ISSN 0976 – 3333

Available Online at www.ijpba.info.

International Journal of Pharmaceutical & Biological Archives 2011; 2(3):914-920

ORIGINAL RESEARCH ARTICLE

Preparation And Optimisation Of Valsartan Bilayered Sustained Release Matrix Tablets

M.Soumya[*1], M. Saritha[2]

[1]Nova College of Pharmacy, Jangareddygudem Andhra Pradesh,India
[2] Associate Professor, Dept.of Pharmaceutics, Nova College of Pharmacy,Jangareddygudem , Andhra Pradesh, India.

Received 28 Apr 2011; Revised 01 May 2011; Accepted 16 Jun 2011

ABSTRACT

The purpose of the present investigation was to develop and optimize bilayered sustained release matrix tablets of Valsartan. The tablets contained an immediate releasing layer with the loading dose of the drug and a sustaining layer with maintenance dose of drug prepared by wet granulation method. The immediate releasing layer is directly compressed on to the sustaining layer. Sodium starch glycholate was used as super disintegrant and Eudragit RSPO and Eudragit RLPO were used as polymers. The drug polymer interaction was investigated by FTIR and DSC and their results directed further course of formulation. Valsartan tablets were evaluated for various post compression parameters like Tablet hardness, Friability, Weight variation, Drug content and In vitro dissolution. The results were found to be within the acceptable limits. A 3^2 full factorial design was applied to systematically optimize the drug release profile. The amounts of Eudragit RSPO (X1) and Eudragit RLPO (X2) were selected as independent variables. The time required for 90% ($t_{90\%}$) drug dissolution was selected as dependent variable. The formulations F1 to F4 showed that the drug release was concentration dependent and followed first order kinetics. While the formulations F5 to F9 showed that drug release followed zero order kinetics. Formulation F9 was selected as an optimized one where the drug from immediate layer was released with in15 min and then sustained for a period of 12 hrs**.** Kinetic treatment to the in vitro release data revealed that the drug release followed zero order non – fickian diffusion with n value greater than 0.45.

Key words: Valsartan,Eudragit RSPO,Eudragit RLPO,Bilayered tablets.

INTRODUCTION

Over the past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled release drug delivery systems.The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. If one were to imagine the ideal drug-delivery system, two prerequisites would be required. First, it would be a single dose for the duration of treatment, whether it is for days or weeks, as with infection, or for the lifetime of the patient, as in hypertension or diabetes. Second, it should deliver the active entity directly to the site of action, thereby minimizing or eliminating side effects.

This may necessitate delivery to specific receptors or to localization to cells or to specific areas of the body. It is obvious that this imaginary delivery system will have changing requirements for different disease states and different drugs. Thus, we wish to deliver the therapeutic agent to a specific site, for a specific time. In other words, the objective is to achieve both spatial and temporal placement of drug[1]. Currently, it is possible to only partially achieve both of these goals with most drug delivery systems.

Valsartan is a member of Angiotensin II Receptor Antagonist class of drugs and is an FDA approved drug for the treatment of hypertension, myocardial infarction and congestive heart failure. Bilayered SR tablets provide an immediate dose required for the normal therapeutic response, followed by the

***Corresponding Author:** M.Soumya**, Email:**dr. soumyamissula@gmail.com,**Phone No:** +91-9491953703

gradual release of drug in amounts sufficient to maintain the therapeutic response for a specific period of time. The major advantage of this category is that, in addition to the convenience of reduced frequency administration, it provides levels that are devoid of the peak and valley effect. They contain two layers formulated from the same drug. The first layer is a fast releasing layer consisting a loading dose of the drug while the second layer is a sustaining layer containing maintenance dose of the drug.

MATERIALS AND METHODS

Valsartan(Torrent research center, Bhat), Eudragit RSPO and Eudragit RLPO are obtained from Rhom pharma.Other ingredients used for the formulation include SodiumStarchglycholate ,lactose magnesium stearate and talc supplied by Loba Chemie pvt.LTD.

Preformulation (Compatibility) Studies:

(a) Fourier Transform Infrared Spectrophotometry (FTIR) [2,3]:

Compatibility study of valsartan with the excipients was determined by I.R. Spectroscopy (FTIR) using Perkin Elmer spectrum RX1 FT-IR spectrometer model. The pellets were prepared at high compaction pressure by using potassium bromide and the ratio of sample to potassium bromide is 1:100.The pellets thus prepared were examined and the spectra of valsartan and other ingredients in the formulations were compared with that of the original spectra.

(b) Differential scanning calorimeter (DSC) [4]:

Differential scanning calorimeter is used to measure the specific heat and enthalpies of transition. When a sample undergoes a thermal transition, the power to the heater is adjusted to maintain the temperature, and a signed proportional to the power difference is plotted on the second axis of the recorder,known as thermogram. The area under the resulting curve is direct measure of the heat of transition. Thermograms were obtained by using a differential scanning calorimeter (Shimadzu DSC 60) at a heating rate 20ºC /min over a temperature range of 50 to 300°C. The sample was hermetically sealed in an aluminum crucible.

Experimental Design:

A 3^2 full factorial design was utilized in the present investigation [5]. Two factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations. The amount of Eudragit RSPO (X1) and the amount of Eudragit RLPO (X2) were selected as independent variables. The time required for 90% in vitro drug dissolution, was selected as dependent variable. This design resulted in 9 batches and it was summarized in (**Table 1.1**).

Table 1.1: Levels Of Factors

Combination	Factors	
	X1	X2
(-1,-1)	-1	-1
(-1,0)	-1	0
(-1,+1)	-1	+1
(0,-1)	0	-1
(0,0)	0	0
(0,+1)	0	+1
(+1,-1)	+1	-1
(+1,0)	+1	0
(+1,+1)	+1	+1

Factor	X1	X2
High level	-1	-1
Middle level	0	0
Low level	+1	+1

Formulation of Bilayered Sustained Release Matrix Tablets of Valsartan:

Calculation of Loading and Maintenance dose [6]:

Theoretical Sustained-release profile needed for valsartan was evaluated based on its pharmacokinetic parameters. The composition of the tablets was presented in (**Table 1.2**). The formuation involves the calculation of loading dose (Di) desired release rate (Ks), maintenance dose (Dm) and total dose needed for valsartan bilayered SR matrix tablets for twice daily administration as follows: -

- Oral dose: 40 mg
- Dosing Interval (τ): 12 hours
- Elimination Half-life ($t_{1/2}$): 6 h
- Time of peak concentration (tp): 2 hours
- Elimination rate constant (Ke): $0.693/ t_{1/2}$
  $= 0.693/6$
- Initial dose (Di): Css.Vd / F
  But, $Css = F.Xo/ Ke.Vd.\tau$
  Thus, $Di = F.Xo / Ke.Vd.\tau * Vd / F$
  $= Xo / Ke. \tau$
  $= 40 / 0.1155*12$
  $= 28.86$ mg
- Desired rate of drug release (Ks): Di * Ke
  $= 28.86 * 0.1155$
  $= 3.3333$ mg / hr
- Maintenance dose (Dm): Ks * τ

= 3.3333 * 12
= 40 mg

- Corrected initial dose (Di^*): Di – (Ks * t_p)
= 28.86 – (3.33 * 2)
= 22 mg
- Total dose (Dt): Dm + Di^*
= 40 + 22
= 62 mg

Table 1.2: Translation Of Coded Levels

Code	Eudragit RSPO (X1)	Eudragit RLPO (X2)
-1	25 mg	25 mg
0	37.5 mg	37.5 mg
1	50 mg	50 mg

Preparation of immediate releasing (Loading dose) layer [7]:

Immediate releasing layer containing 22 mg of valsartan was prepared by direct compression method employing Sodium starch glycholate as super disintegrant.Finally mixed with weighed quantities of talc and magnesium stearate and directly punched over the sustaining layer.(**Table 2.1**)

Table 2.1: Formula For Immediate Release Layer

S.no	Ingredients	Quantity(mg)
1	Valsartan	22
2	Sodium Starch Glycholate	2.2
3	Magnesium Stearate	0.5
4	Talc	0.5

mg-milligram

Preparation of sustaining (maintenance dose) layer:

Sustaining layer containing 40 mg of valsartan as maintenance dose was prepared by wet granulation method .All the materials were first screened though mesh No.40 to break any lumps. Accurately weighed quantity of drug was then mixed thoroughly with required quantity of polymers Eudragit RSPO and RLPO and diluent lactose in a mortar for about ten minutes. The resultant mixture was then granulated with prepared 10% starch mucilage to form a coherent mass. It was then passed through sieve No.16. The formed granules were then dried in an oven at 65º C for 1 hour. The dried granules were then lubricated with calculated quantity of talc and magnesium stearate. Then the granules were sized by passing through sieve No.22. The granules were then punched to form tablets with an average weight of about 200mg/tablet (total tablet) (**Table 2.2**).

Table 2.2: Formula for Sustaining Release Layer

S.N	Formulation code	Valsartan (mg)	Eudragit RSPO(X1) (mg)	Eudragit RLPO (X2) (mg)	Lactose (mg)	Talc (mg)	Magnesium stearate(mg)
1	F1	40	-1	-1	77.8	3.5	3.5
2	F2	40	-1	0	65.3	3.5	3.5
3	F3	40	-1	1	52.8	3.5	3.5
4	F4	40	0	-1	65.3	3.5	3.5
5	F5	40	0	0	52.8	3.5	3.5
6	F6	40	0	1	40.3	3.5	3.5
7	F7	40	1	-1	52.8	3.5	3.5
8	F8	40	1	0	40.3	3.5	3.5
9	F9	40	1	1	27.8	3.5	3.5

Evaluation of Physical Properties of Tablets:

The formulated tablets were evaluated for the following parameters.

1. Thickness:

The thickness and diameter of the formulated tablets were measured by using Vernier calipers.

2. Weight variation:

The formulated tablets were tested for weight uniformity. 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is within the permissible limit [8].

$$\% \text{ Weight Variation} = \frac{\text{Average weight-Individual weight}}{\text{Average weight}} \times 100$$

3. Hardness:

The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Pfizer tablet hardness tester.

4. Friability:

The Roche friability test apparatus was used to determine the friability of the tablets. 20 pre

weighed tablets were placed in the apparatus, which was subjected to 100 revolutions. Then the tablets were reweighed. The percentage friability was calculated using the formula.

$$\% \text{ Friability} = \frac{\text{Initial weight- Final weight}}{\text{Initial weight}} \times 100$$

5. Drug content:

About 50 mg of valsartan was weighed accurately and transferred into a 50 ml volumetric flask. It was dissolved, suitably diluted and made up to volume with Phosphate Buffer pH 6.8.One tablet was powdered and powder equivalent to 50 mg of valsartan was transferred to a 50 ml volumetric flask and was dissolved in Phosphate Buffer pH 6.8. It was sonicated for 30 min and filtered through 0.45 membrane filter. The absorbance after suitable dilutions was measured in a UV-visible Spectrophotometer at 250 nm using PBS pH 6.8 as blank.

6. In vitro release studies:

The release of valsartan from the bilayered tablet was studied in 900 ml of phosphate buffer pH 6.8 as dissolution medium using a USP dissolution paddle apparatus at 50 rpm and 37 ± 0.5^o C. An aliquot (2 ml) was withdrawn at specific time intervals, filtered and diluted to 10 ml with phosphate buffer pH 6.8 and drug content was determined by UV-visible spectrophotometer at 250 nm[9,10]. An equal volume of fresh dissolution medium was replaced to maintain the sink conditions. Dissolution studies were performed for a period of 12 hrs and percentage of drug release was calculated using an equation obtained from a standard curve.

RESULTS AND DISCUSSION:

Preformulation Studies:

The FT- IR Spectrum of pure valsartan drug was compared with the FT- IR spectrum of physical mixture of valsartan (valsartan, Eudragit RSPO and Eudragit RLPO) were showed in (**Fig. 1.1& 1.2**).

The characteristic functional groups of the pure valsartan and physical mixtures of valsartan and polymers showed the peaks at the following wave number region. C-H stretching (Alkane) - 2964.36 cm^{-1},2874.61 cm^{-1};Ketone stretching (Acyclic saturated) – 1732.16 cm^{-1};Hydroxyl stretching (bonded) – 2613.05 cm^{-1}, 2595.55 cm^{-1};N-H bending (Aromatic secondary amine) – 1602.16 cm^{-1},1512.50 cm^{-1};C-N vibration (Aromatic tertiary amine) – 1206.39 cm^{-1},1198.42 cm^{-1},1106.04 cm^{-1};Aliphatic tertiary amine – 1410.82 cm^{-1} . There was no appearance or disappearance of any characteristics peaks. This shows that there is no chemical interaction between the drug and the polymers used .The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions occurred.

Fig 1.1FTIR spectra of pure Valsartan drug.

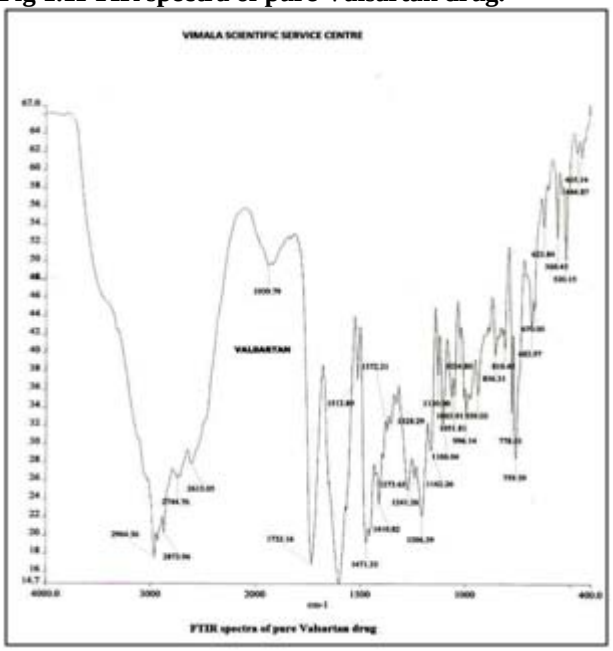
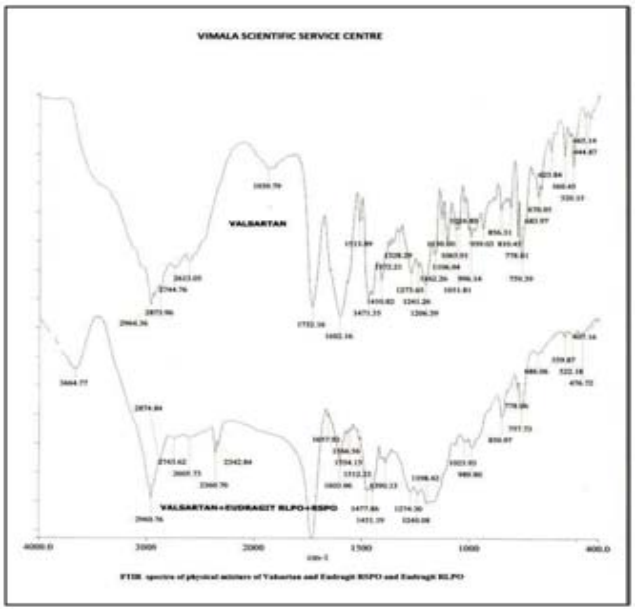


Fig 1.2 FTIR spectra of physical mixture of Valsartan and Eudragit RSPO and Eudragit RLPO.



DSC study:

DSC thermogram of pure drug has shown a melting endotherm at 116.92°C. The thermogram of physical mixture of Valsartan and polymers Eudragit RSPO and Eudragit RLPO also showed

the Valsartan melting endotherm at 116.92°C.and another peak at about 175.1°C, which may be because of the presence of polymers in the physical mixture. The DSC spectra's were shown in the (**Fig 2 & 3**).

The formulation was designed according to the 3^2 full factorial designs where total 9 formulations were prepared with different combination of polymers. All nine formulations were having similar fast releasing layer (**Fig 4**). The quality control tests adopted for the tablets were depicted in the (**Table 3 & 4**). The hardness of the tablets ranged between 5.3±0.07 Kg/Cm^2 to 6.18±0.1 Kg/Cm^2, the thickness of the tablets ranged between 2.38±0.08 mm to 2.56±0.05 mm. The percent friability of the prepared tablets was well within acceptable limit. The percentage friability of all batches ranged from 0.54±0.03 % to 0.79±0.09%. There was no significant weight variation observed between average weight and individual weight. The drug content in all the formulations was with in the range of 99.23±0.02 % to 99.76±0.04%, ensuring uniformity of drug content in the formulations.

The drug release followed first order kinetics for formulations F1 to F4 (**Fig 5**) and formulations F5 to F9 (**Fig 6**) followed zero order kinetics. To ascertain the mechanism of drug release the data was subjected to Higuchi & Korsmeyer Peppas equation [11,12]. Application of Korsmeyer Peppas equation to the data showed that the mechanism of drug release of valsartan from the matrix tablets is governed by non fickian diffusion (slope > 0.45), and the release rate was found to be influenced by the concentration of polymers employed in the preparation of tablets. Formulations F1 to F5 with low polymer concentration released the total drug before 12 hrs while the formulations F6 to F9 with high polymer concentration sustained the drug release till the end of 12 hrs (**Table 5**).

The bilayered tablets showed an initial burst effect to provide a loading dose of the drug, followed by sustained release for 12 hrs, indicating a promising potential of the valsartan bilayered tablet as an alternative to the conventional dosage form. The results of the experimental study confirm that the polymer concentration significantly influence the dependent variable $t_{90\%}$. The tablets of optimized formulation F9(Eudragit RSPO – 50mg and Eudragit RLPO – 50 mg) showed $t_{90\%}$ of 12.06 hrs.

Fig 2: DSC Spectra of Valsartan pure drug.

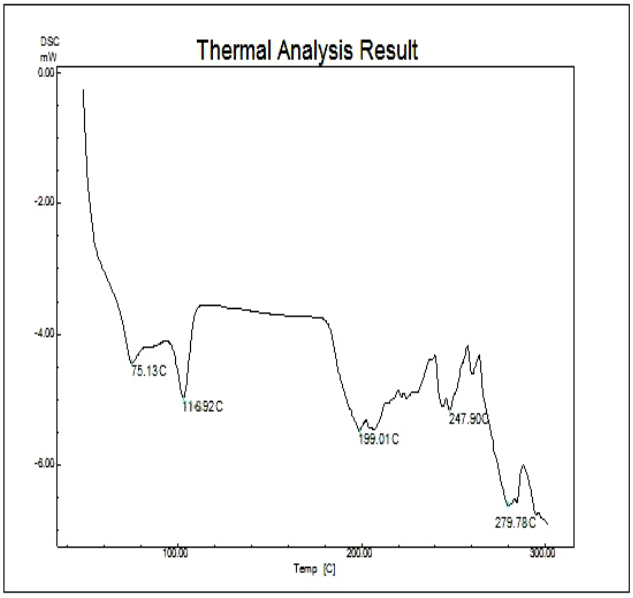


Fig 3: DSC Spectra of valsartan and polymers.

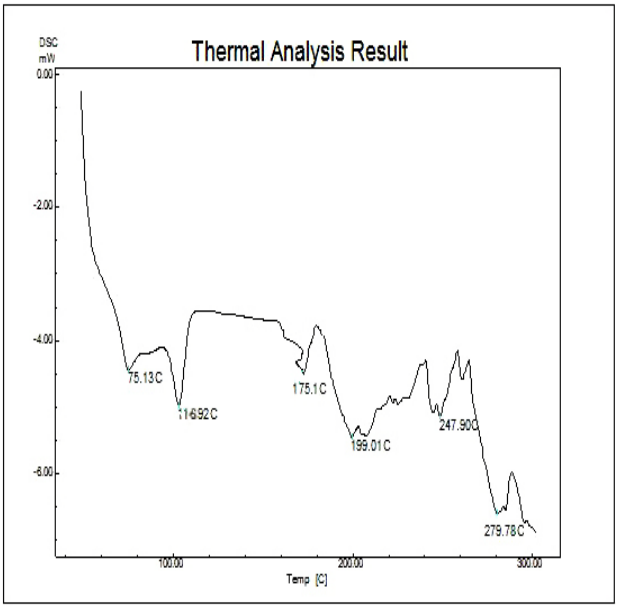


Fig 4: Dissolution profile of SR Valsartan Tablets.

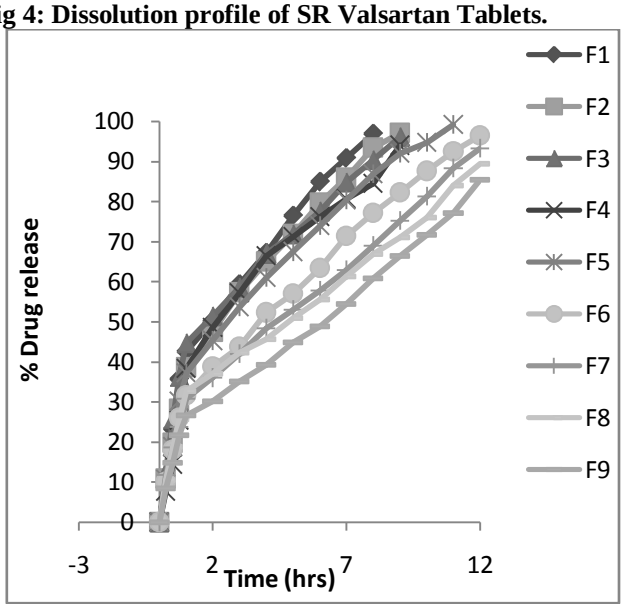


Fig 5: First Order Plots for formulations (F1-F4).

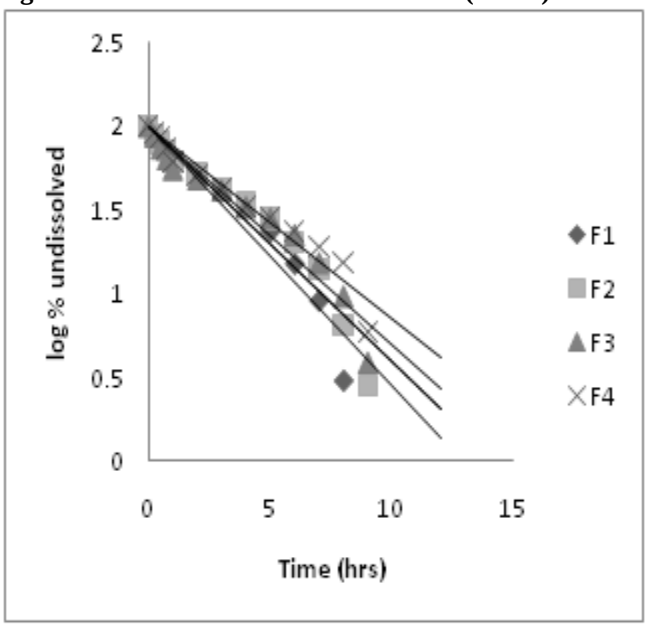


Fig 6: Zero order plots for formulations (F5-F9)

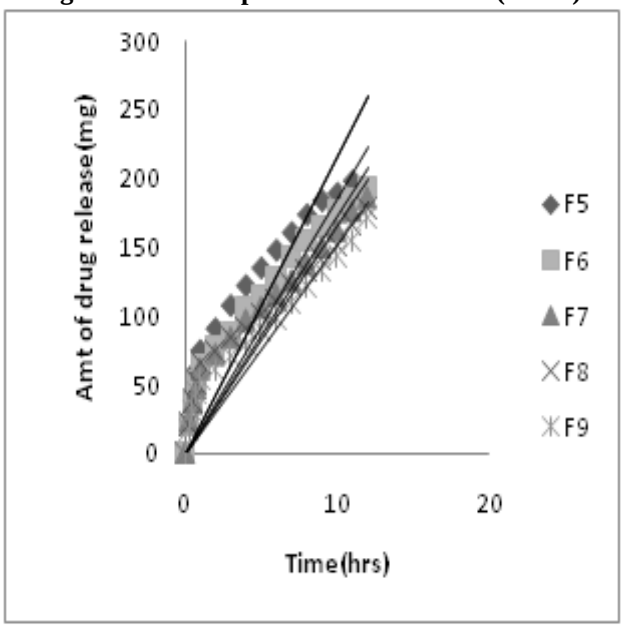


Table 3: Blend Characteristics Of Valsartan Granules

Formulation code	Angle of repose (°)	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index	Hausner's ratio
F1	27.18±0.32	0.4158±0.0009	0.4830±0.0012	13.92±0.39	1.1618±0.0052
F2	28.57±0.20	0.4276±0.0014	0.4807±0.0012	11.04±0.50	1.1242±0.0063
F3	29.42±0.13	0.4045±0.0012	0.4691±0.0006	13.75±0.36	1.1595±0.0049
F4	28.37±0.37	0.4035±0.0021	0.4720±0.0017	14.52±0.48	1.1699±0.0065
F5	28.29±0.58	0.4270±0.0014	0.4676±0.0017	8.682±0.59	1.0951±0.0065
F6	29.19±0.33	0.3973±0.0016	0.4633±0.0016	14.23±0.59	1.1660±0.0070
F7	28.21±0.04	0.4106±0.0008	0.4858±0.0018	15.46±0.30	1.1830±0.0042
F8	26.00±0.28	0.4056±0.0008	0.4680±0.0017	13.31±0.40	1.1536±0.0053
F9	26.28±0.28	0.3926±0.0012	0.4644±0.0016	15.44±0.11	1.1826±0.0016

gm-gram;ml-millilitre

Table 4: Physical Evaluation Of Sr Tablets Of Valsartan

Formulation code	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Weight variation (%)	Drug content uniformity (%)
F1	2.5±0.07	5.52±0.08	0.54±0.03	2.98±0.04	99.29±0.05
F2	2.5±0.15	5.8±0.07	0.64±0.05	3.52±0.05	99.46±0.1
F3	2.44±0.09	5.5±0.07	0.59±0.13	2.7 6±0.04	99.66±0.04
F4	2.38±0.08	5.78±0.08	0.56±0.1	3.29±0.06	99.23±0.02
F5	2.56±0.05	5.3±0.07	0.79±0.06	2.24±0.03	99.49±0.05
F6	2.5±0.11	6.18±0.1	0.54±0.19	2.85±0.05	99.72±0.04
F7	2.4±0.1	5.7±0.07	0.77±0.05	3.55±0.05	99.76±0.04
F8	2.52±0.04	5.4±0.07	0.79±0.09	3.12±0.05	99.52±0.05
F9	2.48±0.08	6.02±0.08	0.69±0.08	3.59±0.05	99.52±0.04

Kg- kilogram;cm-centimetre

Table 5: Kinetic Values Obtained From Different Plots Of Formulations (F1-F9) Of Valsartan

Formulation code	Correlation coefficient (R)				Release rate constant		Exponential coefficient (n)	T_{90} (hrs)
	Zero order	First order	Higuchi	Peppas	zero order Rate constant K_0 ($mg.h^{-1}$)	first order Rate constant K_1 (h^{-1})		
F1	0.9544	0.9656	0.9827	0.9728	21.3980	0.3562	0.5403	6.93
F2	0.9615	0.9825	0.9914	0.9854	19.6180	0.3226	0.5643	7.70
F3	0.9415	0.9481	0.9766	0.9706	17.995	0.2890	0.4817	7.96
F4	0.9456	0.9976	0.9742	0.9646	18.7924	0.2544	0.6032	8.62
F5	0.9660	0.9348	0.9909	0.9836	17.8140	0.3191	0.5352	8.81
F6	0.9753	0.9691	0.9919	0.9884	14.3710	0.2510	0.5253	10.70
F7	0.9784	0.9601	0.9838	0.9843	13.2904	0.1766	0.4759	11.20
F8	0.9702	0.9691	0.9769	0.9831	12.3578	0.1476	0.4757	11.45
F9	0.9891	0.9871	0.9711	0.9855	12.0375	0.1287	0.5201	12.06

mg-milligrams;h-hours

ACKNOWLEDGEMENTS

The authors are thankful to Bactolac Formulations, Hyderabad for providing the adequate laboratories facilities in the execution of this work.

REFERENCES

1. Gwen M. Jantzan, Joseph R. Robinson. Sustained and Controlled release drug delivery systems In: Gilbert S. Banker. Editors. **Modern pharmaceutics.** 4th Edition Revised and expanded. Marcel Dekker Inc; New York. USA.2008 Pg.503-530.
2. Robert M. Silverstein, Francis X. Webster. Infrared Spectrometry. In: Robert M. Silverstein. Editors. **Spectrometric Identification of Organic Compounds**. 6th Ed. John Wiley and Sons. Inc. New York. Pg. 71 – 143.
3. John R. Dyer. Infrared Spectroscopy. In: John R. Dyer. Editors. **Applications of Absorption Spectroscopy of Organic Compounds.** Eastern Economy Edition. Prentice – Hall of India. New Delhi. 2007. Pg. 22 – 57.
4. J. Mendham, R. C. Denney, J. D. Barnes, M. K. J. Thomas. Thermal Analysis. In: J. Mendham. Editors. **Vogel's Textbook of Quantitative Chemical Analysis**. 2006. 6th Ed. Pearson Education Ltd. Pg. 503 – 522.
5. Bolton S, editor. Pharmaceutical statistics. 3rd Edition. New York: Marcel Dekker, pg 326,1997.
6. Loyd V. Allen. Jr. Nicholas G. Poporich, Howard C. Ansel. Tablets. In: Howard C. Ansel. Editors. **Ansel's Pharmaceutical Dosage forms and Drug Delivery Systems**. 8th Ed. Wolters Kluwer (India) Pvt. Ltd. 2007. Pg. 227 – 259.
7. Arthur H. Kibbe. Sodium Starch Glycholate In: Arthur H. Kibbe. Editors. **Handbook of Pharmaceutical Excipients**. 3rd Ed. Pharmaceutical Press. London. Pg. 501 – 504.
8. Nicholas G. Lordi. Sustained release dosage forms In: Herbert A. Lieberman. Editors. **The theory and practice of industrial pharmacy**. 3rd edition (Indian), Varghese publishing house; Mumbai. Pg. 430 – 456.
9. **USP 31 / NF 26.** 2008 Asian ed. Volume – 3, Official Monographs. Pg. 3496 – 3498.
10. J. Mendham, R. C. Denney, J. D. Barnes, M. K. J. Thomas. Thermal Analysis. In: J. Mendham. Editors. **Vogel's Textbook of Quantitative Chemical Analysis**. 2006. 6th Ed. Pearson Education Ltd. Pg. 503 – 522.
11. **Korsmeyer R. W., Gurny R. Peppas**, "Mechanism of Solute Release From Porous Hydrophilic Polymers."In *Int J Pharm***.** 1983, Pg. 25-35.
12. **Higuchi T.**, "Mechanism of Sustained Action Medication: Theoretical Analysis of Rate of Release of Solid Drug Dispersed in Solid Matrix**." In** *J Pharm.Sci*, 1963, Pg. 1145-1149.