Current Trends in Biotechnology and Pharmacy
Vol. 19(2) 2294-2302, April 2025, ISSN 0973-8916 (Print), 2230-7303 (Online)
DOI: 10.5530/ctbp.2025.2.16

Formulation Development and Characterization of Ritonavir Loaded Controlled Release Matrix Tablet

Sujit Shinde[1], Gita Chaurasia[2*]

[1, 2] Department of Pharmaceutics, Siddhant College of Pharmacy, Sudumbare, Pune, Maharashtra-412109, India

***Corresponding Author**: gitagc19@gmail.com

Abstract

The aim of this study was to design Ritonavir loaded controlled-release matrix tablet (CRMT) for the treatment against Human immunodeficiency virus, with an emphasis on the drug's pharmacokinetic and physicochemical characteristics for enhanced therapeutic efficacy and decreased gastrointestinal side effects. The tablet was prepared by using rate-controlling polymers like Hydroxy-propyl methyl cellulose (HPMC) K4M and xanthan gum by direct compression method. Formulation batches F1-F9 were developed, optimized using 3^2 full factorial design and evaluated for pre and post compressional studies. Drug-excipients studies were performed by IR spectra and DSC thermogram. All batches of powder blends were evaluated for particle size, angle of repose, bulk density, tapped density, % Compressibility index and Hausner's ratio. The prepared tablets were characterized for Weight variation, Hardness, Thickness, Friability, % Drug content, % Swelling index and *In-vitro* cumulative drug release study up to12h. Analysis of variance was used to handle acquired data for statistical analysis. In conclusion, maximum drug release 96.29% and swelling index 81.29±0.09%, was observed in F9, after 12 h of studies and found stable under short term stability study as per ICH guideline. The article developed a potential scope in reducing the dose-dependent gastrointestinal toxicity of ritonavir with fewer side effect and a hope in future.

Keywords: Ritonavir, Matrix tablet, Hydroxy-propyl methyl cellulose, Controlled release tablet, Human immunodeficiency virus protease

Introduction

Tablet is the preferred way to provide medications orally, which have advantages including precise dosing, ease of use, patient compliance, cost effective, and extended shelf life (1). Present work aimed development of controlled release tablet to reduce dose-dependent adverse effects and optimize therapeutic benefits. In comparison to traditional delivery systems, matrix-controlled release has shown benefits include longer drug half-lives and enhanced effectiveness, lower toxicity, and better patient comfort. Drug release from a porous monolithic matrix involves the simultaneous penetration of surrounding liquid, dissolution of drug and leaching out of the drug through tortuous interstitial channels and pores (2). Ritonavir, is a Protease inhibitor, inhibits cytochrome P450-3A4 and used to treat HIV/AIDS was selected as suitable candidate for the present work due to suitable biological half- life of ~3-5 h. Literature revealed that the high inter-individual variability in pharmacokinetics was reported with greater than six-fold variability in through concentrations among patients given 600 mg ritonavir every 12 h (3). An approach of developing CRMT of ritonavir to reduce its daily dose frequency and gastrointestinal side effects in

higher dose. For this 300 mg tablet was aimed to develop by direct compression method. The release rate of drug was controlled by using optimized concentration of natural polymers HPMC K4M and xanthan gum by diffusion or dissolution method. Hydrophilic polymer matrix system is widely used for designing oral controlled release delivery systems for long duration towards site of action, because of their flexibility to provide a desirable drug release profile, cost effectiveness, and a broad regulatory acceptance (4,5).

Materials and Methods

Ritonavir was received as a gift sample from Cipla Pt. Ltd. Goa. Xanthan gum, Avicel PH 101, Talc, Magnesium stearate, HPMC K4M were obtained as gift samples by blue cross laboratory, Nashik. The analytical grade chemicals and all other reagents used for the assessment were provided by Research-Lab Fine Chem Mumbai. Freshly prepared distilled water is used throughout the work.

Preformulation study

Physical characteristics

The drug ritonavir was studied visually for organoleptic characteristics such as colour, Odor and appearance. Melting point of drug was determined by glass capillary method whose one end was sealed and kept in melting point apparatus.

Determination of solubility

Accurately weight 5 mg ritonavir was added to 10 ml of different solvents like Distilled water, Methanol, Ethanol, Dimethyl formamide, Di methyl-sulfoxide, Phosphate buffer (PB) (pH 6.8, 7.4 and 7.8) solution in the 10 ml volumetric flask and kept aside for 24 h. After 24 h solutions were diluted suitably and filtered through Whatman filter paper. The drug content was analysed by UV spectrophotometric method in triplicate using equation as follows-

Solubility (mg/ml) = Initial - Final concentration of drug

Loss on drying (LOD)

Weighed1gm of the drug in weighing bottle and kept in the hot air oven at 105^0 C for 2 h and after allowed it to cool. Weighed the contents and the bottle and %LOD was calculated (n=3) as follows-

$$\% \text{ LOD} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} X\ 100$$

Identification of drug

The drug was identified by IR spectra and Differential scanning calorimetry (DSC) methods. Potassium bromide pellet technique was used in the Shimadzu instrument at frequency range of 500-4000 cm^{-1} with scanning speed of 4.0 cm-1 and the graph was recorded. For DSC (STAR*SW 12.10 instrument), a weighted sample was placed in a crucible and thermogram was recorded at scanning rate of 10ºC per min and at 40-150°C.

Quantitative estimation of drug

The UV was used for estimation of the drug by UV-2400 PC series, Shimadzu, Japan, in the present study. The drug concentration was estimated (n=3), in the range 10-50µg/ml in PB pH 7.4 and ethanol mixture (10:1) [PBE mixture]. All aliquots were scanned from 200-400 nm to obtain the value of maximum wavelength and calibration curve was prepared (6).

Drug–excipients compatibility study

Physical mixture of drug and polymers (HPMC K4M and Xanthan gum) was prepared by kneading method in 1:1 molar ratio. All sample was stored and analysed by FTIR and DSC method.

Formulation and development of CRMT

Optimization of polymer concentration by 3^2 full factorial Design

For the present work 3^2 full factorial design selected over 2 factors were evaluated at three possible level (-1, 0, 1) using release retardant polymers HPMC K4M (X_1) in concentration 20, 30, 40 mg and Xanthan gum (X_2) in concentration 30, 40, 50 mg as independent

variable, in 9 batches and % Swelling index (Y) was studied for each as dependant variable up to 12 h (7).

Precompression studies

All batches of polymer were mixed with another excipient to develop CR matrix powder blend and analyzed for different parameters.

Mean particle size determination

Mean vesicle size of prepared formulations F1-F9 was observed by a calibrated electron optical microscope Olympus, India (8). Dilute suspension of all formulation was prepared separately and one drop from each sample was spread on slide; a cover slip was placed over it and observed. The arithmetic mean was determined by following equations. Where, n is the total number of particles counted and d is projected diameter.

$$Arithmetic\ mean = \sum nd / \sum n$$

Bulk and Tapped density

All formulation F1-F9 was evaluated for Bulk density by placing the powder blend in a measuring cylinder of bulk density apparatus and Tapped density was calculated by three tap method and calculated by using the formula (n=3) and reported.

$$\text{Bulk density} = \frac{\text{(Total weight of powder/granules)}}{\text{(total volume of powder/granules)}}$$

$$\text{Tapped density} = \frac{\text{(Total weight of powder/granules)}}{\text{(Tapped volume of powder/granules)}}$$

Compressibility index (CI) and Hausner's ratio

CI was determined by placing the powder formulation F1-F9 each in a measuring cylinder and the volume (V_0) was noted before tapping. After compression again volume (V) was noticed and calculated by follows below equations. Hausner's is the ratio of tapped density to bulk density.

$$CI = \frac{(1-V)}{V0} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{(Tapped density)}}{\text{(Bulk density)}}$$

Angle of repose (θ)

Powder of each formulation F1-F9 was placed in the funnel separately and allowed to flow freely. With the help of vernier callipers the height and radius of the heap were measured and noted in triplicate reading and calculated by formula as follows-

$\tan \theta = h / r$, Where h = height of heap, r = radius of heap

Method of preparation of CRMT

All the ingredients of F1-F9 were weighed accurately and passed through sieve no. 120 and blended thoroughly to obtain uniform mixing and tablets were prepared by direct compression method (9). The machine was adjusted to produce an approximate weight of 300 mg tablet and stored for further study in Table 1.

Evaluation of prepared CRMT

weight variation

Twenty tablets were taken from each formulation and weighed individually. Average weight was calculated as per I.P. (n=3).

Thickness test

Prepared tablets were evaluated for their thickness using a Bernier calliper in millimetre. Average of three readings were taken and the results were tabulated (n = 3).

Hardness test

All formulations CR tablets were evaluated for their hardness using Pfizer hardness tester as per I.P. Average of three reading were taken and tabulated (n = 3).

Friability test

Twenty tablets of each batch were weighed initially (W1) and put it into friability test apparatus by keeping rotation speed of 25 rpm for 4 minutes. Then weighed again after 4 minutes (W2) and % friability has been calculated in triplicate as follows (10)-

$$\%\ \text{friability} = \frac{(W1-W2)}{W1} \times 100$$

Drug content

From each formulation three random-

ly selected tablets were weighed accurately and powdered equivalent to 10 mg of drug. Dissolved by shaking and diluted suitably using PBE mixture into 10 ml volumetric flask. Then, filtered and analysed by UV method against PBE as blank. Averages of triplicate readings were taken and calculated (11).

Percentage swelling index

Three tablets from each formulation were weighed individually (W_1) and immersed in a Petri dish containing PB pH 7.4 for predetermined times (15min, 30min,1h, 2h, up to 12h). After immersion tablets were wiped off the excess surface water and weighed after hydration (W_2). The % swelling index was calculated in triplicate (12).

$$\% \text{ Swelling Index} = \frac{(W2-W1)}{W2} \times 100$$

In-vitro % cumulative drug release study

The drug release profile was studied for each formulation using USP dissolution testing apparatus II using a paddle at 50 rpm with 900 ml PB pH 7.4 at 37±0.5°C. Aliquots of 10 ml were withdrawn at 15 min, 30 min, 1h, 2h, up to 12h respectively and the same volume was replaced with PB pH 7.4. The drug content was analysed by spectrophotometrically. The % cumulative drug release was calculated using calibration curve at 239nm (n=3). The data were studies for different kinetic models (13, 14, 15).

Physical stability study

A protocol of stability study was carried out on optimized formulation for short term stability study conditions at refrigeration temperature (4±2)ºC, room temperature (25±2)ºC and 40ºC, 75% RH as per ICH guidelines for a period of 3 months. After every month time interval physical appearance and residual drug content was determined and reported in triplicate (16).

Results and Discussion

Preformulation studies showed that ritonavir is the off whitish amorphous, odourless, bitter metallic taste powder and has average melting point of 127^{0}C. The drug is found soluble in ethanol, Dimethyl formamide, Di methyl-sulfoxide, insoluble in distilled water and sparingly soluble in buffer solutions. The observed % Loss on drying for drug was 0.02 % w/w within the I.P. limit. Drug showed maximum absorbance at 239nm in PBE mixture in concentration range of 10-50µg/ml, r^2 =0.9998 and Slope y = 0.0162x, that followed Beer-Lambert's law shown in Figure 1.

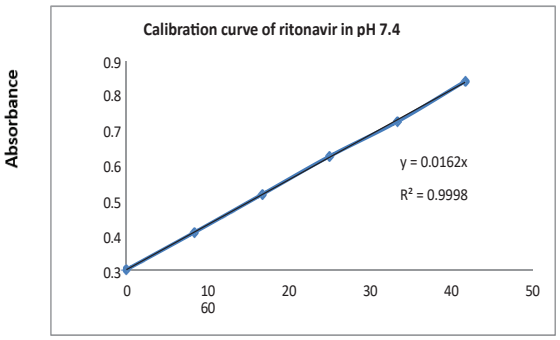

Figure 1: Calibration curve of Ritonavir

Identification and drug–excipients compatibility study (1:1Molar) was carried out by IR and DSC methods. As a result, drug was found no significant interactions with natural polymers used under study. The IR study showed absorption frequencies (cm^{-1}) of common peaks includes; N-H stretching of amines at 3357.3, O-H stretching of aliphatic primary amines at 3330.91, C-H stretching of alkene (3098.88), C-H stretching of alkane (2964.47), C=O stretching of unsaturated ester (1714.67), C=C stretching of conjugated alkane (1620), N-O stretching of nitro compound (1523.57), C-O stretching of alkyl aryl ester (1235.59), C=C bending of alkene (703.20) (17). The DSC thermogram of drug and its physical mixture with selected polymers exhibited little or no change in enthalpy value and found compatible with excipients. For preparing powder blends of selected polymers optimization of different concentration was done by 3^2 full factorial design in nine batches and % swelling index were calculated and reported (n=3) as shown in Table 1.

Table 1: Optimization by 3^2 full factorial design

Batch	HPMC K4 M (X_1)	Xanthan Gum (X_2)	% Swelling index (Y) (mean±SD)
1	20 (-1)	30 (-1)	48.31±0.37
2	20 (-1)	40 (0)	56.82±0.91
3	20 (-1)	50 (1)	71.54±0.10
4	30 (0)	30 (-1)	51.74±0.22
5	30 (0)	40 (0)	63.28±0.54
6	30 (0)	50 (1)	77.65±0.77
7	40 (1)	30 (-1)	54.36±0.36
8	40 (1)	40 (0)	68.34±0.06
9	40 (1)	50 (1)	81.29±0.09

All 9 batches were evaluated and as a result second order polynomial equation was derived from equation $y = b_o+b_1+x_1+b_2x_2+b_3x_1^2 +b_4x_2^2 +b_5\ x_1x^2$, where y is the response (% Swelling index at 2 h). The average results of changing one variable at a time from its low to high value showed by main effect (x_1, x_2) and interaction (x_1x_2) showed the response changes with combined effect of variables. The coefficients corresponding to linear effects (b_1, b_2), interaction (b_5) and quadrate effect (b_3, b_4) were determined from the results of the study. The fitted equation for response was: $Y = [6.1–5.98 \times 10^{-2}\ x_1–2.03\ x_2 \times 10^{-1} + 1.83x_1^2 + 3.45 \times 10^{-2}\ x_2^2 – 1.67\ x_1x_2] \times 10^{-2}$, where values of b_o, b_1, b_2, b_3, b_4 and b_5 were 0.05214, -0.00065, -0.00429, 0.00176, 0.00951and -0.01287 respectively. Before compression powder bed of all formulations were studied for various rheological characteristics like Particle size, bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose shown in Table 2. The results of the studies indicated that the powder bed is easily compressible, and hence can be compressed into a compact mass of tablet.

Table 2: Pre-compressional studies

Formulation code	Mean Particle size (µm, Mean±SD)	Angle of repose(θ) (Mean± SD)	Bulk density (gm/cm^3) (Mean± SD)	Tapped density ($gm/cm,^3$ Mean± SD)	Compressibility index (%) (Mean± SD)	Hausner's ratio (Mean± SD)
F1	98.3±0.12	24.23±0.61	0.31±0.27	0.46±0.42	15.62±0.50	1.20±0.04
F2	102.1±0.36	31.52±0.32	0.38±0.04	0.42±0.65	15.90±0.42	1.35±0.46
F3	108.2±0.53	27.17±0.27	0.34±0.90	0.44±0.12	18.62±0.97	1.71±0.95
F4	96.4±0.31	28.76±0.38	0.37±0.12	0.43±0.08	13.83±0.32	1.15±0.74
F5	106.7±0.22	27.72±0.97	0.34±0.95	0.49±0.32	15.48±0.70	1.26±0.61
F6	104.8±0.13	28.56±0.41	0.40±0.71	0.47±0.09	13.79±0.93	1.39±0.81
F7	94.5±0.64	28.39±0.93	0.39±0.73	0.46±0.18	14.65±0.58	1.20±0.08
F8	103.9±0.54	27.41±0.96	0.35±0.15	0.41±0.34	19.45±0.22	1.23±0.41
F9	97.6±0.09	28.57±0.88	0.37±0.43	0.44±0.94	15.12±0.73	1.14±0.46

Evaluated powder blend of each formulation were directly compressed on 10 station rotary pilot press punching machine to obtained maintenance dose of 300mg as per

the composition shown in Table 3. The formulated CRMT F1-F9 were evaluated for different parameters. The observed values for weight variation (297±0.29 to 303±0.52 mg), Thickness (4.27±0.92 to 4.39±0.55mm), hardness (3.64±0.18 to 4.69±0.23 kg/cm^2), % Friability (0.27±0.68 to 0.35±0.46), and % Drug content (85.42±0.81 to 95.18±0.52) was found. The % swelling index is the water uptake nature of the polymer properties that affect the onset of swelling. Study was carried out for all formulations F1-F9 tablet for a period for 12 h. It was observed that swelling has been increases with increase in amount of HPMC K4M and xanthan gum. Maximum swelling was attained at 12 h. The following order of swelling was ascertained F9 >F6 >F3 >F8 >F5 >F2 >F7 >F4 >F1 resulted in Table 4.

Table 3: Composition of formulation

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ritonavir	100	100	100	100	100	100	100	100	100
HPMC K4M	20	20	20	30	30	30	40	40	40
Xanthan Gum	30	40	50	30	40	50	30	40	50
Avicel PH 101	144	131	124	137	124	114	124	114	104
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Total	300	300	300	300	300	300	300	300	300

Table 4: Evaluation of prepared Tablets

Formulation code	Hardness (kg/cm^2) (Mean± SD)	Thickness (mm) (Mean± SD)	Friability % (Mean± SD)	Weight variation (mg) (Mean± SD)	%Drug content (Mean± SD)	% Swelling Index up to 12 h (Mean± SD)
F1	4.42±0.55	4.32±0.23	0.32±0.12	302±0.62	89.29±0.47	48.31±0.37
F2	4.69±0.23	4.28±0.76	0.29±0.52	298±0.14	93.61±0.56	56.82±0.91
F3	4.79±0.09	4.36±0.14	0.35±0.46	302±0.55	88.52±0.19	71.54±0.10
F4	3.94±0.43	4.39±0.55	0.31±0.38	302±0.67	90.06±0.36	51.74±0.22
F5	4.10±0.92	4.27±0.92	0.29±0.47	297±0.29	91.65±0.72	63.28±0.54
F6	3.78±0.87	4.36±0.09	0.28±0.11	298±0.81	87.22±0.41	77.65±0.77
F7	4.38±0.45	4.33±0.18	0.31±0.09	298±0.49	92.19±0.93	54.36±0.36
F8	4.41±0.29	4.29±0.79	0.29±0.17	303±0.52	85.42±0.81	68.34±0.06
F9	3.64±0.18	4.31±0.98	0.27±0.68	301±0.78	95.18±0.52	81.29±0.09

In vitro % cumulative drug release was studied in F1-F9 using USP dissolution apparatus II (using paddle) under suitable maintained conditions for a period of 12 h. Content of drug was analysed at 239nm by UV method. The obtained data were computed graphically (Graph A). The different kinetic models were studied and observed that data were fitted to linearity in zero order (r^2 = ≥ 0.995), first order (r^2 = ≥ 0.867) and Higuchi model (r^2 = ≥ 0.674) showed in graph B, C and D. Graph E represents Korsemeyer's Peppas released curves (r^2 = ≥ 0.90) for all formulations and n value was found to be ≥ 0.5 which indicate that indicates anomalous or non-fickian diffusion shown in Figure 2. The drug release occurs probably by diffusion, ero-

sion and dissolution methods through polymers. On the basis of all studied evaluation parameters F9 was selected as optimized formulation due to maximum drug release in controlled manner up to 12h, high swelling index. Stability study was carried out on chosen formulation F9. It was observed that no interaction and physical change reported and no significant decrease in residual drug content for a period of 3 months under short term stability study shown in Figure 3.

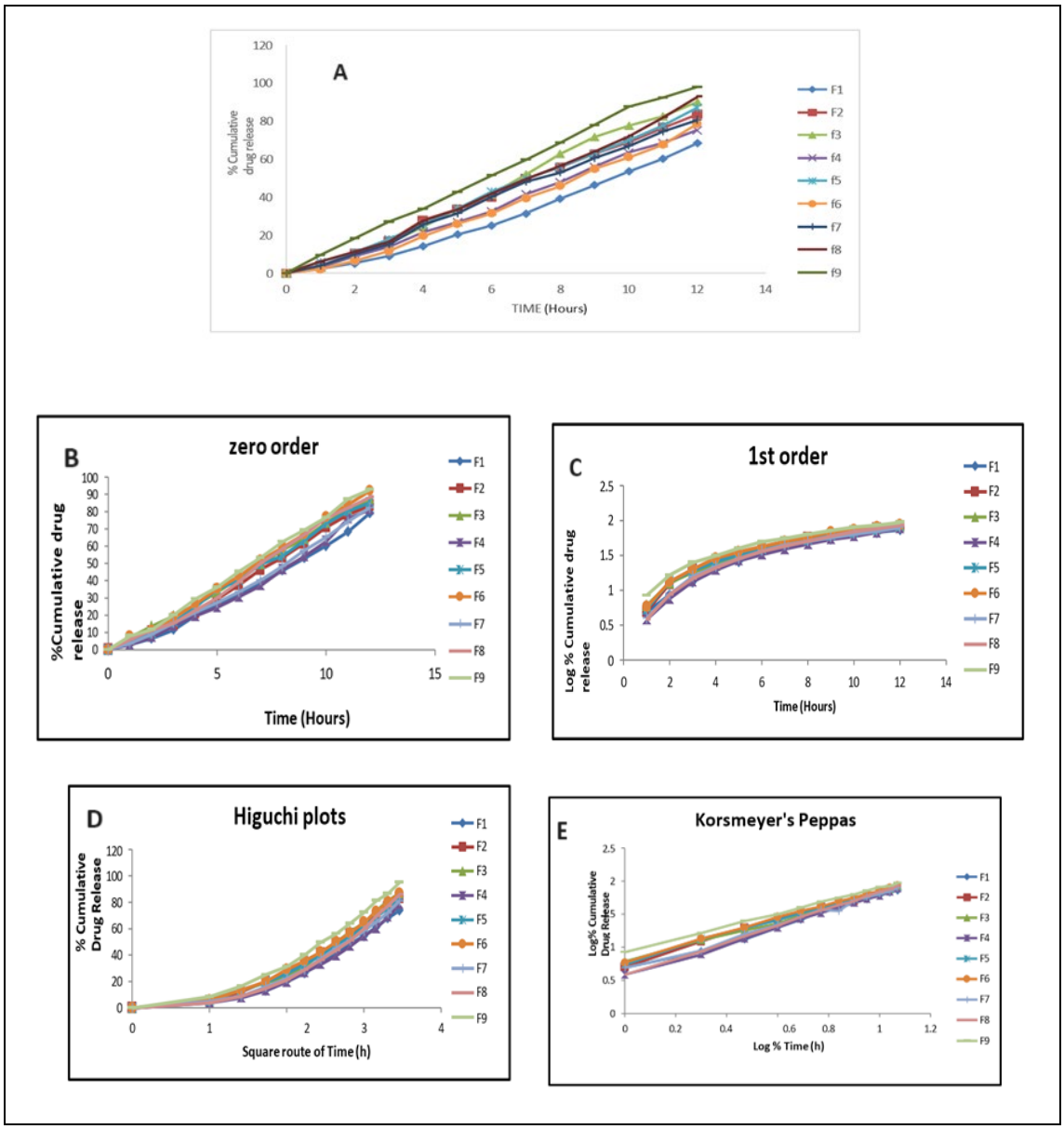

Figure 2: *In Vitro* % cumulative drug release (A) and Kinetic studies of cumulative drug release (B, C, D, E) from F1-F9

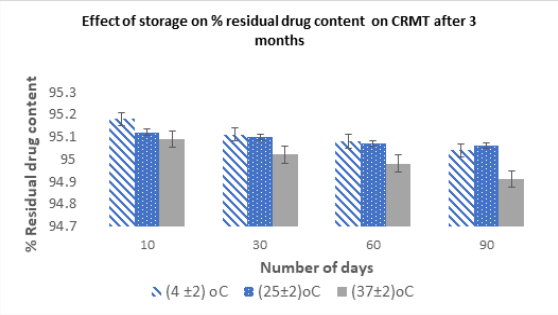

Figure 3: Effect of storage on residual drug content on CRMT after 3 months (Mean± SD)

Conclusion

In conclusion, CRMT of ritonavir was successfully developed to release drug for prolonged duration. The release of 15-20% of drug within first hour could help in the maintaining of minimum effective concentration quickly and avoid the use of loading dose in the formulation. Hence, the developed CRMT of ritonavir can be potentially useful in clinical treatment of HIV.

Conflict of interest

Nil

Acknowledgement

Authors are thankful to Principal, Siddhant college of Pharmacy, Pune for guidance. Also thankful to search engine and library to provide data and support.

References

1. Prajapati, G.B and Patel, R.K. (2010). Design and in vitro evaluation of novel nicorandil sustained release matrix tablets based on combination of hydrophilic and hydrophobic matrix systems. *International Journal of Pharmaceutical Sciences review and research,* 1:33-35.

2. Raghavendra, R.N.G., Prasanna, K.R. and Sanjeev, N.B. (2013). Review on matrix tablets as sustained release. *International Journal of Pharmaceutical Research and Allied Sciences*, 2(3):1-17.

3. British Pharmacopeia, vol 1, London: London stationary office; 2003:495.

4. Ch. Sudha, V.P.L., Narendra, K.R., and Hema, V. (2017). Formulation and evaluation of Zolmitriptan controlled release matrix tablet. *Indian Journal of Research in Pharmacy and Biotechnology,* 5(2): 124-128.

5. Nokhodchi, A., Raja, S., Patel, P. and Asare-Addo, K. (2012). The role of oral controlled release matrix tablets in drug delivery systems. *Bioimpacts*, 2(4):175-87.

6. Mohammad, Y.P., Shakeel, M., Kiran, B. and Irfan, A.A. (2019). Development and validation of UV-Visible spectrophotometric method for estimation of ritonavir in bulk and formulation. *The Pharma Innovation Journal*, 8(4): 30-34.

7. Prajapati, B.G., Patel, G.N. and Solanki, H. (2010). Formulation and statistical optimization of time controlled pulsatile release propranolol hydrochloride compressed coated tablet. *e -Journal of Science and Technology,* 5: 9-19.

8. Martin, A., Swarbrick, J. and Cammarata, A. (1991). Physical Pharmacy, Verghese publishing house, Bombay, Third edition, pp. 492-506.

9. Shambhavi, P., Vasudha, B. and Rajendra, K.J. (2019). Formulation Development and In Vitro Characterization of Zolmitriptan Controlled Release Drug Delivery Systems. *INNOSC Theranostics and Pharmacological Sciences*, 2(1):8-13.

10. Lachman, L., Leiberman, H.A. and Kanig, J.L. (1990). The Theory and Practice of Industrial Pharmacy. Varghese publishing house, Bombay. 3rd Edition. pp.296.

11. Indian Pharmacopoeia, Government of India, Ministry of Health and Family Welfare, Vol. II, 1996, published by Controller of Publications, Delhi, A-147,736.

12. Arora, G., Malik, K., Singh, I., Arora, S. and Rana, V. (2011). Formulation and evaluation of controlled release matrix mucoadhesive tablets of domperidone using Salvia plebeian gum. *Journal of Advance Pharmaceutical Technology & Research,* 2(3):163-169.

13. Higuchi, T. (1961). Rate of release of medicament from ointment bases containing drugs in suspension. *Journal of Pharmaceutical Sciences,* 50:874–5.

14. Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A. (1983). Mechanisms of solute release from porous hydrophilic polymers. *International Journal of Pharm*aceutics,15:25–35.

15. Peppas, N.A. (1985). Analysis of Fickian and non-fickian drug release from polymers. *Pharmaceutica Acta Helvetiae*, 60:110–111.

16. Bajaj, S., Singla, D. and Sakhuja, N. (2012). Stability testing of pharmaceutical products. *Journal of Applied Pharmaceutical Science,* 2(3):129-138.

17. Bonthagarala, B., Dasari, V. and Kotra, V. (2019). Enhancement of solubility and dissolution rate of BCS class II drug ritonavir using liquisolid technique. *International Journal of Pharmaceutical Sciences and research,* 10(5): 2430-2438.