DESIGN, PREPARE, AND CHARACTERIZATION OF ELEMENTARY OSMOTIC PUMP TABLETS OF RITONAVIR

ESLAVATH VENKANNA[1], B. SREEDEVI[1], BHARGAV BHONGIRI[2]*
1-Department of Pharmaceutics, TRR College of Pharmacy, Meerpet, Saroornagar (M), Rangareddy District, Hyderabad.
2-Associate Director, Synpharma Research lab, Dilsukhnagar, Hyderabad, Telangana.

ABSTRACT :
Ritonavir which is oral hypoglycaemic drug belongs to BCS Class IV was selected as a model drug to prepare controlled porosity osmotic pump (CPOP) tablet. The effect of different formulation variables - such as the level of solubility modifier in the core, membrane weight gain, and level of pore former in the membrane - were studied. Drug release was found to be affected by the level of solubility modifier present in the core. Ritonavir release was inversely proportional to the membrane weight but directly related to the initial level of pore former (in the membrane. Controlled porosity osmotic pump (CPOP) based drug delivery system contains active ingredient, osmogens, semi-permeable membrane, channelling agent, and water soluble additives. In this system, when water comes in contact with water-soluble additives, it results in an in situ formation of a Microporous membrane. The main driving force for the release of the drug is osmotic pressure. Osmogens maintain concentration gradient across the membrane. The present study deals with Controlled porosity osmotic pump tablets and its basic components.
Key words: Ritonavir, osmotic drug delivery, osmosis, direct compression technique, coating and in vitro drug release studies.

I.INTRODUCTION

Majority of the oral dosage forms fall in the category of matrix, reservoir, or osmotic systems. Osmotic devices, use technology that delivers the drug at a zero-order rate and minimizes the drug plasma concentration fluctuations, thus reducing the adverse reactions, and improving the patient compliance. Osmotic systems utilize the principles of osmotic pressure for controlled delivery of drugs. Drug release from these systems is independent of pH and other physiological parameters to a large extent.[1]Osmotic drug delivery system (ODDS) has major advantages over other DDS like gastro-retentive and mucoadhesive platforms. ODDS drug release does not depend on pH, hydrodynamic conditions of the body, and agitation intensity.[2]The devices are made up of core and semi permeable membrane that coats the core, having an orifice to release the active material. The core contains an active material and an osmotic agent.[3] 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. It belongs to BCS Class-II drug. Ritonavir is metabolized in the liver, and the half-life5 is 3-5 h .Hence, in the present study the controlled-release 600 mg ritonavir osmotic pump tablets were formulated as a once daily medication using direct compression technique.[4]

II. MATERIALS

Ritonavir was obtained from Micro Labs, HYD. Sodium alginate, HPMC and Sodium chloride were procured fromSynpharma Research Lab, Hyderabad. Other chemicals and the reagents used were of analytical grade.

Methodology

Drug - excipient compatibility studies[5]

The IR absorption spectra of the Ritonavir drug and with different and excipients were taken in the range of 4000-450 cm^{-1} using KBr disc method, 1-2 mg of the substance to be examined was triturated with 300-400 mg, specified quantity, of finely powered and dried potassium bromide. These quantities are usually sufficient to give a disc of 10-15mm diameter and pellet of suitable intensity by a hydraulic press. The scans were evaluated for presence of principle peaks of drug, shifting and masking of drug peaks due to presence polymers and exipients.

Formulation development

Preparation of Ritonavir tablets:[6]

Drug layer composed of Ritonavir. Polymers are weighed accurately and passed through 44#. Pass Sodium

chloride through 60# and mixed properly. The powder are lubricated with Magnesium stearate and talc as a glidant, which is passed through 60#. Blend it in a blender for 5 minutes. The prepared blend was placed in die cavity and compressed by 6 mm round standard concave punches.

Table-1: Formulation table of the Ritonavir osmotic pump core tablets

Ingredients	**F1**	**F2**	**F3**	**F4**
Ritonavir	50	50	50	50
Nacl	10	20	30	40
Magnesium stearate	3	3	3	3
Microcrystalline cellulose	35	25	15	5
Talc	2	2	2	2
Total wt	100	100	100	100

Coating of core tablets[7]Formulation of osmotic pump Tablets by Press Coated Technology. The core tablets were compressed using polymer blend which has composition of HPMC and ethyl cellulose in different concentrations. Half of the coating polymer material was placed in the die cavity, then the core tablet was carefully sited in the centre of the die and cavity was filled on the top with the other half of the coating polymer material. Then the tablet was compressed using Rimektablet machine, with 8 mm punch.

Table-2: Formulation table of the Ritonavir osmotic pump tablets

Ingredients	**F1**	**F2**	**F3**	**F4**
Core tablet	100	100	100	100
HPMC	50	100	-	-
Ethyl cellulose	-	-	50	100

Evaluation parameters[8,9,10]

Weight variation

The prepared osmotic pump tablets are under kept for the weight variation study the randomly about 20 tablets are taken and measure the individual weight of the tablet

$$\text{Percentage Deviation} = \frac{\text{Individual weight} - \text{average weight}}{\text{Average weight}} \times 100$$

Thickness

The prepared tablets are under kept for theThickness by using Verniar calipers.

Hardness test

Thehardness test is also done by using Pfizer hardness tester. The six Tablets were randomly selected from each batch and hardness of each tablet was determined by using a Pharma instruments.

Friability test

The friability test is done by using the friability apparatus. The test is for the knowing of the strength of the tablets. The 10-15 tablets are taken and measure the individual weight of the tablets that is initial weight after that the measured tablets are poured in the Roche friability apparatus. It is operated at 25 rpm for 4mins about 100 revaluations. Tablets were de-dusted and weighed again. The fallowing equation is used for the calculating of the %of friability,

$$\mathbf{F} = \frac{\text{Initial wt} - \text{final wt}}{\text{Initial}} \times \mathbf{100}$$

Drug content estimation

The Ritonavir tablets were tested for their drug content. About to take 20 tablets and crush it properly from curshed powder take 100 mg of the powder that equivalent to the Ritonavir drug substance. The powder is taken in the 100ml of the volumetric flask with the 6.8 pH phosphate buffer solution. The phosphate buffer solution is kept on the sonication for 30mins. The 1ml of solution is taken and it is kept for the absorbance in U.V visible spectroscopy at 269 nm.

In-vitro Dissolution studies[11]

In vitro drug release studies are performed by using USP-II apparatus paddle type .The prepared tablets are under kept in the dissolution studies. The sink condition should be maintained. The temperature is maintained for 37.5^0c. The drug release studies performed for 9hrs. The 1ml of sample is withdrawn from the basket and same amount of sample is placed in the basket to maintain the sink conditions. The 6.8 buffer solution is used for the In-vitro drug release studies. The medium is about 900ml. The sample is withdrawn and under kept for the analysing of the absorbance under U.V at 269 nm.

Stability studies[12]

The success of an effective formulation can be evaluated only through stability studies. The prepared Ritonavir osmotic pump tablets were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 90days.

RESULTS AND DISCUSSION

Compatibility Study

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

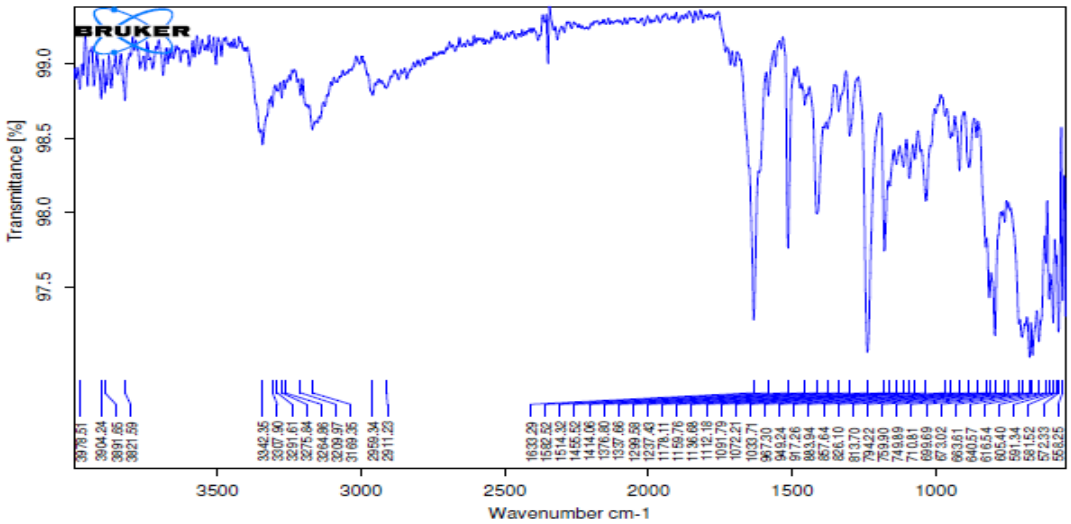

Fig-1: FTIR Spectra of Ritonavir

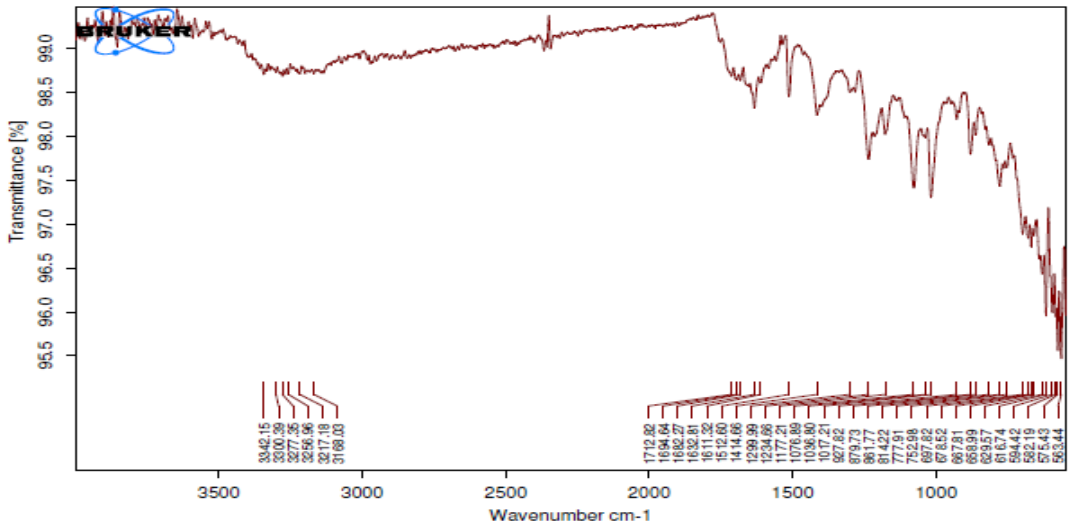

Fig-2: FTIR Spectra of Optimized formulation

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

Evaluation of core Tablets:

Weight variation test: It was carried out as per official method and the average percentage deviation of all the formulation was found to be within the limit (as per USP standard).

Content uniformity: Was also carried out as per official method and it was found that all batches shows good content uniformity. The values for all the formulations were in the ranges from 89.42-95.90%.

Hardness test: States that all the formulations were found in the range 5to 8 kp.

Friability test: Compressed tablets have lose less than 1 %of their weight are generally considered acceptable. All the formulations have less than 1% friability.

Table-3: Results of Evaluation parameters of tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	300	6.09	5.82	0.65	95.90
F2	299	5.99	5.65	0.64	89.42
F3	300	6.05	5.42	0.61	93.80
F4	400	6.12	5.22	0.60	92.82

In vitro drug release studies

Table-4: Cumulative % of drug release of all formulations

Time (hrs.)	F_1	F_2	F_3	F_4
0	0	0	0	0
1	28.44	22.40	20.30	21.52
2	32.51	32.28	29.75	30.52
3	43.79	42.65	34.80	41.21
4	50.72	50.20	48.40	49.85
5	59.18	55.81	52.50	58.62
6	65.22	63.76	60.75	63.86
7	79.21	73.53	71.90	78.82
8	92.32	85.32	86.25	90.12

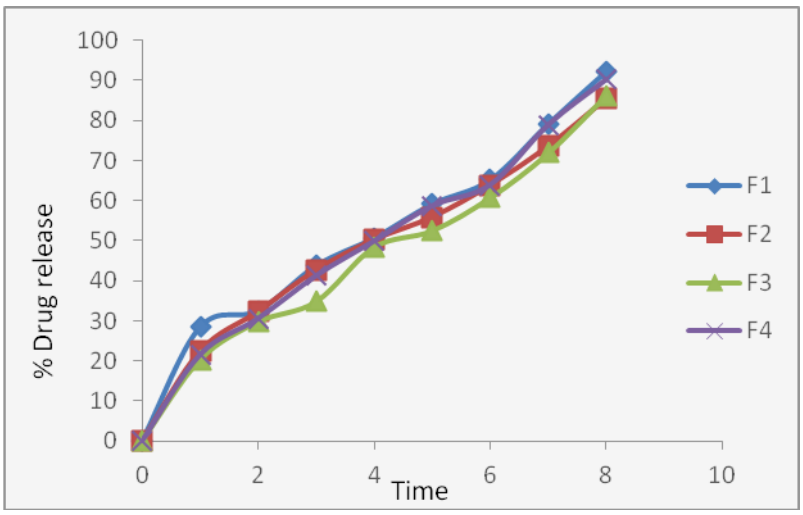

Fig-3: In vitro drug release of all formulations

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-1 after 3

months. Parameters quantified at various time intervals were shown.

Table-5: Results of stability studies of optimized formulation F1

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-1	25^{0}C/60%RH	92.32	92.13	91.24	90.75	Not less than 85%
F-1	30^{0}C/75% RH % Release	92.32	92.08	91.09	90.83	Not less than 85%
F-1	40^{0}C/75% RH % Release	92.32	92.02	90.89	89.89	Not less than 85%

CONCLUSION

Extended release formulations of Ritonavir were developed based on controlled porosity osmotic pump technology. Core tablets of Ritonavir were successfully prepared by direct compression for drug layer using Ritonavir, microcrystalline cellulose, sodium chloride, Magnesium stearate. After compression core tablets coated with HPMC as a polymer. *In vitro* release profile of formulation F1 was found to be release profile were found to be %. Finally the F1 formulation was optimized. The effect of different formulation variable was studied to optimize release profile. Drug release was directly proportional to the pore former, When we increase the concentration of pore former from 30 to 50% along with increase in osmogent ratio, the drug release also found to be increased. Drug release from the developed formulations was found to be independent of Hydrodynamic conditions of the body and depends on pH, because the solubility of the drug is pH dependent.

REFERENCES

1. Theeuwes F. Elementary Osmotic Pump. J Pharm Sci 1975;64; 1987-1991. 3. Theeuwes F, Swanson DR, Guittard G, Ayer A, Khanna S. Osmotic delivery systems for the β-adrenoceptor antagonists metoprolol and oxprenolol: Design and evaluation of systems for once-daily administration. Br J ClinPharmacol. 1985;19; 69S-76.
2. Kaushal AM, and Garg S.An update on osmotic drug delivery patents. Pharm. Tech. 27, 2003, 38-44. Patel NK and Mehta AT. A review on oral osmotically driven systems. Int. J Pharm PharmScim. 5(3), 2013, 1005-1013.
3. Ozdemir N, Sahin J, Design of a controlled release osmotic pump system of ibuprofen. Int J pharmaceutics. 1997;158;91.
4. 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.
5. G.A. McClelland, S.C. Sutton, K. Engle, G.M. Zentner, (1991), The solubility modulated osmotic pump: In vitro/ in vivo release of diltiazem hydrochloride, Pharm Res. 8, 88–92
6. Meena Rani, and Brahmeshwar Mishra, "Comparative In Vitro and In Vivo Evaluation of Matrix, Osmotic Matrix, and Osmotic Pump Tablets for Controlled Delivery of Diclofenac Sodium", AAPS PharmSciTech 2004; 5 (4) Article 71.
7. N.G.Raghvendra Rao, Ashok Yadav " Formulation and evaluation of zero order release glipizide bilayer matrix tablets using natural and synthetic polymers" International Journal of Current Pharmaceutical Research Vol 2, Issue 1, 2010.
8. Nurten Ozdemir ,Jfilide Sahin, "Design of a controlled release osmotic pump systemof ibuprofen", International Journal of Pharmaceutics 158 (1997) 91 9733. N.
9. Giancarlo Santus, Richard Baker W (1995), Osmotic drug Delivery: a review of the patent literature. J Control. Rel.; 35: 1-21
10. G.M. Zentner, G.A. McClelland, S.C. Sutton, (1991), Controlled porosity
11. solubility and resin-modulated osmotic drug delivery systems for release of diltiazem hydrochloride, J. Control. Release 16, 237–244.
12. Prabakaran D, Singh P, Kanaujia P, Jaganathan KS, Rawat A, VyasSP.Modified push-pull osmotic system for simultaneous delivery of theophylline and salbutamol: development and *in vitro characterization*.Int J Pharm 2004;284:95-108.