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Research Article

Formulation, Development and Evaluation of Pulsatile Tablets of Etoricoxib

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Abstract

Aim: This research aimed to develop a pulsatile drug delivery system (PDDS) for etoricoxib, selective COX-2 inhibitor analgesic, to address the limitations of conventional formulations by releasing the drug at specific intervals aligned with the circadian rhythm of pain.

Method: Core tablets containing Etoricoxib were prepared by direct compression with varied concentrations of croscarmellose sodium as a superdisintegrant. The optimized core tablets were coated using hydrophilic (HPMC K4M) and hydrophobic (ethyl cellulose) polymers in different ratios to create press-coated pulsatile tablets with varying lag times. Physical properties hardness, thickness, friability, and disintegration, drug content uniformity, and in vitro release were evaluated.

Results: The core tablets exhibited rapid drug release, with batch C3 showing 98.61% release within 60 minutes. Press-coated formulations with different polymer ratios exhibited varying lag times, with batch F3 achieving the optimal balance—providing a 4-hour lag time and 96.6% drug release over 8 hours. Stability studies confirmed the physical and chemical stability of the optimized formulation (F3) over 6 months under accelerated conditions.

Conclusion: The developed press-coated pulsatile tablets of etoricoxib successfully achieved a controlled lag time and sustained drug release profile, making them suitable for chronopharmacological management of pain.

Keywords: Etoricoxib, Pulsatile Drug Delivery System, Chronopharmacology, Press-Coated Tablets. etc

INTRODUCTION:

Etoricoxib, a selective COX-2 inhibitor, is widely used for the management of chronic and acute inflammatory conditions, including osteoarthritis, rheumatoid arthritis, and gout. However, conventional drug delivery systems may not align with the body's circadian rhythms, where symptoms of these diseases typically intensify in the early morning or late at night. Pulsatile drug delivery systems offer a tailored approach by releasing the drug in a time- or site-specific manner, enhancing therapeutic efficacy while minimizing side effects. These systems are especially beneficial for drugs with chronopharmacological needs, where drug release is required at specific times to achieve optimal therapeutic outcomes.[1] The formulation of pulsatile tablets aims to deliver etoricoxib at a pre-determined time after administration, aligning the drug release with the peak symptom onset. This not only ensures better patient compliance but also maximizes pharmacological outcomes by delivering the right dose at the right time. Such a system can benefit individuals suffering from nocturnal pain or early morning stiffness, where immediate drug availability is crucial.[2]

Etoricoxib offers the advantage of delivering the drug at predefined intervals, ensuring pain relief when it is most needed. This approach aligns with the circadian rhythm of pain, which often intensifies during early morning hours or at specific times during the day.[3] In this study, the formulation of pulsatile tablets involves the use of a core containing etoricoxib, surrounded by a time-controlled release coating. Polymers with varying swelling and erosion properties are employed to achieve the desired lag time. The evaluation of these tablets focuses on parameters such as physical characteristics, drug content, in vitro release profile, lag time, and stability. By optimizing the formulation, the aim is to achieve a predictable and reliable drug release after a specific lag phase. This research aims to provide an effective pulsatile delivery system for etoricoxib, improving pain management while minimizing side effects and enhancing patient compliance.[4]

MATERIALS AND METHOD

Materials

Etoricoxib was supplied as gift sample by Cadila Healthcare (Ahmedabad. India), HPMC and Ethyl

cellulose was purchased from Loba CHem, India. All other solvents and reagents were of analytical grade.

Method

Formulation of Core Tablets of Etoricoxib:

The core tablets were prepared by direct compression technique. The composition of the tablets was showed in Table 1. Three different batches (C1, C2 and C3) of core tablets were made utilizing varied concentration of disintegrating agent (Croscarmellose Sodium). Keeping other materials constant. All the excipients were passed through sieve no.30. The required ingredients were accurately weighed and mixed thoroughly and dry blended with talc and magnesium stearate for 5 min. The resulting blends were subjected to the micromeritic properties and compressed by using 8 mm flat face punch using multi station tablet punching machine.[5]

Table 1: Formulation of Etoricoxib Core Tablets

Sr. No	Ingredients	Batch		
		C1	C2	C3
1	Etoricoxib (mg)	90	90	90
2	Croscarmellose Sodium (mg)	3	4.5	6
3	Magnesium stearate (mg)	1.5	1.5	1.5
4	Talc (mg)	1.5	1.5	1.5
5	Lactose (mg)	54	52.5	51
	Total Wt. (mg)	150	150	150

Formulation of Press Coated Pulsatile Tablet of Etoricoxib

All the ingredients were accurately weighed and passed through sieve no.70 and thoroughly mixed for 5 min. Initially half quantity of the mixture of two polymers (HPMC and ethyl cellulose) with different weight ratio was filled in the die of 12mm diameter and then gently compacted to make a powder bed with a flat surface. The optimized core tablet was then carefully placed in the centre of powder bed. The die was filled with the remaining of coating mixture so that powder bed was compressed directly using 12mm flat punch to produce desired press coated tablets. Five formulations were prepared using different concentration of coating polymer. Formulations of press coated tablet were shown in table 2. The press coated tablets were further evaluated for hardness, thickness, content uniformity, friability and disintegration and dissolution time.[6,7]

Table 2: Composition of Press Coated Tablets

Sr. No	Ingredients (mg)	Batch				
		F1	F2	F3	F4	F5
1	Core Tablet	150	150	150	150	150
2	HPMC K4M	200	150	100	50	-
3	Ethyl Cellulose	-	50	100	150	200
	Total Wt. (mg)	350	350	350	350	350

EVALUATION

Evaluation of Powder Blend

Bulk Density and Tap Density

An accurately weighed quantity of the granules (W) was carefully poured into the graduated cylinder and the volume (vo) was measured. Then the cylinder was dropped at 2-second intervals onto a hard wooden surface three times, from a height of one inch. The volume was recorded and the bulk density was calculated.

Bulk density = weight of sample /volume noted.....(1)

Tap density was calculated by measuring final volume(Vf) after 50 taps on wooden surface from 6-inch height and was expressed in g/cm3. The tapped density was calculated using formula

Tapped Density = Wt of Powder / Tapped Vol. of Powder……(2)

Compressibility Index and Hausner Ratio

The Compressibility index and Hausner ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative

importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there arefrequently greater inter particle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio. The compressibility index and Hausner ratio may be calculated using measured values for bulk density and tapped density as follows:

Compressibility Index (%) =

Tapped Density – Bulk Density/ Tapped Density X 100..... (3)

Hausner ratio = Tapped Density / Bulk Density..... (4)

Angle of Repose

The flow characteristics are measured by angle of repose. Improper flow of powder is due to frictional forces between the particles. These frictional forces are quantified by angle of repose. Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

Evaluation of Core and Press Coated Pulsatile Tablets[66,67,68,69]

Thickness:

Control of physical dimension of the tablet such as thickness is essential for consumer acceptance and tablet uniformity. The thickness of the tablet was measured using Vernier calipers. It is measured in mm.

Hardness:

The Mansanto hardness tester was used to determine the tablet hardness. The tablet was held between a fixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of hardness of the tablet. Hardness was expressed in Kg/cm2.[8]

Friability:

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 mins dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were re- weighed and the percentage loss in tablet weight was determined.

Weight Variation Test:

The weight of the tablet being made in routinely measured to ensure that a tablet contains the proper amount of drug. The IP weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average.[9]

Uniformity of drug content:

Ten tablets of various formulations were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in methanol, the drug content was determined measuring the absorbance at 233 nm after suitable dilution using a UV/Visible Spectrophotometer.[10]

Disintegration Test:

The test for disintegration was carried out in the USP disintegration test apparatus. To test the disintegration time of core tablets, one tablet was placed in each tube and the basket rack was positioned in a 1-liter beaker containing 6.8 phosphate buffer solution at 37 °C ± 1 °C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.[11]

In Vitro Drug Release Studies:

Drug Release of the prepared core and press coated pulsatile tablets was determined using U.S.P. II (type II) dissolution rate test apparatus. 900 ml of phosphate buffer pH 6.8 was used as dissolution medium. The rotation of paddle was fixed at 50 RPM and the temperature of 37+0.5ºC was maintained throughout the experiment. Samples of 5 ml were withdrawn at known time intervals and were replaced with same volume of fresh dissolution media after each withdrawal. The samples were analyzed spectrophotometrically on double beam UV/Visible spectrophotometer at λ max 233 nm. The results in the form of percent cumulative drug released was calculated.[12]

Stability Studies:

The accelerated stability studies were carried out according to ICH guidelines on optimized formulation. The formulation was packed in strip of aluminum foil and was stored in stability chamber maintained at 40°C and 75% RH (Zone III conditions as per ICH Q1 guidelines) for 6 month. The Tablet were evaluated before and after 6 months for change in appearance, Hardness, drug content and In vitro release.[13]

RESULTS AND DISCUSSION

Pre Compression Parameters:

The results of micromeritic properties were showed in table 3. Bulk density values obtained in the range from 0.421- 0.471gm/cc for all the formulations and The tapped density values obtained in the range from 0.512-0.552gm/cc. Angle of repose ranged between (25.32-28.50), the compressibility index ranged between 14.15 to 15.44 and Hausner's ratio ranged between (1.19 - 1.24), confirmed good flow properties of the powder blend. Thus the powder showed better flow properties and were non aggregated.

Table 3: Micromeritics properties of powder blend of core tablets formulation

Batch	Bulk density (g/cc)	Tapped density (g/cc)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose(θ)
C1	0.435	0.550	14.15	1.19	25.32
C2	0.471	0.552	15.24	1.24	27.62
C3	0.421	0.512	15.44	1.21	28.50

Post Compression Parameters

Weight Variation: The weight of tablets of all formulation batch C1 to C3 was passed and found within pharmacopoeial standards.

Hardness: The hardness of tablets was found in the range from 3 to 3.5 kg/cm^2 for formulation C1 to C3 is found to be optimum and indicate tablets able to withstand mechanical shock.

Friability: The friability value of all tablets batch formulation C1 to C3 were found to be less than 1% indicating good mechanical strength of tablets.

Drug Content: Good uniformity of drug content was found within and among the different types of tablet formulation. The values ranged from 95.65 to 96.72%.

Thickness: It varies from 3.1 to 3.2 for formulation C1 to C3 is found to be optimum and indicated well distribution of pure drug.

Disintegration Time : Disintegration time for formulation was found in the range of 30 to 45 sec and found within pharmacopoeial standards. Batch C3 showed least disintegration time of 30 sec when compared with other formulation may due to higher concentration and wicking action of disintegrating agent, croscarmellose sodium. The results of post compression parameters are shown in table 4.

Table 4: Post Compression parameters of Core Tablets Formulation (C1 to C3)

Batch	Weight Variation	Hardness (Kg/cm2)	Friability (%)	Thickness (mm)	Drug Content (%)	Disintegration Time (sec)
C1	150 ± 1.4	3.5± 0.35	0.94	3.2± 0.50	95.66	45± 1.12
C2	151± 1.2	3± 0.47	0.98	3.1± 0.34	96.12	40± 1.51
C3	150± 1.2	3.5± 0.52	0.92	3.2± 0.31	96.72	30± 0.74

(SD ± Mean of n=3)

In Vitro Drug release of Core Tablets of Etoricoxib

The *in vitro* drug release studies of rapid release core tablet were carried out in phosphate buffer pH 6.8. The drug release from core formulations containing C1 prepared with 2% of croscarmellose sodium showed 92.32 % at 60 min. Formulation C2 prepared with 3% of croscarmellose sodium showed 95.41 % drug release at 60 min, while formulation C3 prepared with 4% of croscarmellose sodium showed drug release of 98.61 % at the end of 60 min. All the formulation showed rapid drug release because of presence of super disintegrating agent croscarmellose sodium. Among the formulation batch C3 showed fastest drug release compare to other formulations. The results indicated that as the concentration of superdisintegrant increased the drug release was increased. Data for in vitro drug release of core tablets was shown in figure 1.

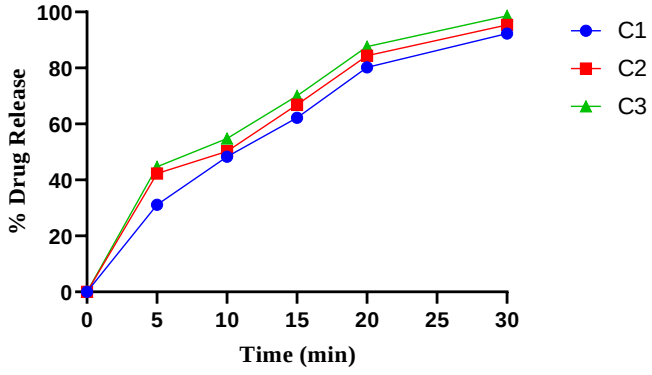

Figure 1: In vitro drug release profile of Etoricoxib core tablets formulation

Evaluation of Press Coated Pulsatile Tablet of Etoricoxib

Press coated pulsatile tablets of etoricoxib was prepared by using varying concentration of hydrophilic polymer HPMC K4M and hydrophobic polymer ethyl cellulose. The composition of formulations is shown in table 5. Among the formulations, batch C3 was considered as optimized formulation on the basis of faster disintegration and drug release and was used for press coating so as to produce pulsatile tablets. The tablets were prepared by direct compression method. The pulsatile tablets of Etoricoxib were subjected to post compression analysis.

The hardness of the tablets prepared by direct compression method was determined by using Monsanto Hardness tester. The mean hardness of coated tablets was found within the range was 5.8 ± 0.32 to 6.3 ±0.36 kg/cm^2 indicating good crushing strength. The mean thickness of coated tablets was found within the range of 4.50± 0.35 – 4.53± 0.33 mm for the pulsatile tablets. The drug content uniformity of all formulations was carried out and was found to be within the range 96.30 % to 98.42 % which found within acceptable limit. Weight variation for all the tablets batch formulations F1 to F5 passes the test and was within pharmacopoeias limit. Friability test for all batches was less than 1% indicating good mechanical strength of tablets. The lag time of the press coated tablets was measured by determining the time for which there is no release of drug, batch F1 prepared with HPMC K4M alone showed 0 hours of lag time which may due to hydrophilic nature of polymer. Batch F2, F3, F4 and F5 showed 1 hour, 4 hours, 3 hours and 4 hour of lag time respectively. Batch F3 and F5 showed highest lag time of 4 hours. Evaluation data of coated tablets are shown in table 5.

Table 5: Evaluation of Press Coated Pulsatile Tablets (F1 to F5)

Batch	Weight Variation	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Drug Content (%)	Lag Time (Hr)
F1	351 ± 0.23	6 ± 0.42	0.62	4.51± 0.52	97.61	0
F2	353± 0.41	5.8 ± 0.32	0.51	4.53± 0.33	98.12	1
F3	351± 0.57	6 ± 0.57	0.46	4.50± 0.35	98.42	4
F4	349±0.22	6.2 ±0.21	0.52	4.52±47	97.36	3
F5	352±0.25	6.3 ±0.36	0.54	4.51±64	96.30	4

(SD ± Mean of n=3)

In Vitro Drug release of Press Coated Pulsatile Tablets

Tablets were subjected to dissolution in 6.8 pH phosphate buffer. The dissolution study of these formulations was performed in order to understand the effect of different polymers and their increasing concentrations. The formulation was optimized on the basis of desired value of lag time and dissolution profile. Batch F1, formulated with HPMC alone showed 0 hour of lag time and 92.7 % drug release at the end of 8 hours. Batch F2, F3 and F4 prepared with varying amount of HPMC and EC showed 90.26%, 96.60% and 86.825 drug release at the end of 8 hours respectively. Batch F5 prepared with polymer EC showed lag time of 4 hours and 41.32 % of drug release in 8 hours, high lag time and low drug release may due to hydrophobic nature of EC polymer. Among the formulations batch F3 gives sufficient lag time and optimum drug release and hence considered as optimum formulation. The % cumulative drug release versus time data for all formulations batch is shown figure 2.

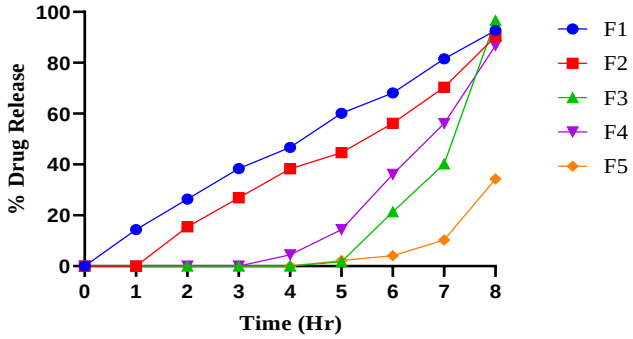

Figure 2: % Drug Release of Press Coated Tablets of Etoricoxib (F1 to F5)

Stability studies

Pulsatile tablets formulation showing optimum lag time and drug release, was selected for stability studies. According to ICH guidelines, optimized formulations F3 were stored at 40^{0}C temperature and 75% relative humidity (RH) for a period of 6 months. Formulation was evaluated for appearance, hardness, drug content and *In vitro* release. At the end of 6 month no significant difference was observed in hardness, drug content and in vitro drug release. From the stability study it was concluded that press coated pulsatile tablets formulation F3 was found to be stable.

CONCLUSION

The aim of the present study was the formulation of pulsatile tablets of Etoricoxib Hydrochloride by press coating technique that could release the drug in pulsatile manner. The core tablets and press coated pulsatile tablet of Etoricoxib Hydrochloride was prepared by direct compression technique. The core tablets were formulated using super disintegrating agent croscarmellose sodium and pulsatile tablets ware by using polymer HPMC and Ethyl cellulose in various concentration. The optimized formulation of F3 showed optimum lag time of 4 hour and release maximum drug in 8 hour. The developed formulation was found to be stable during the stability studies. Thus, it was concluded that the novel time-controlled chronotherapeutic pulsatile tablets drug delivery system containing Etoricoxib can successfully utilized for the chronotherapeutics management of pain.

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