ISSN: 0974-2115
www.jchps.com Journal of Chemical and Pharmaceutical Sciences

Formulation and Optimization of Controlled Porosity Osmotic Pump Tablets of Ritonavir

Chinmaya Keshari Sahoo[1], Surepalli Ram Mohan Rao[2], Muvvala Sudhakar[3], P. Shashikala[4]
[1]Department of Pharmaceutics, University College of Technology, Osmania University, Hyderabad, Telangana-500007.
[2]Mekelle Institute of Technology, Mekelle University, Mekelle, Ethiopia.
[3]Department of pharmaceutics, Malla Reddy College of Pharmacy, Maisammaguda, Secunderabad, Telangana-500014.
[4]Faculty of Pharmacy, University College of Technology, Osmania University, Hyderabad, Telangana-500007.

ABSTRACT

The current work deals with the formulation and characterization of ritonavir controlled porosity osmotic pump (CPOP) tablets. Wet granulation method was adopted to develop tablets of ritonavir. Core tablets were incorporated with HPMCE5 LV polymer, different concentrations of fructose as osmogen and additives. The coating of CPOP formulations were done by the incorporation of cellulose acetate as wall forming material, poly ethylene glycol as flux regulating agent, and sorbitol acts as pore forming material in SPM. FTIR, DSC, pre compression parameters, post compression parameters, in vitro dissolution study and scanning electron microscopy study were carried out for formulated batches. Optimized batch released about 97.13% at the completion of 14hrs.The optimized formulation RF5 releases drug in such a way that it follows zero order release via non-Fickian transport (anomalous) mechanism of exponent n value 0.792.Agitation intensity and p^H of dissolution media does not affect the drug release of optimized formulation, but it is directly related to osmotic pressure of dissolution media. The porosity nature of SPM was observed through SEM study, it confirms that less pores were observed in before dissolution of SPM of tablet and after dissolution study more pores were found out in SPM. Short term stability study was carried out on RF5 batches at 40±2ºC/75±5% RH for three months. From the study it was observed that permissible variations in weight variation, % friability, drug content and in vitro dissolution study.

KEY WORDS: Ritonavir, wet granulation, CPOP, in vitro dissolution study, stability study.

1. INRODUCTION

Controlled release formulations is the part of modified drug release dosage form which covers a wide range of prolonged (Chein, 1992) action of drug release. The drug release from controlled formulations was rate controlled in predetermined rate and time specific as predetermined time. Osmotic pressure (Sahoo, 2015) principle is utilized for osmotic controlled drug delivery system (OCDDS) to control the delivery of active ingredients. The drug released from OCDDS does not dependent on p^H media, hydrodynamic condition of the body and agitation intensity.

Current work is to develop CPOP tablets. The difference between inside and outside of SPM as drug delivery power can be controlled by osmotic pressure of CPOP tablets. CPOP tablets were developed where the delivery orifices were generated due to addition of water leachable additive (Zenter, 1985) in SPM. The coating of core tablets was made by cellulose acetate as wall forming material and to this in situ micro pore former sorbitol is added. Once CPOP tablets exposes to water of biological system the water soluble additive solubilizes, as a result of which an osmotic pumping system is created in the core.

Hence water diffusion occurs through the SPM (Verma, 2000) and creating an osmotic pressure gradient which controls the release of drug.

Globally AIDS is considered a dangerous disease that is infected with human immune deficiency virus. AIDS in final stage where the CD4+ count declines to 200cells/µL. Out of various treatments now antiretroviral (Sahoo, 2017) therapies plays a vital role for controlling of AIDS. Ritonavir belongs to class protease inhibitor an antiretroviral drug. It declines the number of virus in the body. The drug attaches to protease active site and stops breaking of viral polyproteins causing generation of immature non-infectious viral particles. Ritonavir falls in the category of organic compounds known as n-carbamoyl-alpha amino acids and derivatives. It belongs to BCS Class-II drug. Ritonavir is metabolized in liver and the half-life of drug is 3-5 hrs (Biswas, 2013). Hence dose frequency can be reduced to avoid these side effects by means of controlled release dose.

2. MATERIALS AND METHODS

Materials: Ritonavir was obtained from Hetero Drugs Pvt. Ltd. India. Mannitol and Fructose was purchased from Qualigens Fine Chemicals, India. Cellulose acetate (CA) was obtained from Eastman Chemical Inc, Kingsport, TN. Sorbitol, HPMC E5LV, polyethylene glycol (PEG) 400,600,1500,4000,6000, Magnesium stearate and talc were procured from S.D. Fine Chemicals Ltd, Mumbai, India. Microcrystaline cellulose (MCC), PVPK30 were collected from Signet Pharma, Mumbai, India. All other solvents and reagents used were of analytical grade

Compatibility studies:

Fourier Transform Infrared Spectroscopy (FTIR): Infrared spectrum of individual samples, drug and drug with mixture of optimized batch was observed using Bruker FTIR spectrophotometer. The pellet was scanned (Jilakara, 2013) in the between the range 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 were triturated thoroughly for 3-5mins in mortar compressed into disc by applying 10kg/cm to form a transparent pellet in hydraulic press.

Differential Scanning Calorimetry (DSC): Physical mixtures of active ingredient and individual excipients in 1:1 ratio were taken and investigated by DSC (Shimadzu DSC-50, Japan).The weighed quantity 5mg of individual samples, physical mixture of drug and additives were collected in DSC pan. The sample pan was crimped for effective heat conduction and scanned (Banerjee, 2015) in the temperature range of 50-300^{0}C. The rate of heating was 20^{0}C min^{-1} and the thermogram observed was reviewed for evidence of any interactions

Methods:

Preparation of osmotic pump tablets: Wet granulation technique was adopted for the development of CPOP tablets each containing 600mg ritonavir. The composition of different formulations was reported in table.1. All the excipients were sifted through mesh size 30 excluding lubricant and glidant. Lubricant and glidant were sifted through mesh size 80. Mortar and pestle is used for blending of all the ingredients by geometric dilution except lubricant and glidant. Aqueous solution is added for moistening the mixture and it is sieved by mesh size 30. The wet sieved granules were dried at 60ºC for 3-4 hrs by using hot air oven. Mesh size 30 is used for sifting of dried granules, then it is mixed with magnesium stearate and talc. The granules of mixture was compressed by concave punches of 10 station rotary compression machine (Minipress, Karnavati, India) to get round tablets.

Table.1. Composition of osmotic pump ritonavir tablets

Ingredients (mg)	RF1	RF2	RF3	RF4	RF5
RV	600	600	600	600	600
MCC	170	150	130	110	90
PVP K30	50	50	50	50	50
HPMC E5LV	100	100	100	100	100
Fructose	20	40	60	80	100
Magnesium stearate	5	5	5	5	5
Talc	5	5	5	5	5
Total weight(mg)	950	950	950	950	950

Coating of core tablets: The solution for coating was prepared taking required ingredients from table.2, and acetone was added quantity sufficient maintaining proper viscosity of solution. Spray pan coating method is used for coating of tablets by a perforated pan (GAC-205, India). Hot air is supplied to tablet bed by rotating lower speed 5-8 rpm initially. The tablets were coated by carrying out with the rotation speed of 10-12 rpm. The spray rate of solution is maintained between 4-6 ml/min. The air pressure for atomization was 1.75 kg/cm^2. The inlet temperature was 50ºC and the outlet temperature was 40ºC.Coated tablets were dried at 50ºC for 12 hrs.

Table.2. Coating composition for controlled porosity osmotic pump tablets

Formulation code	CA (g)	PEG 400 (g)	PEG 600 (g)	PEG 1500(g)	PEG 4000 (g)	PEG 6000 (g)	Sorbitol (g)	Acetone (ml)
RF1	6	2	0	0	0	0	0.4	300
RF2	6	0	2	0	0	0	0.8	300
RF3	6	0	0	2	0	0	1.2	300
RF4	6	0	0	0	2	0	1.6	300
RF5	6	2	0	0	0	2	2	300

Evaluation of granules: Pre compression parameters (Sahoo, 2015) such as angle of repose, bulk density, tapped density and compressibility index (Carr's index) was determined for granules blend. Fixed funnel method was adopted to determine angle of repose. The bulk density and tapped density were determined by bulk density apparatus (SISCO, India).

The Carr's index (Cooper, 1986) can be calculated by the following formula.

$$\%\text{Carr's index} = \frac{et - eb}{et} \times 100 \quad (1)$$

Where e_t is the tapped density of granules and e_b is bulk density of granules.

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

Evaluation of tablets (Sahoo, 2015):

Thickness: Vernier caliper (Absolute digimatic, Japan) is used to measure the thickness of individual tablets.

Measurement of coat thickness: After 14hrs of dissolution the SPM was collected from dissolution media and dried at 40^{0}C for 1hr.Thickness was measured by using electronic digital calipers (Absolute digimatic, Japan)

Hardness: Monsanto hardness tester (Sisco, India) is used to determine hardness of tablets.
Friability: Roche friabilator (SISCO, India) is used to determine friability (Panda, 2015) of tablets. Twenty tablets of known weight ($W_{initial}$) were de-dusted in plastic chamber of friabilator for a fixed time of 100 revolutions in 4 minutes and weighed again of weight (W_{final}). The percentage of friability can be determined by the equation.

$$\%\text{Friability} = F = \left(1 - \frac{W\ final}{W\ initial}\right) \times 100 \quad (2)$$

Where, $W_{initial}$ and W_{final} are the weight of the tablets before and after the test respectively.
Weight variation test (Sirisha, 2012): The weight variation test is done by weighing 20 tablets individually in weighing balance (Shimadzu, Japan) calculating the average weight and comparing the individual tablet weights to the average. The % weight deviation is determined and matched with USP specifications
Uniformity of drug content test: Powder is made after triturating 10 CPOP tablets from each formulation with mortar and pestle. The powder weight equivalent to 1 tablet is dissolved in a 100ml volumetric flask filled with 0.1N HCl using magnetic stirrer for 24hr. Solution was strained by Whatman filter paper No.1 diluted suitably and analyzed spectro photometrically
Diameter of tablet: The diameter of individual tablets is measured by using vernier caliper (Absolute digimatic, Japan).
***In vitro* dissolution studies:** USP apparatus type II (Lab India 8000) at 75 rpm was used to determine drug release of tablets.

The dissolution medium was 0.1N HCl (pH 1.2) for first 2hrs and then changed to phosphate buffer pH 6.8 from 3-14 hr (900 ml), maintained at 37±0.5^{0}C.At each time point 5 ml of aliquote is taken and it was replaced with 5 ml of fresh medium. The drug release at different time interval was measured by UV-visible spectrophotometer (UV-1800, Shimadzu, Japan)
***In vitro* drug release kinetic studies (Sahoo, 2015):** In order to investigate the mode of release from formulations, the drug release data of formulation was analyzed zero order kinetics, first order kinetics, Higuchi model, Korsmeyer and Peppas and Hixson-Crowell equations.
Effect of osmogen concentration: Keeping all the parameters for tablet constant different osmogen (Vidyadhara, 2014) concentrations is used to develop tablets. The drug release is compared with the different osmogen concentration of formulated batches by using USP-II dissolution apparatus.
Effect of pore former concentration: SPM for various batches were prepared by taking different concentrations of pore former (Gondaliya, 2003). Pore former effect on *in vitro* dissolution profile is compared and number of formation of micropores were observed.
Effect of membrane thickness: Tablets with varying coating thicknesses were developed. Thickness (Kanakal, 2009) effect on in vitro dissolution study was demonstrated.
Effect of osmotic pressure: Osmotic pressure (Reza, 2011) effect was demonstrated by adding different amount of mannitol of an osmogen to produce 30 atm, 60 atm and 90 atm respectively in dissolution media 0.1N HCl for 2hrs and phosphate buffer pH 6.8 for remaining hrs. In vitro dissolution study was performed in USP type II (Paddle) apparatus at 75 rpm maintained at 37±0.5^{0}C and compared for various dosage forms.
Effect of pH: The pH effect for developed formulations were observed by performing the in vitro dissolution studies of optimized batch in different media (Kumaravelrajan, 2011) 0.1 N HCl (pH 1.2), phosphate buffer pH 6.8 and phosphate buffer pH 7.4 in USP type II dissolution apparatus at 75rpm. The temperature was maintained at 37±0.5°C. The release was studied at specified time intervals.
Effect of agitation intensity: Agitation intensity effect were observed by performing the *in vitro* dissolution studies of optimized batch in USP Type II (Paddle) dissolution apparatus containing 0.1NHCl for first 2hrs and phosphate buffer pH 6.8 for remaining hours at different rotational speeds of 50, 100 and 150rpm with maintaining temperature at 37±0.5°C. The aliquots were taken at predetermined intervals and analyzed by UV spectrophotometer.
Scanning Electron Microscopy (SEM): In order to observe the mechanism of drug release and surface morphology from the developed formulations surface coated tablets before and after dissolution studies was examined using scanning electron microscope (Leica, Bensheim, Switzerland).
Accelerated stability studies: The packed tablets in air tight container was kept in stability chambers (Thermo lab Scientific equipment Pvt.Ltd., Mumbai, India) maintained (Kanagale, 2007) at 40±2^{0}C/75±5% RH conditions for accelerated testing) for 3 months. Tablets were subsequently taken off and examined for physical characteristics such as hardness, friability, drug content, *in-vitro* dissolution study etc.

3. RESULTS ANS DISCUSSION

FTIR studies: .In the optimized formulation peaks at 3328.22, 2851.24, 2040.71, 1394.00, and 1016.59 cm^{-1} were due to presence of the drug ritonavir (Figures.1, 2), peak at 3673.51, 1646.80, 1523.70, and 754.71 cm^{-1} were due to presence of the polymer HPMCE5LV. In the formulation the peaks present due to fructose were 2097.34, 1923.37,

and 833.73 cm^{-1}. Hence it can be confirmed that the major peaks of drug 3328.22, 2851.24, 2040.71, 1394.00, and 1016.59 cm^{-1} remain unchange and no interaction was found between the drug and excipients.

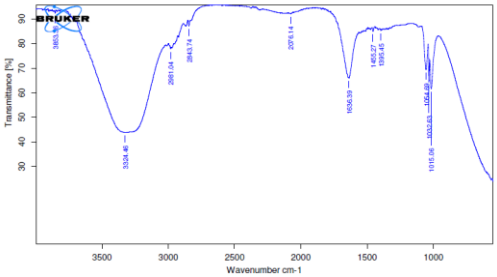


Figure.1. FTIR spectroscopy study of pure ritonavir

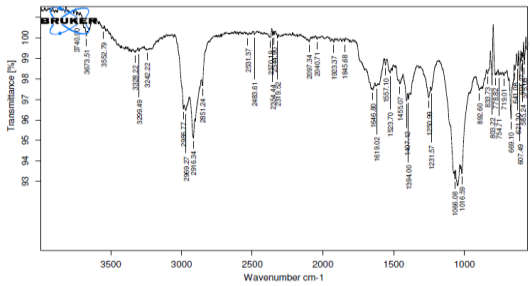


Figure.2. FTIR spectroscopy study of RF5

DSC thermograms: Endothermic peak at 122.5^{0}C (Figure.3) is obtained from DSC thermogram which is corresponding melting point of drug. DSC thermogram showed an endothermic peak at 124.7^{0}C in RF5 formulation (Figure.4). Hence physical mixture showed that there was compatibility with the drug.

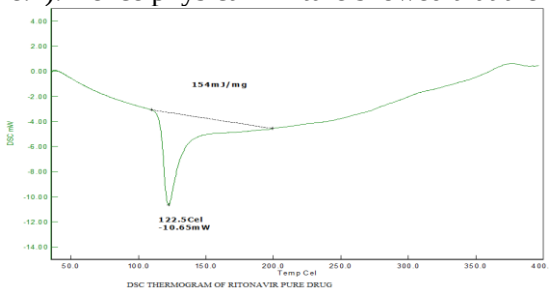


Figure.3. DSC thermo gram of ritonavir

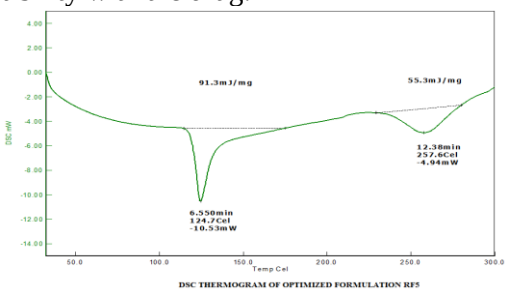


Figure.4. DSC thermo gram of RF5

Pre compression parameters: The formulated blend for various batches were determined for angle of repose, bulk density, tapped density, Carr's index and Hausner's Ratio. The angle of repose of granules of various batches was in the range of 24.11±0.07 to 29.11±0.08.The bulk density of granules were determined in range 0.514±0.06 to 0.521±0.12 gm/ml, tapped density falls in between 0.554±0.06 to 0.566±0.12 gm/ml, the Carr's index values were in the range of 5.95±0.08 to 8.65±0.11, and Hausner's ratio values were ranges of 1.06±0.08 to 1.09±0.06.It is given in Table.3.

Table.3. Pre compression parameters of powder blend

Formulation code	Angle of repose (degree)[a]± S.D	Bulk density (gm/ml)[a]± S.D
RF1	29.11±0.08	0.519±0.07
RF2	28.56±0.06	0.515±0.08
RF3	26.32±0.07	0.514±0.06
RF4	25.20±0.06	0.517±0.08
RF5	24.11±0.07	0.521±0.12

Formulation code	Tapped density (gm/ml)[a]± S.D	Carr's Index (%)[a]± S.D	Hausner's Ratio[a]± S.D
RF1	0.557±0.08	6.82±0.08	1.07±0.06
RF2	0.554±0.06	7.57±0.08	1.07±0.06
RF3	0.559±0.08	8.05±0.06	1.08±0.08
RF4	0.566±0.12	8.65±0.11	1.09±0.06
RF5	0.554±0.14	5.95±0.08	1.06±0.08

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

Post compression parameters: Thickness, coat thickness, hardness, friability, weight variation, drug content and diameter of tablet for various batches were determined as post compression parameters. The thickness of formulated tablets was determined in between 4.49±0.08 to 4.63±0.06 mm, coat thickness falls between 101.3±2.9 to 499.29±3.6 µm, the hardness values were in between of 5.9±0.16 to 7.0±0.16kg/cm^2, the friability values were in range of 0.12±0.06 to 0.27±0.04, average weight of tablet was in between 948.9±1.03 to 952.1±1.14 mg, drug content of tablet was in between 98.07±2.14 to 100±1.03 and diameter of tablets values were ranges of 12±0.03 to 12.09±0.02 mm. It is mentioned in Table.4.

Table.4. Post compression parameters of controlled porosity osmotic pump 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
RF1	4.49±0.08	499.29±3.6	5.9±0.16	0.21±0.06
RF2	4.63±0.06	401.3±3.4	6.4±0.13	0.17±0.03
RF3	4.57±0.04	302.1±3.7	6.1±0.14	0.27±0.04
RF4	4.55±0.02	201.2±3.4	6.5±0.15	0.15±0.07
RF5	4.50±0.04	101.3±2.9	7.0±0.16	0.12±0.06

Formulation code	Average wt.of 1tablet(mg)[b] ± S.D	%Drug content (%)[a] ± S.D	Diameter(mm)[a] ± S.D
RF1	948.9±1.03	98.07±2.14	12.09±0.02
RF2	951.4±1.12	98.39±1.08	12.05±0.03
RF3	950.6±1.13	100±1.03	12.01±0.04
RF4	952.1±1.14	99.68±1.06	12±0.05
RF5	950.1±1.13	99.03±1.16	12±0.03

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

***In vitro* drug dissolution study:** RF1, RF2, RF3, RF4, and RF5 formulations exhibited 83.88, 84.98, 86.46, 87.82, and 97.13% respectively of ritonavir at 14hrs.It is shown in figure.5.

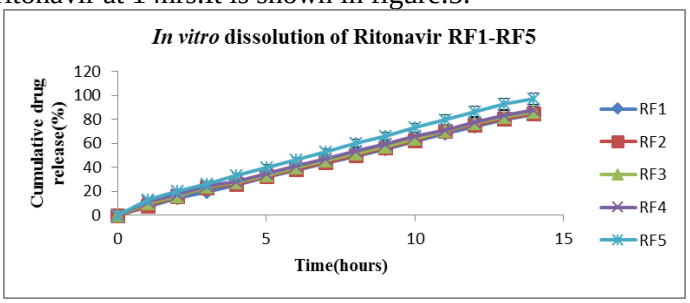


Figure.5. *In vitro* release profiles showing Ritonavir release from various fabricated formulations RF1-RF5

Kinetic model: From the kinetic study it is observed all formulation follows non-Fickian transport mechanism.

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
RF1	0.999	6.018	0.948	0.122	0.932	24.54	0.999	6.870	0.951	0.979	0.147
RF2	0.998	6.012	0.946	0.126	0.936	24.59	0.997	8.053	0.888	0.977	0.149
RF3	0.998	6.061	0.939	0.131	0.939	24.82	0.995	9.120	0.840	0.974	0.154
RF4	0.997	6.109	0.938	0.135	0.944	25.10	0.994	10.000	0.809	0.975	0.158
RF5	0.996	6.771	0.847	0.207	0.948	27.87	0.994	11.614	0.792	0.944	0.207

Effect of osmogen concentration: Due to osmogent the release profile of drug enhanced. It is clear that the drug release is directly related to osmogen concentration. It is depicted in figure.6.

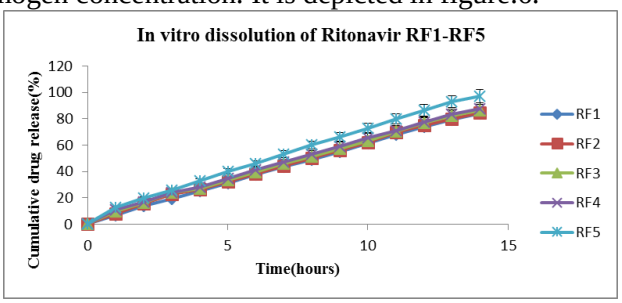


Figure.6. *In vitro* release profiles showing Ritonavir release from various fabricated formulations RF1-RF5 having different concentrations of osmogen

Effect of pore former: Release profile from prepared formulations is shown in figure.7. It is clearly evident that the level of sorbitol had a direct effect on drug release. As the level of pore former increases the membrane becomes more porous after coming contact with aqueous environment resulting in faster drug release.

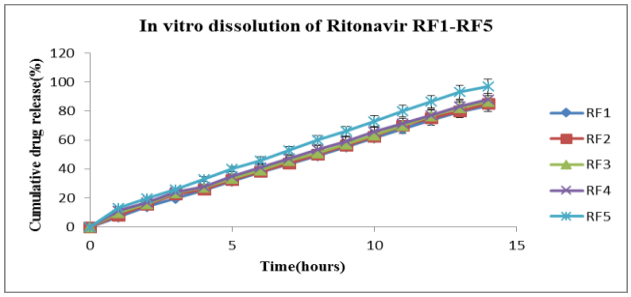


Figure.7. *In vitro* release profiles showing Ritonavir release from various fabricated formulations RF1-RF5 having different concentrations of pore former

Effect of membrane thickness: Release profile of ritonavir from these formulations is shown in figure.8. It is clearly evident that drug release decreases with increase in coating thickness of the semi permeable membrane.

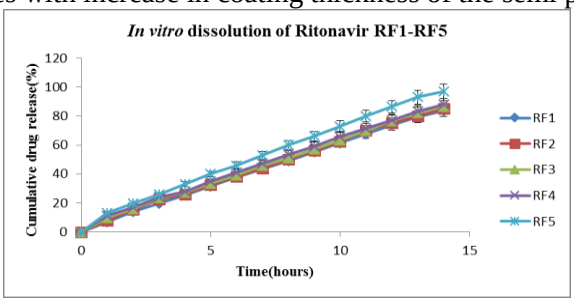


Figure.8. *In vitro* release profiles showing Ritonavir release from various fabricated formulations RF1-RF5 having different membrane thickness

Effect of osmotic pressure: The drug release results were inversely proportional to the osmotic pressure on dissolution media. This finding confirms that the mechanism of drug release is by osmotic pressure. The drug release for RF5 was obtained to be 88.81% for 30 atm, 83.42% for 60 atm and 80.14% for 90 atm respectively. It is depicted figure.9.

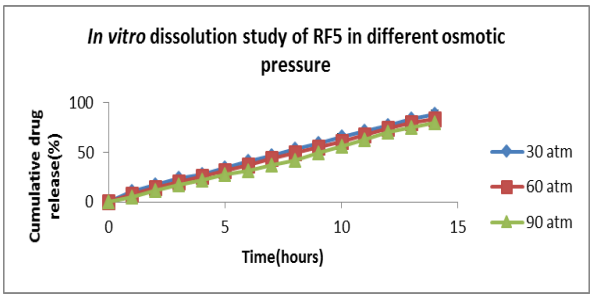


Figure.9. *In vitro* release profiles showing Ritonavir release from best RF5 in different osmotic pressures

Effect of pH: From the results for optimized formulation it was observed that the pH effect on release media has no significant difference in the release profile, demonstrating that the formulated batch showed pH independent release. It was depicted in figure.10.

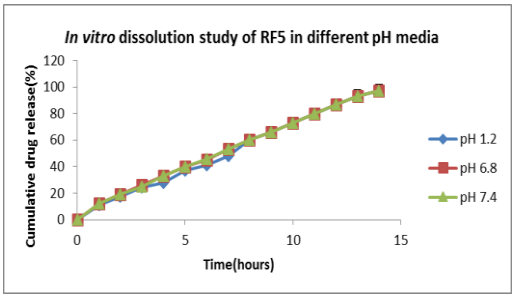


Figure.10. *In vitro* dissolution study of best formulation RF5 in various pH media

Effect of agitation intensity: From the result of drug release the optimized batch showed that the release of ritonavir from CPOP was independent of agitation intensity. It is depicted in figure.11.

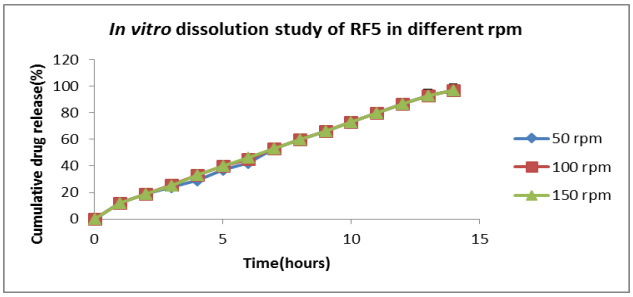
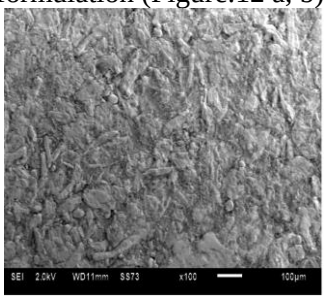


Figure.11. *In vitro* dissolution study of best formulation RF5 in various agitation speed

SEM analysis: SEM study confirmed that before dissolution less pores were found in the SPM, but after dissolution comparatively more numbers of pores were found in the membrane might be due to leaching or removal of active ingredient from the formulation. The porosity nature of the membrane was due to the presence of pore forming agent sorbitol in the formulation (Figure.12 a, b).



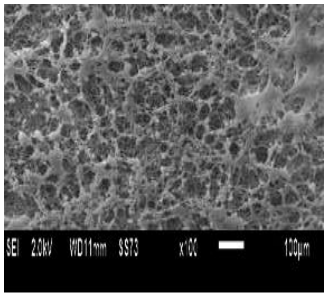


Figure.12. (a) SEM image of RF5 before dissolution, (b) SEM image of RF5 after dissolution

Stability studies: The optimized formulation does not change significantly in physical appearance, thickness, hardness, friability, weight variation and drug content and % drug release. It is shown in table.6.

Table 6. Comparative physicochemical characterization of RF5 at accelerated conditions

Sl.no.	Parameters	Initial	After 30 days	After 60 days	After 90 days
1.	Physical appearance	Pale white, circular, concave smooth surface without any cracks	No change	No change	No change
2.	Thickness(mm)[a] ± S.D	4.50±0.04	4.50±0.04	4.49±0.03	4.49±0.07
3.	Hardness(kg/cm^2)[a] ± S.D	7.0±0.16	7.0±0.16	6.9±0.15	6.8±0.12
4.	Friability(%)[a] ± S.D	0.12±0.06	0.12±0.06	0.11±0.08	0.11±0.03
5.	Weight variation(mg)[b] ± S.D	950.1±1.13	950.1±1.13	949.9±1.14	949.8±1.12
6.	Drug content(%)[a] ± S.D	99.03±1.16	99.03±1.16	98.78±1.12	98.26±1.11
7.	Diameter(mm)[a] ± S.D	12±0.03	12±0.03	12±0.03	11.99±0.02

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

4. CONCLUSION

The desired release of ritonavir from CPOP was gained through careful monitoring of the selected formulation variables. It was evident that increase in concentration of osmogen the drug release from the system was found to be increased.

5. ACKNOWLEDGEMENTS

The authors would like to acknowledge the contributions of Pharmaceutics Department, Faculty of Pharmacy, University College of Technology Osmania University, Hyderabad, Telangana, India for providing necessary facilities to carry out the research work. This study was part of a Ph.D thesis under Osmania University, Hyderabad.

REFERENCES

Banerjee A, Verma P.R.P, Gore S, Controlled porosity solubility modulated osmotic pump tablets of Gliclazide, AAPS Pharm Sci Tech, 16 (3), 2015, 554-568.

Biswas M, Gupta RN, Parhi R, Sethi KK, Sahoo S.K, Formulation and in vitro evaluation of gastroretentive floating drug delivery system of ritonavir, Turk. J. Pharm. Sci. 10 (1), 2013, 69-86.

Chein YW, Novel Drug Delivery Systems ed by Chein YW, Marcel Dekker, Inc., New York, USA, 1992, 139-196.

Cooper J, Gunn C, Powder flow and compaction. In: Carter SJ, eds. Tutorial Pharmacy, New Delhi, India, CBS Publishers and Distributors, 1986, 211-233.

Gondaliya D, Pundarikakshudu K, the Fabrication and Evaluation of the Formulation Variables of a Controlled-Porosity Osmotic Drug Delivery System with Diltiazem Hydrochloride, Pharmaceutical Technology, 2003, 58-68

Jilakara V.S, Chowdary Y.A, Formulation and evaluation of sustained release matrix tablets of zidovudine, Int.J.Pharm.Sci.Rev.Res.18 (1), 2013, 143-149.

Kanagale P, Lohray B.B, Misra A, Davadra P, Kini R, Formulation and Optimization of Porous Osmotic Pump based Controlled Release System of Oxybutynin, AAPS Pharm SciTech, 8 (3), 2007, E1-E7.

Kanakal M.M, Sakeena M.H.F, Azmin M.N, Yusrida D, Effect of Coating Solvent Ratio on the Drug Release Lag Time of Coated Theophylline Osmotic Tablets, Tropical Journal of Pharmaceutical Research, 8 (3), 2009, 239-24.

Kumaravelrajan R, Narayanan N, Suba V, Development and evaluation of controlled porosity osmotic pump for Nifedipine and Metoprolol combination, Lipids in Health and Disease, 10, 2011, 51

Panda N, Reddy AV, Reddy GVS, Panda KC, Formulation Design and in vitro Evaluation of Zolmitriptan Immediate Release Tablets using Primojel and AC-Di-Sol, J. Pharm. Sci. & Res.7 (8), 2015, 545-553.

Reza K.H, Sancheti V.N, Kumaravelrajan R, Formulation and optimization of aceclofenac monolithic osmotic pump, International Journal of Pharmaceutical Sciences Review and Research, 6 (2), 2011, 42-47.

Sahoo C.K, Rao S.R.M, Sudhakar M, Evaluation of controlled porosity osmotic pump tablets: a review, Research J. Pharm. and Tech, 8 (12), 2015, 119-125.

Sahoo C.K, Rao S.R.M, Sudhakar M, Kokkula S, The kinetic modeling of drug dissolution for drug delivery systems: an overview, Der Pharmacia Lettre, 7 (9), 2015, 186-194.

Sahoo C.K, Rao S.R.M, Sudhakar M, Sahoo N.K, Advances in osmotic drug delivery system, J of Chemical and Pharmaceutical Research, 7, 2015, 252-273.

Sahoo C.K, Sahoo N.K, Rao S.R.M, Sudhakar M, A Review on Prevention and Treatment of Aids, Pharm Pharmacol Int J , 5 (1), 2017, 00108.

Sahoo C.K, Sahoo N.K, Rao S.R.M, Sudhakar M, Satyanarayana K, Areview on controlled porosity osmotic pump tablets and its evaluation, Bulletin of Faculty of Pharmacy, Cairo University, 53 (2), 2015, 195-205.

Sirisha V.N.L, Kumarrao Y.K, Eswaraiah M.C, Formulation and evaluation of lamivudine and zidovudine extended release tablets, Int. J. of Research in Pharmaceutical and biomedical Sciences, 3 (4), 2012, 1759-1763.

Verma R.K, Krishna D.M, Garg S, Formulation aspects in the development of osmotically controlled oral drug delivery systems, J control release, 79, 2000, 7-27.

Vidyadhara S, Sasidhar R.L.C, Rao V.U.M, Babu C.H.S, Lakshmi D, Harika, Formulation and evaluation of verapamil hydrochloride osmotic controlled release matrix tablets, Asian J Pharm, 8, 2014, 102-109.

Zenter G.M, Rork G.S, Himmelstein K.J, The controlled porosity osmotic pump, J control release, 1, 1985, 269-282.