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DESIGN AND IN VITRO CHARACTERIZATION OF KETOPROFEN CORE IN CUP PULSATILE TABLETS FOR CHRONOMODULATED DRUG THERAPY.

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ABSTRACT

The aim of the present investigation is to intend, develop and evaluate a pulsatile drug delivery containing a core-in-cup based system of dry coated tablet of ketoprofen based on chronomodulated approach for management of Rheumatoid Arthritis. This pulsatile system contained a core tablet surrounded by an impermeable outer shell and top cover layer. Core tablet contained the active ingredient acting as reservoir, ethylcellulose was used to form an impermeable outer shell, the top cover layer contained different hydrophilic polymers like SodiumAlginate, HPMCK4M, Sodium carboxymethylcellulose with different concentrations. The formulations were evaluated for various pre-compressional and post-compressional parameters. The effect of polymer properties and quantity of top cover layer, on the lag time and drug release was investigated. From the results it was evident that the lag time increased with increase in concentration of the plug layer, whereas drug release decreased. Plug layer polymers showed a lag time with rank order: SA<NaCMC<HPMC. The *in vitro* release studies revealed that the formulations containing HPMCK4M showed enhanced release when compared with other formulations. It was marked that there was no specific interaction between the drug and polymers from FTIR study. Optimized formulation was stable for three months under normal storage conditions. In conclusion a stable core-in-cup tablets of ketoprofen were successfully formulated which provided a desirable lag time followed by a required drug release and complied with chronotherapeutic objective of rheumatoid arthritis.

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INTRODUCTION

Oral controlled drug delivery systems release the drug with constant or variable release rates. The oral controlled release system shows the distinctive pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), there by sustained therapeutic action. But there are certain conditions which require release of drug after a lag time i.e., chronopharmacotherapy of disease which shows circadian rhythms in their pathophysiology[1]. A number of common diseases which shows circadian rhythms in their pathophysiology comprise rheumatoid arthritis, allergic rhinitis [2], hypertension [3, 4] and cancer [5].

Treatment of this disease condition happening in the initial hours may be not suitable toward utilizing customary quick immediate release dosage structure. Hence, chronotherapeutic medication conveyance framework (ChDDS) might make handy for such patients since the medication is discharged during a foreordained lag time. Chronotherapeutics alludes all the will a medication strategy previously, which in vivo medication accessibility is timed to match those rhythms for disease, in place will streamline restorative results, furthermore minimize side impacts [6,9,10]. It will be outlined such medication discharge will be adjusted to a way that ensures that greatest centralization of the medication regardless may be arrived at in the maximum intensity of the disease state.

Chronomodulated drug delivery system (ChDDS) can be distinct as a system where drug is released suddenly after a well-defined lag time according to the circadian rhythm of the disease [11,12]. ChDDS can be classified according to the pulse-regulation of drug release into three main classes; time-controlled pulsatile release (single or multiple unit system), internal stimuli induced release and external stimuli-induced pulsatile release systems [13]. PDDS can also be classified according to the dosage form into three main types; capsules, pellets and tablets among which the 'core-in-cup' tablet system.

The core-in-cup tablet system consists of three different parts: a core tablet, containing the active ingredient, an impermeable outer shell and a top cover plug layer of a soluble polymer [14].

An effort of investigation was done to design and evaluate ketoprofen core-in-cup pulsatile tablets to optimize the drug release after a certain lag time to meet therapeutic needs concerning to particular pathological state in Rheumatoid Arthritis.

MATERIALS

Ketoprofen, crosspovidine, Hydroxy Propyl Methyl Cellulose K4M (HPMC 4000) was obtained from Hetero Drugs, Hyderabad, India. Ethyl cellulose, Sodium Alginate (SA, 200 cps of 1% w/v aqueous solution), Sodium CarboxyMethylCellulose (NaCMC, 1500 cps of 1% w/v aqueous solution) was obtained from S.D. Fine Chem. Ltd., Mumbai. All other chemicals were also procured from S.D. Fine Chem. Ltd., Mumbai.

METHODS

FlowabilityStudies

An amount for 2 g from blend mix starting with every formulation was loaded into a 10 ml measuring cylinder. Initial bulk volume should be measured; further cylinder was allowed to tap from the height of 2.5 cm. The tapped frequency to measure the tapped volume of the blend was 25 ± 2/min. The bulk density (BD) and tapped density (TD) were calculated by using the bulk volume and tapped volume. The Compressibility Index (Carr's Index) (%) and the Hausner ratio were calculated as follows[7]:

$$\text{Carr's Index}(\%) = \frac{\text{TBD-FBD}}{\text{TBD}} \times 100$$

$$\text{Hausner Ratio} = \frac{\text{TBD}}{\text{FBD}}$$

Preparation of ketoprofen core tablets by Direct Compression Method:

The composition of ketoprofen core tablets was depicted in Table 1. Accurately measured quantities of drug, superdisintegrant, diluent were passed through sieve no. 45 seperately, mixed by geometric addition technique, taken and blended properly for 15 min to it glident and antiadherant were added finally, then 100mg blend was weighed and compressed using 6mm flat punches on 16 station tablet punching machine. (Cadmach, Ahmedabad, India).

Table 1: Formulation of ketoprofen core tablets.

Ingredients	Weight(mg)
Drug	50
Cross povidone	4
Microcrystalline cellulose 102	40
Talc	4
Magnesium stearate	2
Total weight (mg)	100

Table 2: Formulation of ketoprofen pulsatile tablets:

Formulation code	Core tablet	Ethyl cellulose	Sodium Alginate	HPMC K4M	Sodium CMC	Total weight (mg)
KPT1	100	150	30			280
KPT2	100	150	60			310
KPT3	100	150	90			340
KPT4	100	150	120			370
KPT5	100	150		30		280
KPT6	100	150		60		310
KPT7	100	150		90		340
KPT8	100	150		120		370
KPT9	100	150			30	280
KPT10	100	150			60	310
KPT11	100	150			90	340
KPT12	100	150			120	370

Preparation of Ketoprofen core-in-cup pulsatile tablets (KPT):

An impermeable coating cup consisting of ethylcellulose was applied underneath and around the core tablet. Ethylcellulose powder (90 mg) was filled into a die of 10mmflat punches and then was quietly flattened to make a powder bed with a flat surface. The core tablet was cautiously placed in the midpoint of the powder bed, and then the gap between the core tablet and the die was filled manually with 60 mg of ethylcellulose so that the surrounding surfaces of the core tablet were fully covered. Different plug polymers (Table 2) were added at the top of the core tablet surrounded by the cup. The tablet was compressed to produce the desired core-in-cup pulsatile system[14].

Physical characterization of tablets:

The prepared core and pulsatile tablets were characterized for different physical parameters like weight variation, thickness, hardness, friability and drug content uniformity.

Drug Content of core and pulsatile tablets:

Tablets were finely powdered and quantity of the powder equivalent to 10 mg of ketoprofen was properly weighed and transferred to volumetric flask containing 100 ml phosphate buffer (pH 6.8) and mixed methodically for one hour on a rotary shaker and the solution was filtered by passing through 0.45µm filter and the filtrate obtained was diluted duly and estimated for ketoprofen content at 260 nm using double beam UV spectrophotometer (Shimadzu Corporation, Japan, UV-1700).

Lag Time

The lag time was determined by visual observation of the pulsatile tablet in USP type II paddle apparatus, medium: pH 1.2 buffer 0.1 N HCl for two hours followed by phosphate buffer, pH 6.8, maintained at 37±0.5ºC, with 50 rpm until the outer coat was ruptured and removed. Lag time was recorded as time point when outer coat of pulsatile tablet is ruptured and removed (n=3) [8,15].

***In vitro* dissolution studies for the prepared tablets:**

In vitro drug release studies of core tablets were conducted using USP type II dissolution apparatus at 50 rpm speed and 37 ± 0.5°C temperatures in 900 ml phosphate buffer pH 6.8 as dissolution media for one hour. *In vitro* drug release studies for ketoprofen pulsatile core-in-cup tablets were conducted using USP type II dissolution apparatus at 50 rpm speed and 37 ± 0.5°C temperature in 900 ml dissolution media (pH 1.2 buffer 0.1 N HCl for first two hours and then in phosphate buffer pH 6.8 from three to twelve hours). An aliquot of 5 ml was withdrawn at definite predestined time intervals and replaced with the same volume of dissolution medium maintained at same temperature. The withdrawn samples were filtered by passing through 0.45µm filter and the filtrate obtained was diluted properly and estimated for ketoprofen content at 260 nm using double beam UV spectrophotometer (Shimadzu Corporation, Japan, UV-1700).

Stability Studies

The stability of ketoprofen in developed optimized formulation was assessed at ambient temperature by placing the tablets at room temperature in a desicator for three months. The physical appearance, physicochemical properties of tablets and drug release studies were conducted at the end of three months to understand the stability of products[7].

Fourier Transform Infra Red (FTIR) Studies

The FTIR spectra of ketoprofen, core tablet formulation and optimized formulation were recorded between 400 to 4000 cm^{-1} with FTIR spectrometer (Shimadzu, Model 84005, Japan) to detect the drug-excipients interactions. The FTIR spectra for the test samples were obtained using KBr disk method, the resultant spectra were compared for any possible changes in the peaks of the spectra[16].

Differential Scanning Calorimetry (DSC) Studies

Differential scanning calorimetry (DSC) is a frequently used thermo analytical technique that generates data on melting endotherms. DSC spectra of drug ketoprofen and optimized formulation physical mixture of core and pulsatile tablets were performed utilizing DSC (DSC60, Shimadzu, Japan). Samples of 3–4 mg were encapsulated and hermetically sealed in flat bottomed aluminum pan with crimped on lid. The pans were positioned on sample pan holder. Samples were allowed to equilibrate for 1 min and then heated in an atmosphere of nitrogen over a temperature range from 0 to 400°C with a heating rate of 20°C/min. An empty aluminum pan is served as reference. Nitrogen was used as a purge gas, at the flow rate of 30 mL/min for all the studies [20].

RESULTS AND DISCUSSION

Flowability Studies

In direct compression process, it is required that the powder blend should possess good flow and compacting properties. The core tablet powder blend exhibited an angle of repose, Carr's index and Hausner ratio of 26°±1.4°, 19.22±0.3% & 1.09± 0.4 respectively. According to USP, values for angle of repose 31-35° generally indicate good flow property. A Hausner ratio of less than 1.25 and Carr's index of 16-20 indicates fair flow. The above result indicates a good flow property and it is suitable for direct compression.

Physical characterization of tablets:

Different evaluation parameters of ketoprofen core tablets are depicted in Table 3 which compiled with the official requirements. The disintegration time of core tablet was found to be 52±3.5seconds.

All the pulsatile core-in-cup tablets of different batches compiled with the official requirements of uniformity of weight as their weights were within the limits (Table4). The hardness of the tablets ranged from 6.2 to 6.5 kg/cm^2 and the friability values were less than 0.5% indicating that the tablets were compact and hard. The thickness of the tablets ranged from 4.3 to 6.2 mm. All the formulations showed 97.01 to 99.98 % of ketoprofen content indicative of suitability of formulation of tablets.

Table3:Physical characterization of ketoprofen core tablet.

Parameter	Observation
Thickness	3.32±0.45mm
Diameter	6.01±0.01 mm
Hardness	3.2±0.45kg/cm^2
Weight variation	104.16±0.47mg
Friability (%)	0.415(%)
Disintegration time	52±3.5sec

Each value represents the mean ±SD (*n* =3).

Table 4: Physical characterization of ketoprofen pulsatile core-in-cup tablets.

Formulations	Hardness (kg/cm2)±SD	Thickness (mm)±SD	Diameter (mm)±SD	Weight variation (mg)±SD	Friability (%)	Drug content (%)±SD
KPT1	6.5±0.25	4.81±0.13	10.06±0.23	281.5±0.32	0.42±0.83	99.65±1.33
KPT2	6.6±0.66	5.25±0.58	10.07±0.11	313.5±0.62	0.44±0.61	98.76±1.80
KPT3	6.5±0.18	5.81±0.33	10.02±0.38	349.0±0.72	0.34±0.72	97.67±1.30
KPT4	6.5±0.29	6.23±0.43	10.01±0.12	372.0±0.86	0.45±0.87	97.01±1.09
KPT5	6.3±0.55	4.35±0.47	10.01±0.42	283.0±0.53	0.43±0.71	97.87±1.18
KPT6	6.5±0.35	5.22±0.23	10.02±0.43	318.4±0.68	0.43±0.35	99.98±1.06
KPT7	6.2±0.56	5.83±0.69	10.06±0.33	341.8±0.71	0.47±0.63	98.01±1.25
KPT8	6.5±0.18	6.25±0.35	10.07±0.21	372.0±0.77	0.39±0.42	97.32±1.25
KPT9	6.5±0.59	4.35±0.27	10.00±0.22	282.0±0.87	0.39±0.72	99.99±1.89
KPT10	6.4±0.33	5.32±0.33	10.00±0.27	311.5±0.64	0.38±0.58	97.87±1.18
KPT11	6.5±0.20	5.83±0.59	10.02±0.51	340.0±0.76	0.45±0.71	98.89±1.06
KPT12	6.4±0.48	6.24±0.28	10.03±0.15	375.0±0.84	0.43±0.43	97.01±1.25

Lag Time and *In Vitro* Drug Release Studies

The drug release studies of core formulation conducted in pH 6.8 buffer showed complete release of drug within 30 min. The drug release from core tablet was 79.46±1.84% at 10 minutes was considered to be optimized, it can be used in the preparation of pulsatile tablets because the drug release revealed more than the Q limit of 75% within 30 minutes.

Suitable plug polymers like Sodium Alginate, HPMC K4M & Sodium CMC were selected for designing ketoprofen pulsatile core-in-cup tablets. Further to choose the most appropriate plug polymer and to know which concentration of the polymer gives the required lag time all the formulations (Table 2) were subjected to drug release studies.

The pulsatile tablets of ketoprofen containing Sodium Alginate i.e., KPT1, KPT2, KPT3 & KPT4 showed a lag time less than and nearly two hours, but all the formulation showed more than 90% drug release and formulation KPT4 the release extended up to seven hours (Figure 1).

Figure 2 shows the *in vitro* release profile of formulations containing HPMC K4M (KPT5 to KPT8). KPT5, KPT6, KPT7 & KPT8 showed a lag time of 3 h, 4 h, 6 h & 7 h with drug release of 96.92% at 8 h, 97.19% at 9 h, 98.74% at 10 h& 97.96% at 11h, respectively.

The formulations containing SodiumCMC (KPT9 to KPT12) KPT9, KPT10, KPT11 & KPT12 showed a lag time of less than four hours with a maximum drug release for nearly 8 hours (Figure 3).

The profiles relevant to the core-in-cup pulsatile tablets showed that a lag phase was allowed before the release of the active agent. The delayed duration clearly depended on the viscosity grade and amount of hydrophilic polymer (hydroxyl propyl methyl cellulose) which was utilized as the plug polymer. [14]

Upon contact of the core-in-cup tablet with medium, those plug layers, comprising of SA, NaCMC and HPMC, absorbs water. Consequently, those polymer swells and stretches. As the contact time increases, the swelling of the plug further extends, builds a obstruction which postpones the contact of fluids with the surface of the core tablet. It may be additionally suggested that the swelling of the plug layer might destabilize the plug itself gradually bit by bit prompts its disintegration or evacuation. Therefore, the swelling and deterioration of the plug polymer control the rate by which the plug layer polymer erodes. At the end, according to the properties of each polymer, the plug is completely eroded and water ingress into the core increases heavily resulting in required drug release [12,17].

In formulations containing PKT1-PKT4, Sodium Alginate shrinks at low pH. In gastric fluid the hydrated Sodium Alginate is converted into a porous, insoluble alginic acid skin. After passed into the higher pH medium, the alginic acid is converted to soluble viscous layer. The pH dependent behavior and rapid dissolution of sodium alginate in higher pH range results in release of ketoprofen at pH 6.8. Sodium Alginate can be used as a biological on-off switch with which the release of drugs can be controlled by the external pH change due to its swelling behavior [12, 17].

In formulations containing HPMC K4M (PKT5 to PKT8), the sensitivity of HPMC gel (plug layer) to pH changes is not significant in comparison with the NaCMC or SA gels. Its rheological properties are not influenced by the medium pH. The system keeps its elastic characteristic at pH1.0, which determines its ability to retain the network structure for a long period of time. In pH 6.8, the elastic viscosity is almost the same. This behavior indicates the absence of entanglement coupling [18].

In formulations containing NaCMC (PKT9-PKT12), NaCMC, as a polyelectrolyte gel, is very sensitive to pH changes. In phosphate buffer pH 6.8, NaCMC gels show a lower dynamic viscosity in comparison with that in an acid medium. It has a liquid-like character and looser structure of NaCMC. This behavior is typical for normal solutions of conformationally disordered (random coil) polymers interacting by physical entanglement. The weak gel structure determines the ability of NaCMC polymer chains to disentangle from the polymer network and dissolve. This results in a faster erosion of hydrogel matrix and enhances the drug release [12, 18].

According to the prior facts, NaCMC was expected to show faster dissolution behavior. Unexpectedly, Sodium Alginate exhibited much faster dissolution upon elevating the pH of the medium when compared to NaCMC. This could be resulted from the higher viscosity grade of NaCMC relative to that of SA. NaCMC, with the higher viscosity, displays the most rapid and the greatest bulk swelling which lasts longer than SA. After maximum swelling of both polymers was achieved, a tendency to rapid decrease of swelling was observed, which appeared to be greater for SA, followed by NaCMC. Apparently, NaCMC, the polymer with the maximum volume increase, exhibited the slower drug release [12,14].

As HPMC K4M, was characterized by its high viscosity, gel layer was sufficiently resistant to extensive erosion even after thorough hydration which was accompanied by path length increase [19]. Therefore, it was logic to get the lowest drug release in comparison with Sodium Alginate and NaCMC which have lower viscosities.

Accordingly, *in vitro* release rate of ketoprofen from KPT7 was the most convenient one among the previously studied tablet formulations showing an optimum lag time of 6hrs followed by a drug release after changing pH from1.2 to 6.8.

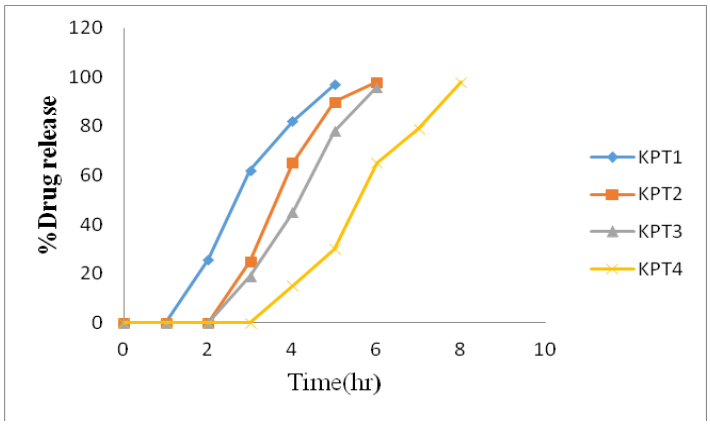

Figure 1: Cumulative percentage drug release of ketoprofen from KPT's containing sodium alginate.

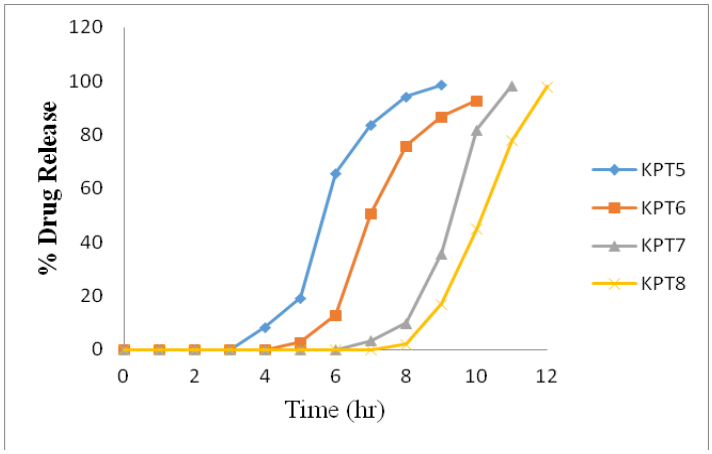

Figure 2: Cumulative percentage drug release of ketoprofen from KPT's containing HPMC K4M.

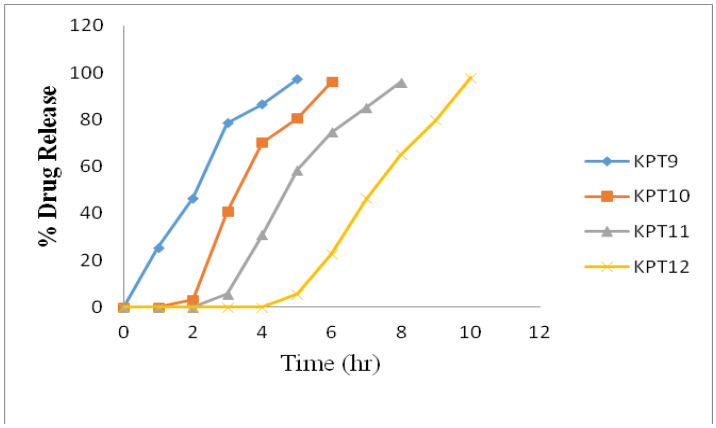

Figure 3: Cumulative percentage drug release of ketoprofen from KPT's containing Sodium CMC.

Stability Studies

The physico chemical parameters of the optimized formulation (KPT7) at initial time and after 3 months was shown in table 5. The results reveal that there was no significant change in the physic chemical parameters of the optimized formulations. Further the dissolution profile of the formulation was observed to be similar with f_2 value of 89.This suggests the developed KPT7 formulation was stable over the period of study.

Table 5: Physical evaluation of the optimized formulation (KPT7) after 3 months.

Formulations	Weight Variation (mg)	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Drug Content (%)	Lag time (hr)
KPT7(0month)	341±0.71	6.2±0.56	0.47±0.63	5.83±0.69	98.01±1.25	6.20±0.27
KPT7(3months)	343±0.43	6.2±0.33	0.42±0.51	5.74±0.13	97.43±0.49	6.30±0.21

FTIR Studies

In order to investigate if there is any interaction between added excipients and ketoprofen in the core-in-cup tablet, the FTIR of the ketoprofen, core tablet formulation and the optimized formulation KPT7 were determined as shown in Figure 4,5&6. All the characteristic peaks observed for both drug and excipient remained unchanged and the spectra data was superimposed. This observation ruled out that there is no possibility of chemical interaction and modification between the ketoprofen and added excipients during the formulation process.

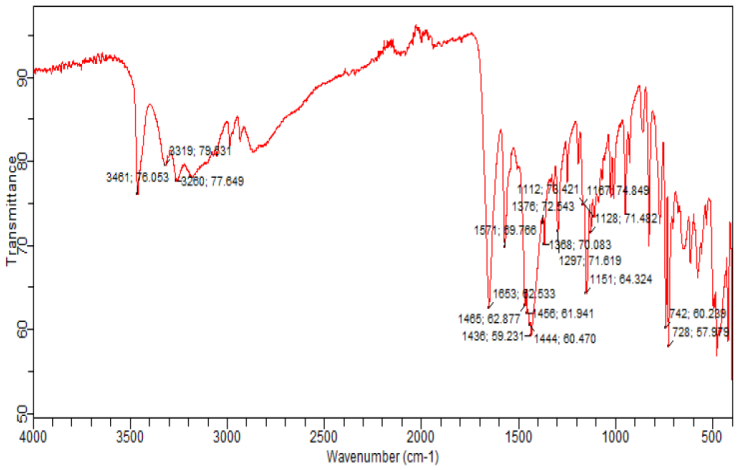

Figure 4: FTIR spectra of ketoprofen.

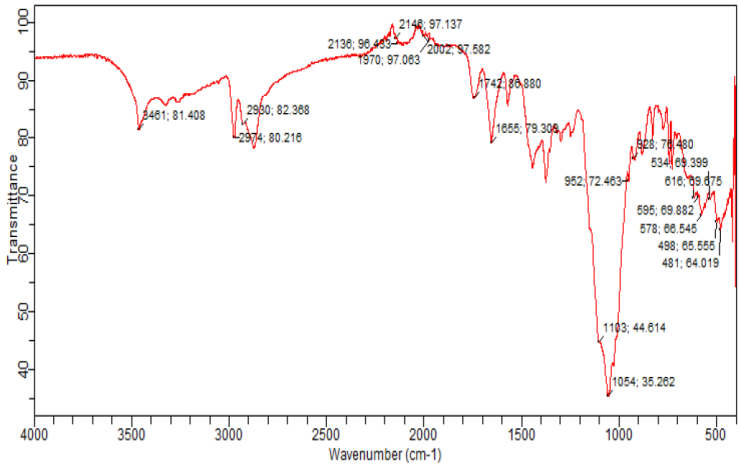

Figure 5: FTIR spectra of ketoprofen core tablet.

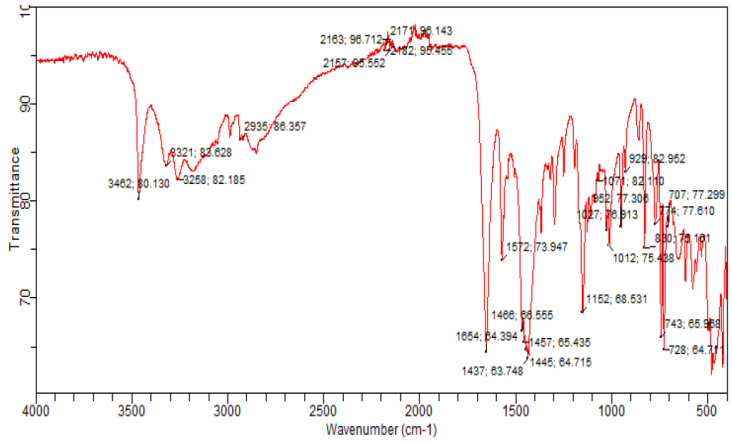

Figure 6: FTIR spectra of optimized ketoprofen pulsatile formulation (KPT7).

Differential Scanning Calorimetry (DSC) Studies

DSC studies were performed to understand the nature of the drug in the optimized tablet. DSC curves obtained for pure drug and optimized pulsatile formulation were shown in Figure 7&8. A sharp endothermic peak corresponding to the melting point of ketoprofen was found at 255.6°C which is almost similar to an endothermic peak corresponding to the melting point of ketoprofen in optimized formulation at 258.2°C.

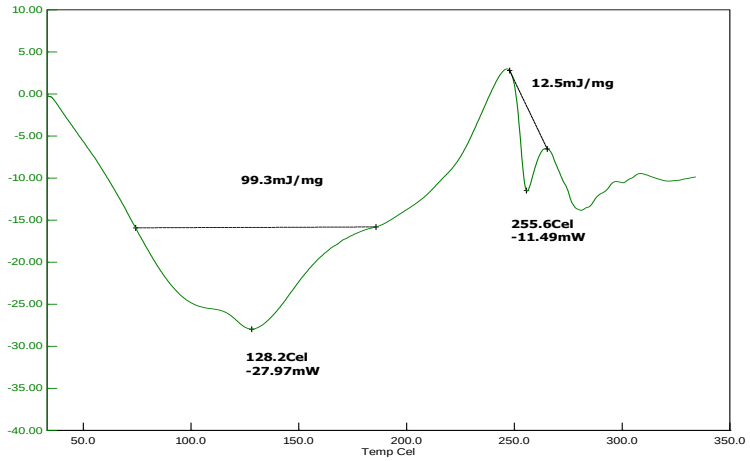

Figure 7: DSC of ketoprofen.

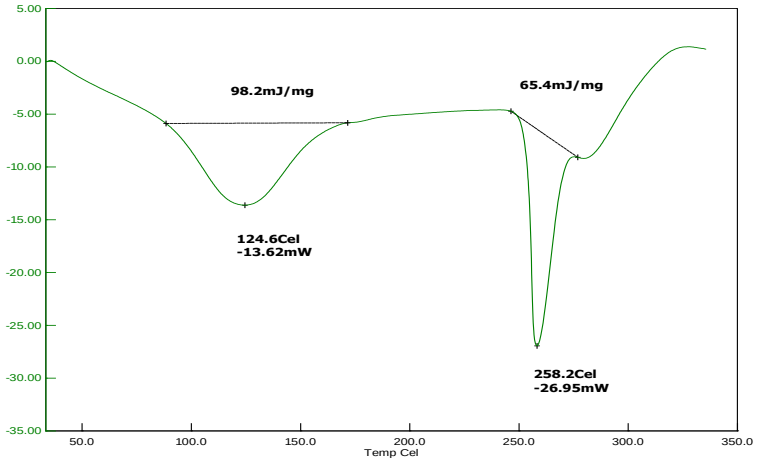

Figure 8: DSC of ketoprofen pulsatile formulation (KPT7).

CONCLUSION

A chronomodulated pulsatile core-in-cup drug delivery system for oral use was formulated and evaluated. From the results it is suggested that the chronomodulated system released the drug after a certain lag time, which could be modified by factors like quantity of material in the top layer, viscosity of the polymer characteristics which were important in controlling the lag time and drug release. The lag time increases by increasing the quantity of the hydrophilic top cover layer. Thus, it can be concluded that the top cover layer and especially the erodible polymeric material, from which this layer consists, regulate the performance of the system. Formulation KPT7 with a predetermined lag time of 6 h with drug release of 98.74% was taken as the optimized formulation and it was observed that there was no chemical interaction throughout the process of formulation.

Thus this approach of core-in-cup pulsatile/programmable release may be supportive to patients to relieve pain rheumatoid arthritis with morning surge, additionally this type of formulations can also be extended for variety of drugs which are suitable for chronotherapy.

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