Research Article

Semisolid Matrix-Filled Hard Gelatin Capsules of Candesartan Cilexetil

C Aparna*, Gannarapu Hima Sree
Sri Venkateshwara College of Pharmacy,86, Hitech City Road, Vittal Rao Nagar, Madhapur, Hyderabad, Telangana 500081, India.
Affiliated to Osmania University, Hyderabad, Telangana, India.
***Corresponding author's E-mail:** caprn1971@gmail.com

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ABSTRACT

Candesartan cilexetil, an anti-hypertensive drug belonging to BCS Class II, exhibits low solubility and bioavailability. The present study was to develop semisolid matrix-filled hard gelatin capsules containing candesartan cilexetil to enable controlled release, improve bioavailability, and reduce the lag time of drug release. Solid dispersions of the drug were prepared using PEG6000 and PEG4000 as carriers and converted to semisolid matrix using Gelucire50/13, and Labrafil M 2130 CS as carriers. The drug exhibited the highest solubility in the carriers PEG6000 and PEG4000 and hence were selected as carriers for the formulation of solid dispersions. Solid dispersion was prepared using the fusion and solvent evaporation method. The formulation F3, prepared by the fusion method, demonstrated a higher drug release of 91.24 ± 0.74% within 75 minutes. Hence, it was chosen to prepare a semisolid matrix, using Gelucire50/13 or Labrafil M 2130 CS. The semisolid matrix prepared using Labrafil M 2130 CS released 98.2±0.75% in 10 minutes whereas the marketed formulation released 63.84±0.69% at the end of 90 mins. The solid dispersions and semisolid matrix were characterized using SEM and XRD. The SEM revealed that the drug was uniformly embedded in the solid dispersion and semisolid matrix. The XRD results showed that the intensity of the peaks decreased in the solid dispersions and semisolid matrix, indicating the conversion of the drug from crystalline to amorphous form which explains the improvement in dissolution rate.

Keywords: Candesartan cilexetil, Solid dispersion, Semisolid matrix, Fusion method, Solvent evaporation.

INTRODUCTION

Solubility, the phenomenon of dissolving the solute in a solvent to give a homogenous system, is one of the important parameters for achieving the desired concentration of drug in systemic circulation for a desired (anticipated) pharmacological response. Solubility is a major challenge for formulation development [2]. Various strategies, including solid dispersion, salt formation, solubilization, and particle size reduction, are commonly used to enhance dissolution rates, oral absorption, and bioavailability. Among these methods, Solid dispersion is particularly effective for improving the solubility of poorly water-soluble drugs.

Solid dispersion (SD), introduced in 1961, refers to the molecular-level dispersion of one or more active ingredients within a hydrophilic inert carrier matrix, increasing drug solubility and dissolution rates [3]. Several preparation techniques for SD have been reported, including co-evaporation, co-precipitation, spray drying, freeze drying, fusion method, solvent evaporation, hot-melt extrusion, lyophilization, and the solvent-melt method. SD transforms the drug's crystalline structure into an amorphous form, resulting in higher porosity.

Candesartan cilexetil (CC), an ester pro-drug of candesartan is an Angiotensin II receptor blocker, primarily used to treat hypertension. As a BCS Class II drug, CC has low solubility, high permeability, and exhibits poor bioavailability (15%). Solid dispersions of candesartan cilexetil (CC) were prepared by the fusion method and solvent evaporation method. and converted to a semisolid matrix and filled into hard gelatin capsules to improve the dissolution rate of the drug and reduce lag time.

MATERIALS AND METHODS

Materials:

Candesartan cilexetil was a kind gift sample from Smilax Laboratories Pvt. Ltd. Methanol and PEG4000 were obtained from Avantor Performance Materials India Pvt. Ltd. Hydrochloric acid and PEG6000 were procured from SD Fine Chem Limited, Mumbai. Gelucire50/13 and Labrafil M 2130 CS were gift samples from Gattefosse SAS.

Method:

Method development for analysis of Candesartan cilexetil:

1) Determination of λmax of Candesartan cilexetil in 0.1N HCl:

10 µg/mL solution of CC was prepared in 0.1 N HCl and scanned in 200-400nm wavelength using UV-vis Spectrophotometer (®T60 UV spectrophotometer) to determine the λmax.

2) Construction of calibration curve of candesartan in 0.1N HCl:

From the 100µg/mL solution, various samples of 0.6, 1.2, 1.8, 2.4, 3.0, and 3.6 milliliters were transferred into a 10-milliliter volumetric flask, and the volume was made up to 10ml using HCl to prepare 6, 12, 18, 24, 30, and 36 µg/mL. The absorbance of these samples was measured using a UV spectrophotometer at a wavelength of 254nm, and the process was carried out in triplicate. The standard graph was plotted with concentration on the x-axis and

absorbance on the y-axis.

PREFORMULATION STUDIES:

1) Determination of the melting point of Candesartan cilexetil:

The melting point of a sample was determined using capillary melting point tubes.

2) Solubility by shake flask method:

Solubility studies of candesartan cilexetil were performed to select the suitable carrier for the solid dispersion formulation. The carrier was taken in a vial and the drug was added to it to get a saturated solution. PEG6000, HPMC E15, Poloxamer188, PEG4000, Gelucire44/14, and PVP K30 were the carriers used for the solubility studies. PEG6000 and PEG4000 were melted then the drug was added into it. Vials were shaken at 200 rpm on a rotary shaker for 48 hrs. The suspension was filtered, and the absorbance of these samples was measured using a UV spectrophotometer at 255 nm.

3) Fourier transform infrared spectroscopy (FTIR):

The drug excipient interactions in the formulations prepared were studied using Shimadzu FTIR. The spectra were scanned over the 4000-400/cm frequency range with a resolution of 4[1/cm]. FTIR can detect changes in functional group bonding caused by structural alterations or the absence of a crystal structure.

APPROACHES OF PREPARATION OF FORMULATIONS:

PREPARATION OF SOLID DISPERSIONS:

The solid dispersions were prepared by using Fusion and Solvent evaporation techniques.

Hot Melt Method (Fusion method) [4]:

The weighed amounts of carriers (PEG6000 or PEG4000) were melted in a China dish and placed in a water bath, weighed amount of the drug was added to the molten carrier. The mixture was then allowed to freeze in an ice bath, cooled, and subsequently passed through an 18-micron sieve to get solid dispersion. Six solid dispersion formulations were prepared by varying the drug-to-carrier ratios of 1:1, 1:5, and 1:10 are mentioned in Table 1 from (F1 to F6).

Solvent evaporation method:

The weighed quantities of the drug and carriers (PEG6000/PEG4000) were added in a beaker, and mixed uniformly. Subsequently, 5 ml of methanol was added to the mixture and allowed to evaporate, the resulting mixture was then collected and passed through an 18 µm sieve to obtain the solid dispersion. Six solid dispersion formulations were developed by altering the drug-to-carrier ratios to 1:1, 1:5, and 1:10 are mentioned in Table 1 from (F7 to F12).

Table 1: Formulation of Solid Dispersion by the Fusion Method and Solvent Evaporation Method

Code	Drug: Carrier	Drug (gm)	PEG 6000 (gm)	PEG 4000 (gm)
F1	1:1	1	1	-
F2	1:5	1	5	-
F3	1:10	1	10	-
F4	1:1	1	-	1
F5	1:5	1	-	5
F6	1:10	1	-	10
F7	1:1	1	1	-
F8	1:5	1	5	-
F9	1:10	1	10	-
F10	1:1	1	-	1
F11	1:5	1	-	5
F12	1:10	1	-	10

Table 2: Formulation of semisolid matrix capsules

Ingredients	G1 (mg)	L1 (mg)
Solid dispersion (F3)	223	223
Gelucire50/13	20	-
Labrafil M 2130 CS	-	20

Preparation of semisolid matrix capsules (SSM):

The semisolid matrix was prepared by the melting method. The best-selected SD formulation was weighed. Semisolid matrix forming agents Gelucire 50/13(G1) or Labrafil M 2130 CS(L1) were weighed and melted in a water bath at 80 °C. The weighed quantity of SD was added to the molten mass and stirred to obtain a homogeneous melt. The heated mixture was poured into a preheated plastic injector and transferred into hard gelatin capsules.

EVALUATION OF FORMULATIONS:

1) In vitro dissolution, studies were carried out for solid dispersions prepared by both the fusion method and solvent evaporation method:

Dissolution studies were carried out for solid dispersions using USP type II apparatus (paddle type) containing 900 ml of 0.1N HCL at 100 rpm. The temperature of the medium was

maintained at 37 ± 0.5°. A 5 ml aliquot of samples was withdrawn at regular intervals for 90 minutes and replaced with an equal volume of fresh dissolution medium. The samples were filtered and analyzed by UV spectrophotometer at 254 nm.

In vitro, drug release studies were also carried out for the marketed drug (Actinsar 16mg) in a similar method.

2) In vitro dissolution of Semisolid matrix capsules (SSM):

Dissolution studies were carried out for semisolid matrix filled into hard gelatin capsules, using a USP type II apparatus, containing a dissolution medium of 900 ml of 0.1N HCL at 100 rpm. An aliquot of 5-milliliter samples was taken out at regular intervals for 30 minutes and replaced with an equal volume of the buffer. After calibrating the UV spectrophotometer with the appropriate blank, the obtained samples were analyzed at 254nm.

3) Drug Content:

The formulation was accurately weighed and taken in 10ml of volumetric flask. The substances were then dissolved in a small quantity of 0.1N hydrochloric acid, and the final volume was adjusted to 10ml with 0.1N hydrochloric acid. The resulting solution was filtered using a 0.45um filter, and the stock solutions were then diluted. Using a UV spectrophotometer absorbance was measured at a wavelength of 254nm.

CHARACTERISATION OF CANDESARTAN CILEXETIL:

1) Scanning Electron Microscopy:

Scanning electron microscope was used to study the surface morphology of solid dispersion and semisolid matrix formulation. The samples were fixed on a brass stub using double-sided tape and then gold coated in a vacuum by a sputter coater and examined at a magnification of 100x.

2) XRD:

To confirm the amorphous form transition of Candesartan cilexetil after preparation of semisolid matrix, the pure form of drug, solid dispersion, and semisolid matrix were analyzed in *XRDML, with intended wavelength type of K-α l radiation, generated at 30 mA and 45 kV. over a 2θ range of 4° to 40°, with the specific range determined by the step size.

RESULTS AND DISCUSSION

Analytical method development for Candesartan cilexetil:

The absorption maximum of Candesartan was determined to find a suitable wavelength for analyzing the drug sample.

1) Determination of λmax in 0.1N HCl:

10 µg/ml solution was scanned in the spectrophotometer to determine the absorption maxima. The absorption maxima of the drug in 0.1N HCl was found to be 254nm are seen in Fig 1(i).

2) Construction of calibration curve of Candesartan cilexetil in 0.1N HCl:

The standard graph was plotted to determine the concentration of the unknown sample in 0.1N HCl are seen in Fig 1(ii), the equation for the standard graph was found to be y= 0.01993x + 0.15373, with an R^2 value of 0.9955. Therefore, the graph is linear in the range of 6 to 36 µg/ml.

PREFORMULATION STUDIES:

1) Determination of the melting point of Candesartan cilexetil:

The melting point is measured to determine the purity of the sample. Candesartan melting point was found to be 163°C which is the same as the value reported in literature. Hence, our sample is pure.

2) Solubility studies:

Among the carriers selected for the solubility study, the drug exhibited maximum solubility in PEG6000, PEG4000, and HPMC E15 as seen in Fig.1(iii)

PEG6000 and PEG4000 were selected as carriers to prepare solid dispersion.

3) Fourier transform infrared spectroscopy (FTIR):

The FTIR analysis was carried out to determine the trace of any intermolecular interactions and the stability of the drug. The FTIR spectra of the candesartan, formulation F3 i.e. solid dispersion with PEG6000 as a carrier (drug: carrier ratio 1:10) prepared by the fusion method and semi-solid matrix with Labrafil M 2130 CS (L1) are shown in Fig 2.

The drug exhibited peaks at 3462.34 cm^{-1} and 3385.18 cm^{-1} corresponding to N-H Stretching (Primary Amine); 2939.61 cm^{-1} and 2860.53 cm^{-1} corresponding to C-H Stretching (Alkane); 1710.92 cm^{-1} corresponding with C=O Stretching; 1618.33 cm^{-1} corresponding with N-H Bending.

The solid dispersion (F3) exhibited peaks at 3462.34 cm^{-1} and 3385.18 cm^{-1} corresponding to N-H Stretching (Primary Amine); 2920.32 cm^{-1} and 2891.39 cm^{-1} corresponding to C-H Stretching (Alkane); 1720.56 cm^{-1} corresponding with C=O Stretching; 1612.54 cm^{-1} corresponding with N-H Bending.

The semisolid matrix (L1) exhibited peaks at 3462.34 cm^{-1} and 3385.18 cm^{-1} corresponding to N-H Stretching (Primary Amine); 2922.25 cm^{-1} and 2852.81 cm^{-1} corresponding to C-H Stretching (Alkane); 1689.70 cm^{-1} corresponding with C=O Stretching; 1629.90 cm^{-1} corresponding with N-H Bending.

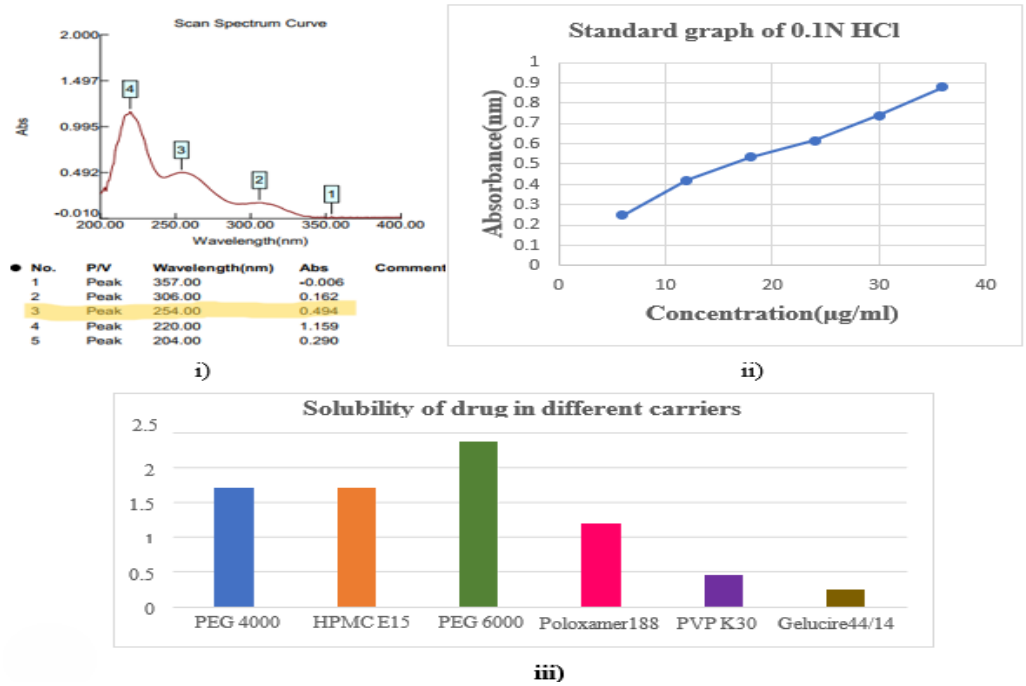


Figure 1: i) λmax of Candesartan cilexetil in 0.1N hydrochloric acid. ii) Standard graph of candesartan cilexetil in 0.1N hydrochloric acid. iii) Solubility of candesartan cilexetil in different carriers.

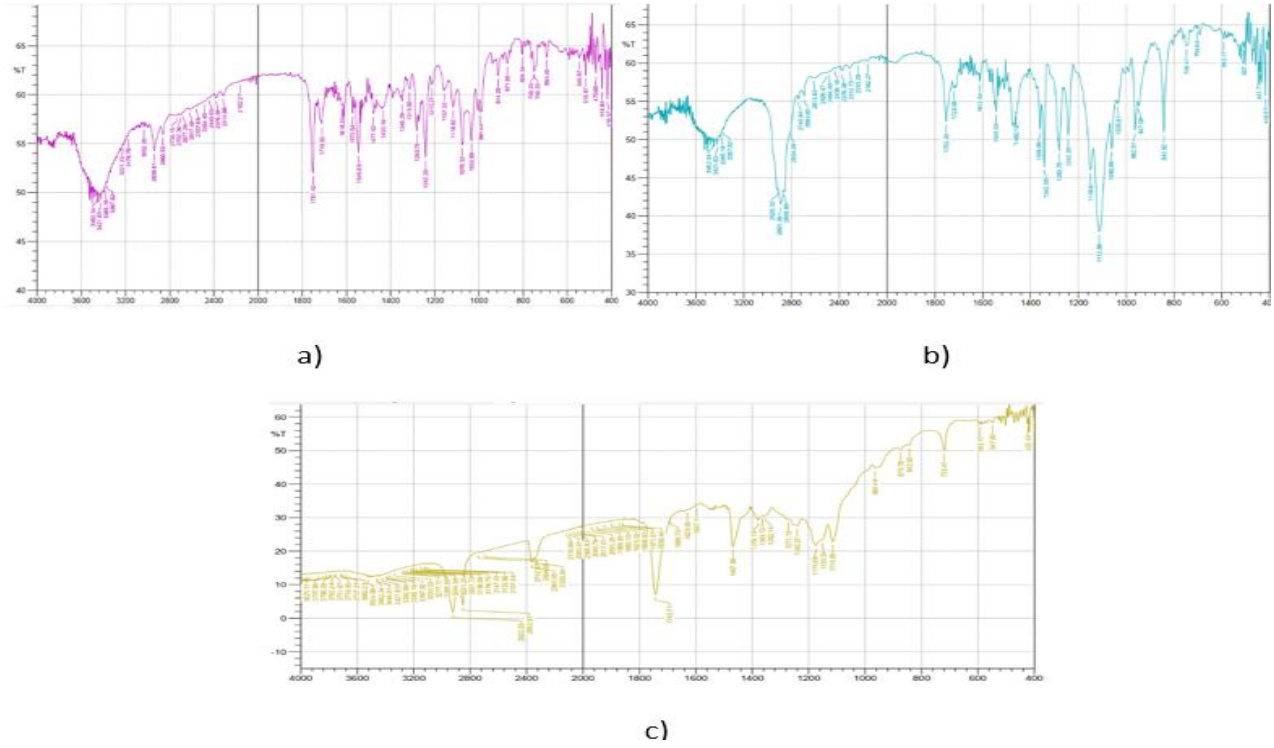


Figure 2: a) FTIR Spectrum of Candesartan. **b)** Solid dispersion (F3). **c)** Semisolid matrix(L1).

As seen in Figure 2. The FTIR Spectrum of Pure drug, Solid dispersion of PEG6000 (F3), and semisolid matrix of Labrafil M 2130 CS (L1) indicated no change in the position of the peaks. Hence it can be concluded that there are no drug excipient interactions.

Preparation of Solid dispersion

Based on solubility studies, PEG 6000 and PEG 4000 were selected as carriers, as the drug was more soluble in these polymers. Solid dispersions were prepared using the fusion method and solvent evaporation method using PEG6000 and PEG4000 as carriers.

EVALUATION OF SOLID DISPERSIONS:

1) In-vitro drug release studies with fusion method:

The solid dispersions were filled into hard gelatin capsules and in-vitro dissolution studies were carried out. The drug release from the formulations was observed for 90 minutes in 0.1N hydrochloric acid. The cumulative amount of drug release was higher for the F3 solid dispersion. i.e.,

91.24±0.74% in 75 minutes. The drug release pattern exhibited by the formulations is displayed in Fig 3 (A).

2) In-vitro drug release studies with solvent evaporation method:

Dissolution studies were also carried out for solid dispersions prepared by solvent evaporation in 0.1 N HCl, using a USP type II apparatus. Results are shown in Fig 3 (B).

The dissolution rate was higher for formulation F3 containing PEG6000 in a ratio of 1:10 prepared by the fusion method (91.24±0.74% in 75 min) compared to the other formulations. This may be due to favorable interaction between the drug and polymer.

The fusion method is advantageous over the solvent evaporation method as it eliminates the use of solvents, enhances stability, aids the uniform distribution of ingredients, reduces processing time, and allows high active ingredient loading. Hence Formulation F3 was selected for the preparation of the semisolid matrix.

Evaluation of semi-solid matrix:

Dissolution studies were performed for the semisolid matrix and marketed drug (Actinsar 16mg).

The semisolid matrix was filled into hard gelatin capsules and dissolution studies were carried out in 0.1N hydrochloric acid using USP type II apparatus. The In-vitro drug release studies are shown in Fig 3 (C).

As seen in Fig 3 (C), the drug release for formulation G1 was 96.17±1.43% at the end of 30 minutes, for formulation, L1 was 98.2±0.75% at the end of 10 minutes, and formulation F3 was 112.16±0.26% at the end of 90 minutes, and the marketed drug was 63.84±0.42% at 90 minutes. The formulation L1 i.e., the semisolid matrix of Labrafil M 2130 CS exhibited faster drug release as the Labrafil M 2130 CS improved the solubility of the drug and it is compatible with it.

Drug Content:

Drug content profile of formulations SD (F3), G1, and L1 was determined. The maximum drug content was obtained for a semisolid matrix made with Labrafil i.e. L1 formulation (91.7%) than a semisolid matrix made with Gelucire G1 (89%), and Solid dispersion F3 (86.8%).

CHARACTERISATION OF SOLID DISPERSION AND SEMI-SOLID MATRIX:

1)Surface Morphology:

The surface morphology of the prepared Candesartan solid dispersion and semi-solid matrix was studied by scanning electron microscopy.

As seen in the above figures, the drug is in the form of long crystals, the long crystals are not seen in the solid dispersion and semisolid matrix, and the drug is uniformly embedded in the solid dispersion and semisolid matrix. We can see that the crystallinity of the drug is lost.

2) XRD:

XRD was used to study the crystalline state. XRD studies of pure drug, formulation F3, and semi-solid matrix of Labrafil M 2130 CS (L1) were performed.

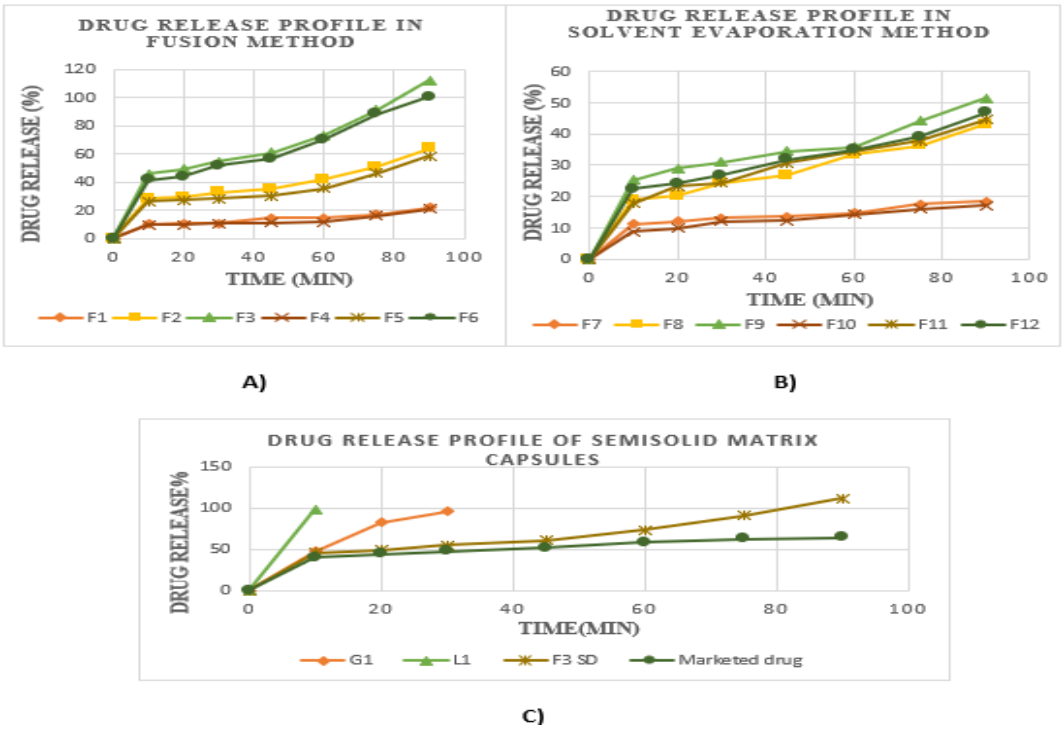
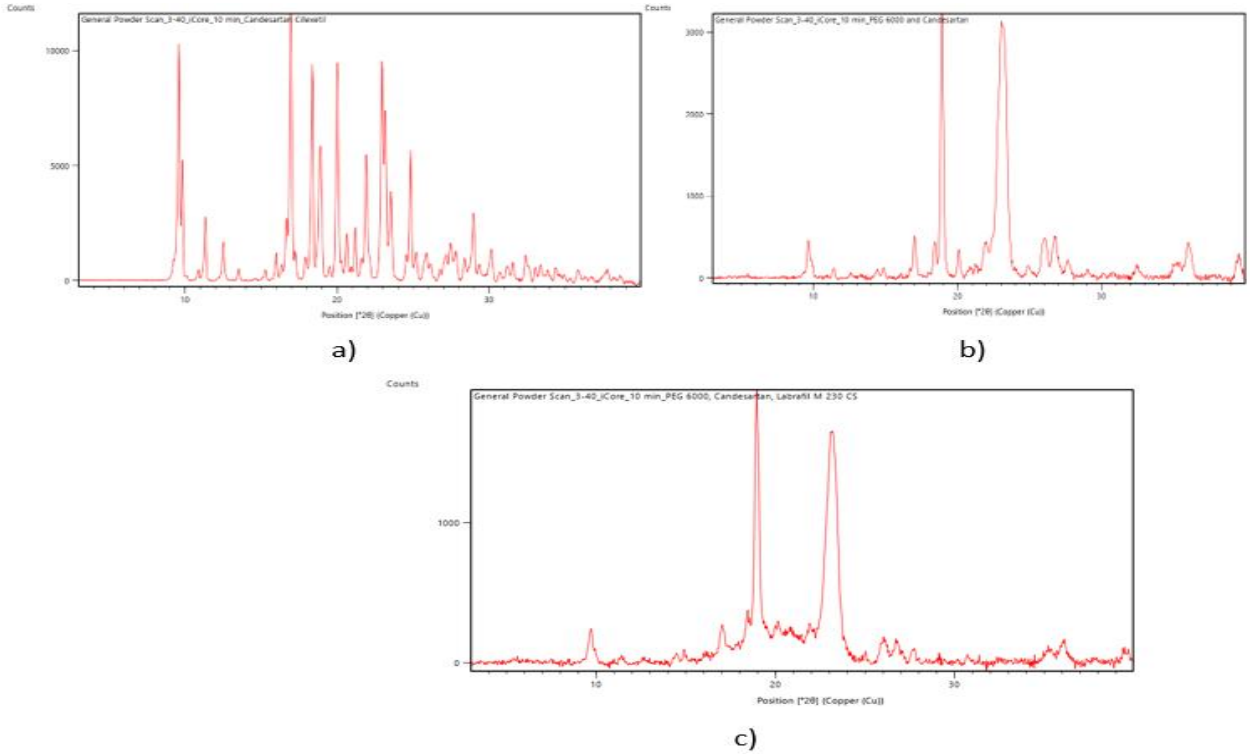


Figure 3: A) Drug release profile of PEG6000 and PEG4000 by the fusion method. **B)** Drug release profile of PEG6000 and PEG4000 by the Solvent Evaporation method. **C)** Drug release profile of semi-solid matrix capsules.

A) B) C)

Figure 4: A) Pure drug of Candesartan cilexetil. B) Solid dispersion with PEG6000 (F3). C) Semi-solid matrix of Labrafil M 2130 CS (L1).



a) b)

c)

Figure 5: a) XRD of pure drug, b) XRD of solid dispersion (F3), c) XRD of semisolid matrix (L1)

Characteristics of °2Θ peaks of candesartan were observed at 9.5908°, 16.9627°, 18.375°, 20.0256°, and 22.948°. (b) shows the peaks at 18.905° and 23.0.131°. At these 2Θ values, peak heights reduced from around 11,000cts to 3143cts. (c) The peaks were observed at 18.9314° and 23.4214°. height of peaks reduced from 1621.16cts to 1075.16cts.

The intensity of peaks decreased compared to the pure drug as the drug was loaded into a semisolid matrix uniformly.

CONCLUSION

Candesartan cilexetil, a poorly water-soluble drug, has been successfully developed into solid dispersions, and the semisolid matrix was filled into hard gelatin capsules. The solid dispersions increased the drug's solubility and improved its dissolution rate. The semisolid matrix made with Labrafil M 2130 CS reduced the lag time for drug release and further enhanced the dissolution rate.

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