



FORMULATION AND CHARACTERIZATION OF SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

This study aimed to Formulated sustained release matrix tablets of Ketoprofen and evaluated to release the drug in a controlled manner over a period. Matrix tablets were prepared by direct compression method, using polymers like HPMC K100M, Ethyl cellulose, HPMC+EC, IPA+PVP, Lactose. Matrix tablets were prepared by wet granulation method using different polymers. Tablets were evaluated for *in vitro* drug release profile in 0.1N hydrochloric acid. The thickness and hardness of prepared tablets were 4.28 ± 0.05 to 4.58 ± 0.06 mm and 6.29 ± 0.02 kg/cm² to 6.82 ± 0.01 kg/cm², respectively. Percentage friability of all the formulated tablets was found between $0.418 \pm 0.02 \pm 0.02$ to $0.682 \pm 0.06\%$. which indicates the good mechanical strength of the tablets. Drug release was retarded with an increase in polymer concentration due to the gelling property of polymers. The *in vitro* drug release from the proposed system was best explained by Higuchi's model, indicating that drug release from tablets displayed a diffusion-controlled mechanism. The results clearly indicate that guar gum could be a potential hydrophilic carrier in developing oral controlled drug delivery systems. Based on the study results, formulations F9 was selected as the best formulation.

Keyword: Matrix tablets, Ketoprofen, *In vitro* Drug release.

1. INTRODUCTION

The main destination of any drug delivery system is to furnish a contributing to quantity of a drug to a suitable region in the body and that the required drug concentration can be attained promptly and then being maintained. The drug delivery system should distribute a drug at a rate dictated by the require of the body for particular length of time. Regarding this existing points there are two important aspects to delivery system, said as, spatial placement and temporal delivery. Spatial placement connected to targeting a drug to particular organ, tissues, cells, or even sub cellular area; whereas temporal delivery system deals to controlling the rate of dosage form to the targeting region. Sustained release tablets and capsules are mostly taken only once or twice daily, compared with immediate release tablet form that may have to take 3 or 4 times a day to attain the same required drug to produce the effect. Typically, the sustained release dosage form to furnish at once release the active component that give the what we are desired for cure of disease, followed by remaining quantity of drug should be release and maintained the therapeutic effect over a predetermined length time or prolonged period. The sustaining of drug plasma levels furnish by sustained release dose often times to eliminate the require for night dose administration, which suitable not only the patient but the care given as well. The bulk of research can be focusing toward oral dosages that improve the temporal aspect of drug delivery. This approach is a continuously developing in the pharmaceutical industry for sustained release oral drug delivery system. The sustained release system for oral use of administration are mostly solid and based on dissolution, diffusion or a combination of both, erosion mechanisms, in the power to directing the drug release. A delivery system containing hydrophilic and hydrophobic polymers and waxes are mixed with active component to furnish drug action for a prolonged length of time. The concept of modified release dosage products was previously used to describe various types of oral extended release dosage forms, including sustained release, sustained action, prolonged action, slow release, long action and retarded release.

2. EXPERIMENTAL WORK

2.1 Preformulation studies

a. Organoleptic properties:

The colour, odour and taste of the drug were recorded using descriptive terminology.

b. IR spectrum interpretation:

The infrared spectrum of pure Ketoprofen was recorded and spectral analysis was done.

c. Loss on drying:

Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified condition. The test can be carried out on the well mixed sample of the substance.

$$\text{Loss on Drying} = \frac{\text{Initial weight of substance} - \text{Final weight of substance loss}}{\text{Initial weight of substance}} \times 100$$

d. Melting point: Melting point of the drug was determined by capillary tube method.

e. Solubility study:

Appropriate quantity of drug was weighed and added to the suitable volume of solvent like Ethanol, water, Acetonitrile, Acetone, Propylene glycol, Ethylene glycol, n-Propanol

f. Analytical methods:

Determination of λ max:

50 mg of Ketoprofen was accurately weighed and transferred to a 50 ml volumetric flask. It was dissolved in sufficient amount of Methanol and volume was made up to 50 ml with Methanol. Exactly 10ml of the stock solution was pipetted out and was diluted to 100 ml with Methanol. The spectrum was recorded in the range of 260 nm.

7.2 Compatibility testing of drug with polymer:

FTIR study was carried out to check compatibility of drug with polymers. Infrared spectrum of Ketoprofen was determined on Fourier transform Infrared Spectrophotometer using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run followed by drug with various polymers by using FTIR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.

Differential scanning calorimetry (DSC):

Any possible drug polymer interaction can be studied by thermal analysis. The DSC study was performed on pure drug, and polymers, drug+HPMC K15M, drug+Carboxy methylcellulose and drug+ Xathan gum. The study was carried out using a Shimadzu. The 2 mg of sample were heated in a hermetically sealed aluminum pans in the temperature range of 25-300°C at heating rate of 10°C /min under nitrogen flow of 30ml/min.

Formulation of Ketoprofen sustained release matrix tablets:**Table 7.1: Composition of Ketoprofen matrix tablets**

Ingredients(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ketoprofen	50	50	50	50	50	50	50	50	50
HPMC K100M	40	60	80	-	-	-	-	-	-
Ethyl cellulose	-	-	-	40	60	80	-	-	-
HPMC+EC	-	-	-	-	-	-	40	60	80
IPA+PVP	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Lactose	100	80	60	100	80	60	100	80	60
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5
Total weight	200	200	200	200	200	200	200	200	200

Preparation of granules:

Granules for Ketoprofen matrix tablets were prepared by wet granulation technique using various percentages of HPMC K15M, carboxy methyl cellulose and xanthan gum as release retardant polymers. The required quantity of drug, various polymers and other ingredients were mixed thoroughly and a sufficient volume of granulating agent (isopropyl alcoholic solution of polyvinyl pyrrolidone) was added slowly. After enough cohesiveness was obtained, the wet mass was sieved through sieve No.8. The granules were dried at 60 C for 30 minutes and then the dried granules were passed through sieve No.16. Talc and magnesium stearate were finally added as a glidant and lubricant respectively.

7.3 Evaluation of granules:

a. Angle of repose: The angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the granules cone respectively.

b. Loose bulk density:

The loose bulk density of granules was determined using the following formula.

Loose bulk density = Total weight of granules / Total volume of granules

c. Tapped bulk density:

The Tapped bulk density of granules was determined by the following formula.

Tapped bulk density = Total weight of granules/ Tapped volume

d. Hausner ratio:

Hausner ratio is the ratio between tapped density and bulk density. Hausner ratio less than 1.25 indicates good flow properties while Hausner ratio greater than 1.25 shows poor flow of granules.

e. Carr's compressibility index:

The compressibility index of the granules was determined using following formula.

Carr's compressibility index (%) = [(TBD-LBD)/ TBD] ×100

7.3 Preparation of tablets:

The evaluation of granules showed excellent flow properties. The granules were compressed into tablets on 16 station rotary tablet compression machine using 11 mm round, biconcave punches. The compressed tablets were evaluated for various parameters viz. appearance, thickness, diameter, hardness, friability, weight variation, drug content and *in vitro* drug release studies.

7.4 Evaluation of Sustained release matrix tablet of Ketoprofen:

i. Appearance:

The tablets were visually observed for capping, chipping, and lamination.

ii. Thickness and diameter:

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined using a vernier caliper. Ten tablets from each type of formulation were used and average values were calculated.

iii. Weight variation test:

For weight variation, 20 tablets of each type of formulation were weighed individually on an electronic balance, average weight was calculated and individual tablet weight was then compared with the average value to find out the deviation in weight.

iii. Hardness:

For each type of formulation, the hardness value of 10 tablets was determined using Monsanto hardness tester.

iv. Percentage friability :

Friability is the measure of tablet strength. Percent friability (% F) was calculated as follows,

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

v. Content uniformity:

Content uniformity was determined by accurately weighing 20 tablets and crushing them in mortar with the help of a pestle. Then an accurately weighed quantity of powder equivalent to 25 mg of drug was transferred

to a 50 ml volumetric flask. Then added few ml of methanol and made upto 50ml with methanol. The solution was filtered through whatmann filter paper. 5 ml of the filtrate was diluted to 50 ml with Methanol. Then 3 ml of the resulting solution was again diluted to 10 ml with Methanol.

vi. In-vitro dissolution studies:

The *in-vitro* dissolution studies were performed using USP type I dissolution apparatus at 50rpm. Dissolution test was carried out for a total period of 8 hours using 0.1N HCl (pH 1.2) solution (900 ml) as dissolution medium at $37 \pm 0.5^\circ$ for first 2 h, and pH 7.4 phosphate buffer solution (900 ml) for the rest of the period An aliquot (5ml) was withdrawn at specific time intervals and absorbance was determined by U.V. spectrophotometer at 260 nm. The release studies were conducted in triplicate.

7.5 Stability study:

ICH guideline specifies the length of study and storage conditions

Long-Term Testing: $25 \text{ C} \pm 2 \text{ C}$ at $60\% \text{ RH} \pm 5\%$ for 12 Months

Stability studies were carried out at accelerated condition ($40 \text{ C} \pm 2 \text{ C}$ at $75\% \text{ RH} \pm 5\% \text{ RH}$) for the optimized formulation. The matrix tablets were stored at $40 \text{ C} \pm 2 \text{ C}$ at $75\% \text{ RH} \pm 5\% \text{ RH}$ for accelerated temperature in closely packed with aluminium foil for 3 months. The samples were withdrawn after periods of 1st month, 2nd month and 3rd month. The samples were analyzed for its hardness, drug content and *in vitro* drug release.

Summary and Conclusion

In present investigation an attempt has been made to design and develop Ketoprofen sustained release matrix tablets using HPMC K100M, and ethyl cellulose, as release retarding polymers. Ketoprofen is widely used as a centrally acting muscle relaxant; therefore have been selected to prepare sustained release dosage forms. An ideal matrix formulation prepared with different polymers and diluents concentrations should release its content in a sustained profile a reasonable length of time and preferably with Korsmeyer-peppas kinetic. The active pharmaceutical ingredient Ketoprofen was evaluated for its physical characteristics, analytical profiles and drug polymer compatibility study. The granules were prepared by wet granulation method. The prepared granules were evaluated for Angle of repose, Bulk density, Tapped density and Carr's index. The results obtained were found to be satisfactory and within the specified limits.

After compression parameters like Thickness, Hardness, Weight variation, Friability, content uniformity and *In-Vitro* release studies were evaluated. Result of the present study demonstrated that hydrophilic polymers could be successfully employed for formulating sustained release matrix tablets of Ketoprofen. The investigated sustained release matrix tablet was capable of maintaining constant plasma concentration upto 10 hours. This can be expected to reduced the frequency of administration and decrease the dose dependent side effects. The efficacy and safety of Ketoprofen tablet dosage form are expected to offer optimum therapeutic efficacy and improved patient compliance. In the present study the effect of types and concentration of polymer were studied on *In-Vitro* drug release. It shows that increase in concentration of polymer results in the sustained drug release

for 10 hours. The study has revealed that by increasing concentration of polymer, release rate of drug was retarded and results confirmed that the release rate from hydrophilic matrix tablets depends on type and concentration of polymer.

According to stability study it was found that there was no significant change in hardness, drug content and *in vitro* dissolution of optimized formulation (F9). In the present work the sustained release matrix tablets of Ketoprofen were formulated using hydrophilic polymers such as HPMC, ethyl cellulose and by wet granulation method. In this work only physiochemical characterization, formulation and *in-vitro* evaluation matrix tablets of Ketoprofen was done. Along with *in-vitro* release study *in-vivo* release behavior of drug is also important. So in future *in-vivo* release study using different models are required to set the *in-vitro in-vivo* correlation which is necessary for development of successful formulation and also long term stability studies are necessary.

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