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DESIGN AND CHARACTERIZATION OF BILAYER TABLETS OF ETODOLAC USING SOME SYNTHETIC AND NATURAL POLYMERS

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Abstract:

Etodolac, a non-steroidal anti-inflammatory drug, is used to manage rheumatoid arthritis associated symptoms via inhibition of cyclooxygenase pathways and other inflammatory mediators. Controlled release medication decreases the frequency of administration and diminishes the sleeping problems, yet the morning complications are not exterminated. Therefore, researches were directed towards designing bilayer tablets of Etodolac using some synthetic and natural polymers to include a fast release layer for rapid onset of action, beside a sustained release layer for drug level maintenance. Direct compression was followed to manufacture the tablets of Etodolac. Optimized formulation IF-7 of Instant release layer and optimized formulation of F-7 for control release used for formulation of Bi-layer tablet. Further bilayer tablets were evaluated for general appearance, thickness and diameter, hardness, friability, uniformity of weight, drug content and dissolution rate studies. the Bilayer tablets of Etodolac could be formulated using HPMC K4, HPMC K15 and Xanthan gum polymer, which is much more effective in treating inflammation.

Key words: *Etodolac, Anti-inflammatory, Bilayer tablets, formulation, Evaluation*

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INTRODUCTION:

The development of sustained or controlled drug delivery systems has got momentum over the past decade due to immense focus on the marketing of new drug molecules as the combination of these new drug molecules has increased to counter multiple diseases that require different dosage regimens [1]. Bilayer tablet has patient compliance and is beneficial for either sequential release of two drugs in combination or sustained and immediate release of the same drug one as initial and other as a maintenance dose [2]. Therefore, this report aims to shed light on the significance of bilayer tablets in the drug delivery system and to counter challenges that are faced in its manufacturing. Besides, numerous techniques for its formation and various bilayer tablets use for different diseases are also analyzed in this article.

Today, several countries, including the developing and the developed ones, have started to consider using combination therapy for treating several diseases and ailments that require long-term therapies like diabetes, cardiovascular diseases, and hypertension. More than 90% of the modern formulations are to be orally ingested. This shows the popularity of this formulation type over the world thus, a majority of the researchers prefer to focus on it. The main objective of controlled drug delivery is the reduction of the dose frequency. According to these findings, a bilayer tablet has been proposed. One of its layers is made for ensuring the instant extraction of the drug and aims to reach a high serum concentration in a brief time. Its second layer is a controlled release hydrophilic matrix that aims at maintaining an efficient plasma level for a long time. The pharmacokinetic benefit depends on the fact that the immediate release of the drug from the first layer results in rising blood concentration suddenly. Nevertheless, the blood level gets steadier after the drug release from the second sustaining layer. The objective of opting for the controlled, or sustained, delivery systems are the reduction of the dose frequency or increasing the efficacy of the drug [3]

Nevertheless, these mediums of drug delivery are mechanically difficult to manufacture and it is not easy to foretell their long-term mechanical properties because of the inferior mechanical and compression characteristics of the basic materials used in the manufacturing of the drug layers, the elastic disparity of the layers, inadequate hardness, imprecise individual mass control, cross- contamination amongst the layers, decreased yield, and their affinity of delaminating at the interface between the layers throughout and after the different production stages following the compaction process. Thus, the main issue that has to be dealt with in the proper and detailed understanding of the main sources of the issues in both macro and micro scales and the development of effective remedies for their solution during the solid dosage delivery design [4].

Among the main issues are the insufficient adhesion and bonding at the interface between the adjacent compacted layers that are mostly caused by an interfacial crack resulted in residual stresses in the tablet, spreading a finite distance in the tablet and resulting in delamination, or layer-separation, that is not visible instantly after compaction, such as during packaging, storage, or shipping. Moreover, if the compacted layers are excessively hard or soft, they won't be able to adhere firmly which could result in negotiated mechanical integrity. Some other issues in the development process are the establishment of the layer sequence order, the elastic disparity of the adjacent layers, layer weight ratio, the damping force of the first layer, and cross-contamination between layers [5].

Etodolac, a non-steroidal anti-inflammatory drug, is used to manage rheumatoid arthritis associated symptoms via inhibition of cyclooxygenase pathways and other inflammatory mediators. Etodolac is a selective COX-2 inhibitor, which inhibits only *cyclo*-oxygenase-2 mediators. It causes less gastrointestinal complication compared to the majority of other NSAIDs. Controlled release medication decreases the frequency of administration and diminishes the sleeping problems, yet the morning complications are not exterminated. Therefore, researches were directed towards designing bilayer tablets of Etodolac using some synthetic and natural polymers to include a fast release layer for rapid onset of action, beside a sustained release layer for drug level maintenance.

MATERIAL AND METHODS:

Preparation of instant layer of Etodolac:

Fast dissolving (Instant Layer) tablets of Etodolac were prepared by direct compression method after incorporating different super disintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60.

Magnesium stearate as lubricant and talc as glidant were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included Angle of repose, Bulk

density, Tap density, Carr's index and Hausner's ratio.

The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Nine different formulations of Etodolac were prepared and each formulation contained one of the three disintegrant in different concentration[6]. Each tablets weighing 150mg, were obtained. Composition of tablets is mentioned in Table 1.

Table 7.1: Composition of Etodolac fast dissolving tablets

Ingredients(mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Etodolac	100	100	100	100	100	100	100	100	100
Sodium Starch glycolate	10	15	20	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	10	15	20	-	-	-
Crospovidone	-	-	-	-	-	-	10	15	20
Microcrystalline cellulose	25	20	15	25	20	15	25	20	15
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	10	10	10	10	10	10	10	10	10
Total weight	150	150	150	150	150	150	150	150	150

Method for Preparation of Etodolac control layer tablets

Direct compression was followed to manufacture the floating tablets of Etodolac. Eight different formulations (F1, F2, F3, F4, F5, F6, F7, & F8) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed as per given in table 2 and all the formulation were used for further evaluations parameters[7]. Polymers selected for tablets are: Xanthan gum, Gaur gum, Karaya gum.

Table 2: various formulations of Etodolac control layer tablets

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Etodolac	300	300	300	300	300	300	300	300
HPMC K4	90	120	-	-	-	-	30	40
HPMC K15	-	-	90	120	-	-	30	40
Xanthan gum	-	-	-	-	90	120	30	40
PVP K30	15	15	15	15	15	15	15	15
Talc	5	5	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10	10	10
Lactose	80	50	80	50	80	50	80	50
Total Weight	500	500	500	500	500	500	500	500

Evaluation of tablets:
All the tablets were evaluated for following different parameters which includes;

Thickness and diameter:
Thickness and diameter of tablets were determined using Vernier caliper. Five tablets from each batch were used, and an average value was calculated.

Drug content:
Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably analyzed for drug content by UV spectrophotometer at a λ max of 276nm using of 0.1 N HCl as blank.

Hardness:
For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach).

Friability
The friability of a sample of 10 tablets was measured using a Friability tester (Electro Lab). Ten tablets were weighed, rotated at 25 rpm for 4 minutes. Tablets were reweighed after removal of fines (dedusted) and the percentage of weight loss was calculated.

Uniformity of weight:
Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated[8].

Dissolution rate studies:
In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.5ºC and rpm of 75. One Etodolac tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 10 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 10 hours using 10ml pipette. The fresh dissolution medium (37^0C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCl and take the absorbance at 276nm using spectroscopy.

Evaluation of Bilayer tablets:
Formulation development of bilayer tablet:
Optimized formulation IF-7 of Instant release layer and optimized formulation of F-7 for control release used for formulation of Bi-layer tablet.

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Uniformity of weight:
Twenty tablets were randomly selected from each batch individually weighed, the average weight and standard deviation of 20 tablets was calculated.

Drug content:
Twenty tablets were taken and amount of drug present in each tablet was determined[61]. The tablets were crushed in a mortar and the powder equivalent to 10mg of Etodolac was transferred to 10ml standard flask. The powder was dissolved in 10 ml of 0.1 N HCl and made up to volume with 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was further diluted 0.2 ml to 10 ml suitably 10 ppm solutions of and determines the Conc. of drug at 276nm for Etodolac.

Dissolution rate studies:
In vitro drug release was performed according to the USP dissolution apparatus II at 50 rpm and 37±0.5ºC temperature over a 12 hrs period for Etodolac bilayer tablets using an automated paddle dissolution system (Labindia). A minimum of 6 tablets per batch were tested.

The media used was 0.1N HCl at a pH 1.2 and a volume of 900 ml was maintained at 37±0.5°C. Test sample (1ml) was withdrawn at particular time interval and replaced with fresh dissolution media maintained at the same temperature and the

concentration of dissolved drug was determined using U.V. (Labindia 3000 plus) spectrophotometer.

RESULTS AND DISCUSSION:

The thickness of the tablets was reported in the micrometer (mm).The thickness of tablet indicates that, die fill was uniform. The thickness depends on the size of the punches (8 mm) and the weight of one tablet (150mg). The value of thickness ranges between 2.3±0.2 to 2.5±0.1mm.

Friability determines the strength of the tablets. The friability for all the formulations was below 1% indicating that the friability was within the prescribed limits. The results of friability test indicate that the tablet possesses good mechanical strength. The friability value ranges from 0.622±0.035 to 0.775±0.042.

The mean hardness values were measured for all the formulation using Monsanto hardness tester. The hardness value ranges from 3.4±0.1 to 3.6±0.1kg/cm^2.

Twenty tablets were randomly selected from each formulation and evaluated. The average weight of each formulation was recorded. The obtained data were almost uniform. The values of tablets average weight ranging from 348±4 to 355±4mg. All the tablets passed weight variation test as the % weight variation was within the USP Pharmacopoeia's limits of ±5% of the weight.

The % drug content of all the formulated tablets were found within the limit. % drug content value of Etodolac was within 98.85±0.45% to 99.78±0.32%.The results within the range indicates uniform of mixing. The Table no 5.13 shows the % drug content in each formulation.

The disintegration time of instant layer of Etodolac IF1, IF2, IF3, IF4, IF5, IF6, IF6, IF7, IF8 and IF9 was found to be 120 ± 5, 110 ± 4, 98 ± 3, 125 ± 4, 115 ± 4, 99 ± 5, 110 ± 6, 83 ± 4 and 98 ± 6 respectively. The minimum disintegration time was found in formulation IF7 (83 ± 4), select as optimized formulation.

Direct compression was followed to manufacture the floating tablets of Etodolac. Eight different formulations (F1, F2, F3, F4, F5, F6, F7, & F8) were prepared by direct compression. The control layer also evaluated for pre-compression and post-compression properties.

In vitro dissolution study was performed for optimization of control layer of Etodolac. Formulation F7 showed release from formulation 33.21, 40.23, 60.32, 71.12, 78.89, 82.23, 89.98, 95.59 and 99.12% after 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0 and 12 Hrs.

Optimized formulation IF-7 of Instant release layer and optimized formulation of F-7 for control release used for formulation of Bi-layer tablet. Further bilayer tablets were evaluated for general appearance, thickness and diameter, hardness, friability, uniformity of weight, drug content and dissolution rate studies.

Table 3: Results of post-compression parameters of Etodolac fast dissolving tablets

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)	Disintegration time (sec.)
IF1	3.4±0.1	0.658±0.014	150±5	2.4±0.2	98.85±0.45	120 ± 5
IF2	3.5±0.2	0.652±0.021	155±4	2.3±0.2	98.87±0.65	110 ± 4
IF3	3.6±0.1	0.612±0.032	148±6	2.3±0.1	99.12±0.25	98 ± 3
IF4	3.5±0.1	0.715±0.025	145±2	2.4±0.3	99.45±0.36	125 ± 4
IF5	3.5±0.1	0.689±0.015	155±4	2.5±0.1	99.65±0.41	115 ± 4
IF6	3.5±0.2	0.775±0.042	147±5	2.4±0.2	99.78±0.32	99 ± 5
IF7	3.6±0.1	0.645±0.032	146±6	2.5±0.1	99.74±0.26	110 ± 6
IF8	3.5±0.2	0.658±0.022	144±2	2.4±0.3	99.18±0.41	83 ± 4
IF9	3.5±0.1	0.622±0.035	158±3	2.5±0.1	99.25±0.33	98 ± 6

Table 4: Results of post compression properties of Etodolac control layer tablets

F. code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.5±0.2	5.2±0.3	498±4	0.858±0.014	98.89±0.25
F2	3.4±0.1	5.3±0.2	495±6	0.658±0.023	99.85±0.32
F3	3.5±0.3	5.1±0.3	498±5	0.489±0.018	98.89±0.14
F4	3.6±0.2	5.4±0.2	502±8	0.558±0.024	99.56±0.25
F5	5.5±0.2	5.3±0.4	505±2	0.658±0.036	99.28±0.36
F6	3.4±0.3	5.4±0.2	504±1	0.856±0.025	99.56±0.52
F7	3.4±0.2	5.2±0.2	503±7	0.658±0.025	99.23±0.45
F8	3.4±0.2	5.1±0.2	502±3	0.758±0.014	99.12±0.36

Table 5: *In-vitro* drug release study of tablets

Time	% Cumulative Drug Release							
(hr)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	55.56	45.54	43.23	40.23	38.89	35.56	33.21	30.12
1	75.56	58.89	55.56	52.32	45.65	42.23	40.23	38.89
1.5	85.56	88.89	80.25	75.65	68.89	65.65	60.32	55.65
2	99.89	98.29	89.98	85.65	78.38	73.25	71.12	65.65
3	-	-	98.89	92.25	85.56	80.32	78.89	70.23
4	-	-	-	98.65	90.23	86.69	82.23	78.32
6	-	-	-	-	99.52	92.23	89.98	85.56
8	-	-	-	-	-	99.85	95.59	90.23
12	-	-	-	-	-	-	99.12	93.32

Table 6: Post-compression parameters of optimized formulation of bilayer tablets

Formulation	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)	Etodolac (% Label Claim)
1.	6.5	0.754	Passes	5.23	99.45

Table 7: Results of Dissolution rate studies of bilayer tablets

Time (Hour)	% Drug Release
	Etodolac
0.5	15.65
1	25.65
1.5	36.65
2	55.65
4	65.58
6	73.32
8	85.65
10	92.32
12	99.85

CONCLUSION:

Etodolac is used in the treatment of rheumatoid arthritis, osteoarthritis, and other inflammatory diseases. Upon oral administration, it is reported to cause ulcerative colitis, gastrointestinal irritation, edema and peptic ulcer. Etodolac usually administered at doses of 400 mg per day. The pharmacokinetic and pharmacodynamics of the drug makes it suitable for administration through oral route. The formulation of Etodolac in the form of oral tablets is a satisfactory tool to achieve its best therapeutic efficacy, since it is well absorbed and well tolerated throughout the GI tract. A study involving preparation and evaluation of instant layer of Etodolac, matrix layer of Etodolac as well as bilayer tablets of both the drug were made. Physicochemical parameters of instant layer, matrix layer and bilayer tablets were performed. In conclusion, the Bilayer tablets of Etodolac could be formulated using HPMC K4, HPMC K15 and Xanthan gum polymer, which is much more effective in treating inflammation.

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