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Solubility enhancement of antihypertensive agent by solid dispersion technique

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Abstract

The present study was aimed to increase the solubility of the poorly water soluble drug Telmisartan by using polymers like Gelucire 43/01, Poloxamer 407, PVP K-30 and HPMC E4 and PEG 6000. Solid dispersions were prepared by fusion method. Saturation solubility studies, in-vitro dissolution of pure drug, physical mixtures and solid dispersions were carried out. All the polymers were found to be effective in increasing the dissolution rate of Telmisartan in solid dispersions when compared to pure drug. Also FT-IR spectroscopy, differential scanning calorimetry and X-ray diffractometry studies were carried out in order to characterize the drug and solid dispersion.

Key-Words: Solid dispersion, Telmisartan, PVP K-30, HPMC, Fusion method.

Introduction

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be rate determining step for appearance of medicinal effect, therefore efforts to increase dissolution of drug with limited water solubility is often needed. Many methods are available to improve these characteristics, including salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of these methods and involved a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method.¹

Telmisartan is chemically described as 4'-[(1,4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl)methyl]-[1,1'-biphenyl]-2-carboxylic acid. Telmisartan is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base. Telmisartan interferes with the binding of angiotensin II to the angiotensin II AT₁-receptor by binding reversibly and selectively to the receptors in vascular smooth muscle and the adrenal gland. As angiotensin II is a vasoconstrictor, which also stimulates the synthesis and release of aldosterone, blockage of its effects results in decreases in systemic vascular resistance.

Telmisartan does not inhibit the angiotensin converting enzyme, other hormone receptors, or ion channels. Studies also suggest that telmisartan is a partial agonist of PPAR γ , which is an established target for antidiabetic drugs. This suggests that telmisartan can improve carbohydrate and lipid metabolism, as well as control insulin resistance without causing the side effects that are associated with full PPAR γ activators.

Following oral administration, peak concentrations (C_{max}) of telmisartan are reached in 0.5-1 hour after dosing. Food slightly reduces the bioavailability of telmisartan, with a reduction in the area under the plasma concentration time curve (AUC) of about 6% with the 40 mg tablet and about 20% after a 160 mg dose. The absolute bioavailability of telmisartan is dose-dependent. At 40 mg and 160 mg, the bioavailability was 42% and 58%, respectively.^(1,2)

So, in order to enhance oral bioavailability, solubility enhancement can be achieved via solid dispersion formation by using hydrophilic polymers.

Material and Methods

A gift sample of Telmisartan was received from Unichem laboratories, Nasik and all other polymers were obtained from S.D. fine chemical (India).

Estimation of Telmisartan¹

An U.V. Spectrophotometric method based on the measurement of absorbance at 216 nm in a 0.1 N HCL containing 1% w/v of sodium lauryl sulphate was used for the estimation of telmisartan. The method was validated for linearity, accuracy, precision and interference. The method obeyed Beers law in the

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concentration range of 2-10 µg/ml ($r=0.9994$). When a standard drug solution was repeatedly assayed ($n=6$), the relative error and coefficient of variation were found to be 0.90% and 1.1% respectively. No interference by the excipients used in the studies was found.

Physical mixture of Telmisartan^{1,11-12}

Physical mixtures of Telmisartan at three different mass ratios (1:1, 1:2, 1:3 and 1:4) were prepared. The mixtures were passed through a sieve no. 60. The prepared mixtures were then filled in glass bottles, sealed and stored in a desiccator until further use.

Phase Solubility Studies²⁻⁴

The phase solubility studies were carried out according to the method reported by Higuchi and Connors. Excess amount of Telmisartan was added to the screw capped vials containing 20 ml of aqueous carrier solution at various concentrations and placed on a rotatory shaker and agitated at room temperature for 48 hours. After equilibrium, the solutions were carefully filtered through Whatman No.41 filter paper and after appropriate dilution; solutions were analyzed at 292 nm by using UV- visible spectrophotometry.

Solid dispersion of Telmisartan (Fusion method)³⁻⁶

Accurately weighed amounts of carrier(s) were placed in an aluminum pan on a hot plate and melted, with constant stirring, at a temperature of about 60°C. An accurately weighed amount of Telmisartan was incorporated into the melted carrier(s) with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. The pan was then removed from the hot plate and allowed to cool at room temperature. It was then scrapped, dried and was passed through sieve no. 60 and stored in a desiccator until further evaluation.

Characterization of solid dispersions:

5.6.1 Saturation Solubility Studies⁷⁻⁸

The saturation solubility studies were carried out to determine the solubility of pure drug and solid dispersions. Weighed amount of solid dispersions were added to 250 ml conical flasks containing 25 ml of distilled water. The sealed flasks were shaken for 24 hrs at $37 \pm 0.5^\circ\text{C}$. Then aliquots were filtered through whatman filter paper. The concentration of Telmisartan was determined by UV spectrophotometer at 363 nm. Saturation solubility studies were also performed in biorelevant media i.e. Fasted state and fed state simulated intestinal fluid.

% Practical Yield^{1,9}

Percentage practical yield is calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production. Solid

dispersions were collected and weighed to determine practical yield (PY) from the following equation.

Practical Mass (Solid dispersion)

$$\text{PY}(\%) = \frac{\text{Practical Mass (Solid dispersion)}}{\text{Theoretical Mass (Drug + carrier)}} \times 100$$

Theoretical Mass (Drug + carrier)

Drug content^{1,9-10}

10 mg of solid dispersions were weighed accurately and dissolved in 10 ml of methanol. The solution was filtered, diluted suitably and drug content was analyzed at 216nm by UV spectrophotometer. Each sample analyzed in triplicate. Actual drug content was calculated for all batches using the equation as follows:

$$\text{Drug content \%} = \frac{\text{Tact}}{\text{Tss}} \times 100$$

Actual Telmisartan content in weight
quantity of solid dispersion

$$= \frac{\text{Theoretical amount of Telmisartan in solid dispersion}}{\text{Theoretical amount of Telmisartan in solid dispersion}} \times 100$$

FT-IR Studies^{4-5,11}

Structural changes and lack of a crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy. The FT-IR spectra was obtained by using an FT-IR spectrometer-430(JASCO, Japan). The samples (Pure drug, PMs and SDs) were previously ground and mixed thoroughly with potassium bromide at 1:100(sample: KBr) ratio, respectively. The scanning range was 4000-400 cm^{-1} .

XRPD Studies^{3-4,12}

The X-ray diffraction patterns were obtained at room temperature using Philips Analytical X-ray BV (PW 1710) with Cobalt as anode material and graphite monochromatic operated at a voltage of 40 Kv. The samples were analyzed in the 2θ angle range and process parameters were set as: scan size of 0.025° (2θ), scan step time of 1.25 s and time of acquisition of 1 h. Also degree of crystallinity (DC) of the product was calculated using the following equation,

$$\text{DC} = \frac{S_{\text{cr}}}{S_{\text{cr}} + S_{\text{am}}} \times 100$$

DSC Studies³⁻⁵

The DSC measurements were performed on DSC-821(Metter Toledo DSC, Switzerland). Differential Scanning Colorimetry with a thermal analyzer. All accurately weighed samples were placed in sealed pans, before heating under nitrogen flow (20ml/min) at a scanning rate of $10^\circ\text{C}/\text{min}$ from 25°C - 250°C . An empty aluminum pan was used as blank.

In vitro Dissolution studies^{1,3-4}

The release profile of an entrapped drug predicts how a delivery system might function and gives valuable insight into its in vivo behavior. In vitro release profile for each solid dispersion as well as pure drug was performed using USP XXII Type II dissolution apparatus. Sample equivalent to 10 mg of Telmisartan was added to 900ml of 0.1 N Hydrochloric acid containing 1% w/v sodium lauryl sulphate at 37± 0.5°C and stirred at 50 rpm. Aliquot of 5 ml was withdrawn at time intervals of 5, 10, 15, 20, 30, 45, 60, and 90 min. The withdrawn volume was replenished with the same volume of dissolution medium in order to keep the total volume constant. The absorbance of the samples was measured at λ_{max} 363 nm after suitable dilution if necessary, using appropriate blank. Results of in vitro drug release studies obtained from absorbance data were shown graphically as cumulative percentage drug released versus time.

Stability studies¹¹⁻¹²

The stability of solid dispersions was checked by storing the tightly sealed vials at 40°C and 75%RH. Periodically samples were removed and analyzed for their stability.

Results and Conclusion

The phase solubility studies were performed to determine stoichiometric proportions of Telmisartan and carriers- PXM 407, Gelucire 43/01, PVP K-30, PEG 6000 and HPMC E4. The effects of polymers concentration at room temperature on solubility are shown in Figure 1.

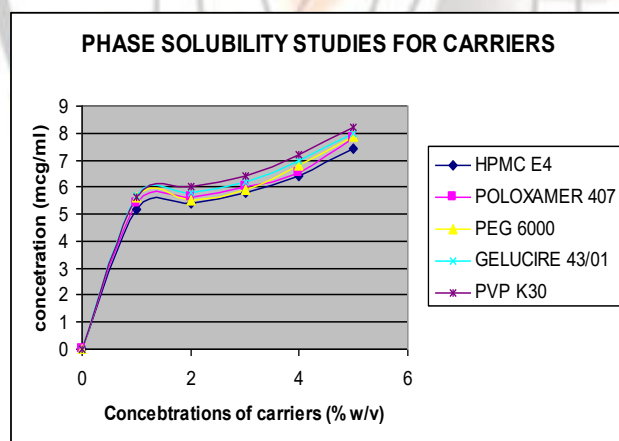


Fig. 1: Phase solubility diagram for Telmisartan and carriers

The plot of drug solubility against polymer concentrations at room temperature indicated a linear

relationship between drug and polymer solution i.e. the solubility of Telmisartan increased with increasing carrier concentration.

Solid dispersions of Telmisartan were prepared by fusion method using five different polymers: Poloxamer 407, Gelucire 43/01, HPMC E4, PVP K30 and PEG 6000. The results for saturation solubility studies are as shown in Table 1.

Table 1: Saturation solubility studies for drug and solid dispersions

Polymer	Solubility in DW	FaSSIF	FeSSIF
Telmisartan	35.35	28.65	25.84
PXM 407 SD	1212.57	987.48	769.34
Gelucire 43/01SD	1138.97	996.37	765.49
HPMC E4 SD	1273.85	1047.65	897.34
PVP K30 SD	946.79	845.12	685.15
PEG 6000 SD	1037.76	885.47	664.64

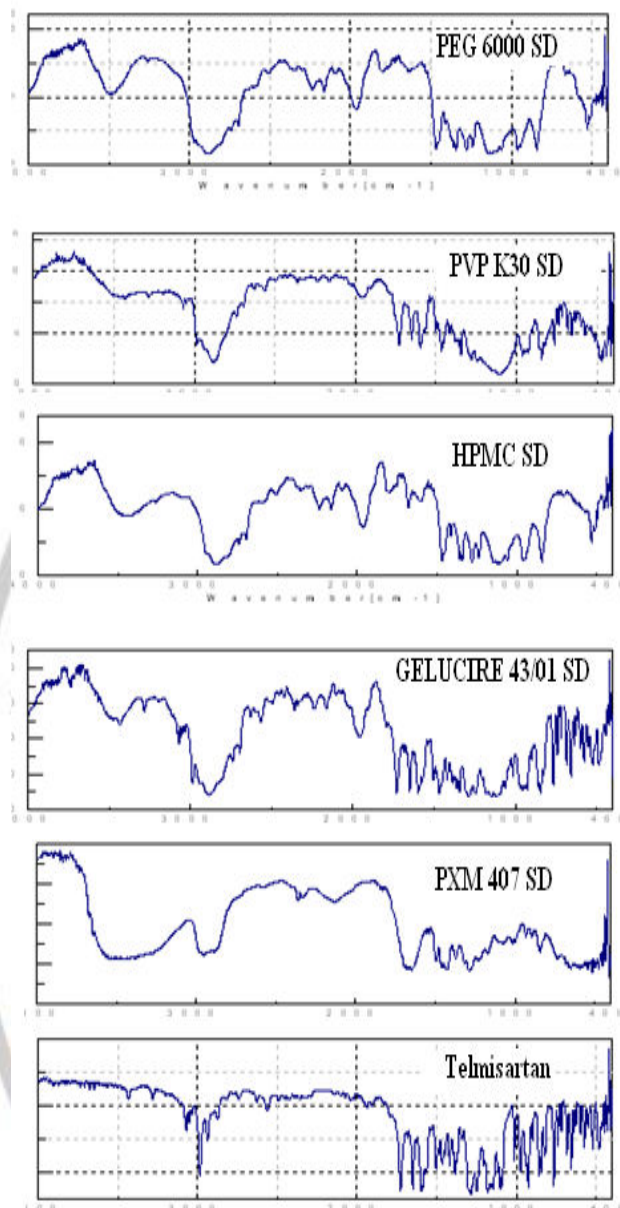
All solubility values are in µg/ml, SD: Solid Dispersion, DW: Distilled water, FaSSIF: Fasted state simulated intestinal fluid, FeSSIF: Fed state simulated intestinal fluid

It was found that solubility of Telmisartan was increased in the solid dispersions of the carriers. The solubility was found to be increased in not only water but also in fasted state and fed state simulated intestinal fluids.

The practical yield was found to be in the range of 93-97 %. As the amount of carrier increased (1:1, 1:2) the practical yield also increased, but the practical yield was found to be decreased as the drug/carrier ratio was increased to 1:4.

The content of Telmisartan in each preparation was assayed by UV spectroscopy. The assay values were between 97% and 99% of the theoretical values.

FT-IR spectroscopic studies conducted for possible drug: carrier interactions. FT-IR spectra of pure drug Telmisartan, and solid dispersions which are as shown in Figure 2 indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its solid dispersion.



SD: Solid dispersion

Fig. 2: FT-IR Spectra of Telmisartan and solid dispersions

XRPD Spectra of Telmisartan and its solid dispersions are as shown in Figure 3. It shows that degree of crystallinity of Telmisartan was found to be decreased due to complex formation between drug and carrier with the possibility of formation of amorphous solid dispersions.

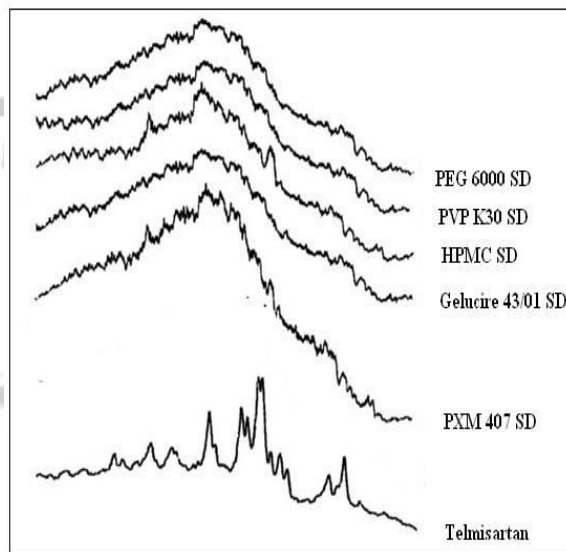


Fig. 3: XRPD Spectra of Telmisartan and solid dispersions

The DSC spectra of pure drug and solid dispersions are as shown in Figure 4a and 4b. It revealed complex formation between drug and carriers as all the peaks of drug are disappeared.

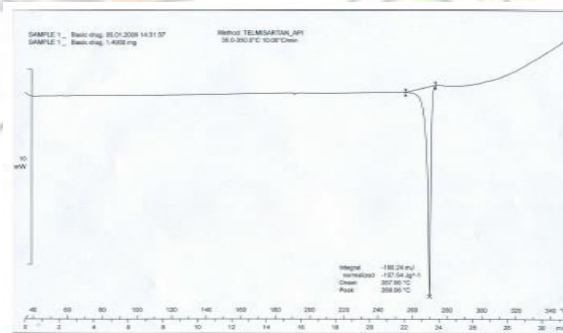


Fig. 4a: DSC spectra of Telmisartan

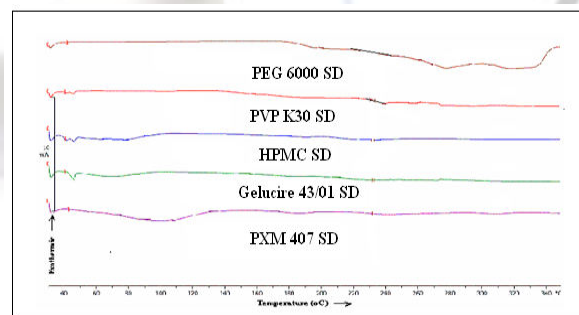


Fig. 4b: DSC Spectra of solid dispersions of Telmisartan

In vitro dissolution profile for Telmisartan and its solid dispersions are as shown in Figure 5a and 5b.

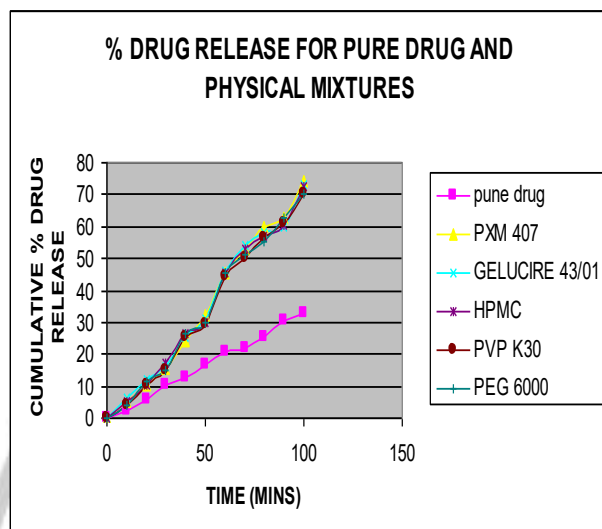


Fig. 5a: Dissolution profile for Telmisartan and its physical mixtures with carriers

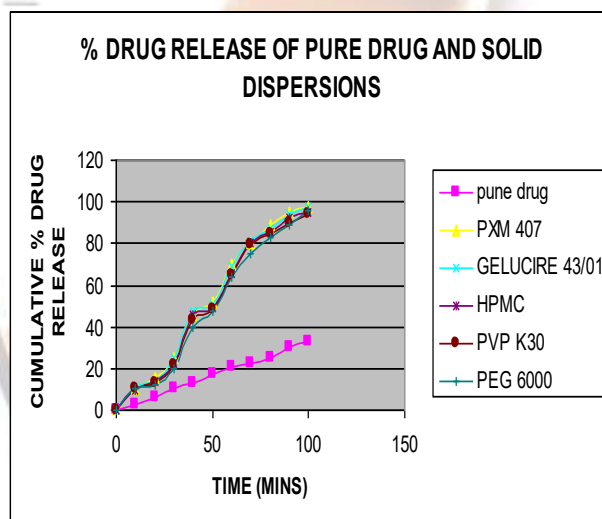


Fig. 5b: Dissolution profile for Telmisartan and its solid dispersions

The dissolution rate of Telmisartan was studied using 0.1 N Hydrochloric acid containing 1% w/v sodium lauryl sulphate as dissolution media. The dissolution rate of pure drug and its physical mixtures was found to be 32.89% for pure drug, 74.185% for PXM 407PM, 73.298% for Gelucire 43/01 PM, 72.285% for HPMC E4 PM, 70.147% for PVP K30 PM, and 70.358% for PEG 6000 PM in 100 mins whereas solid dispersions (1:4) shows 97.337% for PXM 407 SD, 97.284% for Gelucire 43/01 SD, 95.174% for HPMC E4 SD,

94.338% for PVPK30 SD and 96.175% for PEG 6000 SD drug release. The solid dispersions prepared using 1:1 and 1:2 ratio showed marked drug release between 90.435-93.467% in 100 mins.

In vitro release studies reveal that there is marked increase in the dissolution rate of Telmisartan in all the solid dispersions when compared to pure Telmisartan itself. The increase in dissolution rate is in the order of:

PXM 407 > Gelucire 43/01 > HPMC E4 > PVP K30 > PEG 6000.

The dissolution rate of Telmisartan in solid dispersion was strongly dependent on the relative concentrations of the carrier. As the concentration of the carrier in the solid dispersion increased, the dissolution rate also increased. This may be attributed to the increase in the wettability, conversion to amorphous form and solubilisation of the drug due to hydrophilic carrier and solubilizing effect of surfactants.

For stability studies, drug content and assays of solid dispersions were performed and the drug was found to be stable in the solid dispersion forms.

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