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Research paper

Colon-specific double-compression coated pulsatile tablets of ketorolac tromethamine: Formulation development and pharmacokinetics

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ABSTRACT

In the recent pharmaceutical research, pulsatile drug delivery has been of interest to achieve improved drug therapies. The present study is aimed to formulate and study the pharmacokinetics of colon-specific pulsatile ketorolac tromethamine tablets using double-compression coating method. In this, inner compression coat made of sodium starch glycolate as swelling layer and outer compression coat (release controlling layer) contains sodium alginate and hydroxypropyl methylcellulose K 15M. From the *in vitro* drug release studies, F5 tablets showed 5.02 ± 0.16% drug release in 5 h and it was progressively expanded to 99.78 ± 0.64% in 24 h that demonstrate the colon-specific drug release. From the stability studies, F5 formulation showed the good stability and it was proved by calculating the similarity factor i.e., 83.92. From the pharmacokinetic evaluation, immediate release core tablets producing peak plasma concentration (C_{max}) was 4425.23 ng/ml at 2 h T_{max} and colon-specific double-compression coated tablets demonstrated C_{max} = 3456.47 ng/ml at 10 h T_{max}. The area under curve values for the core and double-compression coated tablets were 10128.53 and 17467.62 ng-h/ml respectively and the mean resident time was 4.21 h and 10.34 h respectively. In conclusion, development of ketorolac tromethamine double-compression coated pulsatile tablets is a promising way to achieve colon-specificity.

1. Introduction

To achieve the colon-specific drug delivery, development of pulsatile tablets is one of the promising time- and site-specific systems that release the drug in colon after a predetermined lag time [1]. Incorporation of this lag time into the tablets is depending on the nature of therapeutic application and is depending upon the polymer used and thickness of compression coating [2]. Colonic pulsatile drug delivery is required especially for the treatment of some common diseases, such as bronchial asthma, hypertension, angina pectoris, allergic rhinitis and rheumatoid arthritis with mainly night or early morning symptoms [3]. Some of the recent research examples on colon-specific pulsatile drug delivery systems are colon targeted pulsatile system of flurbiprofen for colonic inflammation [4], pulsatile systems for targeted drug delivery of celecoxib for prophylaxis of colorectal cancer [5], time and pH dependent colon specific pulsatile delivery of theophylline for nocturnal asthma [6].

The current pharmaceutical tabletting research is focusing more on solvent less compression coating rather than the solvent coating. Compression-coated tablets offer coating methodology free of solvents which is safe and inexpensive that doesn't require special coating equipment and the coating formed through compression offers higher stability as compared with film coating [7]. Some of the recent research examples on compression coated tablets are ketorolac tromethamine-sodium alginate compression coated tablets [2], flurbiprofen-sodium alginate compression coated tablets [8], flurbiprofen-guar gum compression coated tablets [9], 5-fluorouracil-hydroxypropyl methylcellulose compression coated tablets [10], 5-fluorouracil compression coated tablets [11], ketorolac tromethamine-hydroxypropyl methylcellulose compression coated tablets [7], flurbiprofen double-compression coated mini-

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tablets [12] etc. Although sufficient research was done on compression coated tablets, very little information available for double compression coating technology. The present study is differed from above literature that based on double-compression coating method to achieve pulsatile colon-specific drug release.

In the present study, ketorolac tromethamine (KTM) was selected as the model drug. KTM is a non-steroidal anti-inflammatory drug and is one of the widely used drugs for long-term treatment of rheumatoid arthritis and colonic inflammation [13]. Rheumatoid arthritis is a circadian rhythms sensitive disease and it requires time-dependent drug release for maximum therapeutic benefit. By considering these factors, colon-specific KTM double-compression coated pulsatile tablets were prepared using inner compression coat as swelling layer and outer compression coat as release controlling layer.

2. Materials

Ketorolac Tromethamine was gift sample from Bright Labs, Hyderabad, India. HPMC K15M, Sodium alginate and Sodium starch glycolate are obtained as a gift sample from MSN Laboratories, Hyderabad, India. All other chemicals used were of analytical grade.

3. Experimental methods

3.1. Preparation of KTM core tablets

In this study, the core tablets were prepared with the help of direct compression method by incorporating 20 mg of KTM as the active ingredient. KTM and excipients other than glidant and lubricant were passed through 60 # sieve and blended for 5–10 min in poly bag. The resultant blend was lubricated with the addition of lubricant and glidant and finally compressed into tablets (80 mg) using 6 mm round flat punches (Table 1).

3.2. Preparation of KTM double-compression coated tablets

The prepared core tablets were coated with different polymers using double-compression coating method (compositions shown in Table 2). At first, the core tablets were coated with inner compression coat using sodium starch glycolate as swelling layer, then treated with HPMC K15M/sodium alginate as release controlling outer compression coat. Each layer adjusted to 80 mg weight and the inner layer compressed using 8 mm and outer layer compressed using 10 mm circular flat punches by placing half of the coating material in die cavity, then cautious placing of cores in middle and finally placing the remaining half of coating material.

3.3. Evaluation of compression coated tablets

After the successful compression coating, the prepared tablets were evaluated for various physical parameters like weight variation, hardness, friability and drug content uniformity. Randomly picked twenty tablets of each formulation were weighed using an electronic weighing balance (AW 120, Shimadzu Corporation, Japan) and calculated the average weights to check the weight variation. Then to check the mechanical strength and integrity of prepared tablets, hardness and friability were measured. The tablet hardness was measured using Monsanto hardness tester and friability was determined using Roche friabilator (Electro lab, Mumbai, India). To check the drug content uniformity of each formulation, randomly selected ten tablets were crushed, and the aliquot of powder equivalent to 50 mg of drug was dissolved in suitable quantity of pH 7.4 phosphate buffer solution. Solution was filtered and diluted and drug content determined by HPLC method at 319 nm using UV detector.

3.4. In vitro drug release study

In vitro drug release studies (n = 3) were planned using USP type II dissolution apparatus at 50 rpm speed and 37 °C ± 0.5 °C temperature in 900 ml dissolution media (0.1 N HCl for first 2 h; 3–4 h in 5.5 pH buffer and then in phosphate buffer pH 7.4 from 5 to 24 h). An aliquot (5 ml) was withdrawn at specific time intervals and replaced with the same volume of pre-warmed fresh dissolution medium. The withdrawn samples were filtered analyzed by HPLC method at 319 nm using UV detector. Then the dissolution data was also used to calculate the mean dissolution time (MDT-the sum of different release fraction periods during dissolution studies divided by the initial loading dose) [14], T10% and T80% (time in hours to take 10% and 80% drug release, respectively) to explain the drug release from compression-coated tablets [7].

3.5. Stability studies

According to the ICH guidelines, stability studies were designed on F5 compression coated tablets to check the stability of KTM. Three replicates of F5 tablets were sealed in aluminum coated inside with polyethylene pack and stored at 40 ± 2 °C and 75 ± 5% RH in the humidity chamber for six months [15]. Then the collected samples after six months of storage were used to measure the drug content and *in vitro* dissolution rate [16]. Finally the data was used to calculate the similarity index between dissolution rates of tablets before and after storage. At this point, the data was statistically analyzed using paired *t*-test to test the significance of difference at level of significance 0.05.

3.6. In vivo study in healthy volunteers-Drug administration

The present study was designed using crossover design by dividing twelve healthy human volunteers (avg age = 25 years) into two groups. During the first phase of study, an immediate release core tablets (dose 20 mg) was administered to group I volunteers (n = 6) and F5 colon-specific double-compression coated tablets

Table 1
Composition and characterization of KTM core tablets.

Ingredients	Quantity (mg)	Core tablet evaluation parameters	n	Observed values
KTM	20	Weight variation (mg)	20	80.42 ± 1.74
Avicel PH 102	53.6	Core thickness (mm)	20	1.83 ± 0.02
Crospovidone	4	Core diameter (mm)	20	6.08 ± 0.02
Talc	1.6	Hardness (kg/cm^2)	6	2.94 ± 0.59
Magnesium stearate	0.8	Friability (%)	6	0.42
Core weight	80	Disintegration time (sec)	3	37.92 ± 1.37
		Content uniformity (%)	3	100.36 ± 1.82
		% Drug release in 15 min (Q_{15})	3	99.98 ± 0.63