ORIGINAL ARTICLE

Chronotherapeutic Press-coated Tablets of Tramadol Hydrochloride: Formulation and *In vitro* Evaluation

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Abstract

Aim: The current investigation is aimed to develop and evaluate chronotherapeutic press-coated tablets (PCTs) of tramadol hydrochloride (TH) for rheumatoid arthritis. **Materials and Methods:** The core tablets were prepared with crospovidone and cross caramellose sodium as superdisintegrants. The PCTs containing TH in the inner core were prepared by compression coating with hydroxypropylmethyl cellulose (HPMC) E50 and HPMC E100 in varying ratios. The formulations were characterized for various pre- and post-compressional parameters. The effect of polymer properties and quantity of polymer on the lag time and drug release was investigated. **Results and Discussion:** The inner core tablet prepared with superdisintegrants showed desirable release pattern compiled with standard limits. The PCTs characterized for physicochemical properties and drug content are within the official limits. The swelling studies revealed that as a concentration of HPMC increased the swelling index was increased. The lag time values of PCTs (PCT1-PCT5) were found to be in the range of 2-7 h indicating that the lag time increased as the polymer concentration was increased. Optimized formulation PCT4 showed a predetermined lag time of 5 h with drug release of 98.74%. Fourier transform infra-red and differential scanning calorimetry study showed no evidence of interaction between the drug and polymers. The stability studies of selected PCT (PCT4) conducted at ambient temperature over 3 months showed similar dissolution profile with similarity factor f2 (61). **Conclusion:** The PCTs were successfully formulated with a combination of polymers HPMC E50 and HPMC E100 provided the better chronotherapeutic release characteristics.

Key words: Compression coating, press-coated tablets, tramadol HCL

INTRODUCTION

Oral controlled drug delivery system releases the drug with constant rate to maintain drug concentration in the human body, regardless of the patient physiological conditions. These dosage forms offer many advantages such as reduction in dose of the drug, prevention of peak-valley fluctuation, nearly constant drug levels at the site of action, reduced dosing frequency, promoting drug efficacy, and improved patient compliance.[1] However, long-term constant drug concentrations in the human body can cause problems such as resistance, tolerability and drug side effects [2] and activation of the physiological system. People are different in their physiological and biochemical conditions due to the circadian rhythm during any 24 h period, and as a result, the constant drug delivery into the body seems unnecessary and undesirable. However, there are certain diseases such as allergic rhinitis, cardiovascular diseases, asthma, cancer, peptic ulcers, rheumatoid arthritis, and osteoarthritis shows circadian rhythms in their pathophysiology. Hence, chronomodulated systems are gaining a lot of interest and attention these days as these systems deliver the drugs on specified time as per

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Received: 01-05-2017
Revised: 23-05-2017
Accepted: 31-05-2017

the pathophysiological need of the disease resulting in improved patient therapeutic efficacy and compliance.[3] Chronomodulated system is also known as pulsatile system or sigmoidal system. The pulsatile drug delivery system is a system that releases the drug at the fast or controlled rate with a programable lag time after administration. These systems are useful for the drugs having chronopharmacological behavior (where night time dosing is required), first pass effect and having specific site of absorption in gastrointestinal tract (GIT).

Compression coating or press coating technique is one of the simple and unique approaches of a pulsatile drug delivery system which offers many advantages. Thick coating can be applied rapidly and no special coating solvent or coating equipment is required for manufacturing of the tablet.[4] It has been used to protect hygroscopic, light sensitive, oxygen labile or acid labile drug,[5] to combine and separate different therapeutic drugs,[6] and to modify a drug release pattern (delayed pulsatile and programmable release of different drugs in one tablet).[7] Compression coated tablets are composed of an inner core immediate release tablet surrounded by an outer barrier hydrophilic/hydrophobic polymer layer. The outer polymer layer can erode or rupture or dissolve after a certain lag time, after which the drug is released from core tablet. The rupturing of the barrier is obtained by an expanding core on water penetration through the barrier coating such as swelling agents.[8] Hydroxypropylmethyl cellulose (HPMC) is a synthetic released retardant that is widely used as an extended release agent in pharmaceutical industry.[9]

Rheumatoid arthritis is a chronic systemic autoimmune disorder that causes inflammation of the joint and tissue around the joint, as well as other organs in the body.[10] The symptoms of rheumatoid arthritis are stiffness, warmth, swelling, and pain of one or more joints of the body which is characterized by diurnal variation in circulating levels of cytokines,[11] interleukin-6 or tumor necrosis factor ά. Due to this diurnal variation, many symptoms and signs are manifested particularly early in the morning on waking[12] or followed prolonged inactivity.[13]

Tramadol HCL (TH) is a synthetic, centrally acting aminocyclohexal analgesic that acts as an opioid agonist. It has a modest affinity for μ receptor that can be used for moderate to severe pain. It also appears to modify the transmission of pain impulses by inhibition of norepinephrine and serotonin reuptake.[14] It has a half-life of 5-6 h. The dose of TH is 50-100 mg daily by oral route in divided doses. It has good oral bioavailability and good absorption throughout the GIT. Most of the water-soluble drug formulations release drug at a faster rate and likely to produce toxic concentration of the drug on oral administration.[15] TH belongs to BCS Class-I drugs having high solubility and permeability and likely producing toxic concentration with side effects of nausea and vomiting, which can be prevented by pulsatile delivery to retard the drug release.[16]

The objective of the current investigation is to design and evaluate TH pulsatile press coated tablets (PCTs) so as to optimize the drug release after a certain lag time expecting an improvement in its bioavailability and to meet therapeutic needs relating to particular pathological conditions.

MATERIALS AND METHODS

Materials

TH, crosscaramellose sodium (CCS), crospovidone (Kollidon® CL-M), HPMC E50 (50 mPa.S, 2% solution), and HPMC E100 (100 mPa.S, 2% solution) were obtained as a gift sample from Hetero Drugs, Hyderabad, India. All other chemicals used were of analytical grade.

Methods

Drug solubility studies

The drug solubility study was conducted in different media (distilled water, 0.1 N HCL pH1.2 and phosphate buffer pH6.8 and pH7.4). A known excess amount of drug TH was added to a flask containing 25 ml of each medium. The flasks were shaken for 24 h on a rotary shaker at 37°C, and then they were left aside to attain equilibrium for another 24 h. Solutions were filtered through a 0.45 μm filter paper. The filtrate was diluted suitably and analyzed at 271 nm by an ultraviolet (UV) - spectrophotometer (Shimadzu Corporation, Japan, UV-1700).[17]

Precompression studies of rapid release core tablet blend

Flowability of the precompression blend of rapid release core tablet was evaluated by angle of repose, compressibility index (%Carr's index) and Hausner's ratio[18] and were calculated using the following formulae.

$$\text{Tan } \theta = \frac{h}{r} \quad (1)$$

In which θ is the angle of repose, h is the height of the cone of powder blend and r is the radius of the cone base.

$$\text{Carr's Index}(\%) = \frac{TB - BD}{TD} \times 100 \quad (2)$$

$$\text{Hausner's Ratio} = \frac{TD}{BD} \quad (3)$$

In which TB is the tapped density and BD is the bulk density.

Preparation of rapid release core tablet

TH core tablets were prepared by direct compression method as shown in Table 1. TH and excipients (varying concentration of CCS and crospovidone; mannitol) were accurately weighed, passed through 40 mesh sieve and mixed in a poly bag for 5 min. Then, the obtained blend was mixed with magnesium stearate and aerosol for another 5 min, and the resultant mixture was directly compressed into tablets with 9 mm round flat punches using 16 stationrotary punching machine (Cadmach, Ahmedabad, India). The amount of TH was 100 mg, and the final weight of the tablet was adjusted to 250 mg (Table 1).

Physical characterization of rapid release core tablets

The prepared core tablets were characterized for thickness, diameter, weight variation, hardness, friability, and disintegration time as per standard procedure.[17,19-21]

Drug content of rapid release core tablets

Tablets were finely powdered and a quantity of a powder equivalent to 100 mg of tramadol hydrochloride was weighed and mixed with 100 ml of phosphate buffer pH 6.8 in volumetric flask, on a rotary shaker. Periodically, the content was shaken for complete dissolution and it was kept aside for 1 h. The mixtures were filtered through 0.45 µm filter, and the filtrate was diluted suitably and analyzed at 271 nm by a UV - spectrophotometer (Shimadzu Corporation, Japan).[22]

In vitro drug release studies of rapid release core tablets

The *in vitro* dissolution study of the rapid release core tablet was carried out in 900 ml of phosphate buffer pH 6.8 for 1 h using USPXXIV Type II dissolution apparatus (Electro lab, TDT-08L) at a rotation speed of 50 rpm and at temperature of 37 ± 0.5°C. At different time intervals, 5 ml of sample was withdrawn and analyzed at 271 nm by UV - spectrophotometer. (Shimadzu Corporation, Japan).

Preparation of PCTs

The selected core tablet (RRCT6) was press coated with different compositions of HPMC E50 and HPMC E100 polymer blend as coats shown in Table 2. Half the quantity of the coating material was placed in the die cavity, and then the selected core tablet was carefully placed in the center of the die cavity, and finally, it was filled with the other half of the coating material. The coating material was compressed using 11 mm round, flat and plain punches using 16 station rotary punching machine (Cadmach, Ahmedabad, India) to give the PCTs.

Each formulation contains 1% magnesium stearate and aerosol.

Physicochemical characterization of PCTs

The prepared PCTs were characterized for thickness, diameter, weight variation, hardness, friability, and drug content as per same procedure followed by rapid release core tablet.[17,19,20,22]

Swelling index of PCTs

The swelling index of all PCTs was calculated using USPXXIV Type I dissolution apparatus (Electro lab, TDT-08L) in 900 ml of 0.1 N HCL for the first 2 h, followed by phosphate buffer pH 6.8 at a rotation speed of 50 rpm maintained at temperature of 37 ± 0.5°C. Tablets were withdrawn at a predetermined time intervals over 60 min period, blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, AUW220D). The study was conducted in triplicate. Swelling index was calculated using the following equation 4:

$$\text{Swelling index}(\%) = \frac{Wt - Wi}{Wi} \times 100 \quad (4)$$

Where Wt is the final weight of the tablet after swelling and Wi is the initial weight of the tablet.

Table 1: Composition of TH rapid release core tablet formulations

Formulation	TH (mg)	Cross carmellose sodium (mg)	Cross povidone (mg)	Magnesium stearate (mg)	Aerosil (mg)	Mannitol (mg)	Total weight (mg)
RRCT1	100	5	-	1	1.5	137.5	250
RRCT2	100	7.5	-	1	1.5	135	250
RRCT3	100	10	-	1	1.5	87.5	250
RRCT4	100	-	5	1	1.5	137.5	250
RRCT5	100	-	7.5	1	1.5	135	250
RRCT6	100	-	10	1	1.5	87.5	250

TH: Tramadol hydrochloride

Lag time and *in vitro* drug release studies of PCTs

The lag time and *in vitro* dissolution study of the PCTs were carried out in 900 ml of 0.1 N HCL for the first 2 h, followed by phosphate buffer pH 6.8 using USPXXIV Type II dissolution apparatus (Electro lab, TDT-08L) at a rotation speed of 50 rpm and at temperature of 37 ± 0.5°C. At predetermined time intervals, 5 ml of sample was withdrawn and analyzed at 271 nm by UV - spectrophotometer (Shimadzu Corporation, Japan). Lag time is the time before the drug release has started or the time in which <10% of the drug has released. However, the lag time was recorded until 10% of the drug was released.[19]

Drug-excipient compatibility studies

Fourier transform infra-red (FTIR) studies

IR spectra of pure drug TH and optimized formulation physical mixture were recorded between 400 and 4000 cm^{-1} by a FTIR (Shimadzu, Model 84005, Japan). Each sample was mixed with KBr (FTIR grade, Aldrich, Steinheim, Germany) and compressed at 70 kN with a hydraulic press.[23]

Differential scanning calorimetry (DSC) studies

DSC spectra of pure drug TH and optimized physical mixtures were determined using DSC (DSC60, Shimadzu, Japan). The weight of 3-4 mg samples were encapsulated in an aluminum pan and hermetically sealed and was positioned on sample pan holder. Samples were heated in an atmosphere of nitrogen (flow rate, 30 mL/min; heating rate, 20°C/min) over a temperature range from 0 to 400°C.[24]

Table 2: Composition of TH PCT formulations

Ingredients (mg)	Formulation code				
	PCT1	PCT2	PCT3	PCT4	PCT5
HPMC E50	250	187.5	125	62.5	0
HPMC E100	-	62.5	125	187.5	250

PCT: Press-coated tablet, HPMC: Hydroxypropylmethyl cellulose, TH: Tramadol hydrochloride

Table 3: Solubility of TH in different medium

Medium	Solubility (mg/ml)
Distilled water	1.892
0.1 N HCL	1.725
Phosphate buffer pH 6.8	2.017
Phosphte buffer pH 7.4	0.981

TH: Tramadol hydrochloride

Stability studies

The preliminary stability of selected PCT4 was conducted at ambient temperature, i.e., at room temperature 30 ± 2°C in a desiccator over a period of 3 months. At the end of 3 months, the tablets were examined for any physical characteristics, drug content, *in vitro* drug release.

RESULTS AND DISCUSSION

Drug solubility studies

The drug solubility studies were conducted to assess the fate of drug in different pH conditions which revealed that drug is readily soluble over a pH range of pH 1.2-pH 6.8. However, the solubility was decreased at phosphate buffer pH 7.4 (Table 3).[22]

Precompression studies of rapid release core tablet blend

The different rapid release core formulations blend was evaluated for angle of repose, compressibility index, and Hausner's ratio. The results of precompression parameters were shown in Table 4. For direct compression of materials, it is required to possess good flow and compacting properties. According to USP, values for angle of repose <30° generally indicate good flow property. If Carr's index and Hausner ratio of powder blend values are of about 11-15 and <1.12-1.18 generally indicates a good flow. The angle of repose values has ranged from 23.9° to 28.4° indicating excellent to good flow property as per USP. Bulk density and tapped density values have ranged from 0.33 to 0.42 and 0.39 to 0.5 g/cc, respectively. The values of % Carr's index and Hausner's ratio ranged from 12.86 to 16.00 and 1.07 to 1.19, respectively, indicating good flow property.

Table 4: Precompression parameters for rapid release core tablet blend

Formulation	Angle of repose (θ)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner's ratio
RRCT1	24.3	0.35	0.40	14.63	1.07
RRCT2	26.7	0.39	0.45	13.33	1.15
RRCT3	24.5	0.42	0.50	16.00	1.19
RRCT4	28.4	0.38	0.44	12.86	1.16
RRCT5	23.9	0.36	0.40	13.29	1.07
RRCT6	26.9	0.33	0.39	15.38	1.18

Physical characterization of rapid release core tablets

The thickness and diameter of core tablet were found within the range of 3.01 ± 0.03 mm to 3.15 ± 0.08 and 9.00 ± 0.06 mm to 9.03 ± 0.02 mm, respectively, which showed a uniform thickness and diameter as shown in Table 5.

The hardness and friability of the core tablet were found within the range of 4.01 ± 0.02 to 4.2 ± 0.02 kg/cm^2 and 0.40% to 0.54%, respectively, which was within the pharmacopeia limits as shown in Table 5.

The weight variation of core tablet was found within the range of 246.0 ± 0.08-250.0 ± 0.07 mg, which was within the pharmacopeia limits, as shown in Table 5.

The disintegration time of core tablet was found within the range of 38.4 ± 1.07 s to 65.8 ± 0.05 s, i.e., <1 min, as shown in Table 5. From the results, the formulations containing crospovidone (RRCT4-RRCT6) showed less disintegration time when compared with formulations containing CCS (RRCT1-RRCT3) because it has an excellent wicking nature. Crospovidone has a finer particle size distribution which improves mixing and minimizes changes in swelling properties on the tablet surface resulting from atmospheric humidity, so it swells only to a very less extent. When the formulations containing CCS (RRCT1-RRCT3) comes in contact with water, it swells to a large extent to disintegrate the tablet. Furthermore, it has a fibrous nature that allows intraparticulate as well as extraparticulate wicking of water at low concentration levels.[25]

Drug content of rapid release core tablets

The drug content of core tablet was found within the range of 97.56 ± 2.03-99.01% ± 0.09, i.e., within the pharmacopeia limits as shown in Table 5.

In vitro drug release studies of rapid release core tablets

The *in vitro* drug release studies of rapid release core tablet were carried out. The drug release from rapid release core formulations containing CCS (RRCT1-RRCT3) showed 79.6 ± 1.68% at 60 min, 88.8 ± 1.54% at 60 min and 95.5 ± 1.78% at 60 min, respectively. The drug release from formulations containing crospovidone (RRCT4-RRCT6) showed 96.4 ± 1.98% at 60 min, 98.90 ± 1.54% at 45 min and 99.1 ± 1.78% at 30 min, respectively. The results indicated that as the concentration of superdisintegrant increased; the drug release was increased [Figure 1].

When formulations containing crospovidone compared with the formulations containing CCS, the drug release was more because it is a synthetic insoluble, swellable, cross-linked polymer with a rapid wicking effect which rapidly wicks solvents into the particle to speed up swelling and enhance disintegration and dissolution of tablets.

Physicochemical characterization of PCTs

The thickness and diameter of PCTs were found within the range of 3.85 ± 0.09 - 3.71 ± 0.02 mm and 11.00 ± 0.05 mm

Table 5: Physicochemical characterization of TH rapid release core tablets and PCT

Formulation	Hardness[a] kg/cm^2)	Thickness[a] (mm)	Diameter[a] (mm)	Weight variation[a] (mg)	Friability (%)	Drug content[a] (%)	Disintegration time[a] (s)
RRCT1	4.20±0.02	3.12±0.04	9.00±0.06	249.5±1.30	0.42	97.56±2.03	65.8±0.05
RRCT2	4.20±0.06	3.01±0.03	9.01±0.07	248.5±0.60	0.54	98.67±1.80	59.7±1.02
RRCT3	4.10±0.01	3.15±0.08	9.03±0.02	250.0±0.07	0.40	97.67±2.30	54.4±0.04
RRCT4	4.01±0.02	3.07±0.03	9.01±0.01	247.0±0.08	0.35	99.01±0.09	49.8±1.07
RRCT5	4.20±0.02	3.12±0.03	9.00±0.02	248.0±0.07	0.48	98.89±1.06	44.8±0.70
RRCT6	4.09±0.04	3.03±0.09	9.01±0.03	246.0±0.08	0.52	99.01±0.25	38.4±1.07
PCT1	6.20±0.01	3.85±0.04	11.00±0.09	500.5±0.60	0.38	99.56±1.03	-
PCT2	6.20±0.05	3.71±0.02	11.01±0.40	498.2±0.70	0.45	98.67±2.80	-
PCT3	6.60±0.04	3.85±0.09	11.00±0.05	501.0±0.60	0.46	97.67±1.40	-
PCT4	6.20±0.09	3.79±0.04	11.00±0.07	499.0±0.09	0.48	99.69±1.76	-
PCT5	6.01±0.04	3.74±0.05	11.01±0.03	500.0±0.07	0.49	99.81±0.25	-

[a]Each value represents the mean±SD (*n*=3), SD: Standard deviation, PCT: Press coated tablets, TH: Tramadol hydrochloride

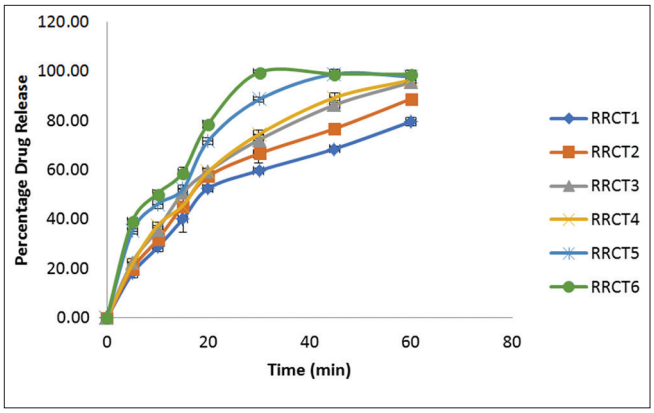

Figure 1: *In vitro* drug release profile of TH core tablets. [a]Each value represents the mean ± standard deviation (*n*=3)

- 11.01 ± 0.04 mm, respectively, which showed a uniform thickness and diameter as shown in Table 5.

The hardness and friability of the PCTs were found within the range of 6.01 ± 0.04 - 6.60 ± 0.04 kg/cm^2 and 0.38-0.49%, respectively, which was within the pharmacopeia limits as shown in Table 5.

The weight variation of PCTs was found within the range of 498.2 ± 0.7 to 501.0 ± 0.60 mg, which was within the pharmacopeia limits, as shown in Table 5.

Drug content of PCTs

The drug content of PCTs was found within the range of 97.67 ± 1.40% - 99.81 ± 0.25%, i.e., within the pharmacopeia limits as shown in Table 5.

Swelling index of PCTs

A direct correlation between swelling index and lag time was observed from the obtained results [Figure 2]. The lag time was found to be increased with increasing swelling index. Higher swelling indices were observed in a formulation containing higher amount of HPMC E100. This may be due to the uptake of water and swelling of the polymer which is hydrophilic and forms a gel upon hydration. As the concentration of HPMC E100 increased in formulations (PCT1 to PCT5) containing polymer blend, swelling index was increased.

Lag time and *in vitro* drug release studies of PCTs

The lag time of the PCT was measured by determining the time for which there is no release or <10% release of the drug from the dosage form. The lag time values of PCTs (PCT1-PCT5) were found within the range of 2 ± 1.08 h - 7 ± 1.54 h. The selected formulation (PCT4) formulation showed release lag time of 5 ± 1.06 h.

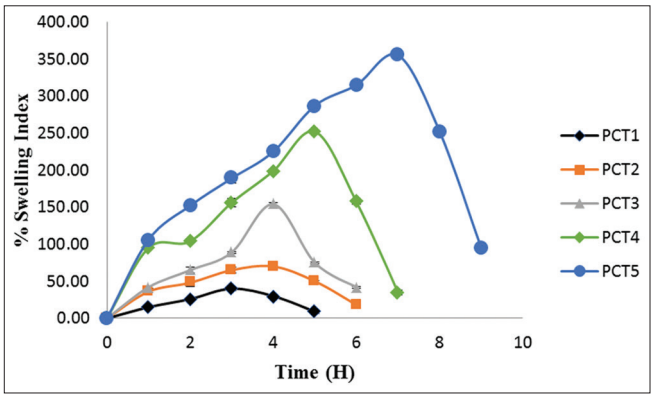

Figure 2: Swelling index of TH press-coated tablets. Each value represents the mean ± standard deviation (*n*=3)

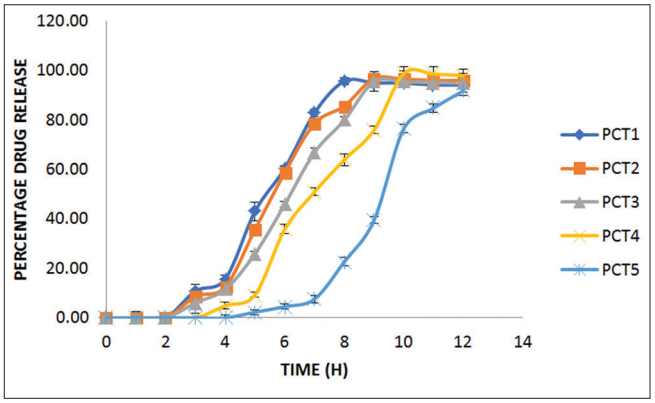

Figure 3: *In vitro* drug release profile of TH press coated tablets. [a]Each value represents the mean ± standard deviation (*n*=3)

The drug release from press coated formulations (PCT1-PCT5) showed 95.6 ± 1.25% at 8 h, 96.65 ± 2.86% at 9 h, 95.5 ± 3.86% at 9 h, 98.74 ± 2.86 at 10 h, and 91.76 ± 1.86% at 12 h, respectively [Figure 3]. The results concluded that an increase in the viscosity grade and polymer quantity showed an increased in lag time and decrease of the release rate of the drug from the system.[26]

Drug-excipient compatibility studies

FTIR studies

The FTIR spectra of pure drug TH and optimized formulation (PCT4) were showed the principal peaks at similar wave numbers [Figure 4] indicating no interaction between drug TH and excipients. The FTIR spectra of pure drug TH showed characteristic peaks at 3637 cm^{-1} (OH stretching), 3438 cm^{-1} (NH stretching), at 2932 cm^{-1} (aliphatic CH stretching), at 1586 cm^{-1} (aromatic C=C stretching), and at 753 cm^{-1} (substituted benzene ring) which were similar to characteristic peaks of optimized formulation at 3670 cm^{-1}, 3470 cm^{-1}, 2921 cm^{-1}, 1577 cm^{-1}, and 750 cm^{-1}.

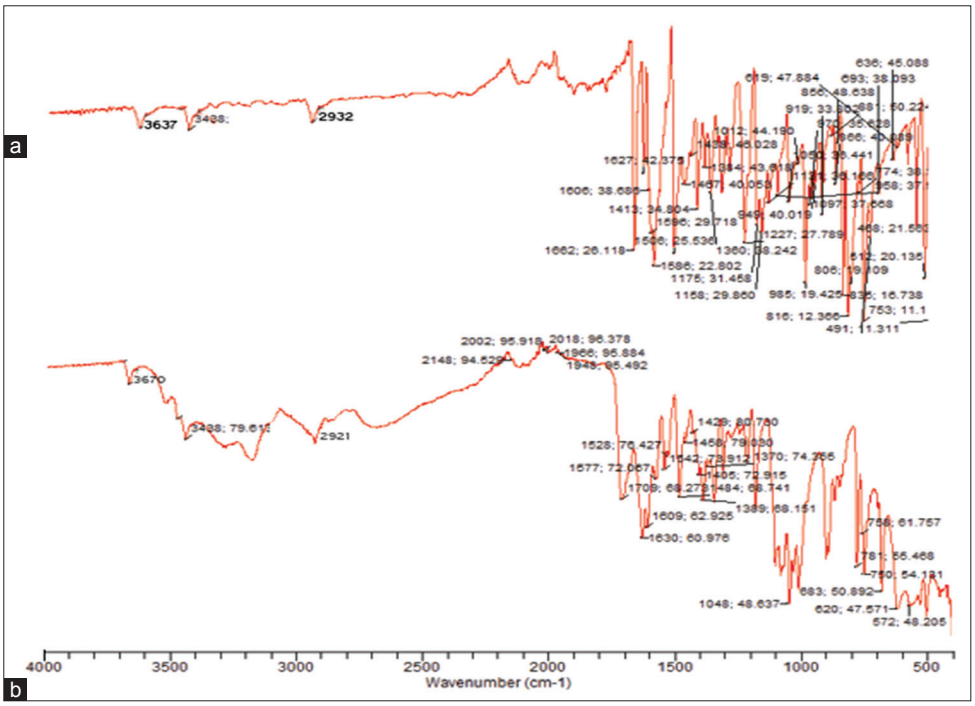

Figure 4: Fourier transform infra-red spectra of (a) pure drug (TH), (b) optimized formulation press coated tablets4

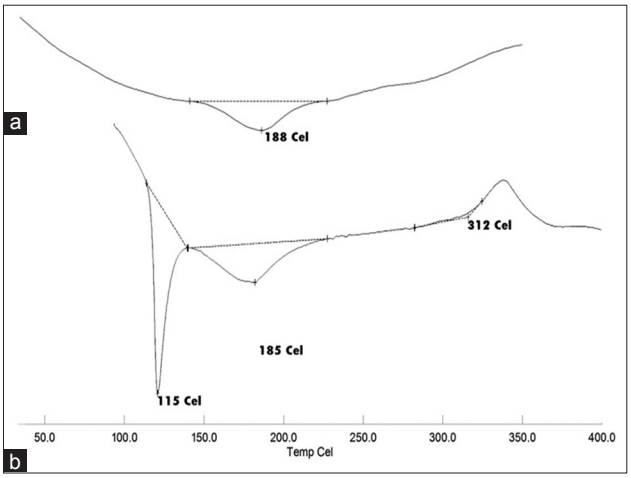

Figure 5: Differential scanning calorimetry spectra of (a) pure drug (TH), (b) optimized formulation press-coated tablets4

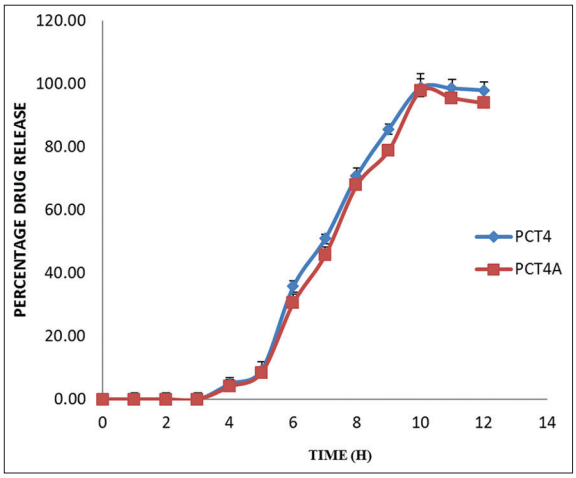

Figure 6: *In vitro* drug release profile of optimized formulation before storage press-coated tablets4 (PCT4) and after storage (PCT4A). [a]Each value represents the mean±standard deviation (*n*=3)

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 formulation (PCT4) were shown in Figure 5. A sharp endothermic peak corresponding to the melting point of TH was found at 188°C which is almost similar to an endothermic peak corresponding to the melting point of TH in optimized formulation at 185°C.

Stability studies

Stability studies of the selected formulation (PCT4) were conducted by subjecting formulation to an examination of physical appearance, drug content studies and *In vitro* dissolution studies [Figure 6]. The physical examination of tablets showed no change in the physical appearance of the tablet. Drug content of selected formulation after storage for 3 months was found to be 99.02 ± 2.26%, which is almost similar to optimized formulation 99.69 ± 1.76, i.e., within limits. *In vitro* drug release studies concluded that there is no significant difference in formulation before and after storage with similarity factor f2 (61) [Figure 6].

CONCLUSION

A chronomodulated PCT for oral use was developed and evaluated. The formulation consisted of a core tablet press

coated with an outer polymer blend. PCT4 compression coated tablets are capable of protecting the drug from being released in the upper region of the GI system. The results suggested that the lag time was increased by increasing the viscosity of the outer coat hydrophilic polymer. In contrast, drug release was found to be decreased. Optimized formulation PCT4 showed a predetermined lag time of 5 h with drug release of 98.74%. There is no modification and/or chemical interaction throughout the process of formulation. Hence, from the above study, it was concluded that the combination of HPMC E50 and HPMC E100 is suitable for the development of chronotherapeutic drug delivery systems with TH.

Thus, this approach can provide a useful means for pulsatile/programable release and may helpful for patients with rheumatoid arthritis.

ACKNOWLEDGMENT

The author Ramya Krishna T is more thankful to Dr. Suresh B and Dr. Jaswanth A (guides) for his valuable support and to Hetero Drugs, Hyderabad for gift sample of TH and other excipients. The author is also thankful to Dr. Sanjeev Kumar Subudhi, Dr. J Venkateshwar Rao and management of Talla Padmavathi Pharmacy College for the infrastructure provided and encouragement.

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Source of Support: Nil. **Conflict of Interest:** None declared.