



Formulation and Evaluation of Etodolac Tablets as Immediate Release

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ABSTRACT

The development of an immediate release (IR) dosage form can minimize the problems associated with controlled release systems of etodolac tablets with its higher ability to release drug into blood circulation, increased bioavailability and patient acceptability. In the present study, an effort has made to formulate and evaluate an immediate release etodolac tablet works against the rheumatoid arthritis and human prostate cancer. These immediate release etodolac tablets were prepared by wet granulation process. Eighteen formulation trials were taken to optimize the final formula. From these, formulation F18 have been optimized as a final formulation. Pre-formulation studies were evaluated to measure the flow properties of pre-compressed powder blend of formulations. Then, post-compression studies include weight variation, thickness, hardness were conducted to evaluate the physical parameters of the final formulation. In vitro drug release studies were conducted to know the intrinsic drug releasing ability of etodolac tablets in dissolution medium. In addition, IR etodolac tablets shown a good stability profile. All results from pre and post-formulation studies were within the acceptable limits which are prescribed by USP. These results suggesting that optimized F18 was a stable formulation, suitable for preparation of immediate release etodolac tablet and also has good dissolution profile with that of innovator product.

Keywords: Immediate release dosage form , Etodolac, In vitro dissolution studies.

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INTRODUCTION

The immediate release drug delivery system is intended to design for fast release of drug in aqueous medium and rapid absorption into the blood circulation. An integration and comparison of pharmacokinetic and pharmacodynamic principles in design of immediate release dosage form lead improve therapeutic efficacy¹. These immediate drug release systems also provide satisfactory clinical performance with an appropriate safety. On the other hand, Controlled release and Sustained release drug delivery systems have several drawbacks such as Decreased systemic availability², increased first pass metabolism and pH-dependent solubility. To avoid these problems, immediate release dosage forms has been developed, which minimizes the difficulties of controlled drugs and also enhances patient acceptability. In the current research work, an attempt was made to formulate and evaluate an Immediate release etodolac tablet used in the treatment of inflammation caused by rheumatoid arthritis. The dissolution testing as a Prognostic Tool for Immediate Release Dosage Forms³. Jennifer B. Dressman *et al* studied the importance of dissolution testing in regulation of post-approval changes during new product developments⁴. Several factors play a significant role in the dissolution stability of immediate release oral dosage form⁵. For example. The functionality of hydrophilic excipients (starch and cellulose substances) is also a determining factor in effective drug dissolution⁶. Various researchers reported the significant and comparison studies of *in vitro*- *In vivo* correlations of immediate release dosage forms^{7, 8}. Etodolac is a selective cyclo-oxygenase-2 non-steroidal anti-inflammatory drug used to treat symptoms of pain and inflammation caused by arthritis or osteoarthritis. It is rapidly absorbed and shows elimination half-life of 6-8 h⁹. The racemic forms of etodolac shows significant effect in inhibition of tumor development and also in prevention of B-cell chronic lymphocytic leukemia^{10,11}. Various studies reported that etodolac was formulated in different solid dosage forms such as hard gelatin capsule¹², chewable tablet¹³, controlled release matrix tablet¹⁴, etc. Furthermore, the synthesis and biological evaluation of five metabolites of etodolac was also studied¹⁵. The chronic oral administration of etodolac can cause the formation of ulcers in gastrointestinal tract¹⁶. But the risk of acute myocardial infarction associated with NSAIDs is less in etodolac compared to naproxen¹⁷.

MATERIALS AND METHOD

Etodolac was procured from Fleming Lab.Ltd. Croscarmellose Sodium and Sodium Starch Glycolate were obtained from AVEB Chemicals. HPC and HPMC-E5 were taken from Colorcon Asia Pvt.Ltd, USA. Other ingredients include Microcrystalline cellulose (Sigachi chloro

chemicals Pvt.Ltd), Povidone-K30 (VVF Ltd, Maharashtra state), Lactose Monohydrate (DMV International), Aerosil (Degussa, Belagaum), Magnesium stearate (Feroo Industries, UK). And other chemicals were consumed of laboratory grade.

Formulation Development

Direct compression method (F1 TO F3):

Weigh (Electronic balance, Mettler Toledo, USA) accurately ETODOLAC, HPC, MCC pH 102, Croscarmellose sodium and pass in sieve no. 40 and mix in a ratio as per method. Then, mix the blend in a double cone blender (Erweka) for 10 minutes. Weigh croscarmellose sodium, magnesium stearate accurately, pass through sieve no. 60 and add to the above blend. The compression of tablets by Rotary tablet punching machine (Rimek, Mumbai) using 18mm punches. In this process, super disintegrant are added in intra granulation and extra granulation for better disintegration of the tablet.

Wet Granulation (F4 TO F18):

Weigh (Electronic balance, Mettler Toledo, USA) accurately ETODOLAC, LACTOSE, MCC pH 101, SODIUM STARCH GLYCOLATE pass through sieve no. 40 and mix in geometric ratio and blend for 15 minutes in Rapid Mix Granulator (Anchor, Mumbai). Add binder solution (PVP K30 for F4-F12, hydroxypropyl cellulose (Klucel) for F13-F14, hypromellose (HPMC-E5) for F15-F18) to the above blend and granulate. Then, transfer the wet mass through sieve no. 12 and dry at 60°C. Pass these dried granules in sieve no. 20. After sieving, add magnesium stearate and blend for 2 min. The tablet was punched by Rotary tablet punching machine using 18mm punches.

The composition of all formulation trials was shown in table 1 and 2.

Table 1: The composition of formulation trials (F1-F9) of Etodolac

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Etodolac	504.33	504.33	504.33	504.33	504.33	504.33	504.33	504.33	504.33
Lactose Monohydrate	-	-	-	80	-	9.0	9.0	75.67	80.00
MCC 101	-	-	-	104.42	227.7	161.67	158.92	57.00	77.75
MCC 102	54.7	54.2	53.7	-	-	-	-	-	-
Sodium Starch Glycolate	-	-	-	37.50	40	37.5	37.50	55.00	40.00
Croscarmellose Sodium	40	40	40	-	-	-	-	-	-
PVP K-30	-	-	-	20.00	16	30.0	35.25	20.00	20.00
Hypromellose (klucel)	40	40	40	-	-	-	-	-	-
Colloidal Silicon Dioxide	1.0	1.5	2.0	-	4.0	-	-	2.0	-
Magnesium Stearate	10.0	10.0	10.0	3.75	8.0	7.5	5.0	11.0	7.25
Purified Water	-	-	-	QS	QS	QS	QS	QS	QS

Table 2: The composition of formulation trials (F10-F18) of Etodolac

Ingredients	F10 (mg)	F11 (mg)	F12 (mg)	F13 (mg)	F14 (mg)	F15 (mg)	F16 (mg)	F17 (mg)	F18 (mg)
Etodolac	504.33	500.00	500.00	504.33	504.33	500.00	500.00	500.00	500.00
Lactose Monohydrate	80.00	12.50	12.50	-	-	12.50	12.50	12.50	12.50
MCC PH 101	52.50	107.90	102.90	202.87	200.87	100.90	102.90	105.40	107.90
MCC PH 102	-	-	-	-	-	-	-	-	-
Sodium Starch Glycolate	40.00	-	40.00	-	-	40.00	40.00	40.00	40.00
Croscarmellose Sodium	-	-	-	40.0	40.0	-	-	-	-
PVP K-30	20.00	25.00	30.00	-	-	-	-	-	-
HPMC-e5	-	-	-	-	-	32.00	30.00	27.50	25.00
Hypromellose	-	-	-	40.0	40.0	-	-	-	-
Colloidal Silicon dioxide	-	7.30	7.30	0.8	0.8	7.30	7.30	7.30	7.30
Magnesium Stearate	7.50	7.30	7.30	10.0	12.0	7.30	7.30	7.30	7.30
Purified Water	QS	QS	QS	QS	QS	QS	QS	QS	QS

PRE-FORMULATION STUDIES¹⁸

Bulk density:

Apparent bulk density (Bulk density apparatus, Electrolab, Mumbai) was determined by pouring a weighed quantity of blend into a graduated cylinder and measuring the volume and weight. The apparent bulk density was calculated by the following formula

$$\text{LBD} = \text{Weight of the powder} / \text{Volume of the packing}$$

Tapped Density:

Apparent tapped density (Tap Density Tester, Electrolab, Mumbai) was determined by the following formula

$$\text{TBD} = \text{Weight of the powder} / \text{volume of the tapped packing}$$

Compressibility Index:

The compressibility index of the granules was determined by the Carr's compressibility index.

The formula of carr's index (%) as follows

$$\text{Carr's index (\%)} = [(TBD - LBD) \times 100] / TBD$$

Hausner ratio:

Hausner ratio was determined as the ratio between the tapped density to that of the bulk density.

$$\text{H.R} = \text{Tap Density} / \text{Bulk Density}$$

Compatibility studies:

In these studies, the effect of intimate contact of a drug with excipient was studied. In some combinations, this intimacy could affect the stability of the drug due to incompatible drug

excipient interactions. Therefore, compatibility between drug and excipients is more important to the formulator in selecting appropriate excipients.

Post-Compression Studies^{19,20,21}

Thickness:

Thickness of tablets was measured by dial calliper (Mitutoya, Japan) and average was calculated.

Hardness:

The hardness (Tablet hardness tester, Schleuniger hardness tester) of ten tablets was measured using a Monsanto hardness tester. The hardness of tablet is expressed in kg/cm².

Weight variation test:

Twenty tablets were selected at random and their average weight was determined using an electronic balance (Shimadzu Aux200, Japan). In this test, an individually weighed tablets were compared with average weight.

Dissolution Procedure²²

The drug release of etodolac was measured by USP dissolution apparatus II (paddle type). Dissolution medium: Phosphate buffer (pH 6.8); Temperature: 37± 0.5⁰C; Rotations: 100 rpm. The dissolution was carried in 1 litre of dissolution medium and exposed to the above conditions. 5 ml of aliquot was withdrawn from dissolution medium at regular time intervals, i.e 5, 10, 20 and 30min. Then the sample was filtered through whattman filter paper, finally the amount of Etodolac dissolved was measured by using UV spectrometry at the wave length of 274 nm. The drug release Percentage was calculated from a standard curve. The drug release profile of all formulations was shown in the graph (times vs. percentage release).

Assay Procedure²²

20 Tablets were accurately weighed and powdered. The powder equivalent to 1000mg of etodolac was transferred to a 500 ml volumetric flask. Add 300 ml of mobile phase containing a mixture of acetonitrile, water, and phosphoric acid (100: 100: 0.05), shaken for 15 min, sonicated for 5min, cooled and allowed to settle for 10 min. Then, 10ml of the solution was pipette out to a 100 ml volumetric flask, add mobile phase up to the mark and correctly mixed then Finally the diluted solution was passed through a filter (0.45 µm). The drug content of etodolac immediate release tablet was analysed by using HPLC (Schimadzu LC-20A, Japan); Detector: UV 274 nm; Column: 4.6-mm x25-cm; 5-µm (packing L1); flow rate: 1.5 mL/min.

Stability testing²³

According to Q1A (R2) guidelines, Stability studies were conducted under realtime (25⁰C, 60%

RH), accelerated storage (40⁰C, 75% RH) and intermediate conditions (30⁰C, 65% relative RH) and determined time intervals; initial, 3, 6, 9 and 12 months.

RESULTS AND DISCUSSION

In the current study, an immediate release tablets were prepared by direct compression (F1-F3) and wet granulation method (F4-F18). All pre-formulation properties and compatability studies were conducted to know the flow properties of different formulation trails. In the present study, these values were found to be in a range of 0.325-0.451g/mL and 0.387-0.614 g/mL respectively. Thereby, the compressibility index and Hausner ratios were calculated and these values were found to be in the range of 16.071- 30.0% and 1.191-1.43 respectively. From the results, it was noticed that the pre-formulated granules had shown (Table 3) good to poor Carr's index values and fair to poor Hausner's ratio values. Among all, F6 and F18 were showing good Carr's index and Hausner's ratio values. That indicates these formulations had good flow properties than the rest of the formulations.

Table 3: Lubricated Powder Characteristics of Formulations (F1-F18)

Formulation	Bulk density G/ml	Tapped density G/ml	Hausner ratio	Compressibility Index%
F1	0.436	0.614	1.40	28.985
F2	0.403	0.569	1.41	29.09
F3	0.436	0.538	1.23	28.90
F4	0.429	0.594	1.385	27.778
F5	0.444	0.584	1.315	25.926
F6	0.325	0.387	1.191	16.071
F7	0.411	0.588	1.43	30.0
F8	0.403	0.559	1.38	27.809
F9	0.417	0.550	1.318	24.1
F10	0.451	0.564	1.25	20.03
F11	0.413	0.586	1.42	29.51
F12	0.422	0.575	1.36	28.02
F13	0.339	0.428	1.262	20.775
F14	0.376	0.498	1.324	24.390
F15	0.414	0.542	1.31	23.61
F16	0.425	0.535	1.26	20.56
F17	0.435	0.548	1.26	20.62
F18	0.448	0.541	1.20	17.20

The compatibility studies are essential not only for knowing the knowledge about drug-excipient interactions and also for selecting an appropriate excipient combination with API during formulation development. In the present investigation, the compatible excipient combination for etodolac was identified by conducting studies for 3 months. From all results, it was confirmed that etodolac (API) was not having any impurity when it was studied as an individual

component. Further more, API in combination with all excipients had shown less % of impurities as it was specified by the USP. In conclusion, it was interpreted that there was no interference for API in combination with diluents and other excipients. The results of drug-excipient compatibility studies of all formulation trials at different time periods were shown in figure 1,2 and table 4,5 and 6.

Table 4: Drug-Excipient Compatibility Initial Results

Name of the ingredient	API: Excipient Ratio	Max unknown Impurity (RT)	Total Impurities
Etodolac	NA	NIL	NIL
Lactose monohydrate	NA	NA	NA
Cellulose microcrystalline101	NA	NA	NA
Cellulose microcrystalline 102	NA	NA	NA
Sodium starch glycolate	NA	NA	NA
Povidone K 30	NA	NA	NA
HPMC-E5	NA	NA	NA
Hydroxypropyl cellulose	NA	NA	NA
Magnesium stearate	NA	NA	NA
Colloidal silicon dioxide	NA	NA	NA
Etodolac: Lactose monohydrate	1:10	0.01	0.01
Etodolac : microcrystalline 101	1:10	0.01	0.01
Etodolac : microcrystalline 102	1:10	0.02	0.02
Etodolac : Sodium starch glycolate	1:5	NIL	NIL
Etodolac : Povidone K 30	1:5	NIL	0.01
Etodolac : HPMC-E5	1:5	NIL	0.01
Etodolac : Hydroxypropyl cellulose	1:5	NIL	0.01
Etodolac : Magnesium stearate	1:0.5	NIL	NIL
Etodolac : Colloidal silicon dioxide	1:0.5	NIL	NIL

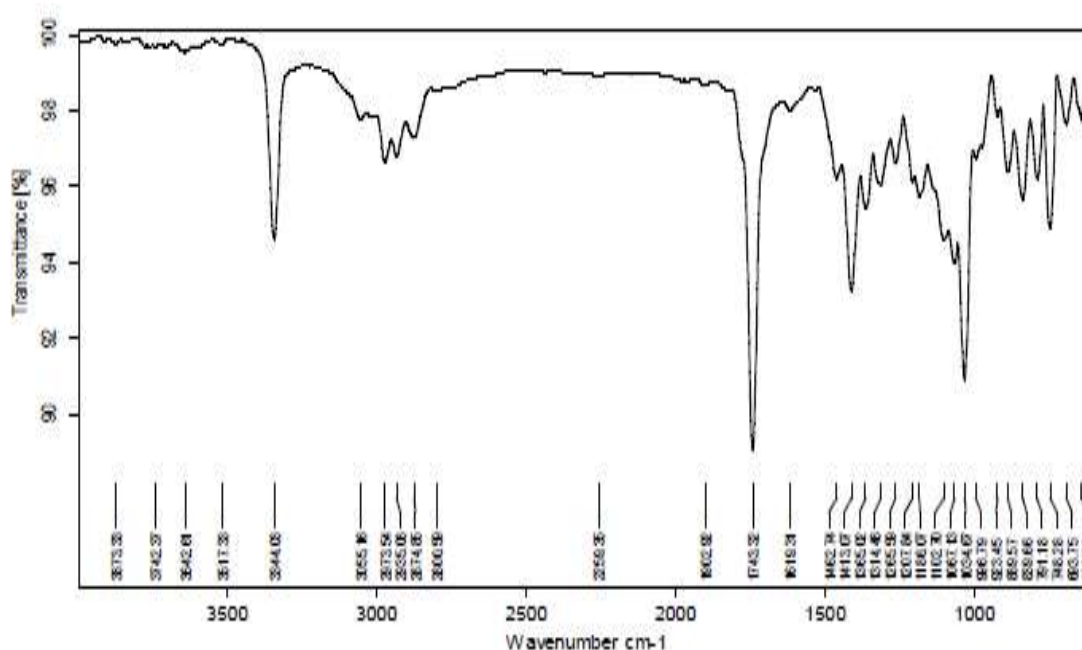
Table 5: Drug-Excipient Compatibility 1st Month Results

Name of the ingredient	API: Excipient Ratio	Max. unknown Impurity (RT)	Total Impurities
Etodolac	NA	NIL	NIL
Lactose monohydrate	NA	NA	NA
Cellulose microcrystalline 101	NA	NA	NA
Cellulose microcrystalline 102	NA	NA	NA
Sodium starch glycolate	NA	NA	NA
Povidone K 30	NA	NA	NA
HPMC-E5	NA	NA	NA
Hydroxypropyl cellulose	NA	NA	NA
Magnesium stearate	NA	NA	NA
Colloidal silicon dioxide	NA	NA	NA
Etodolac: Lactose monohydrate	1:10	0.01	0.01
Etodolac : microcrystalline 101	1:10	0.01	0.01
Etodolac : microcrystalline 102	1:10	0.02	0.02
Etodolac : Sodium starch glycolate	1:5	NIL	NIL

Etodolac : Povidone K 30	1:5	NIL	0.01
Etodolac : HPMC-E5	1:5	NIL	0.01
Etodolac : Hydroxypropyl cellulose	1:5	NIL	0.01
Etodolac : Magnesium stearate	1:0.5	NIL	NIL
Etodolac : Colloidal silicon dioxide	1:0.5	NIL	NIL

Table 6: Drug-Excipient Compatibility 2nd Month Results

Name of the ingredient	API: Excipient Ratio	Max unknown Impurity (RT)	Total Impurities
Etodolac	NA	NIL	NIL
Lactose monohydrate	NA	NA	NA
Cellulose microcrystalline 101	NA	NA	NA
Cellulose microcrystalline 102	NA	NA	NA
Sodium starch glycolate	NA	NA	NA
Povidone K 30	NA	NA	NA
HPMC-E5	NA	NA	NA
Hydroxypropyl cellulose	NA	NA	NA
Magnesium stearate	NA	NA	NA
Colloidal silicon dioxide	NA	NA	NA
Etodolac: Lactose monohydrate	1:10	0.01	0.01
Etodolac : microcrystalline101	1:10	0.01	0.01
Etodolac : microcrystalline 102	1:10	0.02	0.02
Etodolac : Sodium starch glycolate	1:5	NIL	NIL
Etodolac : Povidone K 30	1:5	NIL	0.01
Etodolac : HPMC-E5	1:5	NIL	0.01
Etodolac : Hydroxypropyl cellulose	1:5	NIL	0.01
Etodolac : Magnesium stearate	1:0.5	NIL	NIL
Etodolac : Colloidal silicon dioxide	1:0.5	NIL	NIL

**Figure 1: FTIR Spectrum of Etodolac**

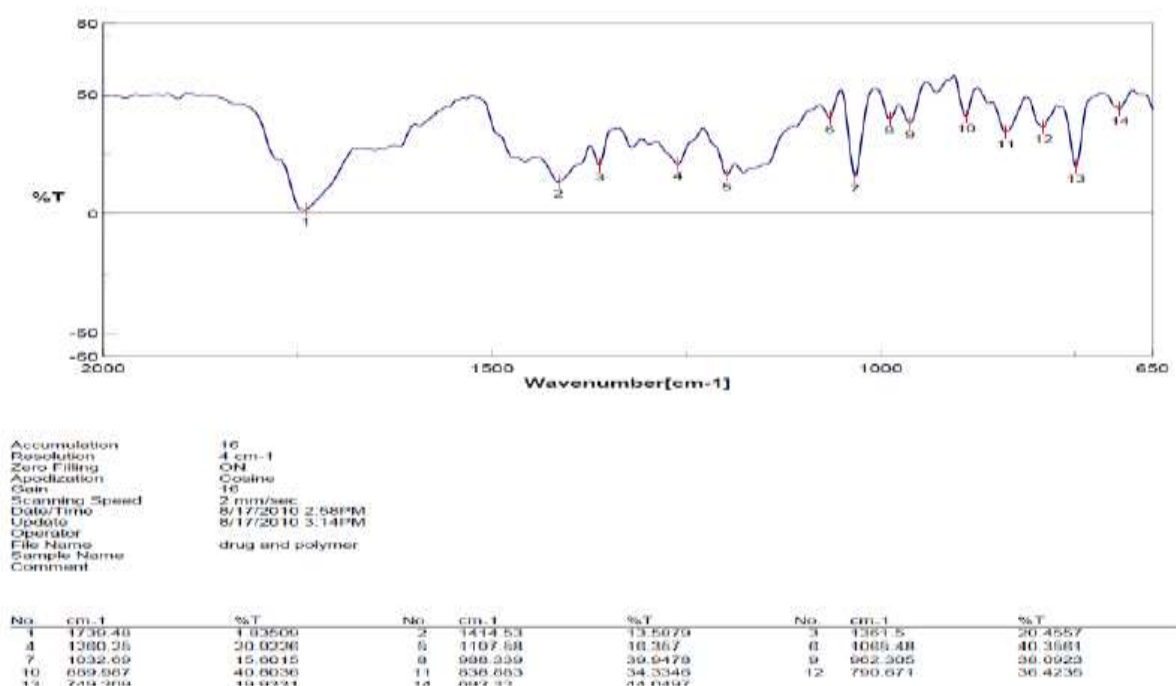


Fig.2: FTIR Spectrum of Optimized formulation

The weight variation of All formulations was varied from 642.00 -807.00 mg with minimum standard deviation values indicate that the uniform distribution of excipients and drug in the tablets. All the formulated tablets were passed weight variation test as the % weight variation was within the IP limits of 5% of the weight. The results were within the limit specified by the IP. The thickness of tablets in the range of 6.30-6.72 mm in with minimum standard deviation values, it assumed that the tablets show uniformity in thickness. The hardness of the tablets was found to be 3.0-14.8 kp. The hardness of tablet varied due to the increased concentration of the excipient in formulations. The physical properties of different batches of developed tablets are given in Table 7.

Table 7: Physical Parameters Of Formulations

Formulation	Thickness (mm)	Hardness (Kp)	Avg. Tab Wt. (mg)
F1	6.3	3	648
F2	6.35	3.5	642
F3	6.42	4.0	654
F4	6.64	12.4	798
F5	6.51	12.8	796
F6	6.42	13.1	745
F7	6.49	12.9	742
F8	6.55	9.2	727
F9	6.65	10.5	728
F10	6.48	11.2	731
F11	6.52	11.8	734

F12	6.60	12.6	724
F13	6.72	13.8	802
F14	6.68	14.2	807
F15	6.48	14.8	728
F16	6.53	14.5	734
F17	6.60	14.0	726
F18	6.55	13.5	730

The optimized formulation trial (F18) was selected on the basis of their In-vitro dissolution profile in dissolution media (phosphate buffer pH-6.8 at $37 \pm 0.5^{\circ}\text{C}$). From the results, it was observed that F18 showed the maximum drug release of 98.2%, which was higher than RLD (innovator product) and other formulations as it was shown in Table. The comparative drug release profile of all trial formulations including optimized formulation F18 with that of the reference listed drug (RLD) as shown in figure. 3 and table 8. In addition, both formulations F18 and RLD were shown (fig. 4 and table 9) above 75% drug release within 5min. Therefore, it was concluded that F18 was a suitable formulation for preparation of immediate release tablets.

Table 8: Comparison of dissolution profiles with that of the RLD

Time (Minutes)	5	10	20	30
F1	70.4	73.8	74.6	75.2
F2	73.5	74.8	75.4	78.3
F3	74.2	76.5	77.8	82.1
F4	67.0	99.5	99.5	100
F5	68.3	88.4	95.6	98.3
F6	65.4	82.3	90.6	93.2
F7	74.3	89.2	96.4	95.3
F8	77.8	90.2	98.2	96.5
F9	73.2	86.5	90.6	92.7
F10	71.4	85.2	91.6	93.8
F11	68.5	82.6	90.8	91.1
F12	67.4	81.5	88.6	90.3
F13	74.3	87.6	97.3	96.1
F14	75.2	86.5	96.8	95.7
F15	76.8	88.6	93.8	93.5
F16	77.2	85.9	92.7	94.8
F17	78.3	89.0	95.4	95.7
F18	79.6	92.8	96.7	98.2
RLD	78.8	93.9	97.0	97.8

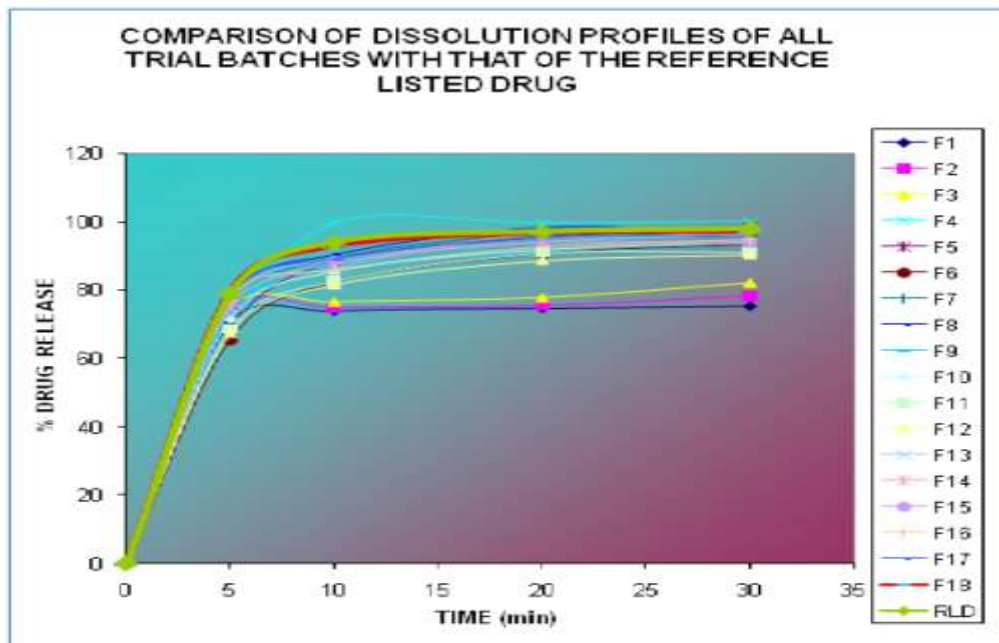


Figure 3: The dissolution profiles of all the formulations

Table 9: Comparative dissolution profiles of F18 and RLD

Time (Minute)	0	5	10	20	30
F18	0	79.6	92.8	96.7	98.2
RLD	0	78.8	93.9	97.0	97.8

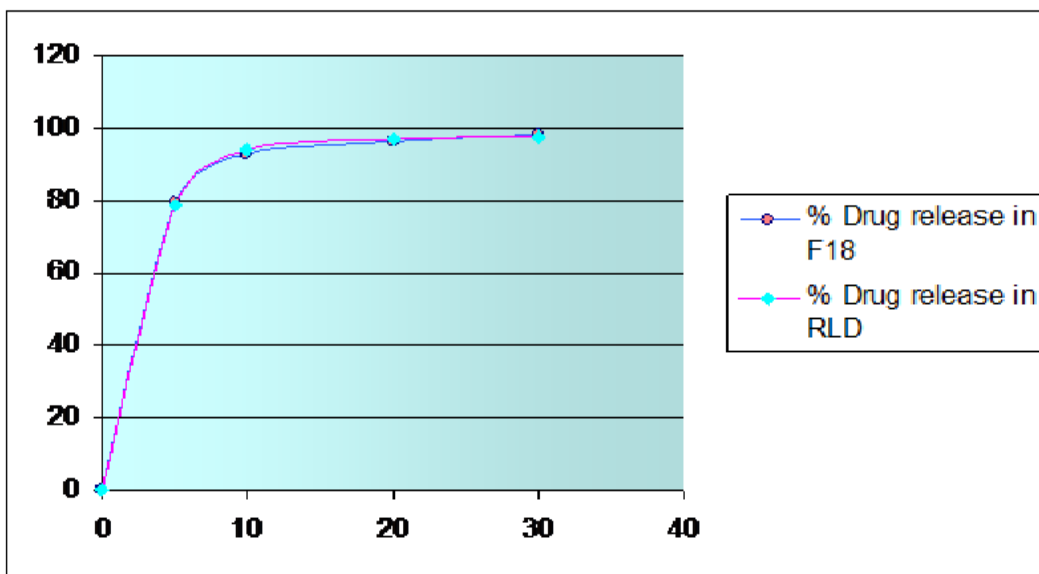


Figure 4: The dissolution profiles of F18 and reference listed drug (RLD)

Stability studies showed that there was no significant difference in the in vitro disintegration times and in vitro dissolution rates of the formulation F18 during the storage of 12 months. The results of stability studies were found to be complied with the tablet specifications. All results obtained during stability studies have been found within established limits. In addition, no

incompatibility was observed between the product and the packaging material. The drug contents of the etodolac immediate release tablet for three consecutive months were found (table 10) to be 98.8, 98.4 and 98.2% respectively. These values were within the limits as specified by USP. As per the above stability data, immediate release Etodolac tablets are stable and comply with that of the specification in the USP.

Table 10: drug content and dissolution profile of etodolac at different time periods

Tests	Initial	1 st month	2 nd month	3 rd month
Assay	99.3	98.8	98.4	98.2
Dissolution(30 min)	96.7	96.1	95.5	94.2

CONCLUSION

The optimization of formula is an essential step to develop an effective formulation in terms of safety, therapeutic efficiency and patient acceptability. In this study, eighteen formulation trails were taken to optimize the final formulation. All the pre-formulation and post compression studies were conducted for an optimized formulation (F18). The results of these evaluation studies were within the limits as specified by USP. Therefore, it was concluded that the optimized etodolac formulation was a stable and more reliable formulation to prepare an immediate release etodolac tablet.

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