Formulation of Gastroretentive Floating Drug Delivery System of Indomethacin

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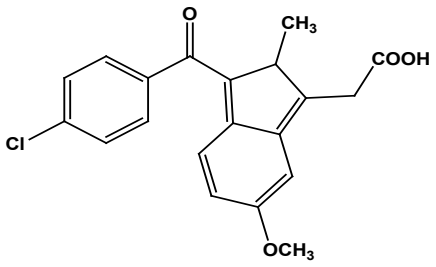
ABSTRACT

Indomethacin (NASID) is used as potent anti-inflammatory drug with prompt antipyretic action, mainly used for the treatment of osteoarthritis with half-life of 4.5 hours. The basic objective of present work was to prepare floating delivery system of Indomethacin for once a day formulation using gas formation technique for prolonging the gastric residence time, so that the dosage regimen and gastric irritancy can be reduced. Indomethacin was estimated in the formulation by using UV/Visible spectrophotometer (Shimazdu UV-1700) at 321 nm.
Tablets were evaluated for various parameters and it was observed that the formulation having 75 mg of Indomethacin, 34% HPMC K4M, 12% sodium bi-carbonate and 20% of lactose shows better result having 96.37% drug release within 24 hr with floating lag time of 155 seconds and floating time of 22 hr. It was also observed that as the concentration of gas generating and channeling agent increases, the chances of burst release and tablet erosion increases simultaneously. In the present study it was concluded that the floating drug delivery system with reduced floating lag time and sustained drug release of Indomethacin was obtained and could be a promising gastro-retentive drug delivery system.

Keywords: Floating drug delivery, Floating time, HPMC, Channeling agent.

INTRODUCTION

Indomethacin, 2-[1-(4-cholorobenzoyal)-5-methoxy-2methyl-indol-3-yl] acetic acid, mol wt= 357.787g/mol (fig 1), a nonsteroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic properties, is used to treat osteoarthritis and control acute pain.



Indomethacin has been known for years and has been the most successful non-steroidal anti-inflammatory agent available for the treatment of inflammatory diseases such as rheumatoid arthritis and osteoarthritis. The use of indomethacin in the traditional pharmaceutical forms such as tablets and capsules requires administration of three or four unit doses per day. Most patients on this therapeutic regimen are elderly and are often on treatment of other disease states, such as hypertension, depression etc. Accordingly, it is important for the convenience of the patient and more particularly to ensure compliance by the patient to the particular therapeutic regimen that the number of unit doses per day is kept to a minimum.

In addition to patient convenience and compliance, it is important, particularly in the treatment of rheumatoid arthritis, to maintain a continuous anti-inflammatory serum concentration of Indomethacin. This is difficult to accomplish with the traditional pharmaceutical forms of

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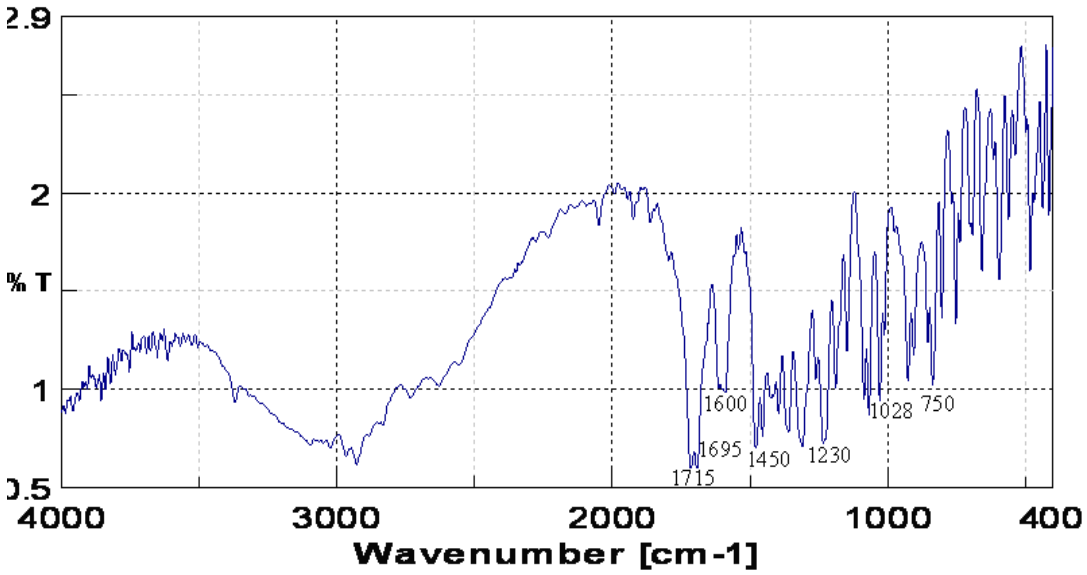

Figure 1: IR spectra of Indomethacin.

Indomethacin which are rapidly absorbed providing high serum concentrations and then slowly metabolized causing low serum concentration leading to three or four times a day administration of drug.

But, when taken orally against chronic inflammatory and pain conditions, adverse events often occur, such as general serious gastrointestinal reaction (even stomach perforation), central nervous system symptoms (dizziness, vertigo etc.), liver function damage, inhibition of hematopoietic system and allergic reaction.[1]

Meanwhile, its inconvenience in use is also a problem, such as pretty high frequency of administration (25 mg, tid) and long period of treatment.[2]

Floating dosage forms enable the sustained delivery of drugs in the gastro-intestinal tract[3] by retaining in the stomach and assists in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.[4]

Miyazaki et al. (1988) developed floating granules with the help of chitosan and compared the release rate with commercial Indomethacin capsules and a sustained release Indomethacin capsule. In contrast with the rapid release of a commercial conventional capsule form and sustained release from the chitosan granules was observed.[5]

In the present investigation floating tablets of Indomethacin were prepared by effervescent approach using HPMC K 4M. The aim of the work was to evaluate the effect of gel-forming polymer HPMC K 4M on floating properties and release characteristics of Indomethacin tablets.

MATERIALS AND METHODS

Materials

Indomethacin IP/BP was received as Gift sample from Wintac Limited, Bangalore India. Hydroxypropylmethyl cellulose was received as generous gift sample from Colorcon Asia Pvt Ltd, India. Magnesium stearate, hydrochloric acid, sodium bicarbonate and citric acid anhydrous (hereafter referred to as citric acid) was purchased from S.D. Fine-Chem Ltd, Ahmedabad, India. Lactose and purified talc were purchased from E. Merck (India) Ltd., Mumbai. All other ingredients were of laboratory grade.

Methods

Characterization Of Drug And Polymer

FTIR spectra of Indomethacin, from 4000 cm^{-1} to 400 cm^{-1}, was obtained using FTIR spectrophotometer (Shimadzu, Japan) according to KBr pellet method and compared with standard reference spectra of Indomethacin. The IR spectra of physical mixture of drug and HPMC K4M were recorded to determine the suitability of selected excipients for the formulation of gastro-retentive formulation of Indomethacin using Infrared spectrophotometer.

Preparation of Floating Tablets of Indomethacin

The ingredients were weighed accurately and mixed thoroughly. Granules were prepared by wet granulation method. HPMC K4M and Indomethacin were mixed homogeneously by pestle mortar. Lactose was used as filler and channeling agent. Sodium bi carbonate and citric acid was used as effervescent agent. Ethanol is used

as granulating agent. Granules were prepared by 40/60 mesh screen and the granules (40 mesh) were dried in conventional hot air oven at 45°c

To these Granules, talc (1% w/w) and magnesium stearate (1% w/w) were added as a glidant and lubricant respectively. Tablets were compressed using 9 mm die/punch set in a single punch tablet compression machine (Lab Tech. instruments).

Characterization of Granules and Prepared Tablets

The flow properties of granules (before compression) were characterized in terms of angle of repose, Carr index and Hausner ratio.[6] For determination of angle of repose (θ), the granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0cm above hard surface. The granules were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The $\tan^{-1}$ of the (height of the pile / radius of its base) gave the angle of repose.

Granules were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess granules were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there was no more decrease in the volume. Bulk density (ϱb) and tapped density (ϱt) were calculated. Hausner ratio (HR) and Carr index (CI) were calculated according to the two equations given below:

$$HR = \varrho t / \varrho b$$

$$CI = (\varrho t - \varrho b) / \varrho t$$

Uniformity of Weight and Hardness of Tablets

The test was performed according to Indian pharmacopoeia. 20 tablets were selected at random, weighed together and individually for the determination of weight of tablets.[6] The mean and standard deviations were calculated. Five tablets were selected at random and the hardness of each tablet was measured on Monsanto hardness tester.

Uniformity of Content

The test is not obligatory for tablets containing more than 10 mg or more than 10 % w/w of active ingredient. So the test was performed as per the USP,[7] A tablet was crushed and dissolved in 60 ml of methanol after mixing the content in 10 ml of water , volume was make up with volume with methanol. Diluted the clear portion of the solution up to 25 µg/ml and absorbance were at 321 nm. The test was performed in triplicate for each batch.

Friability

The friability test was carried out in Roche Friabilator.[6] Ten tablets were weighted (Wo) initially and put in a rotating drum. Then the tablets were subjected to 100 falls of 6 in. height. After completion of rotation, the tablets were again weighted (W).

$$\% \text{ Weight loss or friability} = (1 - W/Wo) \times 100$$

Total Floating Time and Floating Lag Time Determination

The buoyancy of the tablets was studied at 37±0.5°C in 100 ml of simulated gastric fluid at pH 1.2 without pepsin, as per USP.[8] At the same time total *in vitro* floating time was carried out as per the method described by **Rosa et al**. by placing the tablet in same media as used for the lag time determination.[9] The duration of tablet floatation was observed visually in triplicate for each batch of tablets.

In Vitro Dissolution Test[10,11]

In-vitro release studies were carried out in the dissolution test apparatus USP Type II. The tests were performed out in 900 ml of (SGF+1%SLS) for 24 hrs at 75 rpm at 37±0.5°C.[12] Ten ml of the aliquot were withdrawn at different predetermined specified time intervals and filtered. Sample was analyzed at 321 nm using UV/Visible spectrophotometer (Shimazdu UV-1700, Japan) using corresponding blank. The withdrawn volume was replaced with an equal volume of pre-warmed (37°C) media. The percentage drug release was calculated using the calibration curve and was plotted against function of time to study the pattern of drug release from tablets.

RESULT

Characterization of Drug and Polymer

An FTIR spectrum of the pure indomethacin is mentioned in (fig1). The FTIR spectrum of drug and polymer showed no significant shift or reduction in intensity of peaks of Indomethacin as shown in (fig 2).

Flow Properties of Granules

The granules prepared for compression of floating tablets were evaluated for their flow properties (Table 2). Angle of repose was in the range of 24.28 to 28.26 in granules containing methocel K4M. Bulk density ranged between 0.531 to0.605gm/cm^3 in granules containing methocel K4M. Tapped density ranged between 0.612 to 0.687 gm/cm^3, Carr's index was found to be 11.29 to 14.49 and Hausner ratio ranged from 1.116 to 1.161 for granules of different formulations.

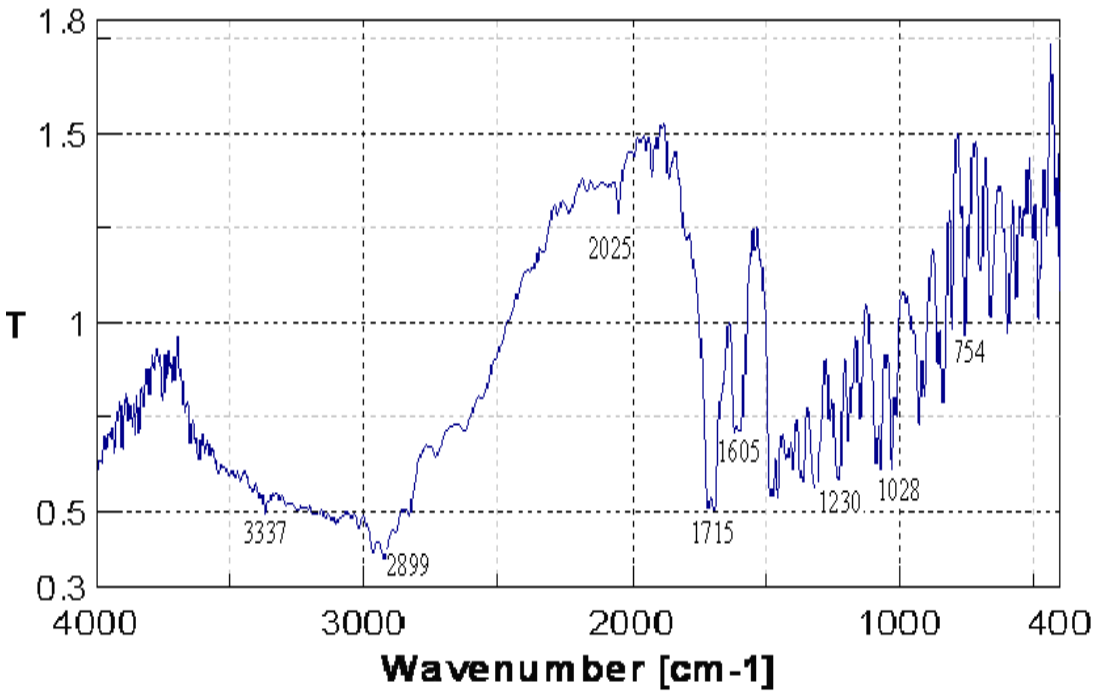

Figure 2: IR spectra of the physical mixture of Indomethacin and HPMC K4M.

Table 1. Composition of floating tablet of Indomethacin

Ingredient	P1	P2	P3	P4	G1	G2	G3	G4	G5	G6
Indomethacin	75	75	75	75	75	75	75	75	75	75
HPMC K 4M	60	75	85	100	85	85	85	85	85	85
Sodium bicarbonate	25	25	25	25	-	-	30	35	30	30
Sodium carbonate	-	-	-	-	25	-	-	-	-	-
Potasium carbonate	-	-	-	-	-	25	-	-	-	-
Lactose	40	40	40	40	40	40	40	40	45	50
Citric acid	5	5	5	5	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Table 2. Flow Properties of Granules

Code	Angle of repose	Bulk Density	Tapped density	Hausner ratio	Carr Index
P1	24.281 ± 0.261	0.531 ± 0.041	0.621 ± 0.043	1.169	14.49
P2	25.321 ± 0.290º	0.528 ± 0.025	0.612 ± 0.053	1.159	13.72
P3	26.410 ± 0.402º	0.542 ± 0.044	0.632 ± 0.073	1.116	14.2
P4	28.160 ± 0.363º	0.552 ± 0.026	0.631 ± 0.064	1.143	12.51
G1	26.342 ± 0.532º	0.541 ± 0.048	0.620 ± 0.071	1.146	12.74
G2	25.625 ± 0.374º	0.544 ± 0.081	0.614 ± 0.063	1.159	11.40
G3	27.561 ± 0.380º	0.593 ± 0.087	0.687 ± 0.043	1.158	13.68
G4	27.840 ± 0.972º	0.605 ± 0.086	0.682 ± 0.089	1.127	11.29
G5	28.262 ± 0.850º	0.591 ± 0.028	0.681 ± 0.077	1.152	13.22
G6	26.879 ± 0.571º	0.587 ± 0.043	0.682 ± 0.062	1.161	13.10

Table 3. Physicochemical characterization of Indomethacin Floating tablet

Code	Uniformity of weight (mg)	% drug Content	Hardness kg/ cm^2)	Friability %	Floating Lag time (s)	Total floating time (h)
P1	4.05 ± 0.11	96.65 ± 0.421	3.31 ± 0.42	0.632	230	14
P2	4.15 ± 0.17	97.15 ± 0.322	3.64 ± 0.33	0.621	158	16
P3	4.32 ± 0.08	98.05 ± 0.241	3.53 ± 0.41	0.624	150	22
P4	4.67 ± 0.14	96.95 ± 0.621	3.82 ± 0.26	0.608	130	28
G1	4.17 ± 0.12	97.48 ± 0.465	3.23 ± 0.26	0.649	257	21
G2	4.32 ± 0.19	98.10 ± 0.473	3.22 ± 0.43	0.684	230	20
G3	4.25 ± 0.16	97.67 ± 0.387	3.22 ± 0.32	0.698	140	21
G4	4.31 ± 0.21	97.35 ± 0.412	3.08 ± 0.23	0.696	109	22
G5	4.06 ± 0.26	98.31 ± 0.352	3.16 ± 0.45	0.679	150	22
G6	4.31 ± 0.21	98.15 ± 0.532	3.08 ± 0.23	0.698	155	22

These values indicate that the prepared granules exhibited good flow properties.

Evaluation of Floating Tablets

The floating tablets of Indomethacin were prepared by effervescent technique using HPMC K4M, sodium bicarbonate, citric acid and lactose. The magnesium stearate and talc were used as lubricant and glidant, respectively. The results of the physico-chemical characterization are shown in (Table 3). The weight of the tablet varied between 238 mg to 262 mg for different formulations with low standard deviation values, indicating uniformity of weight. The variation in weight was within the range of 4.05 ± 0.11 % to 4.67 ± 0.14 in all the batches, complying with pharmacopoeial specifications.[13] The content of the tablet was found to be drug in between 96.65± 0.421 to 98.31 ± 0.352.

The hardness for different formulations was found to be between 3.3 to 4.0 kg/cm^2 indicating satisfactory mechanic strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet.

The data obtained from *in vitro* dissolution studies were fitted in different models viz. zero order, first order[14] and Higuchi square root law, Korsemeyer's equation[15] as mentioned in the (Table 4). The correlation coefficient value of all the formulations showed that the formulations did not follow zero order release pattern as shown in(fig 3 & 4).

When the data were plotted according to the first order equation, the formulations shows a fair linearity, with correlation coefficient values between 0.9035 and 0.9776, which indicates greater the concentration faster, the release rate of drug from tablet, shown in (fig. 5 and 6),

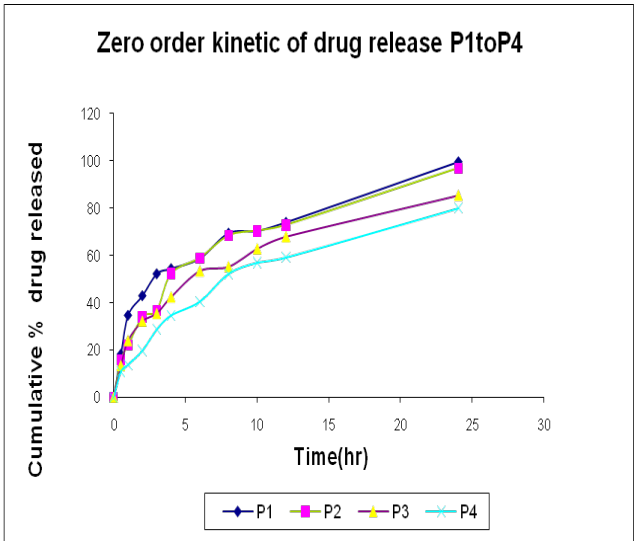

Figure 3: Zero order release kinetic treatment of batch P1to P4

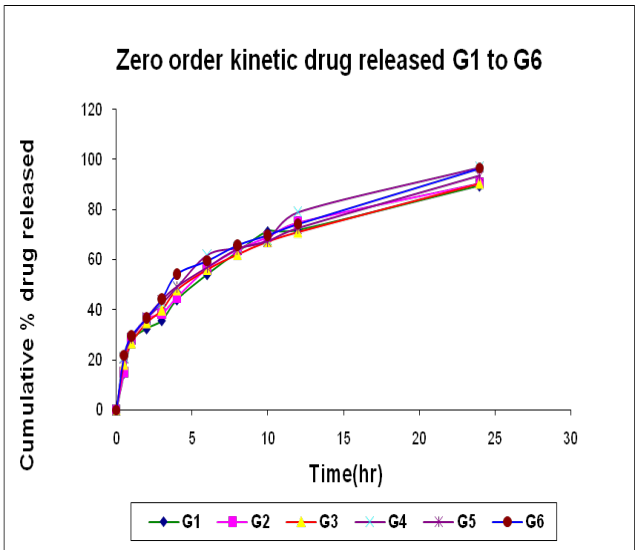

Figure 4: Zero order release kinetic treatment of batch G1to G6

Table 4. Kinetics of *In Vitro* Indometacin Release from Floating Tablets

Code	Zero order (r^2)	First order (r^2)	Higuchi plot (r^2)	Korsemeyer Model	
				(n)	(r^2)
P1	0.7616	0.9039	0.9538	0.32	0.9842
P2	0.8042	0.9501	0.9738	0.46	0.9688
P3	0.8111	0.9608	0.9805	0.41	0.9904
P4	0.8675	0.9776	0.9888	0.47	0.9854
G1	0.8111	0.9713	0.9732	0.41	0.9712
G2	0.7893	0.9748	0.9718	0.38	0.9833
G3	0.7979	0.9592	0.9782	0.39	0.9919
G4	0.8060	0.9606	0.9783	0.39	0.9915
G5	0.7986	0.9512	0.9775	0.37	0.9947
G6	0.7921	0.9465	0.9735	0.36	0.9945

To confirm the exact mechanism of drug release from these tablets, the data were fitted according to Higuchi's kinetics and Korsemeyer's equation, the *in vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's equation as the plots (Fig 7 and 8) shows high linearity (r^2= 0.9538 to 0.9888).

This represents the release process under the drug diffusion through polymer matrix. To confirm the diffusion mechanism, the data were fitted to Korsmeyer's equation, formulations shows linearity with exponent value (n) ranging from 0.32 to 0.47. This n value figure 3: ever, indicates the coupling of swelling and diffusion mechanism so called as Fickian diffusion.

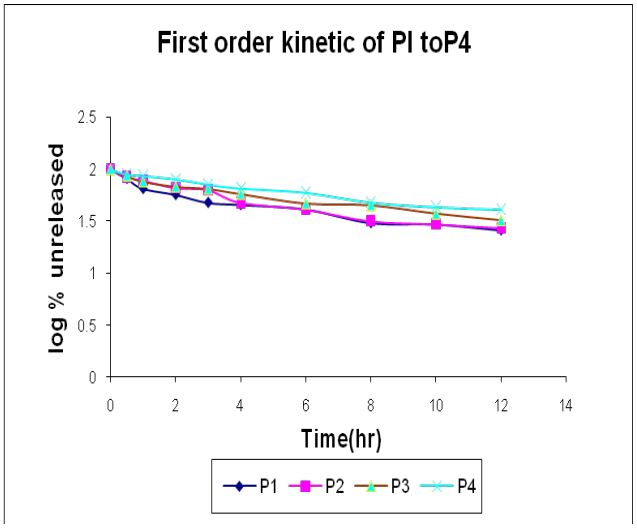

Figure 5: First order release kinetic treatment of batch P1 to P4

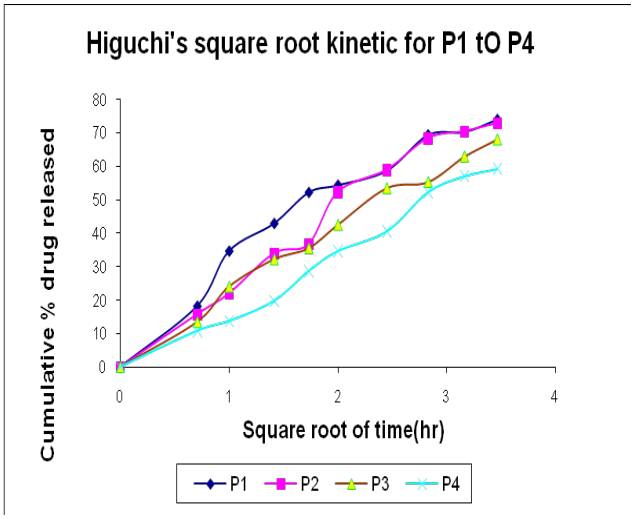

Figure 7: Higuchi's square root kinetic treatment of batch P1to P4

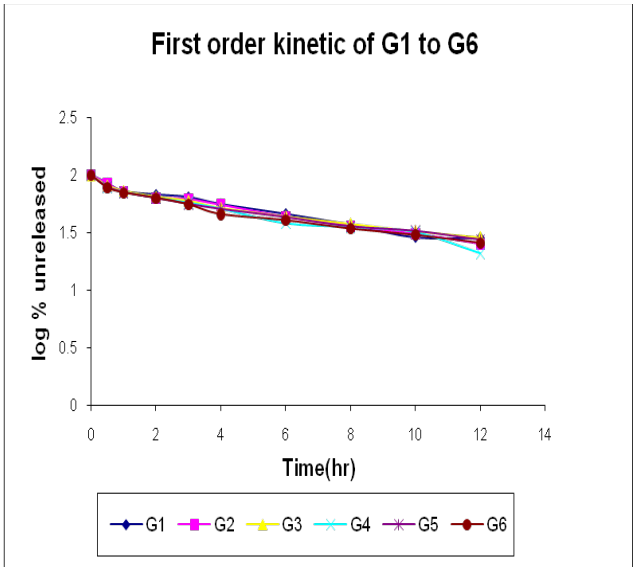

Figure 6: First order release kinetic treatment of batch G1to G6

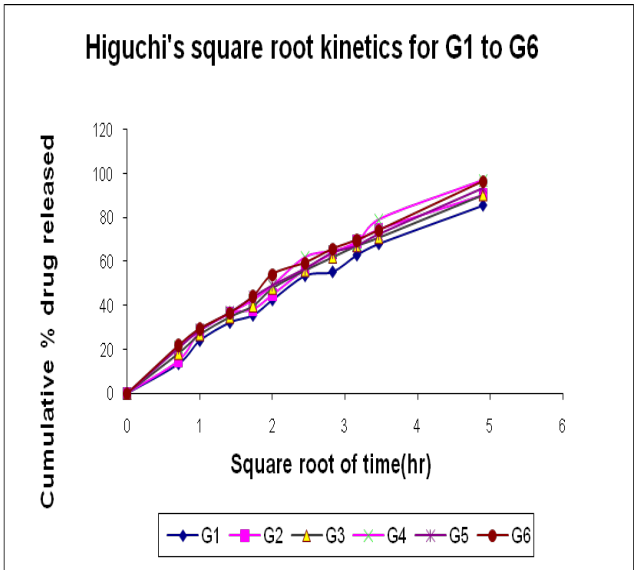

Figure 8: Higuchi's square root kinetic treatment of batch G1to G6

DISCUSSION

All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid). The combination of sodium bicarbonate and citric acid rather than the potassium bicarbonate and calcium carbonate provided desired floating ability and therefore this combination was selected for the formulation of the floating tablets. It was observed that the gas generated is trapped and protected within the gel, formed by hydration of polymer (methocel), thus decreasing the density of the tablet below one and tablet becomes buoyant. The tablet swelled radially and axially during *in vitro* buoyancy studies. It was observed that the low concentration of HPMC K4M causes the disintegration of the tablet before the desired time while excess amount of polymer leads to the trapping of drug release, so the concentration of lactose was optimized to get the optimum release because it was observed during the study that addition of lactose causes better release of the drug from the matrix which shows the channeling property of lactose. All the batches of tablets were found to exhibit short floating lag times due to presence of sodium bicarbonate and citric acid. Decrease in the citric acid level increased the floating lag time and tablets were found to float for longer duration. The treatment by zero order plot, first order plot, higuchi plot and korsemayer shows the release process under the drug diffusion through polymer matrix

CONCLUSION

From the above observations, we concluded that Indomethacin may reside in the stomach for a longer period of time when it is administered in the form of floating tablets in comparison with the conventional system. This system has suggested that the floating tablets could serve as candidate for novel oral delivery that may reduce the doses regimen of Indomethacin and possibly of other drugs, which are aimed to produce a local action and specifically absorbed through the upper region of the GIT.

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