Advances in Bioresearch
Adv. Biores., Special Issue (3) 2025: 01-14

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585. SPL3.25.114

Advances in Bioresearch

Design and Characterization of Candesartan Cilexetil Rapimelts

Angilicam Avinash[1]*, Srikrishna Theerdhala[2], Dommaraju R. Aruna Kumari[3], Himabindu Peddapalli[1]
[1] Department of Pharmaceutics, School of Pharmacy, Anurag University, Hyderabad, Telangana, India.
[2]Department of Pharmaceutics, Swathi College of Pharmacy, Nellore, Andhra Pradesh, India
[3]Department of Pharmaceutics, Seven Hills College of Pharmacy, Tirupati, Andhra Pradesh, India.
Corresponding Author Email: avinash.angilicam3@gmail.com

ABSTRACT
Present research work was designed to improve the solubility of candesartan cilexetil (CC) by surface solid dispersion technique and to develop the CC rapimelts. CC is an anti-hypertensive drug which belongs to BCS Class II having low solubility (5µg/ml) and therefore low oral bioavailability (15%). In the present study, SSDs of CC with water insoluble carriers like aerosil 200, potato starch and sodium starch glycolate were prepared by a co-evaporation method in the weight ratios of 1:2, 1:4 and 1:6 and the optimized surface solid dispersion (SSDs) was oppressed in the development of rapimelts. SSDs were characterized by differential scanning calorimetry (DSC), powder x-ray diffractometry (PXRD), scanning electron microscopy (SEM) and infrared spectroscopy (IR) and evaluated for drug content and in vitro dissolution studies.The results revealed that the dissolution of SSG/CC SSDs was improved greatly at SSG/CC ratios of over 6/1 when compared with that of remaining ratios of SSG which shows 90.58% of drug release within 60 minutes. The above optimized SSDs were formulated as rapimeltsby direct compression using superdisintegrants like crospovidone (CP), (R1-R3), croscarmellose sodium (CCS), (R4-R6) andco-processed superdisintegrants (R7-R9).CC rapimelts were evaluated for pre-compression and post compression parameters. Amongst the formulations prepared (R1-R9), R9 was found to be effective formulation comprising of co-processed superdisintegrants of CP and CCS in weight ratio of 1:3 shows the drug release of 98.17% within 15min. The infrared spectroscopy suggests that there was no chemical interaction between candesartan cilexetil and polymers.
Keywords*: Candesartan cilexetil, Co-processing technique, Surface solid dispersion, Superdisintegrants, Rapimelts*

Received 09.04.2025 Revised 21.05.2025 Accepted 20.06.2025

How to cite this article:
Angilicam A, Srikrishna T, Dommaraju R. A K, Himabindu P. Design and Characterization of Candesartan Cilexetil Rapimelts. Adv. Biores. Special Issue [3] 2025. 01-14

INTRODUCTION

Solubility is a significant physicochemical factor affecting absorption of drug and its therapeutic efficiency (1). Formulation development would lead to be failure if drug having poor aqueous solubility. The low dissolution rate and low solubility of drug substances in water in aqueous GIT fluid frequently leads to inadequate bioavailability (2,3). The effort to improve dissolution of poorly and practically insoluble drugs remains one of the most challenging tasks in drug development (4). Candesartan cilexetil (CC) is a newer class of antihypertensive drug comes under angiotensin II receptor antagonist (5). Clinical trials indicate that CC is effective and safe in the treatment of hypertension (6). CC is safe under the dosages of 4 to 32 mg, with these dosages, systolic blood pressure is reduced by 8-12 mmHg and diastolic pressure is reduced by 4-8 mmHg. One of the major problems with it is its low solubility in biological fluids, which results into poor bioavailability after oral administration (15%) and delayed onset of action. It also shows high first pass effect which further reduces the oral bioavailability (7). Surface solid dispersion technique has been used to increase the solubility, dissolution and subsequently the bioavailability of much poorly water soluble drugs (8). The surface solid dispersion (SSD) technique has been introduced with newer advantages in development of dissolution characteristics of poorly soluble drugs. The method has successfully overcome some common limitations of SD like tackiness and difficulty in handling (9,10). The carriers used in SSD are generally water insoluble, porous materials and hydrophilic in nature. In this technique, drug particles are deposited on the surface of the inert carrier leading to reduction in particle size of the drug and thereby enhanced dissolution. The release of drug from the carrier material depends

on hydrophilic nature, particle size, porosity and surface area of the carrier (11). Larger the effective surface area available for adsorption of the drug, better the release rate (12,13). The tablet is the most commonly used dosage form now-a-days because of its convenience in terms of self-administration, compactness and ease in manufacturing. But, geriatric, pediatric and psychiatric patient's experiences difficulty in swallowing conventional tablets, which leads to reduced patient compliance. To overcome these problems, researchers have developed advanced drug delivery system known as rapimelts/ fast dissolving tablets (FDTs). Fast dissolving tablets are also called as dispersible tablets, fast disintegrating tablets, orally disintegrating tablets, quick disintegrating tablets, mouth dissolving tablets, rapid dissolving tablets, porous tablets, quick melt tablets and rapid melt tablets. Patients with persistent vomiting while travelling or those who have little or no access to water are suitable candidates for FDT (14,15). The formulation is more helpful for the bed-ridden people and patients who have the swallowing difficult. The advantages of FDTs is to improve patient's compliance, quicker onset of action, enhanced bioavailability, good stability and when compared to conventional tablet the amount of drug that is subjected to first pass effect is reduced in rapimelts and which make these tablets popular as a dosage form of choice in the present market. Mouth dissolving tablets are formulated mainly by two techniques first use of super disintegrants like cross carmellose sodium, sodium starch glycolate and cross povidone. Another method is enlarging pore structure of the tablets by freeze drying and vacuum-drying. The bioavailability of some drugs may be increased due to absorption of drugs in oral cavity and also due to pre-gastric absorption of saliva containing dispersed drugs that pass down in to the stomach (16). Candesartan cilexetil is the model drug which is used in the treatment of the hypertension. The basic approach in the development of the rapimelts is by using co-processed super disintegrants. Cross povidone and croscarmellose sodium are the super disintegrants used in this formulation. Co-processed super disintegrants were prepared solvent evaporation method (17). The present investigation deals with the development of an effective and stable rapimelts of candesartan cilexetil having adequate hardness, rapid disintegration time and quicker action (18).

MATERIAL AND METHODS

Candesartan cilexetil (Strides Arcolab Limited, Bangalore), SSG (HiMedia Pvt. Ltd. Mumbai), Potato starch (Central drug house, New Delhi), Aerosil 200 (HiMedia Pvt. Ltd. Mumbai), Methanol (HiMedia Pvt. Ltd. Mumbai), CCS, MCC, Citric acid, Magnesium stearate (Sd fine chemicals Ltd., Mumbai), Crospovidone (Sri Krishna pharmaceuticals, Hyd.), Mannitol, Potassium dihydrogen phosphate, di-sodium hydrogen phosphate, sodium chloride (Merck Pvt. Ltd., Mumbai.) and Talc (Otto chemicals, Mumbai.).

Preparation of candesartan cilexetil surface solid dispersions

SSDs of candesartan cilexetil with a hydrophilic carrier were prepared in different ratios of drug–carrier. The coevaporation method was used for the preparation of SSD in the present study. In this method, 0.5 g of candesartan cilexetil was accurately weighed and dissolved in a minimum amount of methanol in which hydrophilic carrier was suspended. The solvent was evaporated using a water bath at 45^{0}C.The obtained solid was ground, sieved through a sieve no. 60 and store in air tight containers (19). The formula was shown in Table 1.

Table 1: Composition of different formulations of surface solid dispersions

Ingredients	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Candesartan cilexetil (gms)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aerosil (gms)	1	2	3	---	---	---	---	---	---
Potato starch (gms)	---	---	---	1	2	3	---	---	---
SSG (gms)	---	---	---	---	---	---	1	2	3
Solvent (methanol) (ml)	10	10	10	10	10	10	10	10	10

Evaluation of candesartan cilexetil surface solid dispersions

Percentage yield

Percentage yield is calculated to know about percent yield or efficiency of the method and thus it helps in selection of appropriate method of production. The final weights of the prepared surface solid dispersions were taken and percentage yield was calculated by using the given formula (20). The results were shown in Table 2.

Table 2: % practical yield and drug content of CC SSDs

Formulation code	Formulation	% Yield	% Drug content
F1	Candesartan: aerosil (1:2)	89.33	90.12
F2	Candesartan: aerosil (1:4)	94.4	87.98
F3	Candesartan: aerosil (1:6)	94	89.31
F4	Candesartan: Potato starch (1:2)	97.33	93.05
F5	Candesartan: Potato starch (1:4)	96.4	90.25
F6	Candesartan: Potato starch (1:6)	92.28	91.58
F7	Candesartan: SSG (1:2)	93	93.19
F8	Candesartan: SSG (1:4)	92.66	92.79
F9	Candesartan: SSG (1:6)	94.75	94.12

$$\%\text{yield} = \frac{\text{Practical yield}}{\text{Theoretical yield}} \times 100$$

Drug content

Equivalent weight of prepared surface solid dispersions containing 10 mg drug were taken and transferred into 10 ml methanol. Then take 1 ml from above solution and diluted up to 10 ml with phosphate buffer p^H 6.8 and repeat the same again with 1 ml from above solution. The solutions obtained were filtered through a 0.45µ membrane filter and diluted accordingly. The absorbance of the above serially diluted solutions was measured at 224 nm. Percentage of drug content was calculated by using the given formula. The results were shown in Table 2.

$$\%\ \text{Drug content} = \frac{\text{Observed value}}{\text{Actual value}} \times 100$$

***In vitro* dissolution studies**

In vitro dissolution studies of pure candesartan cilexetil and surface solid dispersions were conducted with the USP type II apparatus (paddle type). The dissolution studies were performed using 900 ml phosphate buffer of pH 6.8 as dissolution medium at 37±0.5°C with 50 rpm speed. Samples of each preparation equivalent to 10 mg of drug were added into the dissolution medium. The sample of 4 ml aliquots were withdrawn periodically (15, 30, 45 and 60 min) and filtered through 0.45µ membrane filter. The withdrawn sample was replaced every time with same quantity of fresh dissolution medium. The filtered solutions were diluted suitably and the samples were analyzed for their drug content by using UV spectrophotometer at wavelength of 224 nm. Percentage of drug dissolved at various time intervals was calculated by plotting time on X- axis against percent cumulative drug release on Y-axis. The results were shown in Table 3 and Figure 1.

Table 3: Comparative dissolution data surface solid dispersion of CC

Time (min)	% Cumulative drug release (mean± S.D.)									
	Pure drug	CC : Aerosil			CC : Potato starch			CC : SSG		
		F1	F2	F3	F4	F5	F6	F7	F8	F9
15	3.86±0.45	30.59±0.16	35.64±0.60	36.82±0.21	24.84±0.13	28.11±0.96	29.3±0.28	29.3±0.11	30.29±0.45	30.59±0.16
30	14.05±0.17	41.67±0.51	43.75±0.30	52.47±0.79	43.75±0.75	48.8±0.11	55.73±0.79	45.54±0.34	52.47±0.34	65.04±0.46
45	24.84±0.45	52.47±0.60	58.11±0.12	69.3±0.45	56.62±0.55	62.66±0.15	71.67±0.15	58.11±0.62	65.63±0.45	74.34±0.69
60	33.56±0.17	62.66±0.62	72.27±0.86	84.24±0.13	69.3±0.17	79.49±0.16	87.21±0.51	71.67±0.79	81.27±0.60	90.58±0.16

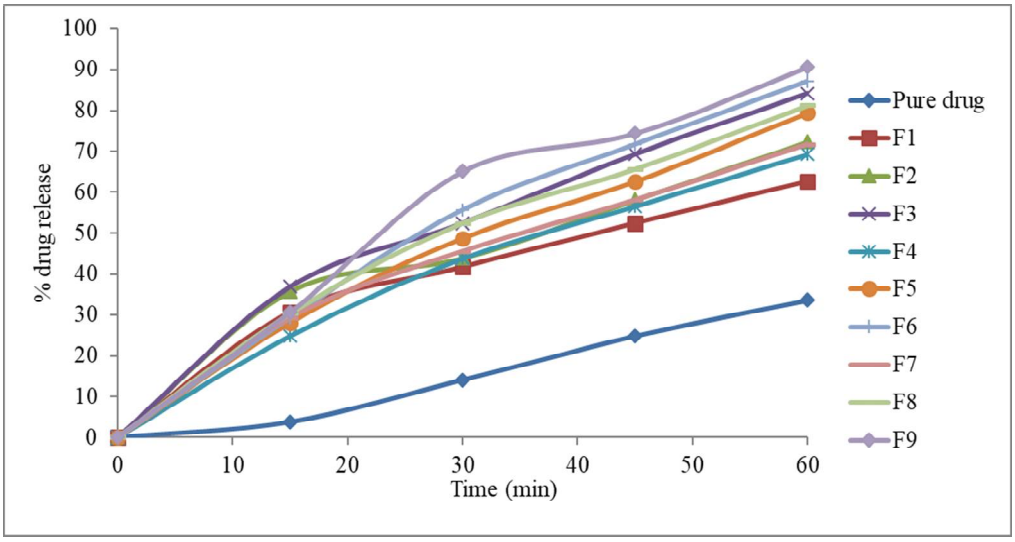


Figure 1: Dissolution profile of candesartan cilexetil surface solid dispersions

Characterization of candesartan cilexetil surface solid dispersions

Drug polymer interaction (FTIR) Study

IR spectroscopy was performed on Fourier transformed infrared spectrophotometer (840, Shimadzu, Japan). The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr - press and the spectra were scanned in the wave number range of 4000 - 500 cm^{-1} (21–24). The results were shown in Table 4.

Table 4: FT-IR interpretations of pure drug and excipients

Functional group	Characteristic peaks	Observed peaks			
		Candesartan cilexetil (CC)	CC : Aerosil 200	CC : SSG	CC : Potato starch
C-H (Aromatic bending)	680-860 cm^{-1}	748.42 cm^{-1}	748.42 cm^{-1}	752.28 cm^{-1}	748.42 cm^{-1}
C-N (stretching)	1020-1250 cm^{-1}	1033.90 cm^{-1}	1030.04 cm^{-1}	1076.34 cm^{-1}	1033.90 cm^{-1}
C-O-C (stretching)	1050-1300 cm^{-1}	1242.22 cm^{-1}	1242.22 cm^{-1}	1280.80 cm^{-1}	1157.35 cm^{-1}
N-H (bending)	1580-1650 cm^{-1}	1612.58 cm^{-1}	1612.58 cm^{-1}	1612.58 cm^{-1}	1612.58 cm^{-1}
C=O (stretching)	1690- 1760cm^{-1}	1716.74 cm^{-1}	1755.32 cm^{-1}	1755.32 cm^{-1}	1716.74 cm^{-1}
C-H (stretching)	2850-3000 cm^{-1}	2939.67 cm^{-1}	2943.53 cm^{-1}	2939.67 cm^{-1}	2939.67 cm^{-1}

Scanning Electron Microscopy

The shape and surface morphology of the surface solid dispersions was studied by using scanning electron microscope. Surface solid dispersions were mounted directly onto the SEM sample stub using double-sided sticking tape and coated with gold film of thickness 200 nm under reduced pressure (0.001 mm of Hg). The surface solid dispersions were viewed at an accelerating voltage of 10KV (25,26). The results were shown in Figure 2.

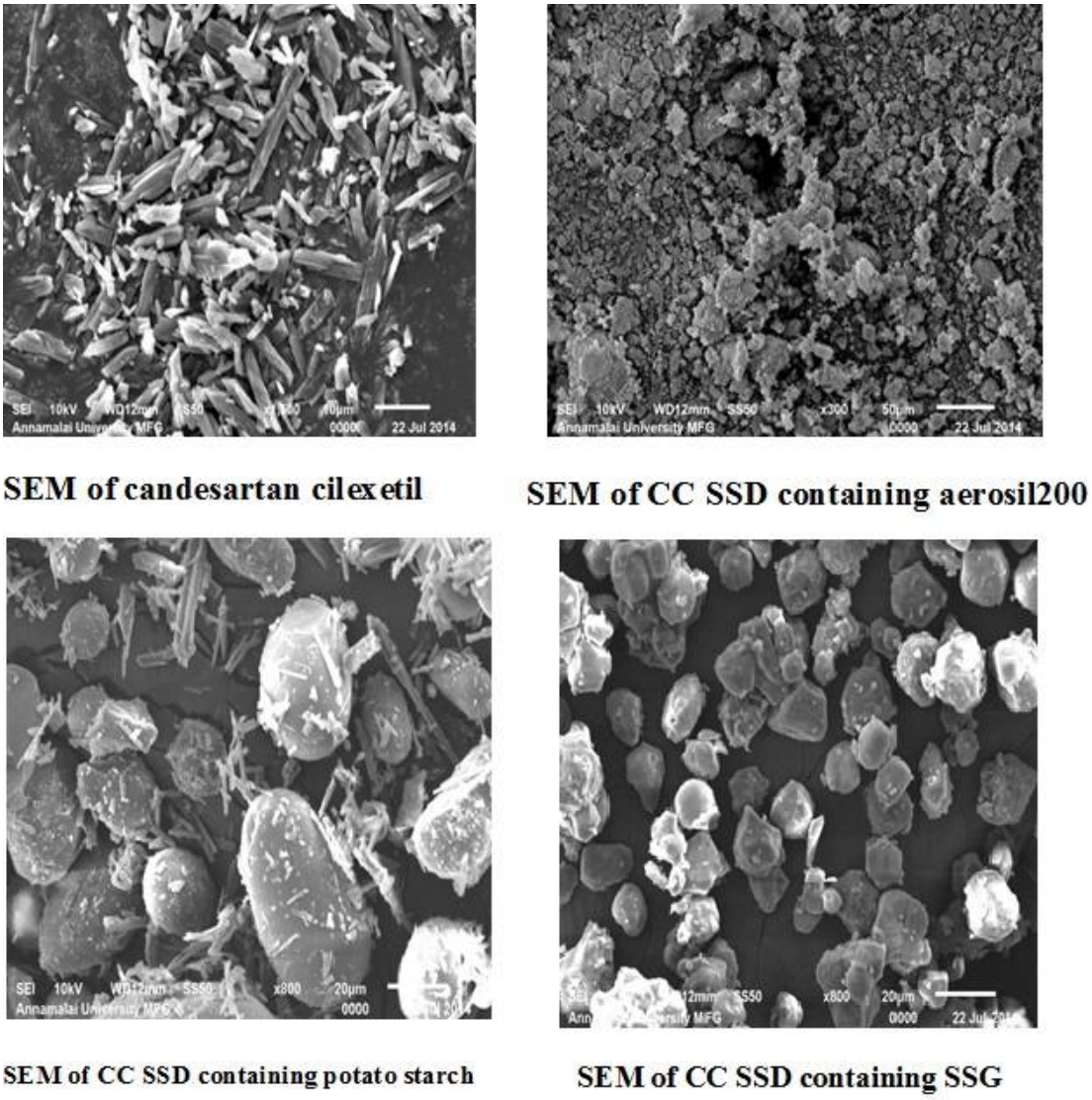


Figure 2: SEM of pure drug candesartan cilexetil and its formulations with aerosil 200 (F1-F3), potato starch (F4-F6) and SSG (F7-F9)

Differential Scanning Calorimetry

Thermal characteristics of drug and drug excipients mixture were studied using a differential scanning calorimeter to ascertain that the drug is in pure form and there is no chemical interaction between the drug and the excipients during preparation and storage. DSC measurements were performed on a Mettler-Toledo 812 instrument at a heating rate of 5°C/min, starting from 40 to 320°C (27). The results were shown in Figure 3.

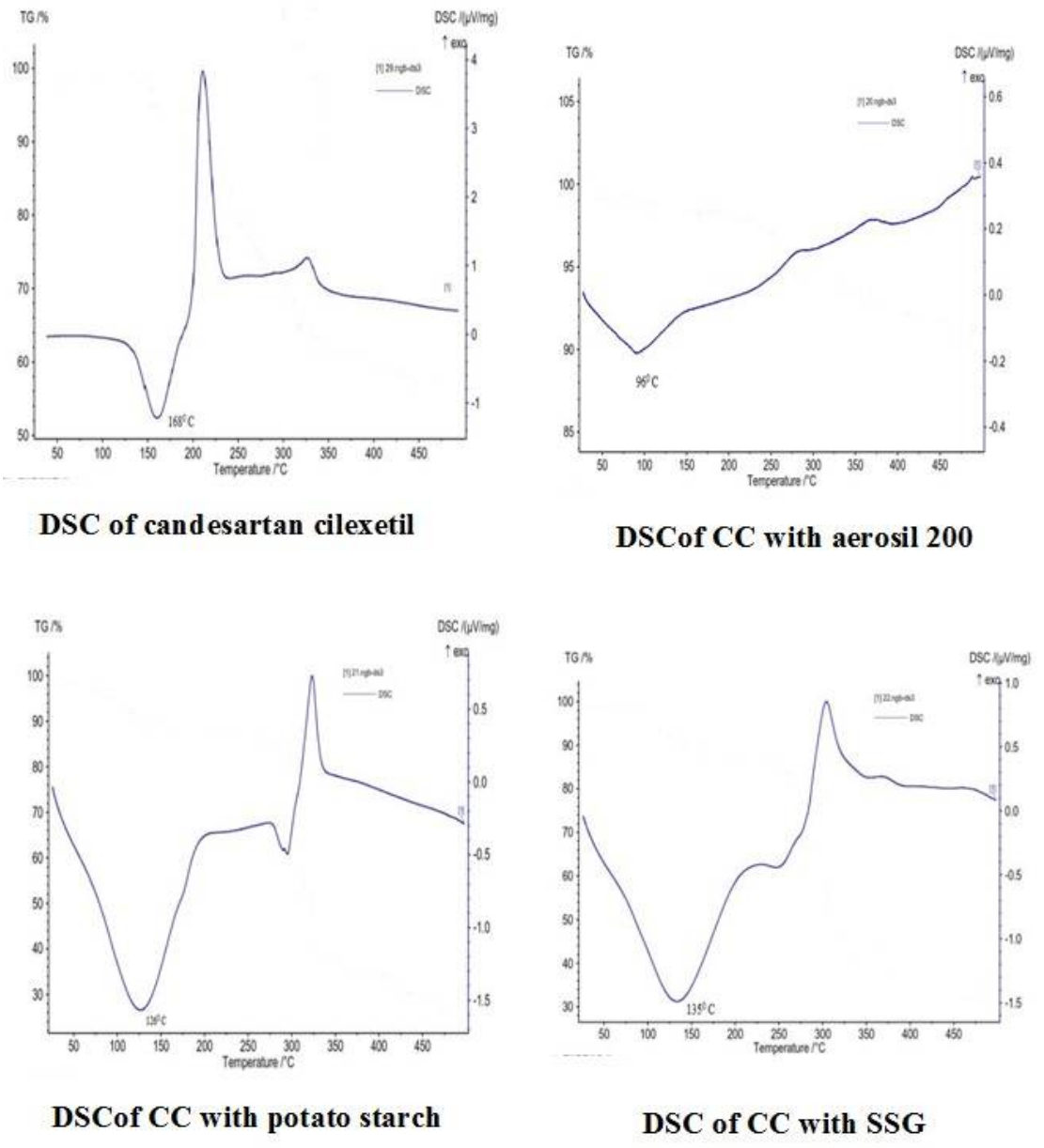
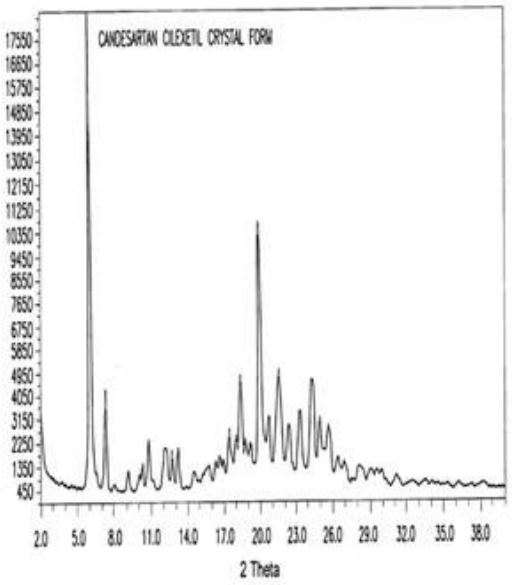


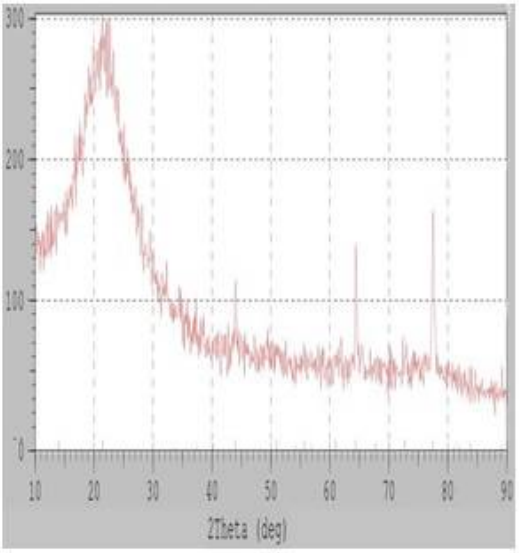
Figure 3: DSC of pure drug candesartan cilexetil and its formulations with aerosil200 (F1-F3), potato starch (F4-F6) and SSG (F7-F9)

X-ray diffractometry (XRD)

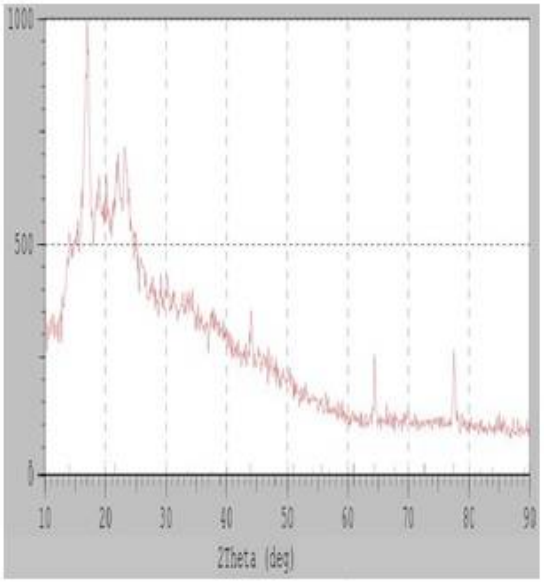
In order to determine the physical state of the drug before and after surface solid dispersions preparations, the XRD patterns of the pure drug and the formulations were investigated using an X-pert pro and Pro-Anac diffractometer. The samples were irradiated with monochromatized CuKα radiation, and the scanning range (2θ) was from 2–50°. The voltage and current were set to 35kv and 35mA, respectively. X-ray patterns were analyzed using an X-pert data collector and X-pert data viewer V-2.0 software (21,28–30). The results were shown in Figure 4.



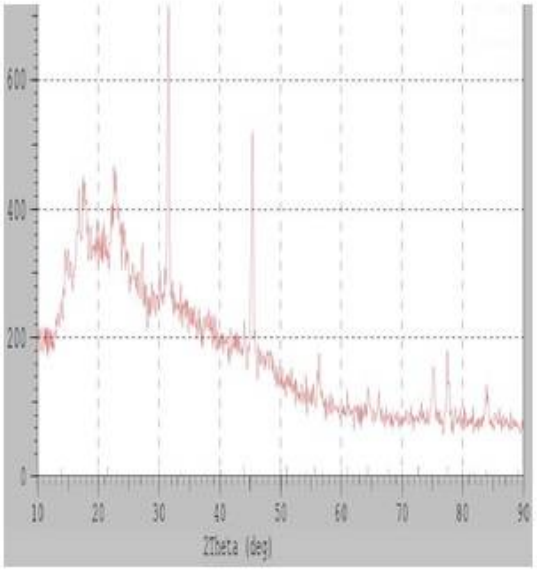
XRD of candesartan cilexetil



XRD of CC with aerosil 200



XRD of CC with potato starch



XRD of CC with SSG

Figure 4: XRD of pure drug candesartan cilexetil and its formulations with aerosol 200 (F1-F3), potato starch (F4-F6) and SSG (F7-F9)

Co - processing of superdisintegrants

Co-processed superdisintegrants were prepared by solvent evaporation method. A blend of crospovidone and croscarmellose sodium in the ratio of 1:3 was taken in a beaker and 10 ml of ethanol was added to it. The contents of the beaker were mixed thoroughly and stirring was continued till most of ethanol was evaporated. The wet coherent mass was granulated through # 44 mesh sieve. The wet powder was dried in a hot air oven at 60º C for 20 minutes. The dried granules were sifted through # 44 mesh sieve (17).

Preparation of candesartan cilexetil rapimelts

Candesartan cilexetil rapimelts were prepared by direct compression method using candesartan cilexetil optimized SSD.The amount of complex equivalent to 8 mg of drug per tablet were taken and mixed with directly compressible diluents and co-processed superdisintegrants in a mortar with the help of pestle. The blend was then compressed using 8 mm round faced punch by using tablet punching machine (31). The total weight of tablet was 200 mg. The formula was shown in Table 5.

Table 5: Preparation of candesartan cilexetil rapimelts

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
SSD complex	Equivalent to 8 mg of CC	Equivalent to 8 mg of CC	Equivalent to 8 mg of CC	Equivalent to 8 mg of CC	Equivalent to 8 mg of CC	Equivalent to 8 mg of CC	Equivalent to 8 mg of CC	Equivalent to 8 mg of CC	Equivalent to 8 mg of CC
Crospovidone	2.5	5	10	__	__	__	__	__	__
CCS	__	__	__	2.5	5	10	__	__	__
Co-processed superdisintegrants	__	__	__	__	__	__	2.5	5	10
Mannitol	94.05	91.55	86.55	94.05	91.55	86.55	94.05	91.55	86.55
MCC	20	20	20	20	20	20	20	20	20
Camphor	20	20	20	20	20	20	20	20	20
Citric acid	3	3	3	3	3	3	3	3	3
Aerosil 200	2	2	2	2	2	2	2	2	2
Mg. Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200	200	200

*8 mg of candesartan cilexetil ≈ 54.45 mg of SSD complex

Pre compression studies of Rapimelts

The powder blend was subjected for the following studies (32).

- Angle of repose
- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio

Angle of repose

The angle of repose of powder material was determined by the funnel method. Accurately weighed powder materials were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the tip of the heap of the powders. The powders were allowed to pass through the funnel freely onto the surface. The diameter and height of the powder cone was measured and angle of repose was calculated by using the given formula. The results were shown in Table 6.

$$\tan\theta = \frac{h}{r}$$

Where,

h = height of the powder cone

r = radius of the powder cone

Table 6: Physical parameters of powder blend

Formulation code	Bulk density (gm/ml) ± S.D.	Tapped density (gm/ml) ± S.D.	Carr's index (%) ± S.D.	Hausner's ratio ± S.D.	Angle of repose (º) ± S.D.
R1	0.461±0.003	0..545±0.004	15.34±1.27	1.181±0.017	27.58±0.74
R2	0.463±0.003	0.544±0.004	14.98±1.10	1.176±0.015	27.10±0.47
R3	0.435±0.002	0.521±0.004	16.42±0.09	1.196±0.001	27.13±0.99
R4	0.417±0.002	0.508±0.003	17.77±0.01	1.216±0.001	27.3±0.74
R5	0.426±0.002	0.510±0.003	16.33±0.56	1.193±0.005	26.66±0.18
R6	0.437±0.002	0.523±0.004	16.47±0.09	1.197±0.001	26.06±0.42
R7	0.419±0.002	0.510±0.003	17.77±0.01	1.216±0.001	27.40±0.73
R8	0.428±0.002	0.510±0.003	16.00±0.99	1.186±0.015	28.68±0.94
R9	0.432±0.002	0.516±0.004	16.25±0.20	1.193±0.002	27.97±0.74

Bulk density and tapped density

A quantity of 4gms of powder material from each formula was taken into a 10 ml measuring cylinder. After the initial volume was noted, the cylinder was tapped continuously until no further change in volume was observed. Then bulk density (BD) and tapped density (TD) were calculated by using the formula given below. The results were shown in Table 6.

$$BD = \frac{\text{Weight of the powder}}{\text{Initial volume}}$$

$$TD = \frac{\text{Weight of the powder}}{\text{Tapped volume}}$$

Carr's index

The Compressibility of the powder blend was determined by Carr's compressibility index. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is a simple test to evaluate the bulk density and tapped density of a powder and the rate at which it is packed. The formula for Carr's Index is given below. The results were shown in Table 6.

$$\text{Carr's index } (\%) = \frac{TD - BD}{TD} \times 100$$

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by using the following formula. The results were shown in Table 6.

$$\text{Hausner's ratio} = \frac{TD}{BD}$$

Post compression studies of Rapimelts

Thickness

Tablet size can be measured using digital vernier calipers (33). 3 tablets were taken and their thickness was measured and the average thickness for each tablet was calculated. The results were shown in Table 7.

Table 7: Physical parameters of candesartan cilexetil rapimelts

Formulation code	Hardness (Kg/cm^2) ± S.D.	Thickness (mm) ± S.D.	% Friability ± S.D.	% Weight variation± S.D.
R1	4.6±0.23	3.78±0.09	0.54±0.10	1.88±2.20
R2	4.6±0.57	3.45±0.05	0.97±0.02	1.78±2.10
R3	4.7±0.25	3.26±0.17	0.73±0.30	1.89±2.23
R4	5.1±0.76	2.85±0.01	0.80±0.21	3.14±2.53
R5	5.3±0.28	2.79±0.16	0.65±0.18	2.82±2.45
R6	4.6±0.28	3.79±0.03	0.72±0.14	2.82±2.45
R7	4.5±0.45	3.77±0.03	0.53±0.03	2.56±4.68
R8	4.6±0.28	3.69±0.17	0.54±0.10	2.49±1.97
R9	4.5±0.50	3.73±0.07	0.45±0.36	2.44±0.52

Hardness

It is the force essential to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because too much crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using monsanto hardness tester. The results were shown in Table 7.

Friability test

Friability of the tablets was determined using Roche friability. This instrument subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. Tablets that lose less than 1% of their weight are acceptable as IP. The results were shown in Table 7.

$$\%\text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Weight variation

The weight variation test is done by weighing 20 tablets individually, calculating average weight and comparing the individual tablet weights to the average weight. If not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit then the tablets meet the USP standard. The results were shown in Table 7.

$$\%\text{ Weight variation} = \frac{\text{Average weight} - \text{Initial weight}}{\text{Average weight}} \times 100$$

Evaluation of candesartan cilexetil rapimelts

Disintegration test

It is time required by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes with the bottom containing a 10 mesh sieve. The basket is set a frequency of 28-32 cycles per minute in a medium of 900 ml which is

maintained at 37 ± 2° C. The tablets were placed in the tubes and the time required per complete pass away of tablet particles through 10# mesh sieve was considered as disintegration time of tablet (34). The results were shown in Table 8.

Table 8: Evaluation tests of candesartan cilexetil rapimelts

Formulation code	Disintegration time (sec) ± S.D.	*In-vitro* dispersion time (sec) ± S.D.	Wetting time (sec) ± S.D.	Water absorption ratio (%) ± S.D.	% Drug content ± S.D.
R1	43±1.52	84±2.51	86±2.00	84.42±3.13	97.05±0.75
R2	37±1.52	69±1.52	60±3.46	85.76±5.91	95.05±0.57
R3	25±2.51	55±3.60	44±4.04	92.78±2.86	95.59±0.56
R4	55±3.51	92±2.00	98±3.00	86.03±2.49	94.99±0.09
R5	46±2.51	76±3.78	67±2.08	90.93±3.05	94.12±0.56
R6	30±2.00	68±2.00	53±3.00	97.88±5.95	93.45±0.75
R7	33±1.52	74±2.51	66±1.52	84.73±0.45	92.12±0.56
R8	27±1.52	49±1.52	40±2.08	89.07±0.34	94.38±0.75
R9	21±2.08	32±2.64	34±0.57	94.72±0.28	94.45±1.78

***In-vitro* dispersion time test**

To determine dispersion time 10 ml measuring cylinder was taken in which 6 ml of simulated salivary fluid of p^H 6.8was added and tablet was placed in it. Time required for complete dispersion was noted. Three tablets from each formulation were selected randomly and the average dispersion time was determined (35). The results were shown in Table 8.

Wetting time

Five circular tissue papers of 10 cm diameter are placed in a petridish. Ten millimeters of simulated salivary fluid of p^H 6.8 containing a water-soluble dye, was added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet was noted as the wetting time. Three tablets from each formulation were selected randomly and the average wetting time was determined (35). The results were shown in Table 8.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of simulated salivary fluid of p^H 6.8. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R), was determined using following equation,

$$R = \frac{W_a - W_b}{W_b} \times 100$$

Where,

$\mathbf{W_b}$ is weight of tablet before water absorption

$\mathbf{W_a}$ is weight of tablet after water absorption.

Three tablets from each formulation were selected randomly and the average water absorption ratio was determined (36). The results were shown in Table 8.

2.8.5. Drug content

Five tablets were taken and powdered; the powder equivalent to 8 mg of candesartan cilexetil was dissolved in 100 ml of simulated salivary fluid of p^H 6.8, filtered, diluted suitably to 10 mcg/ml concentration and analyzed at 224 nm using UV-Visible spectrophotometer (37). The results were shown in Table 8.

***In vitro* dissolution studies**

In vitro dissolution studies of candesartan cilexetil rapimelts were conducted with the USP type II apparatus. The dissolution studies were performed using 900 ml simulated salivary fluid of p^H 6.8 containing 0.35% tween 20 as dissolution medium at 37±0.5°C with 50 rpm speed. A tablet of each formulation containing 8 mg of drug was added into the dissolution medium. The sample of 4 ml aliquots were withdrawn periodically (3, 6, 9, 12 and 15 min) and filtered. The withdrawn sample was replaced regularly with same quantity of fresh dissolution medium. The filtered solutions were diluted and analyzed for their drug release by using UV spectrophotometer at wavelength of 224 nm. Percentage of drug dissolved was calculated by plotting time on X- axis against percent cumulative drug release on Y-axis (38–40). The results were shown in Table 9 and Figure 5.

Table 9: Comparative dissolution data of candesartan cilexetil rapimelts

Time (min)	% Cumulative drug release (mean± S.D.)								
	Formulation containing crospovidone			Formulation containing CCS			Formulation containing co-processed superdisintegrants		
	R1	R2	R3	R4	R5	R6	R7	R8	R9
3	33.83 ± 0.54	35.72 ± 0.55	36.30 ± 1.10	32.59 ± 1.11	34.90 ± 0.84	35.13 ± 0.28	38.08 ± 0.28	39.54 ± 0.27	41.10 ± 1.67
6	46.75 ± 0.82	49.32 ± 0.55	50.61± 1.11	45.00± 0.28	48.21 ± 0.84	49.36 ± 1.13	50.48 ± 1.15	53.25 ± 1.12	55.20 ± 0.56
9	59.41± 0.26	61.46 ± 2.24	63.49 ± 0.55	57.52 ± 1.40	61.67 ± 0.28	62.91 ± 0.84	62.60 ± 0.57	66.70 ± 0.55	70.64 ± 1.12
12	70.59 ± 1.37	73.67 ± 1.41	77.61± 0.28	68.93 ± 1.41	72.80 ± 0.28	75.74 ± 0.28	74.38 ± 1.15	80.22 ± 1.41	84.57 ± 1.13
15	82.61 ± 1.10	85.15 ± 0.57	93.38 ± 1.93	79.21 ± 0.82	84.39 ± 0.27	89.03 ± 0.57	87.04 ± 1.43	94.61 ± 1.11	98.17 ± 0.27

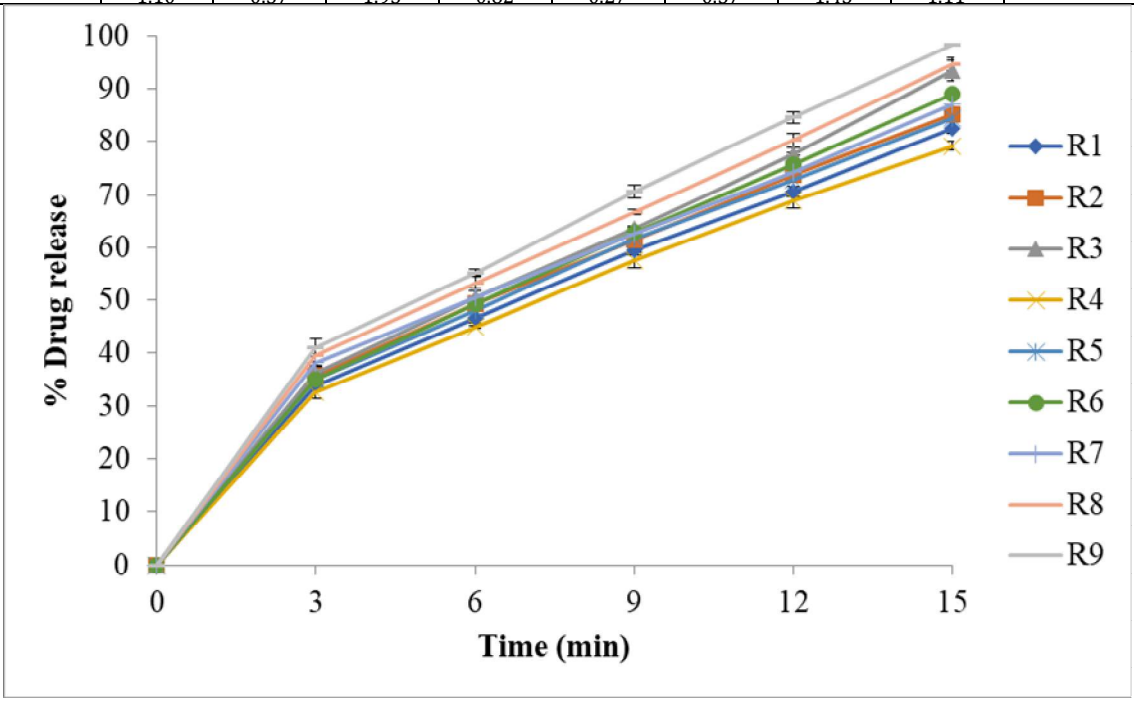


Figure 5: Comparative dissolution profile of candesartan cilexetil rapimelts (R1-R9)

RESULTS AND DISCUSSION

Nine formulations of surface solid dispersions of candesartan cilexetil were prepared and weighed accurately. % yield was found in the range of 89.33-97.33% as shown in table 2. The drug content was found in between of 87.98-94.12% as shown in table 2. From the results, it was found that the percentage drug release of pure candesartan cilexetil was very low and found to be 33.56% in 60 minutes. Out of nine formulations, F9 formulation showed the highest percentage drug release i.e., 90.58% within 60 minutes when compared to that of pure drug. However, all the nine formulations gave a significant improvement in the solubility as compared to that of the pure drug. The results were shown in Table 3 and figure 1. From the FTIR data, it was found that there were no new bands observed in the spectrum, which confirms that no new chemical bonds were formed between the drug and the excipients. The FTIR spectra were shown in Table No.4.

Scanning electron micrographs reveals the surface morphology of pure drug (CC) and SSD containing aerosil 200, potato starch and SSG. The results were shown in figure 2. Characteristic needle shaped crystals of candesartan cilexetil were observed in the scanning electron micrograph as shown in figure 2. SEM of SSDs reveals irregular and spherical shaped particles with small size which provide additional surface for deposition of the drug. It clearly shows surface solid dispersions reduce the crystallinity of candesartan cilexetil which aids for solubility enhancement. The reduced crystallinity of candesartan cilexetil in the SSDs was shown in figure 2.

DSC thermograms of pure drug (CC) and SSDs containing aerosil 200, potato starch and SSG are shown in Figure 3. The DSC thermogram of candesartan cilexetil showed a sharp endothermic peak at 168^0C followed by an exothermic peak which is due to decomposition of the drug. DSC thermogram of SSD containing aerosil 200 showed endothermic peak at 96^0C. DSC thermogram of SSD prepared with potato starch showed endothermic peak at 126^0C. DSC thermogram of SSD comprising SSG showed endothermic peak at 135^0C. DSC thermograms of SSDs showed decrease in melting point which indicates decrease in crystalline nature of candesartan cilexetil into amorphous state. The surface solid dispersion of DSC thermograms of candesartan cilexetil indicates that there is no interaction between the drugs and excipients which can be accessed from the peaks in the DSC thermograms. The DSC graphs of the surface solid dispersion were shown in Figure 3.

XRD patterns of pure drug and SSDs containing aerosil 200, potato starch and SSG were shown in Figure 4. The diffraction patterns of SSDs indicate changes in the crystalline nature of the drug. The diffraction pattern of the pure drug candesartan cilexetil shows a highly crystalline nature, indicated by numerous distinctive peaks at a diffraction angle of 2θ values of 6, 7.5, 18.5, 20, 21.5 and 24.5 throughout the scanning range; on the other hand, PXRD of surface solid dispersions shows a significant decrease in the crystallinity, as evident by the disappearance of sharp distinctive peaks. It can be predicted that a larger proportion of candesartan cilexetil has been converted to the amorphous form.

The bulk density of all formulations, powder blend containing excipients was found to be in the range of 0.419 to 0.463 gm/ml, while the tapped density was observed between 0.508 to 0.545 gm/ml. From the values of bulk density and tapped density the values for compressibility index and hausner's ratio were calculated. The values for compressibility index were found between 14.98 to 17.77 %. The values for hausner's ratio were found in between 1.176 to1.216. All these values are within the specified limit which indicates good flow properties. Angle of repose was found to be less than 30 which indicate good flow of powder. Overall, these values indicate good flow properties of powder blend, uniform die fill and better compression ability. The results were shown in Table.6.

Hardness test for all formulations was carried out and observations obtained were in the range of 4.6 to 5.1 kg/cm^2. Hardness for all formulations was observed to be proper, which signify that crushing strength of all formulations was maintained after direct compression. The thickness of all formulations was found to be uniform as it was obtained in the range of 2.45 to 2.74 mm. Friability test was conducted for all formulations, % friability was found to be in the range of 0.53 to 0.97. Friability test for all formulations indicated that % friability was less than 1%, which showed the I.P specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation. The % weight variation of all formulations was found to be in the range of less than 3.14%. None of the tablet was found to deviate from the average weight of tablets (variation with deviation less than ± 7.5, which complies with USP specification) signifies that there is uniformity in flow of powder blend which leads to uniform die fill. The results were shown in Table 7.

Co-processing by solvent evaporation gives more synergy between the superdisintegrants than individual superdisintegrants. R9 formulation shows better results of all formulations. Disintegration time for all formulations was found to be in the range of 21 to 55 sec. Wetting time of tablets are found in the range of 34 to 98 sec. and the water absorption ratio was found in the range of 84.42 to 97.88 %. As the porosity of formulation is increased by the super disintegrating agents and water uptake is increased due to increased capillary action, the formulation is showing less wetting time. The less wetting time helps in the quick dispersion of the formulation when come in contact with the saliva and having linear relationship with disintegration time.

Disintegration study explained that there was decrease in disintegration time with successive increase in concentration of superdisintegrants but comparatively co-processed superdisintegrants take less time for disintegration with respect to the formulations containing individual superdisintegrants. Such a difference in disintegration time between both of these formulations indicates that co-processed formulation might be increase in capillary action of superdisintegrants which might have led to improved water uptake. *In vitro* dispersion time indicates complete dispersion of formulation in the saliva and it was found to be in the range of 32 to 92sec and it is due to more porosity of superdisintegrant. Quick dispersion of formulation favors fast disintegration of formulation. Drug content of all formulations was observed between 92.12 to 97.05%. Drug content for all formulations showed uniformity which indicated that there was uniform flow and uniform distribution of drug. The results were shown in Table.8.

Candesartan cilexetil rapimelts were prepared by direct compression method. All the formulations viz. R1-R9 has shown increased cumulative dissolution profiles. Out of 9 formulations, R9 containing co-processed superdisintegrants showed highest drug release. From the results it was revealed that co-

processed superdisintegrants showed better drug release than individual superdisintegrants. Co-processed superdisintegrants prepared by solvent evaporation method shows synergism as the superdisintegrants undergoes homogenous distribution in presence of solvent. The results were shown in Table 9 and Figure 5.

CONCLUSION

Candesartan cilexetil solubility was enhanced by the surface solid dispersion technique using carriers like SSG, potato starch and aerosil 200. Amongst the formulations prepared (F1-F9), F9 formulation containing candesartan cilexetil and SSG 1:6 ratios were considered as optimized formulation in which percentage drug release was found to be 90.58% within 60 minutes in comparison with that of the pure drug dissolution of 33.56% only within 60 minut0es. This effect may be due to fine particle size of candesartan cilexetil adsorbed over carriers resulting in a higher surface area of drug exposed to the dissolution media and improved wettability of the drug particles which contribute to high drug dissolution rate. SEM studies reveal the crystalline nature of pure drug whereas surface solid dispersions showed decrease in crystallinity which is further confirmed by DSC and XRD studies. Using optimized SSD rapimelts of candesartan cilexetil were successfully prepared by using direct compression method. From the present work it concludes that the co-processing of excipients could lead to the formation of excipients with superior properties such as better flow, low moisture sensitivity, superior compressibility and rapid disintegrating ability. Amongst the formulations prepared (R1-R9), R9 was found to be effective formulation comprising of co-processed superdisintegrants of crospovidone and croscarmellose sodium in weight ratio of 1:3 shows the drug release of 98.17% within 15min. Thus, from the present work it reveals that the solvent evaporation of co-processing gives the better results than the individual superdisintegrants.

ACKNOWLEDGEMENT

The authors would like to thankful Strides Arcolab Limited, Bangalore for providing gift sample of Candesartan cilexetil.

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