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Designing the formulations in circadian rhythm activity with chronotherapeutic drug delivery system using ramelteon

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***Abstract*---**Ramelteon is an orally sleep promoting agent that is chemically designated as (S)- N- [2-(1,6,7,8-Tetrahydro-2H-indeno-[5,4b] furan-8-yl) ethyl] propionamide and contains one chiral centre. Ramelteon is a neutral compound with no acid or base functional groups, and as such, its aqueous solubility is independent of pH. The activity of Ramelteon at the MT1and MT2 receptors is believed to contribute to its sleep-promoting properties, as these receptors, acted upon by endogenous melatonin, are thought to be involved in the maintenance of the circadian rhythm underlying the normal sleep-wake cycle. These maintenance of circadian rhythm can be well controlled by designing the formulations with chronotherapeutic drug delivery system. This article summarizes to design, develop and evaluate the chronotherapeutic drug delivery system with various approaches using control release polymers like Eudragit RSPO, Hydroxy propyl methyl cellulose (HPMC), Ethyl cellulose etc., the approaches like compression coating technique, pulsatile drug delivery system and coating technique. The main objective of controlling the drug release pattern is to achieve the lag time of 2

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hours followed by drug release profile for 4 hours. Also an attempt has been made to conclude on various approaches studied which can be used in the treatment of circadian rhythm using Ramelteon API.

Keywords---approaches of chronotherapeutic drug delivery system, jet lag phase disease, insomnia, Ramelteon, compression coated technique, pulsatile drug delivery, coating technique.

Introduction

The word circadian is derived from the Latin circa which means "about" and dies which can be defined as "a day". Normally, circadian rhythms are self-sustaining, endogenous oscillations that are synchronized according to internal biologic clocks related to the sleep-wake cycle[1].Depending on the period of time and its rhythmic cyclic nature the rhythms can be broadly classified into circadian rhythm, Ultradian rhythm, Infradain rhythm, Circamenusal rhythm, Circannual rhythm, Circaseptan rhythm and Coupled rhythm. Understanding the rhythms and developing the formulations with different approaches is a challenging task to the formulator. These circadian rhythms can be treated by designing the formulations with chronotherapeutic drug delivery systems.

Chronotherapeutic drug delivery systems can be designed with various approaches like, Contin^{R} ,Oros^{R} , Codas^{R} , Ceform^{R} , Diffucaps^{R} , Egalet^{R} , Port^{R} ,Timerx^{R} , Pulsy^{TM} , Chronotropic^{TM} , Physicochemical modification of API. The objective of the present work is to design the formulations with different approaches like compression coating technique, pulsatile drug delivery system and coating technique. To achieve the desired drug release of the drug various polymers been utilized for different approaches like Eudragit RSPO, Hydroxyl propyl methyl cellulose (HPMC), Ethyl cellulose etc., Ramelteon is a drug used in the treatment of insomnia and jet lag phase disease. Ramelteon is a drug been selected to study the chronotherapeutic drug delivery system for different approaches and its impact on the in vitro drug dissolution studies.

Materials and Methods

Materials

Ramelteon API was gifted from Zydus cadila, India. Eudragit RSPO was gifted from Evonik industries. Ethyl cellulose and hydroxyl propyl methyl cellulose and other excipients were available in the department.

Preparation of Chronotherapeutic drug delivery system

Approach 1 with compression coating technique

Core tablets has been prepared with the various composition details as below in table number 1. Where all the excipients along with the Ramelteon API were co-sifted through #40 sieve and the magnesium stearate were sifted through #60 mesh. The blend was compressed using round shaped punches using compression machine. The tablet weight kept constant to maintain 100mg/tablet. Coating layer

of HPMC, Ethyl cellulose were sifted through #40 sieve and magnesium stearate sifted through #60 sieve and blended well. The coating layer was carefully spread in equal proportions (50 mg each) both above and below the core tablets and compressed with round shaped punches using compression machine.

Table 1
Quantitative composition details of core tablets

Details		Core tablets (mg/tablet)			Coating layer (mg/tablet)		
Sl no	Ingredients/Batch umber	CT -1	CT -2	CT-3	CC-1	CC-2	CC-3
1	Ramelteon	8	8	8	Core tablets of CT-2		
2	Eudragit RSPO	5	10	15			
3	Lactose Monohydrate	58	53	48			
4	Microcrystalline cellulose	27.2	27.2	27.2			
5	Colloidal silicon dioxide	0.3	0.3	0.3			
6	Magnesium stearate	1.5	1.5	1.5			
Total weight of the tab (mg)		100	100	100			
Ethyl cellulose		-	-	-	69.3	49.5	29.7
Hydroxy propyl methyl cellulose K4 M		-	-	-	29.7	49.5	69.3
Magnesium stearate		-	-	-	1	1	1
Total weigh of the tablet					200*	200*	200*

*Core tablets of CT 2 (100mg/tablet) and coating layer (100mg/tablet) produces 200mg /tablet.

Approach 2 with Pulsatile drug delivery system
Formation of Hydrogel Plug

The Hydrogel plug was prepared by compressing by different ratios of Hydroxy propyl methyl cellulose and ethyl cellulose passed through # 30 sieve and compressed under Rotary compression machine.

Table 2
Composition of the Hydrogel Plug

Ingredients	Pulsatile -Plug Composition (mg/capsule)		
Batch number	PCT1	PCT2	PCT3
Hydroxy propyl methyl cellulose	39.6	79.2	NIL
Ethyl cellulose	39.6	NIL	79.2
Magnesium stearate	0.8	0.8	0.8
Total weight of the tablet in capsule	180	180	180

Formation of pulsatile dosage form

Around 100 Empty hard gelatin capsules of Size “0” is been taken. A Cap and Body been separated and the Capsule body is being placed on the wire mesh. Empty Glass beaker has been taken and added 25ml of 15% of formaldehyde solution, to this a pinch of Potassium permanganate was added and placed in the desiccator. The wire mesh containing capsules body has been placed on the

beaker and the desiccator was tightly closed. The hard gelatin capsule body has been made to react with formaldehyde vapours for 12 hours. The capsules were removed and placed in hot air oven at 40^0C for 30 minutes and dried at room temperature for 12 hours on filter paper to facilitate the removal of residual formaldehyde. The Capsules containing Ramelteon core tablets were then plugged with the Hydroxy propyl methyl cellulose and Ethyl cellulose plugs. The capsule body has been locked with the capsule Cap.

Approach 3 with Coating technology

Eudragit RSPO can be successfully used as a film forming agent for developing formulation of chronotherapeutic drug delivery system as a non-enteric coating polymer. The formulation of the coating solution can be adjusted to provide the drug to deliver at a predetermined rate with a specific lag time (MM Kanakal, June 2009)[22]. Eudragit RSPO added slowly in 50 percent of diluent mixture (Acetone, Isopropyl alcohol and water) under mechanical stirrer and continued stirring for around 60 minutes till the Eudragit polymer is completely dissolved. In remaining 50 percent of diluent mixture (Acetone, Isopropyl alcohol and water) added talc and triethyl citrate and stirred under mechanical stirrer and continued stirring for around 15minutes. Both the solutions have been stirred for about 110 to 15 minutes. The Core tablets of CT2 has been selected and coated using the below composition to achieve a different weight build ups like 5 percent, 8 percent and 12 percent to the tablet weight. The coated tablets have been analysed for the weight variation, thickness and in vitro dissolution profile.

Table 3
Composition of the coating formula

Sl no	Ingredients	Percentage
1	Eudragit RSPO	62.50
2	Triethyl citrate	6.25
3	Talc	31.25
4	Acetone*	342.90
5	Iso propyl alcohol*	514.20
6	Water*	42.90

*Evaporated during drying

In vitro dissolution study

Drug release of the Ramelteon tablets was carried out using electro lab dissolution test apparatus, The USP 2 paddle method was been selected to perform the dissolution profile of the Ramelteon. The dissolution test was being carried out using 900 ml, water, at a speed of 50 rpm paddle. The formulation was placed inside the dissolution vessel .10ml of sample was withdrawn at time interval of 1,2,3,4,5 and 6 hours. The volume of dissolution medium was adjusted to 900ml by replacing 10ml of dissolution medium after withdrawal of sample. Each sample was analyzed at 286 nm in UV visible spectrometer against reagent blank. The drug concentration was calculated using standard calibration curve.

Results and Discussion

Approach 1: Evaluation of compression coated tablets

Compression coated tablets were evaluated for physical evaluation. The tablets weight variation, friability was found well within the pharmacopeia limits.

Table 4
Physical characteristics of compression coated tablets

Batch number	Average weight (mg) ± SD*	Thickness (mm) ± SD*	Hardness (N) ± SD#	% Friability
CC 1	201.4 ± 1.90	3.28 ± 0.03	34.97 ± 3.22	0.099
CC 2	200.5± 2.06	3.23 ± 0.04	36.57 ± 2.48	0.100
CC 3	200.0± 1.52	3.24 ± 0.05	35.90 ± 1.40	0.149

*n=10, # n= 6.

Core tablets of CT1, CT2 and CT3 has been analysed for the dissolution profile, in which the batch number CT1 produced the dissolution within 3 hours, whereas the batch number with CT2 and CT3 produced the dissolution profile for 4 hours. Considering a marginal difference in dissolution profile between CT2 and CT3 and the quantity required of Eudragit RSPO less in CT2 could be an advantage in terms of cost, batch number CT2 has been selected as an optimized core formulation. With the ratio of CC1 of coating layer tablets produced a desired lag time of 2 hours followed by dissolution profile for 4 hours and this may be due to combination of Hydrophobic nature of ethyl cellulose and hydrophilic nature of HPMC. As the ratio of HPMC increases the swelling nature of pattern also increases the desired lag time and target dissolution profile of 4 hours was achieved but complete release at the 6th hour was not achieved.

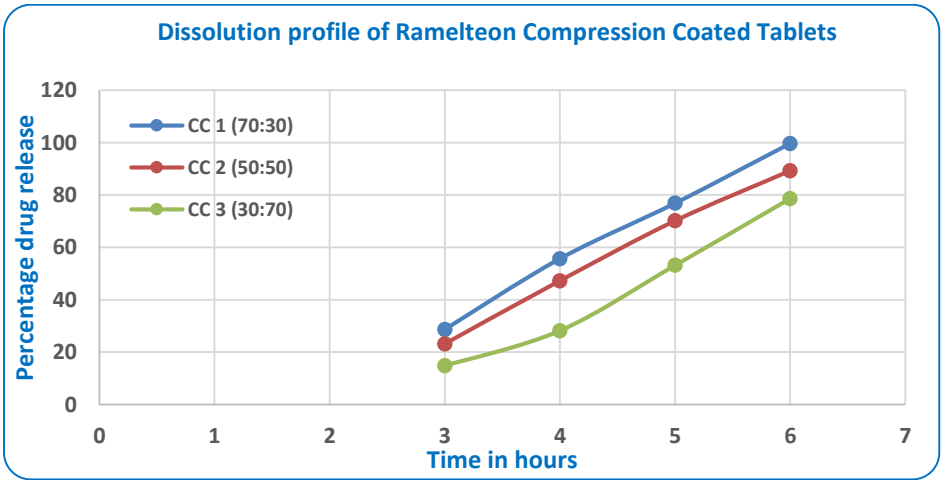

Figure 1. In vitro dissolution profile of compression coated tablets in water

Approach 2: Evaluation of Pulsatile drug delivery system

Few formaldehydes treated capsule body were found to be shrunk or in different shapes and may be due to loss of moisture. It was also observed that the capsules before treating where found to be slightly sticky when touched with the wet hand. But after treating with the formaldehyde, capsule body were found non sticky even touched with the wet hand. And the capsules were found to be odourless and lockable. The treated and untreated capsules were measured for the length and the diameter using Vernier calliper. The treated capsules show a slight difference in dimensions.

Table 5
Hard gelatin capsules Dimensions before and after Formaldehyde treatment

Test Parameters	Before formaldehyde treatment (mm)	After formaldehyde treatment (mm)
Average Capsule Length (Closed cap & Body)	21.3	20.4
Average length of the Capsule body	18.3	17.4
Average Diameter of the capsule Body	7.3	7.1

Table 6
Physical evaluation parameters for Hydrogel plug

Sl no	Physical parameter	PCT1	PCT2	PCT3
1	Weight (mg)	79.3	80.2	78.5
2	Hardness (N)	16.9	14.10	15.18
3	Thickness (mm)	2.73	2.70	2.71

The selection of the hydrogel plug was challenging. The hydrogel plug HPMC alone produces enormous swelling observed compare to the hydrogel plug of Ethyl cellulose and the lag time observed around 3 hours. Where as in case of combination of Ethyl cellulose and HPMC produces a desired lag time of 2 hours which may be due to the swelling nature of HPMC and rupture nature of ethyl cellulose. The core tablets of CT1, CT2 were selected and placed in treated capsule along with the combination of the hydrogel plug and studied for the in vitro dissolution behaviour. The core tablets CT2 with a combination of the hydrogel plug maintained a lag time of 2 hours, but complete drug release was not achieved with a time of 6 hours. But in case of the core tablets with CT1 with a combination of the hydrogel plug maintained a lag time of 2 hours and complete drug release was achieved with a time of 6 hours. However, it's been concluded that the ratio of the hydrogel plug polymer & Core tablets Eudragit RSPO is a key factor to achieve the desired lag time and release profile of the Ramelteon drug.

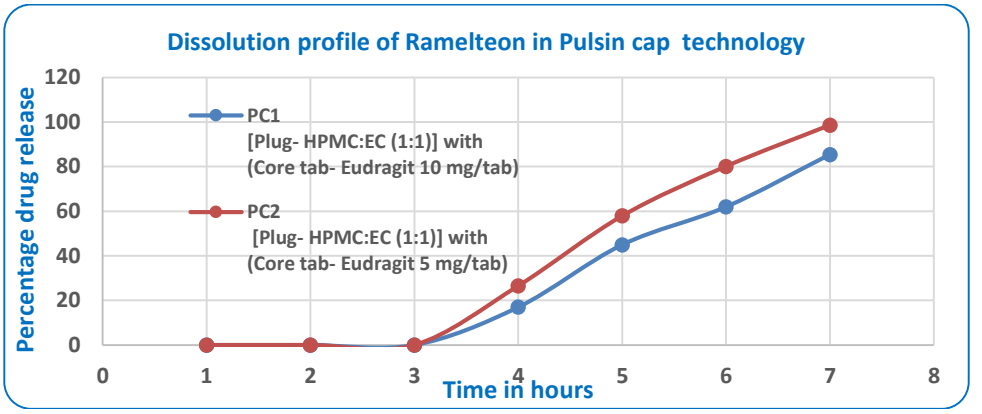

Figure 2. In vitro dissolution profile of Pulsin cap in water

Approach 3: Evaluation of Coating technology

Coated tablets have been evaluated for the tablet weight, thickness and dissolution profile. The drug delivery system consisted of a core coated with Eudragit polymer with PEG 4000. The swelling layer consist of the pH independent Eudragit polymer which also acts as a semipermeable membrane when it comes in contact with the dissolution medium. The lag phase of the dosage form has been made with an attempt by controlling the percentage of coating on the core tablets through a non-enteric coating polymer. The lag time can be controlled with thickness of the coating layer and the dissolution release profile can be controlled with the quantity of the polymer used in the formulation. Coated tablets indicated that as the build-up of the coating increases the thickness of the tablets also increases. The build-up of the polymer plays a critical role in releasing the drug profile and its maintaining the lag time. The lag time was increased with increase percentage of coating build up to the core weight of the tablet. This could be the reason related to the mechanical strength & thickness of the coating material. The tablets coated with different percentage of build-up shows a lag time of 2 hours. Batch number with FC1 shows a complete release in 6 hours whereas tablets coated with 8 % and 12 % didn't show complete release in 6 hours.

Sl no	Batch number	Core weight of the tablet (mg)	Tablet weight after coating (mg)*	Coating thickness*
1	FC1	99.4	104.9±0.47	0.10 ±0.02
2	FC2	99.4	107.8±0.77	0.20±0.02
3	FC3	99.4	112.2 ±0.60	0.28 ±0.05

*Mean ± % Deviation (n=10)

Figure 3. In vitro Dissolution profile of Ramelteon coated tablets.

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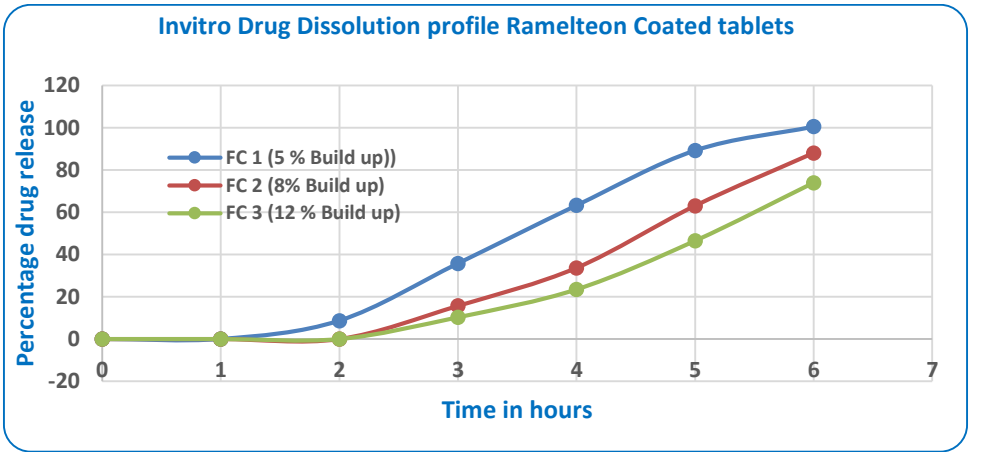

Figure 3. In vitro Dissolution profile of Ramelteon coated tablets

Differential scanning calorimetry (DSC)

The Ramelteon API and the finished dosage form (CC1) was analysed for DSC study to understand the impact on the API and the excipients used in the formulation along with the application of compression force during compression of the tablet. The endothermic peak observed for an Ramelteon API with a sharp peak about 119.82 °C with an onset of melting at 115.69 °C. The endothermic peak observed for an Ramelteon tablets with a sharp peak about 116.89 °C with an onset of melting at 112.91 °C. Also an additional peak observed in the tablets about 143.43^{0}C which could be a melting point of a magnesium stearate which ranges from 117^{0}C to 150^{0}C. The endothermic peak of the finished formulation matches with the endothermic peak of the Ramelteon API indicates the formulation is stable along with the process parameters as shown in Figure number 4 and Figure number 5.

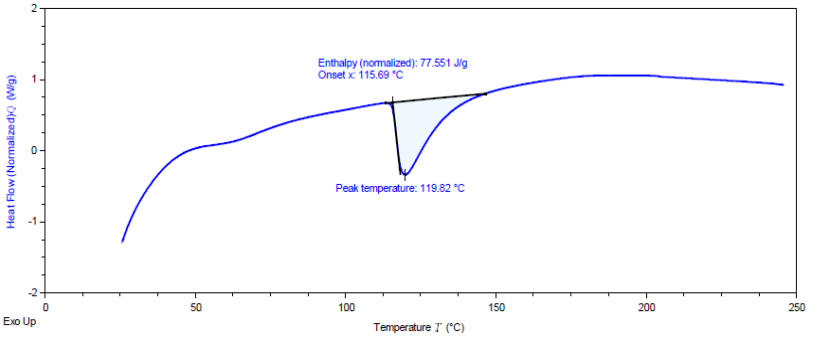

Figure 4. DSC Thermogram of the Ramelteon API

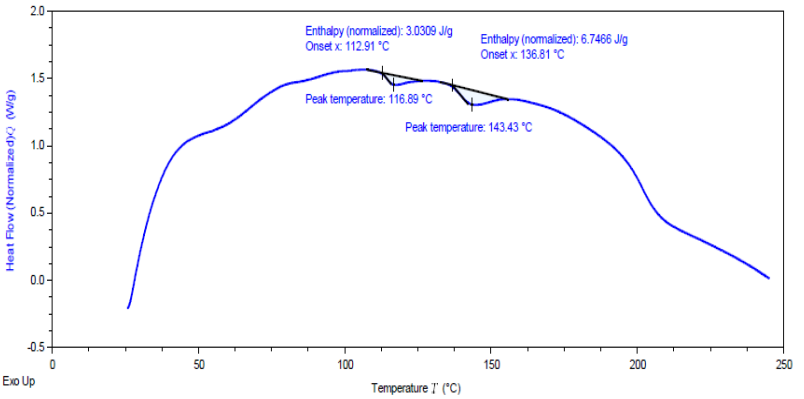

Figure 5. DSC Thermogram of the Ramelteon API and the finished formulation

Conclusion

Circadian rhythm is a process which occurs naturally that regulates the sleep wake cycle associated with several physiological, biochemical behavioural processes in humans and entrainment to light- dark cycle. Chronotherapeutic drug delivery system is an approach in the treatment of circadian rhythms. The present study focused to design and develop with different approaches of the chronotherapeutic release of a Ramelteon drug used in the circadian rhythm by preparing with compression coated approach, pulsing cap approach and coating technique. Compared to all three approaches first approach compression coating technique involves less processing steps which is scalable to industrial scale. second approach involve hard gelatin capsule which needs to be treated with formaldehyde vapours & separate fabrication of hydrogel plug and a dedicated equipment required for the usage for industrial scale. The third approach involves the usage of organic solvents to coat the core tablets. Hence compare to all three approaches compression coating technique to achieve a target of lag phase of 2 hours and a dissolution profile release of 4 hours involves the usage of less equipment in processing the dosage form which can be scaled up to industrial scale using single compression machine with suitable change parts. Further the compression coating technique involving Ramelteon API can be validated in the treatment of jet lag phase disease, circadian rhythm with chronotherapeutic drug delivery system based on the in vivo studies.

Conflicts of interests

Declare none

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