CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.804916

**Available online at:** http://www.iajps.com *Research Article*

# FORMULATION AND EVALUATION OF SUSTAINED RELEASE DOSAGE FORM OF KETOPROFEN

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**Abstarct:**

*Sustained release Ketoprofen matrix tablets were prepared by direct compression method. The nature of the polymer influences the physical and release characteristics of the matrix tablet. The hydrophobic polymer, Ethyl cellulose has retarded the drug release from the tablet and the hydrophilic polymer, HPMC (15 cps) has release the drug. While making the combination of both hydrophilic and hydrophobic polymers i.e HPMC and Ethylcellulose with optimized ratio (F7) leads to sustained release of drug from matrix tablet for 12 hours was observed*

**Key words:** *Ketoprofen, HPMC (15 cps), Ethyl cellulose*

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*Please cite this article in press as K. Rekha Rani et al,* ***Formulation and Evaluation of Sustained Release Dosage Form of Ketoprofen****, Indo Am. J. P. Sci, 2017; 4[05].*

## INTRODUCTION:

Conventional medication systems that require multi-dose therapy are not without problems. With a view to overcoming these problems, the current trend in pharmaceutical research is to design and develop new formulations, thereby enhancing the therapeutic efficacy of existing drugs. Moreover, the impetus for research into drug delivery can be attributed to the exorbitant cost and large development period involved in 'new drug development' with concomitant recognition of the therapeutic advantages of Controlled / Sustained drug delivery. Sustained Release systems include any drug delivery system that achieves slow release of drug over an extended period of time.

Ketoprofen (KP) is a poorly water-soluble non-steroidal anti-inflammatory, antipyretic and analgesic drug, frequently used for the treatment of rheumatoid arthritis, osteoarthritis, anklylosing spondylitis, a variety of other acute and chronic musculoskeletal disorders and mild to moderate pain is a potent non-steroidal anti-inflammatory drug that inhibits prostaglandin synthetase cyclooxygenase. Its oral administration is associated with a high risk of adverse effects such as irritation, ulceration of the gastrointestinal tract, oedema, dizziness, and peptic ulceration when taken orally for a prolonged period. These attributes make KP a good candidate for controlled release dosage forms. Microspheres are one of the multiparticulate drug delivery systems and are prepared to obtain prolonged drug delivery, improve bioavailability or stability and target drug to specific sites. They have played a vital role in the development of controlled/sustained release drug delivery systems. The Eudragits are a family of polymers based on acrylic and methacrylic acids suitable for use in orally administered drug delivery systems. They have been used in the microencapsulation of drugs. Some dissolve rapidly at clearly defined pH values, whereas two grades, Eudragit ® RL and RS, are insoluble in aqueous media water and digestive juices, but swell and are permeable, which means that the drugs can be released by diffusion. Therefore, the permeability of drug through Eudragit RS and/or RL is independent on the pH of the digestive tract Eudragit®RS100 is a water-insoluble polymer that is widely used as a wall material for sustained release microspheres due to its biocompatibility, good stability, easy fabrication and low cost.

## EXPERIMENTAL METHOD:

**Materials**

Ketoprofen, Eudragit RL 100, Ethylcellulose, Hydroxyl propyl methyl cellulose 15 cps, Lactose, Micro crystalline cellulose, Starch, Magnesium stearate, Talc all the chemicals used were lab grade.

Tablets of Ketoprofen were prepared by direct compression. Ketoprofen and excipients are weighed accurately and passed through 60# mesh sieve separately. The drug and polymers was mixed by small portion of both each time and blending it to get a uniform mixture and kept aside. Then the ingredients were added, mixed in geometrical order and are compressed for tablets.

**Table.1 Formulation of Ketoprofen sustained release tablets**

| Ingredients | F1 (mg) | F2 (mg) | F3 (mg) | F4 (mg) | F5 (mg) | F6 (mg) | F7 (mg) | F8 (mg) |
|---|---|---|---|---|---|---|---|---|
| Ketoprofen | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| HPMC 15 cps | 50 | 50 | 70 | 70 | 50 | 50 | 70 | 70 |
| Eudragit RL 100 | 20 | 40 | 20 | 40 | | | | |
| Ethyl cellulose | - | - | - | - | 20 | 40 | 20 | 40 |
| Lactose | 260 | - | 240 | - | 260 | - | 240 | - |
| Microcrystalline cellulose | - | 240 | - | 220 | - | 240 | - | 220 |
| Starch | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Magnesium stearate | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Talc | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Total (mg) | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |

**Pre-compression evaluation:**

**Micromeritic properties**

**a) Angle of repose :**

The angle of repose of powder was determined by the fixed funnel method. The accurately weighed powder was taken in a funnel. The height (h) of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$ ---------- (1)

Therefore, $\theta = \tan\text{-}1h/r$

Where, $\theta$ = angle of repose,

h = height of the pile,

r = radius of the pile base.

**b) Bulk densidty:**

Both loose bulk density (LBD) or bulk density and tapped bulk density (TBD) were determined. Powder from each formulation, previously lightly shaken to break any agglomerates formed was introduced into a 10 ml measuring cylinder. After 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. The tapping was continued until no further change in volume was noted.

Bulk density is calculated by using formula

Bulk density = weight of powder / bulk volume of powder

Tapped density = weight of powder / tapped volume of powder

**c) Compressibility index and husner's ratio**:

The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index. The compressibility index and the hausner‟s ratio are determined by measuring both the bulk volume and the tapped volume of a powder.

Compressibility Index (%) = (TBD – LBD) × 100 / TBD

Hausner's ratio = TBD / LBD

Where, LBD = weight of the powder/volume of the packing,

TBD = weight of the Powder / tapped volume of the packing.

**Post-compression evaluation**

**Physical appearance:**

The tablets are visually observed for capping, chipping, lamination and changes in colour.

**Tablet thickness:**

The thicknesses of the tablets can be determined by using Vernier calliper. Five tablets are required, and average values are calculated. Variation in tablet may cause problems in counting and packaging. Tablet thickness should be controlled within a ±5% of a standard value.

**Hardness:**

Hardness testing determines that tablet was able to withstand mechanical shocks while handling. The hardness of the tablets is determined by using Monsanto hardness tester. It is expressed in $kg/cm^2$. 10 tablets are randomly picked and hardness of the tablets is determined.

**Weight variation:**

20 tablets are selected randomly and weighed individually to check for weight variation.

**Friability:**

20 tablets from each batch are selected randomly and weight. The friability of tablets is determined by using Roche Friabilator for 100 revolutions. The friabilator is operated at 25 rpm for 4 min. The tablets are subject to combine effect of abrasion and shock in a plastic chamber and dropping a tablet at height of 6 in. in each revolution. The tablets were removed, de-dusted and weighed again. It is expressed in percentage (%). % Friability of tablets less than 1% is considered acceptable. The % friability was then calculated by using formula:

$$\%\text{Friability} = \frac{(\text{Initial Weight} - \text{Final Weight})}{\text{Initial Weight}} \times 100$$

**In vitro dissolution study:**

Rotating basket (USP method I) was adopted for the dissolution study of all tablet formulations. Ketoprofen dissolution media would be pH 7.4 phosphate buffers. The pH value of 7.4 was chosen in order to achieve a maximum drug release from the tablet, since the drug is poorly soluble at low pH conditions. Temperature of dissolution medium should maintain at 37 ± 0.5 °C and the rotating speed adjusted to 100 rpm. Samples of 5 ml are taken at time intervals of 0.5, 1, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0 10.0, 12.0, 18.0 and 24 h and filtered using filter paper of 0.45 µm. Then all samples should be observed spectrophotometrically (UV–Visible spectrophotometer evolution 60, Thermo Scientific) with wavelength of 260 nm and note their respective absorbance. Then, the per cent release is calculated for all tablets from the standard curves. The dissolution experiments were conducted in triplicate.

## RESULTS AND DISCUSSION:

**Table 2: standard graph of Ketoprofen**

| S.NO | CONCENTRATION (µg/ml) | ABSORBANCE (at 260 nm) |
|---|---|---|
| 1 | 10 | 0.221 |
| 2 | 20 | 0.422 |
| 3 | 30 | 0.647 |
| 4 | 40 | 0.832 |
| 5 | 50 | 1.102 |

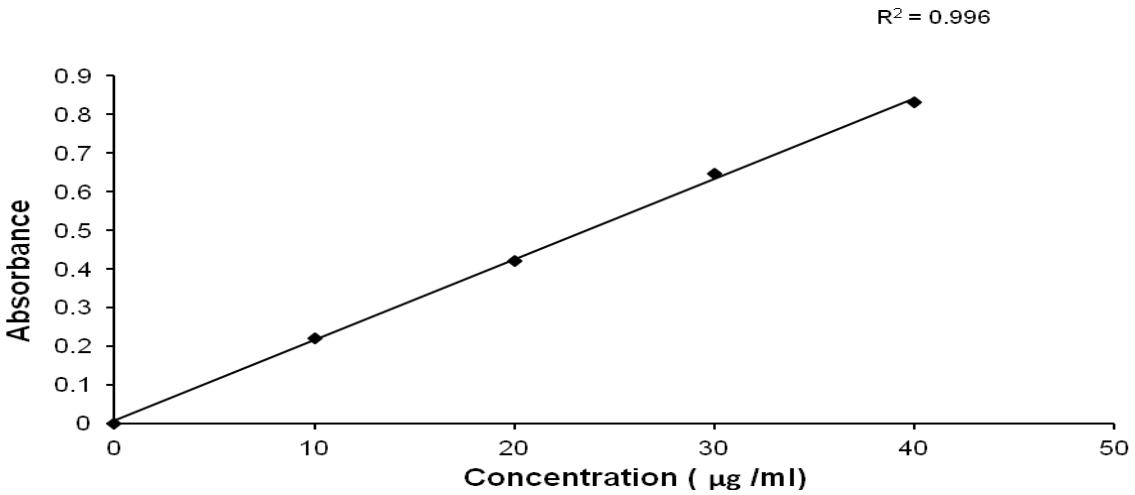


**Fig 1: Calibration Curve of Ketoprofen**

**Preformulation studies of blend:**

**Evaluation of mixed blend of drug and excipients**

**Table 3: Preformulation evaluation**

| Formula | Angle of repose (θ) | Bulk density (gm/cm$^3$) | Tapped density (gm/cm$^3$) | Compressibility index (I) | Hausner,s ratio |
|---|---|---|---|---|---|
| **F1** | 30.13 | 0.43 | 0.48 | 10.41 | 1.11 |
| **F2** | 27.46 | 0.46 | 0.52 | 11.53 | 1.13 |
| **F3** | 26.13 | 0.42 | 0.48 | 12.50 | 1.14 |
| **F4** | 28.21 | 0.38 | 0.45 | 15.55 | 1.18 |
| **F5** | 25.22 | 0.46 | 0.56 | 14.28 | 1.16 |
| **F6** | 28.57 | 0.48 | 0.55 | 12.72 | 1.14 |
| **F7** | 26.43 | 0.39 | 0.43 | 11.30 | 1.10 |
| **F8** | 28.26 | 0.45 | 0.51 | 11.76 | 1.13 |

**Evaluation of Ketoprofen sustained release tablets**

The physical parameters like weight variation, hardness, thickness, drug content of the prepared tablets were within the pharmacopoeia limits. The results of the test were tabulated with the standard deviation

**Table 4: Evaluation of tablets**

| Formulation | Weight variation | Hardness (kg/cm$^2$) | Thickness (mm) | Friability (%) | Content Uniformity (mg/tab) |
|---|---|---|---|---|---|
| **F1** | 499±0.7 | 4.0±0.13 | 3.65±0.02 | 0.7±0.01 | 99.00±1.55 |
| **F2** | 500±0.5 | 5.4±0.15 | 3.48±0.03 | 0.5±0.02 | 101.00±2.20 |
| **F3** | 499±0.6 | 4.6±0.13 | 3.42±0.02 | 0..6±0.01 | 99.55±1.10 |
| **F4** | 500±0.8 | 4.3±0.14 | 3.75±0.04 | 0.8±0.03 | 101.00±2.20 |
| **F5** | 499±0.7 | 4.8±0.16 | 3.80±0.03 | 0.6±0.01 | 99.75±0.55 |
| **F6** | 500±0.6 | 5.0±0.15 | 3.84±0.02 | 0.6±0.03 | 102.00±2.20 |
| **F7** | 500±0.5 | 4.5±0.15 | 3.66±0.03 | 0.7±0.02 | 99.50±3.00 |
| **F8** | 498±0.6 | 5.0±0.14 | 3.88±0.02 | 0.5±0.01 | 99.23±1.13 |

**Table 5: Drug release profile of marketed product, F1, F2, F3, F4**

| Time (hrs) | Marketed product % drug Release | F1 Cumulative % drug release | F2 Cumulative % drug Release | F3 Cumulative % drug Release | F4 Cumulative % drug Release |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 13.5 | 42.72 | 49.13 | 23.93 | 30.78 |
| 4 | 65.5 | 63.15 | 68.52 | 47.73 | 52.36 |
| 6 | 78.4 | 84.72 | 88.34 | 67.34 | 76.92 |
| 8 | 89.68 | 94.85 | 96.58 | 86.26 | 87.48 |
| 10 | 96.58 | - | - | 96.30 | 99.50 |
| 12 | - | - | - | - | - |

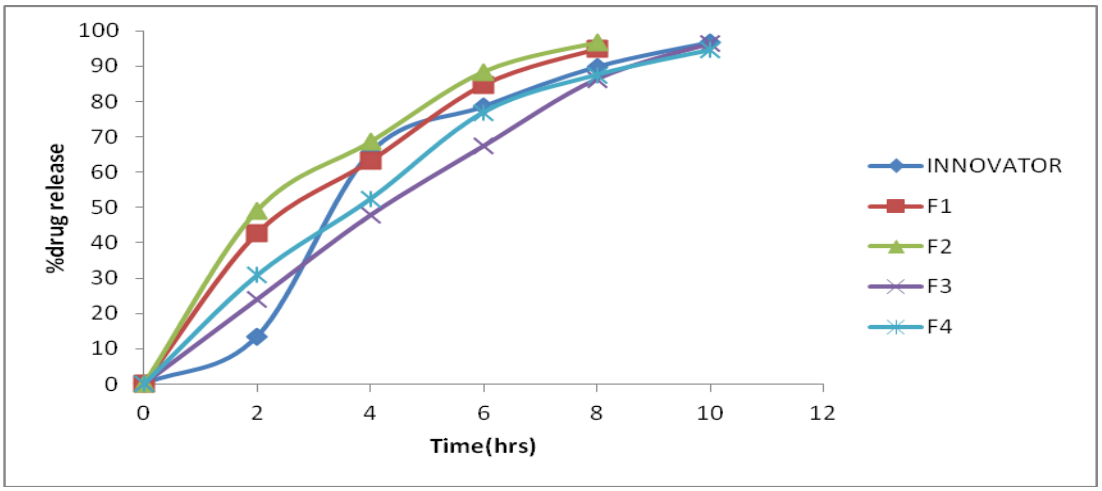


**Fig 2: Drug release profile of innovator and F1, F2, F3, F4 Formulations**

**Drug release profiles of F5, F6, F7, F8, Formulations:**

**Table 6: Drug release profile of innovator F5, F6, F7, F8.**

| Time (hrs) | Marketed % drug Release | F5 Cumulative % drug Release | F6 Cumulative % drug release | F7 Cumulative % drug Release | F8 Cumulative % drug Release |
|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 13.5 | 32.72 | 35.67 | 20.96 | 17.85 |
| 4 | 65.5 | 51.87 | 51.87 | 47.20 | 42.72 |
| 6 | 78.4 | 73.24 | 73.24 | 65.60 | 63.15 |
| 8 | 89.68 | 88.69 | 89.59 | 71.20 | 78.12 |
| 10 | 96.58 | 98.26 | 97.68 | 94.90 | 92.58 |
| 12 | - | - | - | 98.9 | 93.78 |

The above figure shows the *In vitro* release profiles of Ketoprofen sustained release tablets of formulations F5, F6, F7, F8 effect of HPMC (15 cps) and ethyl cellulose polymer on the release profile of Ketoprofen was studied. The formulation F7, F8 combination of HPMC (15 cps) and ethyl cellulose showed 98.9% and 93.78% respectively for 12hr. The formulation F7 showed 98.9% up to 12hrs.

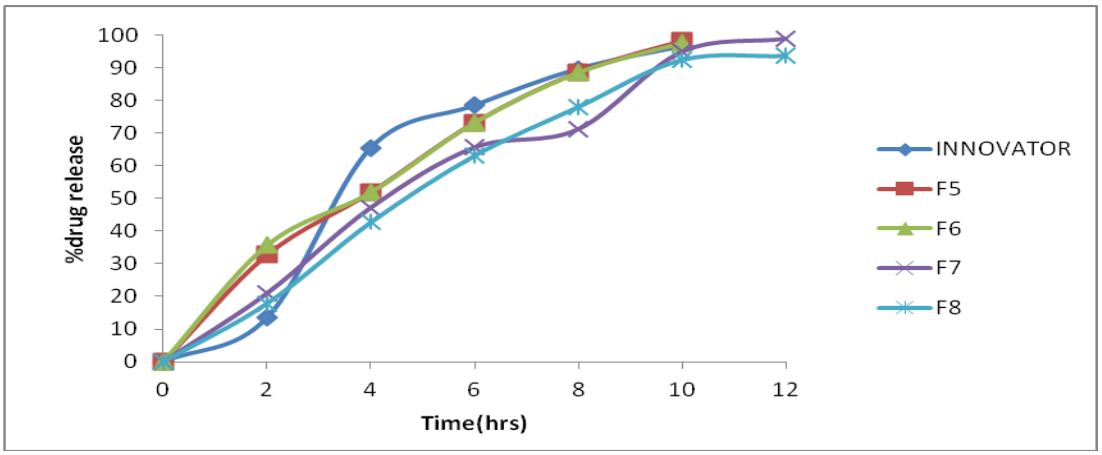


**Fig 3: Drug release profile of marketed product (KETOFEN) and F5, F6, F7, F8 Formulations**

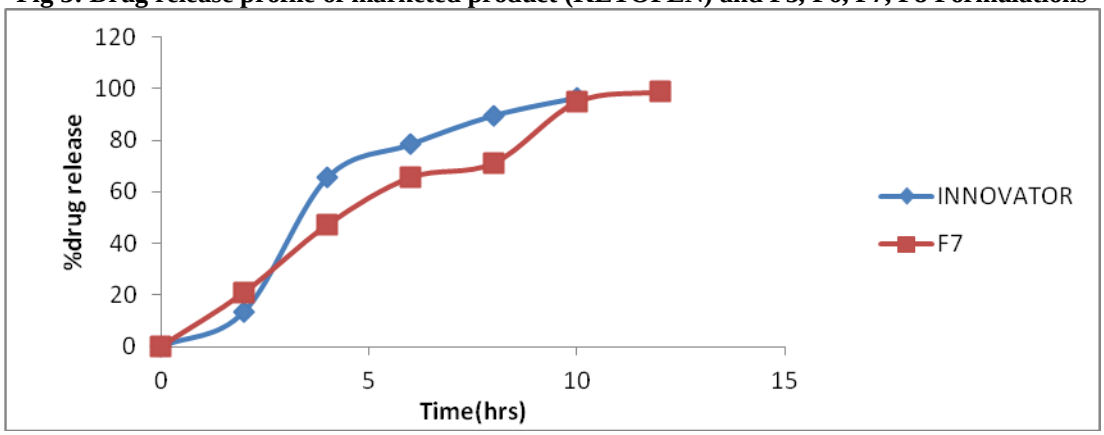


**Fig 4: Drug release profile of marketed product (KETOFEN) and Optimized (F7) Formulation**

## SUMMARY AND CONCLUSION:

**Summary:**

The purpose of the present study was formulation development and evaluation of Ketoprofen sustained release matrix tablets of strength 100 mg. Direct compression technique was chosen to develop a finished pharmaceutical product. Various formulations (F1-F8) were taken. In these trials, drug: excipient ratio was varied and the effect of diluents, and various polymers like Eudragit RL 100, HPMC 15 cps, and ethyl cellulose on the performance tablets was studied. All the formulations showed angle of repose below $30^0$ that mean they show free flowing property. All the formulation has hausner's ratio between the 1.10 to1.5. It indicates all the formulation show better flow property. The physical parameters like weight variation, hardness, thickness, drug content of the prepared tablets were within the pharmacopoeial limits. The total weight of each formulation was maintained constant. The weight variation of tablets was within the limit of 7.5% as specified. , Hardness ranges 4.3 to 5.4 $kg/cm^2$ and the friability loss of less than 1% in weight is generally acceptable. Content uniformity 99.55% to 101 % mg/tab was found.Among all formulation F7 showed in-vitro drug release 98.9% for 12hrs. And which is showed better release than marketed product (KETOFEN) hence considered as most promising preparation.

**Conclusion:**

The Sustained release Ketoprofen matrix tablets were prepared by direct compression method. The nature of the polymer influences the physical and release characteristics of the matrix tablet. The hydrophobic polymer, Ethyl cellulose has retarded the drug release from the tablet and the hydrophilic polymer, HPMC (15 cps) has release the drug. While making the combination of both hydrophilic and hydrophobic polymers i.e HPMC and Ethylcellulose with optimized ratio (F7) leads to sustained release of drug from matrix tablet for 12 hours was observed.

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