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Original Article

Compression Coating Technique and its Formulation in Circadian Rhythm Activity with Chronotherapeutic Drug Delivery System

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ABSTRACT

Background: Circadian rhythms is a natural process that regulates the sleep wake cycle which is associated with several physiological, biochemical, endocrine, behavioural processes in humans and entrainment to light-dark cycle. The activity of Ramelteon is believed to contribute to its sleep-promoting properties and thought to be involved in the maintenance of the circadian rhythm underlying the normal sleep-wake cycle. A tablet can be given before 2 hr of bed time, so the Ramelteon drug shows its effect throughout the night by releasing the active content with lag time followed by sustained action to promote the sleep. **Materials and Methods:** Chronotherapeutic drug delivery system were prepared by compression coating technology using pH independent, hydrophilic and hydrophobic polymers. **Results:** Drug excipient compatibility indicated that the Ramelteon Active pharmaceutical ingredient (API) is compatibility with the excipients proposed. The X-ray Diffraction (XRD) studies indicated that the crystalline form of the Ramelteon API existed in the finished formulation. **Conclusion:** The core tablets containing Eudragit RSPO 10mg/tablet and ratio of Ethyl cellulose: Hydroxy propyl methyl cellulose (HPMC) of 70:30 in the outer coating material yielded a desired lag time of 2 hr and drug release for a period of 4 hr to achieve a chronotherapeutic drug delivery system. Ramelteon is an excellent candidate in designing chronotherapeutic drug delivery systems and further *in vivo* studies can be explored in the treatment of circadian rhythm with sleep wake cycle disorders.

Keywords: Ramelteon, Compression coated, Sleep disorders, Jet lag phase, Sleep wake cycle, Eudragit.

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INTRODUCTION

Broad inter subject variability in patients has been observed in the recent years for the diseases and to respond for the treatment is becoming challenge. So customized medicinal treatment is required to ensure maximum clinical effectiveness and to reduce side effects with its toxicities. A new audit alerts shows the absence of steady clinical advantages utilizing the current customized medication ideas upgrading remedial systems and its technology is a prerequisite to envelope both the specialties of the patient pathology and the patient heredity qualities and the way of life.[1]

The leaves of specific plants and trees open during day and close around evening time, demonstrating a clear rhythmicity.[2] Similarly, numerous elements of the human body fluctuate extensively in a day. Human circadian rhythm is based on sleep-activity cycle, is subjective by our genetic makeup and hence, affects the body's capacities day and night with a time span of 24 hr.[3] Four of them are related to the patient's endogenous circadian framework like delayed sleep phase syndrome, advanced sleep phase syndrome, non–24-hr sleep–wake syndrome, and irregular sleep–wake rhythm.

Tuning drug delivery to the body's circadian rhythms has been the tricky objective of a select band of medication convenience. The knowledge of focusing on delivery to the specific time of day when there is maximal clinical manifestation of a disease has obvious advantages, and there is no shortness of resourcefulness in planning formulations for time-delayed drug release.

One of the most feasible technology for tuning body's circadian rhythms activity is with chronotherapeutic drug delivery system. The term, 'Chrono pharmaceutic drug delivery system', is used to describe a kind of formulating the drug which can cause changes in the circadian rhythm leads to changes in the plasma drug levels.[3] The Chronotropic innovation identifies with an oral convenience intended for time-sensitive pulsatile release of drug, which is generally referred to as the release of drugs after a certain period of time may be called as predetermined lag phase starting at the time of administration.

The objective of the proposed work is an attempt to formulate and evaluate chronotherapeutic drug delivery system of a drug using different polymers that may facilitate maintenance of robust circadian clocks using Ramelteon API. To achieve the objective pH independent polymers such as Eudragit RSPO was selected in the core matrix along with other excipients such as microcrystalline cellulose and lactose monohydrate to control the drug release over a period of time with direct compression technique. And in the outer layer both hydrophobic and hydrophilic polymers were selected such as ethyl cellulose and Hydroxy propyl methyl cellulose to control the lag time of the drug release. The impact of the hardness on dissolution were also studied on the core tablets. The swelling study was studied on the compression coated tablets.

MATERIALS AND METHODS

Materials

Ramelteon was received as a gift sample from Zydus cadila, Ahmedabad, India. Eudragit RSPO was received as gift sample from Evonik industries. Ethyl cellulose from dupont and hydroxyl propyl methyl cellulose was received as a gift sample from Colorcon Asia Pvt Ltd. Other excipients were available in the department.

Methods

Preparation of Core tablets

Core tablets of Chronotherapeutic drug delivery system has been fabricated with the direct compression technique using variable quantitative composition of the Eudragit RSPO polymer as shown in Table 1. The Ramelteon along with excipients were passed through #40 sieve and the magnesium stearate passed through #60 sieve and blended well to produce uniform mixing. All the three formulation were compressed using compression machine using round shaped punches. Reconciliation of Eudragit RSPO quantity has been carried out with lactose monohydrate to maintain the target weight of 100mg/tablet.

Preparation of Coating Layer

Different quantitative composition of chronotherapeutic drug delivery system of Ramelteon coating layer was fabricated as shown in Table 2. Coating layer polymers of Ethyl cellulose and Hydroxy propyl methyl cellulose were sifted through #30 sieve and the magnesium stearate were sifted through #60 sieve. Both the polymers according to the composition and the lubricant magnesium stearate were blended.

Preparation of Compression Coating Tablets

Compression coated tablets of Ramelteon were fabricated by placing the compressed core tablets in the Centre of die cavity of compression machine with different weight ratios of coating layer, Ethyl cellulose and Hydroxy propyl methyl cellulose. The coating layer was carefully placed 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)		
Sl. No	Ingredients/Batch umber	CT -1	CT -2	CT-3
1	Ramelteon	8	8	8
2	Eudragit RSPO	5	10	15
3	Lactose Monohydrate	58	53	48
4	Microcrystalline cellulose (Avicel PH 102)	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

Table 2: Quantitative composition details of compression coated tablets.

Ingredients	Compression Coated tablets				
Core tablet Batch number	CT-2				
Coating layer	mg/tab				
Batch number	CC-1	CC-2	CC-3	CC-4	CC-5
Ratio	1 :0	0:1	70: 30	50: 50	30:70
Ethyl cellulose	99	0	69.3	49.5	29.7
HPMC K4 M	0	99	29.7	49.5	69.3
Magnesium stearate	1	1	1	1	1
Total	100	100	100	100	100

Swelling index

Water uptake study of the compression coated Ramelteon tablets was determined. Each formulated tablet was kept in the Centre of the petri dish containing 75ml of the water and the amount decreased against time was noted. The dimensional changes observed in terms of the increase in tablet diameter and/or thickness over time. Water uptake was measured in terms of percent by using following formula.

$$WU = \frac{(W_t - W_0)}{W_0} \times 100$$

W_t = Weight of dosage form at time t.

W_0 = Initial weight of dosage form

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 drug release.

The dissolution test was being carried out using 900 ml, water, at a speed of 50 rpm paddle. The tablets were placed inside the dissolution vessel. 10ml of sample was withdrawn at time interval of 1,2,3,4,5 and 6 hr. The volume of dissolution medium was adjusted to 900ml by replacing 10ml of dissolution medium after withdrawal of sample. Each sample was analysed at 286 nm in UV visible spectrometer against reagent blank. The drug concentration was calculated using standard calibration curve.

RESULTS

In the present study, the chronotherapeutic drug delivery system was been prepared by direct compression technique using pH independent polymer like Eudragit RPSO in core tablets along with Lactose monohydrate and microcrystalline cellulose as a diluent, colloidal silicon dioxide as a glidant, and the magnesium stearate as a lubricant. The coating layer contains a polymers of Ethyl cellulose and the Hydroxyl propyl methyl cellulose.

Drug excipient compatibility study

Drug excipient compatibility study was being understood with FTIR spectrum with a range of 4000-400 cm^{-1} using KBR disc method. Ramelteon API along with the excipient used in the finished formulation has been exposed to 40°C/75 %RH for 4 weeks and the FTIR analysis has been performed and depicted in Figure 1 and Figure 2.

Physical evaluation of core tablets

Core tablet compressed were evaluated for physical evaluation. The physical description of the tablets was found to be white to off white colour. The tablets weight variation, friability was well within the pharmacopeia limits and represented in Table 3.

In vitro drug dissolution tests of core tablets

Core tablets drug dissolution was controlled through pH independent polymer like Eudragit RSPO and water-soluble excipients like lactose monohydrate.

In vitro dissolution profile of the core tablets from the below Figure 3 indicates that the tablets with Eudragit RSPO with 10mg/tablet and 15mg/tablet shows the desired release profile of the drug with a duration of 4 hr.

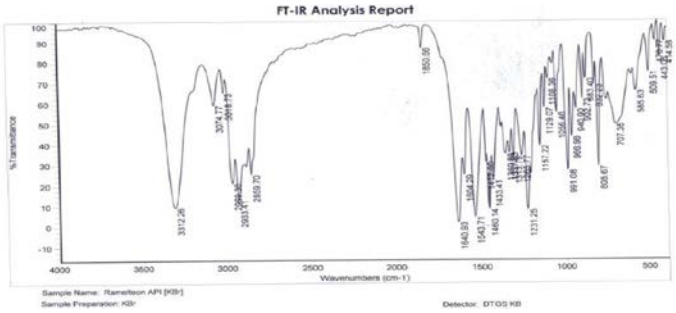

Figure 1: FTIR spectrum of the Ramelteon API. Y axis represents % Transmittance and X –axis represents wave numbers (cm^{-1}).

Figure 2: FTIR spectrum of the Ramelteon tablet - Physical mixture samples. Y axis represents % Transmittance and X –axis represents wave numbers (cm^{-1}).

Table 3: Physical characterization of the core tablets.

Batch number	Average weight (mg) + SD*	Hardness (N) + SD#	Friability
CT 1	99.5 + 2.77	16.98 + 1.80	0.397
CT 2	99.4 + 2.80	16.00 + 2.44	0.297
CT 3	100.6 + 1.43	16.72 + 1.33	0.198

*n=10, # n= 6.

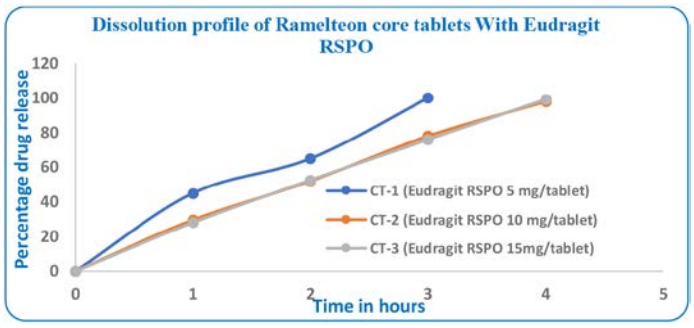

Figure 3: *In vitro* dissolution profile of Ramelteon core tablets in water. The y-axis represents % drug release and the x-axis denotes times in hours. Data represent mean ± standard deviation, n = 3.

Impact of the hardness on the physical evaluation of the core tablets

The optimized formulation of core tablets CT 2 i.e., Eudragit RSPO 10 mg /tablet has been evaluated for the impact of hardness study from 10 Newton's to 30 Newton's in compression machine and represented in Table 4.

With increase in the Tablet hardness from 10 Newton's to 30 Newtons the friability is within the specification limits. It is also observed that

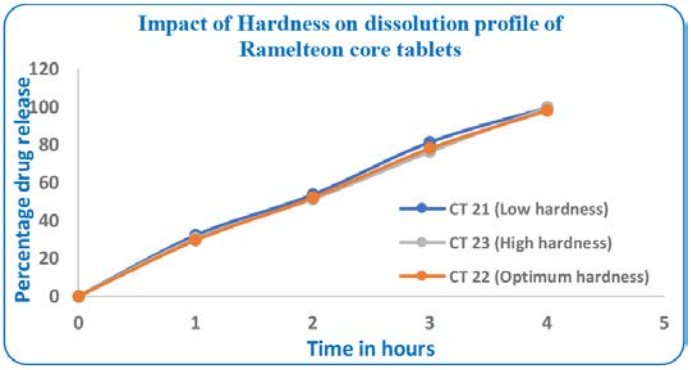

Figure 4: Impact of Hardness on dissolution profile of Ramelteon core tablets. The y-axis represents % drug release and the x-axis denotes times in hours. Data represent mean ± standard deviation, n = 3.

Table 4: Physical characterization of the core tablets with change in hardness.

Batch number	Average weight (mg) + SD*	Hardness (N) + SD#	% Friability
CT 21	99.7 + 2.12	10.72 + 1.55	0.793
CT 22	99.4 + 2.80	16.00 + 2.44	0.297
CT 23	99.4 + 1.63	33.47 + 2.98	0.099

*n=10, # n= 6.

Table 5: Physical characteristics of compression coated tablets.

Batch number	Average weight (mg) + SD*	Hardness (N) + SD#	% Friability
CC 1	199.9 + 2.38	36.98 + 0.97	0.198
CC 2	200.2 + 1.81	36.63 + 1.94	0.248
CC 3	201.4 + 1.90	34.97 + 3.22	0.099
CC 4	200.5+ 2.06	36.57 + 2.48	0.100
CC 5	200.0+ 1.52	35.90 + 1.40	0.149

*n=10, # n= 6.

increase in the hardness form 10 Newtons to 30 Newtons a very slight decrease in thickness and friability value. Also it has seen that the increase in hardness has not been lead in significant difference in the dissolution profile as represnted in Figure 4, this may be due to the nature of the Eudragit RSPO polymer which is insoluble and the formulation which is a continuous matrix. The formation of pores and cracks during dissolution study facilitate the drug release. More over Eudragit RSPO releases the drug in diffusion pattern and not with erosion pattern of the tablets during dissolution. This variation in the hardness causes relatively small change in the porosity and therefore release rate is not being affected.

Physical characteristics of compression coated tablets

Compression coated tablets were evaluated for physical evaluation. The physical description of the tablets was found to be white to off white colour. The tablets weight variation, friability was found well within the pharmacopeia limits. The optimized core tablets with Eudragit RSPO with formulation code of CT2 has been selected for further optimization to evaluate the impact of lag time over the dissolution profile. Initially the hardness around 35 Newton's has been kept constant for all the compress coated tablet and the data is represented in Table 5 and Figure 5.

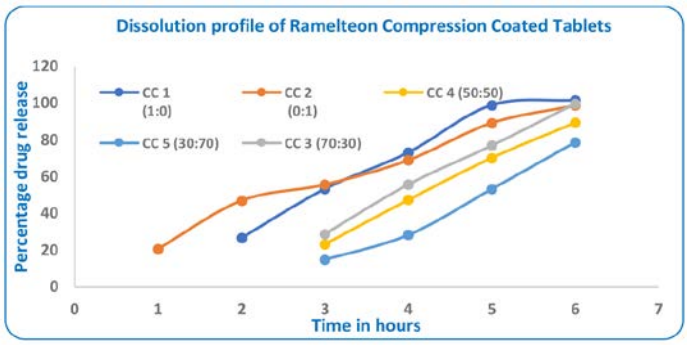

Figure 5: *In vitro* dissolution profile of compression coated tablets in water. The y-axis represents % drug release and the x-axis denotes times in hours. Data represent mean ± standard deviation, *n* = 3.

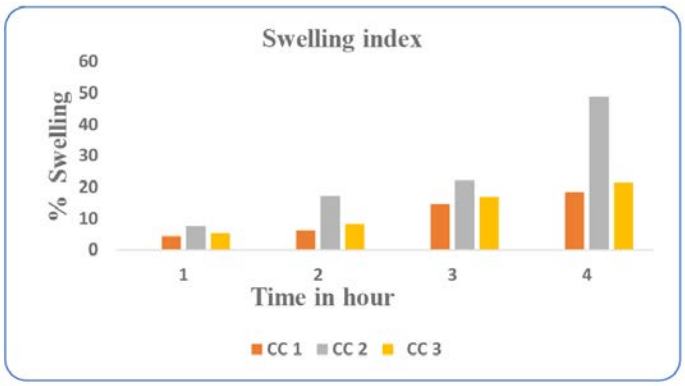

Figure 6: Swelling index behavior of CC1, CC2 and CC3. The y-axis represents % swelling and the x-axis denotes times in hours. Data represent mean ± standard deviation, *n* = 3.

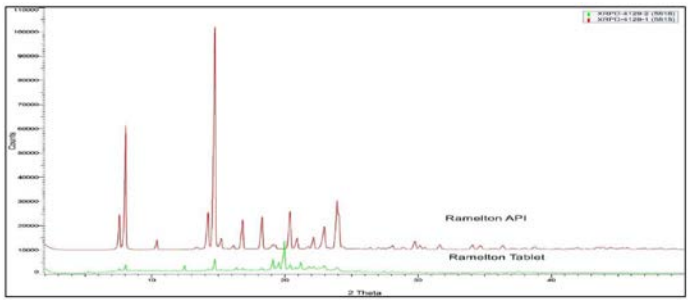

Figure 7: Overlay XRD diffractogram of the Ramelteon API and the finished dosage form.

Swelling index

Swelling study has been carried out for the three compression coated dosage forms CC1, CC2 and CC3 for 4 hr. The results of swelling index against time (hr) was plotted in Figure 6.

XRD Study

The Ramelteon API and the optimized formulation of the finished dosage form (CC3) was analysed for XRD study. XRD diffractogram shown in Figure 7.

DISCUSSION

The optimized core tablets formula (ie., Eudragit RSPO 10 mg/tablet) was chosen to execute the trials with different levels of compression coating polymer and to study its impact on the dissolution profile. The selection and the ratio of the coating polymers were challenging.[4] The ratio of the coating polymer i.e., Ethyl cellulose and the Hydroxy propyl methyl cellulose was optimized to achieve the desired lag time of 2 hr followed by complete release of the drug.

Based on the trials executed with compression coated tablets the ethyl cellulose (CC1) alone in the outer coat dint able to withstand a lag time of 2 hr. Also, its observed that the tablets coated with ethyl cellulose alone separated in two parts and allowed the core tablets exposed to the dissolution medium. This lag time may be due to the penetration of the dissolution medium through the lateral surface of the tablets and complete release was observed within 5 hr. The compression coated tablets with HPMC alone (CC2) was achieved lag time of 1.0 hr against the target of 2 hr, also it was observed that duration of the drug release was prolonged over a period time, this may be due the hydrophilic nature of the HPMC polymer and formation of the swelling and pores around the core tablets.[5]

Dissolution method was selected based on the solubility studies suggested by the office of generic drug media.[6] With the ratio of Ethyl cellulose: HPMC (70:30) (CC3) desired lag time of 2 hr was achieved with a target dissolution release profile of 4 hr from the core tablets. This may be due the combination of the hydrophobic and hydrophilic nature of the polymers.

As the ratio of the HPMC in the coating layer increases (CC4 and CC5) the swelling pattern also increases and desired lag time and target dissolution profile of 4 hr was achieved but complete release at the 6th hr was not achieved. This may be due to the swelling behaviour of the HPMC polymer followed by viscous gel layer formation surrounding the core tablets.

Swelling study results indicated that as the time increases the swelling increases. This may be due to the hydrophilicity of polymer as water absorbs gradually. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or has dispersed, the hydration swelling and release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form. In the present study, the higher swelling index has found for tablets of batch CC 2 i.e. With HPMC compression coating alone. And the swelling has found less with the formulation CC1, this may be due to the hydrophobicity of the ethyl cellulose polymer and less water uptake. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity hence from the above results it can be concluded that linear relationship exists between swelling process and viscosity of polymer of formulations.

The XRD peak indicates crystalline nature of the drug will remain same in the finished product. The presence of numerous distance peaks in XRD study spectrum in Ramelteon indicated that Ramelteon was present in a crystalline material with major characteristic peaks appearing at a diffraction angle of 2 theta at 7.59,8.04, 14.24, 14.74,16.83, 18.29, 20.4, 22.97 and 23.99, Finished dosage form showed similar major characteristic diffraction peaks indicating the presence of Ramelteon in crystalline form in the final formulation. Also from the public domain information it indicates Ramelteon has no known polymorphs.[7] Thus it indicates the Ramelteon in its finished dosage form is stable.

However, based on the results the dosage form formulation indicates that the ratio of the outer polymer is a key factor to achieve the desired lag time and release profile of the drug for the chronotherapeutic drug delivery system.

CONCLUSION

FTIR spectrums indicates the Ramelteon API is compatibility with the proposed excipients in the formulation. XRD studies indicates the formulation is stable with formulation parameters and the process parameters.

The Core tablets prepared with different percentage of Eudragit polymers i.e., 5mg, 10mg and 15mg /Tablet produced a tablets. Whereas tablets fabricated with Eudragit RSPO 10mg/tablet and compression coating polymer with Ethyl cellulose: HPMC 70:30 produced a desired dissolution profile with a lag time of 2 hr and dissolution profile of 4 hr. Also this compression coating technique doesn't involve any solvents/ liquids during manufacturing process and which is also an easy to scale up to the industrial scale. Further there are various approaches in designing the chronotherapeutic drug delivery system in the treatment of circadian rhythm which needs to be explored to achieve a desired therapeutic response along with *in vivo* studies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Manjunath PN, Seth AK, Anand KR, Vivekanadan S. Approaches on chronotherapeutic drug delivery system and its impact on Circadian Rhythm. Int J Pharm Res. 2021;13(2).
2. Ballesta A, Innominato PF, Dallmann R, Rand DA, Lévi FA. Systems chronotherapeutics. Pharmacol Rev. 2017;69(2):161-99. doi: 10.1124/pr.116.013441, PMID 28351863.
3. Kumar RS, Radha GV, Deepthi KL, Sujitha P. An update on chronotherapeutic drug delivery systems. Indo Am J Pharm Res. 2015;5(09):2857.
4. Fan TY, Wei SL, Yan WW, Chen DB, Li J. An investigation of pulsatile release tablets with ethyl cellulose and Eudragit L as film coating materials and cross-linked polyvinyl pyrrolidone in the core tablets. J Control Release. 2001;77(3):245-51. doi: 10.1016/s0168-3659(01)00508-9, PMID 11733092.
5. Maroni A, Zema L, Del Curto MD, Loreti G, Gazzaniga A. Oral pulsatile delivery: Rationale and chronopharmaceutical formulations. Int J Pharm. 2010;398(1-2):1-8. doi: 10.1016/j.ijpharm.2010.07.026, PMID 20655998.
6. Manjunath PN, Seth AK, Anand KR, Satish CS. Designing the formulations in circadian rhythm activity with chronotherapeutic drug delivery system using ramelteon. IJHS. 2022;6;Suppl 3:2599-609. doi: 10.53730/ijhs.v6nS3.6139.
7. Available from: https://formulationdiary.com/Home/Details/RAMELTEON [cited 6/6/2022].
8. Fukui E, Uemura K, Kobayashi M. Studies on applicability of press-coated tablets using hydroxypropyl cellulose (HPC) in the outer shell for timed-release preparations. J Control Release. 2000;68(2):215-23. doi: 10.1016/s0168-3659(00)00261-3, PMID 10925130.
9. Watanabe Y, Mukai B, Kawamura K, Ishikawa T, Namiki M, Utoguchi N, *et al.* Preparation and evaluation of press-coated aminophylline tablet using crystalline cellulose and polyethylene glycol in the outer shell for timed-release dosage forms. Yakugaku Zasshi. 2002;122(2):157-62. doi: 10.1248/yakushi.122.157, PMID 11857956.
10. Lin SY, Li MJ, Lin KH. Hydrophilic excipients modulate the time lag of time-controlled disintegrating press-coated tablets. AAPS Pharm Sci Tech. 2004;5(4):e54. doi: 10.1208/pt050454, PMID 15760051.
11. Sungthongjeen S, Puttipipatkhachorn S, Paeratakul O, Dashevsky A, Bodmeier R. Development of pulsatile release tablets with swelling and rupturable layers. J Control Release. 2004;95(2):147-59. doi: 10.1016/j.jconrel.2003.10.023, PMID 14980764.
12. Gohel MC, Soni CD, Nagori SA, Sarvaiya KG. Modulation of venlafaxine hydrochloride release from press coated matrix tablet. Indian J Pharm Sci. 2008;70(3):292-7. doi: 10.4103/0250-474X.42974, PMID 20046735.
13. Bansal J. Circadian cycle and chronotherapy: Role in the treatment of various biological disorders. World Appl Sci J. 2014.ISSN 1818-4952;32(5):825-38.
14. Sunil SA, Srikanth MV, Rao NS, Uhumwangho MU, Latha K, Murthy KV. Chronotherapeutic drug delivery systems: An approach to circadian rhythms diseases. Curr Drug Deliv. 2011;8(6):622-33. doi: 10.2174/156720111797635559, PMID 21831038.
15. Neeharika MS, Jyothi BJ. Chronotherapeutics: An optimizing approach to synchronize drug delivery with circadian rhythm. Crit Rev. 2019;2(4):31-40.
16. Devdhawala Mehul G, Seth Avinash K. Current status of chronotherapeutic drug delivery system: An overview. J Chem Pharm Res. 2010;2(3):312-28.
17. Venkatesh GM, Stevens PJ, Lai JW. Development of orally disintegrating tablets comprising controlled-release multiparticulate beads. Drug Dev Ind Pharm. 2012;38(12):1428-40. doi: 10.3109/03639045.2011.653365, PMID 22356215.
18. Kulkarni, Mahandra Jaiswal, Jawale, Sathish V. Shirolkar, Kasture. Development and evaluation of press coated tablets for chronopharmaceutical drug delivery using gellable and permeable polymers. Scholars Research Library. 2010;2(4):482-97.
19. Vadlamudi HC, Prasanna RY, Rubia YB, Vulava J, Vandana KR. *In vitro* Characteristics of Modified Pulsincap Formulation with Mesalamine for Ulcerative Colitis Treatment. Indian Drugs. 2014;51(3):35-43. doi: 10.53879/id.51.03.p0035.
20. Seshasayana A, Sreenivasrao B, Prasannaraju Y, Narayan CPS, Ramanamurthy. K, Studies on release of rifampicin from modified pulsincap technique. Indian J Pharm Sci. 2001;63(4):337-9.
21. Kadam VD, Gattani SG. Formulation and evaluation of a pulsatile drug delivery system using time- and pH-dependant polymers. Pharm Dev Technol. 2010;15(1):57-63. doi: 10.3109/10837450902980254, PMID 19552544.
22. Raghavendra K, Koland M. An *in-vivo* Evaluation of Chronotherapeutical Drug Delivery System for the treatment of hypertension. Saudi J PharmSci. 2017;3(6B):643-7.
23. Qureshi J, Amir M, Ahuja A, Baboota S, Ali J. Chrono modulated drug delivery system of salbutamol sulphate for the treatment of nocturnal asthma. Indian J Pharm Sci. 2008;70(3):351-6. doi: 10.4103/0250-474X.43000, PMID 20046744.
24. Sangalli ME, Maroni A, Foppoli A, Zema L, Giordano F, Gazzaniga A. Different HPMC viscosity grades as coating agents for an oral time and/or site-controlled delivery system: A study on process parameters and *in vitro* performances. Eur J Pharm Sci. 2004;22(5):469-76. doi: 10.1016/j.ejps.2004.05.002, PMID 15265517.
25. Bandameedi Ramu, Shanmugan P. Chrono therapeutic drug delivery system. Drug metabolism and toxicology. J Drug Metab Toxicol. 2015;6:5.
26. Center for drug evaluation and research. Application number 21-782. Chemistry review (s). Applicant Takeda Global Research and Development Center;475 half day road Lincolnshire:IL60069.

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