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Original Article

FORMULATION AND *IN VITRO* EVALUATION OF RAMELTEON TABLETS FOR COLON DRUG DELIVERY SYSTEM BY COMPRESSION COATING

TRINADHA RAO M., PARIMALA Y.*, YAMINI M., PHANINDRA CVS, SRINIVASA RAO Y.

Department of Pharmaceutics, Vignan Institute of Pharmaceutical Technology, Duvvada, Visakhapatnam 530049, India
***Email: thrinadh_81@rediffmail.com**

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ABSTRACT

Objective: Ramelteon, is a sleep agent that selectively binds to the MT_1 and MT_2 receptors in the suprachiasmatic nucleus (SCN), instead of binding to $GABA_A$ receptors. In the present research work, the formulation of ramelteon targeted to colon by using various polymers developed.

Methods: Colon-targeted tablets were prepared in two steps. Initially, core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethylcellulose, Eudragit RLPO and L100 were used as enteric coating polymers. The precompression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to physical characterization, drug content, *in vitro* drug release and kinetics of drug release.

Results: Among all the formulations, F4 formulation was found to be optimized as it was retarded the drug release up to 18 h and showed maximum of 99.25% drug release. It followed the first-order kinetics mechanism. All the formulations having Korsmeyer-Peppas 'n' values are in the range of 0.540 to 0.818. Hence, it was concluded that the prepared formulations followed non-Fickian diffusion.

Conclusion: An effective and stable remelteon colon targeted formulation developed for treating insomnia.

Keywords: Ramelteon, Colon targeted drug delivery system, Ethylcellulose, Eudragit RLPO, Eudragit L 100

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INTRODUCTION

Now a days a novel oral colon-specific drug delivery system (CDDS) has been developed as one of the site-specific drug delivery systems. This delivery system, by means of the combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the gastrointestinal (GI) tract, but rapidly releases drug in the colon following oral administration. First, as for treating localized colonic diseases, i.e. ulcerative colitis, Crohn's disease and constipation etc., the optimal drug delivery system, such as CDDS, should selectively deliver drug to the colon, but not to the upper GI tract [1, 2]. Second, the colon is referred to as the optimal absorption site for protein and polypeptide after oral administration, because of the existence of relatively low proteolytic enzyme activities and quite long transit time in the colon. Finally, CDDS would be advantageous when a delay in absorption is desirable from a therapeutically point of view, as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythms, such as nocturnal asthma, angina and rheumatoid arthritis. There were currently a few strategies to achieve colonic specificity, such as use of pH sensitive polymers and pressure-controlled CDDS. The aim of this study was to explore the feasibility of the colonic microorganism to develop CDDS by using paracetamol as a model drug. Polysaccharides, the polymer of monosaccharides retains their integrity because they are resistant to the digestive action of gastrointestinal enzymes [3]. The matrices of polysaccharides are assumed to remain intact in the physiological environment of the stomach and small intestine, but once they reach in the colon, they are acted upon by the bacterial polysaccharides and results in the degradation of the matrices. A large number of polysaccharides such as amylose, guar gum, pectin, chitosan, inulin, cyclodextrins, chondroitin sulphate, dextrans, dextrin and locust bean gum have been investigated for their use in colon targeted drug delivery systems [4, 5]. The most important fact in the development of polysaccharide derivatives for colon targeted drug delivery is the selection of a suitable biodegradable polysaccharide. As these polysaccharides are usually soluble in water, they must be made water-insoluble by cross linking or hydrophobic derivatization, very important is an optimal proportional of the hydrophobic and hydrophilic parts, respectively and the number of free hydroxyl groups in the polymeric molecule. The present study includes the preparation of ramelteon colon targeted tablets by using compression coating technology.

MATERIALS AND METHODS

Materials

Ramelteon was obtained as gift sample from Dr. Reddys Laboratories, Hyderabad, Andhrapradesh.

Formulation of remelteon tablets

Ramelteon colon targeted tablets were prepared by using compression coating technology. Initially, internal core tablet containing drug and super disintegrate was formulated. For the prepared core tablet compression coating is done by using various compositions of polymers. Ethyl cellulose, Polymethacrylate polymers such as Eudragit RLPO and Eudragit S100 are used as polymers for compression coating [6, 7].

Formulation of core tablet

The core tablets are formulated by using 8 mg of the drug molecule, Cross carmellose sodium as super disintegrate, Micro crystalline cellulose as diluent, talc and magnesium stearate as Glidant and Lubricant, respectively. The composition of core tablet was given in below table 1.

Table 1: Composition of core tablet

Ingredient name	Quantity (mg)
Ramelteon	8
Cross carmellose sodium	32
Talc	3
Magnesium stearate	3
MCC pH102	34
Total weight	80

Total weight of the core tablet was fixed as 80 mg. The tablets are prepared by using 6 mm flat punch. Then the prepared core tablets are subjected to compression coating by using various compositions of polymers.

Formulation of compression coated tablets

The prepared core tablets were subjected to compression coating by using various compositions of polymers such as Ethylcellulose, Eudragit L 100 and Eudragit S 100 as coating materials [8, 9]. The composition of coating layer is given in below table 2.

Table 2: Composition of the coating layer

Ingredient name	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ethyl cellulose (mg)	40	80	----	----	----	----	40	----	40
Eudragit RLPO (mg)	----	----	40	80	----	----	40	40	----
Eudragit L 100 (mg)	----	----	----	----	40	80	----	40	40
Magnesium stearate (mg)	3	3	3	3	3	3	3	3	3
Talc (mg)	3	3	3	3	3	3	3	3	3
MCC pH 102 (mg)	174	134	174	134	174	134	174	134	174
Total weight	220	220	220	220	220	220	220	220	220

Compression coating layer was divided into two equal portions i.e., 110 mg of each quantity. Half of the quantity of powder blend was placed in the die cavity, core tablet was placed exactly in the middle of die cavity and then remaining quantity of powder blend was placed over the core tablet so that the powder blend should cover all the sides and top side of core tablet uniformly. Then the tablets are compressed by using 9 mm flat-surfaced punch using 8 station tablet punching machine with the hardness of 4-4.5 kg/cm^2. Then the prepared compression coated tablets are evaluated for various post-compression parameters as per standard specifications.

Physical characterization of fabricated tablets

Hardness

The hardness of the tablet was determined by using a Monsanto hardness tester and expressed in kg/cm^2 [10, 11].

Uniformity of thickness

The thickness of the three tablets was measured using Vernier calipers. The extent to which the thickness of each tablet deviates from±5% of the standard value was determined.

Friability

Percentage friability is calculated by given formulae that tells how much resistant to abrasion during manufacturing and packaging.

$$\% \text{ Friability} = \frac{(W1-W2)}{W1} x100$$

W_1=Weight of tablets before test, W_2=Weight of tablets after the test.

Weight variation

Individual weights of 20 tablets were taken and the average weight was calculated by using the following formula and variation should not be more than 5 %.

$$\text{Weight variation} = \frac{\text{Weight of tablet} - \text{Average weight}}{\text{Average weight of tablets}} x100$$

Determination of drug content

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Ramelteon were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV–Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**

Drug release studies of ramelteon core tablets

The core tablets containing 8 mg Ramelteon of were tested in (pH 6.8), for their dissolution rates. Dissolution studies were performed using USP paddle-type sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at respective 256 nm [12, 13].

Drug release studies of compression coated ramelteon tablets

The release of ramelteon from coated tablets was carried out using USP paddle-type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the first 2 h as the average gastric emptying time is about 2 h. Then, the dissolution medium was replaced with enzyme-free simulated intestinal fluid (SIF, pH 7.4) and tested for drug release for 3 h, as the average small intestinal transit time is about 3 h, and finally, enzyme-free simulated intestinal fluid (SIF, pH 6.8) was used up to 18 h to mimic colonic pH conditions.

Drug release was measured from compression coated Ramelteon tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with the fresh medium; samples were withdrawn at various time intervals were analyzed spectrophotometrically at 254 nm, 256 nm and 257 nm, respectively. All dissolution runs were performed for six batches. The results were given with deviation [14, 15].

Kinetics of *in vitro* drug release

In vitro release data is applied to all the formulations (F1-F12) as per the given table 3 by using the equation and find the release mechanism.

Table 3: Kinetics of drug release

Type	Equation	Parameter
Zero order	$Q_t = Q_0 + K_0 t$	Cumulative percentage drug release vs. Time in hours
First order	$Q_t = Q_0 e^{-Kt}$	Log cumulative percentage remained vs. Time in hours
Higuchi	$Q = K_h t^{1/2}$	Cumulative percentage drug release vs. Square root of time
Korsmeyer peppas	$F = (Q_t/Q) = K_m t^n$	Log cumulative percentage of drug release vs. Log time

Qt= Cumulative amount of drug release at time "t". Q0=Initial amount of drug release, Q=Total amount of drug release in dosage forms, N= Diffusion of release exponent, T= Time in hours, K_0, K, K_h, K_m are release rate constants of Zero, First, Higuchi, Korsmeyer peppas

RESULTS AND DISCUSSION

Determination of absorption maxima

A solution of containing the concentration 10 µg/ml was prepared in 0.1N HCl, 7.4 pH and phosphate buffer 6.8pH respectively, UV spectrum was taken using a Double beam UV/VIS

spectrophotometer. The solution was scanned in the range of 200–400.

Preparation calibration curve

10 mg of drug was accurately weighed and dissolved in 10 ml of 0.1N HCl, 7.4 PH, and 6.8 PH in 10 ml volumetric flask, to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution (2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then final concentrations were prepared 2, 4,6, 8, 10, with 0.1N HCl, 0.5, 1, 1.5 and 2 7.4 pH, and 1,2,3,4 and 5 with 6.8 pH. The absorbance of standard solution was determined using UV/VIS spectrophotometer at 254 nm, 256 nm and 257 nm. Linearity of the standard curve was assessed from the square of correlation coefficient (r2), which was determined by least-squares linear regression analysis. The graph plotted concentration vs. Absorbance [16, 17].

Fourier transforms infrared spectroscopy

Preformulation studies

Preformulation studies can be defined as investigations of physical and chemical properties of a new drug substance; either of the pure substance or of its combinations with other excipients. It is a phase of the research and development process that is required to develop stable, safe and effective dosage forms. These are also used for the determination of suitable excipients for the formulation of dosage forms.

Drug-excipient compatibility study

Drug excipient compatibility studies carried out by FTIR spectroscopy. The FTIR of pure drug and physical mixture of drug and excipient were studied. From FTIR, there was no significant change in the peaks of pure drug and excipient mixture [18]. Therefore it can be inferred that there was no specific interaction observed between the drug and the excipient, as shown in fig. 2

Physical characterization of coated tablets

All the formulations were prepared according to the formula given in table 1. The prepared tablets were evaluated for various physical properties as indicated in table 4. The results of evaluation studies can be summarized as follows:

The thickness of the formulations was found to be in the range of 4.40±0.5 mm to 4.9±0.5 mm. the crushing strength of tablets is found to be 4.1 to 4.5 kg/cm2. The loss in total weight of the tablets that is friability is less than 1%. Weight variation was found to be in the range of 1.18 to 1.65%. this shows that all the parameters are within limits and having good compressibility. Drug content is found to be 98.45 % to 99.89% for all the formulation and having within limits.

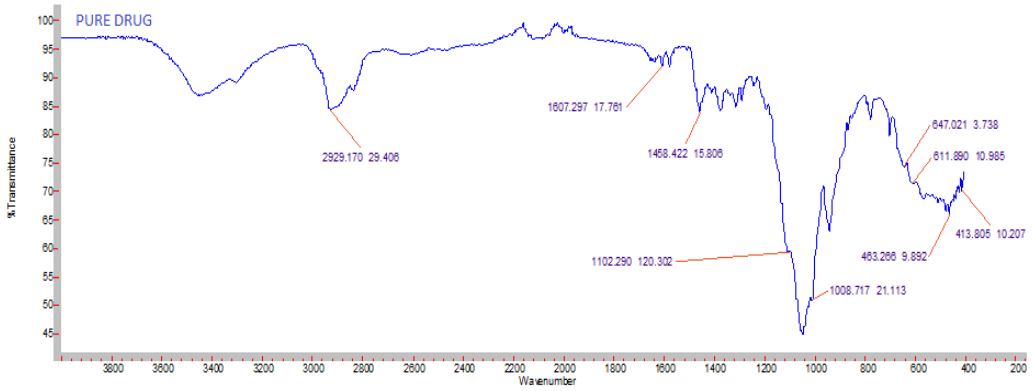

Fig. 1: FTIR spectrum of pure drug

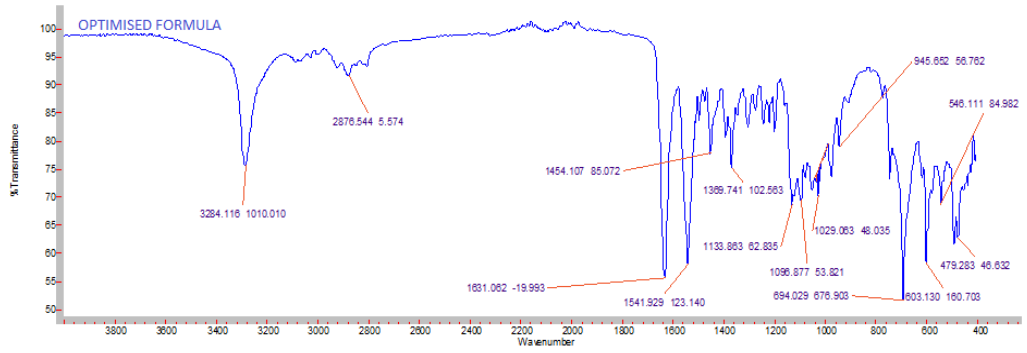

Fig. 2: FTIR spectrum of optimized formulation

Table 4: *In vitro* quality control parameters for compression coated tablets

Formulation codes	Weight* variation (mg)	Hardness* (kg/cm2)	Friability* (%loss)	Thickness (mm)	Drug content* (%)
F1	303.1±2.03	4.5±0.26	0.51±0.11	4.8	99.77±0.58
F2	304.2±3.04	4.2±0.19	0.53±0.19	4.9	99.47±0.61
F3	299.1±2.98	4.4±023	0.52±0.15	4.9	99.35±0.78
F4	309.3±3.47	4.5±0.17	0.56±0.17	4.9	99.89±0.45
F5	310.3±2.87	4.4±0.24	0.57±0.16	4.7	99.15±0.54
F6	311.5±1.99	4.2±0.31	0.46±0.11	4.5	98.57±0.49
F7	303.4±3.75	4.1±0.17	0.53±0.19	4.4	98.45±0.48
F8	304.6±4.12	4.3±0.19	0.48±0.18	4.7	99.66±0.51

F9	299.4±3.75	4.5±0.21	0.56±0.19	4.6	99.15±0.61

*mean±SD(n=3)

***In vitro* drug release of tablets**

Table 5: *In vitro* drug release profile for coated formulations (F1-F9)

Time (h)	F1*	F2*	F3*	F4*	F5*	F6*	F7*	F8*	F9*
0.5	4.76±0.65	5.98±0.50	6.89±0.15	7.58±0.15	3.89±0.36	4.98±0.10	6.85±0.44	7.65±0.57	4.25±0.55
1	10.55±0.51	11.55±0.32	15.66±0.31	16.98±0.78	12.55±0.26	12.55±0.56	14.82±0.38	10.76±0.55	8.95±0.67
2	10.47±0.21	17.48±0.15	22.69±0.15	25.23±1.32	19.77±0.32	22.57±0.61	21.03±0.61	18.19±0.66	14.3±0.50
3	30.68±0.32	25.44±0.56	35.63±0.50	33.64±0.55	26.76±0.21	30.86±0.46	28.6±0.84	20.98±0.56	19.88±0.60
4	43.75±0.61	36.55±0.61	48.87±0.59	34.39±0.79	32.85±0.66	36.28±1.21	33.35±0.72	23.65±0.90	24.89±0.82
5	49.79±0.82	38.62±0.76	52.45±0.56	45.85±0.67	38.75±0.76	38.12±0.55	45.26±0.38	27.05±0.59	28.18±0.55
6	50.06±0.93	42.29±0.61	54.98±0.31	46.54±0.70	43.38±0.45	45.99±0.21	46.27±0.85	36.48±0.35	35.67±0.59
7	55.65±0.15	46.72±0.55	57.72±1.11	56.77±0.61	45.23±0.70	48.37±0.71	54.25±0.72	42.68±0.70	45.35±0.75
8	58.39±0.40	53.57±1.05	59.93±0.61	59.48±0.40	50.55±0.66	55.85±0.55	60.93±0.46	49.19±0.44	48.93±0.90
9	67.98±0.67	58.85±0.68	65.53±1.80	62.75±0.55	57.28±0.75	57.93±0.90	65.33±0.93	55.82±0.21	52.08±0.90
10	68.79±0.81	65.45±0.67	67.56±0.72	65.18±0.86	63.49±0.95	59.35±0.81	66.09±0.71	59.89±0.80	58.15±0.78
11	70.35±0.52	70.89±1.00	72.83±0.44	70.57±0.72	67.76±0.68	69.78±0.84	69.37±0.70	65.55±0.40	63.65±0.82
12	73.36±0.85	72.35±0.78	75.48±0.78	74.38±0.26	79.66±0.65	73.75±0.75	70.45±0.66	69.45±0.60	65.09±0.57
13	77.57±0.78	76.36±0.61	77.15±0.55	79.97±0.55	83.76±0.59	76.45±0.57	73.26±0.93	72.85±0.92	69.71±0.75
14	81.64±0.44	82.69±0.70	82.36±0.87	85.28±0.68	85.18±0.26	78.57±0.38	77.25±0.62	78.98±0.57	73.38±0.95
15	84.55±0.47	85.93±0.61	84.78±0.78	90.96±0.31	88.67±0.56	82.18±1.81	80.8±0.55	84.53±0.66	76.45±0.75
16	86.69±0.32	86.32±0.78	87.99±0.55	93.55±0.32	90.32±1.05	85.36±1.39	85.36±0.87	85.75±0.66	80.27±0.60
17	88.89±0.61	89.87±0.70	89.43±1.25	95.18±1.25	91.86±0.40	87.13±0.68	87.85±0.32	88.74±0.55	82.89±0.81
18	90.16±0.92	90.98±1.06	93.19±0.56	99.25±0.66	90.98±0.66	90.18±0.76	89.26±0.74	89.05±0.46	85.99±0.95

*mean±SD(n=3)

Table 6: Release kinetics data of ramelteon

Formulation	Zero Order (R2)	First Order (R2)	Higuchi (R2)	Korsmeyer-Peppas	
				(R2)	n
F1	0.917	0.988	0.975	16.117	0.6127
F2	0.975	0.974	0.981	12.48	0.703
F3	0.925	0.971	0.988	19.72	0.54
F4	0.978	0.851	0.986	15.37	0.645
F5	0.973	0.956	0.97	11.744	0.735
F6	0.969	0.978	0.987	14.11	0.649
F7	0.950	0.982	0.989	15.91	0.605
F8	0.987	0.96	0.956	8.86	0.818
F9	0.984	0.981	0.987	9.05	0.789

Kinetics of drug release

Kinetics of *in vitro* drug release

In vitro release data obtained is applied to all the formulations (F1-F9) as per the table 2. The kinetic profiles of all formulations were shown in table 6. The correlation coefficient (r) values in the analysis of release data as per various models are given table 6. Analysis of the release data as per zero order and first-order kinetic models indicated that the drug release from matrix tablets followed first-order kinetics. All the formulations followed first order kinetics. This implies that the drug release is dependent on one of the concentrations. The correlation coefficient (r) values were higher in first order model when compared to zero-order models. The r-values were also higher in the Higuchi and Peppas equation models indicating that the drug release from the ramelteon tablets also obeyed these two models. When the release date are analyzed as per Peppas equation, the release exponent '*n*' is an empirical parameter characterizing the release mechanism [19, 20]. Mechanism of drug release may be determined based on the values of the diffusion exponent, if the value of n is 0.5 it indicates that the drug release mechanism is explained by a Fickian diffusion-controlled release, whereas if *n* equal to 1.0, it indicates that the drug release mechanism approaches to zero order release. If *n* value is from 0.5 to 1, it implies that the release mechanism is non-Fickian diffusion or chain relaxation control release. The n value of the formulations was in the range of 0.540 to 0.818.

Hence, it was concluded that the prepared formulations followed non-Fickian diffusion. The drug release from all the batches followed by non-ficikian diffusion mechanism as Higuchi's fit shows high correlation coefficient values [21]. Among all the formulations F4 formulation was found to be optimized as it was retarded the drug release up to 18 h and showed maximum of 99.25% drug release.

CONCLUSION

In the present research work formulation of ramelteon targeted to colon was prepared by using various polymers. Colon-targeted tablets were prepared in two steps. Initially, core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethylcellulose, Eudragit L100 and Eudragit RLPO were used as enteric coating polymers. The pre-compression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests. Among all the formulations, F4 formulation was found to be optimized as it was retarded the drug release up to 18 h and showed maximum of 99.25% drug release. It followed the first order kinetics mechanism.

CONFLICT OF INTERESTS

The authors declare that they do not have any financial and personal relationships with other people or organisation that could in appropriately influence their work.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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