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IJPBS |Volume 3| Issue 1 |JAN-MAR |2013|194-202

Research Article
Pharmaceutical Sciences

ROLE OF HYDROPHILIC POLYMER ON ETODOLAC FLOATING TABLETS

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ABSTRACT

The purpose of this research was to prepare floating matrix drug delivery system of Etodolac. Floating matrix tablets of Etodolac were developed to prolong gastric residence time. Rapid gastrointestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of the administered dose. Floating matrix tablets containing 100 mg Etodolac were developed using different hydrophillic combinations. The tablets were prepared by direct compression method, using polymers such as hydroxypropylmethylcellulose (HPMC K15, k4m), Carbomer 971p and other standard excipients. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of sodium bicarbonate on drug release profile and floating properties were investigated. The formulation was optimized on the basis of acceptable tablet properties, floating lag time and total duration of floating and in vitro drug release. The resulting formulation produced tablets with optimum hardness, uniform thickness, consistent weight uniformity and low friability. The results of dissolution studies, floating lag time indicated that formulations F9 exhibited good and controlled drug release up to 18hrs as the polymer concentration increases the dissolution rate was decreased. Applying the linear regression analysis and model fitting showed the selected formulation F9 showed diffusion drug release mechanism followed first order kinetics.

KEY WORDS

Etodolac; Floating tablets; HPMC, carbopol; Sustained release

INTRODUCTION

Etodolac belongs to a class of nonsteroidal anti-inflammatory drugs (NSAIDs). Other members of this class include aspirin, ibuprofen (Motrin, Advil, Nuprin, etc.), naproxen (Aleve,Naprosyn), indomethacin (Indocin), nabumetone (Relafen) and numerous others. These drugs are used for the management of mild to moderate pain, fever, and inflammation. They work by reducing the levels of prostaglandins, which are chemicals that are responsible for pain and the fever and tenderness that occur with inflammation.

Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. The purpose of controlled release systems is to maintain drug concentration in the blood or in target tissues at a desired value as long as possible. In other words, they are able to exert a control on the drug release rate and duration. In recent years, considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery system because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance[1].

The need for Gastroretantive dosage forms (GRDFs) has led to extensive efforts in both academic and industry towards the development of such drug delivery systems. Prolonging the gastric residence of a dosage form may be of therapeutic value. Amongst the methods available to achieve this, floating dosage forms show considerable promise[2].

Floating tablet of Etodolac will have the following advantages than other conventional dosage forms;

1. Improved drug absorption, because of increased GRT and more time spent by the dosage form at its absorption site
2. Delivery of drugs for local action in the stomach
3. Minimizing mucosal irritation by drugs, by drug releasing slowly at a controlled rate
4. Treatment of gastrointestinal disorders such as gastro-esophageal reflux
5. Ease of administration and better patient compliance

Hence the present work has been proposed. The aim of this proposed work is to role of HPMC on floating tablets of Etodolac.

MATERIALS AND METHODS

Etodolac gift sample from Bioleo analytical labs, prashanthinagar. HPMC K15, HPMC K4M, Carbopol940, lactose, $NaHCO_3$, Magnesium sterate was obtained from Drugs India, Hyderabad. All reagents and solvents used were of analytical grade satisfying pharmacopoeial standards.

The Compositions of formulations with different polymers are given in the following tables (1.6). Accurately weighed quantities of hydrophilic polymers, Lactose were taken in a mortar and mixed geometrically. To this mixture required quantity of Etodolac was added and mixed slightly with pestle. This mixture was passed through 32# and later collected in a plastic bag and blended for 5 min. Later sufficient quantity of Magnesium Stearate was added and the final blend was again passed through 32#.

Then they obtained blend was mixed thoroughly for 10 min and compressed into tablets with 8.7 mm round concave Punches and corresponding dies at a hardness of 5.5 kg/cm twelve station tablet punching machine. Here each tablet weight is kept constant for 250mg[3].

EVALUATION PARAMETERS

The prepared floating tablets were evaluated for Uniformity of weight using 20 tablets, Hardness, Friability, I*n Vitro* buoyancy, Swelling behavior (Water uptake studies) and *In Vitro* dissolution studies.

(1) Hardness*:*

The hardness of ten tablets was measured using Hardness tester. Mean and standard deviation were computed and reported. It is expressed in kilopascal (kp)[5].

(2) Friability*:*

The friability of the tablets was determined using thermionic friabilator. It is expressed in percentage (percentage). 10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for four minutes. After four minutes the tablets were weighed again. The % friability was then calculated using the formula[5].

$$\%\text{Friability} = \frac{\text{initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

(3) Weight variation:

Twenty tablets were selected at random and the average weight of the tablets was determined. The weight of individual tablets was compared with the average weight[6].

(4) Drug content uniformity:

Prepared tablets were accurately weight and finely powdered by pestle in a mortar. A weighed portion of each powder equivalent to 1 mg/ml of prepared tablet was transferred in to a volumetric flask and the drug was extracted with methanol as the solvent. The contents of the flask were sonicated for 10 min and diluted with 0.1 N HCl as the solvent. The samples were analyzed spectrophotometrically at 274 nm[6].

(5) In Vitro Buoyancy Studies

The in vitro buoyancy was determined by floating lag time, per the method described by the tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time[7].

(6) Swelling study

Swelling of hydrophilic polymer such as Hydroxy Propyl Methyl Cellulose greatly depends upon the contents of the stomach and the osmolarity of the medium. This eventually influences the release, slowing action and the residence time. For each formulation, one tablet was weighed and placed in a beaker containing 200 ml of 0.1 N Hcl. After each hour the tablet was removed from beaker and weighed again up to 8 hours. The percentage weight gain by the tablet was calculated by using the formula[7].

Swelling index (S.I) = $\{(W_t-W_o)/W_O\}$ x 100

Where, S.I. = swelling index

Wt = Weight of tablet at time t

WO = Weight of tablet before immersion.

(7) In Vitro Dissolution Studies

The release rate of Etodolac from floating tablets (n = 3) was determined using *United States Pharmacopeia (USP)* 23. Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 mL of 0.1N HCl, at 37 ± 0.5°C and 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus hourly for 18 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45-µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 274 nm using a Shimadzu UV-1601 UV/Vis double-beam spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

(8) Stability Study

The selected batch (F9) was kept at 40° C with 50% RH and the samples were withdrawn at 30, 60 and 90 days for physical and *in vitro* evaluation of drug release.

(9) Drug release Kinetics:

Zero order release rate kinetics

To study the zero order release kinetics the release rate data are fitted to the following equation

$F= K_0t$

Here, F is the fraction of drug release

K_0 is the rate constant

T is the release time

First order model

This model has also been used to describe absorption and /or elimination of some drug, the release of the drug which followed first order kinetic can be expressed by the equation

$LogC = logC_0-Kt/2.303$

Where, C_0 is the initial concentration of drug

K is the first order rate constant

t is the time

Higuchi release model

To study the Higuchi release kinetics, the release rate data was fitted to the following equation

$F = K_H.t^{1/2}$

Where, F is the amount of drug release

K_H is the release rate constant

t is the release time

Korsmeyer and peppas model

The release rate data were fitted to the following equation,

$Mt/M8 =K_M.t^n$

Where, Mt/M8 is the fraction of drug release
K_M is the release constant
t is the release time

RESULTS AND DISCUSSION

Flow Properties:

Etodolac along with other excipients were evaluated for bulk density, tap density, angle of repose, compressibility and Hausner ratio, before proceeding to direct-compression. The physical parameters are recorded in **Table 1.1.**

[a] Angle of repose: 26 to 30 indicating good, 30-35 indicating passable.

[b] Compressibility index: 19 to 23 indicating passable and 25-28 indicating poor.

[c] Hausner ratio: 1.24 to 1.34 indicating passable and 1.35 to 1.39 indicating poor.

Table No 1.1 Preformulation parameters of Etodolac

Formulation	Bulk Density (gm/cm^2)	Tapped Density(gm/cm^2)	Carr's Index	Hausner's Ratio	Angle of Repose
F1	0.390	0.500	22	1.28	28.1
F2	0.378	0.510	25.88	1.35	30.9
F3	0.387	0.496	22	1.28	27.2
F4	0.364	0.506	28.06	1.39	31.3
F5	0.393	0.510	22	1.32	32.6
F6	0.416	0.516	19.37	1.24	34.6
F7	0.374	0.514	27.23	1.37	28.3
F8	0.388	0.526	26.23	1.36	26.7
F9	0.396	0.511	25.50	1.29	29.4

Evaluation Studies

The important parameters in the production of tablets were evaluated and reported in **Table 1.2.** The weight variation of the tablets was within the range. The thickness varied from 4.1± 0.1 mm. The hardness varied from 5.5 ± 1.0 kg\cm^2 found satisfactory. The friability test was passed. The percent content uniformity was 100 ± 2 and therefore was satisfactory.

Table No 1.2 Evaluation studies of Etodolac

Formulation	Average weight of tablets (mg)	Hardness (Kg/cm2)	Friability (%)	% Drug content	Buoyancy lag Time (sec)	Total floating time (hrs)
F1	250	5.5	0.19	100.01	113	>20
F2	249	5.2	0.14	100.31	129	>20
F3	248	5.5	0.21	101.31	174	>20
F4	248	5	0.15	101.20	150	>20
F5	250	5.2	0.12	99.77	165	>20
F6	252	5	0.21	100.52	140	>20
F7	251	5	0.40	98.21	96	>20
F8	250	5.2	0.13	99.58	109	>20
F9	250	5.5	0.20	100.97	105	>22

Swelling index

The swelling studies were conducted on matrix tablets of Etodolac on the basis of weight. The weight was taken after 12 hours. The data are recorded in **Table 1.3.** Swelling was uniform for all formulation.

Table No 1.3 Swelling index

Formulation	Swelling index (%)			
	Time (hr)			
	1	4	8	12
Fl	12.06	22.46	63.21	87.74
F2	14.04	29.94	70.38	98.56
F3	18.29	40.34	81.92	109.95
F4	13.31	34.52	72.77	99.39
F5	20.38	45.74	79.8	115.18
F6	26.62	55.75	91.07	122.50
F7	22.04	44.08	80.67	105.3
F8	27.45	54.89	90.65	119.76
F9	32.86	63.63	99.80	131.6

Kinetics Data

The Higuchi equation suggests that the drug release by diffusion.

Table No 1.4 Dissolution table of formulations in 0.1N HCL

Time in hrs	1hr	2hr	4hr	6hr	8hr	10hr	12hr	14hr	16hr	18hr
F1	32.36	42.57	55.86	68.58	78.21	84.95	95.9			
F2	26	38.14	51.62	65.5	75.21	78.8	87.07	94		
F3	23.3	33.52	47.2	54.7	61.64	76.5	77.25	85.72	96.51	
F4	33.51	45.46	59.91	80.9	96.7					
F5	30.05	42.95	55.09	72.23	87.84	97.86				
F6	25.62	37.75	49.9	64.73	78.98	88.61	98.28			
F7	36.6	50.08	67.42	89	96.31					
F8	24.07	35.63	52.78	66.07	80.9	90.73	95.93			
F9	21.57	34.29	43.53	53.75	60.1	66.65	74.74	82.83	91.88	98.44

STABILITY STUDIES

Table No.1.5: Stability Data of Formulation 9 at 30±2°c/65 ± 5%RH and 40 ± 2°C / 75 ± 5% RH

Time (Days)		Hardness (kg/cm²)	Drug content (%)	Floating lag time (s)
0		5.67 ± 0.14	99.76 ± 0.81	36.10 ± 0.36
30	At 30 ± 2°C 65 ± 5%RH	5.57 ± 0.10	99.06 ± 0.50	37.50 ± 0.2
	At 40 ± 2°C 75 ± 5%RH	5.57 ± 0.10	98.80 ± 0.70	37.7 ± 0.3
60	At 30 ± 2°C 65 ± 5%RH	5.50 ± 0.05	98.14 ± 0.30	38.7 ± 0.3
	At 40 ± 2°C 75 ± 5%RH	5.50 ± 0.05	97.21 ± 0.45	39.2 ± 0.4

Table No.1.6 Formulation table of Etodolac

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Etodolac	100	100	100	100	100	100	100	100	100
Lactose monohydrate	102.5	82.5	77.5	102.5	82.5	77.5	102.5	82.5	77.5
HPMC k4m	25	37.5	50	--	--	--	--	--	--
Carbomer 971p	--	--	--	25	37.5	50	--	--	--
HPMC k15	--	--	--	--	--	--	25	37.5	50
$NaHCO_3$	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
MS	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Tablet weight	250	250	250	250	250	250	250	250	250

FIGURES

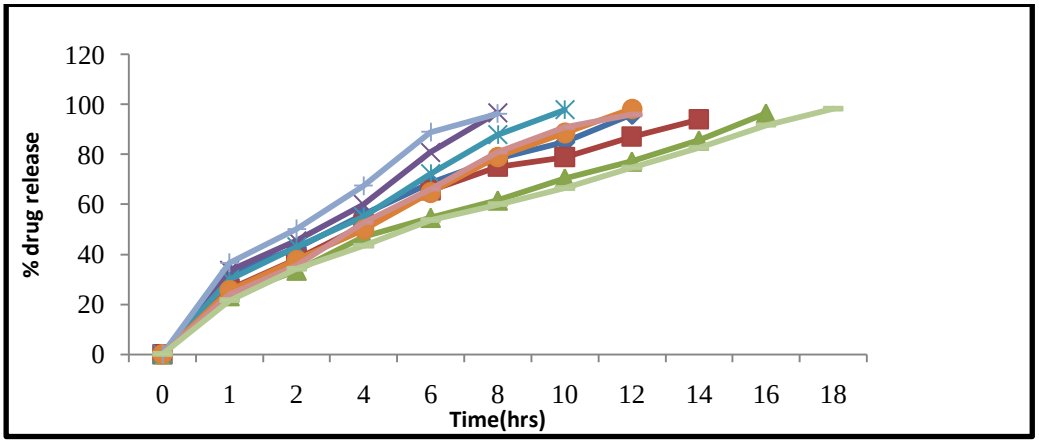

Fig 1.1: Graphs of Dissolution Studies

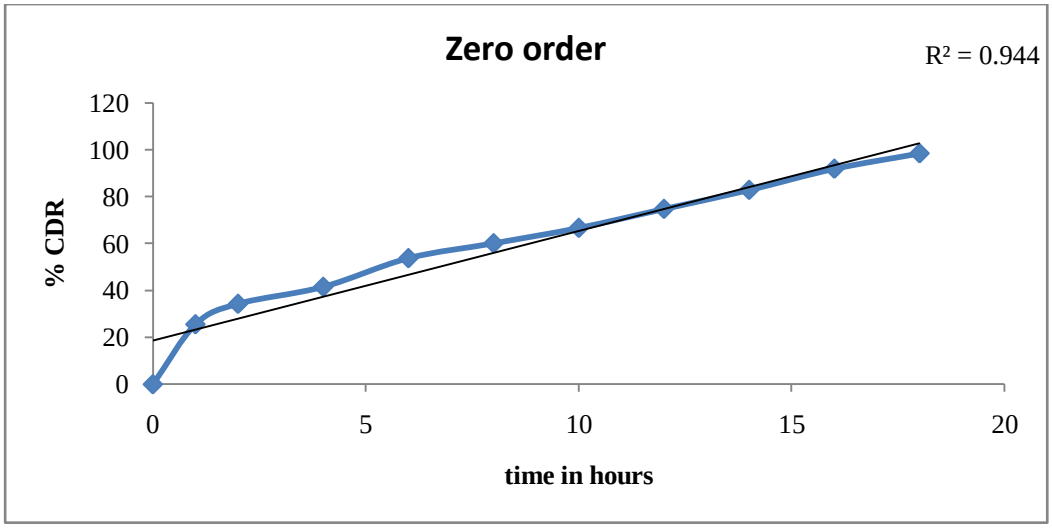

Fig No.1.2: Zero order kinetic graph

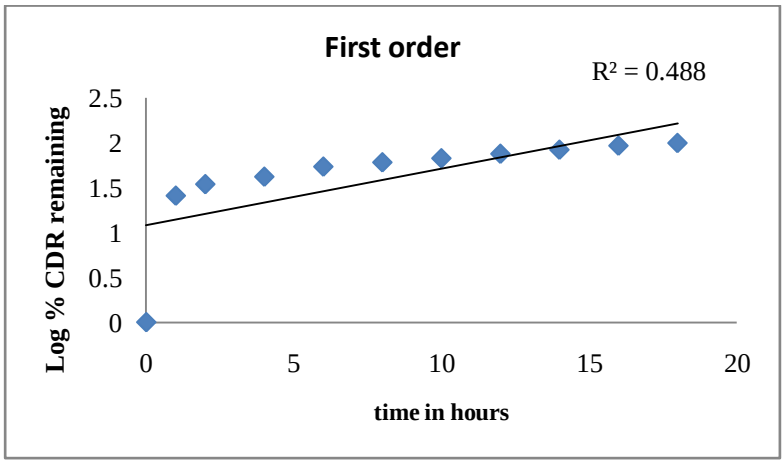

Fig No.1.3: First order kinetic graph

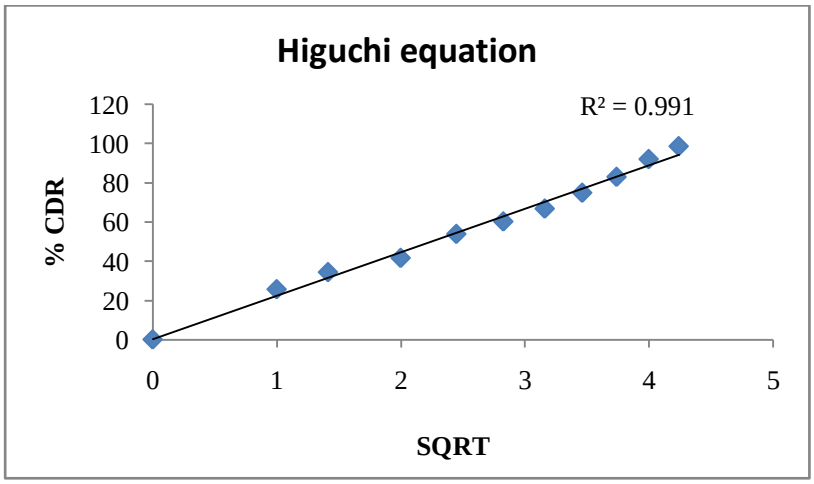

Fig No.1.4.Higuchi equation graph

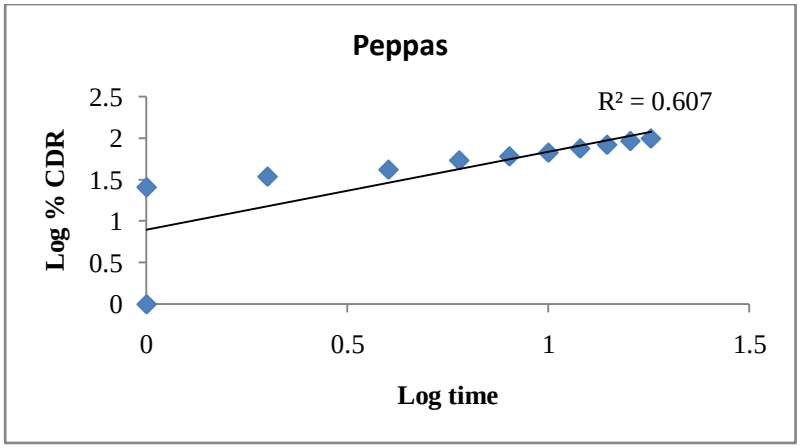

Fig No.1.5:Peppas-korsemeyer equation graph

CONCLUSION

Drug release was delayed efficiently by hydrophilic polymers SR as a matrix forming excipient and was found to be governed by Higuchi model. For estimating food effects on application of floating oral drug delivery effects it is of great importance to study floating performance not only regarding floating duration but floating strength as well. All formulations remained float for a time interval of 18 h and showed an increased floating strength for samples with a higher polymer/drug ratio. As the polymer concentration increases lag floating time and release rate was retarded.

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