug content:

20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 200 mg of Celecoxib was transferred in to a 100 ml volumetric flask and the volume adjusted to 100ml with 0.1N HCl. Further 1ml of the above solution was diluted to 100 ml with 0.1N HCl and the absorbance of the resulting solution was observed at 258nm. From the absorbance value, drug content is determined[8].

***In-vitro* Buoyancy studies:**

The *in-vitro* buoyancy was determined by floating lag time and total floating time. The tablets were placed in a 100ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time (FLT) and the duration of the time the tablet constantly floats on the dissolution medium was noted as the Total Floating Time (TFT)[9,10].

Swelling Index Studies:

The swelling behavior of dosage form was measured by studying its weight gain. The swelling index of tablets was determined by placing the tablets in the basket of dissolution apparatus using dissolution medium as 0.1N HCl at 37±0.5°C. After 1, 4 and 6h each dissolution basket containing tablet was withdrawn, blotted with tissue paper to remove the excess water and weighed on the analytical balance (Schimadzu, AX 120)[9,10].The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula.

$$\textbf{\textit{Swelling index}} = \frac{\textbf{\textit{Wet weight of tablet} - \textbf{\textit{Dry weight of tablet}}}}{\textbf{\textit{Dry weight of tablet.}}}$$

In-Vitro Dissolution Studies of Tablets:

900ml 0f 0.1 HCl was placed in the vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temperature of 37±0.5°C. Tablet was placed in the vessel and the vessel was covered, the apparatus was operated for 12 hours at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fresh buffer was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometrically at 258 nm[11].

Release Kinetics

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to four popular release models such as zero-order, first-order, higuchi and Korsmeyer Peppa's equations. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from the matrix systems was studied by using Higuchi equation and Korsmeyer Peppa's equations[12].

RESULTS AND DISCUSSION:

Precompression evaluation:

The powder blend of the formulations is subjected to precompression evaluation and the results are given in the table-5. Bulk density values and tapped density values have been used to determine the hausner's ratio and carr's index values and the results were found to be in the range of 1.15-1.17 and12.68-14.73 % respectively. The angle of repose values were in the range of 24^0 02'-28^0 38'. All these values suggest that powder blend has good flow properties.

Table.5: Evaluation of pre-compression parameters of floating tablets of Celecoxib

Formulations	Angle of repose (θ)	Bulk density gm/cc	Tapped density gm/cc	Carr's Index	Hausner's ratio
F1	25^0 65'	0.330	0.387	14.73	1.17
F2	25^0 73'	0.311	0.36	13.61	1.16
F3	25^0 16'	0.326	0.381	14.44	1.17
F4	26^0 68'	0.327	0.378	13.49	1.16
F5	26^0 89'	0.343	0.395	13.16	1.15
F6	27^0 58'	0.367	0.425	13.65	1.16
F7	28^0 38'	0.31	0.355	12.68	1.15
F8	26^0 42'	0.319	0.366	12.84	1.15
F9	24^0 02'	0.392	0.458	14.41	1.17

Post compression evaluation:

The results of the evaluation studies are represented in the table-6. The in-process quality control tests have shown that the results obtained were within specified pharmacopeial limits. Buoyancy lag time was found to be increasing with increase in concentrations of gums, where as the buoyancy lag time was less in the formulations containing HPMC. Low buoyancy lag time of 3.52 sec was found in the formulation F1. All the formulations remained floating for more than 6 hours in the simulated gastric fluid.

Table.6: Post compression evaluation parameters of Celecoxib floating Tablets

Formulation	Avg. Weight(mg)	Hardness (kg/cm^2)	Friability (%)	% Drug content	Buoyancy Lag time (sec)	Thickness (mm)
F1	399	6.4	0.56	98.32	3.52	3.77
F2	401	6.3	0.59	99.10	3.68	3.81
F3	398	6.2	0.52	98.45	4.38	3.89
F4	402	6.4	0.50	99.10	18	3.78
F5	400	6.7	0.54	99.45	4	3.92
F6	399	5.6	0.52	98.19	5.35	4.01
F7	398	6.1	0.49	98.50	18.58	3.92
F8	402	6.2	0.53	99.14	9.16	3.89
F9	401	5.8	0.55	99.18	20.38	3.98

In-vitro dissolution study:

The % Cumulative drug release of the formulations F1-F4 has shown that they were not able to sustain the drug release for 12 hrs. Formulations F5, F6, F7 and F9 have shown a very slow release in drug release, which were not fulfilling the objective of the study. Formulation F8 have shown a maximum of 96.41% drug release at the end of 12 hours. F8 formulation was optimised based on the floating behaviour ie., the floating lag time of 9.16 sec and sustained release profile with 96.41% drug release. The results of the study are represented in the table-7 and figure-1.

Table.7: Dissolution data of celecoxib floating tablets

Time (hr)	Cumulative percentage drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	10.81	17.21	15.81	9.16	6.21	9.21	10.42	10.26	8.21
1	28.24	27.21	25.42	15.18	11.42	15.62	17.13	16.14	14.11
2	49.21	39.12	40.72	25.12	21.83	24.44	26.62	24.21	21.71
3	71.72	50.62	60.39	35.24	30.62	35.61	37.61	36.24	33.62
4	84.26	78.62	75.25	59.28	39.24	40.75	50.13	50.16	39.74
6	99.21	99.13	83.21	80.21	50.74	51.84	60.72	69.22	49.62
8	--	--	97.42	99.71	58.81	56.68	69.12	78.41	57.21
10	--	--	--	--	69.72	68.86	81.62	85.72	69.64
12	--	--	--	--	73.84	77.24	87.42	96.41	73.42

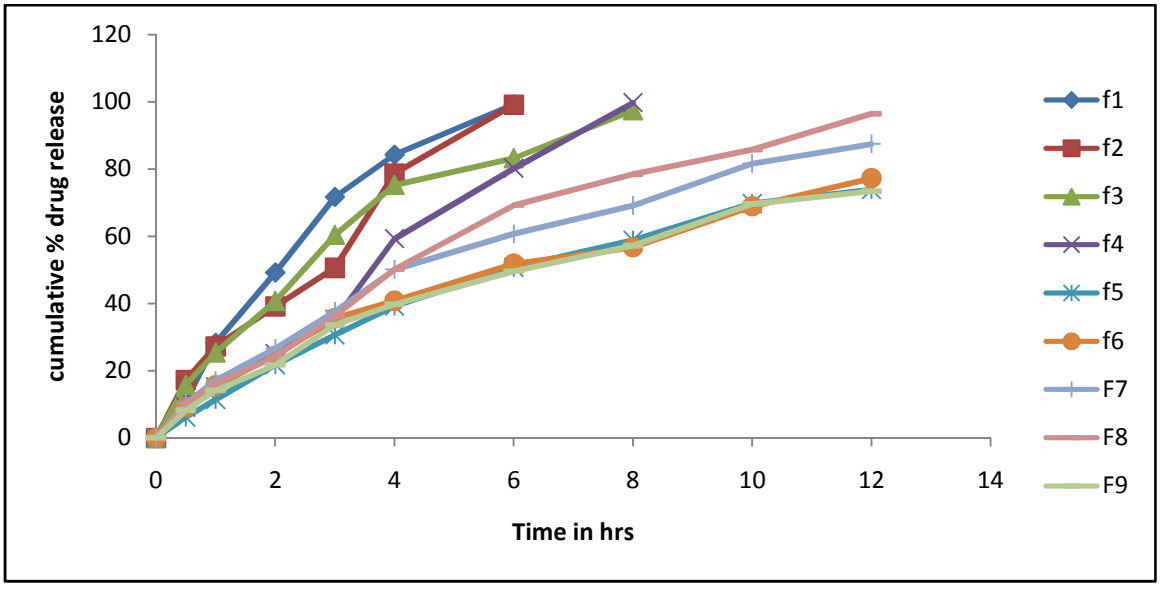

Figure.1: Dissolution profile of celecoxib Floating Tablet

Kinetic modeling and mechanism of drug release:

In-vitro drug release data of all the formulations was subjected to kinetic study by linear regression analysis according to zero order and first order kinetic equations, Higuchi and Korsmeyer-Peppas models to ascertain the mechanism of drug release. The results of linear regression analysis are summarized in table-8.

Table.8: Release Kinetics for the optimized formulation

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	8.006894479	-0.10600297	30.18526628	1.838325514
Intercept	9.444940674	2.071976147	-9.94351820	0.2014586
R 2	0.957911558	0.940678078	0.974800334	0.84427973

The optimized formulation F8 was found to exhibit zero–order kinetics and the mechanism of drug release is by higuchi model ie., drug release is by diffusion.

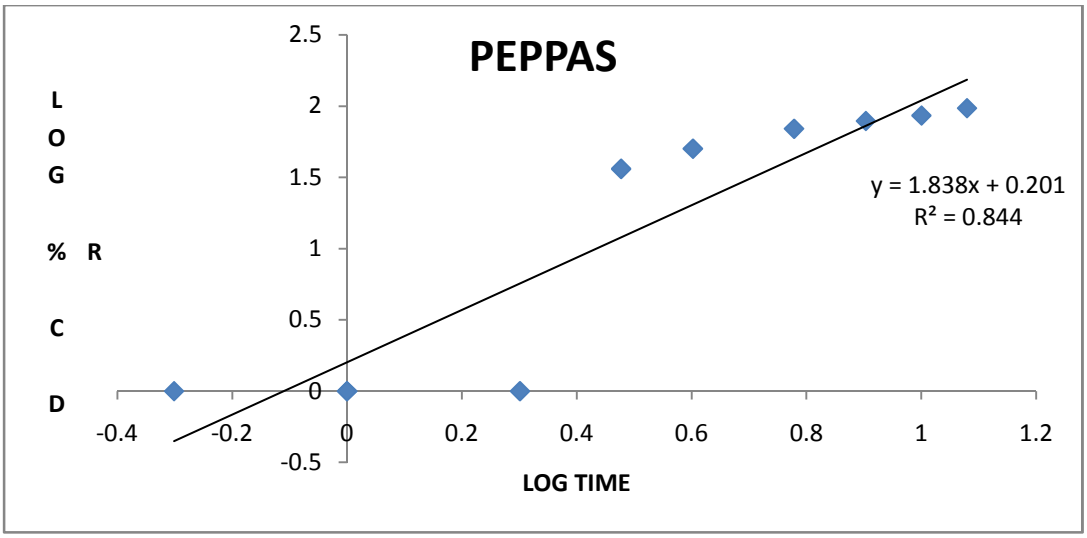

Figure.2: Peppas model for optimized F8 formulation

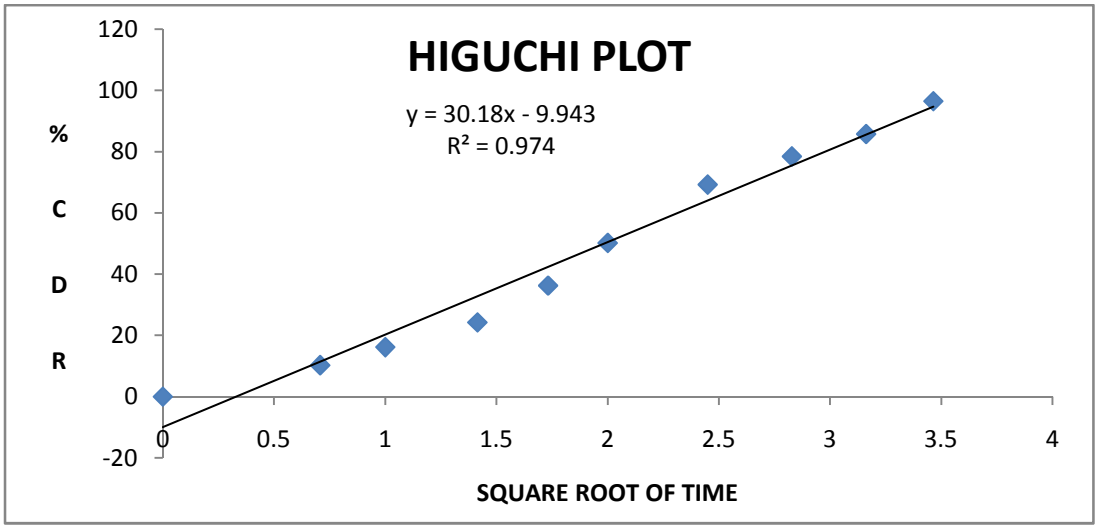

Figure.3: Higuchi model for optimized F8 formulation

Figure.4: First order release model for optimized F8 formulation

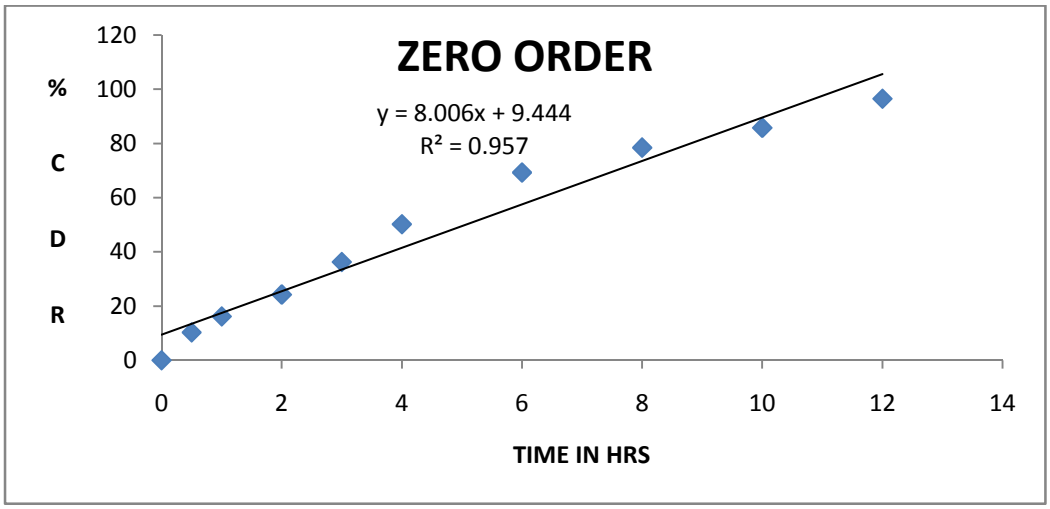

Figure.5: Zero order release model for optimized F8 formulation

CONCLUSION

Gastro retentive floating tablets of Celecoxib were developed by using HPMC K4M, xanthan gum and Guar gum, which could retain in the stomach for longer periods of time delivering the drug to the site of action, i.e., stomach. The pre-compression parameters of all formulations showed good flow properties and these can be used for tablet manufacture. The post-compression parameters of all formulations were determined and the values were found to be satisfactory. From the floating nature and *in-vitro* dissolution studies of the formulations, it was concluded that the formulation F8 is the best formulation. As a result of this study it was be concluded that the floating tablets prepared by using guar gum and HPMC K4M in optimized concentration can be used to increase the GRT to deliver the drug in a controlled manner. The concept of formulating floating tablets of Celecoxib offers a suitable and practical approach in serving desired objectives of gastro retentive floating tablets.

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