Research Article

Formulation and Evaluation of Fast Dissolving Tablets of Candesartan Cilexetil by Sublimation Technique

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ABSTRACT

The purpose of this investigation was to develop fast dissolving tablets (FDTs) of Candesartan cilexetil by sublimation technique using camphor as subliming agent together with croscarmellose sodium and crospovidone as superdisintegrants. The prepared formulations were evaluated for pre-compressional and post-compressional parameters. The compatibility of drug with other ingredients was checked by FTIR studies, the results revealed that there was no interaction between dug and other excipients. The values of pre-compressional parameters were within prescribed limits and indicated good free flowing properties. In all the formulations the hardness test indicates good mechanical strength. Friability of all formulations was less than 1. Drug content was found to be high (≥ 101.02%) and uniform in all the formulations. The tablet thickness was found to be 3.10 to 3.16 mm. The weight variation results revealed that average percentage deviation was less then ± 7.5 %, which provides good uniformity in all formulations. The disintegration time of the tablets found to be in the range of 21 to 40 sec. The formulations CCC_4,CCU_4, 50 % of drug released in 1.02, 2.42 min, and 90 % of drug released in 3.37, 6.19 min. Stability study carried out as per ICH guidelines for three months and results revealed that upon storage disintegration time of tablets decreased significantly ($p<0.05$). The release of drug from the CCC_4 formulation was quick when compared to other formulations. It was concluded that fast dissolving tablets with improved Candesartan cilexetil dissolution could be prepared by sublimation of tablets containing suitable subliming agent.

Keywords: Fast dissolving tablet, Candesartan cilexetil, subliming agent, super disintegrant, camphor.

INTRODUCTION

Candesartan cilexetil (Fig.1) is chemically 2-Ethoxy-3-[21-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] -3Hbenzoimidazole- 4-carboxylic acid 1- cyclohexyloxycarbonyloxy ethyl ester.[1] Candesartan cilexetil is a prodrug of Candesartan – a compound that inhibits binding of angiotensin II to the AT_1 – receptor. Candesartan cilexetil is hydrolyzed to Candesartan during absorption from the gastrointestinal tract.[2] It is mainly used in the treatment of hypertension. The typical dose of Candesartan cilexetil is 16 mg per day in patients who are not volume depleted. It may be given once or twice daily with total daily doses ranging from 8 mg to 32 mg.[3]. Tablet formulation containing 4 mg and 8 mg Candesartan cilexetil are available in market.

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing. However, geriatric and pediatric patients experience difficulty in swallowing conventional tablets, which leads to poor patient compliance. To overcome this weakness, scientists have developed innovative drug delivery systems known as fast dissolving tablets. Their characteristic advantages such as administration without water, anywhere, any time lead to their suitability to geriatric and pediatric patients. They are also suitable for the mentally ill, the bedridden and patients who do not have easy access to water. The benefits, in terms of patient compliance, rapid onset of action, increased bioavailability, and good stability make

these tablets popular as a dosage form of choice in the current market[4,5]. The fundamental principle used in the development of the fast-dissolving tablet is to maximize its pore structure. Researchers have evaluated spray dried materials[6] and plastic materials[7] for development of such tablets. Vacuum-drying[8-13] and freeze-drying[14-17] techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and yields a fragile and hygroscopic product. Therefore, a vacuum drying technique was adopted in the present investigation after addition of a subliming agent to increase porosity of the tablets. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly.

In the present study, an attempt was made to develop dissolving tablets of Candesartan cilexetil and to investigate the effect of subliming agent on the release profile of the drug in the tablets.

MATERIALS AND METHODS

Candesartan cilexetil was gift sample from Hetero Labs. Ltd. Medak district. (AP). Croscarmellose sodium, crospovidone, camphor, aspartame, mannitol, talc, magnesium stearate, and all the other chemicals used were of pharmaceutical grade.

Fourier transform infrared (FTIR) spectroscopy

The Fourier-transform infrared spectra of Candesartan cilexetil and mixture Candesartan cilexetil with other excipients were obtained by using FTIR spectroscopy – 5300 (JASCO Japan). Samples were prepared by KBr pressed pellet technique. The scanning range was 400 -4600 cm^{-1} and the resolution was 4 cm^{-1}. The spectra are shown in Fig. 2.

Preparation of tablet

Candesartan cilexetil 4 mg was taken and mixed with mannitol, directly compressible microcrystalline cellulose, super disintegrant, aspartame and camphor, (10%) in plastic container. Magnesium strearate and talc were passed through sieve No. 60 and blended with initial mixture in the plastic container followed by direct compression of blend (Table 1). After compression the tablets were collected and vacuum dried at 60^0C until the constant weight is obtained to ensure the complete removal of sublimable component to make a tablet porous.

Evaluation of tablets

Tablet was evaluated for hardness, friability, weight variation, thickness, disintegration time, wetting time, water absorption ratio, drug content and stability study. The Pfizer hardness tester and roche friabilator were used to test hardness and friability loss respectively. In weight variation test, 20 tablets were selected at random and average weight was determined using electronic balance. Tablets were weighed individually and compared with average weight. Disintegration time was determined using USP Tablet disintegration test apparatus using 900 ml distilled water at room temperature. Thickness of tablets was determined by using dial caliper, wetting time study, a piece of tissue paper folded twice was kept in culture dish containing 6 ml of distilled water. A tablet having small amount of amaranth powder on upper surface was kept on tissue paper. A time required to develop a red color on upper surface of tablet was recorded as the wetting time. For drug content analysis, a total 10 tablets were weighed and powdered. The powder equivalent to 4 mg of Candesartan cilexetil was taken and dissolved in phosphate buffer 6.8. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically at 255 nm. Using 900 ml of buffer monitored *in vitro* dissolution of Candesartan cilexetil from tablets at 37 ± 0.5^0C at 50 rpm using programmable dissolution tester. Aliquots were withdrawn at 1 min time intervals. Aliquots, following suitable dilution were assayed spectrophotometrically at 255 nm. The stability study of the tablets were carried out according to ICH guidelines by

storing tablets in stability chamber at 40 ± 2^0 C / 75 ± 5% RH for 3 months

RESULTS AND DISCUSSION

FTIR studies revealed that there was no physico-chemical interaction between Candesartan cilexetil and other excipients. The pure drug Candesartan cilexetil showed characteristic absorption at 2941 cm^{-1}, 1752cm^{-1}, 1714cm^{-1}, 1614 cm^{-1}. This absorption peak at 2941 cm^{-1} was due to stretching of C-H bond, the peaks at 1752cm^{-1} and 1714cm^{-1} were due to two C-O bonds (carbonyl group) and peak at 1614 cm^{-1} was due to C-N bond. These peaks were present in IR scan of all formulations, so it was conformed that, presence of undisturbed drug in the formulations. Hence there were no drug-excipient interactions.

The flow properties of the powder mixture are important for the uniformity of mass of tablets; the flow of powder mixture was before compression of tablets. The values of pre-compressional parameters were within prescribed limit as per USP XXVII and indicate good flow properties. The results are shown in table 2. The post compressional parameters results are shown in table 3 and 4. In all the formulations the hardness test indicates good mechanical strength. The hardness of all tablets found between 2.4 to 3.1 kg/cm^2. Friability of all formulation was less than 1%, which indicates the tablets had good mechanical resistance. Drug content was found to be high (≥101.02 %) and uniform in all formulations. The tablet thickness was found to be 3.10 to 3.14 mm. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than ± 7.5%, which provide good uniformity in all formulations. The disintegration time of all tablets found to be in the range of 21 to 40 sec. The tablets prepared by vacuum drying technique rapidly exhibit high pores and disintegrate the tablets rapidly. It may be due to their lowest hardness and maximum pore structure was responsible for faster water uptake; hence it facilitates wicking action of superdisintegrants in bringing about faster disintegration. Wetting time is closely related to the inner structure of the tablet. The wetting time of all formulations were found to be in the range of 42 to 54 sec. The dissolution profiles of all formulations are shown in Fig. 3 & 4. Out of eight formulations, the formulation CCC_4 show faster drug release within 4 min. *In-vitro* profile of Candesartan cilexetil shown in Fig. 5 and in Table 5. The $t_{50\%}$ and $t_{90\%}$ values changed with changing concentration of superdisintegrants. The formulations CCC_4 and CCU_4, 50 % of drug released in 1.02, 2.42 min, and 90 % of drug released in 3.37, 6.19 min

The stability studies results revealed that, the disintegration time, wetting time was decreased significantly (Table 6). During the sublimation procedure all the formulations were kept in vacuum dryer at 45^0C for 60 min. at this time sum amount of subliming agent may be left in the formulations after vacuum drying. But in case of stability study, the selected formulations were kept at 40^0C for 90 days. This extended expose time may leads to evaporation of subliming agent, which may left after sublimation techniques leads to increased formation of pores in the tablets. So, the disintegration and wetting time of tablets were decreased after stability study.

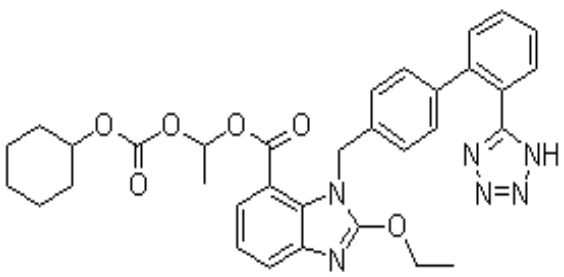

Fig. 1: Structure of Candesartan cilexetil

Table 1: Formulation of Candesartan cilexetil FDTs

Ingredients	Formulation Code							
	CCC_1	CCC_2	CCC_3	CCC_4	CCU_1	CCU_2	CCU_3	CCU_4
Candesartan cilexetil	4	4	4	4	4	4	4	4
Croscarmellose sodium	2.5	5	7.5	10	--	--	--	--
Crospovidone	--	--	--	--	2.5	5	7.5	10
Mannitol	67.5	65.0	62.5	60.0	67.5	65.0	62.5	60.0
MCC	10	10	10	10	10	10	10	10
Camphor	10	10	10	10	10	10	10	10
Aerosil	1	1	1	1	1	1	1	1
Aspartame	3	3	3	3	3	3	3	3
Magnesium stearate	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1
Total wt (mg)	100	100	100	100	100	100	100	100

Table 2: Precompressional parameters of Candesartan cilexetil FDTs

Formulation code	Angle of repose* (degree) ±SD	Bulk density* (g/cc) ± SD	Tapped density* (g/cc) ± SD	Carr's index* (%) ± SD	Hausner's Ratio* ± SD
CCC_1	21.55 ± 1.36	0.48 ± 0.02	0.53 ± 0.01	15.13 ± 1.12	1.15 ± 0.01
CCC_2	23.64 ± 1.10	0.43± 0.01	0.47 ± 0.02	14.59 ± 1.17	1.17 ± 0.04
CCC_3	26.22 ± 1.17	0.43 ± 0.01	0.49 ± 0.01	14.33 ± 1.27	1.16 ± 0.01
CCC_4	21.48 ± 1.23	0.42 ± 0.02	0.52 ± 0.01	14.42 ± 1.08	1.15 ± 0.01
CCU_1	24.33 ± 1.53	0.47 ± 0.01	0.51 ± 0.01	14.25 ± 1.49	1.16 ± 0.01
CCU_2	24.25 ± 1.29	0.42 ± 0.01	0.48 ± 0.01	14.55 ± 1.23	1.16 ± 0.01
CCU_3	23.29 ± 1.22	0.41 ± 0.01	0.49 ± 0.01	15.43 ± 1.44	1.15 ± 0.02
CCU_4	22.36 ± 1.26	0.47 ± 0.02	0.55 ± 0.01	15.18 ± 1.26	1.17 ± 0.03

* Average of three determinations

Table 3: Post-compressional parameters of Candesartan cilexetil FDTs

Formulation Code	Weight variation* (mg) ± SD	Thickness* (mm) ± SD	Hardness* (Kg/cm^2) ± SD	Friability (%)
CCC_1	100 ± 1.20	3.12 ± 0.10	2.4 ± 0.12	0.58
CCC_2	99 ± 1.31	3.10 ± 0.11	3.1 ± 0.14	0.51
CCC_3	98 ± 1.35	3.11 ± 0.12	2.6 ± 0.10	0.56
CCC_4	99 ± 1.09	3.11 ± 0.14	2.5 ± 0.15	0.59
CCU_1	99 ± 0.64	3.10 ± 0.14	2.6± 0.20	0.69
CCU_2	100 ± 1.15	3.14 ± 0.15	2.7 ± 0.21	0.51
CCU_3	101 ± 0.82	3.16 ± 0.05	2.8 ± 0.21	0.74
CCU_4	99 ± 0.58	3.15 ± 0.13	2.7 ± 0.07	0.53

* Average of three determinations

Table 4: *In-vitro* disintegration time, wetting time, water absorption ratio and drug Candesartan cilexetil FDTs

Formulation Code	*In-vitro* disintegration time * (sec) ± SD	Wetting time* (sec) ± SD	Water absorption ratio* ± SD	Drug Content* (%) ± SD
CCC_1	36 ± 1.34	50 ± 1.05	75± 1.12	100.45 ± 1.24
CCC_2	33 ± 1.24	46 ± 1.23	79 ± 1.17	99.78 ± 1.15
CCC_3	30 ± 1.45	44 ± 1.17	80 ± 1.22	99.17 ± 1.53
CCC_4	26 ± 1.22	42 ± 1.12	84 ± 1.16	99.48 ± 1.26
CCU_1	40 ± 1.15	54 ± 1.45	77 ± 1.07	101.02 ± 1.18
CCU_2	34 ± 1.27	46 ± 1.13	82 ± 1.10	99.06 ± 1.14
CCU_3	33 ± 1.35	49 ± 1.56	84 ± 1.22	99.58 ± 1.21
CCU_4	21 ± 1.18	47 ± 1.27	87 ± 1.56	98.47 ± 1.03

* Average of three determinations

Table 5: Release profile of Candesartan cilexetil FDTs

Formulation Code	$t_{50\%}$*	$t_{90\%}$*
CCC_1	3.06	6.19
CCC_2	2.31	5.25
CCC_3	1.49	4.30
CCC_4	1.02	3.37
CCU_1	5.34	9.04
CCU_2	4.14	8.06
CCU_3	3.44	7.07
CCU_4	2.42	6.19

* Average of three determinations

Table 6: Results of stability study

Formulation Code	*In vitro* disintegration time* (sec) ± SD	Wetting time* (sec) ± SD	Drug Content* (%) ± SD
CCC_4	20 ± 1.14	38 ± 1.29	98.11 ± 1.44
CCU_4	19 ± 1.17	39 ± 1.43	99.19 ± 1.35

* Average of three determinations

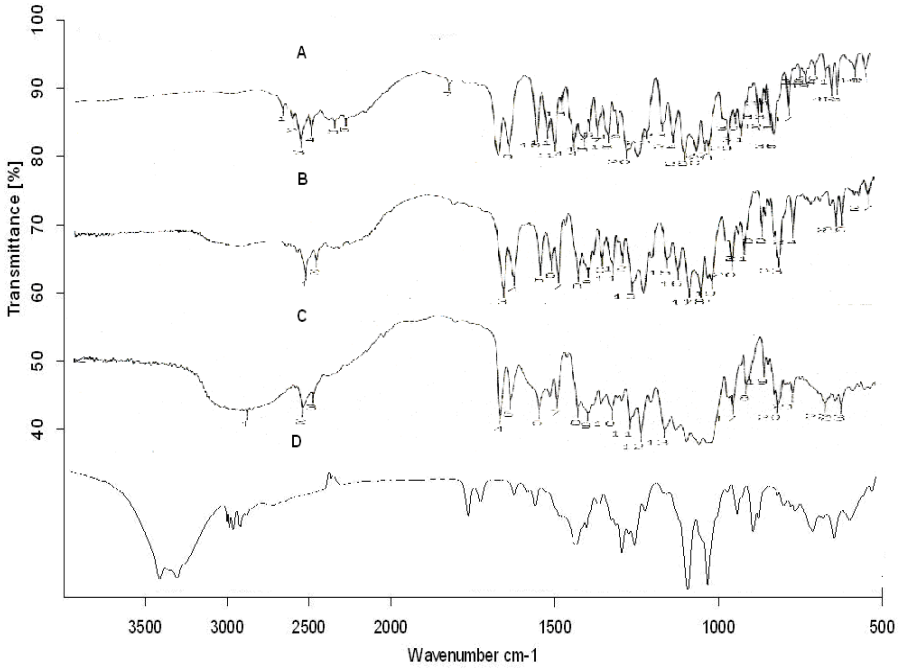

Fig. 2: IR spectrum of Candesartan cilexetil (A), Drug + CCS(B), Drug + CP (C), Drug + Camphor(D)

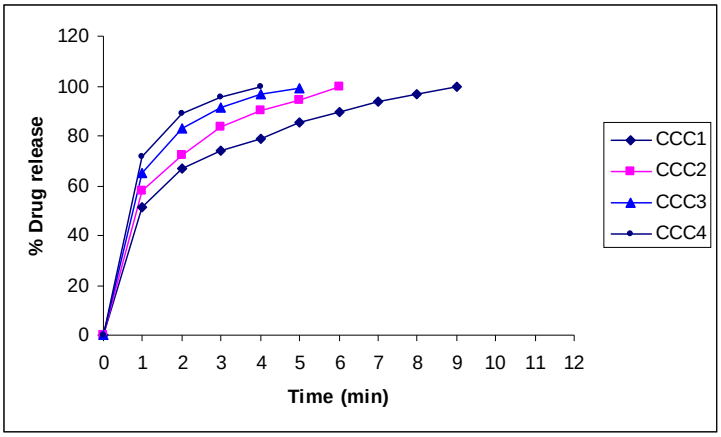

Fig. 3: Dissolution profile of formulations CCC_1-CCC_4

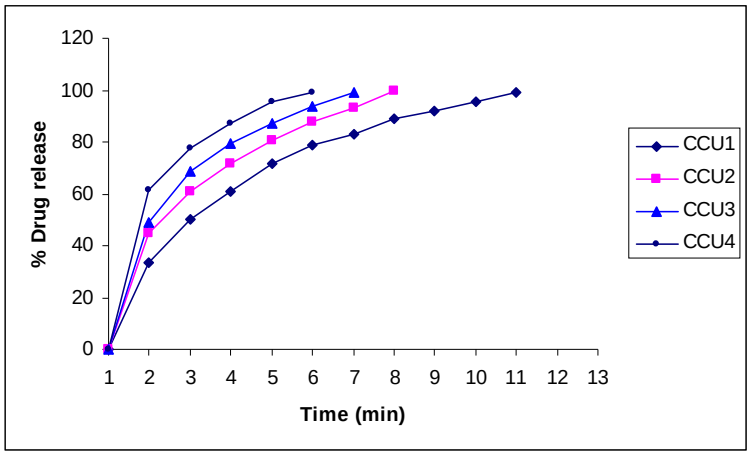

Fig. 4: Dissolution profile of formulations CCU_1-CCU_4

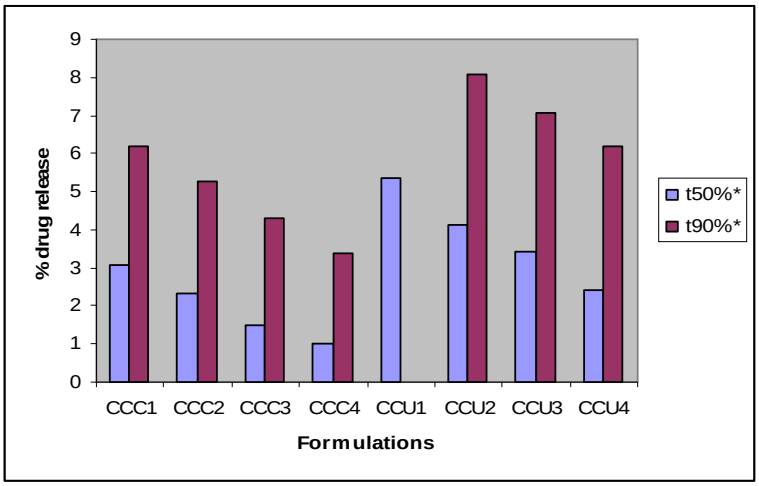

Fig. 5: Comparison of release profile ($t_{50\%}$ and $t_{90\%}$) of different formulations of Candesartan cilexetil by sublimation method

CONCLUSION

The release of drug from the CCC_4 formulation was quick when compare to other formulations. It can be concluded that fast dissolving tablets with improved Candesartan cilexetil dissolution could be prepared by sublimation of tablets containing suitable subliming agent.

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