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FORMULATION AND INVITRO EVALUATION OF GASTRORETENTIVE FLOATING MATRIX TABLETS OF ETODOLAC

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ABSTRACT

In the present work, an attempt has been made to develop *In vitro* Evaluation of Gastroretentive Floating Matrix tablets of Etodolac. Novel method of Gastroretentive Floating Matrix technology was employed to formulate the tablets. All the formulations were prepared by direct compression method using 8mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F4 was considered as best formulation after considering all the evaluation parameters. *In vivo* evaluations were performed later for the selected best formulation.

KEYWORDS: Etodolac, Gastroretentive Floating Matrix, Blend, Direct compression, quality control, parameters.

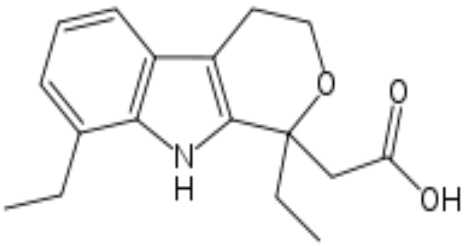
INTRODUCTION

The gastro-intestinal (GI) tract is diversified in its composition at several locations in anatomy, biochemical environment, microbial flora, expression of transporters and absorption characteristics. There are several processes such as chemical/ enzymatic/ bacterial degradation, absorption, precipitation, efflux by P-glycoprotein pump and metabolism by Cytochrome P450 enzymes may occur simultaneously following drug release from a dosage

form in the GI tract. Due to this, the pharmacokinetic profile of drug may be influenced by delivery site. This type of delivery approach found to be unsuitable for drugs that are poorly absorbed from the lower part of the GI tract. The concept of controlled release gastro retentive dosage form (GRDF) was introduced in order to enable continuous delivery of drug substance to the upper part of the GI tract, while minimizing the limitation of poor absorption from the colon. GRDFs are designed such that the dosage form retained in the stomach for a prolonged time period while releasing their content in a continuous and controlled manner. The gastric retention is attained by preventing the dosage form from travelling across the pyloric sphincter. Many alterations in pharmacokinetic and pharmacodynamic profiles of drugs have been reported following drug administration in GRDFS.

Etodolac belongs to a class of drugs called 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. Etodolac blocks the enzyme that makes prostaglandins (cyclooxygenase), resulting in lower concentrations of prostaglandins. As a consequence, inflammation, pain and fever are reduced. The U.S. Food and Drug Administration approved etodolac in January 1991. Post-marketing studies demonstrated that etodolac inhibition of cyclooxygenase is somewhat COX-2 selective similar to celecoxib and other "COX-2 inhibitors." Unlike rofecoxib, both etodolac and celecoxib can fully inhibit COX-1 and are designated as having "preferential selectivity" toward COX-2. Interestingly, the (inactive against COX) r-enantiomer of etodolac inhibits beta-catenin levels in hepatoma cells.

Etodolac



Systemic (IUPAC) name: (RS)-2-(1,8-Diethyl-4,9-dihydro-3H-pyano(3,4-b)indol-1-y1) acetic acid

The effect of etodolac (CAS 41340-25-4) on the inflammatory reactions induced by histamine and bradykinin was compared with that of indomethacin and other nonsteroidal anti-inflammatory drugs. Etodolac (50 mg/kg p.o.), indomethacin (20 mg/kg p.o.), diclofenac Na (20 mg/kg p.o.) and acetylsalicylic acid (200 mg/kg p.o.) had no effect on the increase of vascular permeability induced by histamine or bradykinin and on passive cutaneous anaphylaxis in rats. Etodolac (5, 10 and 20 mg/kg p.o.) suppressed concanavalin A-induced paw edema in rats. Etodolac (10 mg/kg p.o.) and bromelain (10 mg/kg i.v.) significantly suppressed the heat-induced elevation of bradykinin in perfusates of rat paws, but indomethacin (20 mg/kg p.o.) and diclofenac sodium (20 mg/kg p.o.) did not. Etodolac inhibited bradykinin-forming enzyme activity in a concentration-dependent manner. These results suggest that etodolac is a unique nonsteroidal anti-inflammatory drug which can also inhibit bradykinin formation, unlike indomethacin or diclofenac sodium.[1-7] Floating tablet of Etodolac will have the following advantages than other conventional dosage forms;

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

Hence the present work has been proposed with the aim of to formulate and evaluate floating tablets of Etodolac.

MATERIALS AND METHOD

Materials

Etodolac was obtained as gift sample from Yarrow Chem, Mumbai, India. Xanthum gum from Colorcon Asia Pvt. Ltd Goa, India. Guar gum and Micro Crystalline Cellulose procured from Signet Chem. Ltd, Mumbai, Magnesium Stearate, sodium bicarbonate and aerosol from S.D. Fine Chem. Ltd, Mumbai, India.

Methods

Formulation of floating tablets of Etodolac

Floating tablets of Etodolac were prepared by direct compression method employing sodium bicarbonate as gas-generating agent. Xanthgum and guar gum were used as rate controlling polymers. The concentrations of all the ingredients were optimized as shown in table no 1. All the ingredients were weighed accurately. The drug was mixed with the release rate retarding polymers and other excipients, except magnesium stearate, in ascending order of their weight. The powder mix was blended for 20 min to have uniform distribution of drug in the formulation. Then, magnesium stearate was added and mixed for 3 to 5 min (to ensure good lubrication.) The blended powder was compressed in to tablet in 8 station tablet punching machine.

Table No 1: Formulation of Etodolac Floating tablets.

	F1	F2	F3	F4	F5	F6	F7	F8
Etodolac (mg)	400	400	400	400	400	400	400	400
Guar Gum (mg)	200	250	300	350	---	---	---	---
Xanthum Gum (mg)	---	---	---	---	200	250	300	350
MCC (mg)	230	180	130	80	230	180	130	80
$NaHCo_3$ (mg)	150	150	150	150	150	150	150	150
Mg. Stearate (mg)	10	10	10	10	10	10	10	10
Aerosil (mg)	10	10	10	10	10	10	10	10
Total Weight of Tablet (mg)	1000	1000	1000	1000	1000	1000	1000	1000

EVALUATION PARAMETERS

Precompressional parameters

The powder blend of etodolac was evaluated for following parameters

1. Bulk Density
2. Tapped density
3. Compressibility Index
4. Hausners ratio
5. Angle of Repose
6. Drug Excipient compatibility studies

Post compression parameters[8-12]

Tablet Thickness

The Thickness and diameter of the tablets was determined using a Digital Vernier caliper. Ten tablets from each formulation were used and average values were calculated.

Weight variation

20 tablets were selected randomly and weighed accurately and average weight of tablet calculated. Not more than two of the individual weight deviates from the average weight by ± 10 % and none should deviate by more than twice that percentage. The weight variation test would be a satisfactory method of determining the drug content uniformity.

The percent deviation was calculated using the following formula:

$$\%\ Deviation = \frac{Individual\ weight - Average\ weight}{Average\ weight} \times 100$$

The average weight of tablets in each formulation was calculated.

Tablet Hardness

Tablet hardness is defined as the force required to break a tablet. Tablets require a certain amount of strength, or hardness and resistance to withstand the mechanical shocks during handling, manufacturing, packaging and shipping. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Six tablets were taken from each formulation and hardness was determined using Monsanto hardness tester and the average was calculated. It is expressed in Kg/cm2.

Friability Test

The percent loss of drug due to small mechanical forces during handling and shipping can be measured by using Roche friabilator consisting of a plastic chamber which revolves at a speed of 25rpm for 4 minutes. In each revolution the tablets were dropped from a height of 6 inches. For this test 10 tablets were selected from each batch and weighed accurately (Wi) and allowed to rotate for 4 min for 100 revolutions. Finally these were removed from chamber dedusted and weighed again (Wf). The % loss can be calculated using the following formula

$$\%\ Loss = \frac{Wi - Wf}{Wi} \times 100$$

Uniformity of drug content

5 tablets were powdered in a glass mortar and 100 mg of powder was placed in a 100 ml stoppered conical flask. The drug was extracted with 1.2 pH acidic buffer with vigorous shaking on a mechanical gyratory shaker (100 rpm) for 5 hour and filtered into 50 ml volumetric flask through cotton wool. 10ml of above filtrate was diluted to 100ml with 1.2

pH acidic buffer and absorbance was measured at 226 nm against blank using UV Visible spectrophotometer (1800 shimadzu, Kyoto, Japan).

In vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag time.[12,13] The tablets were placed in 250ml beaker containing 200ml of 1.2 pH acidic buffer. The time taken for a tablet to float to the surface of 1.2 pH acidic buffer was determined as Floating lag time and the period upto which the tablet remained floating is determined as Total floating time.

In vitro dissolution studies[15]

The *In Vitro* drug release studies were performed using USP type II (Paddle) apparatus at a rotational speed of 100rpm. 900ml 1.2 pH acidic buffer used as dissolution medium maintained at a temperature of 37^0 C ± 0.5^0 C. A sample of 10ml was withdrawn at a specified time interval for about 24hrs and the same was replaced with pre warmed fresh dissolution media. The collected samples were filtered through Whatman filter paper and diluted if required with 1.2 pH acidic buffer. Absorbance of these samples was measure at 226nm using UV Visible spectrophotometer (1800 shimadzu, Kyoto, Japan).

Curve fitting analysis

The mechanism of drug release from the floating tablets was studied by fitting the dissolution data of optimized formulation in following models.

1. Zero order – Cumulative % drug release Vs Time
2. First order – Log cumulative % drug release Vs Time
3. Higuchi model – Cumulative % drug release Vs Square root of time
4. Korsemeyer and peppas equation – Log cumulative % drug release Vs log time

The mechanism of drug release was decided based on the slope and R^2 values obtained from above models.[16]

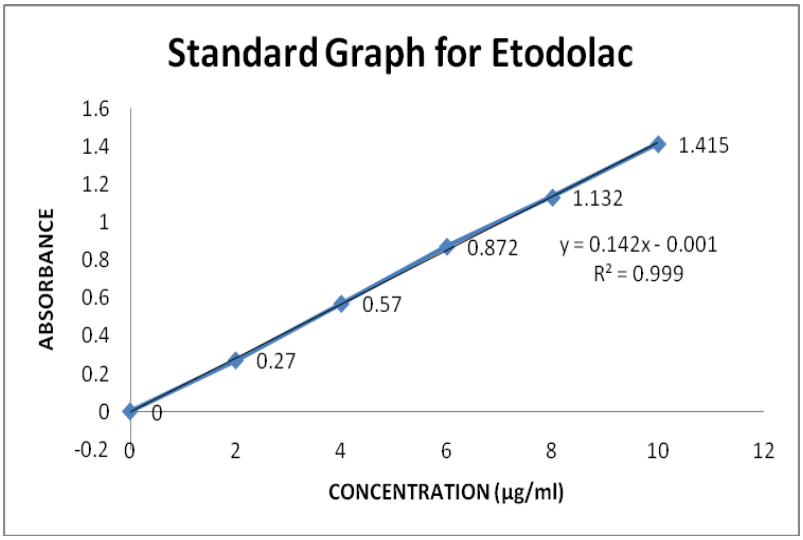
RESULTS AND DISCUSSION

Standard Graph of Etodolac

The standard graph of Etodolac was plotted as per the experimental method using 1.2 pH Acidic buffer which showed good linearity and obeys “Beer – Lamberts” law.

Table No 2: Standard graph of Etodolac.

S.NO	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.27
3	4	0.57
4	6	0.872
5	8	1.132
6	10	1.415



Precompression parameters

The results of Precompression parameters were performed and presented in table no 3 indicating within the limit.

Table No 3: Precompression parameters of powder blend of Etodolac.

Formulation code	Angle of repose (º) ± S.D	Bulk density ± S.D	Tapped density ± S.D	Carr's index(%) ± S.D	Hausner's ratio ± S.D
F1	28.06± 0.31	0.45±0.045	0.52 ± 0.09	15.60±0.2	1.15±0.02
F2	27.58± 0.15	0.45±0.045	0.50 ± 0.07	12.23±0.6	1.11±0.04
F3	28.44± 0.11	0.44±0.044	0.50 ± 0.09	12.58±0.8	1.13±0.08
F4	28.36± 0.13	0.45±0.045	0.52 ± 0.04	15.19±0.1	1.15±0.06
F5	28.52± 0.19	0.44±0.044	0.52± 0.01	15.48±0.6	1.18±0.08
F6	29.32± 0.19	0.45±0.045	0.51 ± 0.04	13.48±0.8	1.13±0.09
F7	29.69± 0.19	0.51±0.045	0.59 ± 0.04	14.48±0.8	1.15±0.09
F8	27.36±0.23	0.45±0.045	0.52±0.04	15.19±0.1	1.15±0.05

Post compression parameters

Hardness of all the formulations was lies in between 10.3 to 10.9kg/cm^2 which indicate all formulations having good mechanical strength.

The average weight of each formulation ranges from 995.25 to 1008.43mg which were uniform and lies within the specifications.

The % friability values below 1% indicating good compact properties. All the formulations of Etodolac tablets range from 0.37 to 0.72%.

The % drug content of all formulations of Etodolac tablets was in between 99.18 to 99.94%

The results were represented in table no 4.

Table No 4: Post compression parameters of Etodolac tablets.

Formulation Code	Hardness (kg/cm^2) ± S.D	Thickness (mm) ± S.D	Weight (mg) ± S.D	Friability (%) ± S.D	Drug content (%) ± S.D
F1	10.3±0.54	5.48±0.20	1008.43±4.36	0.72±0.41	99.18±0.24
F2	10.5±0.75	5.63±0.22	1000.81±4.02	0.37±0.42	99.70±0.38
F3	10.6±0.45	5.78±0.17	1000.14±3.89	0.40±0.38	99.51±0.32
F4	10.9±0.25	5.56±0.05	999.53±3.99	0.46±0.36	99.94±0.21
F5	10.4±0.13	5.44±0.05	1001.08±3.49	0.61±0.34	99.42±0.28
F6	10.6±0.13	5.35±0.06	1001.63±2.99	0.67±0.35	99.91±0.23
F7	10.8±0.14	5.71±0.18	1000.23±2.89	0.63±0.34	99.58±0.24
F8	10.9±0.23	6.64±0.20	995.25±2.88	0.54±0.21	99.26±0.44

***In vitro* buoyancy studies**

All the formulations were evaluated for *in vitro* buoyancy studies in which formulation F4 showed better results as compared with other formulations. The results were represented in table no 5.

Table No 5: Buoyancy character of Etodolac.

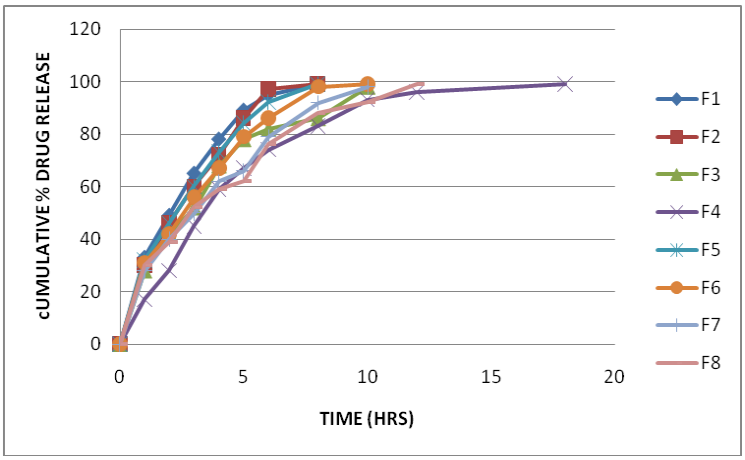
Formulation Code	Floating lag time (sec)	Total floating time (hrs)
F1	76	>10
F2	83	>10
F3	105	>12
F4	64	>16
F5	83	>10
F6	104	>12
F7	112	>12
F8	119	>12

***In Vitro* drug release studies**

The *in vitro* drug release studies were performed using 1.2 pH acidic buffer for 18hrs. Out of all the formulations F4 shown better results represented in table no 6.

Table No. 6: *In vitro* drug release data of Etodolac formulations F1 to F8.

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	33	30	28	17	32	31	28	30
2	49	46	42	28	46	42	40	39
3	65	60	52	45	60	56	50	52
4	78	72	68	59	73	67	62	59
5	89	86	78	67	84	79	66	62
6	95	97	82	74	92	86	79	76
8	99	99	86	83	99	98	92	88
10	-	-	98	93	-	99	98	92
12	-	-	-	96	-	-	-	99
18	-	-	-	99	-	-	-	-



Kinetics of optimized formulation

Formulation Code	Zero Order	First Order	Higuchi	kosermeyer-peppas	
	R^2	R^2	R^2	Slope (n)	R^2
F4	0.799	0.422	0.903	0.523	0.651

CONCLUSION

Gastro retentive dosage form using Guar gum was prepared to develop a sustained release tablets that 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 drug content and *in-vitro* dissolution studies of the formulations, it was concluded that the formulation F4 containing highest concentration of Guar gum is the best formulation. From this study it may be concluded that the floating tablets using guar gum in optimized concentrations can be used to increase the GRT of the dissolution fluid in the stomach to deliver the drug in a sustained manner. The concept of formulating floating tablets of

Etodolac offers a suitable and practical approach in serving desired objectives of gastro retentive floating tablets.

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