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Formulation and Evaluation of Once Daily Sustained Release Bilayered Matrix Tablets of Valsartan Using Different Viscosity Grades of HPMC

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ABSTRACT

In the present study, once daily sustained release bilayered matrix tablets of valsartan containing different viscosity grades of HPMC (K4M, K15M and K100M) were prepared by direct compression method and evaluated for physicochemical parameters and *in vitro* drug release studies. All the physical attributes of bilayered matrix tablets of valsartan (F1 to F6) were found to be within limits and all the matrix formulations provided the drug release up to 24 hrs in a controlled manner without changing their physical integrity in dissolution medium. When the data obtained from *in vitro* drug release studies was fitted to dissolution kinetics, the results showed that the release of valsartan from all the formulations (F1 to F6) followed first order kinetics via Fickian diffusion mechanism. Among all the formulations, F2 (HPMC K4M), F4 (HPMC K15M) and F6 (HPMC K100M) are better formulations as they provided the sustained release of valsartan up to 24 hours and their f_2 value is higher than 50 indicating that the drug release profiles are similar to the theoretical release profile. From the stability studies, it was found that valsartan bilayered matrix formulations were stable after the storage period. FTIR and DSC studies clearly indicated that there is no drug polymer interaction.

INTRODUCTION

Valsartan is an angiogenesis II receptor antagonist that is used for the treatment of hypertension. Valsartan acts by blocking the binding of angiotensin II and angiotensin I receptor in many tissues thereby blocking the vasoconstrictor and aldosterone secreting effect of angiotensin II selectively. The most preferred route for this is oral delivery in the form of tablets. Valsartan have poor water solubility, low bioavailability (approximately 20-25%) and shorter half life (nearly 6 hrs) [1]. Hence sustained release tablet formulation is needed for valsartan to enhance its oral bioavailability and to prolong its therapeutic effect, to reduce dosage frequency and to increase patient compliance.

The most commonly used method of modulating the drug release is to include it in a matrix system [2]. An effort was therefore made to develop simple and effective bilayered sustained release valsartan tablets using a polymer matrix system. The bi-layered tablet concept has been long utilized to develop sustained release formulations. Such a tablet has an Immediate Release (IR) layer and a Controlled Release (CR) layer. The pharmacokinetic advantage relies on the fact that drug release from Immediate Release layer leads to a sudden rise in the blood concentration to achieve the therapeutic concentration. However, the blood level is maintained at steady state with controlled release layer.

HPMC is the most commonly and successfully used hydrophilic retarding agent for the preparation of oral controlled drug delivery systems [3]. Upon contact with the gastrointestinal fluid, HPMC swells, gels and finally dissolves slowly [4]. The gel becomes a viscous layer acting as protective barrier to both the influx of water and the efflux of the drug in solution [5]. As the proportion of the polymer in the formulation increases, the gel formed is more likely to diminish the diffusion of the drug and delay the erosion of the matrix [6]. The efficiency of the hydrophilic matrix in controlling the drug release, in addition to other factors, is dependent on the viscosity of such hydrophilic polymers incorporated in the formulation [7, 8, 9]. Hence, various viscosity grades of HPMC were used for the once daily oral sustained release bilayered matrix tablets of valsartan.

MATERIALS AND METHODS

Materials

Valsartan was obtained from M/s Aurobindo Pharma Pvt. Limited, Hyderabad, India and Hydroxy Propyl Methyl Cellulose K4M, K15M and K100M were obtained from M/s. Colorcon Asia Pvt. Limited, Mumbai, India. Microcrystalline Cellulose, Sodium starch Glycolate, Talc and Magnesium Stearate were of USP/NF grade.

Methods:

Calculation of Theoretical Release Profile of Valsartan:

Theoretical release profile of valsartan for once daily sustained release formulation was calculated by below equation using available pharmacokinetic data.

$$D_T = D_i [1 + 0.693 \times t / t_{1/2}]$$

D_T = Total dose of drug

D_i = Dose of Immediate release part

t = time during which sustained release is desired i.e., 24 hrs

$t_{1/2}$ = Half life of the drug

$$80 = D_i [1 + 0.693 \times 24/6]$$

$$80 = D_i[1 + 2.772]$$

$$D_i = 80/3.772 = 21.21 \text{ mg} = \text{Loading dose}$$

$$\text{Maintenance Dose} = 80 - 21.21 = 58.79/23 = 2.556 \text{ mg/hr}$$

Hence a once daily oral sustained release formulation of valsartan containing a total dose of 80 mg should release 21.21 mg in first 1 hour and 2.556 mg/hr up to 24hrs.

Preparation of Valsartan bilayered matrix tablets:

The bilayered matrix tablets of valsartan containing different viscosity grades of HPMC were prepared by the direct compression method. The composition of Immediate Release (IR) layer and matrix formulations (F1 to F6) is shown in Table No. 1 and Table No. 2 respectively. The drug, polymers and other excipients were used for immediate (IR) and controlled release (CR) layers.

Step 1: The controlled release layer containing drug, matrix materials, diluents, binder and lubricants were mixed uniformly and compressed on 16 station rotary tableting machine (Cadmach Machinery Co., Ahmedabad) using 12 mm round and concave faced punches with hardness between 4-5 Kg/sq. cm.

Step 2: Immediate release layer containing drug, super disintegrating agent, diluent and lubricant were mixed uniformly and compressed over CR layered tablet with hardness between 5-7 kg/sq. cm to obtained bilayered matrix tablet. Tablets were directly compressed by 16 station rotary tableting machine (Cadmach Machinery Co., Ahmedabad) using 12 mm round and concave faced punches.

Table No. 1: Composition of Valsartan Immediate release layer (IR) in bilayered matrix tablets (F1 to F6)

Ingredients (mg)	IR
Valsartan	20
Sodium starch glycolate	3
Microcrystalline cellulose	36.5
Magnesium stearate	0.5
Total weight	60

Table No. 2: Composition of Valsartan bilayered matrix tablets containing different viscosity grades of HPMC (F1 to F6)

Ingredients (mg)	F1	F2	F3	F4	F5	F6
IR	60	60	60	60	60	60
Valsartan	60	60	60	60	60	60
HPMC K4M	270	300	--	--	--	--
HPMC K15M	--	--	210	240	--	--
HPMC K00M	--	--	--	--	210	240
Microcrystalline cellulose	104	74	164	134	164	134
Talc	4	4	4	4	4	4
Magnesium Stearate	2	2	2	2	2	2
Total Weight	500	500	500	500	500	500

***In-Vitro* drug release characteristics:**

Drug release was assessed by dissolution test under the following conditions: n=3, USP type II dissolution apparatus (paddle method) at 50 rpm in 900 mL of the phosphate buffer pH 6.8 till 24 hours, maintained at 37°C ± 0.5°C. An aliquot (5 mL) was withdrawn at specific time intervals and replaced with the same volume of pre-warmed (37°C ± 0.5°C) fresh dissolution medium. The samples withdrawn were filtered through Whatman filter paper (No.1) and drug content in each sample was analyzed by UV-Visible spectrophotometer at 251 nm.

Kinetics of drug release:

The dissolution data of various bilayered matrix tablets of valsartan was fitted into various kinetic models such as zero order [10] {cumulative percentage of drug released Vs. time}, first order [10] {log cumulative percentage of drug remaining Vs. time} and Higuchi's [11] {cumulative percentage of drug released Vs. square root of time} models. For determination of mechanism of drug release data was fitted into Korsmeyer-Peppas [12] equation which was verified by Peppas and Franson [13], Peppas [14], Peppas and Sahlin [15].

$$M_t / M_\infty = Kt^n$$

Where M_t/ M_∞ is fraction of drug released at time `t', `K' represents a constant. The exponent `n' is calculated through the slope of the straight line which indicates mechanism of drug release.

Different mechanisms of drug release

`n' value	Type of Mechanism
less than (<) 0.5	Fickian diffusion
greater than (>) 1	Super case II transport
between 0.5 to 1	Non-fickian diffusion

Similarity Factor (f_2) Analysis:

In vitro release profiles of sustained release bilayered matrix tablets of valsartan were compared with the theoretical release profile which was calculated earlier. The data were analyzed by the following formula [16].

$$f_2 = 50 \log\{[1 + (1/N)\sum (R_i - T_i)^2]^{-0.5} \times 100\}$$

Where N = number of time points, R_i and T_i= dissolution of reference and test products at time i. If f_2 values are greater than 50, it is considered that the drug release behavior of the formulations is similar to the theoretical release profile.

FTIR Studies:

FTIR studies were performed on drug and the optimized formulations using Shimadzu FTIR (Shimadzu Corp., India). The samples were analyzed between wavenumbers 4000 and 400 cm^{-1}.

DSC Studies:

DSC studies were performed for drug and the optimized formulations. Indium/Zinc standards were used to calibrate the temperature and enthalpy scale. Accurately weighed 5-6 mg samples were hermetically sealed in aluminium pans and heated at constant rate of 10°C/min over a temperature range of 40 to 300°C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.

RESULTS AND DISCUSSION

Once daily sustained release bilayered matrix tablets of valsartan (F1 to F6) containing different viscosity grades of Hydroxy Propyl Methyl Cellulose (HPMC) were prepared by direct compression method and tested for physicochemical parameters like uniformity of weight, hardness, thickness, friability and content uniformity. The results of the tests are shown in Table No. 3. All the tablets of different formulations complied with the official requirements of uniformity of weight as their weights varied between 498.2 ± 0.54 and 502.3 ± 0.67 mg. The hardness of tablets of different formulations (F1 to F6) ranged from 7.08 ± 0.30 to 7.41 ± 0.60 kg/cm^2 and the friability values were less than 1.0% indicating that the matrix tablets were compact and hard. The thickness of the matrix tablets ranged from 5.03 ± 0.20 to 5.13 ± 0.25 mm. All the formulations satisfied the content of the drug as they contained 98 ± 5% of valsartan. Thus all the physical attributes of the prepared tablets were found to be practically within control.

Table No. 3: Physicochemical parameters of Sustained release bilayered matrix tablets of Valsartan containing different viscosity grades of HPMC (F1 to F6)

Formulation	Hardness (kg/cm^2) ± S.D.	Thickness (mm) ± S.D.	Weight Variation (mg) ± S.D.	Friability (%) ± S.D.	Drug content (%) ± S.D.
F1	7.16 ± 0.35	5.03 ± 0.20	498.2 ± 0.54	0.39 ± 0.09	99.12 ± 1.47
F2	7.36 ± 0.44	5.06 ± 0.28	500.5 ± 0.80	0.67 ± 0.08	101.22 ± 0.88
F3	7.25 ± 0.57	5.08 ± 0.36	500.6 ± 1.14	0.54 ± 0.04	100.24 ± 1.25
F4	7.08 ± 0.30	5.13 ± 0.25	499.2 ± 0.83	0.58 ± 0.06	99.53 ± 1.87
F5	7.25 ± 0.57	5.07 ± 0.31	502.3 ± 0.67	0.64 ± 0.15	98.28 ± 1.99
F6	7.41 ± 0.60	5.12 ± 0.29	499.0 ± 0.43	0.37 ± 0.02	101.35 ± 1.14

Bilayered sustained release matrix tablets of valsartan containing HPMC K4M (F1, F2), HPMC K15M (F3, F4) and HPMC K100M (F5, F6) were subjected to *in vitro* drug release studies in pH 6.8 buffer for 24 hours. The cumulative percent of drug released from matrix tablets (F1 to F6) at different time intervals is shown in Figures 1-3. Immediate release layer of all the formulations showed the burst release of valsartan within 10 minutes. Presence of super disintegrant (sodium starch glycolate) in immediate release layer showed faster disintegration of the layer. This can be attributed to the extent of water uptake and consequently strong swelling power of this disintegrant causing sufficient hydrodynamic pressure to induce complete disintegration. The percent of drug released from F1, F2, F3, F4,

F5, F6 formulations at the end of 1 hour is 29.34, 27.83, 35.27, 30.56, 33.10, 32.20 respectively. Initial drug release is more in all the formulations due to the presence of Immediate release layer which may be useful to achieve the therapeutic concentration.

All the bilayered matrix tablets of valsartan (F1 to F6) showed the drug release up to 24 hrs in a controlled manner without changing their physical integrity in dissolution medium. Different viscosity grades of hydroxyl propyl methylcellulose (HPMC K4M, HPMC K15M and HPMC K100} were able to form quite viscous gel upon contact with the aqueous fluid and hence retarded the drug release from hydrophilic matrix tablets. Less amount of polymer is required in case of HPMC K15M (F3, F4) formulations and HPMC K100M (F5, F6) formulations when compared with the amount of polymer required for HPMC K4M (F1, F2) formulations to control the drug release up to 24 hrs. This is mainly due to the higher viscosity polymers induce the formation of thicker gel layer after hydration. Increase in the polymer viscosity grade results in a decrease in the drug release rate due to a decrease in the total porosity i.e, release is extended to long period.

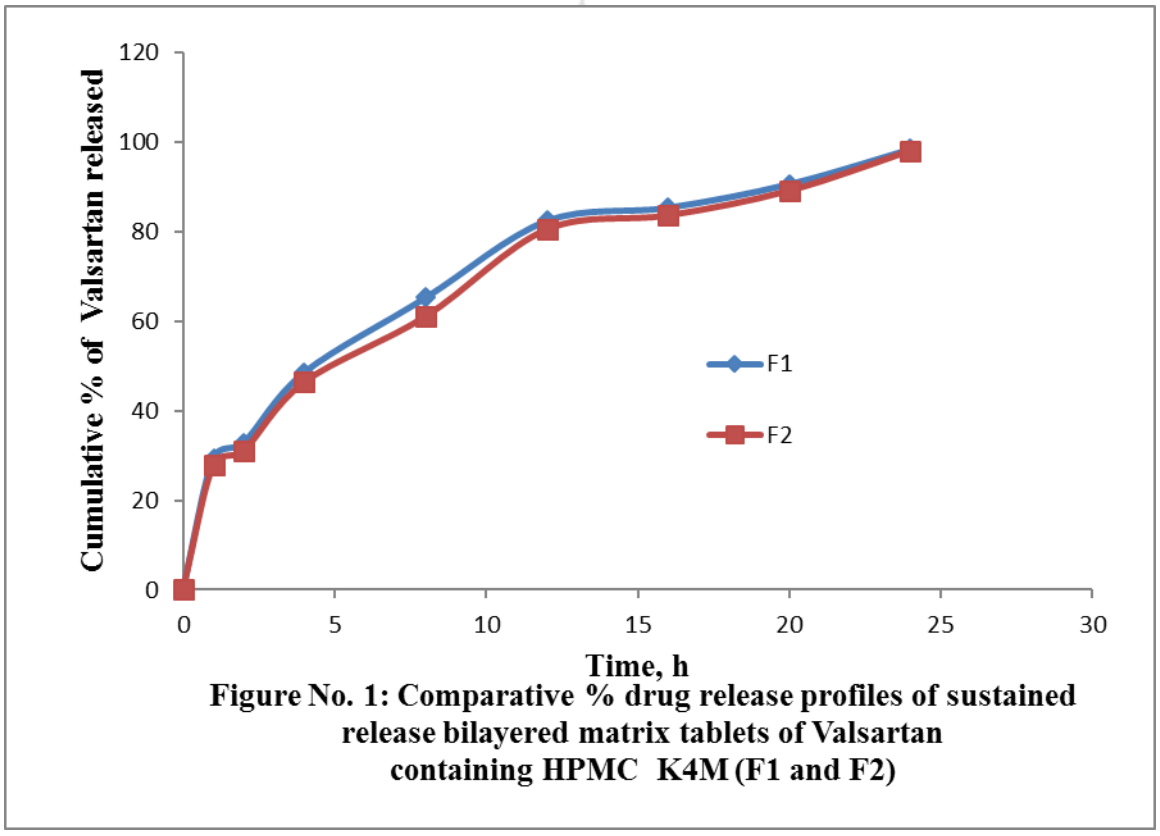

Figure No. 1: Comparative % drug release profiles of sustained release bilayered matrix tablets of Valsartan containing HPMC K4M (F1 and F2)

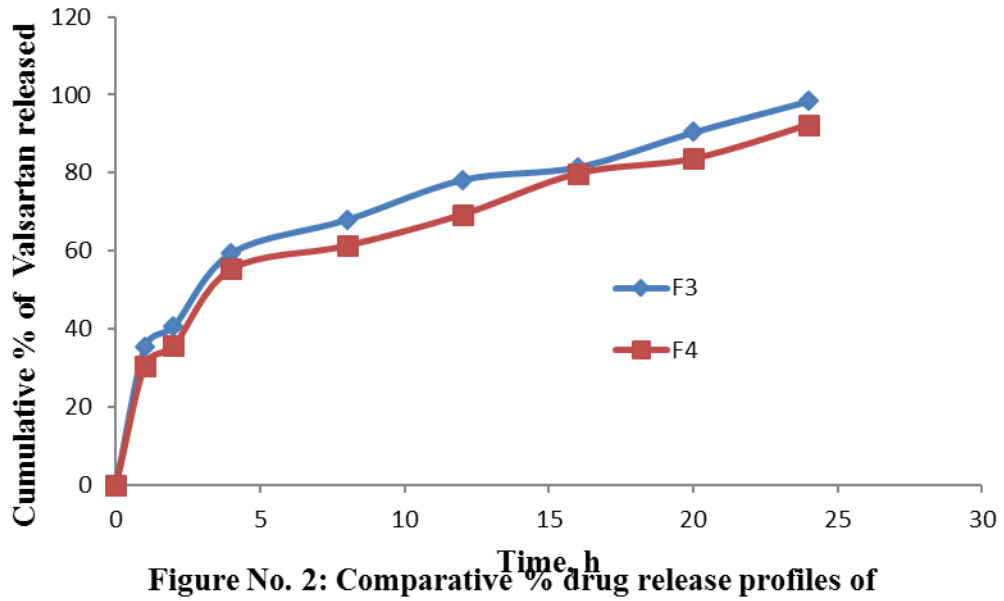

Figure No. 2: Comparative % drug release profiles of sustained release bilayered matrix tablets of Valsartan containing HPMC K15M (F3 and F4)

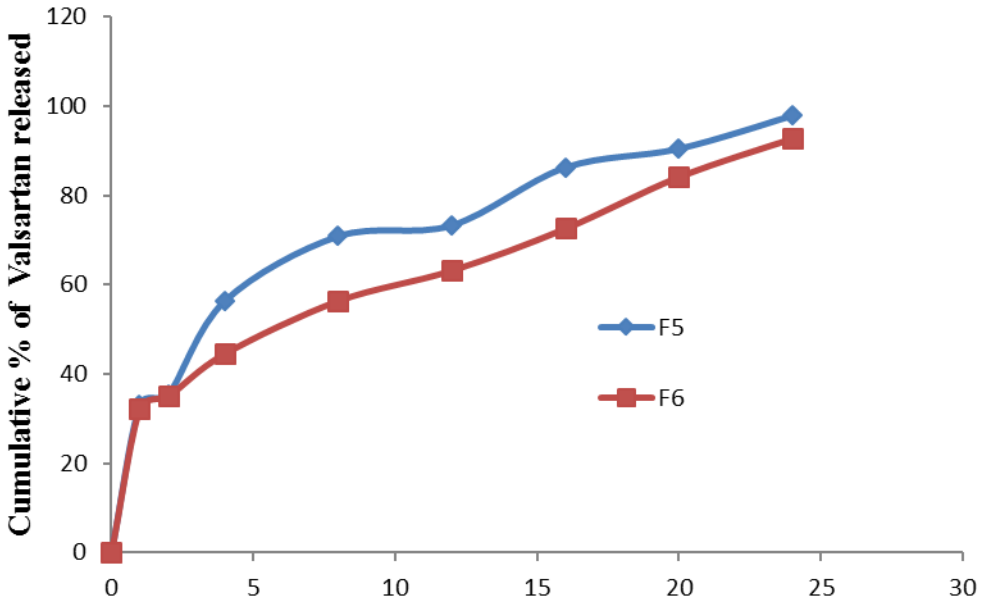

Figure No. 3: Comparative % drug release profiles of sustained release bilayered matrix tablets of Valsartan containing HPMC K100M (F5 and F6)

The data obtained from the in vitro dissolution studies of bilayered matrix tablets of valsartan was fitted to zero order, first order, Higuchi and Korsmeyer peppas equation and the results are shown in Table No. 4. The first order plots of F1 to F6 were found to be fairly linear as indicated by their high regression values (0.8906 to 0.9612) when compared with that of zero order plots (0.8044 to 0.8820). All the formulations (F1 to F6) showed good correlation in Higuchi kinetics (0.9547 to 0.9863), clearly indicating that the drug release mechanism was predominantly diffusion controlled. To confirm the exact mechanism of drug release from these matrix tablets, the data was fitted to Korsmeyer peppas equation. The diffusional exponent values (n) suggested that the release of valsartan from formulations F1 to F6 followed Fickian diffusion (n<0.5). The results of present study indicated that the release of valsartan from bilayered matrix tablets followed first order kinetics via Fickian diffusion mechanism.

Table No. 4: Dissolution kinetics of Valsartan from bilayered matrix tablets containing Different viscosity grades of HPMC (F1 to F6)

Formulation	Zero order		First order		Korsmeyer-peppas		Higuchi	Similarity factor (f_2)
	R^2	K_0 (mg/hr)	R^2	K_1 (hr^{-1})	R^2	n	R^2	
F1	0.8607	3.534	0.9282	0.143	0.9849	0.41	0.9816	47.50
F2	0.8794	3.550	0.9231	0.136	0.9847	0.42	0.9863	51.25
F3	0.8044	3.188	0.8906	0.134	0.9846	0.32	0.9547	43.50
F4	0.8268	3.068	0.9612	0.090	0.9797	0.35	0.9642	53.55
F5	0.8249	3.320	0.9341	0.131	0.9721	0.36	0.9647	44.96
F6	0.8820	3.084	0.9417	0.090	0.9721	0.34	0.9762	61.95

To compare the dissolution profile of each formulation with the theoretical release profile, the similarity factor (f_2) values of all formulations (F1 to F6) were calculated. The f_2 values of the formulations F2, F4 and F6 were higher than 50 indicating the drug release profiles are similar to the theoretical release profile. Among all the formulations, F2 (HPMC K4M), F4 (HPMC K15M) and F6 (HPMC K100M) are better formulations as they provided the sustained release of valsartan up to 24 hours and their f_2 value is higher than 50.

Hence, stability studies were conducted on valsartan bilayered matrix tablets containing various viscosity grades of HPMC (F2, F4 and F6) as per ICH guidelines i.e., at 30 ± 2°C/65 ± 5% RH and 40 ± 2°C/75 ± 5% RH for 3 months to assess their stability with respect to their physical appearance, drug content and drug release characteristics. From the results, it was found that there was no significant difference in the various physicochemical parameters indicating that valsartan bilayered matrix formulations were stable after the storage period.

In FTIR studies, all the characteristic peaks of valsartan (pure drug) were present in the spectrum of drug and polymer mixtures, indicating compatibility between drug and polymer. From the results, it was concluded that there was no interference of the functional group as the principal peaks of the valsartan were found to be unaltered in the drug polymer physical mixtures indicating that they were compatible. DSC study was conducted on valsartan pure drug and optimized formulation containing HPMC K4M. DSC thermogram of pure drug exhibits maximum peak at 105.6°C and similar peaks were observed for the formulation prepared with HPMC K4M at 103.8°C. DSC studies clearly indicated that there is no drug polymer interaction.

CONCLUSION

Once daily sustained release bilayered matrix tablets of valsartan containing different viscosity grades of HPMC (F1 to F6) provided drug release up to 24 hours in a controlled manner without changing their physical integrity in dissolution medium. When the data obtained from *in vitro* drug release studies was fitted to dissolution kinetics, the results indicated that the release of valsartan from bilayered matrix tablets followed first order kinetics via Fickian diffusion mechanism. Among all the formulations, F2 (HPMC K4M), F4 (HPMC K15M) and F6 (HPMC K100M) are better formulations as they provided the sustained release of valsartan up to 24 hours and their f_2 value is higher than 50.

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