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SOLUBILITY ENHANCEMENT OF CLASS -II DRUGS BY SOLID DISPERSION TECHNIQUE

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ABSTRACT

The main objective of the present work is to enhance the dissolution rate of the valsartan by formulating into solid dispersions and the selection of appropriate solid dispersion to be used in the preparation of further formulation development. To accomplish the objective, API characterization and reference product evaluation were carried out. FT-IR studies of the API and excipients showed no marked changes in the spectra confirming the compatibility. Phase solubility studies of valsartan with PEG 6000 and PVP K30 showed proportional increase in solubility with increase in concentration of the polymer indicating that the polymers are suitable as carriers for solid dispersion. Solid dispersion of valsartan with PEG 6000 and PVP K30 were prepared at increasing concentrations of the carrier (1:1, 1:3, 1:5) by solvent evaporation method using Rotary flash evaporator. The dissolution profile of the solid dispersions showed an improved solubility. Solid dispersion (SD6) containing 1:6 ratio of valsartan: PVP K30 showed 94.40±1.79% of drug release by the end of 60 min compared to pure drug which showed 33.01± 0.64%.

Key words: Valsartan, Solid dispersions angiotensin II receptor antagonist, PEG

INTRODUCTION

Oral drug delivery is the simplest and easiest way of administering drugs (Young *et al.*, 2006). Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosage forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities under development these days are intended to be used as a solid dosage forms that originate an effective and reproducible *in vivo* plasma concentration after oral administration (Tetsuya O *et al.*, 2005). Compounds with poor aqueous solubility are increasingly posing challenges in the development of new drugs, since a large number of drugs coming directly from synthesis or from high throughputs screenings have a poor solubility (Sharma DK *et al.*, 2011). The ability to increase aqueous solubility is thus a valuable aid to increase the efficacy for poorly water soluble

drugs (Yolkowsky *et al*., 1981).

Various approaches available to improve drug solubility as well as drug dissolution of poorly aqueous soluble drugs include micronization, formation of inclusion complexes with cyclodextrins, formation of amorphous drugs and formation solid dispersions of drugs using various hydrophilic carriers. Among them, solid dispersion technique has attracted substantial interest as an efficient means of improving the dissolution rate as well as the bioavailability of a wide range of poorly aqueous soluble drugs. Fast and immediate drug dissolution from solid dispersions has been observed due to increased wettability and dispersibility of drug particles, existence of the drug in amorphous form with improved solubility and absence of aggregation of drug particles using various hydrophilic carriers. Increasing cost and complications involved in development and marketing of new drug entities also has forced industries to focus their attention on the development of solid dispersion systems.

Solid dispersions

According to Chiou *et al*., (1971), a solid dispersion is "the dispersion of one or more active ingredients in an inert carrier at solid-state prepared by melting (fusion), solvent or the melting-solvent method". The carrier used has traditionally been a water-soluble or water- miscible polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) or low molecular weight materials such as urea, citric acid and mannitol. However, the proliferation of publications in the solid dispersions area has led to a broadening of these definitions to include water-insoluble matrices such as Gelucires.

The faster the drug is into solution form, quicker the absorption and onset of clinical effects. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. A fraction of pre-gastric drug absorption may bypass the digestive system and metabolism by the stomach acids and enzymes. In such cases, bioavailability of drug is significantly greater than those observed from conventional dosage form.

Valsartan is an angiotensin II receptor antagonist and is widely used in the management of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction following myocardial infarction and in the management of heart failure.

Being a class II drug valsartan shows low solubility and high permeability. Therefore an attempt was made to enhance its solubility by formulating into solid dispersion.

History

Valsartan was first developed by Novartis and was sold under the brand name DIOVAN and it currently holds the largest market share for the drug of its kind in the market. In the USA, Valsartan is registered by the Food and Drug Administration (FDA) for use in the treatment of hypertension in children of 6 years and older and adolescents in the December 2008.

Present and Future Scenario

Diovan (valsartan) was labeled as the world's number one selling high blood pressure medication and accounted for $6 billion in sales in 2010 worldwide. In near future its patent protection on its active ingredient is ready to expire in most of the major territories.

Materials and Methods

Valsartan was obtained from Hetero drugs Ltd, Hyderabad, India. PEG 6000, PVP K30, and others were obtained from Qualikem's fine chem ltd, Vadodara, india and reagents were of analytical grade and procured from commercial sources.

METHODOLOGY

Preparation of Physical Mixtures

Physical mixtures of Valsartan with PEG 6000 and PVP K30 were prepared in different concentrations as shown in table by mixing accurately weighed quantities of drug and polymer in a mortar to get uniform powder. The resulting mixtures were passed through sieve # 80, collected and stored in a closed container away from the light and humidity in desiccators until use.

Preparation of Valsartan Solid Dispersions

Solid dispersions of Valsartan in PEG 6000 and PVPK30 containing 3 different weight ratios (table. 1) were prepared by the solvent evaporation method. Valsartan was dissolved in ethanol to get clear solution. An appropriate amount of carrier was added to a solution of Valsartan in ethanol and dissolved. The solvent was removed under vacuum at 40°C in

a rotary flash evaporator at 45 rpm for 2 hrs. Solid residue was dried in a vacuum oven for 24 hours at room temperature to remove the residual solvent, pulverized and sieved using sieve # 80. Powder samples were stored in a closed container away from light and humidity in a dessicator until use.

Table 1: Formulations for physical mixtures and solid dispersions of Valsartan

Formula	Drug / Carrier	Ratio
PM1	Valsartan / PEG 6000	1:5
PM2	Valsartan / PVP K30	1:5
SD1	Valsartan / PEG 6000	1:1
SD2	Valsartan / PEG 6000	1:3
SD3	Valsartan / PEG 6000	1:5
SD4	Valsartan / PVP K30	1:1
SD5	Valsartan / PVP K30	1:3
SD6	Valsartan / PVP K30	1:5

Determination of percent yield

The percent yield of Valsartan solid dispersions can be determined by using the following expression:

$$\text{Percent yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Determination of percent drug content

Accurately weighed quantities of physical mixtures and solid dispersions, each sample equivalent to 20 mg of Valsartan were separately added to 20 ml of ethanol in stoppered conical flasks. The sealed flasks were agitated on a rotary shaker for 1 hour. The solution was filtered, diluted suitably and was assayed by a UV-Vis spectrophotometer for drug content at 250 nm.

DISSOLUTION STUDIES

Dissolution studies for pure drug, PM and SDS

In-vitro dissolution studies of pure drug, physical mixtures (PM) and solid dispersions (SD) were carried out by using XXIV type II apparatus. Samples equivalent to 40 mg of Valsartan were added to the 900 ml of phosphate buffer pH-6.8 at 37 ± 0.5^0 C and stirred at 50 rpm. An aliquot of 5 ml was withdrawn at different time intervals 10, 20, 30, 40, 50 and 60 mins with a syringe filter. The withdrawn volume was replaced immediately with the same volume of dissolution medium in order to keep total volume constant. The filtered samples were assayed spectrophotometrically at 250 nm using phosphate buffer as blank. The mean of at least three determinations were used to calculate the drug release.

Drug - Excipient Compatibility Study

FTIR studies were carried out to determine the compatibility of excipients with the drug. API and excipients were been thoroughly mixed in predetermined, passed through the 40 # sieve and were analysed.

RESULTS AND DISCUSSION

Drug Excipients compatibility-FTIR spectroscopy

The functional groups present in the drug were identified. The FTIR of valsartan showed intense bands at 3445.98 cm^{-1}, 2963.28 cm^{-1}, 1730.51 cm^{-1}, 1603.48 cm^{-1} and 1066.13 cm^{-1} corresponding to the functional groups NH, C=N, Carboxylate, C=O and CN bending respectively.

The wave numbers of drug were compared with final formulated product IR spectrum. The resulted peaks observed in FTIR are presented in Table No.2. The results revealed that there was no significant disturbance in the principle peaks of pure drug Valsartan. The FTIR spectrum for Valsartan and excipients mixture reveals a broad peak at 3382.46 cm-1 due to N–H bond stretching. From the interpretation it was understood that there was no major shifting in the frequencies of valsartan which indicated that there is no chemical interaction in the formulations.

This further confirms the integrity of pure drug and compatibility of it with excipients.

Table 2: Principle IR peaks of valsartan

valsartan	Valsartan+excipients	Functional group
3445.98	3382.46	Amine(NH)
2963.28	2962.20	C=N
1730.51	1727.67	Carboxylate
1603.48	1604.30	C=O
1066.13	1071.81	C-N

Determination of percent yield

The prepared solid dispersions the percentage yields of all formulations ranging from 80 to 89 (table 3). The yield was relatively higher in case of physical mixtures than in solid dispersions.

Table 3: Percent yield of solid dispersions

Formula	Percent yield
PMI	97.52
PM2	98.21
SD1	84.8
SD2	81.6
SD3	86.9
SD4	89.3
SD5	80.25
SD6	85.7

Drug content of valsartan in Solid Dispersions

The drug content of the prepared solid dispersions was found to be in the range 95-100 indicating the application of the present method for the preparation of solid dispersions with high content uniformity.

6000 have shown a significant enhancement in drug releas characteristics compared to pure Valsartan. The percent drug released from higher ratio of SDs and PM1 in 60mins was found to be 78.93 % and 42.43% respectively.

Table 4: Drug content of valsartan with PEG 6000 and PVP K30 solid dispersions

Formula	Drug / Polymer (w/w)	Ratio	Assay
SD1	valsartan / PEG	1:1	97.61 ±0.92
SD2	valsartan /PEG 6000	1:3	96.01 ±0.23
SD3	valsartan /PEG 6000	1:5	98.33 ±1.48
SD4	Valsartan /PVP K30	1:1	95.16 ±0.36
SD5	Valsartan /PVP K30	1:3	99.32 ±0.25
SD6	Valsartan /PVP K30	1:5	98.31 ±0.38

Dissolution Studies:

Dissolution studies of Valsartan with PEG 6000 PM1 and SDs in phosphate buffer pH - 6.8.The dissolution data for PM1 and solid dispersions were presented in respectively, release profiles were shown in Fig.1. The dissolution profiles for Valsartan SDs and PM1 with PEG6000 have shown a significant enhancement in drug release characteristics compared to pure Valsartan. The percent drug released from higher ratio of SDs and PM1 in 60mins was found to be 78.93 % and 42.43% respectively.

The dissolution profiles of solid dispersions and physical mixtures with PVP K30 were presented in Fig.2. All the values represent mean±SD, where n=3. The dissolution profiles for Valsartan SDs and PM2 with PVP K30 have shown a significant enhancement in drug release characteristics compared to pure Valsartan. The percent drug released from higher ratio of SDs and PM2 in 60mins was found to be 94.90 % and 46.67%.

The dissolution profiles of the SD3 made from PEG 6000 shown significant higher dissolution profiles compared to PM1,SD1 and SD2of the same carrier. The dissolution profiles of the SD6 made from PVP K30 shown Fig.3 significant higher dissolution profiles compared to PM2, SD4, SD5 of the same carrier and also to that of the formulations with PEG 6000.

Therefore it can be concluded that SD6 formulation shows improved dissolution profiles than other formulations.

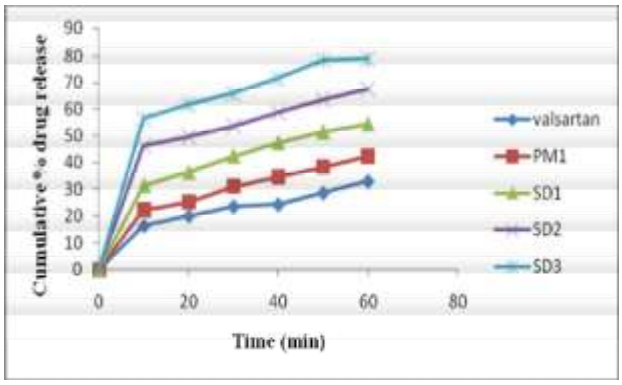

Fig. 1: Dissolution profile of Valsartan and Valsartan with PEG 6000 SDs

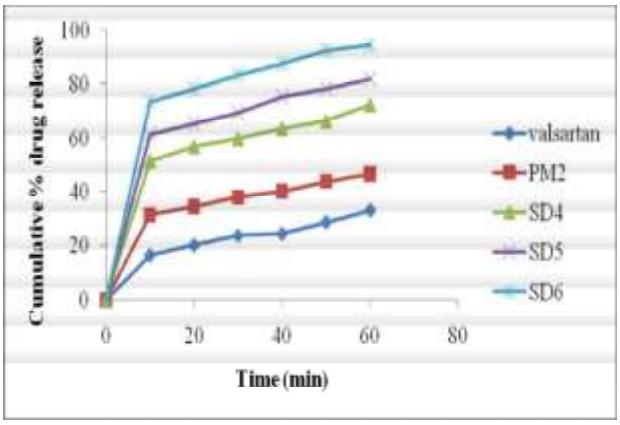

Fig. 2: Dissolution profiles of valsartan and valsartan with PVP K30 SDs

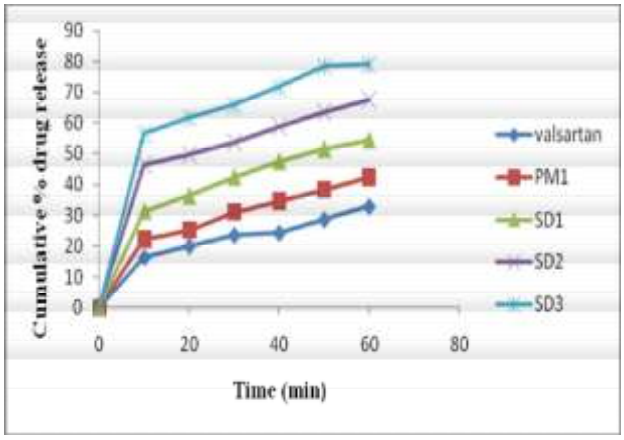

Fig. 3: Dissolution profile of valsartan and valsartan with PEG 6000 and PVP K30 SDs.

CONCLUSION

Solid dispersions of valsartan were prepared by solvent evaporation method using PEG 6000 and PVP K30 as carriers using solvent evaporation technique. Different parameters were evaluated and the Solid dispersion with 1:5ratio of drug and polymer showed enhanced dissolution rate.

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