

Solid State Characterization of the Polymorphic Changes in Candesartan Cilexetil Solid Dispersion with Poly Ethylene Glycol 8000

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Abstract:

Aim: The main aim behind this work is to study the effect of thermal methods used for the formulation upon the candesartan cilexetil properties and to evaluate the changes due to temperature

Method: Melt method was followed to study the polymorphic changes in the candesartan cilexetil solid dispersions. In this method different ratios of drug to carrier were selected for the formulation. Initially the carrier was melted in china dish at 80°C, when the complete carrier was converted to liquid form the weighed amount of drug was added to the liquefied carrier and stirred vigorously to get homogenous mixture and to get uniform coating of the carrier around the drug, then the homogenous mixture was cooled at room temperature to solidify the formulation. The final formulation was then evaluated by DSC, X-RD, FTIR, and HPLC to determine the polymorphic changes in the candesartan cilexetil. It was also evaluated to see whether there is any change in the release of the candesartan cilexetil.

Results: Evaluating the final formulation of the candesartan cilexetil solid dispersion by DSC, the endothermic peak of the formulation has shifted towards the lower temperature. When the formulation was characterized with X-RD the relative degree of crystallinity was found to 0.645, the crystallinity was not reduced in a drastic manner but it has given less intense peaks than the plain candesartan cilexetil. The evaluation by FTIR showed that shift in the peaks due change in polymorphism. HPLC evaluation has given the clear idea that the polymorphic changes have taken place in the formulation of candesartan cilexetil. *in vitro* release studies showed that the solid dispersion formulation have released the drug within 10minutes.

Conclusion: The solid state and, chromatographic characterization of the candesartan cilexetil solid dispersion formulation using melt method have confirmed that whenever the formulations are prepared with elevated temperature may leads to the polymorphic changes in the candesartan cilexetil

Key words: candesartan cilexetil, polymorphism, solid dispersion, thermal methods.

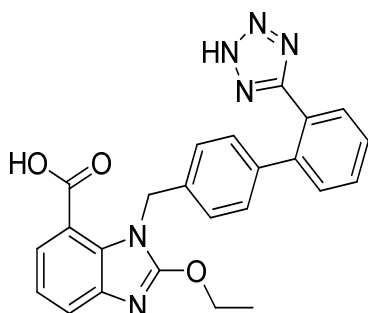
INTRODUCTION:

Many active pharmaceutical ingredients can exist in different physical and morphological forms. Polymorphism is often characterized as the ability of active pharmaceutical ingredient to exist in two or more crystalline phases that have different arrangements or conformations of the molecules in the crystal lattice¹. Polymorphism refers to the occurrence of different crystalline forms of the same drug substance. Polymorphism in this commentary is as defined as in the International Conference on Harmonization (ICH) Guideline Q6A². Polymorphs and/or solvates of a pharmaceutical solid can have different chemical and physical properties such as melting point, chemical reactivity, apparent solubility, dissolution rate, optical and electrical properties, vapor pressure, and density. These properties have a direct impact on the process-ability of drug substances and the quality/performance of drug products, such as stability, dissolution, and bioavailability.

Various conditions in the crystallization processes are the main criteria for the development of different polymorphic forms. These conditions include: Solvent effects (the packing of crystal may be different in polar and nonpolar solvents), Certain impurities inhibiting growth pattern and favor the growth of metastable polymorphs, The level of super saturation from which material is crystallized (in which

generally the higher the concentration above the solubility, the more likelihood of metastable formation), Temperature at which crystallization is carried out, geometry of covalent bonds (differences leading to conformational polymorphism). Change in stirring conditions. Despite the potential implications, polymorphism is not always well understood. In 2006 a new crystal form was discovered of maleic acid 124 years after the first crystal form was studied³.

There are several forms in which a drug can exist as a polymorph they are cubic, monoclinic, hexagonal, rhombohedral, face-centered cubic etc. Polymorphism apart from effecting the physical properties of the drug they can also effect the pharmacokinetic properties such as solubility, dissolution rate, and bio availability, manufacturing properties and stability of the active pharmaceutical ingredient. The polymorphism influences the manufacturing of the pharmaceutical formulation by altering the properties such as mechanical properties, flow properties, compressibility, hygroscopicity, shape and the density of the active pharmaceutical ingredient there by showing alteration in the final formulation of the API. In stability concern the polymorphism also influences the stability of the API. During manufacturing the most stable form will be chosen to ensure its stability^{4,5}.



candesartan belongs to the class II drug of BCS classification. The main intention behind this work is existence of polymorphs of the candesartan.

The main clinical uses of candesartan cilexetil are Angiotensin II receptor antagonist candesartan is indicated for the treatment of hypertension. The CHARM has demonstrated that reduction in the mortality and the morbidity rate was decreased due to the candesartan therapy. Thus the ACE inhibitors are considered as the first line of drugs in the treatment of congestive heart failure. The four year study was performed to know whether candesartan can prevent or can postpone the development of the full-blown hypertension which also called as the prehypertension. In this study first two years half of the population of the trial were given candesartan and the remaining received the placebo, candesartan has helped to reduce the risk by two third in the population. At the end of the study candesartan reduced the risk of hypertension by 15%. More over the side effects were negligible over the placebo, which has shown serious effects. The marketed products like Atacand HCT, Hytacand, Blopress Plus, Advantec and Ratacand Plus are being marketed in combination with thiazide diuretics such as hydrochlorothiazide to have additive antihypertensive activity^{6,7}.

Solubility is the main hurdle for the lower bio availability of the drugs. In the Biopharmaceutical Classification System (BCS) class II drugs are those with low aqueous solubility and high

Membrane permeability and therefore solid dispersion technologies are particularly promising for improving the oral absorption and bioavailability of BCS Class II drugs. It is obvious that for class II drugs the low ability to dissolve is a more important limitation to their overall rate and extent of absorption than their ability to permeate through the membrane. Therefore, the formulation work for class II compounds should focus on the enhancement of aqueous solubility or dissolution rate⁸. Solid dispersion is one of the methods for enhancing the solubility of the drugs. These solid dispersions are also called as the solid solutions in which the carrier is being used to improve the solubility of the active pharmaceutical ingredient which has low solubility. Following are the methods that are employed in the formulation of the solid dispersions. Solvent Evaporation Method, Modified Solvent Evaporation Method, Melting Method, Melt-Solvent Method, Kneading Method, Co-grinding Method, Co-Precipitation Method (Co-Evaporates),

Co-Precipitation with Supercritical Fluid, Spray Drying Method, Dropping Solution Method, Direct Capsule Filling, Lyophilization Technique, Gel Entrapment Technique. In the following methods melt method was selected to study the effect of temperature on the formulated drug^{9,10}.

EXPERIMENTAL:

Materials:

candesartan cilexetil was obtained as a gift sample from aurobindho pharmaceuticals Ltd. Hyderabad. Polyethylene glycol 8000 (PEG8000) was obtained from Himedia chemicals, and all other solvents and reagents used are analytical grade.

Methods:

The solid dispersions were prepared by melt method; three formulations have been prepared in the ratio of 1:1, 1:5, 1:10 drug to carrier ratios. Initially the carrier PEG8000 was weighed according to the ratios of the formulation and transferred to the china dish, then it was melted at 80 °C until the carrier was transformed to the liquid state. Then weighed amount of the drug was added to the liquefied carrier and stirred vigorously to get uniform dispersion of drug in the carrier. Then the dispersion was cooled to the normal room temperature to solidify the drug carrier system. The formulated solid dispersions then lead to the characterization for the polymorphic changes in the drug¹¹.

Characterization:

The formulated solid dispersions were characterized for the polymorphic changes in the formulated drug by Differential scanning calorimetry, FTIR, X-Ray diffraction, and High performance liquid chromatography.

Differential scanning calorimetry: To study the polymorphic changes and the effect of carrier in the drug were studied using Shimadzu QA-100 Thermal Analyzer and the samples were scanned at a rate of 10 °C/min between 20 °C and 200 °C under an inert atmosphere of nitrogen supplied at 40 mL/min.

Powder X-Ray diffraction: Powder X-ray diffraction (XPRD) patterns of candesartan cilexetil and PEG 8000 solid dispersions, were recorded on a Philips P Analytical X'Pert powder X-ray diffractometer (Philips P) using Ni-filtered, Cu K α radiation, a voltage of 40kV and 25mA current. The scanning rate was 1°/min over the diffraction angle range (2 θ) of 5–40 °C.

FTIR Spectroscopy:

FTIR spectra of candesartan cilexetil solid dispersion were taken. About 5mg of sample was weighed and mixed with 100mg of potassium bromide IR powder and compacted under vacuum at a pressure of 12,000 psi for 3min. The so obtained pellet was placed on a suitable holder in perkin elmer IR spectrophotometer (FTIR spectrum RX I) and IR spectrum was recorded from 4000 cm⁻¹ to 400 cm⁻¹ in a scan time of 12 min. The obtained spectra were compared for any spectral fluctuations.

High performance liquid chromatography: The HPLC method was used in this study to determine the polymorphic changes that have been took place during the process of formulation of the solid dispersion of the candesartan cilexetil. Based upon the elution time i.e. retention time, the polymorphic formations were identified. For this RP18 column was used at a flow rate of 0.8mL per minute using mixture of water and acetonitrile with pH adjusted to 3.2 (60:40) as mobile phase .

In Vitro Evaluation of drug release:

Dissolution studies were performed for plain drug, 1:1, 1:5, and 1:10 ratios of drug to the polymer. The USP paddle method was used for all *in vitro* dissolution studies. The dissolution was carried out at pH of 0.1M Hcl(pH 1.2). The stirring rate was 100 ± 1 rpm. The amount of candesartan cilexetil was 10mg in all formulations the formulations were placed in 900ml dissolution medium and maintained at 37 ± 0.5 °c. At appropriate intervals 5ml of the sample was collected and then filtered through 0.45µm filter. The samples were analyzed at 233nm by UV-spectroscopy. The mean value of three determinations was used to calculate the drug release from each formulation.

RESULTS AND DISCUSSION

Differential scanning calorimetry: Differential scanning calorimetry (DSC) has been one of the most widely used calorimetric techniques for studies of the interactions between drug and carrier in the solid state In this study, DSC was applied to evaluate the change in the endotherm of the pure drug carrier and the formulation.

The DSC profiles of pure components and of the respective binary systems in the melting range of the drug, dehydration of the PEG8000, and formulation are shown in (Figure1). The thermal curve of pure candesartan cilexetil was typical of a crystalline anhydrous substance with a sharp endothermic peak at 171.91 °C corresponding to the melting point of the drug. The DSC curve of PEG8000 showed the liberation of crystal water as an endothermic effect peaked at about 56.78°C, The characteristic, well recognizable thermal profile of the drug appeared at the temperature 147.73 ° C corresponding to its melting point of the polymorph of the candesartan cilexetil. Thus we can say that in the formulation the drug has been converted to its polymorphic form.

X-ray powder diffraction (XRPD):

The solid-state form, like as crystalline, polymorphs, solvates or amorphous solids of a drug substance, can have a significant impact on drug's solubility, dissolution rate, stability in a pharmaceutical formulation and bioavailability. A crystal has an ordered arrangement of molecules and atoms, maintained in contact through non-covalent interactions. On the other hand, amorphous solids are characterized by a random state. Although the amorphous solids are often susceptible to changes during storage, the amorphous form of a drug is generally more soluble, due to free energies involved in the dissolution process. This characteristic of solubility is a useful propertyof the polymorphs.

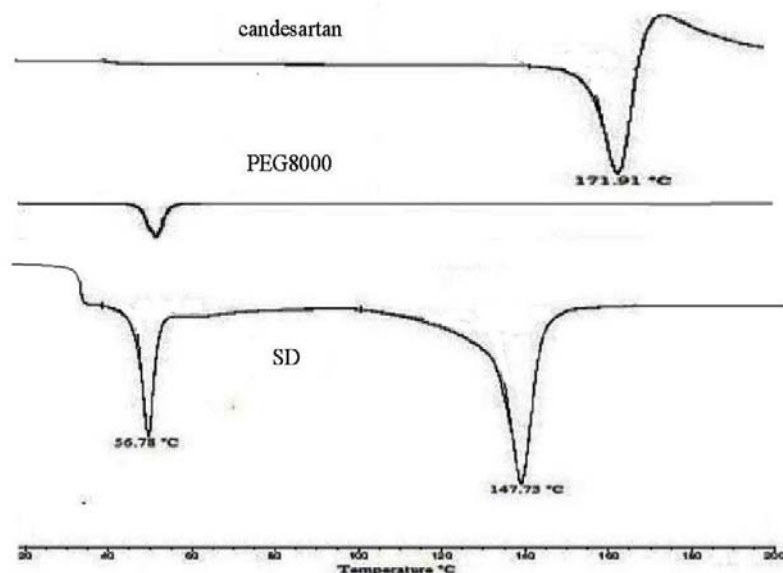


Figure1: DSC thrmogram of plain candesartan cilexetil,PEG8000, and the solid dispersion formulation of the drug and PEG8000.

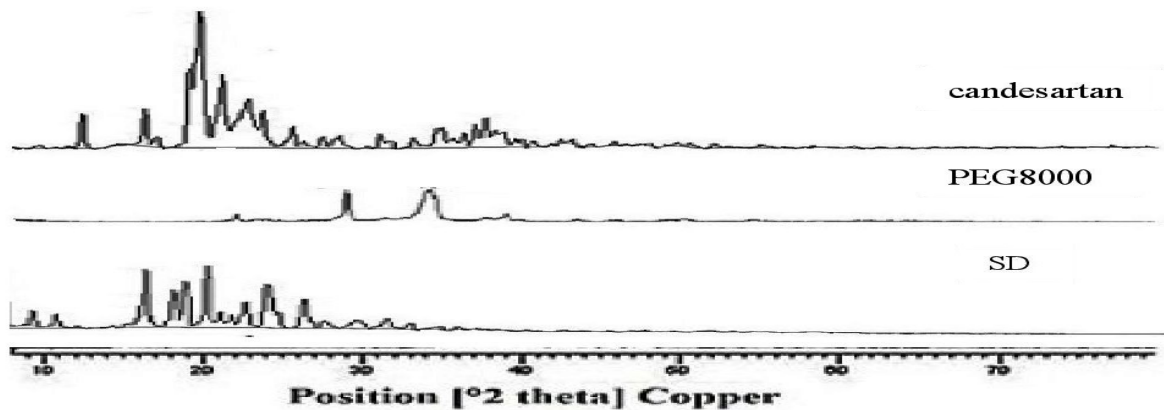


Figure2: X-RD spectrum of plain candesartan cilexetil,PEG8000, and the solid dispersion formulation of the drug and PEG8000.

The XPRD pattern of candesartan cilexetil PEG8000 and solid dispersion formulation are shown in Figure2. Peaks of drugs are intense and sharp, indicates its crystalline nature. Crystallinity was determined by comparing the peaks of the pure drug and the formulation. In the formulation the peaks are sharp but the intensity of the formulation is lower than the pure drug. The crystallinity of the formulation is due to the conversion of the drug into its polymorphic form. Candesartan cilexetil showed sharp peak at 20.90405 (2θ) with highest peak intensity 386 and in formulation at 20.69217 (2θ) with peak highest peak intensity 249. The relative degree of crystallinity (RDC) was calculated according to the equation:

$$RDC = \frac{I_{sam}}{I_{ref}}$$

Where I_{sam} is the peak height of sample and I_{ref} is the peak height at the same angle for the reference with the highest intensity. The peak height at 20.90405 $^{\circ}$ was used for calculating the RDC of solid dispersion formulation and drug. The RDC values of corresponding formulation Was 0.645. However, The characteristic crystalline peak of candesartan

cilexetil was observed for the solid dispersion, but the peak size was reduced which indicates that intensity of crystallinity was decreased.

FTIR spectroscopy:

The FT-IR spectrum gives the detailed information about the functional groups involved in the interaction in the formulation.

The IR spectrum of the drug PEG8000 and solid dispersion formulation were taken. The IR spectrum (figure3) of candesartan cilexetil shows characteristic peak 1835 to 1953 cm^{-1} (C=O functional group), 2957 cm^{-1} (C-H group stretching vibration), 1699 cm^{-1} (carboxyl carbonyl), 1458 cm^{-1} indicates the presence of the C=C aromatic group. The C=O group present in the candesartan cilexetil at 1835 to 1953 cm^{-1} is the group which shows the polymorphic changes in the candesartan cilexetil in the formulation. This is a fingerprint proof for the polymorphic changes in the drug present in the formulation.

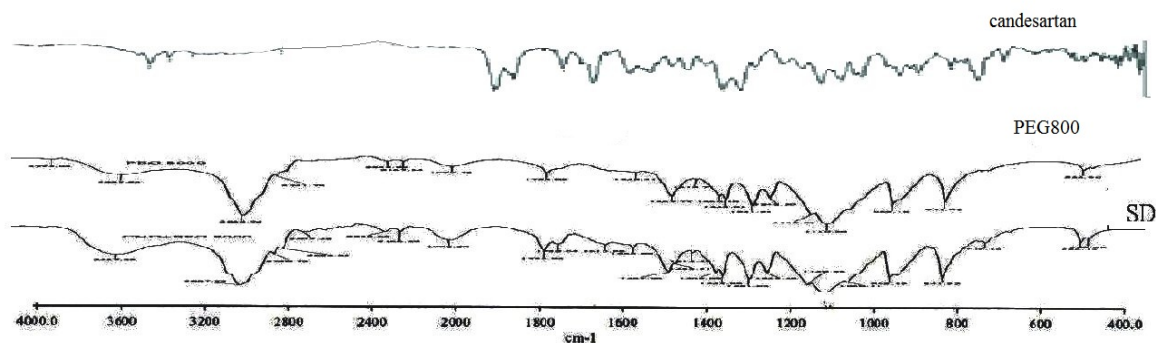


Figure3: FTIR spectrum of plain candesartan cilexetil,PEG8000, and the solid dispersion formulation of the drug and PEG8000.

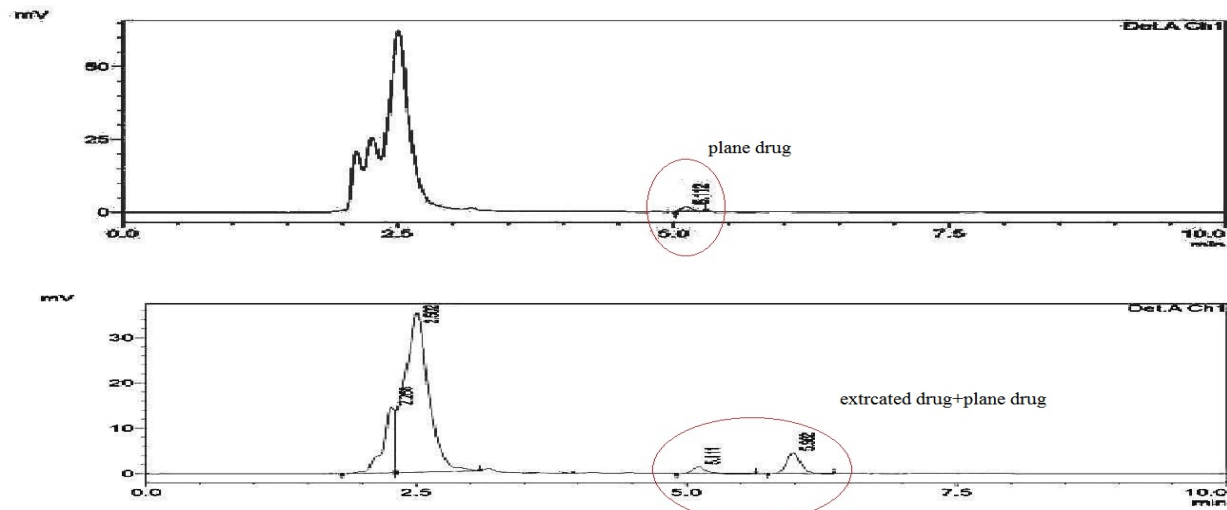


Figure 4: HPLC chromatogram showing the different peaks at different retention times for the plain drug and the extracted drug from the formulation.

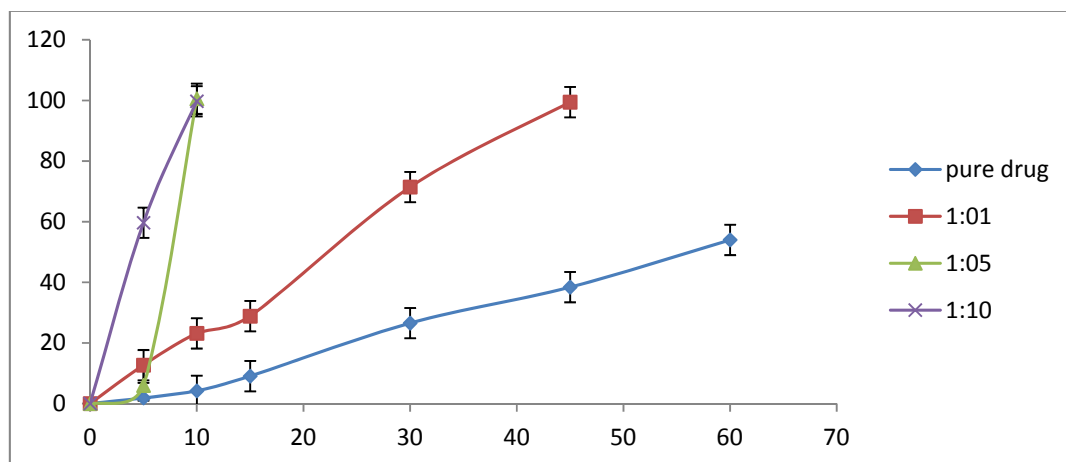


Figure 5: *in vitro* drug release studies from the formulations of 1:1, 1:5, 1:10 drug to carrier ratios of the solid dispersion formulations in 0.1N HCl (pH1.2).

High performance liquid chromatography:

HPLC method for the determination of the polymorphic changes in the candesartan cilexetil in the solid dosage form formulation was found to be very useful technique. In this method 60:40 ratio of water to acetonitrile was used at a pH of 3.2 at a flow rate of 0.8ml/min flow rate and the Column used was RP18.

Initially 20 μ l of the plain candesartan cilexetil was spiked to see where the plain is giving the drug peak. After that the drug was extracted in the methanol and to that same quantity of the plain drug was added to differentiate the drug peak from the polymorphic peak and same quantity of the drug and extract was spiked. It was found that when the plain drug was spiked the plain drug has given the peak at 5.112 and when the extract with plain drug was spiked it has given two peaks

in which one is resembling the plain drug peak at 5.111 retention time and another peak at 5.932 which shows that the extracted drug from the formulation was a polymorphic form of the candesartan cilexetil.

In vitro drug release studies:

The *in vitro* drug release studies were performed in USP II dissolution apparatus using 750 ml of 0.1N HCl medium for 1hr. 1:5 and 1:10 ratios has released the drug within 10minutes, 1:5 has shown burst release after 5minutes and 1:10 has released the drug in linear manner.. The drug release was more for higher ratios of the carrier used when compared to the lower ratios. This may be attributed by the coating of the carrier around the drug molecule which leads to the improved solubility and dissolution rate of the drug.

CONCLUSION:

The present study of polymorphic changes in the drug that has been formulated in the solid dispersion formulation of candesartan cilexetil using PEG8000. The results of the study were characterized by Differential scanning calorimetry, X-Ray Diffraction, FTIR, and HPLC. It was also evaluated for the in vitro release of the drug. The results showed that when the solid dispersion formulation was formulated using melt method that has showed polymorphic changes in the candesartan cilexetil. The reasons for the polymorphic changes may be due to the thermal formulation of the solid dispersion. And here by it can be concluded that formulations of the candesartan cilexetil should not be prepared at elevated temperature which leads to the polymorphic changes in the drug.

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