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Dissolution enhancement of valsartan using natural polymers by solid dispersion technique

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ABSTRACT

Solid dispersions have been widely used to enhance the solubility of poorly water soluble drugs. In this study, solid dispersions of valsartan (VAL) with natural polymers such as hupu gum (HG), guar gum (GG) and xanthan gum (XG) were prepared by kneading technique in the weight ratios of 1:1,1:2,1:3 and1:4.The prepared solid dispersions were investigated by X-ray diffraction, infrared spectroscopy, differential scanning caloriemetry and solubility studies. X-ray diffraction and differential scanning caloriemetry have shown that natural polymers inhibit the crystallinity of valsartan. The infrared spectroscopy suggests that there was no chemical interaction between valsartan and natural polymers. Phase solubility studies showed that the drug solubility was increased as the concentration of polymer content was increased. The prepared solid dispersions were analysed for percentage practical yield, drug content and dissolution studies. The results demonstrated that the dissolution of GG/VAL solid dispersions was enhanced greatly at ratios of over 4/1 when compared with that of remaining ratios of GG which shows 97.90% of drug release within 60 minutes.The drug release from the solid dispersions was found to follow the first-order kinetics, Fitment into Hixson Crowell's cube root model equation suggest the drug release mechanism could be erosion.

Key words: Solid Dispersion, Valsartan, HG, GG, XG, Kneading technique.

INTRODUCTION

Poor aqueous solubility and bioavailability of drugs into the body after administration are two prime issues which are faced by the pharmaceutical industry at the present time. This problem has been the major problem hampering the release of new chemical entities into the market.Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. Every year more than 50% of the potentially active pharmaceutical ingredients get rejected due to the above stated problems.Solid dispersion technology is one of the possible modes that increase the solubility of poorly soluble drugs.Enhancement of aqueous solubility which may lead to increased bioavailability [1, 2].Solid dispersions are defined as "a dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by melting (fusion), solvent or melting-solvent method [3]. There has been tremendous improvement in the usage of these natural polymers as pharmaceutical excipients for oral use. Hence the present work is aimed to explore the applicability of different polymers of natural origin such hupu gum (HG), guar gum (GG) and xanthan gum (XG)in the enhancement of dissolution rate and thereby oral bioavailability of poorly water soluble drug. Valsartan (VAL) was selected as model drug in this study. Valsartan is an angiotensin II receptor antagonist with particularly high affinity towards the type I (AT_1) angiotensin receptor [4] and belongs to BCS Class II [5].Hence, it requires rapid absorption and high bioavailability in patient point of view. The oral bioavailability was found to be 25% in many of the solid unit dosage forms with minimum of 2 hours onset of action [6]. The solid dispersions of valsartan with selected natural

polymers such as HG, GG and XG were intended to prepare at different weight ratios by employing kneading technique.

MATERIALS AND METHODS

Valsartan was procured from A-Z Pharmaceuticals, Chennai as gift sample. Hupu gum, Guar gumand xanthan gumwere obtained from S.D. Fine ChemLtd., Mumbai. All other reagents used were of analytical grade.

Saturation Solubility studies:
Solubility study was carried out on selected BCS Class II drug candidate valsartan by using flask shaker method [7]. Excess valsartan was introduced separately into the amber colored glass vials of 25 ml capacity, each containing 25 ml of distilled water and shaken for 36 hrs at room temperature [8]. The content of each bottle was filtered through 0.4 µ membrane filter. The filtrate was then diluted accordingly and assayed spectrophotometrically.

pH-dependent solubility studies:
The pH-dependent solubilitystudies [9] of valsartan were determined in various fluids such as pH 1.2, pH 6.8 and pH 7.4 buffers. The similar procedure was followed as per above saturation solubility studies.

Phase solubility studies :
Phase solubility studies of valsartan, was carried out to evaluate the possible solubilizing effect of the carrier by adding an excess of drug to 10 ml of aqueous solutions containing increasing concentrations of hupu gum, guar gum and xanthan gum (0–1% w/v) and shaken at 25°C in a temperature controlled bath for 72 hrs. Drug concentrations were assessed spectrophotometrically. The apparent stability constant (K_c) of the drug-gums was calculated according to the following equation [10].

$$K_c = \frac{\text{slope}}{S_0} \times (1\text{-slope})$$

PREPARATION OF SOLID DISPERSIONS BY KNEADING TECHNIQUE:
Accurately weighed quantity of valsartan and selected natural polymers were transferred into a glass mortar and 5 ml of methanol was added to the mixture and triturated for 30 min for homogeneity. Then the mixture was dried at 50°C in the hot air oven until to get constant weight. The dried mass thus obtained was pulverized to fine powder and passed through sieve no. 80. A 2 gm of each sample of prepared solid dispersion formulations were stored in desiccator for further studies [11].

FT-IR Spectroscopy
Fourier Transform Infrared (FT-IR) spectral measurements for valsartan, hupu gum, guar gum, xanthangum and their solid dispersionswere recorded using Thermo-IR 200 FTIR spectrophotometer. Potassium bromide pellet method was employed. The solid dispersions were finely ground with KBr to prepare the pellets under a hydraulic pressure of 600 psi and background spectrum was collected under identical conditions. Each spectrum was derived from 16 single average scans collected in the range of 4000-400 cm^{-1} at the spectral resolution of 2 cm^{-1}.

DSC Thermal Analysis
Thermal analysis of valsartan, hupu gum, guar gum, xanthangum and their solid dispersionswere recorded with Netzsch DSC 200PC (Netzsche, Selb, German). The temperature axis and cell constant of DSC were previously calibrated with Indium. A heating rate of 5/min was employed over a temperature range of 0- 350 with nitrogen purging. The sample was weighed into an aluminium pan was used as reference.

X-Ray Diffraction Study (XRD)
X-Ray diffraction spectra of valsartan, hupu gum, guar gum, xanthan gum and their solid dispersions were recorded on a Seifert 303, Germany X-Ray Diffractometer with Rayflexsoftware using Ni-filtered, CuKα-radiation, a voltage of 40 kV and a current of 25 mA. The instrument was operated in the continuous scan mode over a 2-θ range of 10 to 70° at step time of 0.5 seconds.

PERCENTAGE PRACTICAL YIELD:
Percentage practical yield was calculated to know about percent yield or efficiency of any method [12], thus its help inselection of appropriate method of production. The final weights of the prepared solid dispersions were taken and practical yield was calculated with the following equation.

% practical yield = $\frac{\text{Practical yield}}{\text{Theoritical yield}}$ x 100

DRUG CONTENT UNIFORMITY

Six samples of each batch in which sample containing 10 mg of prepared solid dispersionswere taken and analyzed for their drug content. A 10mg sample of prepared solid dispersion was weighed accurately and transferred into a 100ml standard flasks and volume was made up to 100 ml with 0.1N HCl.The resulting solutions were filtered through a 0.45µ membrane filter and diluted accordingly. The absorbance of the solutions was measured at 249 nm.

***IN-VITRO* DISSOLUTION STUDIES:**

In-vitro dissolution study was conducted for pure valsartan and solid dispersions with the USP type II apparatus (paddle type) using SSF (pH 6.8 buffer) as dissolution medium at 37±0.5°C with 50 rpm speed [13]. The sample of 5ml aliquots were withdrawn periodically and filtered through 0.45µ membrane filter. The filtered solutions were diluted suitably. Samples were analyzed for their drug content by using UV spectrophotometer at wavelength of 249nm. Percent of valsartan dissolved at various time intervals was calculated and plotted against time. The experiment was repeated for six times.

RESULTS AND DISCUSSION

Saturated solubility studies of valsartan were carried out in distilled water and the solubility was found to be 0.567 mg/ml. weakly basic drugs and weakly acidic drugs or salts thereof demonstrated pH-dependent solubility. For weak acids, as the pH value increases, the solubility of the acid also increases due to the contribution from the ionized form. If log P of any drug is exceeding 1, indicating that the compound has a rather hydrophilic character at physiological pH.In case of valsartan, it contains two weakly acidic functions with pKa values of 3.9 and 4.7 and one asymmetric center and (co) exists in solution at physiological pH values as the undissociated acid, the mono-anion and the di-anion.In pH dependent solubility studies of valsartan (Table.No.1)the solubility was low at pH 1.2 and high at pH 7.4. Proportionate increase in solubility was observed at pH 6.8.

Table No.1: pH-Dependent Solubility of Valsartan

S. No.	Formulation Code	Solubility (mg/ml) ± S.D. (n=6)		
		pH 1.2	pH 6.8	pH 7.4
1	VAL	0.116±0.97	0.304±0.66	0.598±0.83

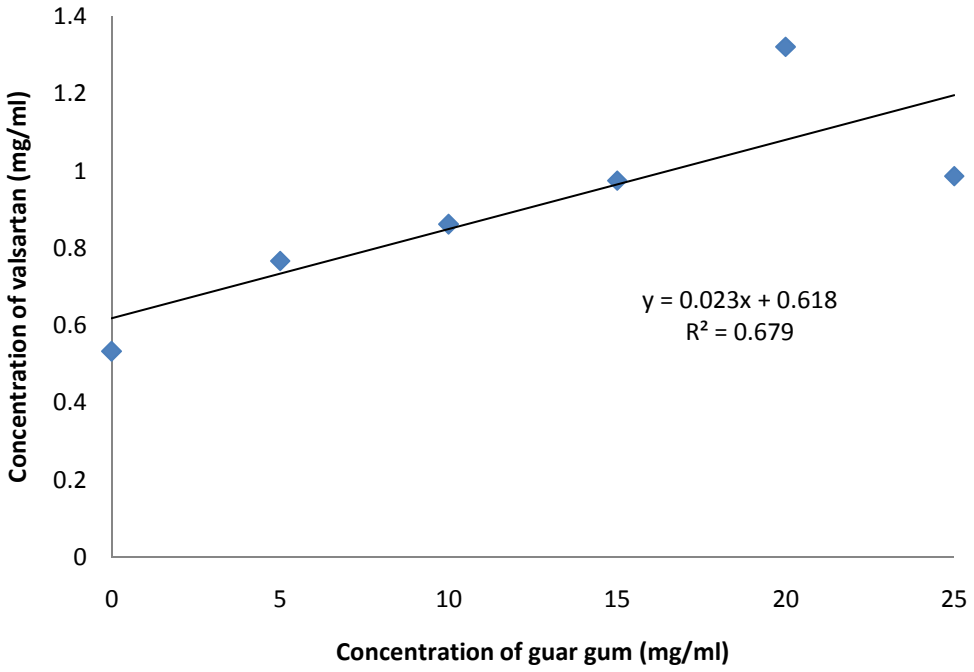


Fig. 1: Phase Solubility of Valsartan in Guar Gum

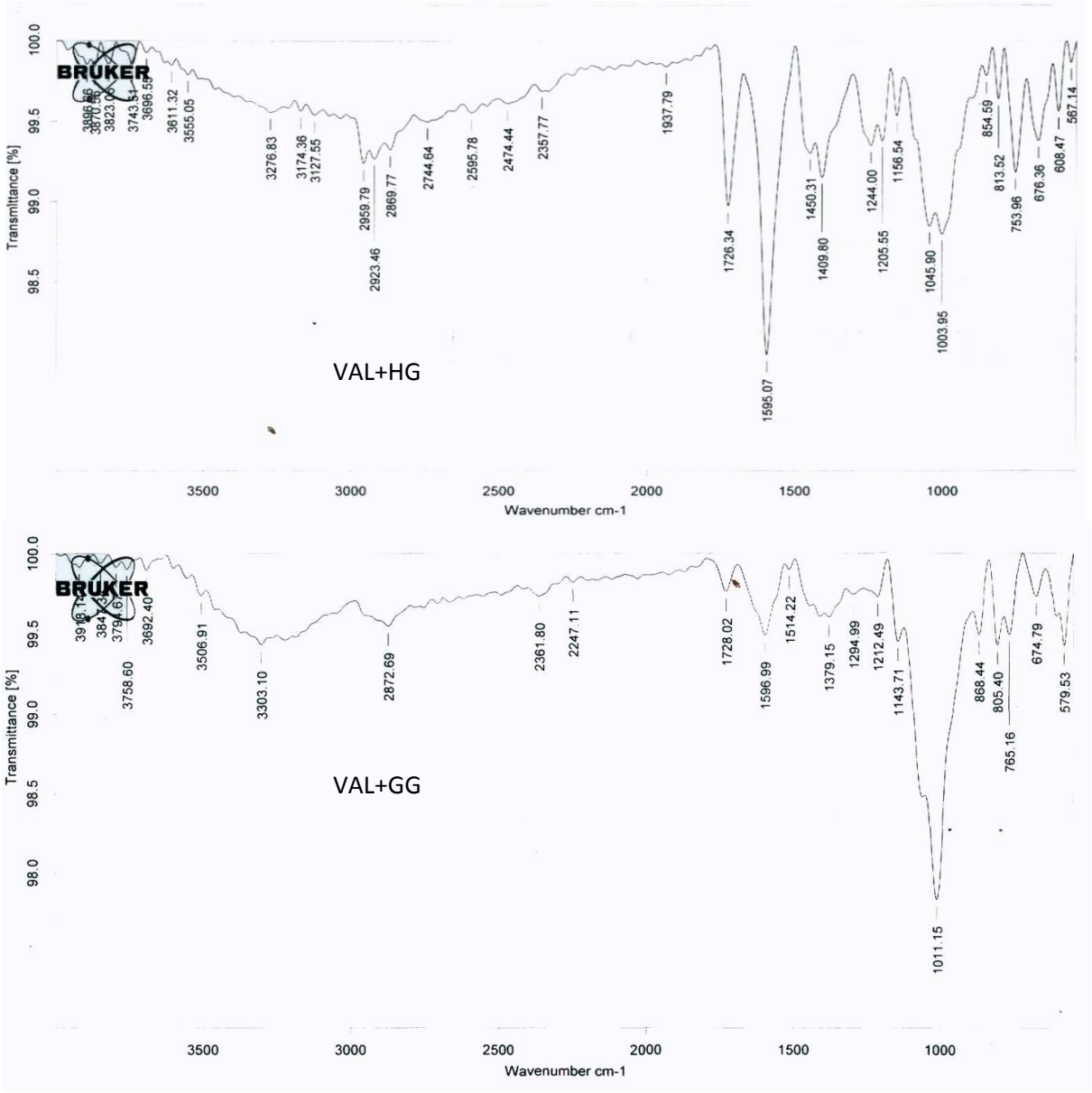
Phase Solubility

The molecular weight of used hydrophilic gums were not defined clearly, the concentrations are expressed in %w/v units in this study. The aqueous solubility of these drugs was increased as a function of the concetration of

thehydrophilic natuarl gums. The hupu gum, guar gum and xanthan gum concentration beyond 0.5% w/v resulted in the formation of the viscous gel and the solubility of the drugs could not be determined. The apparent stability constant values of the selected drugs in various natural polymers are supporting them. The phase solubility studies indicated the role of hydrophilic gums in improving the solubility of the poorly soluble drug. (Fig.1)

FT-IR Spectroscopy:

FT-IR spectra of solid dispersions of VAL and selected natural polymers prepared by kneading method are shown in Fig. 2. The principal absorption peaks of VAL were observed at 1160 cm^{-1} (N-N stretch), 1596 cm^{-1} (N-H bending), 1727 cm^{-1} (C=O stretch), 1204 cm^{-1} (C-N stretch) and 2960 cm^{-1} (methyl bond). Same peaks of N-N and methyl bond were present without much shifting in the spectra of solid dispersions of VAL and carriers suggested no interaction between the drug and the carriers



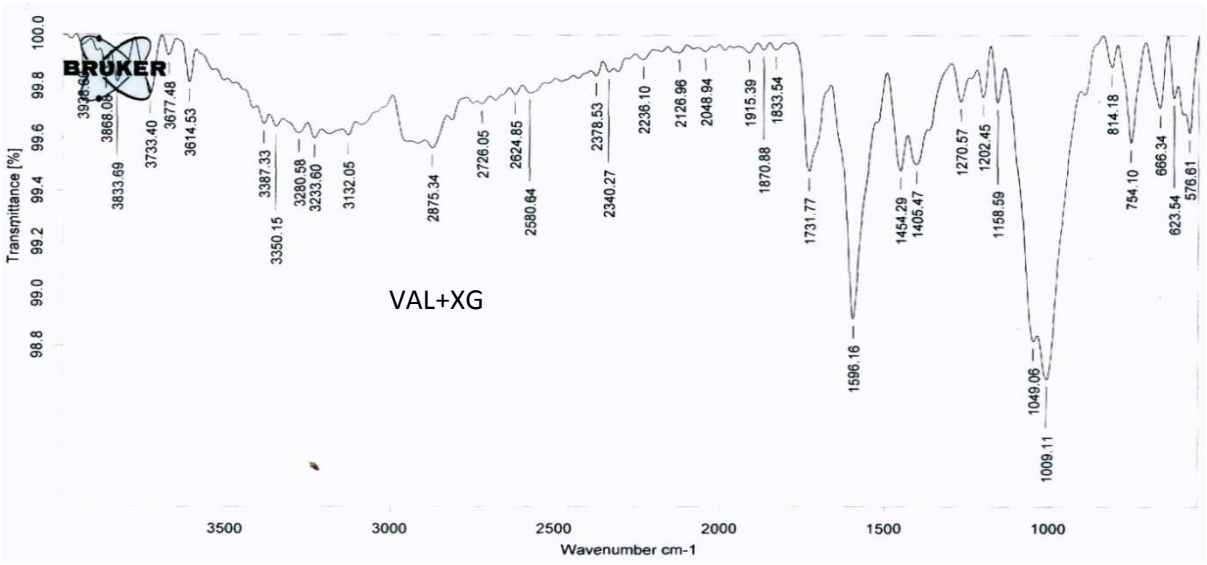


Fig. 2: FT-IR spectra of Valsartan solid dispersions

DSC Thermal Analysis:

From DSC thermograms the melting point of pure drug valsartan was found to be 117°C which the value reported in literature hence the procured drugs are pure forms.The solid dispersion of DSC thermograms of valsartan indicated that there are no interactions between the drugs and selected natural polymers which can be accessed from the peaks in the DSC thermograms. The DSC graphs of the solid dispersion were shown in Fig.3.

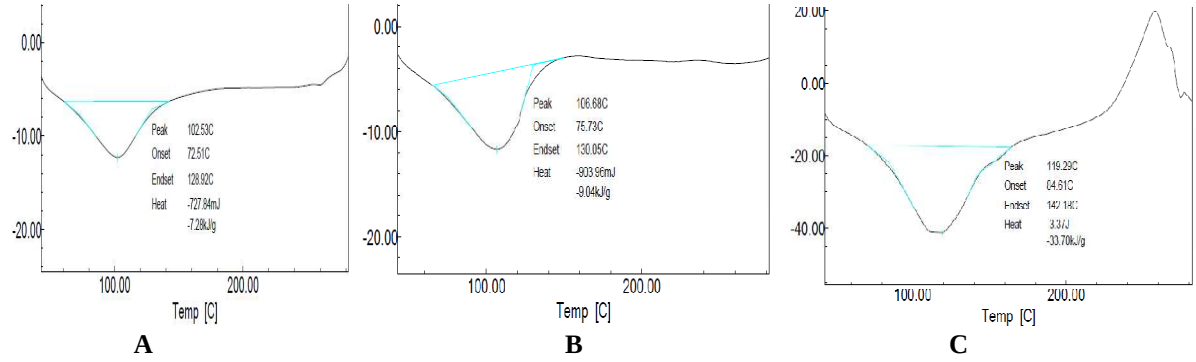


Figure No.3: (A)DSC of valsartan with hupu gum, (B)DSC of valsartan with guar gum and (C)DSC of valsartan with xanthan gum

X-Ray Diffraction Study (XRD):

Valsartan exhibited characteristic diffraction pattern, whereas in the case of solid dispersions with all the carriers, the sharp diffraction peaks have been changed. The intensity of sharp peaks in the diffractograms of solid dispersions reduced considerably indicating the reduced crystallinity of the drug in all the cases of solid dispersions when compared to pure drugs. This may be due to partial conversion of the drugs to amorphous state from crystalline state (Fig. 4)

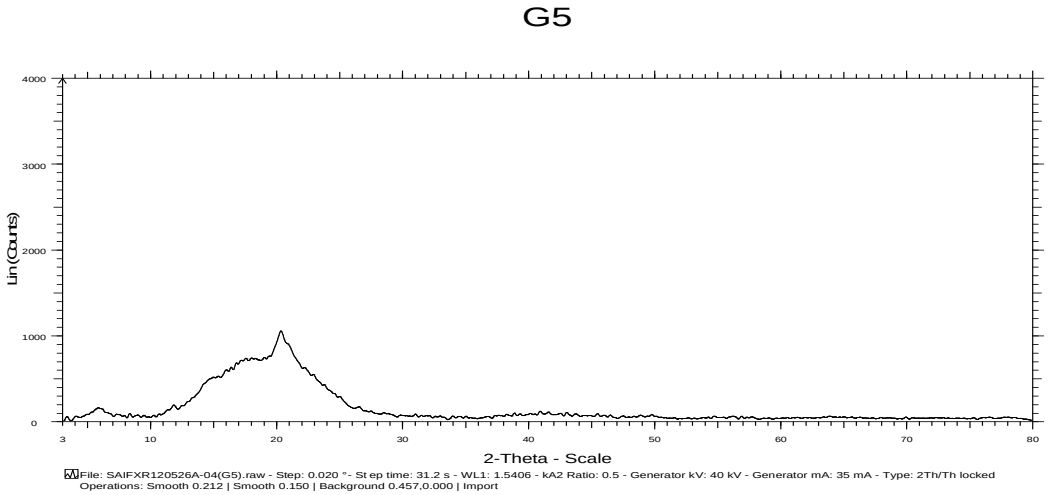


Fig. 4: XRD of valsartan with guar gum

% Practical Yield

All the solid dispersions prepared were found to be fine and free flowing powders. Percentage practical yield of valsartan solid dispersions was in the range of 80.32-94.61 as shown in Table No.2. The percentage yield was low for 1:1 and the high for1:2 (guar gum& xanthan gum).Low s.d. values in the percent practical yields ensured that there was no significant loss of drug during the preparation of solid dispersions. In the preparation of kneading mixtures, the solvent used has no effect on results.

Table 2: % Practical Yield of Solid Dispersions Containing valsartan (mean± S.D.)

Drug: Polymer	Hupu gum	Guar gum	Xanthan gum
1:1	92.73±1.13	80.32±1.23	85.67±1.54
1:2	90.63±0.91	91.57±0.96	94.61±0.88
1:3	92.22±1.98	88.76±1.42	90.34±1.45
1:4	85.42±1.32	87.04±2.12	93.12±0.93

% Drug Content Estimation: Valsartan content was found in the range of 45.63 - 63.23 as shown in Table No.3. The drug content was low for 1:1 of xanthan gum and high for 1:3 of hupu gum.The results revealed that the ratios and method used to prepare solid dispersions have shown no effect on the drug content and uniformity of the solid dispersions.

Table 3: % Drug Content of Valsartan in Solid dispersions (mean± S.D.)

S. No.	Ratio	% Drug content		
		VAL:HG	VAL:GG	VAL:XG
1	1:1	45.63±1.38	49.96±1.65	47.16±1.67
2	1:2	52.40±0.92	54.47±1.18	51.75±1.42
3	1:3	63.23±1.92	57.11±1.68	57.62±1.83
4	1:4	53.67±2.13	62.02±1.14	62.65±1.68

In vitro Dissolution studies

Dissolution study of valsartan and its solid dispersions with HG, GG and XG have exhibited varied release profiles and shown in Fig.5, 6 and 7 in which it was found that solid dispersions with all selected carriers better than pure valsartan dissolution rate.In case of VAL:HG solid dispersions, all ratios viz. 1:1, 1:2, 1:3 and 1:4 have shown increased cumulative dissolution profiles when compared with pure valsartan (Fig. 5). This could be due the presence of natural polysaccharide, hupu gum in its formulation. The hupu gum is having the ability to reduce the crystallinity of selected class II drug VAL. In addition, employing the kneading technique in solid dispersion preparation, it would have reduced the particle/crystal size and facilitated to form the new surfaces/ small crystals and proportionate increase of amorphous portion in VAL. Formation of the new surfaces cause subsequent increase in the effective surface area, which allows the increased wetting of the insoluble/poor soluble drug, valsartan by surrounding bulk liquid and facilitate the wetting of hydrophobic surface, which resulted in the increased solubility and subsequent dissolution. The crystalline drug VAL was adsorbed onto the surface of selected carriers, results in passage of solvent towards the faces and interiors of drug particles. Therefore, increased dissolution profiles were observed for solid dispersions of hupu gum at various time intervals as shown in Fig. 5.

There was two fold increase in cumulative percent of drug dissolved in case of solid dispersion of 1:4 weight ratio at 5 minutes withdrawn sample and whereas similar double increase was observed at 60th minute sample. The dissolution parameters such as, dissolution efficiency at 10, 30 and 60 minutes periods was increased proportionately when compared to pure drug (Table 5). The time point to dissolve 50% of drug is T_{50} was found to 9.42 min for 1:4 weight ratio formulations. The increased dissolution profiles was observed for solid dispersions of guar gum at various time intervals as shown in Fig. 6 which are similar to hupu gum case. There was significant increase in %drug dissolved in case of solid dispersion of 1:4 weight ratios at with function of time. The dissolution parameters such as, dissolution efficiency at 10, 30 and 60 minutes periods was increased proportionately when compared to pure drug (Table 5). The time point to dissolve 50% of drug is T_{50} was found to 7.53 min for 1:4 weight ratio formulations. Solid dispersions of VAL: XG at all weight ratios viz. 1:1, 1:2, 1:3 and 1:4 have shown increased cumulative dissolution profiles. The xanthan gum is also having the ability to reduce the crystallinity of selected class II drug VAL. The increased dissolution profiles was observed for solid dispersions of xanthan gum at various time intervals as shown in Fig. 7 which are similar to hupu gum case. There was significant increase in % drug dissolved in case of solid dispersion of 1:4 weight ratios at with function of time. The time point to dissolve 50% of drug is T_{50} was found to 10.63 min for 1:4 weight ratio formulations (Table 5). The drug release patterns from the solid dispersions have found to be followed the first-order kinetic model and fitment into Hixson Crowell's cube root equation suggest that the drug release mechanism could be erosion (Table No.4).

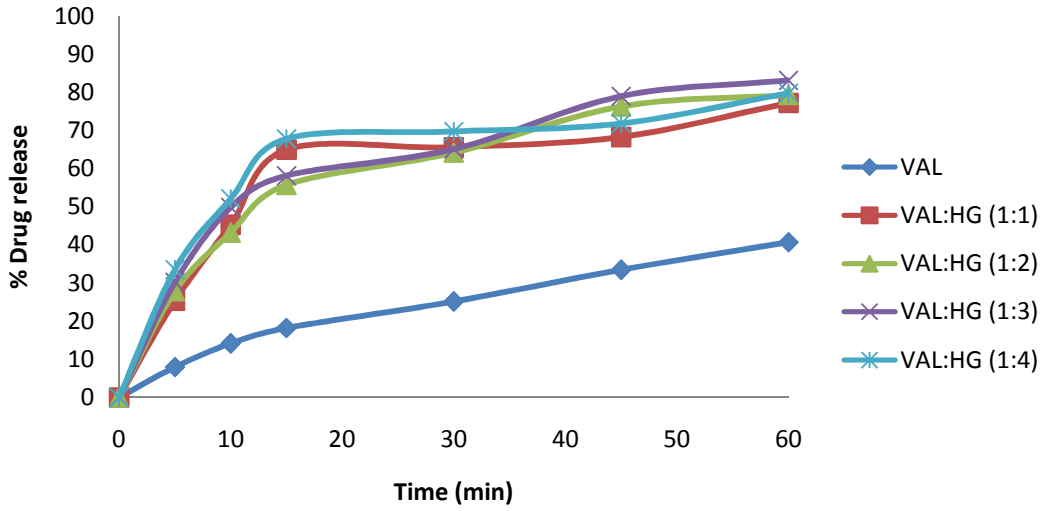


Fig. 5: Percentage drug release of valsartan hupu gum solid dispersions

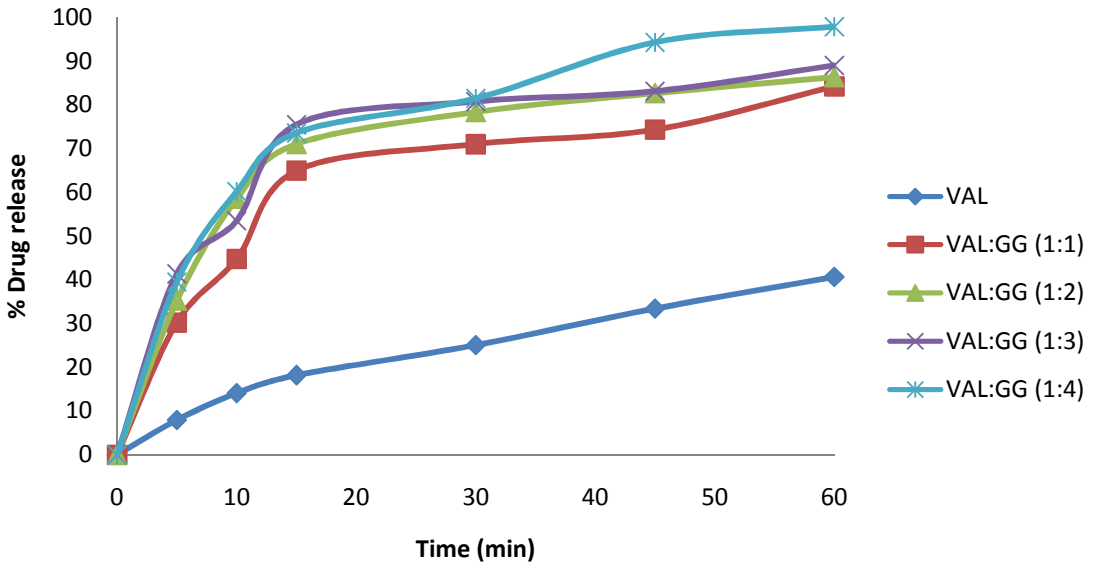


Fig. 6: Percentage drug release of valsartan guar gum solid dispersions

Table No.4: Correlation coefficient (r) & Rate constant (k) values of VAL-HG, VAL-GG and VAL-XG solid dispersions

Model		VAL	VAL:HG (1:1)	VAL:HG (1:2)	VAL:HG (1:3)	VAL:HG (1:4)	VAL:GG (1:1)	VAL:GG (1:2)	VAL:GG (1:3)	VAL:GG (1:4)	VAL:XG (1:1)	VAL:XG (1:2)	VAL:XG (1:3)	VAL:XG (1:4)
Zero-Order	r	0.9972	0.998	0.9863	0.9926	0.9866	0.9892	0.9931	0.9713	0.9842	0.9908	0.9864	0.9927	0.9821
	k	1.415	4.528	4.318	4.987	5.215	4.481	5.857	5.352	6.025	3.854	4.158	4.325	4.854
Higuchi	r	0.9945	0.9859	0.9975	0.9958	0.9973	0.9993	0.9953	0.9976	0.9988	0.9982	0.9999	0.9948	0.983
	k	5.2768	16.1332	14.2047	15.3535	17.2621	16.0418	18.4657	18.724	19.0596	13.6773	14.8329	15.0626	15.5827
First-Order	r	0.9986	0.9998	0.9973	0.9997	0.9992	0.9928	0.9931	0.9861	**0.9987**	0.9964	0.9934	0.9984	0.9969
	k	0.0153	0.0692	0.0565	0.0691	0.0747	0.0677	0.0881	0.089	0.0923	0.0521	0.059	0.0606	0.0664
Baker Landale	r	0.997	0.9684	0.9909	0.9919	0.9884	0.9954	0.9883	0.9983	0.992	0.9929	0.9982	0.9846	0.9948
	k	0.0006	0.0069	0.0048	0.0055	0.0078	0.0068	0.0091	0.01	0.0099	0.0046	0.0056	0.0057	0.006
Peppas	r	0.997	0.9713	0.9629	0.9882	0.9522	0.9919	0.9939	0.9743	0.9982	0.9955	0.9892	0.9993	0.9883
	k	0.7521	0.8509	0.6283	0.6059	0.6375	0.6793	0.6436	0.526	0.5676	0.6993	0.6474	0.7331	0.8432
Erosion	r	0.9982	0.9999	0.9936	0.9984	0.997	0.9999	0.9936	0.9984	0.997	0.9964	0.9936	0.9986	0.9979
	k	0.005	0.0195	0.0172	0.0206	0.0218	0.0195	0.0172	0.0206	0.0218	0.0152	0.0169	0.0174	0.0199
Hixson Crowell	r	0.9982	0.9999	0.9936	0.9984	0.997	0.995	0.9994	0.9873	0.9955	0.9964	0.9937	0.9986	0.9979
	k	0.023	0.0905	0.0797	0.0954	0.1011	0.0884	0.1181	0.11	0.1229	0.0707	0.0786	0.0807	0.0922
Weibul	r	0.9849	0.9702	0.9905	0.9882	0.9865	0.9945	0.9848	0.9621	0.9847	0.9933	0.9974	0.9854	0.957
	k	0.277	0.8181	0.8968	0.9788	0.8906	0.9915	1.1487	1.231	1.9678	0.7902	0.8975	0.9588	1.1966

Table No.5: Dissolution efficiency and T-50 values of VAL-HG, VAL-GG and VAL-XG solid dispersions

	VAL	**VAL:HG (1:1)**	**VAL:HG (1:2)**	**VAL:HG (1:3)**	**VAL:HG (1:4)**	**VAL:GG (1:1)**	**VAL:GG (1:2)**	**VAL:GG (1:3)**	**VAL:GG (1:4)**	**VAL:XG (1:1)**	**VAL:XG (1:2)**	**VAL:XG (1:3)**	**VAL:XG (1:4)**
DE 10	7.54	23.99	24.72	27.57	29.81	26.33	32.28	34.08	34.82	22.24	24.86	24.16	24.23
DE 30	16.04	49.83	46.45	49.01	54.34	51.93	58.91	61.18	61.54	44.68	48.89	49.2	50.54
DE 60	24.61	59.84	60.24	62.79	63.82	63.97	70.71	72.6	76.78	56.7	61.38	62.61	66.05
T 50	0.00	11.20	12.72	10.08	9.42	11.29	8.16	8.55	**7.53**	13.44	12.28	11.98	10.63

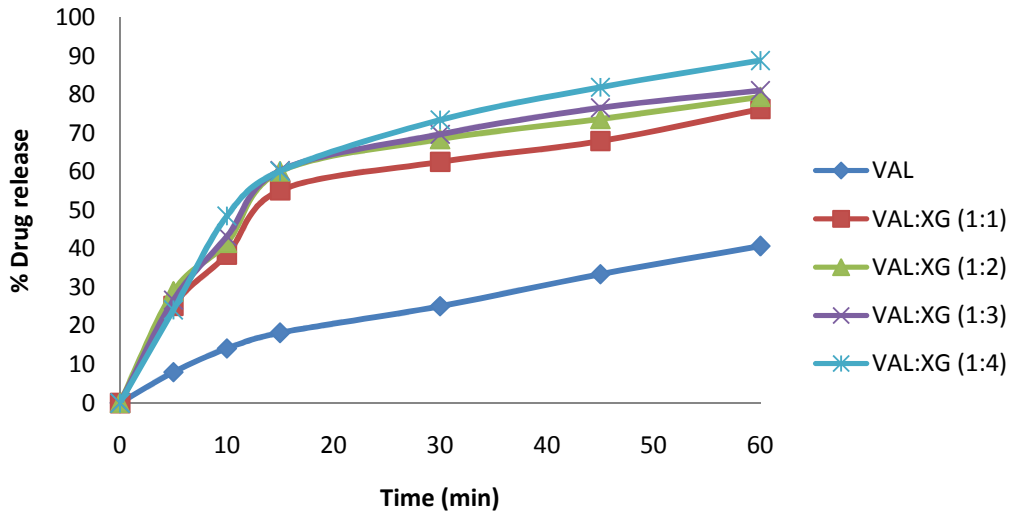


Fig. 7: Percentage drug release of valsartan xanthan gum solid dispersions

CONCLUSION

The results of the present study clearly demonstrated that suitability of selected natural polymers such as hupu gum, guar gum and xanthan gum in the preparation of solid dispersions. These prepared solid dispersions are showing promising results in enhancing the solubility of poorly soluble drug such as valsartan. Amongst the solid dispersions prepared, solid dispersions prepared using guar gum as carrier in 1:4 weight ratio shown the better release of valsartan (97.90%) within 60 min in comparison with that of pure valsartan. Thus, the selected natural polymers (HG, GG and XG) are considered to be very good carriers in increasing the solubility, dissolution rate and thereby bioavailability of poorly soluble drug candidates. Further studies are required to confirm the applicability of these natural polymers in formulation technology.

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