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FORMULATION AND CHARACTERIZATION OF TELMISATAN SOLID DISPERSIONS

Kothawade S. N.[1]*, Kadam N. R.[1], Aragade P. D.[1], Baheti D. G.[1]

[1]Sitabai Thite College of Pharmacy, Shirur (Ghodnadi), Pune-412 210. Maharashtra, India

Corres.author: sachin_kothawade23@rediffmail.com
Ph. No. (02138) 222680.

ABSTRACT: Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. In the present investigation, an attempt was made to improve the solubility and dissolution rate of a poorly soluble drug, Telmisartan. Solid dispersions were prepared using Polyvinyl pyrrolidone (PVP), Polyethylene glycol-1500 (PEG-1500) and Polyethylene glycol-4000(PEG-4000) to increase its aqueous solubility. Telmisartan solid dispersions were prepared in 1:1, 1:2 and 1:4 ratios of the drug to polymer ratio (by weight) using solvent evaporation method. The formulations were characterized for solubility parameters, drug content studies, drug release studies and drug-polymer interactions by using FTIR spectrum. Formulation containing 1:2 ratio of drug: PEG-4000 showed the best release with a cumulative release of 99.49% as compared to 35.82 % for the pure drug. The interaction studies showed no interaction between the drug and polymer. It was concluded that PEG-4000 as a carrier can be very well utilized to improve the solubility of poorly soluble drugs.
KEYWORDS: PEG-4000, Solid dispersion, Solubility, Telmisartan.

INTRODUCTION

The bioavailability of poorly water soluble drug is often limited by its dissolution rate, which in turn is controlled by the surface area available for dissolution. Larger the surface area, higher will be the dissolution rate. Since the surface area increases with decreasing particle size, decrease in particle size, which can be accomplished by conventional methods like trituration, grinding, ball milling, fluid energy micronization, salt formation and precipitation. Although these conventional methods have commonly been used to increase dissolution rate of the drug, there are practical limitation with these techniques, the desired bioavailability enhancement may not be achieved. Therefore formulation approaches are being explored to enhance bioavailability of poorly water soluble drugs. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists. Formulation approach that has shown to significantly enhance absorption of such a drug is to formulate/prepare solid dispersion. The solid dispersion approach has been widely and successfully applied to improve the solubility, dissolution rate and consequently the bioavailability of poorly soluble drugs.[1-4]

Telmisartan is 2-(4-{[4-methyl-6-(1-methyl-1*H*-1,3-benzodiazol-2-yl)-2-propyl-1*H*-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid. Telmisartan is antihypertensive agent. The major draw back of this drug is its low aqueous solubility that delays its absorption from the gastrointestinal tract. Prolonged use of the drug is associated with hypokalemia, hypotension, tachycardia and urinary tract infection.[5]

In the present work solid dispersions of Telmisartan was prepared by solvent evaporation method using various water soluble polymers such as PVP and PEG-4000. The prepared solid dispersions were evaluated for % practical yield, drug content, in-vitro dissolution

rate studies and interactions between drug and polymer using FT-IR spectral studies.

EXPERIMENTAL
Materials
Telmisartan was obtained as a gift sample Cipla, Gao. Polyvinyl pyrrolidone (PVP), Polyethylene glycol 4000 (PEG4000) Sodium Lauryl Sulphate (SLS) and HCL were purchased from SD-Fine Chem. Industries Mumbai. Double distilled water was used for all the experiments.

Estimation of Telmisartan
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 concentration range of 2-10μg/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 study was observed.

Preparation of telmisartan solid dispersions by solvent evaporation method
Telmisartan solid dispersions were prepared by solvent evaporation method using carriers (PVP & PEG-4000) in proportions viz 1:1, 1:2 and 1:4 (drug : carrier). The drug (100mg) and carrier (100, 200 and 400mg) were dissolved in methanol in a china dish and the mixture was heated until the solvent evaporated and a clear film of drug and carrier was obtained. The resultant solid dispersion was scraped out with a spatula. Dispersions were pulverized in a mortar and pestle and passed through a 250μm sieve before packing in an airtight container.

% Practical Yield
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.

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

Drug content
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:

$$\text{Drug content \%} = \frac{T_{act}}{T_{ss}} \times 100$$

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

Infrared spectroscopy
FT-IR spectra of pure Telmisartan, PVP, PEG-4000 and Telmisartan with its solid dispersion were obtained by a Perkin-Elmer Fourier transform infrared spectrophotometer using KBr pellets were prepared by gently mixing the sample with KBr (1:100). The scanning range used was 2000 to 400 cm^{-1}.

1n vitro drug release studies
The release profile of an entrapped drug predicts how a delivery system might function and gives valuable insight into its in vivo behaviour. In vitro release profile for each solid dispersion as well as pure drug was performed using USP XXII type2 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.

RESULTS AND DISSCUSSION
Solid dispersions of telmisartan were prepared by solvent evaporation method using carriers like PVP and PEG-4000. In the present work total nine formulations were prepared and their complete composition is shown in Table 1. The results of % practical yield studies are shown in Figure 1. Percent practical yield increased as the amount of carrier/polymer added to each formulation increased (1:1 and 1:2 ratio of drug: carrier). But as the amount of carrier is increased (1:4 ratio of drug: carrier) the percentage practical yield was decreased. Maximum yield was found to be 99.49% in N-4.

The content of Telmisartan in each preparation was assayed by UV spectroscopy. The assay values were between 96% and 99% of the theoretical values. FT-IR spectroscopic studies conducted for possible drug: carrier interactions. FT-IR spectra of pure drug Telmisartan, PVP, PEG-4000 and Telmisartan with its

solid dispersions were obtained (Figure 5, 6 and 7). Indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its solid dispersion.

The release data obtained for formulations N-1 to N-6 are tabulated in Table 2. Figure 2, 3 and 4 shows the plot of cumulative percent drug released as a function of time for different formulations. Cumulative percent drug released after 90 min was 66.71%, 97.66%, 48.29%, 90.25%, 99.49% and 49.21% for N-1 to N-6 respectively and was 35.82% in 90 min for pure drug Telmisartan.

In vitro release studies reveal that there is marked increase in the dissolution rate of Telmisartan from all the solid dispersions when compared to pure Telmisartan itself. The increase in dissolution rate is in the order of PEG-4000 > PVP. The dissolution rate of Telmisartan in solid dispersion was strongly dependent on the relative concentration of the carrier. As the concentration of the carrier in the solid dispersion increased, the dissolution rate also increased.

From the in vitro drug release profile, it can be seen that formulation N-2 and N-4 containing PEG-4000 (1:1 and 1:2 ratio of drug: PEG-4000) shows higher dissolution rates than PVP. This may be attributed to the increase in the wettability, conversion to amorphous form and solubilisation of the drug due to hydrophilic carrier. But as the amount of PEG-4000 is increased (1:4 ratio of drug: PEG-4000) in formulation, the dissolution rate was decreased. This decrease in dissolution rate may be due to increased viscosity of coating materials.

In the case of solid dispersions of Telmisartan with PVP ratio of 1:1 and 1:2, the dissolution rate was increased while in the case of those prepared in ratio of 1:4, the dissolution rate was decreased. This might be due to formation of viscous layer around the drug particles leading to decrease in the dissolution rate. From the dissolution data, it is clear that the dissolution rate increased with decreasing molecular weight of the carrier. The increase in the dissolution rate may be due to improved wettability by PEG 4000.

CONCLUSION
1) The solid dispersion of Telmisartan was successfully formulated by solvent evaporation method using hydrophilic carriers like PVP and PEG-4000.
2) Percent practical yield increased as the amount of carrier or polymer added to each formulation increased (1:1 and 1:2 ratio of drug: carrier). But as the amount of carrier is increased (1:4 ratio of drug: carrier) the percentage practical yield was decreased.
3) In vitro release studies reveal that there is marked increased in the dissolution rate of Telmisartan from all the solid dispersion when compared to pure Telmisartan itself. The increase in dissolution rate is in the order of PEG-4000>PVP.
4) Formulations containing PEG-4000 (1:1 and 1:2 ratio of Drug: PEG-4000) shows higher dissolution rate than PVP. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilisation of drug due to hydrophilic carrier. But as the amount of PEG-4000 is increased (1:4 ratio of Drug: PEG-4000) in formulation, the dissolution rate was decreased. This degrease in dissolution rate may be due to increased viscosity of coating material.

Table 1. Formulation plan of Telmisartan solid dispersions

Sr. No.	Batch code	Composition	Ratio (Drug:Carrier)
1	N1	Telmisartan + PVP	1:1
2	N2	Telmisartan +PEG 4000	1:1
3	N3	Telmisartan + PVP	1:2
4	N4	Telmisartan +PEG 4000	1:2
5	N5	Telmisartan + PVP	1:4
6	N6	Telmisartan +PEG 4000	1:4

Table 2: In Vitro Release of Pure Drug and Different formulations of Telmisartan solid dispersions

Time (min)	Cumulative percentage drug released						
	Pure drug	N-1	N-2	N-3	N-4	N-5	N-6
5min	2.55	32.21	22.83	52.63	35.79	20.48	23.66
10 min	9.25	43.23	27.54	62.84	37.30	23.93	25.66
15 min	1.12	43.34	37.70	67.02	44.32	25.66	27.70
20 min	13.77	46.63	54.48	74.61	47.72	29.76	29.68
30 min	17.73	52.91	58.87	78.48	57.13	37.26	36.96
45 min	24.40	59.23	64.75	90.25	70.24	44.32	41.00
60 min	29.68	62.80	70.24	92.94	82.41	45.15	44.30
90 min	35.82	66.71	90.25	97.66	99.49	48.29	49.21

Figure 1: % Practical Yield of Different Formulations of Telmisartan solid Dispersions
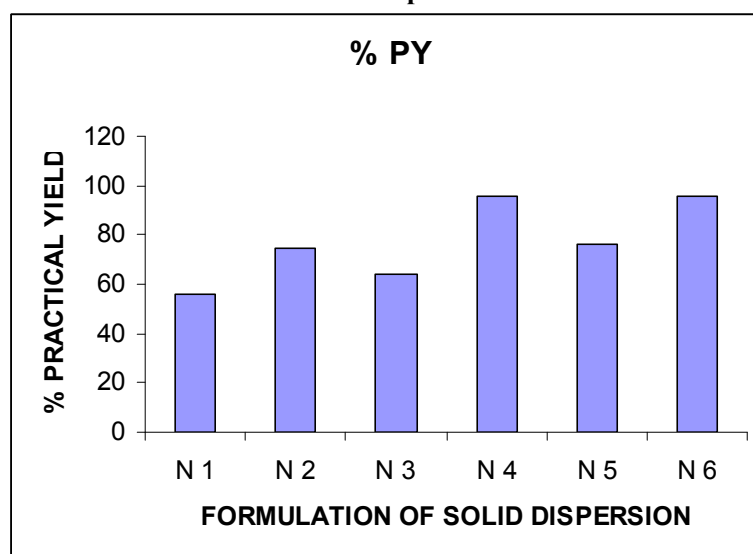
Figure 2: In vitro dissolution profile of solid dispersion of Telmisartan in 0.1N HCL (N-1 to N-2) (1:1)
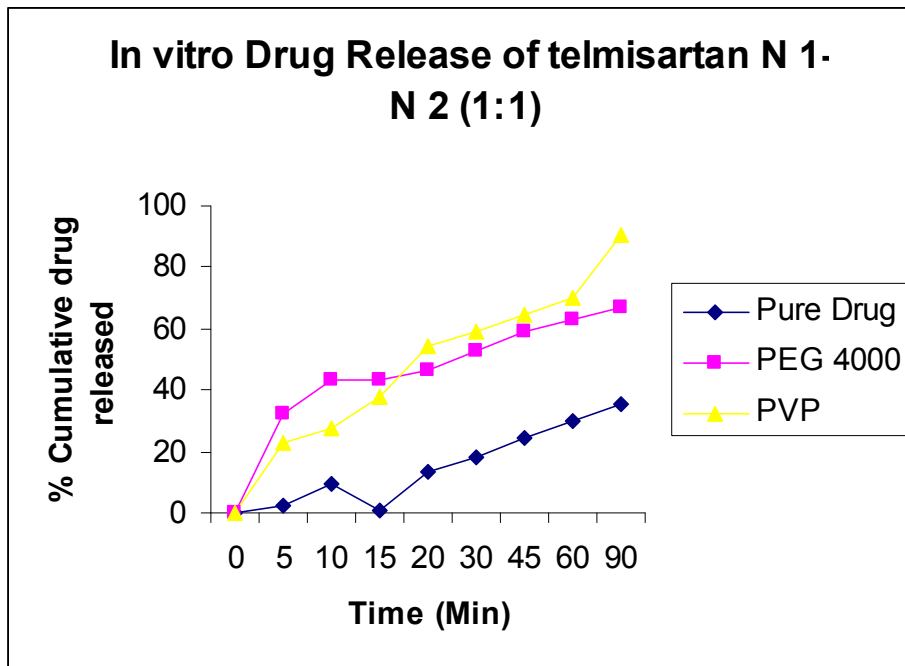

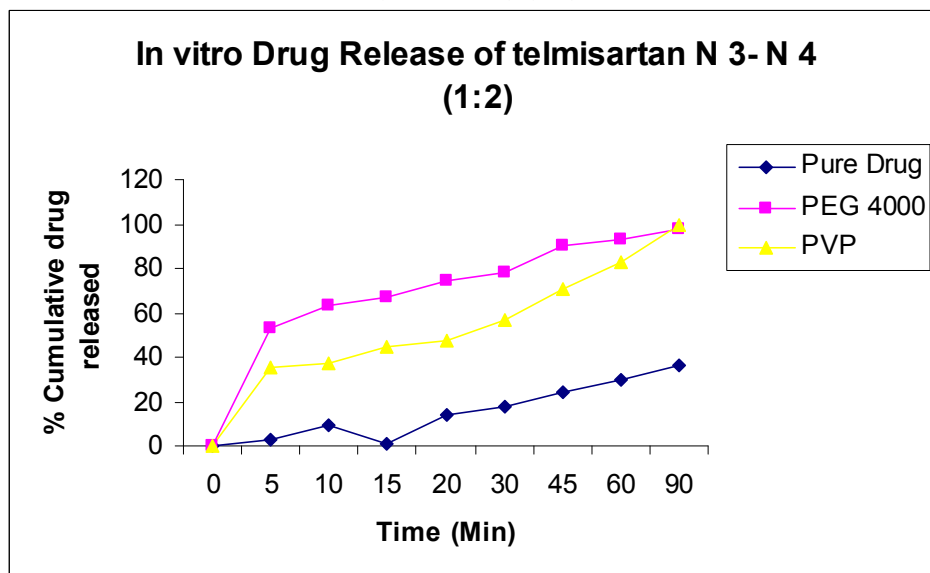**Figure 3: In vitro dissolution profile of solid dispersion of telmisartan in 0.1N HCL (N-3 to N-4) (1:2)**

Figure 4: In vitro dissolution profile of solid dispersion of telmisartan in 0.1N HCL (N-5 to N-6) (1:4)
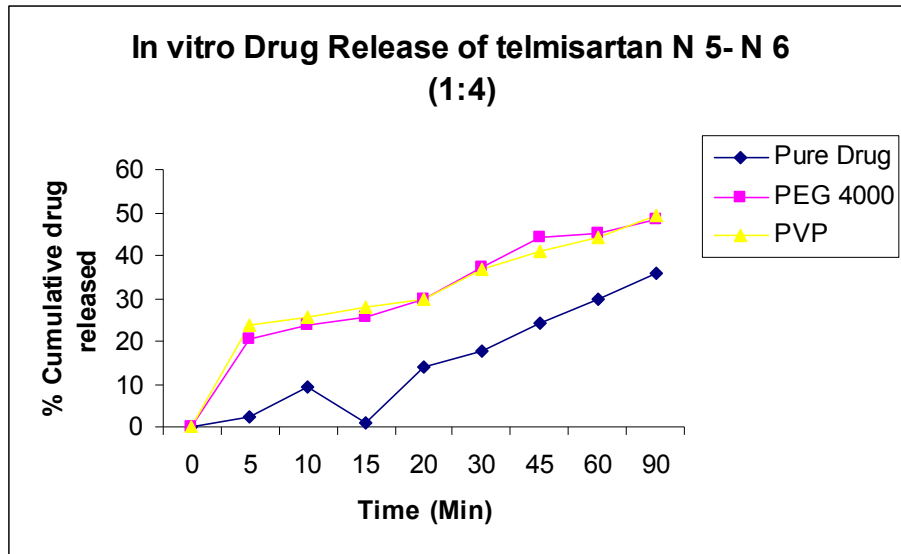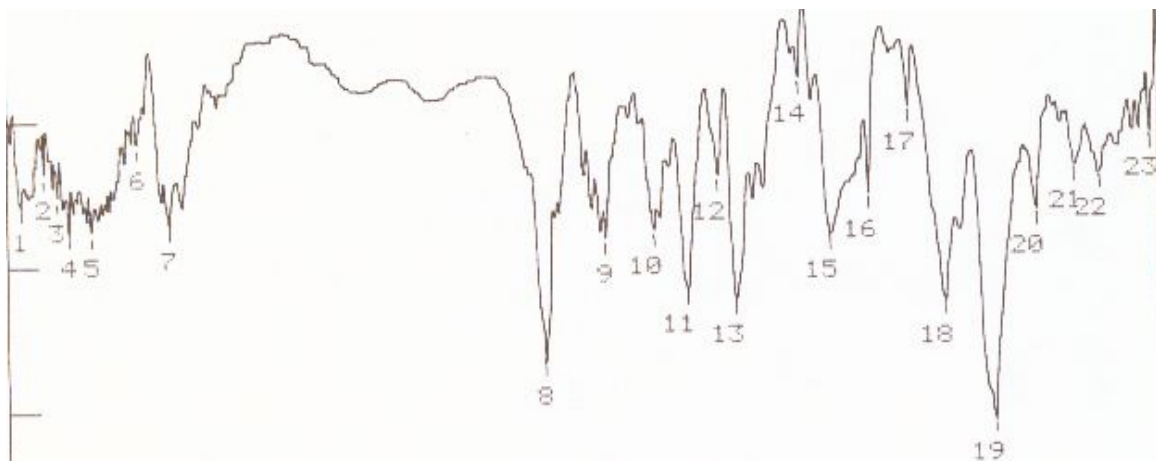

Figure 5: IR Spectrum of Telmisartan

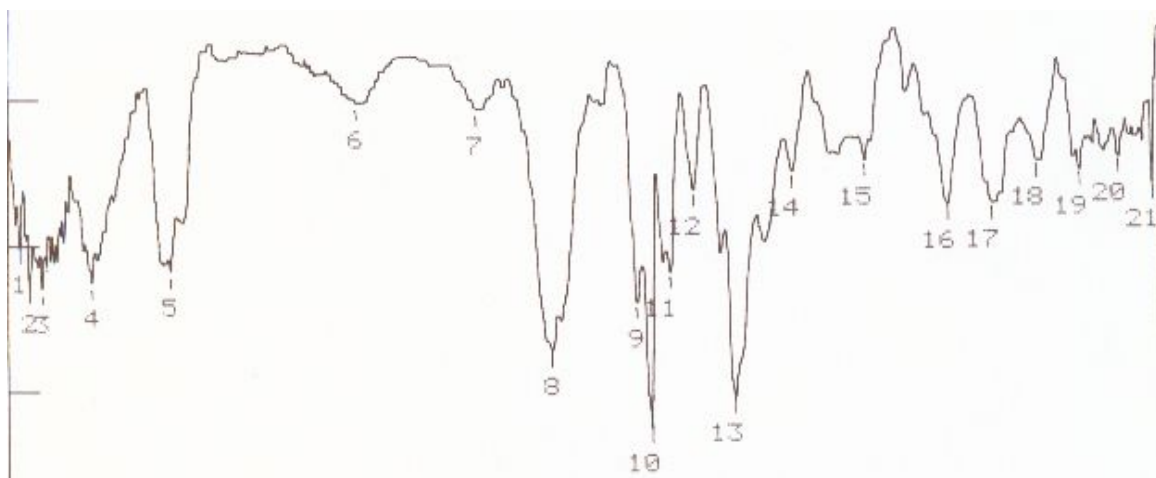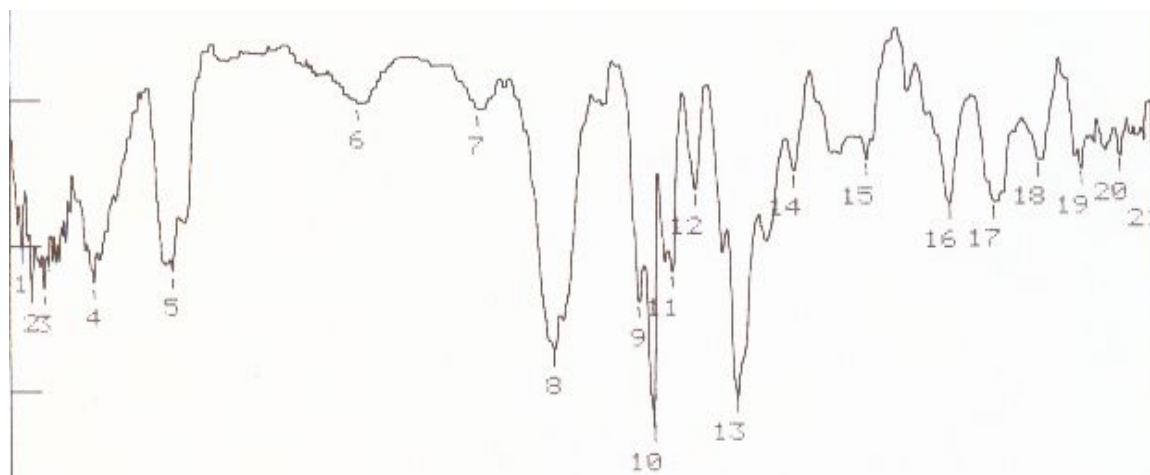**Figure 6: IR Spectrum of Telmisartan with polymer PVP**

Figure 7: IR Spectrum of Telmisartan with PEG-4000

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