



DEVELOPMENT AND *IN VITRO* EVALUATION OF VALSARTAN SUSTAINED RELEASE MATRIX TABLETS AND INFLUENCE OF ETHANOL ON DOSE DUMPING

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ABSTRACT

Valsartan is an angiotensin II receptor blocker indicated for the treatment of hypertension to lower blood pressure. The present work is aimed to formulate and evaluate the sustained release matrix tablets by using valsartan drug to prolong the release of drug for an extended period of time in order to improve reduce dosing frequency and increase the bioavailability of the drug. Prepared tablets were evaluated for weight variation, hardness, friability, drug content and *in-vitro* drug release studies in different ethanol concentrations. From the results, all the tablets were within the pharmacopeial limits. Sustained release matrix tablets of valsartan were evaluated for the effect of HPMC K15M, ethyl cellulose and eudragit RS 100 in different amounts on drug release. The optimized formulation F6 was prepared with ethyl cellulose and released $98.71 \pm 2.69\%$ of the drug in 12hrs and exhibited sustained drug release, follows zero-order kinetics. The optimized formulation was observed that dose-dumping occurred at high concentrations of alcohol in the media. The impact of alcohol was prominently observed in terms of initial rapid release for the drug in the first 2 hours of the high concentration of alcohol.

KEY WORDS

Valsartan, sustained release, ethanol, dose dumping.

INTRODUCTION

Sustained release (SR) dosage form is a type of modified drug delivery system that can be used as an alternative to conventional drug delivery system. Sustained release dosage form, that releases the drugs in a rate-controlled manner over an extended period of time either systemically or to a specified target organ to patients and maintains the plasma drug concentration in therapeutic window except for any fluctuation and increases the therapeutic efficacy of a drug^{1,2}.

Sustained-release dosage forms can better patient compliance, avoid multiple dosing, increase the plasma drug concentration, avoid side effects and overcome the problems associated with conventional system³. Dose dumping can be defined as the rapid unintended release of a large amount of drug from an SR dosage form resulting potentially harmful effects for patients. Co-consumption with alcohol can

complicate matters because it may influence the absorption, metabolism and excretion of drugs⁴⁻⁷.

However, for alcohol-induced dose dumping sustained-released formulations can produce negative side effects, in particular the increased risk of toxicity when the patient consumes excessive amounts of alcohol. Dose dumping becomes a severe safety concern with sustained release products, which contain higher drug concentrations compared to immediate release dosage forms⁸.

Valsartan is an oral antihypertensive agent used for the treatment of hypertension, to lower blood pressure. Valsartan is an angiotensin II receptor antagonist that selectively inhibits the binding of angiotensin II to angiotensin I, which is found in many tissues such as vascular smooth muscle and the adrenal glands. This effectively inhibits the angiotensin I - mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in a decrease in vascular resistance and blood

pressure⁹. Valsartan has a biological half-life of 6hrs as shows bioavailability only 10-35% when administered orally. This short half-life of the drug indicates that the dose to be taken two to three times a day, thereby giving the need for sustained release dosage forms¹⁰. The present aim of this study was to formulate and evaluate the sustained release matrix tablets by using valsartan drug to prolong the release of drug for an extended period of time in order to investigate the influence of various concentrations of hydroalcoholic media on the release rate of valsartan from hypromellose hydrophilic SR matrix tablets.

MATERIALS AND METHODS

Valsartan is a gift sample of Dr. Reddy's labs, Hyderabad, India. Eudragit RS100, HPMC K15M, ethyl cellulose was purchased from Chemi-nova Remedies, Balanagar, India. Lactose was obtained from Lakshmi Chemicals Pvt. Ltd, Hyderabad. Magnesium stearate, Talc was obtained from Nihal Traders Pvt Ltd, Hyderabad. All other ingredients used in this study are either analytical grade or pharmaceutical grade.

Preformulation studies:

Preformulation studies are the first step in the rational development of dosage form of a drug substance, so that this information is useful to develop formulation. Preformulation studies are primarily done to investigate the physico-chemical properties of the drug and to establish its compatibility with other excipients.

Drug-Excipients compatibility studies:

Fourier Transform Infrared (FTIR) Spectroscopy:

FT-IR study was carried out by using an infrared spectrophotometer to find out if there is any possible chemical interaction of valsartan with polymers like HPMC K15M, ethyl cellulose and eudragit RS100 and other excipients. The samples were prepared for FTIR test, as pure drug and as a drug with one polymer among those polymers in 1:1 ratio and sample from optimized formulations.

Pre-compression of the blend:

The powder blend of all formulations was evaluated for an angle of repose, bulk density, tapped density, compressibility index and Hausner ratio¹¹.

Angle of Repose: The angle of repose of granules was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured, and an angle of repose was calculated using the following equation.

$$\theta = \tan^{-1} (h/r)$$

Where, θ = angle of repose, h = height in cm, r = radius in cm

Bulk Density and Tapped Density: An accurately weighed quantity of the granules/powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tablets and after that, the volume (V_f) was measured and continued operation till the two consecutive readings were equal.

The bulk density and the tapped density were calculated using the following formulae.

$$\text{Bulk density: } \rho_b = M / V_0$$

Where, ρ_b = Apparent bulk density, M = Mass of powder blend; V_0 = apparent volume of powder blend

$$\text{Tapped density: } \rho_{\text{tap}} = M / V_f$$

Where ρ_{tap} = Tapped density, M= Weight of powder blend, V_f = Tapped volume of powder blend

Compressibility Index (Carr's Index): Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible of a material is the more flowable.

$$\text{Carr's Index} = [\rho_{\text{tap}} - \rho_b] / \rho_{\text{tap}}$$

Where ρ_b = bulk density, ρ_{tap} = tapped density

Hausner's Ratio: It is the ratio of tapped density and bulk density.

$$\text{Hausner's ratio} = \rho_{\text{tap}} / \rho_b$$

Where; ρ_{tap} = tapped density, ρ_b = bulk density.

Formulation development of valsartan matrix tablets

Valsartan matrix tablets were prepared by direct compression method according to the formula given in Table 1. Accurately weighed quantities of drug, polymer and lactose were mixed in the ascending

order of their weights in a mortar and pestle. The powder was passed through sieve no.60. The whole mixture was collected in a plastic bag and mixed for 15min. To the mixture magnesium stearate was added and mixed for 5min, later talc was added and mixed for 5min. Then the lubricated blend equivalent to 400mg was compressed into tablets with 11mm round plat punches on an 8-station rotary tablet punching machine (Rimek Minidress Karnavati Eng.

Ltd, Ahmadabad, India). The compositions of all formulations (Table 1) were varied by using polymers alone and the combination of polymers in different ratios. Lactose, talc and magnesium stearate were used as diluent, glidant and lubricant respectively. Before tablets preparation, the mixture blends of all the formulation were subjected to compatibility studies and pre-compression parameters.

Table1: Formulation of matrix tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Valsartan	80	80	80	80	80	80	80	80	80
HPMC K15M	80	120	160	--	--	--	--	--	--
Ethyl cellulose	--	--	--	80	120	160	--	--	--
Eudragit RS 100	--	--	--	--	--	--	80	120	160
Lactose	224	184	144	224	184	144	224	184	144
PVP K30	8	8	8	8	8	8	8	8	8
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
Total weight (mg)	400	400	400	400	400	400	400	400	400

Evaluation of matrix tablets of valsartan:

The designed formulations of valsartan tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content^{12, 13, 14}.

Weight variation test:

To study the weight variation, twenty tablets were taken, and their weight was determined individually and collectively on a digital weighing balance. The average weight of tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. The percent deviation was calculated using the following formula:

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

Hardness test:

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under the condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of

6 tablets was determined using Monsanto hardness tester and the average is calculated and presented with standard deviation.

Thickness test:

Tablet thickness is an important characteristic in reproducing appearance ten tablets were taken and their thickness was recorded using vernier calipers. The average thickness for tablets were calculated and presented with standard deviation.

Friability:

It is a measure of mechanical strength of tablets. Roche friabilator (Electrolab, Mumbai, India) was used to determine the friability by the following procedure. Prewighed tablets (10 tablets) were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were reweighed; loss in the weight of tablet is the measure of friability and is expressed in percentage as:

$$\% \text{ Friability} = \frac{[(W1 - W2) / W1] \times 100}{1}$$

Where, W1 = Initial weight of 10 tablets, W2 = weight of 10 tablets after testing

Drug content:

Matrix tablets of valsartan were tested for their drug content. Ten tablets were finely powdered; the powder equivalent to one tablet (400mg) of valsartan was accurately weighed, transferred to a 100ml volumetric flask containing 50 ml of methanol and allowed to stand for 1 hrs with intermittent sonication to ensure complete solubility of the drug. The mixture was made up to the volume with methanol. The solution was suitably diluted, and the absorption was determined by UV-Visible spectrophotometer at 250 nm. The drug concentration was calculated from the calibration curve.

In-vitro drug release studies:

In-Vitro dissolution release behavior was carried out using USP II (paddle type) apparatus in 900 ml of different release media for 12 hours. The temperature of the dissolution medium was kept at $37 \pm 0.5^\circ\text{C}$ and the paddle was set at 50 rpm. 5 ml of sample solution was withdrawn at a specified interval of time and filtered through Whatman filter paper. The absorbance of the withdrawn samples was measured at 250 nm using UV visible spectrophotometer. To simulate possible dose-dumping effects due to pH changes in the GI tract or because of alcohol consumption, the *in-vitro*

dissolution tests were performed in different release media such as 0.1N HCl and 0.1N HCl and 5% (equivalent of several beers), 20% (hard liquor) and 40% (worst case) ethanol (coded 0%, 5%, 20% and 40%, according to the percentage of alcoholic component, v/v) for 2h at $37 \pm 0.5^\circ\text{C}$, referred to the FDA guidance^{15, 16}.

RESULTS AND DISCUSSION

Drug Excipient Compatibility Studies:

FTIR spectrum of pure valsartan, polymers and the optimized formulation were analyzed over the range of $4000\text{--}400\text{ cm}^{-1}$ mentioned in Figure 1. Valsartan showed some prominent and characteristic peaks. The Spectrum of pure Valsartan presented characteristic peaks at 2613.05 cm^{-1} (alcoholic O-H stretching vibration), 2964.36 cm^{-1} (methyl and methylene C-H asymmetric and symmetric stretching vibration), 1732.85 cm^{-1} (C=O stretching vibration), 1602.16 cm^{-1} (N-H bending) and 2874.61 cm^{-1} (superimposed on OH stretching vibration). FTIR spectra of optimized formulations displayed all the characteristic bands of both drug and polymer, without any significant spectral shift. This suggested that there was no interaction between the drug and the excipients.

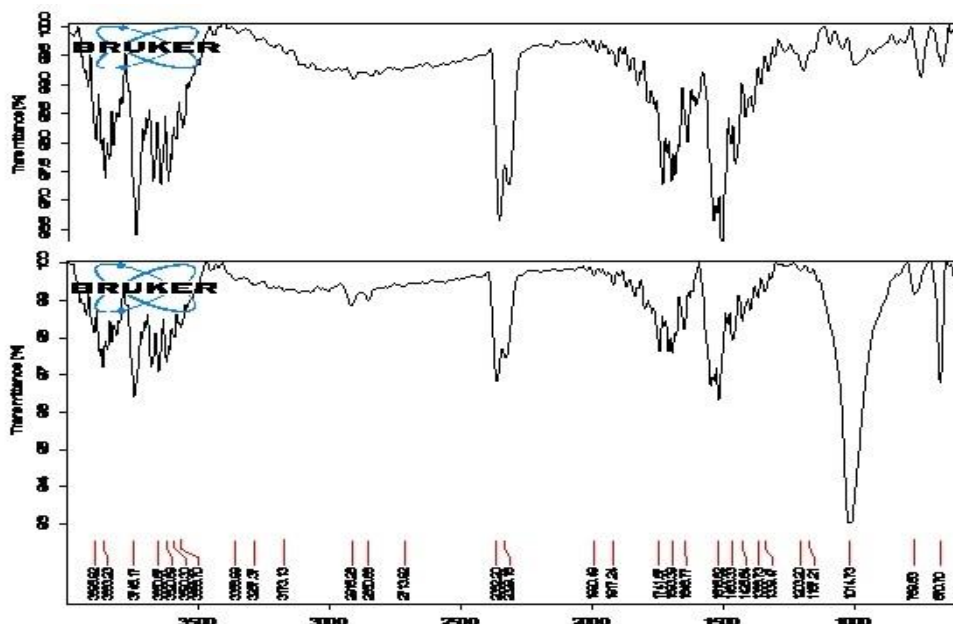


Fig 1: FTIR spectrum of Valsartan pure drug and optimized formulation

Evaluation of final powder blend:

The powder blend of all formulations was evaluated and the results of the Angle of repose and compressibility index (%) ranged from 21.09 ± 0.35 to 29.45 ± 0.46 and 10.66 ± 0.12 to 16.44 ± 0.52 respectively. The results of an angle of repose (<30) indicate good flow properties of the powder. This was further supported by lower compressibility index (or) Carr's index values. Generally, compressibility index values up to 16% result in good to excellent flow

properties. The bulk density and tapped density for all the formulations varied from $0.41 \pm 0.07 \text{ gm/cm}^3$ to $0.49 \pm 0.06 \text{ gm/cm}^3$ and $0.47 \pm 0.05 \text{ gm/cm}^3$ to $0.53 \pm 0.07 \text{ gm/cm}^3$ respectively. The values obtained lies within the acceptable range and no large differences found between loose bulk density and tapped bulk density. All these results indicate that the powder possessed satisfactory flow properties compressibility index (Table 2).

Table.2. Physical Properties of Pre-compression Blend

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	Hausner's ratio
F1	21.09 ± 0.35	0.46 ± 0.06	0.53 ± 0.06	11.35 ± 0.64	1.128 ± 0.14
F2	27.05 ± 1.06	0.47 ± 0.05	0.48 ± 0.05	15.77 ± 0.78	1.187 ± 0.17
F3	28.45 ± 1.01	0.45 ± 0.07	0.51 ± 0.06	15.86 ± 0.48	1.189 ± 0.14
F4	23.56 ± 0.84	0.45 ± 0.04	0.57 ± 0.03	15.62 ± 0.29	1.185 ± 0.18
F5	29.45 ± 0.46	0.42 ± 0.06	0.44 ± 0.05	15.35 ± 0.62	1.181 ± 0.14
F6	23.06 ± 0.54	0.46 ± 0.06	0.53 ± 0.07	13.26 ± 0.69	1.152 ± 0.18
F7	24.82 ± 1.01	0.49 ± 0.06	0.47 ± 0.05	16.44 ± 0.52	1.196 ± 0.15
F8	26.61 ± 0.82	0.41 ± 0.07	0.53 ± 0.09	13.58 ± 0.64	1.156 ± 0.16
F9	22.35 ± 0.51	0.42 ± 0.06	0.52 ± 0.03	10.66 ± 0.12	1.118 ± 0.14

Weight variation, Hardness, Thickness, Friability and Drug content:

All the formulations passed the weight variation and weight of all the formulations was found to be within pharmacopeia limits. All the formulations were tested for hardness by a Monsanto hardness tester. The hardness of tablets was found to be within the range of 5.25 to 5.78 kg/cm^2 . The thickness of all formulations was in the range of 3.40 ± 0.44 to

3.48 ± 0.66 mm. Friability of the formulations was found to be in the range of 0.48 ± 0.11 to 0.91 ± 0.13 which is acceptable according to pharmacopeia limits. It infers the physical stability of the formulations to with stand shock during handling and transport. Drug content of all formulations was found to be in the range of 97.15 ± 0.96 - $101.78 \pm 1.56\%$ which is acceptable range according to pharmacopeia limits (Table 3).

Table.3. Physical Evaluation of matrix tablets

Formulations	Hardness (kg/cm ²)	Thickness (mm)	Weight variation(mg)	Friability	Drug Content
F1	5.72 ± 0.80	3.44 ± 0.52	393.8 ± 1.48	0.48 ± 0.11	104.55 ± 1.31
F2	5.64 ± 0.82	3.42 ± 0.46	397.4 ± 1.21	0.55 ± 0.14	97.15 ± 0.96
F3	5.54 ± 0.95	3.40 ± 0.44	401.4 ± 1.19	0.78 ± 0.16	98.27 ± 1.68
F4	5.25 ± 0.67	3.41 ± 0.45	405.7 ± 0.75	0.91 ± 0.13	101.55 ± 1.56
F5	5.42 ± 0.57	3.48 ± 0.66	409.6 ± 1.14	0.83 ± 0.15	98.24 ± 1.25
F6	5.78 ± 0.86	3.45 ± 0.56	398.4 ± 1.04	0.62 ± 0.15	101.78 ± 1.56
F7	5.47 ± 0.57	3.44 ± 0.71	401.9 ± 0.67	0.82 ± 0.16	99.28 ± 1.99
F8	5.56 ± 0.67	3.42 ± 0.89	404.0 ± 0.43	0.76 ± 0.13	98.35 ± 1.14
F9	5.61 ± 0.31	3.43 ± 0.68	401.2 ± 0.83	0.88 ± 0.12	99.29 ± 0.98

In-Vitro Drug Release Studies

The results of release studies of formulations F1 to F12 were shown in Figure 2 To 6. The most important factor affecting the rate of release from tablets is the drug and polymer ratio. As the percentage of polymer concentration increased, the amount of drug release is decreased. This may be a structural reorganization of the hydrophilic polymer. Increase in concentration of HPMC may result in an increase in the tortuosity or gel strength of the polymer as well as the formation of gel layer with the longer diffusional path. This could cause a decrease in the effective diffusion coefficient of drug and therefore reduction in drug release rate. When the polymer is exposed to the aqueous medium, it undergoes hydration and to form the viscous gelatinous layer. The drug release observed for formulations F1 to F3 was not sufficient to retard the drug release and releases only 10hrs (Figure 2). This phenomenon may be attributed to surface erosion or initial disintegration of the matrix

tablet prior to gel layer formation around tablet core. The drug release retarding effect of formulations F4 to F6 was observed and the results were shown in Figure 3. In ethyl cellulose formulation drug release was retarded with increased of polymer proportion. F6 formulations shown extended drug release up to 12hrs and shown maximum drug release of $98.71 \pm 2.69\%$ and sustained up to 12hrs. The results of release studies of formulations F7 to F9 are shown in Figure 4. In eudragit RS 100 based formulations with the increase of polymer concentration; the release was sustained up to 12hrs. The decrease in drug release is due to increase in eudragit RS 100 content might be ascribed an increase in the extent of gel formation in the diffusion layer and consequently, increase in diffusion length. Based on the drug release studies formulation F6 and F8 selected as optimized formulation, these are evaluated for dose dumping study.

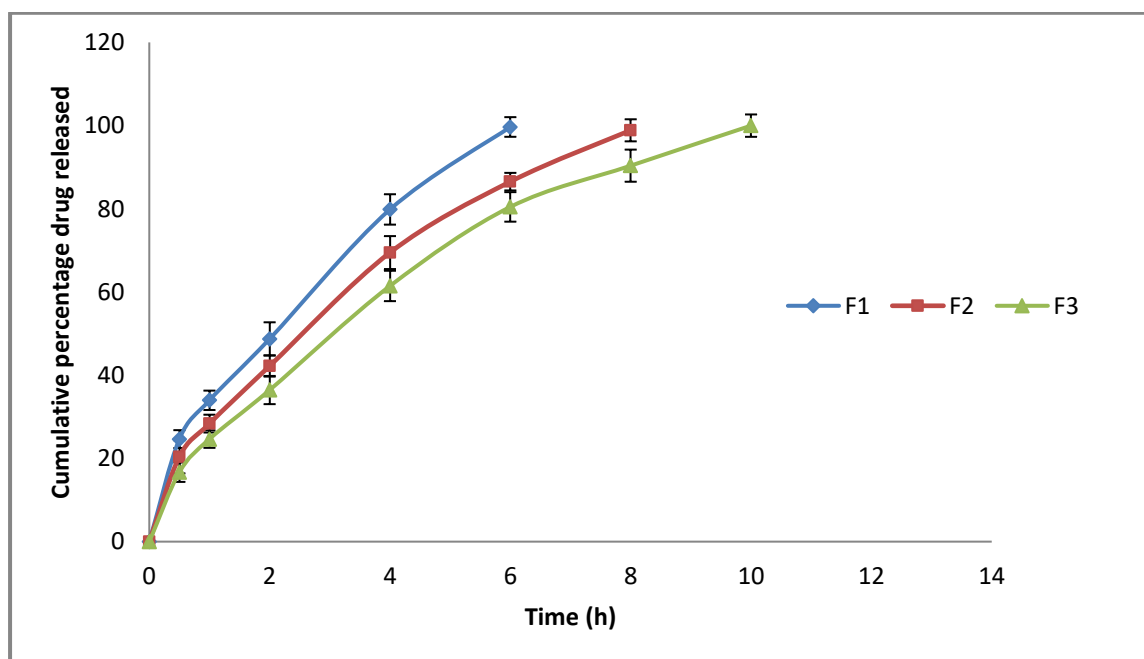


Fig.2 In-Vitro Release Data of Valsartan from HPMC K15M matrix tablets

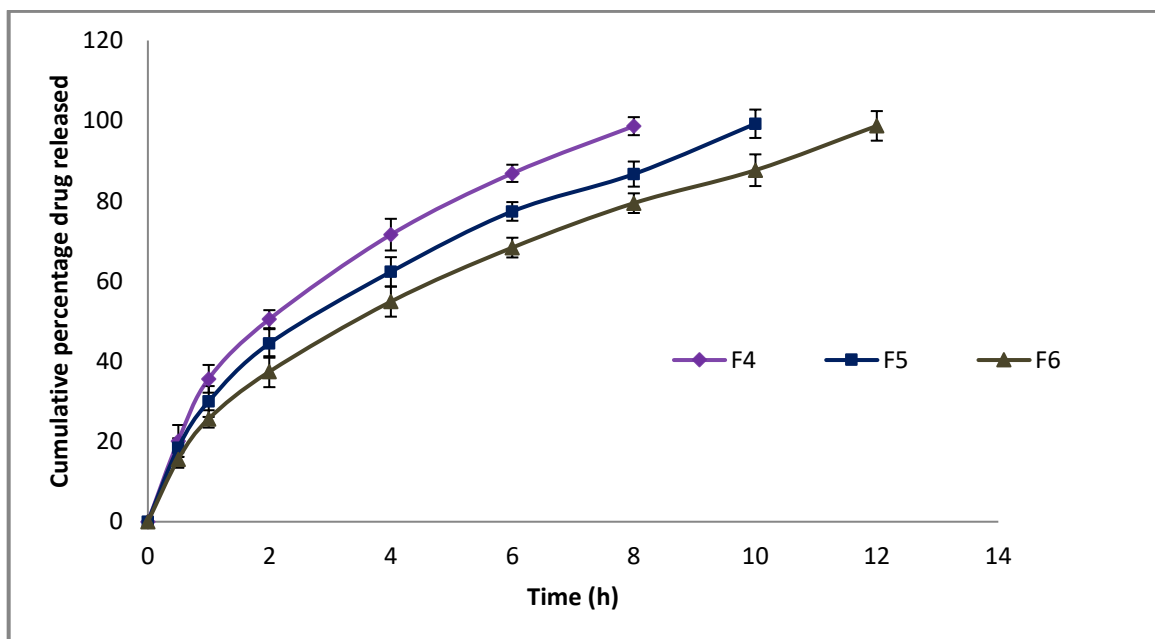


Fig. 3 *In Vitro* Release Data of Valsartan from ethyl cellulose matrix tablets

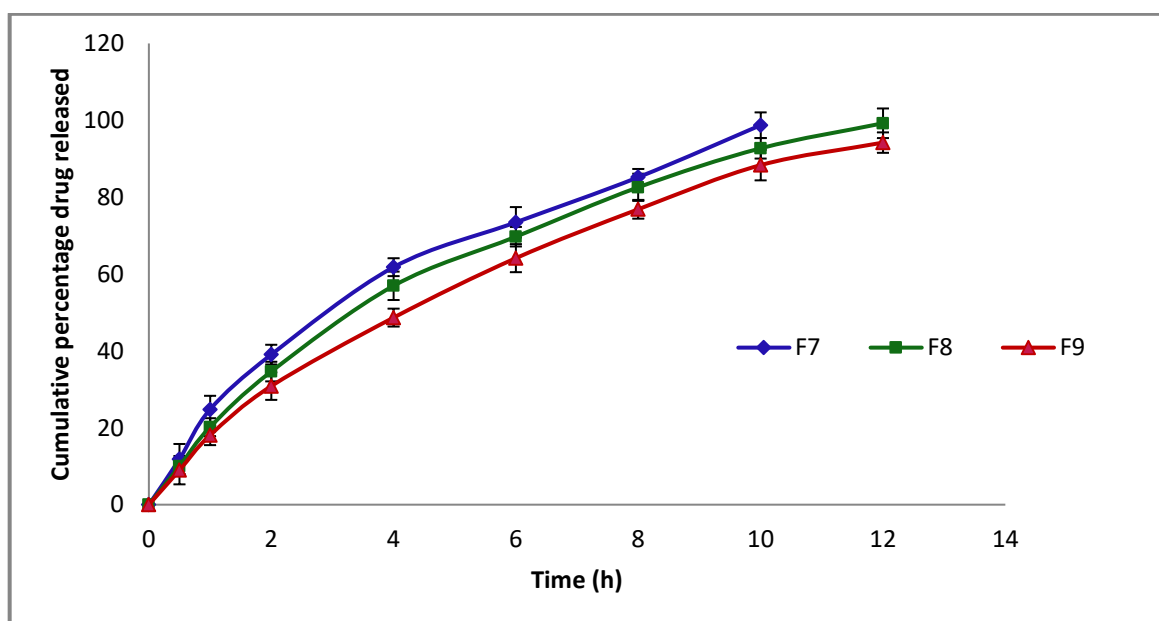


Fig. 4 *In Vitro* Release Data of Valsartan from eudragit RS 100 matrix tablets

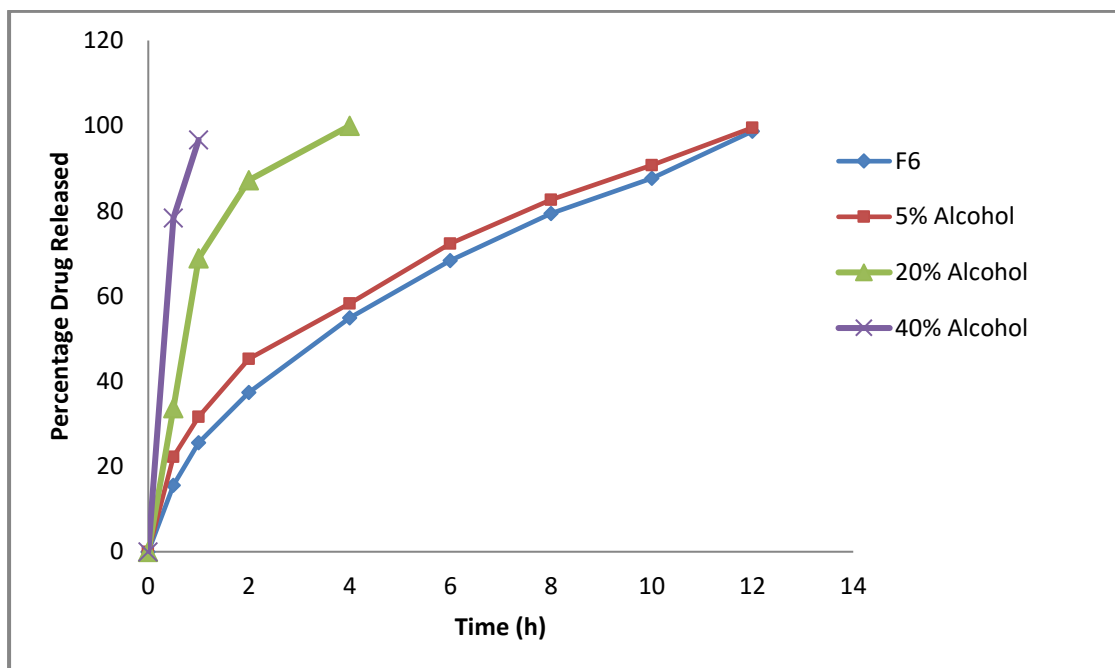


Fig.5 *In-vitro* release data of valsartan from matrix tablets containing ethyl cellulose in presence of ethanol media

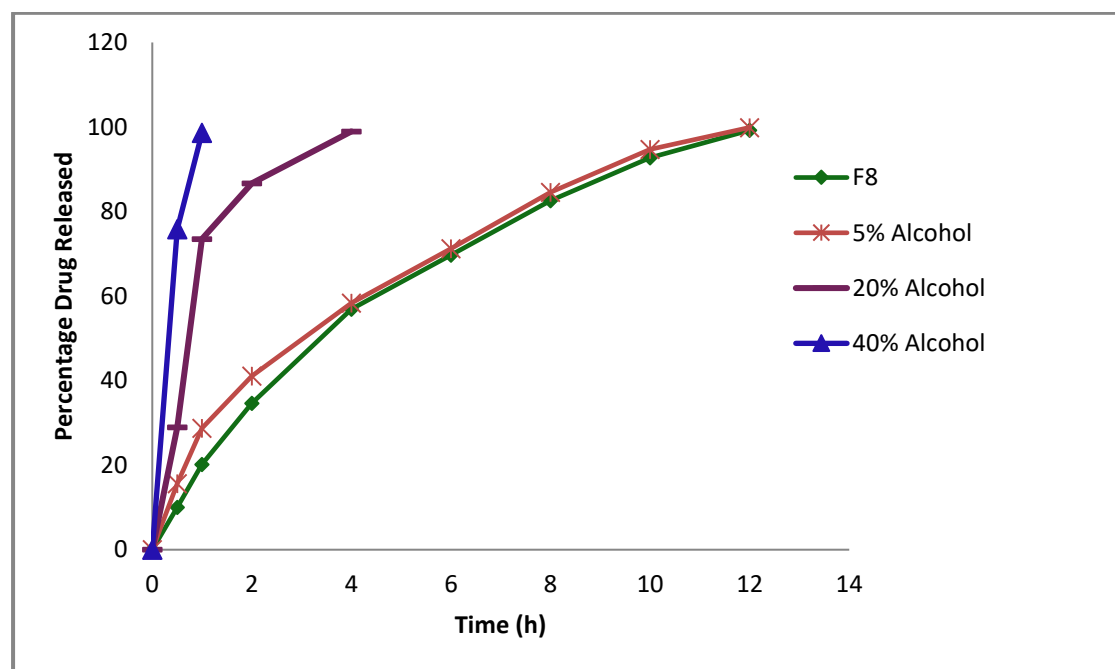


Fig. 6 *In-Vitro* release data of valsartan from eudragit RS 100 matrix tablets in presence of ethanol media

Dose dumping study:

Drug release from matrix tablets containing ethyl cellulose and eudragit RS 100 in presence of ethanol media:

In-vitro drug release studies were performed for matrix tablets containing ethyl cellulose and eudragit RS 100 in presence of different ethanol concentrations i.e., 5%, 20% and 40%. These are water-insoluble polymers; it appears to be very vulnerable to ethanol. Drug release at the 5% ethanol concentration was nearly identical to that observed in 0% ethanol. At higher ethanol concentrations (20 and 40%), the rapid release was seen in first 2 hours. This effect was dependent on ethanol concentration and a higher mean dissolution percentage (%) was reached in the 40% ethanol medium compared to 20% ethanol medium, both of which were significantly higher compared to the 0% ethanol condition. This indicates that the higher amount of drug had been dumped into the dissolution medium within few hours. The results of release studies of formulations were shown in Figure 5 and 6.

CONCLUSION

In the present work, the sustained release tablet dosage form of valsartan was formulated using different polymers in different concentrations and evaluated. It was found that HPMC K15M and did not show promising results, drug release was not retarded up to a desired time. The formulations containing ethyl cellulose and eudragit RS 100 showed maximum drug release along with good sustained release behavior up to 12 hrs. In non-alcoholic media, valsartan sustained release matrix tablets typically released less than 25% of their total drug in 2 hrs. At higher ethanol concentrations (20 and 40%), the rapid release was seen in first 1-2 hrs. This indicates that the higher amount of drug had been dumped into the dissolution medium within few hours. The work presented here suggests that *in vitro* testing can be used to evaluate a formulation's vulnerabilities to an ethanol environment. FDA recommended that makers of modified release formulations conduct investigations to determine the risk of ethanol-induced dose-dumping, whereby

ethanol interacts with the extended-release characteristics to yield unintended, rapid drug release in a short period of time.

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