Research Article

Improvement of Bioavailability and Solubility of Telmisartan by Solid Dispersion Technique using Various Carriers

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ABSTRACT

The objective of this study was to prepare and evaluate solid dispersion of Telmisartan to increase solubility and for enhancement of bioavailability. The solid dispersions were prepared by physical mixture method using PEG 6000, Eudragit L 100 and PVP K 30 as a carrier in various ratios. Optimized solid dispersion was evaluated for % CDR and Time for CDR, FTIR, DSC, SEM, and in vitro drug release study. The results showed that among the various batches containing the polymer being used in the study, F2 formulation containing DRUG: EUD L 100 in the ratio 1:1exhibited significant enhancement in solubility and dissolution profile of the drug. The results were supported by the DSC, FTIR, SEM and stability studies.

Keywords: Solid dispersion, Solubility, Telmisartan, Physical Mixture method.

INTRODUCTION

Telmisartan is 2-(4-{[4-methyl-6-(1-methyl-1H-1, 3-benzodiazol-2-yl)-2-propyl-1H-1, 3-benzodiazol-1-yl] methyl} phenyl) benzoic acid (figure 1). It is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. Generally, angiotensin II receptor blockers (ARBs) such as telmisartan bind to the angiotensin II type one (AT1) receptors with high affinity, causing inhibition of the action of angiotensin II on vascular smooth muscle, ultimately leading to a reduction in arterial blood pressure. Recent studies suggest that telmisartan may also have PPAR-gamma agonistic properties that could potentially confer beneficial metabolic effects.[1, 2, 3]
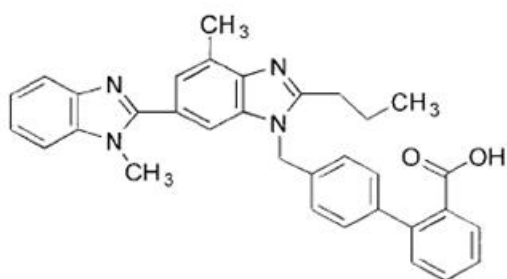

Figure 1: Chemical Structure of Telmisartan

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.

In the present work, Solid Dispersions were successfully prepared by physical mixture method. The optimized Solid dispersions were evaluated for various parameters like mean Dug Content CDR, % CDR, Time and in vitro drug release study.

MATERIALS AND METHODS

Materials

Telmisartan was obtained as a gift sample from Cipla PVT. LTD. Mumbai, (India). All other chemicals and reagents were of analytical grade.

Preparation of Solid Dispersions

Physical Mixture Method

Among the various techniques available Solid Dispersions were prepared by using Physical Mixture technique. The physical mixtures were prepared by weighing the calculated amount of Telmisartan and then the carriers and then mixing them in a glass mortar by triturating. The resultant mixture was passed through 44 – mesh sieve and stored in desiccator until used for further studies.[4]

Experimental design

Initially nine batches of solid dispersion were prepared using individual carriers with Drug: Carrier ratio 1:1, 1:2, 1:3 separately (table 1).

In vitro drug release (Kinetics and Data Analysis):

The in-vitro drug releases of all the solid dispersion formulations were investigated by dissolution study. An accurately weighed amount of solid dispersion equivalent to 40 mg of TEL was added to 900 ml of dissolution medium; 0.1 N HCl and drug release was investigated using the USP rotating paddle dissolution apparatus (Lab India 2000) at 75 rpm and 37.5°C. A percent release study was continued from 10 mins. to 90 mins. The final volume in all cases was 900 ml. The samples were withdrawn from the dissolution medium at various time intervals. 10 ml of sample was diluted to 100 ml with dissolution medium and subjected to UV Spectrophotometric analysis at 296 nm (λmax of TEL). All the samples were analyzed in triplicate.[5]

Table 1: Coded factors with their levels (F1 to F9 Formulations)

Drug :Polymer /Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
TEL:PEG	1:1			1:2			1:3		
TEL:EUD		1:1			1:2			1:3	
TEL:PVP			1:1			1:2			1:3

Fourier transform infrared spectrometry (FTIR)

Fourier transform infrared spectrometry (FTIR) spectra were recorded with a JASCO FTIR-410, JAPAN Spectrophotomer to evaluate the molecular states of pure drug, excipients and all solid dispersion formulations. The spectra were scanned over wavelength region of 400 to 4000 cm^{-1}, resolution of 4 cm^{-1} and accumulation of 20 scans were used in order to obtain good quality spectra by making a pellet of the sample with KBr. The procedure consisted of grinding the sample with KBr in an agate mortar and pestle and compressing the sample in an evacuable KBr die by applying a pressure of 5 tons for 5 min in a hydraulic press, Techno search instrument M-15 KBr press (KBr pellet method). The pellet was placed in the light path and the spectrum was obtained. [6]

Scanning electron microscopy (SEM)

The Surface appearance and shape of the solid dispersions were investigated by scanning electron microscopy. Drug, excipients and all spray dried formulations were mounted onto separate, adhesive coated aluminium pin stubs. Excess powder was removed by tapping the stubs sharply and then gently blowing a jet of particle-free compressed gas across each. The specimen stubs were sputter coated with a thin layer of gold in a JEC-550 Twin coating unit at 10 mA for 4 min using an argon gas purge. The specimens were examined using a scanning electron microscope (SEM, JEOL-JSM-5400). The SEM was operated at high vacuum with an accelerating voltage of 5-10 kV. Secondary electron images were recorded digitally at higher magnification. Particles surface was determined by examining the microphotographs.[5]

Differential scanning calorimetry (DSC)

The phase transition of the pure drug, excipients, solid dispersion formulation batches were studied by thermogram obtained by using Differential scanning calorimeter (Dupont 2000, model SDT- 2960, USA). An empty aluminium pan was used as reference. DSC measurements were performed at the heating rate of 10°C/min from 25 to 350°C using aluminium sealed pan. Sample weight was kept between 5- 10 mg. During the measurement, the sample cell was purged with nitrogen gas. [7]

X-Ray powder diffraction study (XRD)

The crystalline nature of pure drug and all solid dispersion formulation batches were examined by studying its X-Ray diffraction patterns by using powder X-Ray diffractometer (PW- 3710 BASED). It was determined whether the obtained formulation after precipitation is a co-precipitate of individual substances or whether it becomes co-crystal. The operating parameters for instrument were Cu filtered K (α) radiations, a voltage of 40 kV, current of 25 mA and receiving slit of 0.2 In. The instrument was operated over 2θ scale. The angular range was 5 to 50° (2θ) and counts were accumulated for 0.8 second at each step. [8]

Stability Study

Short term stability studies

Stability Study: Stability study for selected preparations was carried out by storing 1 gm of solid dispersions in an amber coloured screw cap bottles at different temperatures and relative humidity for a period of 3 months. The dispersions were visually examined for any physical change and drug content was estimated at the end of three months.[9]

Representative formulations were tested for stability with respect to physical appearance, assay and dissolution, at accelerated (40°C/75% RH) and controlled room temperature (25°C/60% RH) conditions for three months in amber coloured glass containers with 1 gm silica gel desiccant.

RESULTS AND DISCUSSION

Compatibility Studies

After 30 days, samples of drug with excipients stored at room temperature were observed for physical change, No physical change were observed in the sample.

Experimental design

Formulation and Optimization

Results of the % CDR for nine batches of solid dispersion prepared using individual carriers with Drug: Carrier ratio 1:1, 1:2, 1:3 separately are shown in Table No.2

Search for optimum formulations

Among the various formulations optimum formulations were selected on the basis of Desirability factor. Formulations having highest desirability factor were selected among the obtained solutions. Criteria for the selection were primarily based upon the highest possible values of %CDR (> 90.00%) and lowest possible values of Time (< 90 min).

Evaluation of Solid Dispersions

FTIR spectrometry

Fourier transform infrared spectrometry (FTIR) spectra were recorded with a JASCO FTIR-410, Japan Spectrophotomer to evaluate the molecular states of pure drugs: TEL; excipients: PEG 6000, EUD RL PO, PVP K 30, and Solid Dispersion Formulation and are shown in figure 2. Close agreement between the spectra of solid dispersion formulation with FTIR of pure TEL suggested that there were no changes in the structure of TEL prepared by Physical mixture method.

Table 2: Release profile of F1 to F9 formulations

Time in min	% Cumulative drug release (%CDR)								
	F1±S.D.	F2±S.D.	F3±S.D.	F4±S.D.	F5±S.D.	F6±S.D.	F7±S.D.	F8±S.D.	F9±S.D.
0	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00	0±0.00
15	76.75 ±0.11	50.85 ±0.88	9.42 ±0.19	69.68 ±0.56	47.55 ±0.51	7.53 ±0.23	64.98 ±0.68	42.85 ±0.12	6.12 ±0.52
30	83.81 ±0.62	84.75 ±0.65	72.98 ±0.92	74.39 ±0.59	79.57 ±0.92	67.33 ±0.63	69.68 ±0.39	75.8 ±0.57	61.21 ±0.11
45	85.69 ±0.71	88.52 ±0.80	73.92 ±0.39	78.63 ±0.13	80.04 ±0.63	70.15 ±0.42	72.98 ±0.56	77.69 ±0.55	65.92 ±0.64
60	86.16 ±0.33	89.93 ±0.73	81.45 ±0.37	80.51 ±0.81	83.34 ±0.65	79.57 ±0.23	79.57 ±0.72	80.04 ±0.83	71.57 ±0.49
75	89.93 ±0.44	93.23 ±0.67	81.45 ±0.29	85.69 ±0.91	89.46 ±0.57	80.04 ±0.44	81.45 ±0.35	85.22 ±0.51	78.63 ±0.49
90	89.93 ±0.17	99.82 ±0.59	83.81 ±0.18	85.69 ±0.96	91.34 ±0.35	80.98 ±0.47	81.45 ±0.67	88.99 ±0.22	79.1 ±0.72

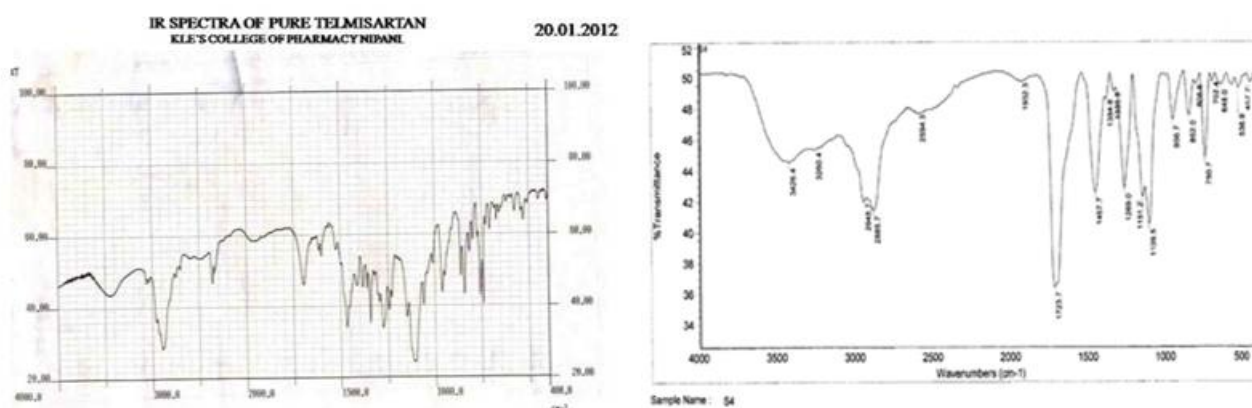S.D= Standard Deviation, CDR= Cumulative Drug Release

Figure 2: FTIR spectra of procured TEL and Solid Dispersion formulation of TEL.

The above mentioned characteristic peaks of pure TEL appear in the spectra of solid dispersion formulation at the same wave no. indicating no interaction between drug and carrier.

Particle Surface Morphology by Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM): Scanning electron microscopy is very helpful in studying the change in the surface topography and shape of the particles of pure

drug and solid dispersions. The batches of engineered crystals covering extreme polymer concentrations from the entire range of experimental batches were taken for SEM studies. Photomicrographs of the pure drug and solid dispersion are shown in Figure No. 3 Photomicrographs of the pure drug and the formulated batches revealed the change in particle shape and surface topography. SEM thus indicates that the polymer has formed a uniform coating over the individual drug particles thus resulting in the formation of spherical particles with improved crystal properties as revealed from later studies.[10]
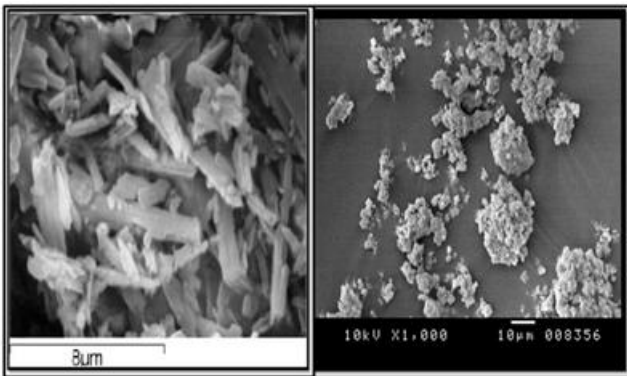

Figure 3: SEM image of pure TEL and Solid Dispersion of TEL

The scanning electron micrograph of pure TEL showed the powder to be of a crystalline flat material, needle like in structure. Many irregular particles with much fragmentation were observed.

The scanning electron micrograph TEL solid dispersion showed the powder to be typical aggregate of amorphous material. Many irregular particles with cluster were observed.

This observation was further confirmed by differential scanning calorimetry and X-ray diffraction study.

Differential Scanning Calorimetry (DSC)

In Differential Scanning Calorimetry (DSC), Comparison of DSC thermograms of drug alone as well as in the presence of polymer give an idea about the glass transition temperature (Tg) of dug in solid dispersions. DSC thermograms of TEL, as well as their solid dispersions prepared by physical mixture method are shown in figure No.4. Pure TEL exhibited a characteristic, sharp endothermic peak at 269.060C which is associated with the melting point of the drug. And indicates the crystalline nature of the drug. However, the characteristic, endothermic peak corresponding to drug melting was broadened and shifted towards a lower temperature with reduced intensity in solid dispersions. This could be attributed to higher polymer concentration and uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in polymer.
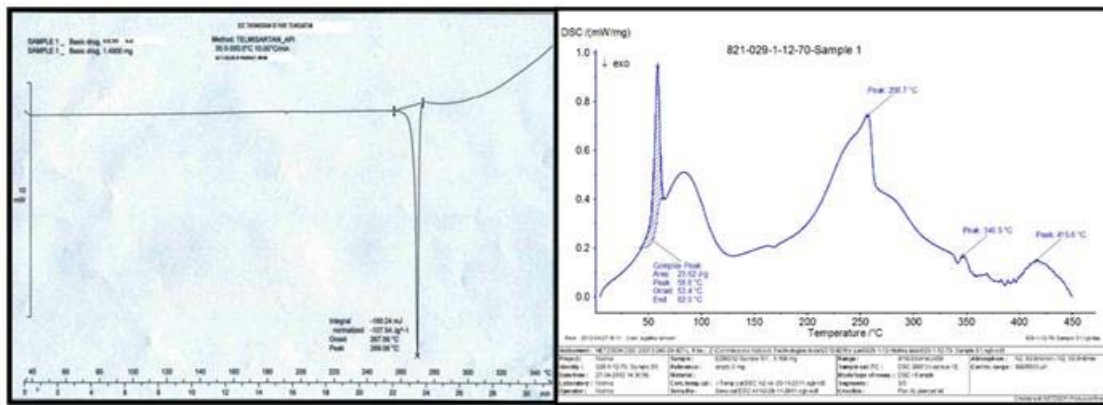

Figure 4: DSC spectrum of pure TEL and Telmisatran Solid Dispersion.
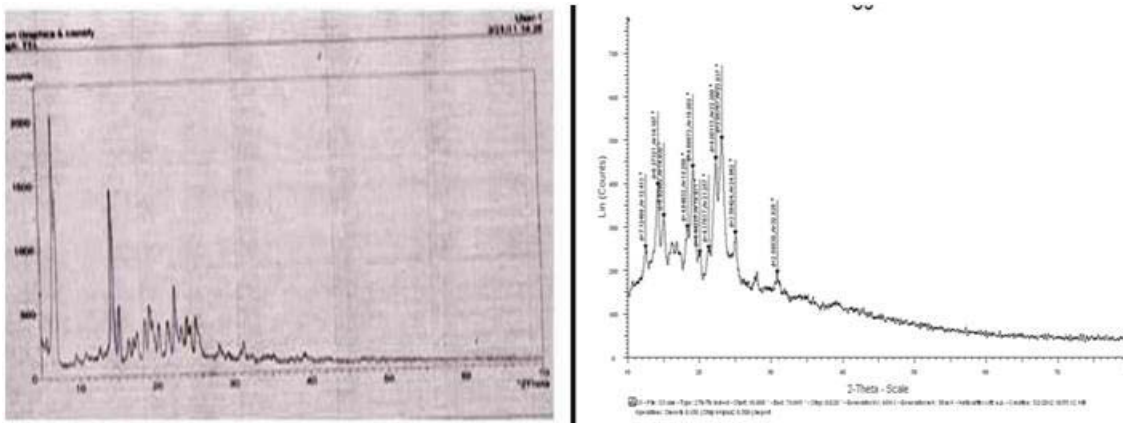

Figure 5: XRD image of Pure TEL and solid dispersion

Table 3: Stability study of optimized formulation

Formulation code	Physical appearance			% Drug Content			% CD (30 mins)		
	Initial	25°C/60% RH, 3M	40°C/75% RH, 3M	Initial	25°C/60% RH, 3M	40°C/75% RH, 3M	Initial	25°C/60% RH, 3M	40°C/75% RH, 3M
R5	Colourless White powder	Colourless White powder	Colourless White powder	86.86	86.63	86.37	99.41	99.32	98.55

X-Ray Diffraction Study (XRD)

The crystalline nature of pure drug and solid dispersion formulation were examined by studying its X-Ray diffraction patterns.

The diffraction pattern of pure TEL was highly crystalline in nature as indicated by numerous peaks. Three peaks at 7.0°, 14.0°, 20.0°, 23.0° and 25.0° were noticeable and the main peak at 7.0° was particularly distinctive. It is known that the lack of a distinctive peak of a drug in SD systems demonstrates that a high concentration of the drug is dissolved in the solid state. Moreover, a large reduction in characteristic peaks indicates an amorphous state.

X ray powder diffraction patterns of pure TEL and solid dispersion are showed in figure No. 5. X-Ray diffractrogram of powder TEL showed sharp diffraction peaks indicating the presence of crystalline form. Reduction of intensity of crystalline peaks was observed in the formulation. These results indicate that TEL is no longer present in crystalline form, and its exits in the amorphous state.

Stability Study

Representative formulations were tested for stability with respect to physical appearance, assay and dissolution, at accelerated (400 C/ 75% RH) and controlled room temperature (25°C/ 60% RH) conditions for three months in amber coloured glass containers with 1 gm silica gel desiccant. The results are appended in Table No. 3. The results indicated the formulations were stable under the tested conditions of storage.

The results from drug content study provide an important information regarding stability of solid dispersion formulation containing TEL. The result of accelerated stability studies as shown in Table No. 3 indicated that the selected formulations did not show any physical changes during the study period and the drug content was found to have close agreement with the drug content of formulation before stability study. This indicates that all formulations were quite stable at accelerated storage conditions.

CONCLUSION

From the results it can be concluded that PEG 6000, PVP K30, Eudragit L 100 can be used to formulate an efficient solid dispersion of Telmisartan with highest % CDR with minimum Time required for cumulative drug release. Thus, the current study is useful for the successful design, development and optimization of solid dispersions for Telmisartan.

A significant enhancement in the aqueous solubility and dissolution profile of the drug is seen. Among the various batches containing the polymer being used in the study namely, Eudragit L 100: PEG 6000: PVP K30 in the ratio 1:1 (Drug: EUD L 100) exhibited significant enhancement in solubility and dissolution profile of the drug. SEM studies revealed the spherical nature of the solid dispersion. Spherical nature indicates improvement in micromeritic properties thus anticipating improved tabletting properties. DSC studies revealed that the lack of melting point of solid dispersion indicated that the drug was present in an amorphous form. Stability studies reveal that the product does not undergo degradation on storage and hence expected to maintain its integrity during storage with reasonable shelf life. Despite the wide application of SDs, an obstacle of the SD method is its limited solubilization capacity.

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