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Research Article

ENHANCEMENT OF CANDESARTAN CILEXETIL DISSOLUTION RATE BY USING DIFFERENT METHODS

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ABSRTACT

The poor solubility and wettability of candesartan cilexetil (CAN) leads to poor dissolution and hence, low bioavailability after oral administration. The aim of this study was to improve the dissolution rate and hence the bioavailability of CAN by preparing solid dispersions (SD)/inclusion complexes (IC) and liquisolid (LS) systems. SD were prepared using polyethylene glycol (PEG) 6000 (hydrophilic polymer) by melting method in different drug-to-carrier ratios (1:2, 1:4 weight ratio), while IC (IC1:1 molar ratio) were made with hydroxypropyl-β cyclodextrin (complexing agent) by kneading method. LS systems were prepared using PEG 400 as the nonvolatile solvent, Avicel PH102 as carrier, Aerosil 200 as the coating material. Based on the drug release studies from SDs, SD1:4 was selected to prepare tablets, because it showed an enhanced dissolution profile in comparison with pure drug and SD1:2 according to two-tailed Student's t-test ($p<0.05$), in order to compare them with IC1:1 tablets, and LS systems and the marketed product. Fourier transform infrared, and differential scanning calorimetry studies indicated no interaction of the drug with the carriers, and provided valuable insight on the possible reasons for enhanced dissolution profile. Dissolution studies showed that LS systems enhanced dissolution profile of CAN compared with SD (SD1:4) tablets, IC1:1 tablets and the marketed product. The overall rank order given for the various formulations when compared with marketed tablets was: LS tablets > SD1:4 tablets > IC1:1 tablet > marketed tablets. Thus, the SD/IC technique and LS systems can be successfully used for enhancement of the dissolution profile of CAN.

Keywords: Candesartan cilexetil, Liquisolid systems, Solid dispirions, Inclusion complexes.

INTRODUCTION

One of the major challenges of present pharmaceutical research is to enhance the dissolution profile, absorption efficiency and bioavailability of water insoluble drugs [1]. The solubility-dissolution behavior of a drug is frequently the rate-limiting step to absorption of drugs from the gastrointestinal tract for orally administered drugs [2,3]. Poor aqueous solubility has always been a very challenging obstacle as it is together with membrane permeability, an essential factor in the limitation of a drug's bioavailability following oral administration. Since an increasing number of newly developed drug candidates in preclinical development phases present poor water-solubility characteristics, there is a great need for formulation approaches to overcome this factor [4]. During the past few years many techniques have been used in attempt to improve solubility and dissolution rates of poorly water soluble drugs which include solid dispersions (SDs) [5-7], inclusion complexes (IC) [4,8,9] and liquisolid (LS) systems [10-12].

Candesartan cilexetil (CAN) is an angiotensin receptor blocker indicated in the treatment of essential hypertension. CAN is a white to off-white powder with a molecular weight of 610.67. It is practically insoluble in water and sparingly soluble in methanol [13]. The poor solubility and wettability of CAN leads to poor dissolution and hence, low and/or variable bioavailability after oral administration. The absolute bioavailability for candesartan is about 40% when CAN is given as a solution and about 14% when given as tablets. Peak plasma concentrations of candesartan occur about 3-4 hrs after oral doses as tablets [14].

The aim of this study was to improve the dissolution rate of CAN using SDs, IC and LS systems and compare the prepared tablets with marketed product. Further, to characterize the interaction of CAN with the carriers various techniques like Fourier transform-infrared (FT-IR), and differential scanning calorimetry (DSC) were used.

METHODS

Materials

CAN (99.8%) from Zhejiang Huanai Pharmaceuticals (China), hydroxypropyl-β-cyclodextrin (HP-β-CD) with a degree of substitution of 4.8 was produced by NIHON Shokuhin Kako Co. Ltd. (Japan), polyethylene glycol 6000 (PEG 6000) from Interpharm Ltd. (UK), Avicel PH 102 from Gujarat Microwax Pvt. Ltd. (India), colloidal silicon dioxide (Aerosil 200) from Degussa (Belgica), PEG 400 from Interpharm Ltd. UK, Crospovidone from BASF (Germany), Mg stereate from Magnesia (Germany). Other chemicals were of analytical grade obtained from Merck (Germany).

Instruments

High performance liquid chromatography (HPLC) instrument (VWR-Hitachi Lachrome Elite®, UK) equipped with pump (Lachrom Elite L-2200 Hitachi, Germany), photo diode array detector (Lachrom Elite L-2130, Hitachi, Germany) and autosampler (Lachrom Elite L-2200 Hitachi, Germany).

FT-IR spectroscopy (Bruker, Vector 22, Germany). Differential scanning calorimeter (METTLER TOLEDO, OH, USA).

Preparation of CAN: HP-β-CD IC

CAN (2 g) and HP-β-CD (4.52 g) were well mixed together in a mortar and then water (4 ml) was added (in portions) so as to obtain a homogeneous paste. The mixture was then ground for 30 minutes. During this process, an appropriate quantity of water was added to maintain a suitable consistency. The paste was dried in oven at 40°C for 24 hrs. The dried complex was pulverized into a fine powder and passed through 355 μm sieve.

SD preparation (melting method)

PEG 6000 (4 g), (8 g) were weighted separately and melted at 70°C, then CAN (2 g) was added to the molten PEG 6000 and stirred for 5 minutes in order to obtain SDs of (1:2), (1:4) weight ratios, respectively. The

system was placed in an ice bath until solidification occurred. The mass was crushed, ground with a mortar and pestle and passed through 355 μm sieve. The samples were kept overnight in a desiccator or until the next experiments.

LS systems preparation

Calculation of liquid load factor

In the current study, PEG 400 was used as the liquid vehicle, microcrystalline cellulose (Avicel PH 102) as the carrier material, and Aerosil 200 as the coating powder. Liquid load factor, L_f, defined as the ratio of weight of the liquid medication and carrier powder in the LS systems, refers to the maximum amount of the liquid medication that can be loaded to the carrier material to produce an acceptably flowable and compressible liquid/powder admixture [15].

L_f is given by the following equation (1):

$$L_f = \frac{W}{Q} \quad (1)$$

Where:
W is the weight of liquid medication and,
Q is the weight of carrier material.
It can also be calculated using the following equation (2):

$$L_f = \Phi + \varphi\left(\frac{1}{R}\right) \quad (2)$$

Where:
Φ is the flowable liquid retention potential for Avicel PH 102=0.005 [15],
φ is the flowable liquid retention potential for Aerosil 200=3.26 [15], and
R is the ratio of carrier (Q) to coating (q) materials; it is given by the following equation:

$$R = \frac{Q}{q} \quad (3)$$

The ratio of Avicel PH 102 to Aerosil 200 was selected at R=20. Thus,

$$L_f = \Phi + \varphi\left(\frac{1}{R}\right) = 0.005 + 3.26\left(\frac{1}{20}\right) = 0.168$$

This calculated L_f is general and does not take in account drug factors. Therefore, it should be adjusted experimentally according to each drug substance and its concentration in the liquid.

The experimental liquid load factor was calculated starting from the L_f value calculated above. Following the calculations of Q and q amounts, a mixture of half of these quantities was added to the liquid medication in a mortar. Two grams of the carrier-coating materials admixture (R=20) was added to the above mixture and angle of repose, Carr's index, and Hausner's ratio were measured. This procedure was repeated until acceptable values of angle of repose, Carr's index, and Hausner's ratio were achieved.

Procedure of preparation

One LS formulation (Table 1), namely, F1, was prepared first by mixing quantities of 8 mg of the solid drug with 92 mg of the liquid vehicle (PEG 400) in such a way to produce a liquid medication mixture with a concentration of CAN, 8%. Then, the liquid mixture was heated to 80-90°C with continuous stirring, until a homogenous mixture was achieved. Afterwards, a binary mixture of the carrier material Avicel PH102 and the coating powder Aerosil 200 (with a ratio of 20:1) was added to the above mixture containing the drug and PEG 400 under constant mixing in a mortar. The quantities of the carrier and coating material, calculated based on L_f value, are enough to maintain acceptable flow and compression properties. Then, 5% (w/w) of the disintegrating material crospovidone was mixed with the previous combination for a period of 5 minutes. Finely, 1% (w/w) of the lubricant Mg stereate was mixed with the last combination for a period of 2 minutes. The final mixture was compressed using a single punch tablet press machine (ERWEKA GmbH AR402, Type EK0, Germany) to achieve a tablet hardness of 5-7 kg cm^{-2}.

Table 1: Formulation of the prepared tablets

Ingredients	Weights (mg/tablet)		
	F1	F2	F3
	LS tablets	SD1: Four tablets	IC1: One tablets
CAN	8	8	8
PEG 400	92	-	-
Avicel PH 102	518	146	162
Aerosil 200 (1% in F2 and F3)	26	2	2
PEG 6000	-	32	-
HP-β-CD	-	-	16
Crospovidone (5%)	34	10	10
Mg stearate (1%)	7	2	2
Total weight (mg)	685	200	200

CAN: Candesartan cilexetil, PEG: Polyethylene glycol, HP-β-CD: Hydroxypropyl-β cyclodextrin

Characterization of the IC, SDs and LS systems

IR-spectroscopy

FT-IR spectroscopy was employed to characterize further the possible interactions between the drug and the carrier in the solid state on a Bruker Vector 22. FT-IR spectra were obtained by the conventional KBr pellet method. The spectra were scanned over a frequency range 400-4000/cm with a resolution of 4/cm.

DSC

DSC analysis was performed using (Mettler Toledo) on 3-4 mg samples. Samples were heated in an aluminum pan at a rate of 10°C/minutes conducted over a temperature range of 25-300°C.

Drug content analysis

First, an amount of the pure drug, SD1:2, SD1:4 and IC1:1 (molar ratio), equivalent to 8 mg of candesartan cilxetil, was accurately weight and transferred to a 50 ml volumetric flask, then 35 ml acetonitrile was added and the solution was then shaked for 10 minutes, and then completed to 50 ml using the same solvent. 5 ml of the last solution was filtered and transferred to a 100 ml volumetric flask, and diluted with a mixture of acetonitrile: Water (60:40 v: v). Then 50 μl of this solution was injected to the HPLC column to determine the amount of CAN according to the following equation:

$$\text{Percentage of CAN} = \frac{\text{Peak area of the sample}}{\text{Peak area of the standard}} \times \frac{\text{Concentration of the standard}}{\text{Concentration of the sample}} \times 100 \quad (4)$$

Then, the drug content in the prepared tablets (Table 1) and the marketed product was assayed as the following: 20 tablets were accurately weight individually, and the average was calculated, then crushed and an amount equivalent to 8 mg of candesartan cilxetil was transferred to a 50 ml volumetric flask, then 35 ml of acetonitrile was added and the solution was then shaked for 10 minutes, and then completed to 50 ml using the same solvent.

5 ml of the last solution was filtered and transferred to a 100 ml volumetric flask, and diluted with a mixture of acetonitrile:water (60:40 v:v). Then 50 μl of this solution was injected to the HPLC column to determine the amount of CAN according to equation (4).

Drug release studies (from SDs and ICs)
USP Type 2 (paddle) method was used. An amount of samples (pure drug, SD1:2, SD1:4, IC1:1) equivalent to 8 mg of drug was dispersed into the dissolution vessel containing 900 ml of 0.05 M phosphate buffer (pH=6.5) containing 0.35% (w: w) tween 20. The dissolution medium was maintained at 37±0.5°C and stirred at 50 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through micro filter (0.45 µm), concentration of CAN was determined using HPLC apparatus. All experiments were carried out 6 times [16].

Tablet preparation (Formula 2 and Formula 3)
The (SD:F2, IC:F3) tablets were prepared by using direct compression.

SD1:4 or IC1:1, Avicel PH102, Aerosil 200, crospovidone were sieved and mixed. Then, Mg stearate was added to the last mixture and mixed for 2 minutes. The obtained blend was then compressed to tablets (Table 1) using a single punch tablet press machine (ERWEKA GmbH AR402, Type EK0, Germany). Compression load was adjusted to produce tablets with a hardness of 5-7 kg/cm.

Disintegration test
The disintegration test was performed using USP disintegration tester, PTZ ATUO 2/EZ (Pharma Test, Germany) and in distilled water as a medium at 37±0.5°C.

Drug release study from tablets
In vitro release study was performed on the prepared tablets and the marketed product using USP Type 2 dissolution apparatus. The dissolution medium was 900 ml of 0.05 M phosphate buffer (pH=6.5) containing 0.35% w: w tween 20. Each test was carried out at 37±0.5°C (n=6) and at a stirring speed of 50 rpm. Each tablet containing 8 mg of CAN was subjected to the dissolution test. The volume of the medium was kept constant during the run by replacing the removed samples with an equivalent amount of fresh dissolution medium to maintain sink condition. Samples were filtered through a 0.45 µm filter and analyzed using HPLC apparatus [16].

Method of analysis
The HPLC system was equipped with a 254 nm detector and (60 mm × 4.6 mm) column that contained 5 µm packing L1 (Intertsil® ODS-3, 60 mm × 4.6 mm is suitable). The system was operated at (30±0.5°C). The mobile phase composed of 570 ml acetonitrile + 430 ml water + 10 ml glacial acetic acid. The flow rate was about 1.5 ml/minutes. The HPLC method was developed and validated.

Statistical analysis of the drug release profile
All the results were expressed as mean values ± standard deviation. The difference between percentages (fractions) of CAN release at each time interval from pure drug, SD1:2, SD1:4, IC1:1 were statistically evaluated by using two-tailed Student's t-test. All data analysis was performed using the Microsoft Excel 2010 software. A confidence limit of $p<0.05$ was fixed for interpretation of the results. Whereas, comparison of different tablet dissolution profiles was made using mathematical methods (difference and similarity factors).

RESULTS

Determination of liquid load factor
Following flow ability studies, experimental liquid load factor that produces LS systems with good flow ability was determined. Table 2 shows the experimental liquid load factor value with the corresponding angle of repose, Carr's index, and Hausner's ratio values. The experimental L_f value is close to the calculated value, which is 0.168. The use of that optimized experimental value of L_f helps reducing the required amounts of carrier and coating materials and consequently reducing tablet size.

To prepare the LS tablets, the R value of 20 was selected because this value is proved to provide LS systems with ideal flow ability characteristics.

Table 2: Flow ability parameters corresponding to the experimental liquid load factor

EXP Lf	Angle of repose (°)	Carr's index (%)	Hausner's ratio
0.193	33.44±0.21	14.24±0.41	1.17±0.01

Characterization of the IC, SDs and LS systems

FT-IR spectroscopy

Fig. 1 shows the FT-IR spectrum of pure CAN. Whereas, Fig. 2 shows the FT-IR spectrum of CAN, SD1:2 and SD1:4.

Fig. 3 shows the FT-IR spectra of CAN, HP-β-CD and IC1:1. Fig. 4 shows the FT-IR spectrum of CAN, Avicel PH102, Aerosil 200 and LS formulation

DSC

Fig. 5 shows the DSC thermograms of CAN (a), PEG 6000 (b), SD1:2 (c), and SD1:4 (d).

Fig. 6 shows the DSC thermograms of CAN (a), HP-β-CD (b), and IC1:1 (c). Fig. 7 shows the DSC thermograms of CAN (a), Avicel PH102 (b), Aerosil 200 (c), LS placebo (d), and LS formulation (e).

Drug content analysis
Table 3 shows the drug content analysis results of SD1:2, SD1:4, and IC1:1. The powders were found homogeneous because they showed a good agreement between theoretical and actual drug contents. Table 4 shows drug content analysis results for the prepared tablets and the marketed product.

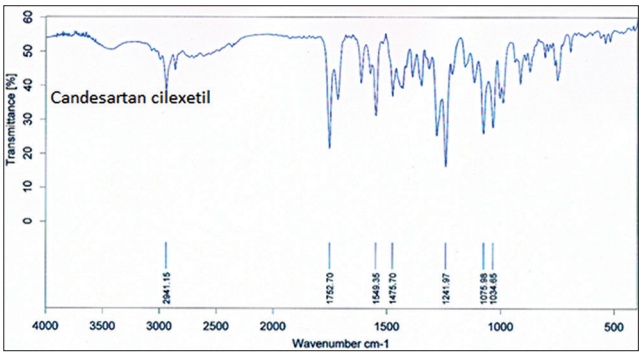

Fig. 1: Fourier transform infrared spectrum of candesartan cilexetil

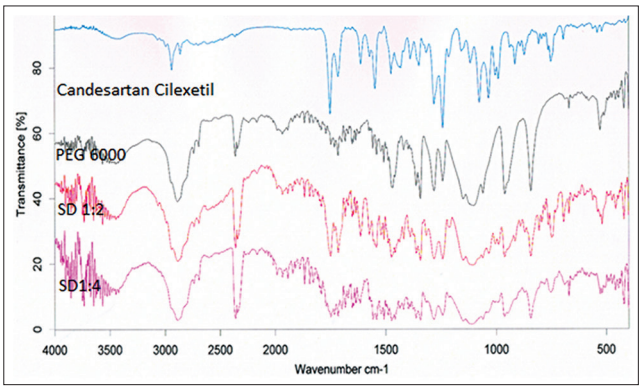

Fig. 2: Fourier transforms infrared spectra of candesartan cilexetil, solid dispersion 1:2 and solid dispersion 1:4

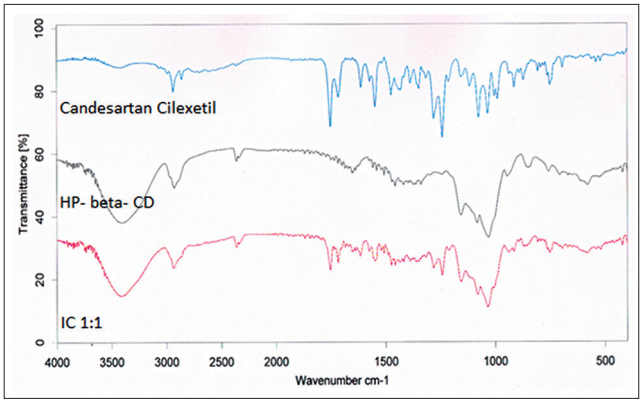

Fig. 3: Fourier transforms infrared spectra of candesartan cilexetil, hydroxypropyl-β cyclodextrin and inclusion complexes 1:1

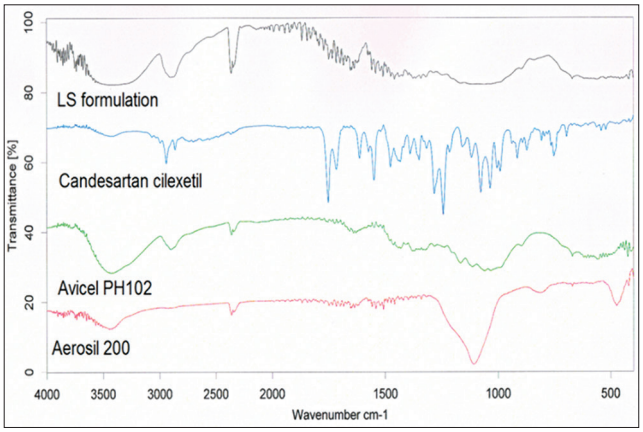

Fig. 4: Fourier transforms infrared spectra of candesartan cilexetil, Avicel PH102, Aerosil 200 and liquisolid formulation

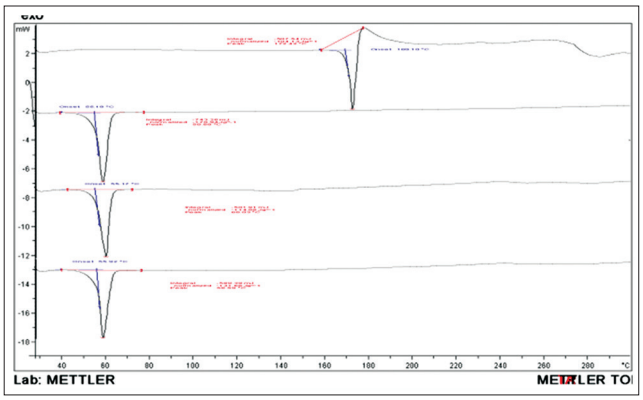

Fig. 5: Differential scanning calorimetry thermo grams of candesartan cilexetil (a), polyethylene glycol 6000 (b), solid dispersion (SD) 1:2 (c) and SD1:4 (d)

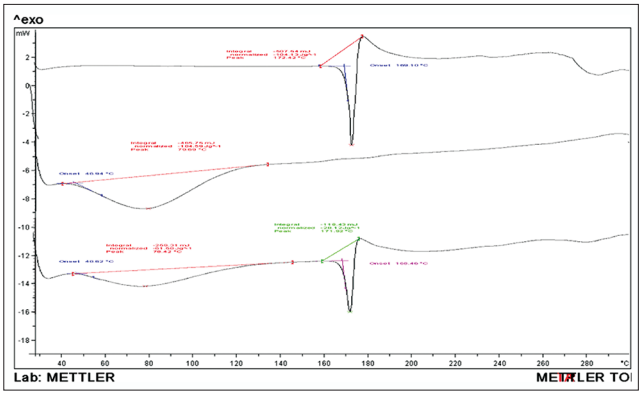

Fig. 6: Differential scanning calorimetry thermo grams of candesartan cilexetil (a), hydroxypropyl-β cyclodextrin (b) and inclusion complexe1:1 (c)

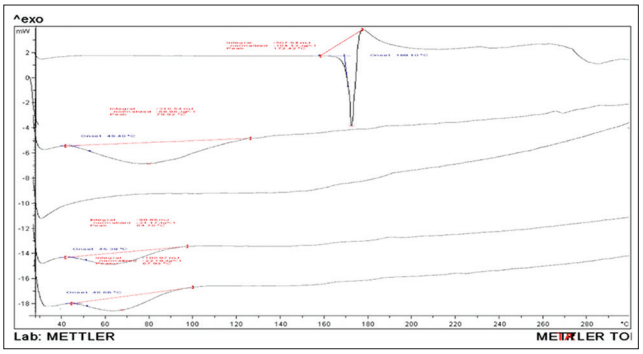

Fig. 7: Differential scanning calorimetry thermo grams of candesartan cilexetil (a), Avicel PH102 (b), Aerosil 200 (c), liquisolid (LS) placebo (d) and LS formulation (e)

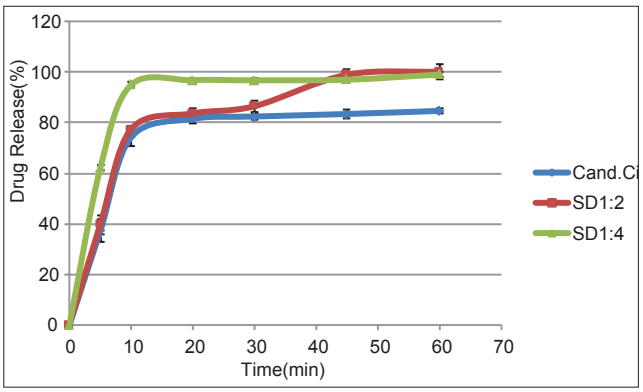

Fig. 8: Dissolution profile of candesartan cilexetil from pure drug, solid dispersion (SD) 1:2 and SD1:4 (weight ratio)

Release rate studies from (SDs and ICs)

Drug release studies were carried out in (0.05M) phosphate buffer (pH=6.5) containing 0.35% w: w tween 20 (Figs. 8 and 9). Blending of CAN with PEG 6000 or HP-β-CD in form of SDs SDs or ICs, respectively, could enhance the release of CAN. Dissolution rate of CAN from SDs and ICs were greater than those for pure drug (CAN alone). The percentage of drug dissolved after 5, 10, 20, 30, 45 and 60 minutes from the pure CAN, SD1:2, SD1:4 (weight ratio) and IC 1:1 (molar ratio) were illustrated in Table 5. It is shown that, the maximum percent amount of drug dissolved after 60 minutes at the dissolution medium was 84.7±1.01%, 100.25±2.8%, 99.10±1.78% and 99.52±0.91% for pure drug, SD1:2, SD1:4, IC1:1, respectively. SD1:4 showed an enhanced dissolution profile compared to pure drug, SD1:2 at the points (5, 10, 20, 30 minutes) according to two-tailed Student's t-test ($p<0.05$). Furthermore, SD1:4 showed an enhanced dissolution profile compared to the pure drug at time points (45 and 60 minutes) according to two-tailed Student's t-test ($p<0.05$). IC1:1 showed an enhanced dissolution profile compared to the pure drug at all-time intervals according to two-tailed Student's t-test compared to pure drug.

Disintegration test

Table 5 shows the disintegration test results of the prepared tablets and the marketed product.

Drug release study from tablets

Fig. 10 shows the percentage of drug dissolved from the prepared tablets and the marketed product. The release profiles showed that the dissolution of CAN was 16.46±3.18% at the first 5 minutes from the marketed tablet Atacand®, whereas it reached 65.47±5.4%, 49.74±4.91% and 45.88±5.94% from LS, SD1:4 tablets and IC1:1 tablet, respectively, at the first 5 minutes. According to the findings of this study and in comparison with other formulations, F1 (LS formulation) was the best formulation producing the best drug release profile, followed by F2 (SD1:4 tablets), followed by F3 (IC1:1 tablets). Table 6 shows the differential factor (F_1) and the similarity factor (F_2) of the prepared tablets compared to the marketed product.

DISCUSSION

Characterization of the IC, SDs and LS systems

FT-IR spectroscopy

The FT-IR spectrum of CAN exhibited characteristic signals at 1752.70/cm and 1715.14/cm for ester –C=O stretching vibration and 1315.96/cm and 1241.93/cm for C–O stretching of aromatic esters [17,18]. Important vibrations detected in the spectrum of PEG 6000 are the OH stretching at 3446.11/cm, C–H stretching at 2888.55/cm and the C–O–C stretching (ether) at 1101.80/cm [17,18]. The spectra of PEG 6000 (SD1:2) (SD1:4) can be simply regarded as the superposition of those of CAN and PEG 6000, and that is clear at region 2500-3500/cm where the characteristic OH stretching band appears in this region, and also the characteristic peaks of CAN in the region 2500-4000, but as we can see there was a shift in the ester C=O stretching vibration from 1715.14/cm to 1728/cm which may be attributed to conversion of CAN from crystal form I to the amorphous form [19]. The minor peaks due to CAN were absent indicating trapping of CAN inside the PEG matrix. However, the major characteristic peaks for CAN were still present. The intensities of two most prominent peaks 2888.55/cm and 1101.80/cm in PEG had doubled in its SD indicating the summation of intensities of drug and carrier at these peaks and probably a slight increase in the crystallinity of PEG.

The IR spectra of HP-β-CD show prominent absorption bands at 3414/cm (for O–H stretching vibrations), 2929.30/cm (for C–H stretching vibrations), and 1157.20, 1083/cm, (C–H, C–O stretching vibration) [17,18]. The FT-IR spectrum of IC1:1 shows the characteristic peaks of CAN at 1752.00/cm, 1716.71/cm with a slight decrease in their intensities. However, the peaks for methyl groups at 1475.14/cm and 1388.08/cm, and the peak for C–O stretching of aromatic esters at 1315.96/cm had disappeared. Also missing from the spectrum were the many minor peaks for C–H in-plane bending of aromatic rings, which occur in the spectrum of CAN. This indicated that the vibrations and bending in some part of the drug molecule was restricted due to a possible formation of an IC [20], Therefore, it is very likely that an aromatic ring in CAN along with a methyl group and a portion of aromatic ester were included within the apolar cavity of HP-β-CD.

The FT-IR spectrum of LS formulation Fig. 4 shows all the characteristic peaks of CAN (1716.90/cm and 1749.43/cm corresponding to carbonyl stretching) (1316.25/cm, 1240.96/cm corresponding to C-O stretching in aromatic esters), which may indicate the absence of any chemical interaction between the drug and excipients [21].

DSC

The DSC curve of CAN shows a sharp endothermic peak at 172.42°C corresponding to its melting, and indicating its crystalline nature [22]. The thermogram of neat PEG 6000 exhibited a sharp endothermic peak corresponding to its melting point at 58.88°C [23]. A complete disappearance of the drug melting peak was observed in PEG 6000 (SD1:2, SD1:4) SDs, which is attributable to the dissolution of drug in the melted carrier before reaching its fusion temperature [24] or to the transformation of CAN from crystal form I to the amorphous form [19].

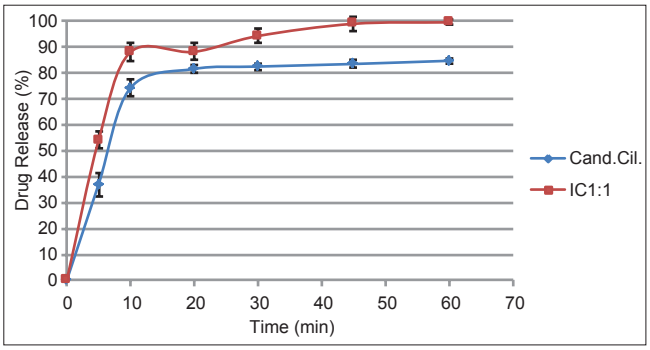

Fig. 9: Dissolution profile of candesartan cilexetil from pure drug and inclusion complex 1:1 (molar ratio)

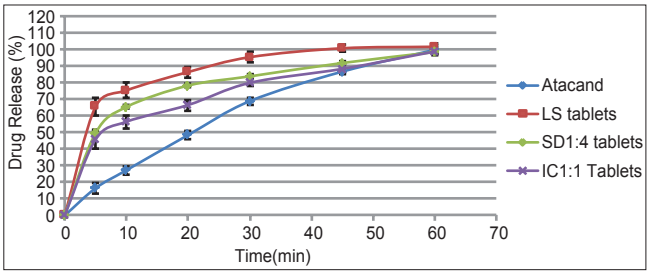

Fig. 10: Dissolution profile of candesartan cilexetil from the prepared tablets and the marketed product

Table 3: Drug content analysis results in SD1:2, SD1:4 and IC1:1 powders

Powder	Drug content (%)
SD1:2	101.43±2.57
SD1:4	100.45±2.31
IC1:1	99.42±2.3

SD: Solid dispersions, IC: Inclusion complexes

Table 4: Drug content analysis results in SD1:4 tablets, IC1:1 tablets, LS systems and the marketed product

Formula	Drug content (%)
SD1:4 tablets	102.17±1.62
IC1:1 tablets	101.16±1.31
LS	102.97±0.50
Atacand®	100.38±0.17

SD: Solid dispersions, IC: Inclusion complexes, LS: Liquisolid

Table 5: Disintegration test results

Formula	Disintegration time (seconds)
SD1:4 tablets	150±7
IC1:1 tablets	113±9
LS	157±10
Atacand®	229.5±5

SD: Solid dispersions, IC: Inclusion complexes, LS: Liquisolid

Table 6: The calculated difference factor and similarity factor of the prepared tablets compared to the marketed product

Formula	IC1:1 tablets		SD1:4 tablets		LS tablets	
	F1	F2	F1	F2	F1	F2
Atacand®	25.99	35.99	35.27	30.21	51.11	23.17

SD: Solid dispersions, IC: Inclusion complexes, LS: Liquisolid

The DSC thermogram of HP-β-CD shows a broad endothermic peak between 40 and 120°C (maximum at 79.69°C), corresponding to the release or evaporation of the water molecules [24]. In the IC1:1 endotherm, the peak corresponding to the loss of water as well as that for the melting of CAN, slightly shifted to lower temperatures (from 79.69 to 78.42 for HP-β-CD) and (from 172.42 to 171.92 for CAN) along with an increase in the intensity of broad peak and while a considerable decrease in the intensity of the peak for drug melting was observed. A possible explanation to this development can be that a part of the drug molecule may have penetrated into the CD cavity and replaced some water molecules exhibiting a more intense endotherm indicating slight increase in the crystallinity of amorphous HP-β-CD [24]. This also suggests the formation of an IC although some free drug may be present.

The DSC thermogram of Avicel PH102 exhibited a broad endothermic peak at 79.92°C that might correspond to the volatilization of adsorbed water [10]. The thermal behavior of Aerosil 200 did not show any sharp peaks, proving that the coating material was almost in an amorphous state [25]. The DSC thermogram of LS placebo shows only one broad endothermic peak at 64.78 corresponding to volatilization of adsorbed water on the Avicel PH102 which exhibit a slight shifting (about 15.14°C) and this might be attributable to the effect of aerosil 200 and PEG 400 as impurities. On the other hand, the LS system thermogram in Fig. 7e displayed a complete disappearance of the characteristic melting peak of CAN, a fact that agrees with the formation of drug solution in the LS powdered system, i.e. the drug was molecularly dispersed within the LS matrix [26].

Release rate studies from (SDs and ICs)

The results of drug release studies from SDs are in agreement with a study of Shaikh and Avachat [24] whose proved that the saturation solubility of CAN in distilled water enhances when preparing it as SDs with PEG 6000 using melt agglomeration, and this enhancement increases with increasing PEG 6000 concentration in the SD. Hence, we chose SD1:4 to prepare the tablets in order to compare them with IC tablets and LS systems.

Disintegration test

The rapid disintegration of the prepared tablet can be explained by using a super disintegrant (crospovidone), besides the presence of Avicel PH102, which exhibits some disintegrant properties [23]. SD1:4 exhibits a longer disintegration time compared to IC1:1 tablets, because PEG 6000 enhances the effectiveness of tablet binders and can prolong disintegration if present in concentrations >5% w/w [23].

Drug release study from tablets

The dissolution behavior can be studied using the classic dissolution rate equation of Noyes–Whitney [26]:

$$D_R = \frac{DA}{h}\left(C_s - C_t\right) \quad (5)$$

In the conditions of our experiment, diffusion coefficient (D) of the drug molecules and the thickness (h) of the static diffusion layer are expected to remain constant. C_s, the saturation concentration or solubility of CAN, and C_t, the actual concentration of the drug in the bulk solution, increases continuously as the drug diffuses to the dissolution medium. LS systems contain either solutions or dispersions, with very fine particle size (high surface area A), of the drug. Ideally, if the drug is completely dissolved in the LS systems, it should diffuse readily to the surrounding environment skipping the dissolution step and resulting in rapid release. In essence, after tablet disintegration, the LS primary particles suspended in the dissolving medium contain the drug in a state of molecular dispersion, whereas the marketed product is merely exposing micronized drug particles. In other words, in the case of LS tablets, the surface of drug available for dissolution is related to its specific molecular surface which by any means, is much greater than that of the CAN particles delivered by the marketed tablets. Significantly increased surface of the molecularly dispersed CAN in the LS tablets may be chiefly responsible for their observed higher and consistent drug dissolution rates [27]. Besides, the PEG 400 acts as a cosolvent with the dissolution medium at the diffusion layer surrounding the particles which increases the saturation solubility of the drug at the diffusion layer, therefore, increasing the concentration gradient ($C_s - C_t$).

The enhanced dissolution rates of SDs may be due to many factors such as decreased particle size of drug, specific form of drug in these SDs, in addition to increase in drug wettability and preventing of drug aggregation by the polymer [28]. Furthermore, PEG 6000 affected the crystallinity of the drug could be considered as an important factor in enhancement the dissolution rate. It is known that the amorphous drug presents the most ideal case for fast dissolution [29]. Moreover, PEG 6000 may form a concentrated diffusion layer into which the drug dissolves prior to its release into the aqueous medium [24]. The improvement of CAN dissolution profile in IC1:1 can be attributed to the local solubilization action of the carrier, operating in the microenvironment on the hydrodynamic layer surrounding the drug particles, which improve CAN wettability [30]. The results from the dissolution study were found to be in constance with that obtained from drug FT-IR and DSC studies. Table 6 shows the calculated difference factor (F_1) and similarity factor (F_2) of the prepared tablets compared to the marketed product. As we can see all tablet formulations shows a better dissolution profile compared to the marketed product.

CONCLUSION

The above studies conclude that the dissolution rate of CAN can be greatly enhanced by preparing it as LS systems using PEG 400 as a vehicle, or by SD tablet with PEG 6000 or by complexing it with HP-β-CD. In effect, the rate and extent of dissolution of CAN can be enhanced thereby improving its bioavailability. Hence, formulation of CAN into LS systems/SD/IC may be a promising tool as the dose of the drug may be decreased and hence side-effects may be minimized.

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