ORIGINAL ARTICLE

Formulation and Evaluation of Candesartan Cilexetil Fast-Dissolving Tablets Using Natural Superdisintegrant

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Abstract

Introduction: Candesartan Cilexetil is a BCS class II drug having low water solubility, which can be enhanced by formulating them in to solid dispersions by using hydrophilic carriers and compressed in to fast dissolving tablets by using natural superdisintegrants. **Materials and Methods:** The solubility and dissolution rate of Candesartan Cilexetil were aimed to be increased in this investigation by employing fusion process to create a solid dispersion with a hydrophilic carrier like PVP or PEG 6000. Additionally, utilising Croscarmelose sodium (CCS) and *Aegle marmelos* as superdisintegrants, the solid dispersion was compressed into fast dissolving tablets. **Results and Discussion:** The drug release increased proportionately with increase in carrier concentration. Among the solid dispersions prepared, the one made with PEG6000 released the medication more rapidly than the one made only with PVPK30 and pure drug. First order kinetics were found to determine the release. **Conclusion:** The prepared solid dispersions were then mixed with super-disintegrants like Croscarmelose sodium (CCS) and *Aegle marmelos* to produce tablets. Such tablet formulations have been observed to release drug more rapidly than tablets prepared from pure drug. FTIR and XRD tests are used to characterise the pure drug and optimised formulation F6. Results showed that there were no drug and excipient interactions.

Key words: Candesartan Cilexetil, croscarmellose sodium and *Aegle marmelos*, fast-dissolving tablets, polyethylene glycol 6000, polyvinylpyrrolidone, solid dispersions

INTRODUCTION

Candesartan cilexetil, the drug candidate, is an angiotensin II receptor blocker used to treat hypertension, congestive heart failure, and myocardial infarction, and is preferred as a first-line treatment for diabetic neuropathy. Candesartan is a lipid-soluble, orally active medication with rapid absorption. It lowers blood pressure and is used to treat hypertension. It is also used to treat congestive heart failure and as a migraine preventative to lessen the severity and duration of migraines.[1,2] The drug candidate candesartan cilexetil is one of the substitutes for treating hypertension that is more tolerated and effective in lowering blood pressure in the number of patients. Candesartan cilexetil appears to have a longer antihypertensive effect than losartan with 2-32 mg daily dose because of its higher binding affinity toward angiotensin II receptor. Candesartan cilexetil is a BCS Class-II drug with low solubility and high permeability; dissolution of drug is the rate-limiting step in the absorption of drug.[3]

Solid dispersions (SDs) are formulations that increase a drug's solubility and bioavailability by dispersing sparingly soluble substances in water-soluble carriers.[4,5] Nowadays, the demand for newer technology has been raised. The oral administration of drug continues to be preferred route because of its advantages and high patient acceptability in comparison to various other routes, as the majority of therapeutic agents

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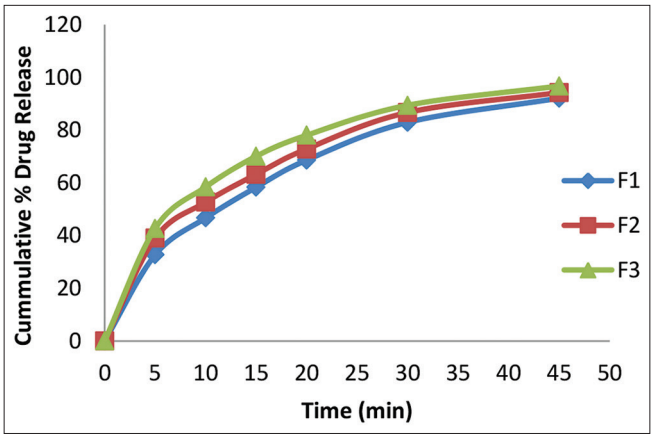

Figure 1: Drug-release profiles candesartan cilexetil tablet formulations using CCPEG-3 solid dispersions with croscarmellose sodium

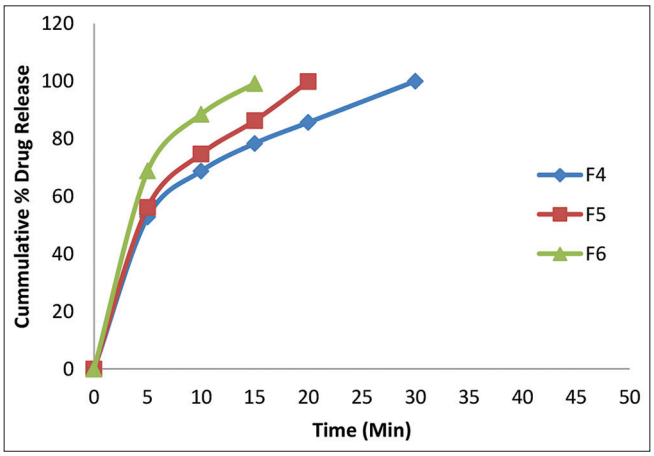

Figure 2: Drug-release profiles of candesartan cilexetil tablet formulations using CCPEG-3 solid dispersions with *Aegle marmelos*

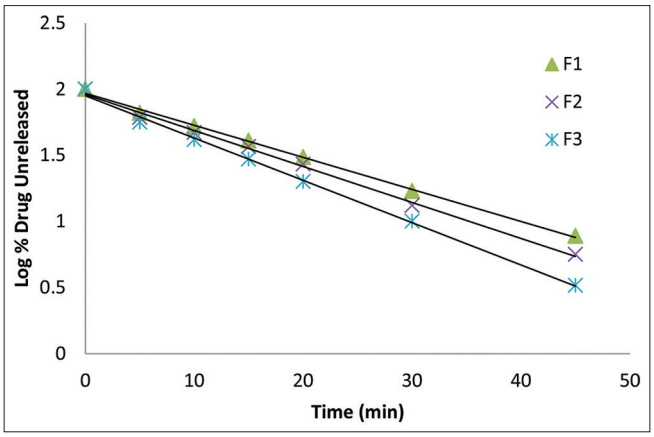

Figure 3: First-order plot of candesartan celixetil tablet formulation using CCPEG-3 with croscarmellose sodium

are employed to achieve a systemic impact. In conventional dosage forms, drug dissolution and bioavailability will be high and show rapid onset of action.[6,7]

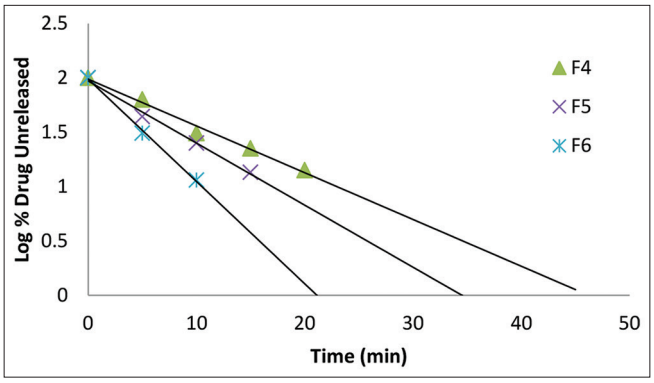

Figure 4: First-order plot of candesartan celixetil tablet formulation using CCPEG-3 with *Aegle marmelos*

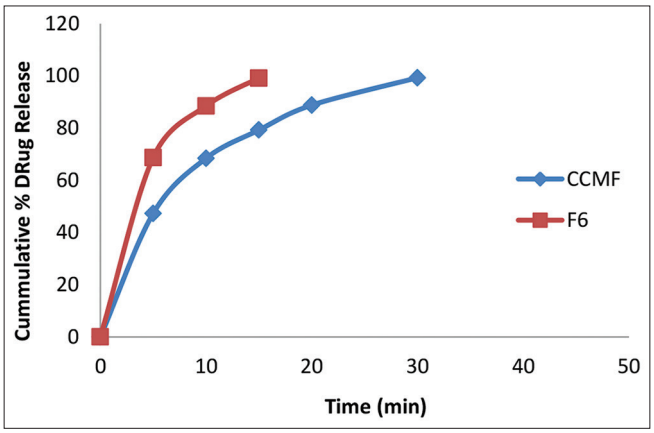

Figure 5: Drug-release profiles of optimized candesartan cilexetil tablet formulations F6 with marketed formulation

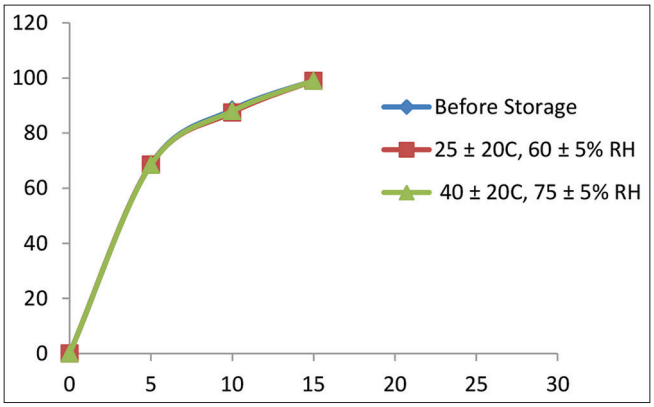

Figure 6: Drug-release profiles of candesartan cilexetil tablet formulation (F6) before and after storage at different conditions

The bioavailability of Class II medications has been improved using lipid-based carriers by formulating them into SDs. The solubility and bioavailability of poorly water-soluble drug can be enhanced using low concentrations of carriers. Low carrier concentrations should cause them to accelerate and enhance the solubility and dissolution of poorly water-soluble drugs.[8-12] Fast-dissolving tablets

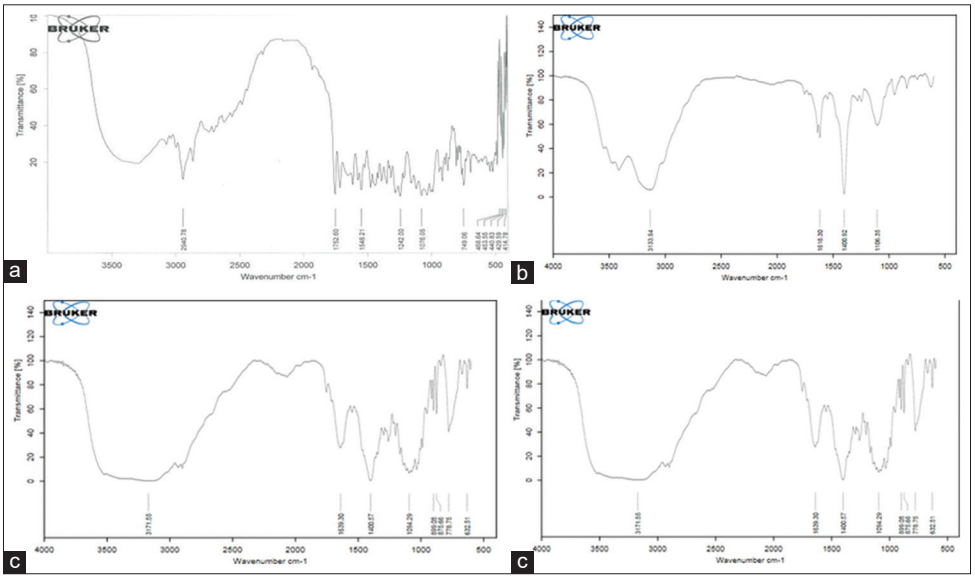

Figure 7: IR interpretations of (a) Candesartan cilexetil (b) Drug + polyvinylpyrrolidone (c) Drug + polyethylene glycol (d) Drug + *Aegel marmelos*

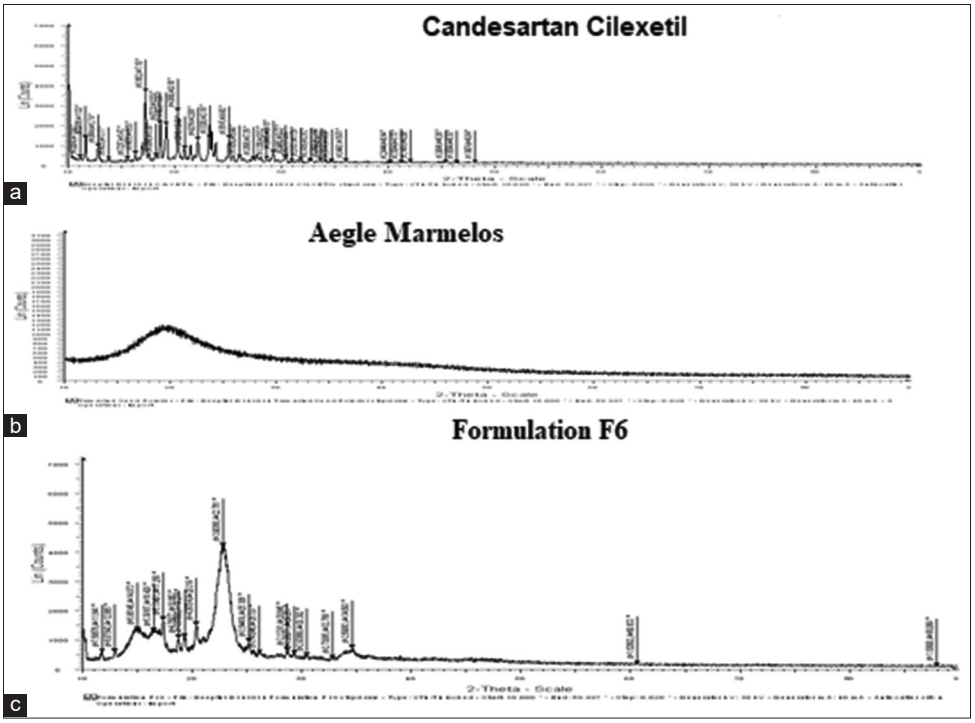

Figure 8: X-ray diffraction graphs of (a) candesartan cilexetil (b) *Aegle marmelos* powder (c) F6 formulation

are also known as orodispersible, mouth-dissolving, rapid-dissolving, and oral disintegrating tablets. There are a few definitions that have been developed by various pharmacopoeias. Uncoated fast-dissolving tablets, when they present in the mouth, they get dissolve or disperse instantly before being swallowed.

When the disintegration tests have been done, fast-dissolving tablets disintegrate within 180 s.[8,9] When the drug is meant for gastrointestinal distribution and absorption, oral disintegrating tablets are meant to dissolve quickly in mouth to promote dispersion before being ingested.[13-15]

The goal of the current investigation was to formulate Candesartan cilexetil as SDs using various carrier concentrations to increase its solubility and to formulate fast-dissolving candesartan tablets using the superdisintegrants croscarmellose sodium (CCS) and *Aegle marmelos* to increase its dissolution rate and comparing them with marketed formulations.

MATERIALS AND METHODS

Materials

Candesartan cilexetil, CCS procured commercially from yucca enterprises, Ltd., Mumbai. *A. marmelos* extracted in the laboratory, micro crystalline cellulose, polyethylene glycol (PEG) 6000, polyvinylpyrrolidone (PVP), magnesium stearate, and talc procured commercially from Loba chemicals, Ltd., Mumbai.

Saturated Solubility Studies of Candesartan Cilexetil

Candesartan cilexetil saturation solubility in various dissolution media has been studied. 500 mg of candesartan cilexetil was weighed and transferred into different Erlenmeyer flasks. 50 mL of dissolution media was transferred to each individual Erlenmeyer flasks and properly sealed. All Erlenmeyer flasks were shaken in REMI incubator shaker with 50 rpm for 24 h at 37°C ± 1°C. The Erlenmeyer flask was then removed from the incubation shaker, and the sample was filtered through Whatmann filter paper. The clear solutions obtained by filtration were diluted with appropriate dissolution media, and absorbance values at 259 nm were recorded using dissolution media as blanks. The absorbance and corresponding solubility were given in Table 1.

Table 1: Saturated solubility studies of candesartan cilexetil

S. No.	Solvent	Amount soluble (candesartan cilexetil) in µg/mL
1.	0.1N HCl (1.2 pH)	149.23
2.	pH 6.8 phosphate buffer	598.31
3.	pH 4.6 acetate buffer	431.30
4.	Distilled water	236.86

PREPARATION OF CANDESARTAN CILEXETIL SDS

Preparation of SDs

The SDs of candesartan cilexetil were prepared using PVP and PEG as carriers by fusion technique.

Fusion Method

A known amount of carrier was melted in a porcelain bowl to form a coalesced mass. Predetermined amount of drug was added to the molten polymer, which was then thoroughly mixed and cooled to room temperature to form a solid mass. The solid mass was then crushed, grounded, and screened with a sieve No. 40. The SD that resulted was placed in a desiccator. The compositions of various SDs were shown in Table 2.

Evaluation of SDs

The prepared SDs were evaluated for physical parameters such as drug content, flow characteristics, and particle size. Sieve analysis was used to determine particle size, and Carr's index and the angle of repose were used to analyze the flow characteristics of SDs.

Table 2: Composition of various solid dispersions of candesartan cilexetil

Formulation code	Formulation	Drug: Carrier	Method used
CCPEG-1	Drug+PEG 6000	1:1	Fusion method
CCPEG-2	Drug+PEG 6000	1:2	
CCPEG-3	Drug+PEG 6000	1:3	
CCPVP-1	Drug+PVP	1:1	Fusion method
CCPVP-2	Drug+PVP	1:2	
CCPVP-3	Drug+PVP	1:3	

*One part is equal to 4 mg, PEG: Polyethylene glycol, PVP: Polyvinylpyrrolidone

Estimation of Candesartan Cilexetil SDs

Candesartan cilexetil SDs were randomly taken from a batch and were placed into 100 mL volumetric flask, then add 70 mL of methanol to the flask. The final volume was make up to 100 mL by adding 6.8 pH phosphate buffer after it had been agitated intermittently for about 15 min. About 10 mL of this solution was taken out, and it was subjected to centrifugation. The centrifuge tube's supernatant solution was removed, collected, and put through another Whatmann filter. The filtrate obtained was then diluted with 6.8 pH phosphate buffer, and the absorbance was measured at 259 nm.

Dissolution Studies on Candesartan Cilexetil

The dissolution studies for the prepared SDs were performed using 900 mL of 6.8pH phosphate buffer using United States Pharmacopoeia (USP) dissolution apparatus type II (paddle). Samples were taken at regular time intervals of 5, 10, 15, 20, 30, and 45 min. Sink conditions were maintained throughout the experiment, by replacing the sample volume with the same volume of fresh medium. The amount of drug dissolved and cumulative percentage drug resealed was determined by using Schimadzu UV-1800 double-beam spectrophotometer at 259 nm. Samples were taken out at regular time intervals and diluted with the same dissolution medium. Dissolution studies were performed in triplicate. The physical parameters of various SDs were given in Table 3. *In vitro* drug release from various SDs was given in Tables 4 and 5 and shown in Figures 1-4.

Table 3: Physical parameters of candesartan cilexetil solid dispersions

S. No.	Solid dispersion	Angle of repose (°)	Carr's index (%)	Particle size (microns)	Drug content (%)
1.	CCPD	19.21	15.23	176±2	------
2.	CCPVP-1	19.45	14.56	175±4	99.95±0.3
3.	CCPVP-2	19.85	13.77	173±3	97.35±0.9
4.	CCPVP-3	19.22	13.25	177±2	98.20±1.1
5.	CCPEG-1	18.65	11.14	178±2	99.15±0.5
6.	CCPEG-2	16.52	13.64	176±5	97.35±2.1
7.	CCPEG-3	13.18	12.85	176±2	97.60±0.9

Table 4: Drug-release profiles of candesartan cilexetil solid dispersions prepared by fusion method using PVPK-30 as carrier

Time (min)	Cumulative % drug released			
	CCPD	CCPVP-1	CCPVP-2	CCPVP-3
0	0	0	0	0
5	13.5±0.12	45.69±0.94	57.87±0.45	71.47±0.75
10	17.7±0.32	56.48±0.67	68.59±0.14	78.99±0.19
15	22.5±0.85	60.98±0.41	73.61±0.57	81.64±0.64
20	28.6±0.94	65.05±0.39	76.15±0.48	84.92±0.18
30	35.3±0.45	68.67±0.13	78.56±0.79	88.76±0.07
45	41.6±0.23	72.6±0.01	80.93±0.91	90.33±0.75

Table 5: Drug-release profiles of candesartan cilexetil solid dispersions prepared using PEG 6000 as carrier

Time (min)	Cumulative % drug released			
	CCPD	CCPEG-1	CCPEG-2	CCPEG-3
0	0	0	0	0
5	13.5±0.12	56.93±0.92	64.53±0.47	77.07±0.76
10	17.7±0.32	67.35±0.65	75.6±0.16	85.9±0.20
15	22.5±0.85	69.62±0.44	80.35±0.59	90.17±0.66
20	28.6±0.94	72.45±0.41	83.55±0.46	94.64±0.20
30	35.3±0.45	76.76±0.15	85.01±0.80	97.85±0.05
45	41.6±0.23	80.08±0.03	88.85±0.93	98.83±0.76

Characterization of SDs

Fourier transform infrared (FTIR) spectroscopy study

To study the interaction between drug and excipients (carrier) used in the preparation of SDs, the FTIR spectra of the candesartan cilexetil pure drug and F6 the optimized formulation was done using a Brucker FTIR spectrophotometer. The samples were prepared using KBr discs method (2 mg sample in 200 mg KBr), at resolution of 4 cm^{-1}. The sampling range was 400–4000 cm^{-1}. The FTIR interpretation was given in Table 14 spectra were shown in Figure 7.

X-ray diffraction (XRD) studies

Physical properties of the prepared SDs were investigated using XRD studies. The XRD patterns of the drug powder and SD were recorded with copper tube anode over the range of 1–40° using an X-ray powder diffractometer. The following were the operational parameters: 45 kV generator tension (voltage); 40 mA generator current; 9/s scan step time; and 0.008° (2Θ). The results indicated that SDs are amorphous in nature, thereby increasing the dissolution of drug. Results were given in Table 15 shown in Figure 8.

Preparation of Candesartan Cilexetil fast-Dissolving Tablets

Candesartan cilexetil tablets were made using the direct compression method from optimized (fusion) SDs. Microcrystalline cellulose (Avicel pH102) was used as a diluent to make tablets with uniform weight variation. Depending on the dissolution studies, one optimized dispersion was chosen from among the SDs, tablets were compressed using CCS and *A. marmelos* powdered extract as superdisintegrants, microcrystalline cellulose (Avicel pH102) as diluent, magnesium stearate as a lubricant, and talc as glidant using a Karnavati punching press. The compositions of various tablet formulations were given in Table 6.

Table 6: Composition of candesartan cilexetil tablet formulations

S. No.	Formulation	Ingredients						
		CCPEG-3 (mg)	Croscarmellose sodium (mg)	*Aegle marmelos* (mg)	MCC pH 102 (mg)	Magnesium Stearate (mg)	Talc (mg)	Total Weight of Tablet (mg)
1.	F1	24	2	-	222.5	1.5	1.5	250
2.	F2	24	4	-	220.5	1.5	1.5	250
3.	F3	24	6	-	218.5	1.5	1.5	250
4.	F4	24	-	2	222.5	1.5	1.5	250
5.	F5	24	-	4	220.5	1.5	1.5	250
6.	F6	24	-	6	218.5	1.5	1.5	250

Table 7: Physical parameters of candesartan cilexetil fast-dissolving tablet formulation

S. No.	Formulation	Weight uniformity (mg)	Hardness (kg/cm^2)	Friability (%) loss	Drug content (mg/tablet)	Disintegration time (s)
1.	F1	249±3	3.0±0.03	0.16	3.90±0.3	42.00±2.4
2.	F2	248±3	3.2±0.07	0.18	3.74±0.3	35.00±1.2
3.	F3	250±1	3.4±0.06	0.16	3.82±0.4	20.42±1.3
4.	F4	249±3	3.5±0.02	0.17	3.72±0.2	41.00±1.3
5.	F5	251±1	3.0±0.04	0.18	3.72±0.2	33.00±1.4
6.	F6	249±2	3.4±0.07	0.17	3.72±0.2	19.00±1.2

Table 8: Drug release profiles of candesartan celixetil fast dissolving tablet formulations using CCPEG-3 solid dispersions with croscarmellose sodium

Time (min)	Cumulative % drug released		
	F1	F2	F3
5	32.72±0.83	39.03±0.41	42.73±0.16
10	46.71±0.92	52.69±0.12	58.45±0.19
15	58.32±1.91	63.22±0.32	70.09±0.09
20	68.61±0.87	72.85±0.24	78.05±0.10
30	82.94±0.53	76.69±0.47	89.41±0.06
45	92.09±0.68	94.85±0.62	96.71±0.02

Table 9: Drug release profiles of candesartan celixetil tablet formulations using CCPEG-3 solid dispersions with *Aegle marmelos*

Time (min)	Cumulative % drug released		
	F4	F5	F6
5	52.72±0.96	56.13±0.75	68.73±0.34
10	68.71±0.41	74.69±0.14	88.45±0.78
15	78.32±0.08	86.22±0.56	99.09±0.12
20	85.61±0.81	99.85±0.71	-
30	99.94±0.07	-	-
45	-	-	-

Evaluation of Physical Parameters of Fast-Dissolving Candesartan Cilexetil Tablets

Physical parameters such as weight uniformity, hardness, friability, and drug content were evaluated for the compressed tablets. Dissolution studies for candesartan cilexetil fast-dissolving tablets were performed using USP type-II apparatus. From the data obtained from dissolution studies, various parameters such as T50, DE30%, zero-order, and first-order release rate constants were estimated. Physical parameters were given in Table 7. Dissolution parameters such as T50 and DE30% were calculated. The dissolution profiles were shown in Figures 1-4.

Accelerated Stability Studies

The formulations with good *in vitro* dissolution characteristics such as CCPEG3 and optimized formulation F6 were subjected to accelerated stability studies, at a temperature and relative humidity (RH) of 25 ± 2°C, 60 ± 5% RH for 6 months and 40±2°C, 75 ± 5% RH for 3 months. Physical parameters and drug release for the selected formulations were evaluated after storage at different conditions given in Table 12. Dissolution profiles from accelerated stability studies were given in Table 13 shown in Figure 6.

RESULTS AND DISCUSSION

The results of saturated solubility studies revealed that Candesartan cilexetil shows a maximum solubility in 6.8 pH phosphate buffer when compared to other dissolution media used. The concentration of drug was measured at a λmax of 259 nm using Schimadzu UV-1800 double-beam spectrophotometer. The absorbance and corresponding solubility values were given in Table 1.

The compositions of the various SDs, prepared by using PVP and PEG 6000 as carriers, are listed in Table 2. To prevent batch-to-batch fluctuation, all dispersions were made under the identical conditions. The features of the dispersions were found to be consistent. The particle size ranges from 174 ± 31 to 79 ± 2 µm for the prepared SDs. The drug content for all the dispersions was highly uniform and it ranges from 3.72 ± 0.3 to 3.9 ± 0.3%.

The prepared Candesartan cilexetil SDs were evaluated for drug release using USP apparatus II with phosphate buffer of pH 6.8. Dissolution studies shown that the SDs dissolve at a faster rate than pure drug. When compared to candesartan cilexetil in its pure form, all formulations T50 and DE30% values showed that the drug dissolves more quickly. Drug release of all the formulations was given in Tables 8 and 9 and shown in Figures 1-4.

Drug release from the formulations follows first-order kinetics. It has been shown that increase in the concentration of carrier in the SDs prepared by fusion method results in increase in dissolution rate of the drug. SD with 1:3 ratio of drug to carrier prepared using PEG6000 showed a faster dissolution rate when compared to other formulations. SDs of CCPEG3 and optimized formulation F6 subjected to FTIR studies to determine drug excipients interaction.

The composition of various tablet formulations was given in Table 6. All the SDs were compressed under the same conditions to avoid processing variables. All the tablets compressed were evaluated for physical parameters such as weight uniformity, hardness, and drug content. The parameters evaluated were consistent and all tablets were within the specified limits of IP. Weight uniformity ranges from 249 ± 2.0 to 251 ± 1mg, hardness was found to be 3.5 ± 0.4 mg/tablet of candesartan cilexetil. The dissolution studies on commercial tablet were also done with USP type-II apparatus using 6.8 pH phosphate buffer. The drug release from optimized formulation was found to be faster when compared to marketed formulations (Candesar 4 mg, Ranbaxy lab, Ltd.). The results were given in Table 10 shown in Figure 5.

Among all the formulations, fast-dissolving tablets with *A. marmelos* as superdisintegrant at 3% concentration tend to dissolve at a faster rate. The order of drug-release rate from the formulations was *A. marmelos* > CCS. Among all the compressed tablet formulations, F6 shows rapid drug release (up to 99.7%) compared to marketed formulation (99.23%). It was observed that the concentration of superdisintegrant increases in the tablet formulation, drug dissolution of sparingly soluble drug candesartan cilexetil also increases due to rapid uptake of water by the superdisintegrant. *In vitro* dissolution parameters of drug were given in Table 11 and shown in Figure 3-4.

Future Scope

It was found that the CCPEG-3 and CCPVP-3 formulations, made by the fusion method with a high carrier concentration,

Table 10: Comparative drug-release profiles of optimized candesartan cilexetil tablet formulations with marketed formulation

Time (min)	Cumulative % drug released	
	CCMF	F6
5	47.31±0.21	68.73±0.34
10	68.42±0.18	88.45±0.78
15	75.23±0.23	99.09±0.12
20	88.76±0.16	-
30	99.23±0.56	-
45	-	-

Table 11: *In-vitro* dissolution parameters of candesartan cilexetil tablet formulations

Formulation	Drug release parameters of candesartan cilexetil tablet formulations						
	T50 (min)	T90 (min)	DE 30%	Zero order		First order	
				R2	K (mg/min)	R2	K (min^{-1})
CCMF	7	12	43.33	0.604	0.745	0.942	0.945
F1	12.5	42	65.95	0.889	2.392	0.928	0.050
F2	9.5	40	71.14	0.896	0.994	0.954	0.552
F3	7	38	71.73	0.898	1.992	0.967	0.264
F4	4	21	99.94	0.880	1.861	0.956	0.057
F5	3	16	-	0.889	1.506	0.959	0.331
F6	2	10	-	0.966	2.598	0.974	0.025

Table 12: Physical parameters of candesartan cilexetil tablet formulations using ccpeg-3 solid dispersions (F6) before and after storage eat different condition

Formulation	Storage condition	Weight uniformity (mg)	Hardness (kg/cm²)	Friability (% w/w)	Drug content (mg/tablet)
F6	Before storage	249±2.0	3.4±0.07	0.17	3.72±0.2
	25±2°C, 60±5% RH	248±3.0	3.2±0.3	0.15	3.07±0.3
	40±2°C, 75±5% RH	248±3.0	3.2.±0.3	0.16	2.96±0.2

RH: Relative humidity

Table 13: Drug release profiles of candesartan cilexetil tablet formulation (F6) before and after storage at different conditions

Time (min)	Before storage	25±2°C, 60±5%RH	40±2°C, 75±5%RH
5	68.73±0.34	68.47±0.12	70.16±0.34
10	88.45±0.78	87.35±0.73	89.05±0.64
15	99.09±0.12	98.98±0.52	99.17±0.68
20	-	-	-
30	-	-	-
45	-	-	-

RH: Relative humidity

Table 14: IR Interpretations

Functional groups present	CC	Drug+*Aegle marmelos*
Aliphatic C-H-stretching	2940.78	2926.87
C-C stretching	1639.30	1651.75
C-N stretching	-	-
O-H-Stretching	-	-
C-F stretching	-	-

Table 15: XRD interpretations

Formulations	Peak presence at degrees(θ)	Nature of peak
Pure drug	17.13	Sharp peak
Tamarind seed powder	18.95,22.27	Sharp peak
F6 formulation	19.14,23.14	Sharp peak

XRD: X-ray diffraction

release the medication more rapidly and are ideal for making tablets. Using a variety of polymers, we can concentrate on candesartan cilexetil. New tablet production methods can be used to extend this study. *In vivo* pharmacokinetic and dynamic studies can be performed on a suitable animal model.

CONCLUSION

Based on investigation it was found that the solubility and dissolution rate of poorly water soluble drug candesartan Cilexetil can be enhanced by formulating in to solid dispersion by fusion method using hydrophilic carriers like PEG 6000 and PVPK-30 at varying ratios and the optimized formulations of solid dispersions CCPEG-3 and CCPVP-3 at 1:3 ratio of drug to polymer were further compressed in to fast dissolving tablets using croscarmellose sodium and *Aegle marmelos* as superdisintegrants. All the tablet formulations were found to be stable and meeting the I.P limits for weight uniformity, friability, drug content and show good invitro drug release characteristics. Among all, the formulation F6 show rapid drug release. It was found that as the concentration of superdisintegrant in the tablet increases than the solubility and the dissolution rate of the drug increased. Characterisation studies revealed that, they were no drug and excipient interactions. Accelerated stability studies were performed on optimized formulation (F6), there were no significant changes observed in drug release after storage at different conditions. The formulation remained unaltered and found to be quite stable.

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