Research Article

Development of Controlled Porosity Osmotic Pump of Ritonavir: Design, Optimization and Characterization

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ABSTRACT

The present study was aimed to develop controlled porosity osmotic pump (CPOP) tablets of ritonavir, a protease inhibitor for the treatment of acquired immune deficiency syndrome (AIDS). Ritonavir tablets were prepared by wet granulation method using controlled release polymer hydroxypropyl methylcellulose (HPMCE5LV) with different concentrations of osmogen sodium chloride. The core tablets were coated with cellulose acetate (CA) as a wall forming material, polyethylene glycols as a flux regulating agent, and sorbitol as a pore forming material in semipermeable membrane (SPM). The formulated tablets were evaluated by Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), micromeritic properties, post compression parameters, *in vitro* drug release (IVDR), and scanning electron microscopy (SEM). Among developed formulations RS5 batch showed 97.24±0.42% drug release at 14 h. Zero order, first order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell models were used to assess the *in vitro* release kinetics of different batches as well as the mechanism of drug release. The results of optimized formulation was found to exhibit zero order kinetics independent of the pH and agitation intensity, but depended on the osmotic pressure of dissolution media. This indicated that mechanism of drug release was due to osmotic pressure. Results of SEM study showed the formation of pores in SPM from where the drug release occurred. Short term stability study at 40±2ºC/75±5% RH for three months was carried out for the optimized batch. The results from stability study indicated that there was no significant change in weight variation, % friability, drug content, and *in vitro* drug release. The present study confirmed that increasing the concentration of osmogen, the drug release from the system also increased, and the system could provide controlled release of the drug.

Keywords: CPOP, AIDS, FTIR, DSC, wet granulation, *in vitro* drug release, stability study.

INTRODUCTION

Controlled release dosage form prolongs the action, and offers continuous release of their active ingredients at predetermined rate and time. Out of various controlled drug delivery systems (DDS), osmotic drug delivery system (ODDS) has major advantages over other DDS like gastro-retentive and mucoadhesive platforms[1]. ODDS drug release does not depend on pH, hydrodynamic conditions of the body, and agitation intensity[2].

The present work was to develop CPOP tablets. CPOP tablet is a novel drug delivery system with characteristic continuous drug delivery rate which is controlled by the osmotic pressure difference between the inside and outside of a semi permeable membrane (SPM) as a drug delivery driving force. The tablet core is made up of drug and excipients, which is surrounded by SPM. SPM is incorporated[3] with different channeling agents of water soluble additives and usually is made up of cellulose acetate (CA) and sorbitol. The core of CPOP tablets delivers drug when it comes into contact with the biological fluid where low levels of water soluble additives are leached from the polymer materials which form a sponge-like structure in the controlled porosity walls. The rate of drug delivery depends upon factors such as SPM water permeability, osmotic pressure of the core formulation, the thickness and total area of the coating.

Human immune deficiency virus causes AIDS a dangerous disease which spreads worldwide. The CD4+ count falls to 200cells/µL at the final stage of AIDS. To control the progression[4] of AIDS antiviral therapy is most useful among other treatments. Ritonavir is a protease inhibitor, an anti-HIV drug that reduces the amount of virus in the body. Ritonavir binds to the protease active site, and inhibits the activity of the enzyme. This inhibition prevents cleavage of the viral proteins resulting in the formation of immature non-infectious viral particles. This compound belongs to the class of organic compounds known as n-carbamoyl-alpha amino acids and their derivatives. It belongs to BCS Class-II drug. Ritonavir is metabolized in the liver, and the half-life[5]is 3-5 h .Hence, in the present study the controlled-release 600 mg ritonavir CPOP tablets were formulated as a once daily medication using wet granulation in order to reduce dose frequency in adults as compared to the conventional 300mg tablet taken twice daily with the goal to enhance patient compliance towards therapy.

MATERIALS AND METHODS

Materials

Ritonavir was obtained from Hetero Drugs Pvt. Ltd. India. Mannitol and sodium chloride were obtained from Qualigens Fine Chemicals, India. Cellulose actate (CA) was obtained from Eastman Chemical Inc. (Kingsport, TN, USA). Sorbitol, HPMC E5LV, polyethylene glycols (PEG400, PEG600, PEG1500, PEG4000, and PEG6000), magnesium stearate and talc were purchased from S.D. Fine Chemicals Ltd, India. Polyvinyl pyrrolidone (PVPK30) and microcrystalline cellulose (MCC) were obtained from Signet Pharma (Mumbai, India) as well as other solvents and reagents used were of analytical grade.

Compatibility studies

FTIR study

Infrared spectra[6] of the individual ingredients, drug, and drug with mixture of optimized formulation were observed using Bruker FTIR spectrophotometer. The scanning range of pellet was 4000 to 400 cm^{-1}, and the IR spectra of samples were observed using KBr pellet method. The sample with KBr in the ratio 1:100 was triturated thoroughly for 3-5 mins. in mortar and compressed into disc by applying10kg/cm to form a transparent pellet using a hydraulic press.

DSC study

Physical mixtures[7] of drug, and individual excipients in the ratio of 1:1 were taken and investigated by DSC (Shimadzu DSC-50, Japan). Individual drug sample as well as physical mixtures of drug and excipients were weighed to about 5 mg in DSC pan. The sample pan was crimped for effective heat conduction, and scanned at the temperature range of 50-300°C. The rate of heating was 20°C min^{-1}, and the thermograms observed were reviewed for evidence of any interactions.

Methods

Preparation of CPOP tablets

Wet granulation method was adopted for the development of CPOP tablets of ritonavir containing 600mg.Table 1 indicates composition of different batches. Ingredients used for the development of CPOP tablets were passed through sieve no 30, but magnesium stearate (lubricant) and talc (glidant) are sifted through sieve no 80.The blending was performed manually using mortar and pestle by the way of geometric dilution without addition of lubricant and glidant. Aqueous solution was used for moistening of mixture and then passed through sieve no 30 followed by drying for 3-4 h in hot air oven. The dried granules are obtained from hot air oven and sifted through sieve no 30 followed by blending with talc and magnesium stearate. 10 Station rotary compression machine (Minipress, Karnavati, India) having standard concave punches were used for compression of homogenous blend to get round tablets.

Table 1: Composition of CPOP ritonavir tablets

Ingredients (mg)	RS1	RS2	RS3	RS4	RS5	RV6
RV	600	600	600	600	600	600
MCC	170	150	130	110	90	190
PVP K30	50	50	50	50	50	50
HPMC E5LV	100	100	100	100	100	100
Sodium chloride	20	40	60	80	100	0
Magnesium stearate	5	5	5	5	5	5
Talc	5	5	5	5	5	5
Total weight(mg)	950	950	950	950	950	950

Coating of core tablets

The coating solution was prepared according to the required ingredients in Table 2, and the solvent acetone was added to maintain desired solution viscosity. Spray pan coating in a perforated pan (GAC-205, Gansons Ltd., India) was used coating of tablets. Hot air was initially supplied to the tablet bed at a lower rotating speed of 5-8 rpm. The rotational speed of coating pan was 10-12 rpm for coating of tablets. Coating solution spray rate was 4-6 ml/min and the pressure for atomization was 1.75 kg/cm^2. The temperature of inlet was 50°C and out let temperature was 40°C.The drying temperature of coating tablet was 50°C for 12h.

Evaluation of granules[8]

Angle of repose (α)

Angle of repose was determined by fixed funnel method where the funnel height was adjusted to funnel tip which touches the apex of the heap of granules. Onto the surface granules were dropped through funnel. Cone radius(R) was determined in cm and the heap height (H) was determined in cm. Angle of repose (α) can be can calculated using following formula.

$$\tan\alpha = H/R \quad (1)$$

$$\alpha = \tan^{-1}(H/R) \quad (2)$$

Table 2: Coating composition for CPOP tablets

Formulation code	CA (g)	PEG 400 (g)	PEG 600 (g)	PEG 1500(g)	PEG 4000 (g)	PEG 6000 (g)	Sorbitol (g)	Acetone (ml)
RS1	6	2	0	0	0	0	0.4	300
RS2	6	0	2	0	0	0	0.8	300
RS3	6	0	0	2	0	0	1.2	300
RS4	6	0	0	0	2	0	1.6	300
RS5	6	2	0	0	0	2	2	300
RV6	6	0	0	0	0	0	2	300

Bulk density (e_b) and tapped density (e_t)

Bulk density apparatus was used to determine bulk density by keeping granules in graduated cylinder. Mass (m) of granules was weighed and bulk volume (Vb) was measured from graduated cylinder. Graduated cylinder of bulk density apparatus having mass (m) of granules allowed to tap 1000 times for a fixed time and then tapped volume (Vt) was determined.

The bulk density can be determined by using given equation

$$e_b = \frac{m}{Vb} \quad (3)$$

The tapped density was measured by using the following formula.

$$e_t = \frac{m}{Vt} \quad (4)$$

Compressibility index (Carr's index)

The Carr's Index[9] can be calculated by the following formula.

$$\%Carr'sIndex = \frac{et-eb}{et} \times 100 \quad (5)$$

Where e_t is the tapped density of granules, ande_b is bulk density of granules.

Hausner's ratio (H_R)

Hausner's ratio can be calculated by taking the ratio of tapped density to the ratio of bulk density.

Evaluation of CPOP tablets[10]

Thickness

Vernier caliper (Absolute digimatic, Japan) was used to determine thickness of tablets.

Coat thickness

Coat thickness can be determined by electronic digital caliper (Absolute digimatic, Japan) which was obtained after dissolution from tablets followed by drying at 40°C for 1hr.

Hardness

Monsanto hardness tester was used to evaluate hardness of tablets.

Friability

Twenty tablets were initially weighed (W_0) together and then placed[11] in the chamber. The friabilator was operated for 100 revolutions and the tablets were subjected to the combined effects of abrasion and shock because the plastic chamber carrying the tablets drops them at a distance of six inches with every revolution. The tablets are then dusted and reweighed (W).The percentage of friability was calculated using the following equation.

$$\%Friability = F = \left(1 - \frac{W}{W0}\right) \times 100 \quad (6)$$

Weight variation test

Twenty tablets were randomly selected from each batch and weighed[12] individually. The average weight and standard deviations of 20 tablets were calculated and compared with the USP criteria.

Drug content

Ten tablets[13] were weighed and powdered. The powder weight equivalent one tablet of ritonavir was dissolved in 100ml of 0.1N HCl using magnetic stirrer (Ricon, Hyderabad, India) in a volumetric flask for 24hrs. The primary stock solution was filtered through Whatman filter paper No.1.From this primary stock solution, solutions were withdrawn with suitable dilution to get desired concentrations and the drug content of formulations were calculated using calibrated standard curve equation.

Diameter of tablet

The diameter of individual tablets was measured by using Vernier caliper (Absolute digimatic, Mitutoyo Corp. Japan).

In vitro dissolution studies

In vitro dissolution test was carried out by using USP type II (paddle) apparatus. Each tablet was put in 900 ml of dissolution medium containing 0.1N HCl (pH 1.2), and stirred at 75 rpm, 37±0.5°C for the first 2 h. The dissolution fluid was then changed to phosphate buffer pH 6.8 maintaining under the same condition for another 12 hr. At specified time intervals an aliquot of 5 ml samples of the solution was withdrawn through 0.45-µm

cellulose acetate filter from each dissolution vessel, and was replaced with the freshly prepared medium. Absorbance of these solutions was measured at specific λ_{max} using a UV/Visible Spectrophotometer (Shimadzu UV-1800, Japan). The drug release was plotted against time to determine the release profile of various batches. Three replicates were performed (n=3) for drug release study.

In vitro drug release kinetic studies

The obtained data from the *in vitro* release study was fitted into various kinetic equations. The kinetic model used were zero order which was plotted as a cumulative amount of drug release versus time, first order as a log cumulative percentage of drug remaining versus time, Higuchi model as a cumulative percentage of drug release versus square root of time, Korsmeyer- Peppas model (KP Model) as a log cumulative percentage drug release versus log time and Hixson-Crowell model as a cube root of drug percentage remaining in matrix versus time[14].

Effect of osmogen concentration

To assess the effect of osmogen concentration on drug release, the formulations were developed with different concentrations of osmogen keeping all other ingredients constant[15, 16]. The drug release was compared at different osmogen concentrations of the formulated batches by using USP dissolution II apparatus.

Effect of flux regulating agents

To determine the flux regulating effects on drug release, the formulations prepared with particular concentration of different flux regulating agents and keeping other excipients constant. USP dissolution II apparatus was used to estimate the drug release of different batches and compared.

Effect of pore former concentration

Different concentrations of pore former[16]were used in SPM formation. To know drug release characteristics and surface morphology in SPM, the *in vitro* drug release data as well as the number of micropores formation were compared.

Effect of membrane thickness

Tablets with varying coating thicknesses[17] were prepared to determine the effect of coating thickness on drug release. The drug release rate was measured in 0.1NHCl for 2 hr and phosphate buffer pH6.8 for remaining 12hr, and compared among various formulations.

Effect of osmotic pressure

The effect on osmotic pressure[18] on the optimized formulation can be studied in media of different osmotic pressure and the release profile with varying osmotic pressure is compared. To increase the osmotic pressure of the release media mannitol can be added to produce 30 atm, 60 atm and 90 atm respectively.

Effect of pH

In order to study the effect of pH of release medium[19] in the drug release of optimized formulation, the *in vitro* release study was carried in dissolution media having different pH media. Dissolution can be carried in 900 ml of 0.1 N HCl (pH 1.2), phosphate buffer pH 6.8 and phosphate buffer pH 7.4 phosphate buffer in USP type II dissolution apparatus. The temperature is maintained at 37±0.5°C. The sample (5ml) was withdrawn at predetermined intervals and analyzed after filtration through 0.45-µm cellulose acetate filter. The percentage cumulative drug release of optimized formulations at various pH was plotted and compared.

Effect of agitation intensity

To demonstrate the effect of agitation intensity[20, 21] on drug release profiles, three different agitation intensities such as 50, 100and 150 rpm were selected for the optimized batch RS5.Dissolution was carried out in USP-II (Paddle) in a suitable dissolution media at 37±0.5°C. The samples were withdrawn at predetermined intervals, and analyzed by UV-Visible spectrophotometer, and the drug release for various batches was compared.

SEM study

For the observation of the mechanism of drug release[22-24] from the developed formulations surface coated tablets before and after dissolution studies was examined using scanning electron microscope (Leica, Bensheim, Switzerland). The surface morphology of coated membrane of optimized formulation film coating before and after dissolution is determined and by comparing the porous morphology the capability of porogen and drug release can be evaluated.

Accelerated stability studies (AST)

The formulation can be evaluated for accelerated stability studies[25-27] as per ICH (The International Conference of Harmonization) guidelines. Stability chambers (Thermo lab Scientific equipment Pvt. Ltd., India) maintained at 40±2ºC/75±5% RH for 3 months was used to AST for packed tablets in air tight container. Physical characteristics, weight variation, %friability, drug content, and in-vitro drug release were evaluated periodically.

RESULTS AND DISCUSSION

FTIR study

Out of six formulations the optimized formulation was RS5. FTIR study was carried out for the optimized formulation. In the optimized formulation RS5peak at 2348.25 and 780.23 cm^{-1} were due to the presence of HPMCE5LV. In the formulation the peaks due to sodium chloride were 1776.73, and 624.68 cm^{-1}. Peaks at 3328.46, 1452.86, and 1407.49 cm^{-1} were due to the presence of ritonavir in the optimized formulation. So from the study it can be concluded that the major peaks of drug 3328.46, 1452.86, and 1407.49 cm^{-1} remained intact, and no interaction was found between the drug,

polymer, and osmogen. Hence the drug-excipient mixture data reveal that no incompatibility was observed between ritonavir and the active ingredients.

DSC study

DSC thermogram showed an endothermic peak at 122.5°C which was corresponding melting point of drug.DSC thermogram showed an endothermic peak at 122.4°C in RS5 formulation. The endothermic peak at 252.1°C was due the excipients in the formulation (Fig. 2b).Hence, the physical mixture demonstrated compatibility between the drug and the excipients.

Evaluation of granules

The angle of repose of granules of various batches was in the range of 23.98±0.06 to 28.15±0.10. The angle of repose is less than 30° usually indicate good flow properties that were noticed for all the formulations of ritonavir. Out of all formulations the optimized formulation RS5 showed excellent flow properties giving angle of repose 23.98°±0.06. Bulk density of granules was found to be in the range of 0.513±0.12 to 0.531±0.12 g/ml, tapped density in the range of 0.554±0.11 to 0.579±0.12 g/ml. Bulk density, and tapped density determinations established that density of granules rely upon the particle packing, and as the granules consolidates the density changes. The Carr's Index values were in the range of 7.40±0.14 to 9.15±0.08.The values of Carr's Index falls between 5-15% showing excellent flow property of granules. Hausner's ratio values were ranges of 1.07±0.03 to 1.10±0.13. The value of Hausner's ratio of granules below 1.25 usually indicates an excellent flow property that was observed for all the formulations of ritonavir. It is given in Table 3.

Post-compression parameters

The range of thickness of tablets was within 4.49±0.12 to 4.65±0.11mm. It was within limits, and the deviations from average value were not more than 5%.The average coat thickness was in the range of 100.3±3.2 to 500.6±2.9 µm. It was within limits. The uniformity in the tablet showed perfect coating while manufacturing of tablets. The hardness values were in the range of 6.2±0.14 to 7.3±0.16 kg/cm^2. Itindicates good handling, and transportation characteristics of tablets under study. Less variation of hardness of tablets indicates uniformity in compression force during tablet punching. The % friability values were in range of 0.11±0.01 to 0.23±0.04. In the current studies the percentage friability for all formulations was within the recommended limits. The average weight of tablet was in the range of 949.9±1.07 to 952.5±1.06 mg. All the formulations fell within the limit. Therefore all formulations passed the test for uniformity of weight as per official requirement. The % drug content of tablet was in the range of 98.39±1.02 to 99.68±1.08 which was within the acceptable limits. Diameter of tablets values were in the ranges of 11.99±0.06 to 12.2±0.02 mm. It was also within limits as shown in Table 4.

Table 3: Micromeritic properties of granules

Formulation code	Angle of repose (degree)[a] ± S.D	Bulk density (g/ml)[a] ± S.D	Tapped density (g/ml)[a] ± S.D	Carr's Index (%)[a] ± S.D	Hausner's Ratio[a] ± S.D
RS1	28.15±0.10	0.531±0.12	0.576±0.14	7.81±0.06	1.08±0.12
RS2	27.52±0.12	0.526±0.13	0.579±0.12	9.15±0.08	1.10±0.13
RS3	26.14±0.14	0.524±0.12	0.573±0.11	8.55±0.11	1.09±0.12
RS4	25.08±0.12	0.520±0.11	0.571±0.14	8.93±0.12	1.09±0.08
RS5	23.98±0.06	0.513±0.12	0.554±0.11	7.40±0.14	1.07±0.03
RV6	25.32±0.06	0.521±0.06	0.565±0.04	7.78±0.04	1.08±0.06

N.B.- All values are expressed as mean± S.D, [a] n = 3

Table 4: Post-compression parameters of CPOP tablets

Formulation code	Thickness of tablet (mm)[a] ± S.D	Coat thickness (µm)[a] ±S.D	Hardness (kg/cm^2)[a] ±S.D	%Friability(%)[b] ± S.D	Average weight of 1tablet(mg)[b] ± S.D	%Drug content (%)[a] ± S.D	Diameter(mm)[a] ± S.D
RS1	4.65±0.11	500.6±2.9	6.2±0.14	0.23±0.04	951.3±1.06	99.35±1.15	11.99±0.06
RS2	4.49±0.12	400.7±3.3	6.4±0.16	0.18±0.06	952.4±1.07	99.68±1.07	12.1±0.03
RS3	4.56±0.09	300.5±3.8	6.8±0.18	0.17±0.04	952.5±1.06	98.39±1.02	12.2±0.02
RS4	4.59±0.09	200.4±3.4	6.7±0.14	0.13±0.03	949.9±1.07	98.71±1.01	12.1±0.03
RS5	4.52±0.04	100.3±3.2	7.3±0.16	0.11±0.01	950.2±1.06	99.68±1.08	12±0.02
RV6	4.55±0.02	201.2±3.4	6.5±0.15	0.15±0.07	952.1±1.14	98.39±1.11	12±0.05

N.B.- All values are expressed as mean± S.D, [a] n = 10, [b] n = 20

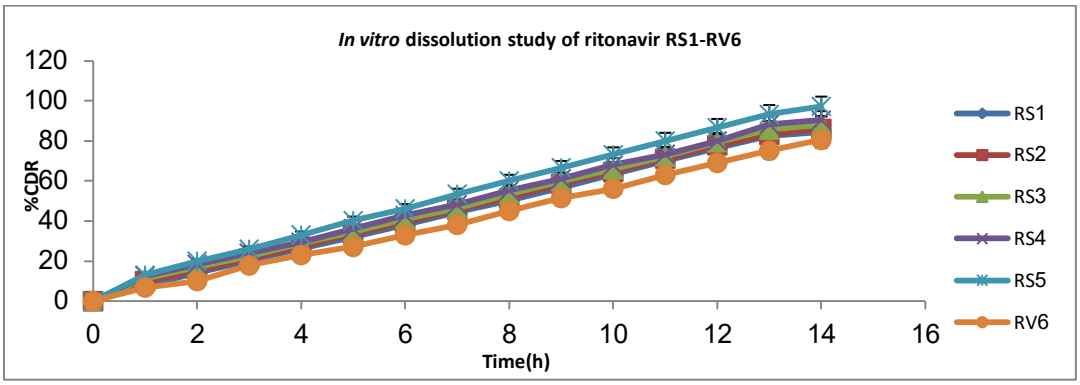


Figure 1: *In vitro* release profiles showing ritonavir release from various osmotic formulations RS1-RV6 (n=3)

In vitro dissolution study

RS1, RS2, RS3, RS4, RS5, and RV6 formulations exhibited 84.46±*0.62*, 85.92±*0.67*, 87.83±*0.51*, 90.34±*1.22*, 97.24±*0.42*, and 80.46±*0.83* %, respectively of cumulative drug release of ritonavir at the end of 14hr.The drug release was maximum in RS5 due to high concentration of osmogen, and drug release was minimum in RV6 due to lack of osmogen. The drug release was higher in RS5 batch as it contained100 mg of polymer and100 mg of sodium chloride. Hence it was confirmed that the drug release depends on the osmotic pressure of the osmogen. The optimized formulation RS5 under study released 13.03% of drug within the first hour as loading dose and the remaining drug was released up to 14 hr in a controlled-release manner as seen in Fig. 1.

Kinetic model

All the formulations showed to be best expressed by zero order equation as the plots showed high linearity. The regression values (R^2) of zero order were higher for all the formulations comparing to other kinetic models. It can be concluded that all the developed formulations follow zero order kinetics. The release exponent n value of Korsmeyer- Peppas model was more than 0.45 in all the developed formulations which indicated a non- Fickian diffusion mechanism of drug release. It is shown in table 5.

Table 5: Fitting of IVDR data in various mathematical models

Models	Zero order		First order		Higuchi		Korsmeyer - Peppas			Hixson-Crowell	
Batches	R^2	K_0	R_1^2	K_1	R_H^2	K_H	R_K^2	K_{kp}	n	R^2	Ks
RS1	0.998	6.153	0.946	0.1289	0.931	25.09	0.998	7.464	0.923	0.977	0.153
RS2	0.998	6.166	0.945	0.1335	0.936	25.21	0.993	8.770	0.859	0.977	0.157
RS3	0.997	6.235	0.933	0.1427	0.939	25.54	0.992	9.817	0.819	0.971	0.163
RS4	0.996	6.318	0.915	0.1543	0.942	25.93	0.989	10.864	0.786	0.964	0.171
RS5	0.996	6.778	0.845	0.2095	0.949	27.91	0.994	11.694	0.791	0.944	0.208
RV6	0.998	5.744	0.944	0.1082	0.915	23.22	0.993	5.942	0.975	0.973	0.134

Effect of osmogen concentration

The concentrations of sodium chloride varied at 20, 40, 60, 80, 100, and 0 mg/tab in RS1, RS2, RS3, RS4, RS5, and RV6 respectively. The cumulative drug release was in order RS5>RS4>RS3>RS2>RS1> RV6. It was observed that the higher concentration of osmogen resulted in the higher osmotic pressure which led to the higher drug release. Hence the osmogen concentrations have a pronounced effect on the release of ritonavir. The optimized ritonavir CPOP tablets RS5 contained NaCl 100mg/tablet which released 97.24±*0.42* % drug at 14 hr as seen in Fig.1.

Effect of flux regulating agents

The concentration of flux regulating agents (PEG400, PEG600, PEG1500, PEG4000 and PEG6000) was 33.3% w/w in the coating solutions RS1, RS2, RS3, RS4and RS5, respectively, and RV6 did not contain any flux regulating agent. The cumulative drug release was in order RS5>RS4>RS3>RS2>RS1> RV6.It was evident that the type of flux regulating agents had a pronounced effect on the drug release as seen in Fig. 1.

Effect of pore former

Batches RS1 to RS5 had the coating composition of pore forming agent (sorbitol) of 6.6%, 13.3%, 20% ,26.6% and 33.3% w/w, respectively. The batch without osmogen RV6 contained 33.3% w/w of sorbitol in the CA membrane. The drug release order for RS1 to RS5 was RS5>RS4>RS3>RS2>RS1 whereas the batch RV6 (no osmogen) despite containing the highest sorbitol still demonstrated the least drug release in all batches. The optimized ritonavir CPOP tablets RS5 containing NaCl 100mg/tablet and the pore former concentration of 33.3% w/w in the CA SPM released the highest drug content of 97.24±*0.42* % at 14 hr. From Fig. 1, it is clearly

evident that as the level of pore former increased the membrane became more porous after coming into contact with the aqueous environment resulting in faster drug release. Hence the pore former concentrations also had a pronounced effect on ritonavir release.

Effect of membrane thickness

The order of coating thickness for RS1 to RS5 is RS1>RS2>RS3>RS4>RS5.The batch RV6 (no osmogen) had a coating thickness of 201.2±3.4 µm. As shown in Fig. 1, it is clearly evident that the drug release decreased with an increase in the coating thickness of SPM.

Effect of osmotic pressure

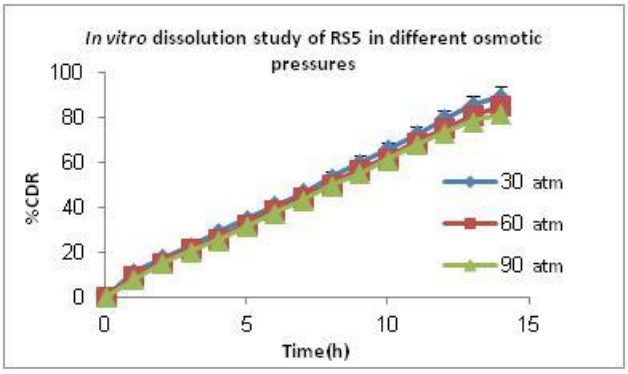
Optimized formulation drug release in dissolution medium showed that the drug release depends on the osmotic pressure of the release medium with inverse relationship. This finding confirmed that the mechanism of drug release is triggered by the osmotic pressure difference between inside of the tablet and the surrounding medium. The drug release for RS5 was found to be 89.23±1.13% for 30 atm, 85.31±1.19% for 60 atm,and81.44±0.98% for 90 atm respectively as seen in Fig. 2a.The optimized formulation RS5 without mannitol under normal atmosphere released drug 97.24±*0.42* % upto the end of 14 hr. Hence, the higher osmotic pressure in the dissolution medium resulted in the lesser drug release comparing to the optimized formulation under normal atmosphere.

Effect of pH

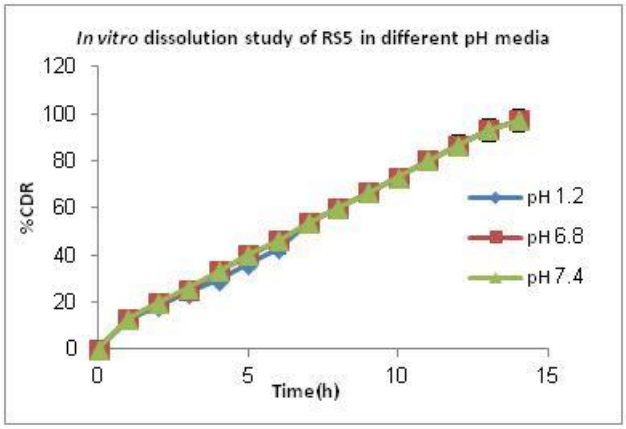
It was found that the drug release was nearly same for end of 6 hr. From the 7th h to end of 14 hr the drug release was same with optimized formulation in each hour of drug release. From the study it showed that there was no significant difference in the release profile. Hence the drug release is independent of pH .It is shown in Fig. 2b.

Effect of agitation intensity

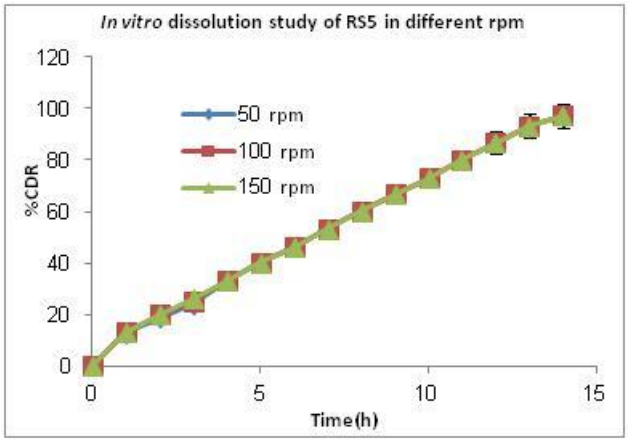
It shows that the release of rtonavir from CPOP is independent of agitation intensity. Hence it can be expected that the release from the developed formulation will be independent of the hydrodynamic conditions of the absorption site. It is shown in figure 2c.



2a



2b

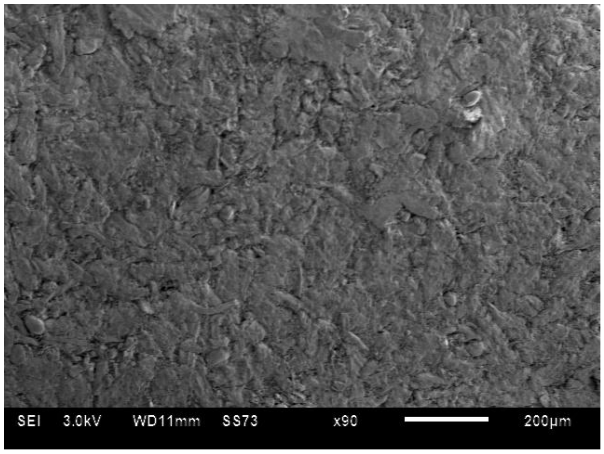


2c

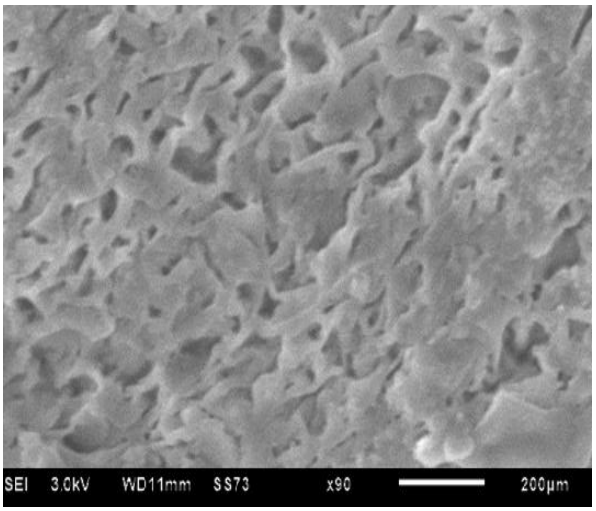
Figure 2: *In vitro* release profiles showing ritonavir release from optimized RS5 in different a) osmotic pressures (n=3) b) pH media (n=3) c) agitation speeds (n=3)

SEM analysis

The coating membrane of the osmotic delivery system before and after dissolution was examined with the help of SEM. Before dissolution (Fig.3a) no pores were found in the coating membrane. After dissolution (Fig. 3b) more numbers of pores were observed in the membrane might be due to leaching or removal of entrapped drug and SPM became porous due to sorbitol.



3 (a)



3 (b)

Figure 3: SEM image of RS5 (a) Before dissolution, (b) After dissolution

Stability studies

Stability study showed that no measure changes of evaluated parameters like physical appearance, thickness, hardness, Friability (%), Weight variation and drug content. The optimized formulation showed little change on *in vitro* dissolution study for 3 months. The % cumulative drug release was $97.24 \pm 0.42, 96.88 \pm 1.41, 96.13 \pm 1.16$, *and* 95.88 ± 1.18 at 0 day, 30 days, 60 days, and 90 days respectively at the end of 14 h.

CONCLUSION

The desired release of ritonavir from CPOP was gained through careful monitoring of the selected formulation variables. It was evident that increase in the concentration of osmogen the drug release from the system was also increased. The optimized formulation RS5 was found to deliver ritonavir in a predetermined rate and time.

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