Development and in Vitro Evaluation of Edotolac Matrix Tablets

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ABSTRACT

The aim of the study was to develop matrix tablets of Etodolac using Eudragit S 100 and HPMC for the treatment of Osteoarthritis. All the formulations (F1 to F5) were evaluated for the physicochemical parameters and were subjected to in vitro drug release studies. The amount of Etodolac released from tablets at different time intervals was estimated by UV spectrophotometer. The formulation F3 released 95.24% of Etodolac. The results of the study showed that formulation F3 is most likely to provide targeting of Etodolac for local action in the colon owing to its minimal release of the drug in the first 5h. The most satisfactory formulation was stable during stability studies conducted for 60 days as per ICH guidelines. Stability studies showed no significant changes in the physicochemical parameters, in vitro drug release. The studies confirmed that, the designed formulation could be used potentially for controlling the drug release.

Keywords: Matrix tablets, Etodolac, Eudragit S 100, HPMC.

INTRODUCTION:

Nearly 50% of the drug delivery systems available in the market are oral drug delivery systems and these systems have more advantages due to patient acceptance and ease of administration[1]. Sustained release dosage form is a modified dosage form that prolongs the therapeutic activity of the drug. Sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect which is followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period of time. sustained release products often times eliminates the need for night dosing, which benefits not only the patients but care given as well because of the sustained plasma drug levels[2].

Sustained release matrix tablet is formulated mainly by wet granulation or direct compression method or by dispersion of solid particle within solid particle within a porous matrix formed by using different polymers like Poly methyl methacrylate (PMMA), Polyglycolic acid, HPMC etc. The matrix controls the release rate of drug. Release retardants like HPMC can aid in sustained release and thus they form core excipient of the formulation. The method involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix core of the retardant, alternatively granulation can be carried out prior to compression. The matrices used may be of hydrophilic, hydrophobic, mineral, or biodegradable types. Thus, sustained release matrix tablets can assure better patient compliance through reduction in total dose and dosage regimen, which can be of great help to treat chronic diseases[3].

Advantages of matrix tablets :

- Prevent drug from degradation.
- Ensure direct treatment at disease site.
- Used to prolong the drug therapy.
- Improved drug utilization.

- Direct access to target tissue.
- Targeted drug delivery to the colon.
- Decrease in dose administration.
- Decrease side effects[4]

Etodolac is a member of the pyranocarboxylic acid group of nonsteroidal anti-inflammatory drugs (NSAIDs). Etodolac is indicated for acute and long-term management of signs and symptoms of osteoarthritis and rheumatoid arthritis, as well as for the management of pain[5].

MATERIALS AND METHODS:

Etodolac, Eudragit S 100, HPMC, Lactose, Starch and Magnesium sterate. All other reagents and solvents were of analytical grade.

PRE-FORMULATION STUDIES:

Compatibility study by FT-IR :
The FT-IR spectrum of the obtained gift sample of a pure drug was obtained by KBr method and compared with standard FT-IR spectra.
Weighed amount of drug (3 mg) was mixed with 100mg of potassium bromide (dried at 40-50^{o}C). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by IR spectrophotometer.
Similar procedure is followed for all relevant excipients used[6].

UV spectrophotometry method was developed for the analysis of drug :
Preparation of buffer reagents: **0.1N HCL:**
0.1 N HCL was prepared by diluting 8.5 ml of concentrated hydrochloric acid to 1000 ml with distilled water.

Phosphate buffer (pH 6.8):
28.80 g of disodium hydrogen phosphate and 11.45 g of potassium hydrogen phosphate were dissolved in water and volume was made up to 1000ml.

Determination of λ_{max} using pH 6.8 phosphate buffer:
Absorbance maximum (λmax) for a drug was determined in pH 6.8 phosphate buffer. Accurately weighed 100 mg of Etodolac was transferred into 100 ml volumetric flask. The drug was then dissolved with 10 ml of methanol and diluted up to the mark with buffer to obtain a concentration of 100µg/ml as stock solution. From the stock solution aliquot was withdrawn to obtain a concentration of 5µg/ml and scanned over the wavelength range of 400 nm to 200 nm using UV-spectrophotometer against same dilutions as blank. The spectrum of absorbance versus wavelength was recorded and analyzed for the absorbance maximum (λmax) and its wavelength.

FORMULATION OF ETODOLAC MATRIX TABLETS :

Table 1: Composition of matrix tablets of Etodolac

Ingredients (mg)	F1	F2	F3	F4	F5
Etodolac	400	400	400	400	400
Eudragit S 100	50	100	-	-	50
HPMC	-	-	50	100	50
Lactose	120	70	120	70	70
Starch	20	20	20	20	20
Mg sterate	5	5	5	5	5
Talc	5	5	5	5	5
Total	**600**	**600**	**600**	**600**	**600**

Method of preparation:
All ingredients are weighed accurately and passed through sieves no 80. All ingredients except magnesium stearate was transferred in to the motor and mixed thoroughly for 5 min to obtain a uniform mixed powder and blend homogenously for 15 min by triturating with the help of pestle. The above blend mixture was granulated with 10% w/v starch paste till a coherent mass was formed and passed through sieve 10 to form granules. The collected granules were dried at 40°C and passed through sieve 20. Granules were lubricated by blending with magnesium stearate and talc evaluated for pre compressional parameter and then subjected for tablet compression.

Pre-compression Parameters:
Determination of angle of repose (θ):
A glass funnel is held in place with a clamp and place a graph paper below it. Approximately weighed quantity of powder is poured through the funnel keeping the orifice of the funnel blocked by the thumb. A gap of 6.4 mm is maintained between the bottom of the funnel stem and the top of the powder pile. Again, the powder is poured through the funnel keeping the orifice of the funnel blocked by the thumb. The height of the heap is measured. The circumference of the heap is marked by pencil and diameter is determined with the help of scale and finally the radius is determined and the angle of repose is calculated using the formula.

$\tan \theta = h/r$

Where,

θ = the angle of repose

h = height of the heap of the powder

r = radius of the heap of the powder

Determination of Bulk Density and Tapped Density:
20 g of the mixed blend (W) was introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals for 100 tapping. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formula.

Bulk density = W / VO

Tapped density = W / VF

Where, W = weight of the initial granules

VO = Initial volume of the granules

VF = Final volume of the granules.

Hausner's Ratio:
It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.
Hausner's Ratio = Tapped density/Bulk density

Compressibility index (Carr's Index):
The flow ability of powder can be evaluated by comparing the bulk density and tapped density of powder and the rate at which it packed down. Compressibility index is calculated

$$\text{Compressibility index}(\%) = \frac{(\text{Tapped density} - \text{bulk density})}{\text{Tapped density}} \times 100$$

Post compression evaluation :
Weight variation :
The variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit[7-8]

Tablet hardness :
The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 5 tablets were chosen randomly and tested for hardness[7-8]

Tablet thickness :
Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using Vernier Caliper. It was determined by checking the thickness of ten tablets of each formulation[7-8]

Friability:
10 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded[7-8]
Percentage friability was calculated by using the formula:

$$\% \text{ Friability} = \frac{\text{Initial weight of the tablets} - \text{Final weight of the tablets}}{\text{Initial weight of the tablets}} \times 100$$

Content Uniformity :
Crush 5 tablets and take average weight of tablet powder equivalent to 400 mg of Etodolac and dissolve in 100 ml of pH 6.8 phosphate buffer. Tablets were allowed to dissolve in the solution and 5 ml of filtrate was diluted to 50 ml with the same buffer and analysed spectrophotometrically at 274 nm[9-10].

***In-vitro* dissolution studies :**
In-vitro dissolution study was performed by using USP Type I Apparatus (Paddle type) at 50 rpm, the dissolution medium was used was pH 6.8 phosphate buffer and tested for next 10 h. At the end of the time period 5 ml of the sample were taken and filtered. 1ml was taken from the filtrate and diluted to10 ml and analyzed spectrophotometrically at 274 nm[9-10].

Release kinetics :
To analyse the mechanism for the drug release and the release rate kinetics of the dosage form, the data obtained was fitted to Zero order, first order, Higuchi matrix and Korsemeyer-Peppas Model. In this by comparing the R value obtained the best fit model was selected.

RESULT AND DISCUSSIONS :

Pre compression Studies

Table 3: Pre-Compression Parameter results

Formulation code	F1	F2	F3	F4	F5
Bulk density (g/cm^3)	0.38	0.41	0.48	0.42	0.43
Tapped density (g/cm^3)	0.49	0.47	0.52	0.46	0.49
Angle of Repose (°)	23	21	27	29	25
Carr's index (%)	25.5	27.4	22.5	24.7	23.1
Hausner's ratio	1.4	1.5	1.2	1.6	1.3

Table 4: Data for post compression studies of the prepared formulation for core tablet

Parameters	F1	F2	F3	F4	F5
Thickness(mm)	4.31	4.14	3.93	4.25	4.27
Hardness(kg/cm^2)	4.8	5.6	5.2	5.0	5.3
Friability (%)	0.42	0.49	0.51	0.50	0.48
Weight variation (mg)	601.3	597.6	602.1	596.4	595.5
Drug content (%)	97.1	96.2	97.6	95.5	97.7

***In vitro* drug release studies :**

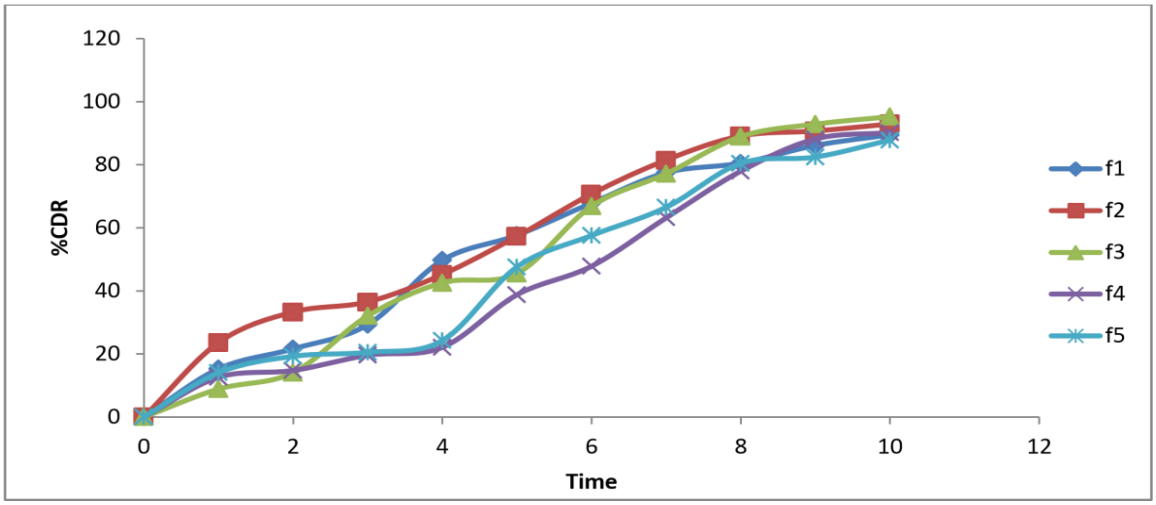

Fig 11: *In vitro* drug release study of formulations (F1 to F5) in phosphate buffer (pH 6.8)

Kinetics modeling :

Table 6: Kinetics modeling data

Formulation code	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Krosmeyer-peppas	
				(r^2)	(n)
F1	0.95	0.69	0.96	0.95	0.74
F2	0.93	0.61	0.97	0.96	0.71
F3	0.94	0.78	0.98	0.94	0.72
F4	0.97	0.75	0.95	0.95	0.76
F5	0.95	0.74	0.92	0.97	0.79

DISCUSSION:

Pre compression studies :

The results of the preformulation studies of Etodolac are shown in table 3. The bulk density and tapped density for granules were found to be 0.38 to 0.48 g/cc and 0.46 to 0.52g/cc respectively. Hausner's ratio with values less than 1.6 indicates good flow and cohesive flow property. The Carr's index value was less than 27%, which confirmed that granules showing excellent flow properties and good compressibility. The angle of repose was found to be 21 to 27^0 thereby confirming the excellent flow property of the granules.

Physical characterization of matrix tablets

Thickness of tablets

All the formulations were evaluated for their thickness using vernier calipers and the results are shown in table 3.The range of all formulations was found to be 3.93 to 4.31mm. The average thickness for all the formulations was found to be within the allowed limit.

Hardness :

Tablet hardness is critical parameter to evaluate the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage. All the tablets formulations were evaluated for their hardness and the results recorded in table 4.All the formulations have an average hardness in between 4.8 to 5.6kg/cm^2 which was found to be acceptable.

Friability :

Friability is determined to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. All the tablets formulations were evaluated for their percentage friability as per the procedure in methodology section 4 and the results are shown in table 4.The average percentage friability for all the formulations was in the range of 0.42% to 0.51%, which was found to be within the limit.

Weight Variation :

As material was free-flowing tablets obtained were uniform weight due to uniform die fill with acceptable variation as per IP standards. All the tablets formulations were evaluated for their uniformity of weight according to the procedure described in methodology section 4 and the results were shown in table 4. The maximum weight was 602.1mg and the minimum observed was 595.5mg. Thus all the formulations were found to be complying with the standards given in IP.

Drug Content :

All the tablet formulations were evaluated for their uniformity of drug content and the results were shown in table 4. The drug content for all formulations was 95.5 % w/w to 97.7% w/w.

In vitro drug release studies :

The prepared matrix tablets were evaluated for *in-vitro* release studies. The drug release from the formulations F1 to F5 showed 98.54% and 89.25% at the end of 10 hours respectively. Formulation F5 shows the drug release of 89.25 % at 10 hours and may release the complete drug at 12 hours

Kinetic studies :

In vitro drug release kinetic study revealed that (Table 6) Etodolac tablet formulation F1 to F5 release drug with Higuchi kinetics, whereas tablet formulation F5 release drug with Zero order kinetic. From the korsmeyer-peppas model, It revealed that the drug release profile tablet formulation F1 to F5 follow non-Fickian transport mechanism.

CONCLUSION:

The present study is to develop matrix tablets of Etodolac for an effective and safe therapy of rheumatoid arthritis. The pre-formulation studies like melting point, flow properties, UV-analysis of Etodolac were complied with IP standards. The FTIR spectra revealed that, there was no interaction between polymer and drug polymers used were compatible with Etodolac.

The physicochemical properties of all the formulations with different concentrations of polymers were shown to be within limits. *In-vitro* drug release studies were carried out for all prepared formulations. F4 formulation was optimized based on the various physic-chemical evaluation parameters. Stability studies were carried out for formulation F4 for three months and the results showed that there is no significant difference in the physicochemical properties and drug release. The present study concludes that the matrix tablets of Etodolac may be a suitable formulation for the treatment of Osteoarthritis. Further, future studies like *in-vivo* bioavailability studies are required to confirm the suitability of the formulation.

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