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Research Article

FORMULATION, EVALUATION AND OPTIMIZATION OF ETODOLAC FLOATING TABLETS

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ABSTRACT

Objective: To formulate and evaluate floating tablets of Etodolac, a gastro retentive drug delivery system. Floating matrix tablets of Etodolac were developed to prolong gastric residence time. **Materials and methods**: Floating matrix tablets containing 500 mg Etodolac were developed using different polymeric combinations. The tablets were prepared by direct compression method, using polymer such as HPMC K4M, HPMC K15M, and HPMC K100M. Formulations were prepared by varying the amount of polymers. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of sodium bicarbonate on drug release profile and floating properties were investigated. **Results and Discussion**: The Preformulation blend showed good flow properties with good angle of repose, bulk density and tapped density parameters. All the prepared formulations were tested for physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeias limits. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good. The ED6 formulation was considered as optimized formulation on the basis of acceptable tablet properties, floating lag time and total duration of floating up to more than 12 hrs and *in vitro* drug release. **Conclusion**: As a result of this study it may be concluded that the floating tablets using a polymer in optimized concentration can be used to increase the GRT of the dissolution fluid in the stomach to deliver the drug in a controlled manner.

INTRODUCTION

The oral ingestion is the predominant and most preferable route for drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drug. Time controlled oral drug delivery systems offer several advantages over immediate-release dosage forms, including the minimization of fluctuations in drug concentrations in the plasma and at the site of action over prolonged periods of time, resulting in optimized therapeutic concentrations and reduced side effects; a reduction of the total dose administered (while providing similar therapeutic effects); and a reduction of the administration frequency leading to improved patient compliance[1].The real issue in the development of oral controlled release dosage form is to extend the duration of action of drug from the small intestine. For the successful performance of oral CRDDS the drug should have good absorption throughout the GIT, preferably by passive diffusion. In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological adversities like short gastric residence time and unpredictable gastric emptying time [2].

MATERIALS AND METHODS

Table 1 List of Materials

S.No.	Name of Chemical	Source
1	Etodolac	A generous gift sample from KP Labs, Hyderabad
2	HPMC K4M	Bright laboratories
3	HPMC K15M	Bright laboratories
4	HPMC K100M	Bright laboratories
5	Sodium bicarbonate	S.D. Fine chemicals Ltd., Hyd
6	Talc	S.D. Fine chemicals Ltd., Hyd
7	Magnesium stearate	S.D. Fine chemicals Ltd., Hyd

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Table 2 List of Equipments

S.No.	Name of Equipment	Manufacturer
1.	Rotary tablet Machine	Karnavati
2.	Digital weigh balance	Shimadzu
3.	Monsanto Hardness tester	Sisco
4.	Vernier calipers	Edison
5.	Roche Friabilator	Biotechnics India
6.	Dissolution apparatus	Lab India
7.	UV-VIS Spectrophotometer	Elico
8.	Hot air Oven	Biotechnics
9.	Disintegration apparatus	DBK

Accurately weighed quantities of HPMC [3,4] polymer and Lactose were taken in a mortar and mixed geometrically, to this required quantity of Etodolac was added and mixed slightly with pestle. Accurately weighed quantity of Sodium bicarbonate [5] was taken separately in a mortar and powdered with pestle. The powder was passed through sieve no. 40 and mixed with the drug blend which was also passed through sieve no 40.

The whole mixture was collected in a plastic bag and mixed for 3 minutes. To this Magnesium stearate was added and mixed for 5 minutes, later Talc was added and mixed for 2 minutes. The mixture was equivalent to 500mg at a hardness of 5 kg/cm^2.

The composition of various formulations was given in table 3.

Table 3 Formulation for Etodolac floating tablets

Ingredients	Formulation (mg)					
	ED1	ED2	ED3	ED4	ED5	ED6
Etodolac	200	200	200	200	200	200
HPMC K4M	100	150	-	-	-	-
HPMC K15M	-	-	100	150	-	-
HPMC K100M	-	-	-	-	100	150
Lactose	105	55	105	55	105	55
$NAHCO_3$	75	75	75	75	75	75
TALC	10	10	10	10	10	10
Magnesium Stearate	10	10	10	10	10	10
Total Wt	500	500	500	500	500	500

Evaluation

Precompression Parameters

Angle of Repose

It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose can range from 0° to 90°. It is related to the density, surface area and shapes of the particles, and the coefficient of friction of the material.

The fixed funnel method was employed to measure the angle of repose[6]. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose (θ) was calculated using the following formula:

$\theta = \tan^{-1}(h / r)$
where θ = angle of repose

Bulk Density

Density is defined as weight per unit volume Bulk density[7], ρb, is defined as the mass of many particles of the material divided by the total volume they occupy and is expressed in grams per cubic centimeter (g/cm^3). The total volume includes particle volume, inter-particle void volume, and internal pore volume. Bulk density is not an intrinsic property of a material; it can change depending on how the material is handled. The bulk density of a powder is determined by measuring the volume of a known mass of powder sample, that may have been passed through a sieve, into a graduated cylinder (Method A), or by measuring the mass of a known volume of powder that has been passed through a volumeter into a cup (Method B) or a measuring vessel (Method C).

The bulk density was calculated, in grams per ml, using the formula:

(M) / (Vo)
Where M = Total weight of the powder blend
V_0 = bulk volume of the powder blend

Tapped Density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped 100 times, then tapped volume [7]was measured and tapped density was calculated, to the nearest graduated unit.

The tapped density was calculated, in gm per ml, using the following formula.

(M) / (V_f)
Where M = Total weight of the powder blend
V_f = Tapped volume of the powder blend

Compressibility Index

The Carr index (also: Carr's index or Carr's Compressibility Index) is an indication of the compressibility of a powder. It is named after the scientist Ralph J. Carr, Jr.

The Carr index is frequently used in pharmaceutics as an indication of the flow ability of a powder. It is determined from the bulk and tapped densities[8] . In a free-flowing powder, the bulk density and tapped density would be close in value; therefore, the Carr index would be small. On the other hand, in a poor-flowing powder where there are greater interparticle interactions, the difference between the bulk and tapped density observed would be greater, therefore, the Carr index would be larger.

The Carr index is calculated by the formula

$$C = 100(1 - \rho_B/\rho_T),$$

Where, ρ_B is the freely settled bulk density of the powder, and

ρ_T is the tapped bulk density of the powder.

Hausners Ratio

The Hausners ratio is a number that is correlated to the flow ability of a powder or granular material. It is named after the engineer Henry H. Hausner (1900-1995). A Hausners ratio greater than 1.25 is considered to be an indication of poor flow ability. The Hausners ratio is calculated by the formula.

$$H = \frac{\rho_T}{\rho_B}$$

Where ρ_B is the freely settled bulk density of the powder, and

ρ_T is the tapped bulk density of the powder.

Post Compression Parameters

Hardness

It is a laboratory technique used by the pharmaceutical industry to test the breaking point and structural integrity of a tablet "under conditions of storage, transportation, and handling before usage". The breaking point of a tablet is based on its shape. In this five tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester[9]. The hardness is usually measured in terms of kg/cm^2.

Friability

The friability test was carried out in an instrument called the Roche friabilator. It is expressed in percentage (%). 20 tablets from each formulation were weighed and tested at a speed of 25 rpm for 4 min.

After removing of dusts, tablets were re-weighed and friability percentage was calculated using the following equation.

$$\text{Percentage friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight Variation

Weight variation was carried out to ensure that, each of tablets contains the proper amount of drug. The test was carried out by weighing the 20 tablets individually using analytical balance[10], then calculating the average weight, and comparing the individual tablet weights to the average.

The percentage of weight variation is calculated by using the following formula:

% Weight variation = (Average weight-Individual Weight) / Individual Weight × 100

Not more than two of the individual weights deviate from the average weight by more than the percentage given in the pharmacopeia and none deviates by more than twice that percentage.

Drug Content Uniformity

Tablet containing 200mg of drug is dissolved in 100ml of pH 1.2 phosphate buffer taken in volumetric flask. The drug is allowed to dissolve in the solvent. The solution was filtered, 1ml of filtrate was taken in 100ml volumetric flask and diluted to mark with pH 1.2 phosphate buffer and analyzed spectroscopically at 226nm. The concentration of Etodolac in mg/ml was obtained by using standard calibration curve of the drug. Drug content studies were carried out in triplicate for each formulation batch.

Disintegration time

The disintegration time for all immediate release formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The medium, water was maintained at a temperature of 37° ± 2°C and time taken for the entire tablet to disintegrate completely was noted. Average of three determinations was taken.

Swelling Index

The extent of swelling can be measured in terms of % weight gain by the tablet[10]. Floating tablets from each batch were individually weighed (W_1) and placed separately in each Petri dish with 50 ml of 0.1N HCl solution. At time intervals of 1, 2, 3, 4, 5, 6, 7 and 8, the tablet was removed from each Petri dish and excess surface water from the tablet was wiped out carefully with filter paper.

Each swollen tablet was reweighed (W_2) and the swelling index (SI) was calculated using the following formula
Swelling Index (S.I.) = {(Wt-Wo)/Wo} ×100
Where, S.I. = swelling index.
Wt = weight of tablet at time t.
Wo = weight of tablet before immersion.

In vitro Buoyancy studies

The *in-vitro* buoyancy [3,4] was determined by the floating lag time. The tablets were placed in a 100 ml beaker containing 1.2 pH acidic buffer. The time required for the tablet to rise to the surface for floating was determined as the floating lag time and further floating duration of all tablets was determined by visual observation.

In vitro Drug Release studies

The *in vitro* drug release study was performed for the floating tablets using USP Type II dissolution apparatus under the following conditions.

Dissolution test parameters

Medium	:	900ml of 01.N HCl
Rotation speed	:	50 rpm
Temperature	:	37±0.5ºC
Sampling Volume	:	5ml
Sampling Time	:	0.5, 1, 2, 4, 6, 8, 10, 12 hours

At predetermined time intervals samples (5 ml) were collected and replenished with same volume of fresh media. The drug content in the samples was estimated using UV-spectrophotometer at 226 nm.

RESULTS AND DISCUSSION

Table 4 Standard graph of Etodolac in 0.1N HCl at 226 nm

Concentration (µg/ml)	Absorbance
5	0.0823
10	0.1016
15	0.3790
20	0.5603
25	0.6037
30	0.6620
35	0.7002
40	0.7919
45	0.8501
50	0.9610
55	1.102
60	1.231

The study started with the construction of standard calibration curves of Etodolac. The λ_{max} of Etodolac in 0.1N HCl was scanned and found to have the maximum absorbance at 226

nm. The standard graph of Etodolac in 0.1N HCl was plotted by taking concentration ranging from 5 to 60 µg/ml and a good correlation was obtained with R^2 value of 0.96.

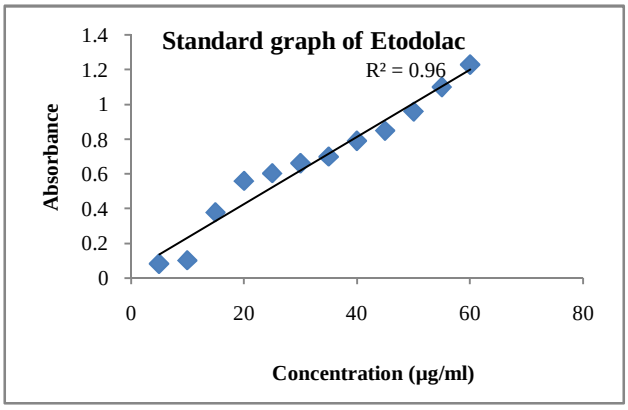

Figure 1 Calibration curve of Etodolac in 0.1N HCl at 226nm

Drug - Excipient Compatibility study by FTIR

Based on the FTIR interpretation results, all the major drug peaks were identified when compared with the physical mixture of drug and polymers, which reveals that there is no chemical interaction between them.

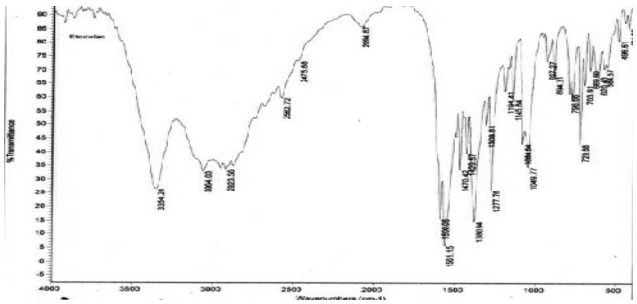

Figure 2 FTIR of Etodolac

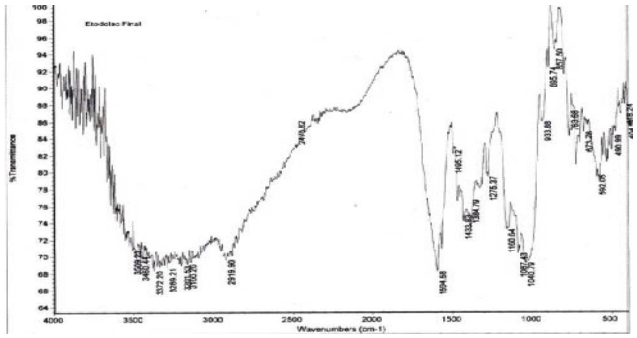

Figure 3 FTIR of Optimized formulation

Pre Compression Parameter Results

The physical properties like bulk density, tapped density, Compressibility index (CI), Angle of repose and Hausner's ratio were calculated and tabulated.

Table 5 Pre Compression Parameter Results

Formulation	Bulk density(g/ml)	Tapped density(g/ml)	Compressibility index	Hausner's ratio	Angle of repose
ED1	0.600 + 0.008	0.712 + 0.008	15.73	1.18	24.26
ED2	0.612 + 0.006	0.734 + 0.008	16.62	1.19	23.32
ED3	0.673 + 0.005	0.776 + 0.008	11.44	1.12	22.77
ED4	0.682 + 0.008	0.780 + 0.008	12.56	1.14	24.06
ED5	0.676 + 0.004	0.793 + 0.008	14.75	1.17	22.18
ED6	0.604 + 0.008	0.708 + 0.008	14.68	1.17	23.06

The results of the Compressibility index, Hausner's ratio and angle of repose of the blends were found to be in the limits and comply with the standards.

Post Compression Parameter Results

All the prepared formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeias limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table 6 Post Compression Parameter Results

Formulation code	Hardness (kg/cm^2)	Weight variation (gm)	Thickness (mm)	Friability (%)	Drug Content (mg/tab)
ED1	4.38 ± 0.070	0.49 ± 0.011	5.884±0.05	0.11 ± 0.008	199.6 ± 0.89
ED2	4.30 ± 0.074	0.50 ± 0.008	5.76±0.06	0.12 ± 0.011	200.0 ± 0.97
ED3	4.67 ± 0.090	0.50 ± 0.011	5.86±0.03	0.11 ± 0.011	198.6 ± 0.82
ED4	4.82 ± 0.070	0.49 ± 0.008	5.76±0.04	0.10 ± 0.008	201.0 ± 0.89
ED5	4.96 ± 0.070	0.50 ± 0.011	5.63±0.06	0.10 ± 0.008	200.2 ± 0.89
ED6	5.02 ± 0.074	0.50 ± 0.008	5.65 ±0.06	0.10 ± 0.011	202.1 ± 0.89

The physical evaluation parameters were also tested. The total weight of each formulation was maintained constant; the weight variation of the tablets were within the permissible limits of 5%, as specified for tablet weighing more than 500 mg (Table 3). Weight of the tablet was fixed at 500 mg and the weight variation for every batch was tested and found within the acceptance limits.

Hardness of the tablet was about 4.8 kg/cm^2 and was maintained for all the batches in order to minimize the effect of hardness on the drug release because the effect of polymer concentration is the only area of interest.

Tablet thickness was also used to assess the quality of tablets. Under uniform conditions of manufacture, the total weight of tablet and thickness were linearly related. The thickness of floating tablets ranged from 5.51 to 5.94 mm and linearly correlated with the weight of the tablets (Table 6). Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion. Drug content uniformity in all formulations was calculated and the dose of active ingredient ranged from 198 to 202mg (Table 6).

Floating properties of floating tablets of Etodolac

All the formulations were tested for floating properties like floating lag time and total floating time. The results of the tests were tabulated.

Table 7 Floating properties results

Formulation code	Floating lag time (sec)	Floating time (hours)
ED1	52	>12
ED2	39	>12
ED3	40	>12
ED4	33	>12
ED5	16	>12
ED6	10	>12

Further, the formulated tablets on immersion in 0.1N Hydrochloric acid media they remain buoyant for 12 hrs with lag time of 10 to 52 seconds. Sodium bicarbonate was added as a gas-generating agent. The optimized concentration of effervescent mixture utilized aided in the buoyancy of all

tablets. This may be due to the fact that effervescent mixture in tablets produced CO_2 that was trapped in swollen matrix, thus decreasing the density of the tablet below 1 making the tablets buoyant. Hydroxy propyl methyl cellulose (HPMC) K4M, K15M, K100M was evaluated varying the sodium bicarbonate portion from 8% to 10%. Finally, lag time was observed less than 1 min for all the formulations. Also the tablet integrity, swelling characteristics were found satisfactory. Floating characteristics like lag time, total floating time for all the formulations were studied and reported (Table 7).

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 8. Swelling was uniform for all formulation.

Table 8 Results of Swelling Index

S.No.	TIME (hrs)	SWELLING INDEX (%)					
		ED1	ED2	ED3	ED4	ED5	ED6
1	1	21.30	20.30	19.12	19.20	19.13	19.10
2	2	29.12	30.12	28.10	26.16	25.14	24.42
3	3	50.11	52.10	50.13	50.00	49.46	46.67
4	4	66.13	68.13	66.10	66.00	63.26	65.92
5	6	73.14	72.24	70.24	70.12	70.00	68.68
6	8	76.26	74.34	73.36	74.08	73.03	71.03
7	10	81.00	80.26	80.18	80.06	80.14	76.00
8	12	91.32	90.36	89.15	89.00	89.00	88.96

***In – vitro* Drug Release data and profiles**

The dissolution conditions used for studying the drug release from the matrix tablets of Etodolac were:

Apparatus : USP Type 2 (paddle)
Agitation speed (rpm) : 50
Medium : 0.1N HCl (pH 1.2), 900ml
Temperature : 37.0 ± 0.5 C
Time : 1, 2, 4, 6, 8, 10, and 12hr
Wavelength : 226 nm

Table 9 Results of Percentage drug release

S.No.	TIME (hrs)	% DRUG RELEASE					
		ED1	ED2	ED3	ED4	ED5	ED6
1.	1	25.64	25.00	20.08	18.64	12.02	11.7
2.	2	32.04	30.06	29.26	28.32	27.06	25.07
3.	4	46.36	46.02	44.00	42.36	40.08	37.67
4.	6	53.64	52.02	49.09	47.37	45.92	43.10
5.	8	70.34	70.00	68.06	60.94	59.96	59.00
6.	10	86.92	84.93	82.96	80.13	70.14	69.36
7.	12	98.15	96.26	96.20	90.43	82.06	80.06

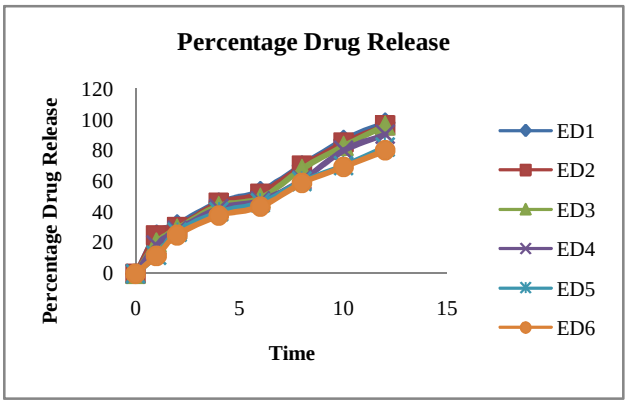

Figure 4 % Drug Release Graph

The % Cumulative drug release of all the formulations sustained the drug release for 12 hrs. The optimized formulation ED6 showed a % drug release of 80.06% for 12 hrs which shows more sustained release compare to all other formulation.

CONCLUSION

Gastro retentive dosage form was prepared to develop a controlled release tablets that could retain in the stomach for longer periods of time delivering the drug to the site of action, i.e., stomach. Etodolac is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties. The tablets were formulated using hydrophilic polymers HPMC K4M, HPMCK15M, HPMC K100M along with effervescing agent sodium bicarbonate.

All the formulations were prepared by direct compression method. The prepared tablets of all the formulations were evaluated for physical characters, tablet density, hardness and friability, swelling index, floating lag time, total floating time, drug content and *in-vitro* drug release. The main aim was to optimize the formulation for more than 12hrs *in-vitro* release with the use of polymers.

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 ED6 i.e. the formulation containing HPMCK100M, lactose, $NaHCO_3$, talc and of Magnesium Stearate is the best formulation with respect to *in-vitro* drug release for more than 12 hrs. As a result of this study it may be concluded that the floating tablets using a polymer in optimized concentration can be used to increase the GRT of the dissolution fluid in the stomach to deliver the drug in a controlled 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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