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Research Article

DEVELOPMENT AND *IN VITRO* EVALUATION OF SOLID DISPERSIONS OF CANDESARTAN CILEXETIL

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ABSTRACT

Objective: The main objective of the present study is the systematic development of solid dispersions of Candesartan cilexetil by solvent evaporation method to enhance the solubility and bioavailability.

Methods: In the present study, 18 formulations of SD were prepared with 1:1 and 1:3 ratios of drug: Carrier and with and without surfactant. There was a significant improvement in the rate of drug release from all 20 SD and the formulation (SD16) comprising Candesartan: Containing Soluplus (1:3 ratio of drug: Soluplus with 2% sodium lauryl sulfate as a surfactant) by a solvent evaporation process.

Results: Final optimized design SD16 contained maximum drug content of 99.08%. In *in vitro* dissolution studies, it shows greater dissolution rate, that is, 99.7±4.2% associated through additional designs and pure drug. The drug was compatible with all the excipients as per the Fourier transform infrared spectroscopy. From powder X-ray diffraction and by (scanning electron microscope) studies, it was evident that crystalline form of Candesartan has been converted into amorphous form within SD design.

Conclusion: From these studies, we can accomplish SD are one of the greatest favorable formulation for Candesartan cilexetil for enhancing the solubility and bioavailability of poorly water-soluble drugs in the effective group of hypertension and other cardiac problems.

Keywords: Candesartan cilexetil, Hypertension, Solid dispersions, Soluplus, Poloxamer, Kolliwax.

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INTRODUCTION

Candesartan is a common drug used for the treatment of hypertension and heart failure. Delivery of candesartan is difficult due to its low aqueous solubility, efflux through intestinal p-glycoprotein and vulnerability to enzymatic degradation in the small intestine [1]. Hence, various formulations are continuously researched and developed of which lipid-based systems are most widely accepted [2]. Low oral solubility and bioavailability are the major hurdles for designing delivery systems with improved pharmacokinetic profiles and therapeutic responses [3]. Drugs belonging to BCS Class II and IV have inspired formulators for the expansion of drug delivery technologies to overcome the effort in their solubilization by biochemical or mechanical alteration of the environment surrounding drug substance/physically altering macromolecular characteristics of aggregated drug particles [4].

To control hypertension Thiazide diuretics, angiotensin-converting enzyme inhibitors, β-blockers, calcium antagonists, and AT1 antagonists are employed mostly to prevent organ damage and reduce the mortality rate. However, most of these undertake extensive first-pass metabolism, frequent administration and have varied bioavailability [5]. The most possible method for increasing dissolution with the help of a water-soluble carrier is to reduce the particle size and thereby increase the surface area of absorption. Several approaches can be utilized to obtain solid dispersions (SD) that enhance solubility and bioavailability such as fusion, fusion dissolution, solvent removal, and spray drying [6]. The term SD refers to two different components, hydrophilic matrix, and hydrophobic drug. Hydrophilic carriers include povidone (polyvinylpyrrolidone [PVP]), polyethylene glycols (6000, 8000, etc.), and many more [7]. Nature of the solvent and the rate and temperature of evaporation are critical factors that can affect the final formulation [8]. This method is unique that thermal decay of drugs can be prevented as low temperature is required for the removal of the organic solvents [9].

The aim of this study is to design and evaluate various formulations of Candesartan SD prepared using different polymer ratios so as to increase the overall solubility and bioavailability of the final formulation.

MATERIALS AND METHODS

Materials

Candesartan cilexetil pure drug was gifted from Aurobindo Pharma Ltd, Hyderabad, India. Poloxamer 407 and PEG 8000 obtained from BASF, Mumbai. Kolliwax GMS was obtained from Signet Chemical Corp. Pvt. Ltd, Mumbai. Soluplus was gifted from BASF, Germany. PVP K-30 was gifted from Dow Chemicals, USA. All other chemicals used are of analytical grade.

Preliminary solubility studies of Candesartan cilexetil

Solubility measurements of Candesartan cilexetil performed according to a published method reported by Higuchi and Connors in 1965 [10]. Excess amount of Candesartan cilexetil existed added to 25 ml aqueous solution of water-soluble carriers such as PEG8000, Soluplus, Kolliwax GMS II, Poloxamer 407, and PVPK-30 screw-capped bottles. Samples are shaken for 24 h at room temperature. Subsequently, suspensions are filtered through Whatman filter paper no 1. Filtered solutions are diluted up to the mark with methanol. Diluted solutions of Candesartan cilexetil analyzed at UV 257 nm.

Preparation of Candesartan cilexetil SD by solvent evaporation method

The calculated amount of Candesartan cilexetil and the employed polymers (Soluplus, Kolliwax GMS, Poloxamer 407, PEG 8000, and PVPK-30) in different drug-polymer ratios (1:1 and 1:3) besides sodium lauryl sulfate (SLS) as surfactant (0 or 2%) (as shown in Table 1) are weighed and mixed together in a porcelain dish. 20 different formulations prepared by a solvent evaporation method. Drug and

Table 1: Composition of Candesartan cilexetil SD

Formulation no and ingredients	Candesartan (g)	PVP K30 (g)	Poloxamer (g)	Kolliwax GMS (g)	Soluplus (g)	PEG 8000	SLS g (%)	Methanol (mL)
SD 1	0.16	0.16	-	-	-	-	0	Qs
SD 2	0.16	0.16	-	-	-	-	2	Qs
SD 3	0.16	0.48	-	-	-	-	0	Qs
SD 4	0.16	0.48	-	-	-	-	2	Qs
SD 5	0.16	-	0.16	-	-	-	0	Qs
SD 6	0.16	-	0.16	-	-	-	2	Qs
SD 7	0.16	-	0.48	-	-	-	0	Qs
SD 8	0.16	-	0.48	-	-	-	2	Qs
SD 9	0.16	-	-	0.16	-	-	0	Qs
SD 10	0.16	-	-	0.16	-	-	2	Qs
SD 11	0.16	-	-	0.48	-	-	0	Qs
SD 12	0.16	-	-	0.48	-	-	2	Qs
SD 13	0.16	-	-	-	0.16	-	0	Qs
SD 14	0.16	-	-	-	0.16	-	2	Qs
SD 15	0.16	-	-	-	0.48	-	0	Qs
SD 16	0.16	-	-	-	0.48	-	2	Qs
SD 17	0.16	-	-	-	-	0.16	0	Qs
SD 18	0.16	-	-	-	-	0.16	2	Qs
SD 19	0.16	-	-	-	-	0.48	0	Qs
SD 20	0.16	-	-	-	-	0.48	2	Qs

SD: Solid dispersions, PVP: Polyvinylpyrrolidone, SLS: Sodium lauryl sulfate

polymer mixtures were dissolved in the least amount of methanol as a common solvent. The solvent was evaporated in an oven at temperature 50°C till complete evaporation. SD thus prepared were pulverized in a mortar and sieved. The fraction of powder that passed through 45 µm sieve was stored in a desiccator and used for further investigations.

Evaluation of Candesartan cilexetil SD

SD obtained from the above method were tested for their percentage practical yield, drug content, and *in vitro* drug release studies.

Percentage practical yield

Percentage of practical yield was calculated to know about percent yield or efficiency of the method so as to help in the selection of a suitable method of production [11].

Drug content

SD equivalent to 16 mg Candesartan cilexetil is weighed accurately and dissolved in 100 ml of methanol. Solution is filtered, diluted with a suitable solvent and drug content is analyzed at λ_{max} 257 nm against blank by UV spectrometer [12].

***In vitro* dissolution study of SD**

USP dissolution test type II apparatus (Electrolab TDT- 06 N, India) is used. Amount of samples equivalent to 16 mg drug was dispersed into a dissolution vessel containing 900 mL phosphate buffer pH 6.5 containing 0.75% Tween 20 at 37°C and stirred at 50 rpm. Samples are withdrawn periodically, filtered and replaced with fresh dissolution medium. After filtration through 0.45 µm microfilter, the concentration of Candesartan cilexetil is determined spectrophotometrically at λ_{max} 257 nm [13].

Characterization

Fourier transform infrared (FTIR) studies

Using Shimadzu FTIR-8700 spectrophotometer, potassium bromide disc method is employed. Pure drug, physical mixtures, and SD are studied. Powdered samples are intimately mixed with dry powdered potassium bromide. This mixture was then compressed into a transparent disc under high pressure using special dies. Disc is placed in IR spectrophotometer using a sample holder, and then the spectrum is recorded [14].

Powder X-ray diffraction (p-XRD)

X-ray powder diffraction patterns were recorded on an X-ray powder diffraction system (Shimadzu, Japan) using copper target, a voltage of 40 Kv and a current of 30 mA. The scanning was done over 2_ range of 5–60° [15].

Table 2: Preliminary solubility studies Candesartan cilexetil in different polymers

Physical mixture	Solubility (mg/ml)
Pure drug	0.417±0.04
Drug+urea	0.57±0.003
Drug+Kolliwax GMS	1.42±0.13
Drug+Aerosil 200	0.89±0.01
Drug+Avicel PH 102	0.99±0.04
Drug+Soluplus	1.69±0.05
Drug+PEG 8000	1.22±0.07
Drug+PVP K 30	1.31±0.11
Drug+Kleptose HPB	1.17±0.02
Drug+Poloxamer 407	1.51±0.12

Scanning electron microscope (SEM) studies

Surface morphology of layered sample was inspected using SEM (Hitachi, Japan). Small amount of powder was manually dispersed onto a carbon tab (double adhesive carbon coated tape) adhered to an aluminum stub. These sample stubs were coated with a thin layer (30Å) of gold by employing POLARON-E 3000 sputter coater. Samples are examined by SEM and photographed under various magnifications with direct data capture images onto a computer [16].

Stability studies

Systematized SD were placed inside sealed 40cc HDPE container with child-resistant cap under controlled temperature environment inside stability chamber (Thermo Lab, India) with a relative humidity of 75%±5% RH and temperature 40°C±2°C for stability studies. Samples were removed after 1, 2, and 3 months and evaluated for percentage drug content and *in vitro* dissolution studies and compared with those SDs tested immediately after preparation [17].

RESULTS AND DISCUSSION

Preliminary solubility studies Candesartan cilexetil

Preliminary solubility studies were carried out to select suitable water-soluble carriers for the preparation of SD. Pure drug solubility was found to be 0.417 mg/ml. From this study, drug and Soluplus in ratio of 1:1 shown highest drug solubility of about 1.69±0.05 mg/ml, almost 4-fold increase paralleled to that of pure drug. For all the water-soluble carriers used in preliminary solubility studies, Avicel PH 102, Colloidal Silicone dioxide (Aerosil 200), and urea have shown low solubility when compared with other carriers and are not included in the preparation of

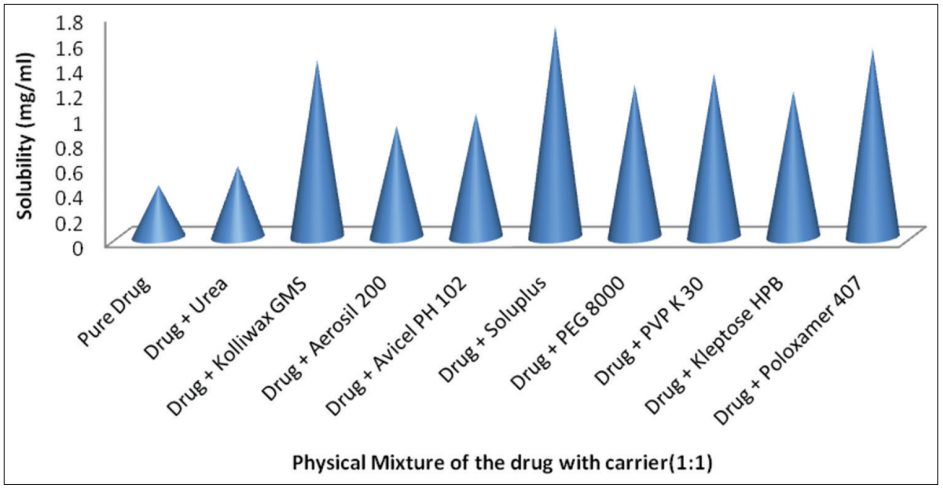

Fig. 1: Solubility studies of Candesartan cilexetil physical mixture

Fig. 2: Candesartan cilexetil solid dispersions

Candesartan cilexetil SD. The graphical representation solubility studies of Candesartan cilexetil physical mixtures are shown in Fig. 1 and Table 2.

Preparation of Candesartan cilexetil SD

Candesartan cilexetil SD were prepared and shown in Fig. 2.

Evaluation parameters

Solubility studies of Candesartan cilexetil SD

Different formulations of Candesartan cilexetil SD were prepared using solvent evaporation method with their respective carriers. After preparation, SD solubility analysis was carried out. Formulation (SD16) with Soluplus in the ratio of 1:3 and SLS showed the highest solubility, that is, 4.599±0.07 mg/ml, almost 11-fold compared to that pure drug (pure drug solubility is 0.417±0.04 mg/ml). Results were tabulated in Table 3 and the graphical representation is shown in Fig. 3.

Percent practical yield and drug content

Results of percent practical yield for all formulations of SD were found to be in the range of 83.88–99.28%; results are shown in Table 4. Maximum yield found to be 99.28% in formulation SD16. The drug content in prepared SD found to be in the range of 86.33–99.08%. Maximum percent drug content, that is, 99.08% found in formulation SD16.

***In vitro* dissolution studies**

Drug release data obtained for formulations SD1-SD20 are tabulated in Tables 5-7, respectively. They show a cumulative percent drug released as a function of time for all formulations. *In vitro* studies reveal that there

Table 3: Solubility studies of Candesartan cilexetil solid dispersions (SD) prepared by a solvent evaporation method

Formulation code	Solubility (mg/ml)*
Pure drug (Candesartan)	0.417±0.04
SD1	2.417±0.07
SD2	2.611±0.13
SD3	2.694±0.22
SD4	2.714±0.08
SD5	2.653±0.02
SD6	2.891±0.03
SD7	3.011±0.02
SD8	3.451±0.04
SD9	2.231±0.03
SD10	2.341±0.04
SD11	2.551±0.01
SD12	2.678±0.03
SD13	3.112±0.04
SD14	3.515±0.03
SD15	4.018±0.04
SD16	4.599±0.07
SD17	1.901±0.02
SD18	1.911±0.03
SD19	1.920±0.02
SD20	1.933±0.02

Table 4: Percent practical yield and drug content for Candesartan cilexetil SD

Formulation	% Practical yield	% Drug content
SD1	95.21±0.02	91.47±0.01
SD2	92.46±0.01	94.77±0.15
SD3	93.68±0.03	86.33±0.11
SD4	83.88±0.11	90.33±0.17
SD5	96.55±0.12	92.47±0.07
SD6	91.68±0.08	94.92±0.09
SD7	91.98±0.04	93.50±0.10
SD8	96.22±0.02	94.52±0.13
SD9	91.87±0.09	91.53±0.15
SD10	94.26±0.14	92.56±0.17
SD11	91.99±0.05	94.57±0.03
SD12	96.12±0.14	91.64±0.13
SD13	91.87±0.31	92.43±0.05
SD14	93.27±0.15	89.37±0.09
SD15	94.26±0.09	92.52±0.07
SD16	99.28±0.10	99.08±0.03
SD17	89.23±0.01	86.01±0.02
SD18	85.23±0.07	87.99±0.07
SD19	86.33±0.09	88.88±0.03
SD20	89.13±0.10	89.03±0.01

SD: Solid dispersions

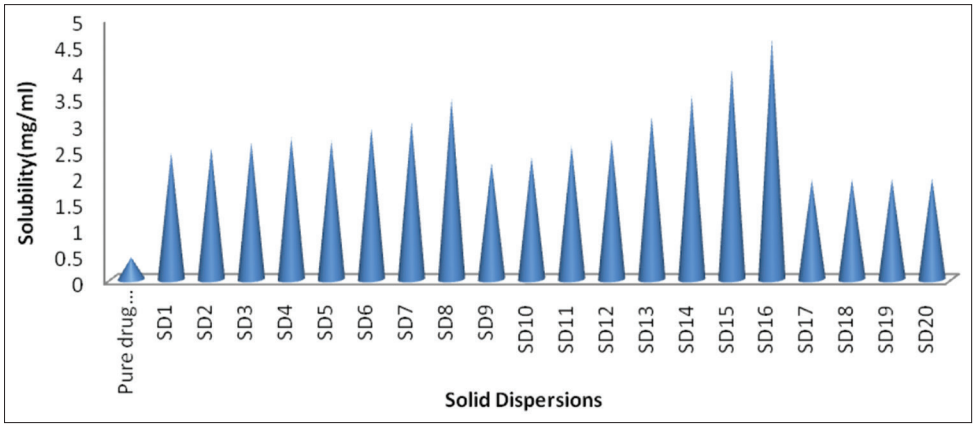

Fig. 3: Solubility studies of Candesartan cilexetil solid dispersion

Table 5: *In vitro* dissolution profile of pure drug and different formulations of Candesartan cilexetil SD1-SD8

Time (minutes)	Cumulative % drug release								
	Pure drug	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8
0	0	0	0	0	0	0	0	0	0
5	3.11±0.43	20.6±2.9	22.6±2.9	26.8±2.0	30.3±2.5	23.3±3.4	26.4±2.9	25.5±1.3	21.5±1.3
10	4.38±0.12	31.7±3.9	32.7±3.9	30.3±2.9	36.9±1.5	31.2±1.4	33.8±2.3	31.0±2.4	31.0±2.4
20	7.01±0.36	50.8±2.0	44.8±2.0	46.5±3.3	48.5±2.7	43.3±2.3	39.5±1.6	35.5±3.3	32.5±3.3
30	12.12±0.73	61.4±1.4	58.4±1.4	55.5±3.8	58.2±2.6	59.1±2.9	45.8±1.8	39.1±2.6	41.1±2.6
45	17.09±0.40	70.7±3.8	69.7±3.8	65.5±1.9	68.5±2.2	63.2±1.4	59.5±1.7	46.0±2.4	45.0±2.4
60	21.22±0.80	81.4±2.2	78.4±2.2	72.9±3.3	79.3±2.9	77.5±3.6	69.9±1.8	66.2±4.3	68.2±1.5
90	25.55±0.64	83.6±1.7	85.6±2.7	88.4±3.1	91.5±2.8	81.8±3.3	84.2±1.2	88.8±3.1	90.9±3.4

SD: Solid dispersions

Table 6: *In vitro* dissolution profile of different formulations of Candesartan cilexetil SD9-SD14

Time in min	Cumulative % drug release					
	SD9	SD10	SD11	SD12	SD13	SD14
0	0	0	0	0	0	0
5	26.6±2.9	25.2±3.7	26.6±2.9	23.6±2.9	26.6±2.9	23.4±2.9
10	36.7±3.9	32.6±1.9	41.7±3.9	33.7±3.9	36.7±3.9	39.8±2.3
20	58.8±2.0	44.6±2.5	53.8±2.0	48.8±2.0	49.8±2.0	51.5±1.6
30	63.4±1.4	56.8±0.55	65.4±1.4	63.4±1.35	58.4±1.4	61.8±1.8
45	77.7±0.8	68.5±0.13	73.7±3.7	72.7±3.6	67.7±3.8	69.5±1.7
60	81.5±2.2	79.9±2.5	83.5±2.9	84.4±2.2	77.4±2.2	79.9±1.8
90	83.22±1.7	84.1±3.8	86.6±1.7	88.8±1.7	89.6±2.7	91.3±1.2

SD: Solid dispersions

Table 7: *In vitro* dissolution profile of different formulations of Candesartan cilexetil SD15-SD20

Time in min	Cumulative % drug release					
	SD15	SD16	SD17	SD18	SD19	SD20
0	0	0	0	0	0	0
5	21.5±1.3	40.1±2.3	23.5±1.3	25.5±1.3	27.5±1.3	29.5±1.3
10	31.0±2.4	59.2±2.8	33.0±2.4	35.0±2.4	37.0±2.4	39.0±2.4
20	55.5±3.3	68.5±2.2	39.5±3.3	41.5±3.3	45.5±3.3	48.5±3.3
30	68.1±2.6	77.2±2.3	43.1±2.6	49.1±2.6	51.1±2.6	53.1±2.6
45	73.0±2.4	89.4±3.0	56.0±0.4	58.0±2.2	61.0±2.12	65.0±2.01
60	84.2±4.3	96.6±1.6	61.2±0.03	65.2±0.25	68.2±1.2	69.2±4.3
90	94.8±3.4	99.7±4.2	72.1±1.12	73.9±1.01	75.2±1.22	79.7±1.44

SD: Solid dispersions

is marked an increase in the dissolution rate of Candesartan cilexetil from all the SD when compared to pure Candesartan cilexetil itself. From the *in vitro* drug release profile, it can be seen that formulation SD16 containing Soluplus (1:3 ratio of drug: Soluplus with surfactant) shows higher dissolution rate, that is, 99.7±4.2% compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of the drug due to the hydrophilic carrier. The graphical representation of SD of SD1-SD8, SD9-SD14, and SD15-SD20 with the pure drug is depicted in Figs. 4-6, respectively.

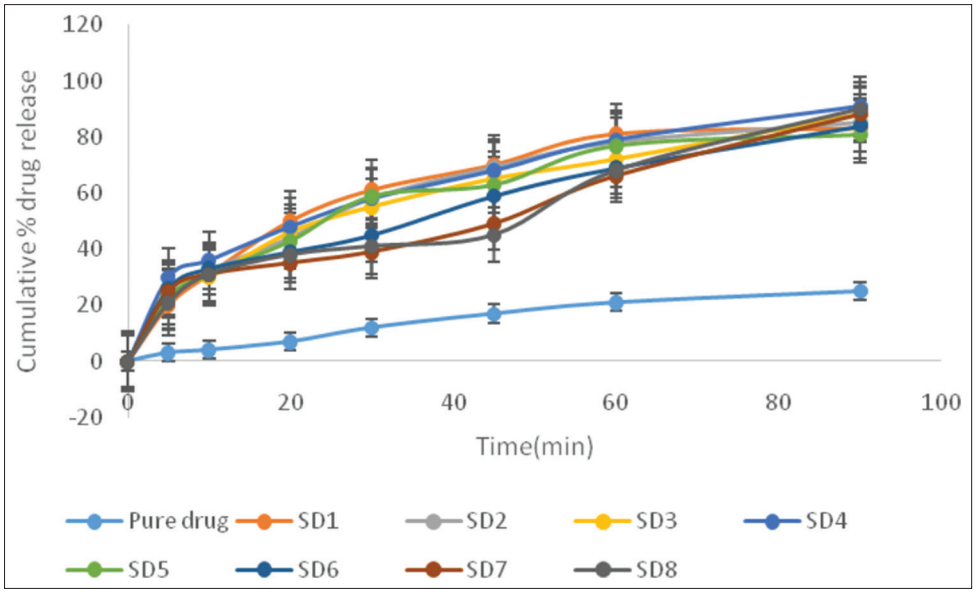

Fig. 4: *In vitro* dissolution profile of the pure drug and different formulations of Candesartan cilexetil solid dispersions (SD1-SD8)

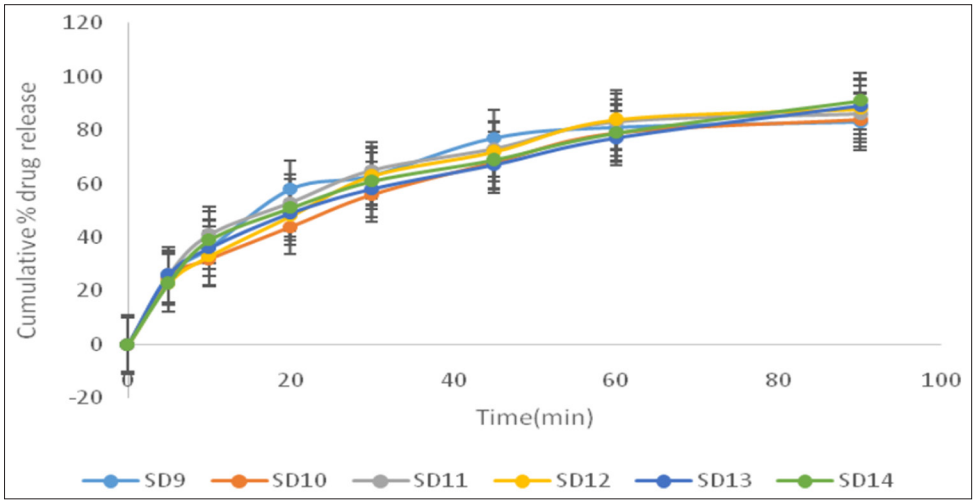

Fig. 5: *In vitro* dissolution profile of different formulations of Candesartan cilexetil solid dispersions (SD9-SD14)

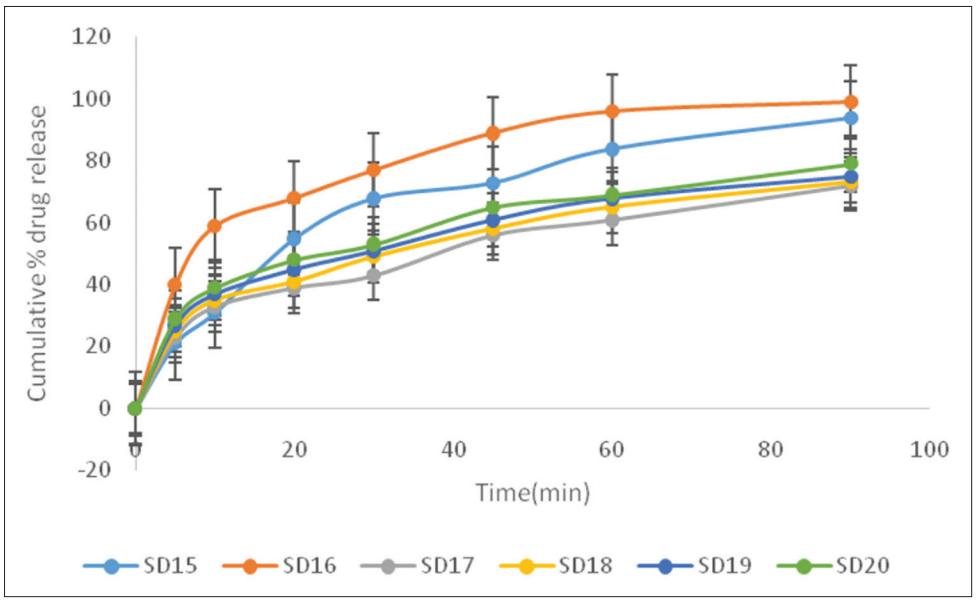

Fig. 6: *In vitro* dissolution profile of different formulations of Candesartan cilexetil solid dispersions (SD15-SD20)

Characterization

FTIR studies

FTIR studies pure drug Candesartan cilexetil, Soluplus, SLS, its physical mixtures and SD conducted (Figs. 7-11). FTIR spectra of Candesartan cilexetil showed characteristic peaks at 2932 cm^{-1} due to C-H slight bend, 1712 cm^{-1} due to C=O stretching, 1115 cm^{-1} due to CO stretching, 1275 cm^{-1} due to C-N stretching, and 3610 cm^{-1} due to N-H bend. IR spectra of physical mixture displayed superimposition Candesartan cilexetil and Soluplus peaks with decreased peak intensity. IR spectra optimized formulation of SD showed a peak corresponding to C-H Candesartan cilexetil shifted from 2932 cm^{-1} to 2865 cm^{1}, which suggests the presence of hydrogen bonding, resulting in an increase in solubility. Other peaks related to C=O, C-O, C-N, and N-H remained unchanged.

X-ray diffraction patterns

XRD studies for Candesartan cilexetil SD carried out to find out whether SD of various drug-polymer ratios are crystalline or amorphous. The presence of numerous distinct peaks in the XRD spectrum of pure Candesartan cilexetil indicates that Candesartan cilexetil present as a crystalline material (Fig. 12). On the other hand, the spectrum of optimized formulation SD16 SD characterized by complete absence of any diffraction peak, which is characteristic of an amorphous compound (Fig. 13). Enhancement in the dissolution rate of the drug from drug-Soluplus-SLS SD is ascribed to marked reduction in crystallinity of the drug.

SEM studies

SEM photographs for pure drug and optimized formulation SD16 are shown in Figs. 14 and 15, respectively. Drug crystals seemed to be smooth-surfaced, irregular in shape and size. In the case of SD, it is difficult to distinguish the presence of drug crystals. Drug surface in SD seems to be more porous in nature. SD appeared as uniform and homogeneously mixed mass with a wrinkled surface. Drug crystals appeared to be incorporated into particles of the polymers. SD looked

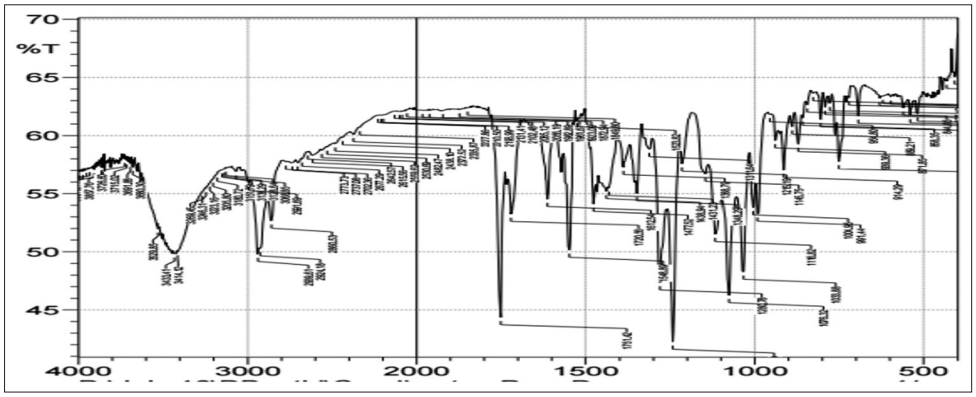

Fig. 7: Fourier transform infrared spectrum of Candesartan cilexetil pure drug

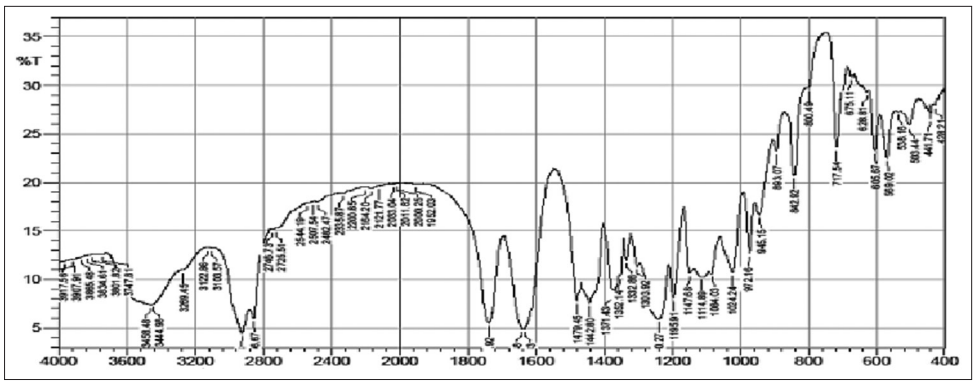

Fig. 8: Fourier transform infrared spectrum of Soluplus

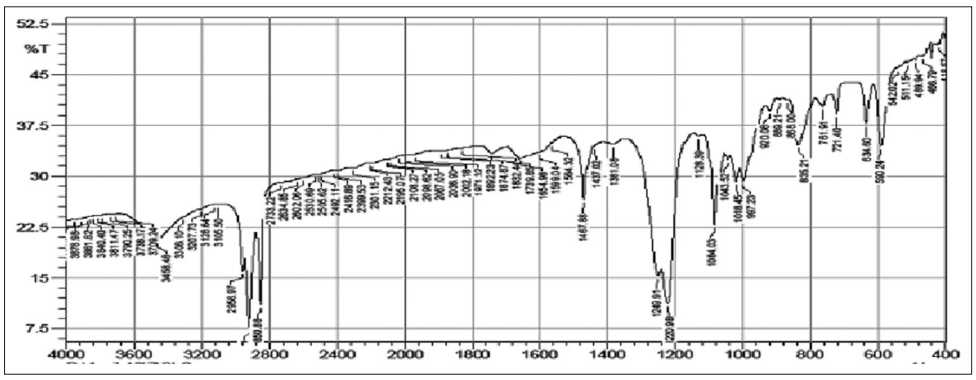

Fig. 9: Fourier transform infrared spectrum of sodium lauryl sulfate

like a matrix particle. Results could be attributed to dispersion of the drug in molten mass of polymer.

Stability studies

Optimized formulation (SD16) was selected for stability studies on the basis of high cumulative percent drug release. Stability studies are conducted for drug content and *in vitro* drug release studies for 3 months at accelerated stability conditions according to the ICH guidelines. The optimized formulation is stable during 3 months period. From these results, it is concluded that optimized formulation (SD16) is stable and retained its original properties with minor differences. The results are summarized in Table 8.

CONCLUSION

From solubility and *in vitro* studies, it can be revealed that there is marked increase in dissolution rate of Candesartan cilexetil from all SD when compared to pure Candesartan cilexetil itself. It can be seen that optimized formulation SD16 containing Soluplus (1:3 ratio of drug: Soluplus with surfactant) shows higher dissolution rate, that is, 99.7±4.2% when compared with other formulations. This may be attributed to the increase in drug wettability, conversion to amorphous form and solubilization of drug due to the hydrophilic carrier. FTIR results confirm the molecular binding of Candesartan cilexetil with Soluplus. DSC and XRD studies also confirm the molecular amalgamation of the drug in an amorphous state with the polymers. From these studies, we

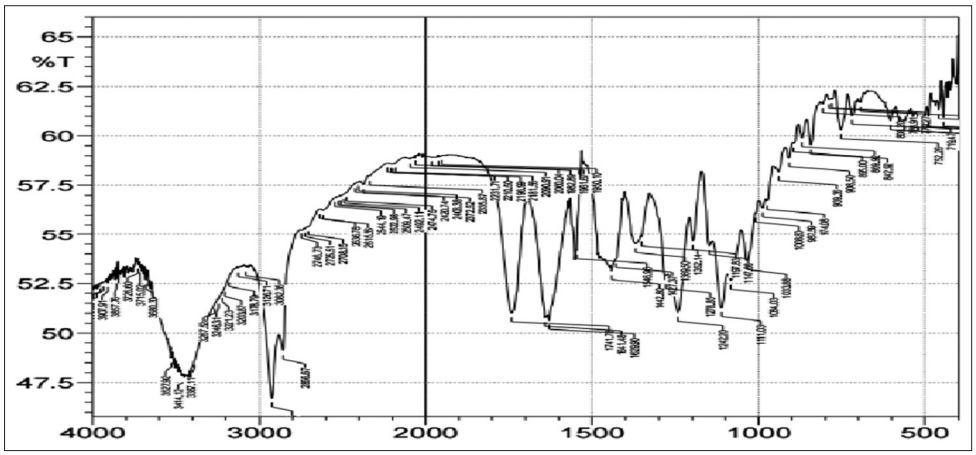

Fig. 10: Fourier transform infrared spectrum of Candesartan cilexetil physical mixture

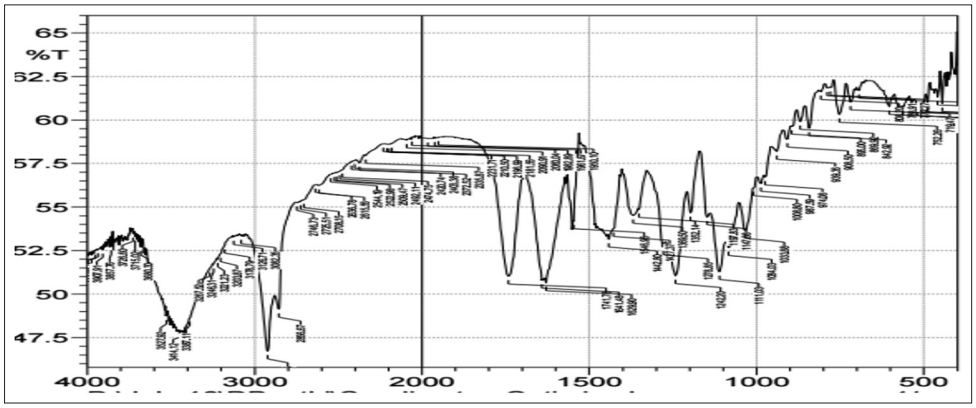

Fig. 11: Fourier transform infrared spectrum of Candesartan cilexetil optimized formulation SD16

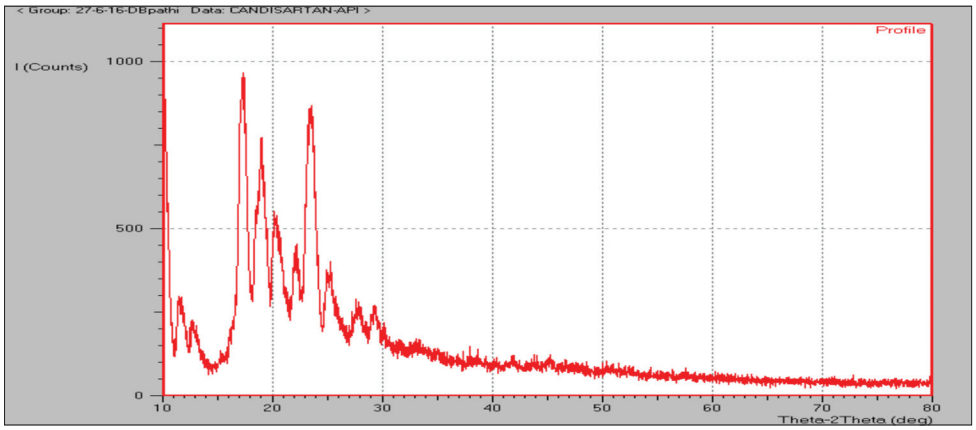

Fig. 12: X-ray diffractograms of Candesartan cilexetil pure drug

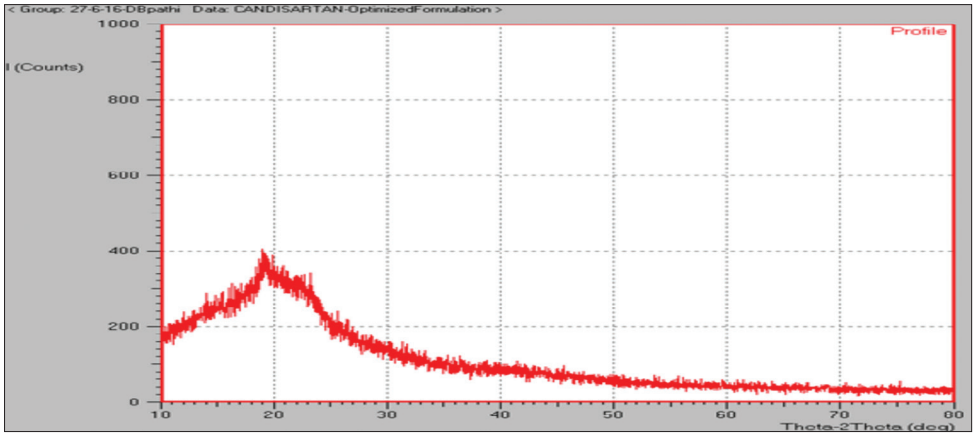

Fig. 13: X-ray diffractograms of Candesartan cilexetil optimized formulation SD16

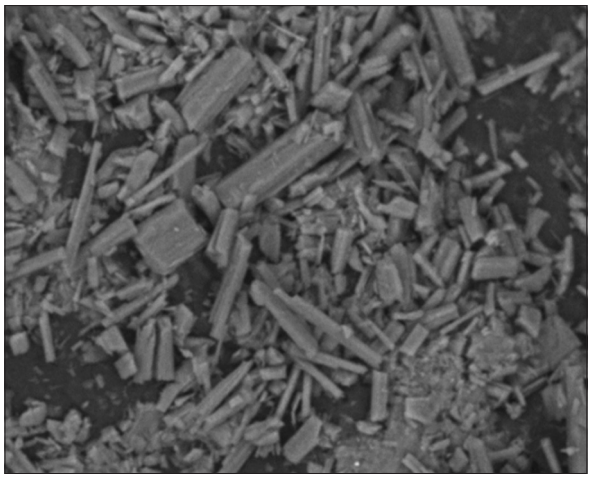

Fig. 14: Pure drug of Candesartan

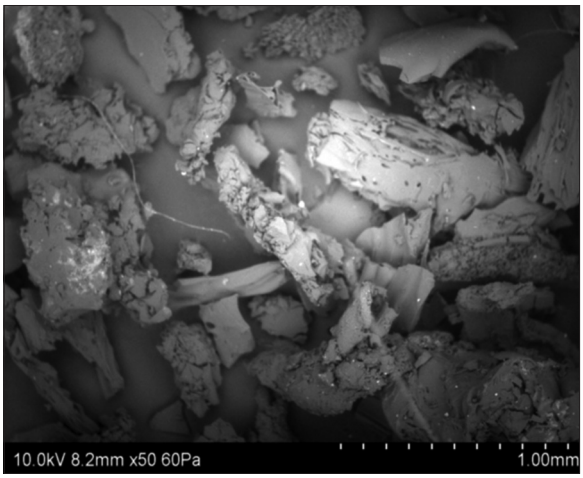

Fig. 15: Candesartan optimized formulation SD16S

can conclude that SD are one of the most favorable formulations for Candesartan cilexetil for the effective management of hypertension and other cardiac problems.

CONFLICTS OF INTEREST

None.

Table 8: Evaluation parameters of optimized formulation (SD16) stored at 40±2°C/75±5%rh

Retest time for optimized formulation (days)	% Drug content	*In vitro* drug release (%)
0 day	99.08	99.70
30 days	98.39	98.55
60 days	97.65	97.45
90 days	96.05	96.15

SD: Solid dispersions

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