The Pharma Innovation

ISSN: 2277- 7695
CODEN Code: PIHNBQ
ZDB-Number: 2663038-2
IC Journal No: 7725

Received: 09-03-2014
Accepted: 14-05-2014

Vol. 3 No. 4. 2014
Online Available at www.thepharmajournal.com

THE PHARMA INNOVATION - JOURNAL

Formulation and *in-vitro* evaluation of oral disintegrating tablets containing solid dispersions of Candesartan Cilexetil

Ramya Krishna S.

1. Jimma University, Jimma, Ethiopia.
   Email: ramya.krishna.seelam@gmail.com

Author for correspondence: Ramya Krishna S, Email: ramya.krishna.seelam@gmail.com

Candesartan Cilexetil is an angiotensin II receptor antagonist used mainly for the treatment of hypertension. The drug is having low solubility in biological fluids which results in poor bioavailability after oral administration. Hence present study was carried to enhance dissolution properties of candesartan cilexetil. Solid dispersions of candesartan cilexetil were prepared by using PEG-6000 as water soluble carries at various proportions 1:1, 1:2, 1:3. The kneading and solvent evaporation methods were used to prepare solid dispersions. The prepared dispersions were made into tablets by the direct compression method.

The release profile was studied in phosphate buffer pH 6.5 containing 0.35% polysorbate 20. It was found that the dissolution rate of tablets containing solid dispersions were higher than those of intact drug. The degree of dissolution rate enhancement depended on the amount of the carrier i.e., the higher the amount of the carrier used; the higher the dissolution rate was obtained. Among the prepared batches formulation F4 gave highest dissolution. The increase in the dissolution rate of the drug may be due to increase in wet ability, hydrophilic nature of the carrier and also possibility due to a reduction in drug crystalline.

Keyword: Candesartan cilexetil, Solid dispersions, Polyethylene glycol.

1. Introduction

Candesartan cilexetil (CAND) is a selective AT_1 subtype angiotensive II receptor antagonist [1, 2]. It is a white to off white powder. The solubility in benzyl alcohol is 0.3 M and the solubility in water is $< 8 \times 10^{-8}$ M. The partition coefficient in octanol/aqueous at pH 1.1, 6.9 and 8.9 is >1000 indicating high hydrophobicity character. In the gastrointestinal tract CAND is converted to candesartan, an angiotensin receptor blocker, which blocks the ability of angiotensin II to raise blood pressure by constricting arteries and veins and so leads to a reduction in blood pressure [3]. It has a pKa value of 6.0 [4]. The drug belongs to class-II according to the biopharmaceutics classification system. Class-II drugs are poorly water soluble but once dissolved, they rapidly pass biological membrane like the gastrointestinal wall [5, 6]. As a consequence, class-II drugs slowly dissolve in the aqueous environment of the gastrointestinal tract after oral administration and result in a poor bioavailability, while increasing the dissolution rate will also improve bioavailability [7, 8]. Preparation of solid dispersions is one of the strategies to increase the dissolution rate of class-II drugs [9]. Solid dispersions consist of two component systems in which the drug is dispersed mono molecularly or as small particles in a hydrophilic matrix. The increased dissolution rate can be attributed to an enhanced surface area of the drug for dissolution, improved wetting of the drug and to an enhanced solubility due to the small size of the drug particle.

[10]. Many studies on the application of solid dispersions or the improved dissolution behaviour of lipophlic drugs have been published. [11] In the present study solid dispersions of CAND were made by taking PEG-4000, PEG-6000 as carriers using kneading and solvent evaporation techniques, and then tablets of the best solid dispersion were made into tablets by the direct compression method. The prepared tablet formulations were evaluated for their quality.

2. Materials and Methods

2.1 Materials

Candesartan cilexetil is obtained as a gift sample from Dr. Reddy's Lab, Hyderabad. PEG 4000, PEG 6000 were purchased from Sd Fine chemicals Limited, Mumbai. Avicel PH-102, Ac-Di-Sol was from FMC Biopolymers. All other chemicals used in the study were analytical grade.

2.2 Methods

2.2.1 Preparation of solid dispersions by kneading method

Accurately weighed amount of CAND and either carrier at various drug to carrier weight ratios [Table 1] were placed in a glass mortar and then the mixtures were kneaded with small volume of methanol for 30 minutes to produce homogeneous dispersion. Once homogeneous dispersions were obtained, samples were allowed to dry at room temperature [13]. After drying the dispersions were pulverized and then sifted through sieve number 60 to obtain uniform size particles. The samples were stored in desiccator until further use.

Table 1: Composition of batches containing Candesartan cilexetil and carriers.

Batches of Kneading Solid Dispersions	Candesartan cilexetil(mg)	PEG 4000(mg)	PEG 6000(mg)	Drug : Carrier ratio	Batches of Solvent evaporation Solid Dispersions
SD1	16	16	-	1:1	SD7
SD2	16	32	-	1:2	SD8
SD3	16	48	-	1:3	SD9
SD4	16	-	16	1:1	SD10
SD5	16	-	32	1:2	SD11
SD6	16	-	48	1:3	SD12

2.2.2 Preparation of solid dispersions by solvent evaporation

Solid dispersions of CAND and either carrier at various drugs to carrier weight ratios [Table 1] were dissolved in methanol to get a clear solution in a dry beaker. The solvent was evaporated at 45℃, and resulting residue was dried in hot air oven for 1 hour and stored for 24 hours in a desiccator. Subsequently, the dispersion was ground in a mortar and passed through sieve number 60 [14].

2.3 Determination of drug content

Drug content was calculated by dissolving solid dispersion equivalent to 10mg of CAND in suitable quantity of methanol, filtered and analyzed by UV-Visible spectrophotometer at 254 nm.

2.4 *In vitro* drug release

Accurately weighed preparations equivalent to 10 mg of CAND were added to 900 ml of dissolution media (0.05 M phosphate buffer pH 6.5 containing 0.35% Polysorbate 20) in a USP dissolution apparatus II and stirred at a speed of 50rpm at 37± 0.5 ℃. 5 ml of aliquots were withdrawn at 10, 20, 30, 45 and 60 minutes from the basket and replaced by 5 ml of fresh dissolution media. The collected samples were analyzed after suitable dilution at 254 nm using UV- Visible spectrophotometer against the blank. Drug release studies were carried out in triplicate. The dissolution of pure CAND was done similarly. The release profile data were analyzed by model-independent and model-dependent approaches [15, 16]. Model-independent approaches are based on

the ratio of the area under the dissolution curve or on mean dissolution time. Percent dissolution efficiency (%DE) at 30 min and 60 min were calculated to compare the relative performance of various concentrations of carriers in solid dispersions [17]. In model-dependent approaches, release data was fitted to kinetic models like zero order, first order, Higuchi matrix and Hixson-Crowell equations to find the equation with the best fit.

2.5 Formulation of CAND fast dissolving tablets

CAND solid dispersion tablets of SD12 composition were prepared by direct compression method using 10 station rotary tablet punching machine. Tablets were prepared by using Ac-Di-Sol as superdisintegrant, Avicel PH-102 as a directly compressible vehicle. The concentration of superdisintegrant varies from 0 to 4% in tablet formulations. All the ingredients [Table 2] were grinded in a glass motor and were passed through mesh number 60. Finally talc and magnesium sterate were added and mixed. The physicochemical properties of blends were evaluated. The mixed blend of drug and excipients was compressed by rotary tablet punching machine using 6 mm flat punches.

Table 2: Composition of CAND Fast dissolving Tablets.

Ingredients	F1	F2	F3	F4
SD12	64 mg	64 mg	64 mg	64 mg
Ac-Di-Sol	-	3 mg	4.5 mg	6 mg
Avicel PH-102	76 mg	73 mg	71.5 mg	70 mg
Talc	5 mg	5 mg	5 mg	5 mg
Magnesium Sterate	5 mg	5 mg	5 mg	5 mg

2.6 Evaluation of CAND fast dissolving tablets

All the prepared tablets were evaluated for drug content uniformity, disintegration time, dissolution time, hardness, friability, wetting time and water absorption ratio. Hardness was measured using Pfizer hardness tester. Friability was determined using Roche friabilator.

2.6.1 Content uniformity

Ten randomly selected tablets of each formulation were weighed and average weight calculated, and then tablets were powdered in a glass mortar. The weight equivalent to 2 mg CAND was weighed and dissolved in 10 ml of methanol. The solution was filtered and estimated by UV-Visible spectrophotometry at 254 nm.

2.6.2 *In vitro* disintegration test

The *in vitro* disintegration time was determined using disintegration test apparatus. One tablet was placed in each of six tubes of apparatus and one disc was added to each tube. The basket assembly was positioned in one litre of 0.05 M phosphate buffer pH 6.5 containing 0.35% polysorbate 20. The time taken for the complete disintegration of the tablet was measured.

2.6.3 *In vitro* dissolution test for tablet formulations

In vitro dissolution studies for all batches of tablets were carried out using the USP paddle method in 900 ml of 0.05M phosphate buffer pH 6.5 containing 0.35% polysorbate 20 as dissolution media, maintained at 37±0.5 ℃ at 50 rpm. 5 ml of aliquots were withdrawn at 10, 20, 30, 45 and 60 minutes from the basket and replaced by 5 ml of fresh dissolution media. The collected samples were analyzed after suitable dilution at 254 nm using UV- Visible spectrophotometer against the blank.

2.6.4 Wetting time and water absorption ratio

A piece of tissue paper folded twice was placed in a petridish containing 6 ml of phosphate buffer pH 6.8. A tablet was placed on the paper and the time for complete wetting was measured. Water

absorption ratio indicated with R was calculated using equation, where W_b is the weight of the tablet before water absorption and W_a is the weight of the tablet after water absorption. $R= (W_a-W_a/W_b) \times 100$.

2.6.5 Stability test

Short-term stability study on the promising F4 formulation was carried out by storing the tablets in amber colored rubber stoppered vial at 40 ℃/75 RH over a period of 45 days [18].

3. Results and Discussion

CAND assay in all prepared dispersions was more than 99% and also low values of standard deviation indicate that the drug was uniformly distributed in solid dispersions. Hence the method used to prepare solid dispersions was found to be reproducible. Cumulative amount of CAND dissolved from pure CAND was lower compared with solid dispersions prepared by kneading method [Figure 1]. The cumulative amount of CAND dissolved is even better than kneaded dispersions in dispersions prepared by solvent evaporation method [Figure 2].

It is evident that dissolution efficiency of pure CAND is very low, about 15.1% and 25.07% of drug being dissolved within 30 min, 60 min respectively. Solid dispersions of CAND with PEG 4000 and PEG 6000 considerably enhanced dissolution within 60 min compared to pure drug. The value of DE_{60min} for pure drug, 25.07% was enhanced to 52.81% in kneading dispersions as well as 75.8% in solvent evaporated dispersions. The obtained values of mean dissolution time (MDT) for pure CAND and solid dispersions were calculated [Table 3].

Table 3: %DE_{30min}, %DE_{60min}, MDT and Release kinetics of prepared solid dispersions

Formulation	DE 30 min	DE 60 min	MDT (min)	Correlation coefficient(r)			
				Zero-order	First-order	H-M model	H-C model
Pure Drug	15.10	25.07	28.62	0.9920	0.9874	0.9883	0.9900
SD1	24.25	45.67	24.05	0.9733	0.9898	0.9898	0.9865
SD2	29.13	49.89	22.49	0.9726	0.9940	0.9920	0.9899
SD3	29.63	50.89	21.75	0.9647	0.9868	0.9868	0.9821
SD4	23.58	46.45	22.73	0.9701	0.9767	0.9790	0.9761
SD5	28.40	50.93	22.55	0.9689	0.9801	0.9847	0.9789
SD6	30.03	52.81	22.38	0.9696	0.9838	0.9803	0.9814
SD7	26.40	48.83	23.91	0.9774	0.9880	0.9876	0.9868
SD8	31.30	53.10	21.70	0.9714	0.9855	0.9862	0.9834
SD9	36.38	57.27	20.13	0.9646	0.9812	0.9852	0.9797
SD10	50.78	69.50	15.00	0.9323	0.9965	0.9699	0.9843
SD11	50.91	70.27	15.10	0.9177	0.9872	0.9580	0.9732
SD12	57.12	75.80	14.00	0.9303	0.9959	0.9674	0.9969

DE_{30min} is dissolution efficiency at 30 minutes, DE_{60min} is dissolution efficiency at 60 minutes, MDT is mean dissolution time, H-M is Higuchi matrix, H-C is Hixson-Crowell.

The MDT of CAND is 25.07 min; it decreased to 14 min for solid dispersions with PEG 6000 at 1:3 ratios. A 2.8 fold increase in the dissolution rate of CAND was observed with PEG 6000 (1:3) solid dispersion. *In vitro* dissolution data was fitted into various kinetic models and correlation coefficient (r) was calculated [Table 3]. The goodness of fit for various models investigated for drug and solid dispersions ranked in the order of First order> Higuchi Matrix>Hixson Crowell cube root law> Zero order. The r values of the first order release model are found to be 0.9767 to 0.9965. Hence, the release of drug from preparations predominantly follows first order kinetics. Among the formulations SD12 has shown maximum dissolution efficiency, less MDT, highest

correlation coefficient value 0.9969 with Hixson Crowell cube root law. Hence, SD12 dispersion was used to make fast dissolving tablets.

The study of various parameters of the formulations revealed that all the tablets were acceptable in regard to amount of candesartan cilexetil, hardness, friability. The results also showed decrease in disintegration time as the concentration of superdisintegrant increases [Table 4]. Higher levels of disintegrants probably made larger pores with continuous network providing enough pressure within a matrix for faster disintegration. The formulation F4 shows maximum % DE 60 min value. The *in vitro* dissolution data was fitted into various kinetic models. The goodness of fit for various models were in order of First order> Hixson-Crowell cube root law > Higuchi matrix > Zero order. *In vitro* release data of formulation F4 was best fitted to first order model with r value 0.9965.

Formulation F4 was subjected to accelerated stability study for a period of 45 days at 40±2 ℃, 75% RH showed no significant changes in both physicochemical properties and dissolution profile at 5% level [Table 5]. We find a tabulated t value of 2.45 (p=0.05), calculated value 0.04 indicates insignificance.

Table 4: Characteristics of fast dissolving tablets

Batch	Drug content (%)*	Friability (%)	Hardness (Kg/cm^2)*	DT** (sec)	%DE 60min	Wetting time(sec)*	Water absorption ratio*
F1	99.87±0.28	0.54	3.2±0.31	25	73.63	25.12±0.24	45.12±0.13
F2	100.04±0.78	0.64	3.1±0.62	18	74.75	24.54±0.67	42.14±0.54
F3	100.45±0.65	0.65	3.2±0.12	12	75.52	24.15±0.34	41.25±0.76
F4	99.98±0.35	0.47	3.3±0.13	10	75.73	23.12±0.56	41.15±0.12

DT** Disintegration time. *Each value represents mean± S.D (n=6)

Table 5: Stability Data of F4

Time	Initial Cumulative % drug release	Cumulative % drug release after 45days
0	0	0
10	55.1	54
20	71.0	71
30	88.1	88
45	96.0	94
60	98.9	96.8

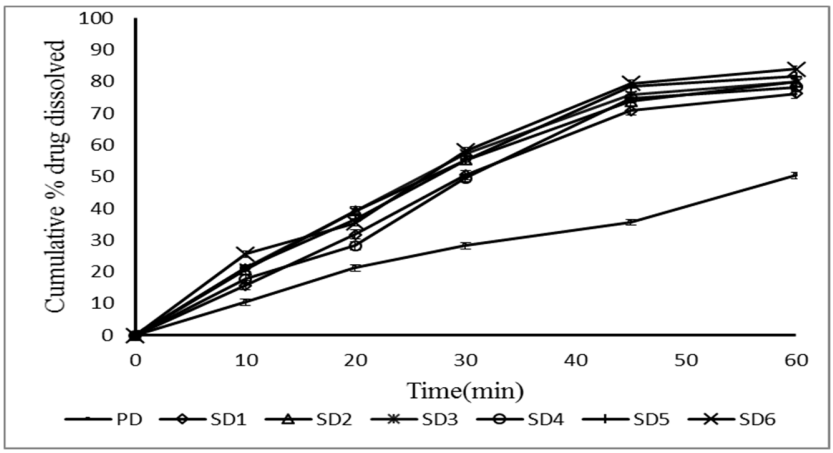

Figure 1: comparative *in vitro* release profile of solid dispersions prepared by kneading method.

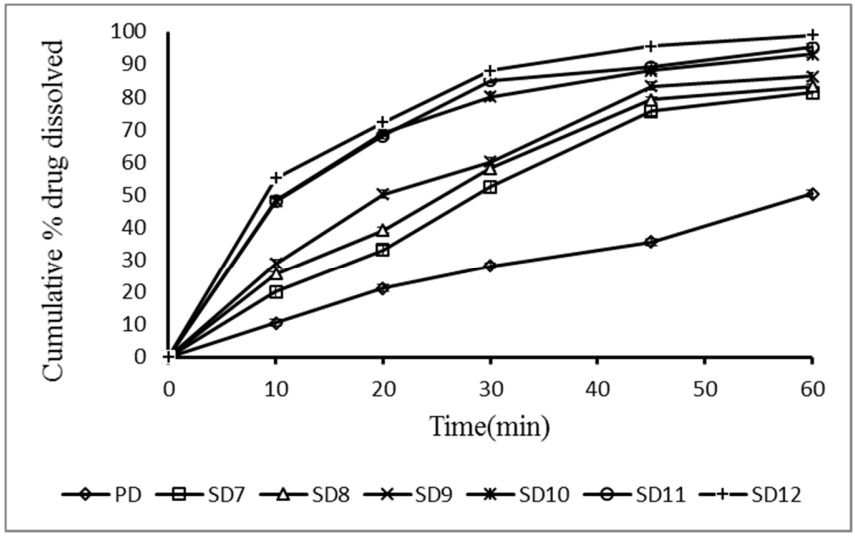

Figure 2: comparative *in vitro* release profile of solid dispersions prepared by solvent evaporation.

4. Conclusion

The study demonstrated that the dissolution rate of candesartan cilexetil can be enhanced by formulating solid dispersions of candesartan cilexetil with PEG 6000. The solubilization effect of PEG 6000, reduction of particle aggregation of the drug, formation of microcrystalline or amorphous drug, increased wettability and dispersibility, and alteration of the surface properties of the drug particles might be responsible for the enhanced dissolution rate. Tablet formulation F4 showed a higher rate of dissolution and acceptable stability.

5. Acknowledgements

The authors would like to express sincere thanks to M/S. Dr. Reddy's Laboratories for providing a gift sample of drug. The authors would also like to express sincere thanks to the management of JIMMA University (department of public health and sciences) for providing the necessary facilities in carrying out this work.

6. References

1. Ross A, Papademetriou V. Candesartan cilexetil in cardiovascular disease. Expert Rev Cardiovasc Ther 2004; 2:829-35.
2. Israili ZH. Clinical pharmacokinetics of angiotensin II (AT1) receptor blockers in hypertension. J Hum Hypertens 2000; 14:S73-86.
3. Al Omari AA, Al Omari MM, Badwan AA, Al-Sou'od KA. Effect of cyclodextrins on the solubility and stability of candesartan cilexetil in solution and solid state. J Pharm Biomed Anal 2011; 54:503-9.
4. Cagigal E, González L, Alonso RM, Jiménez RM. PKa determination of Angiotensin II receptor antagonist (ARA II) by spectrofluorimetry. J Pharm Biomed Anal 2001; 26:477-86.
5. Ku MS. Use of biopharmaceutical classification system in the early drug development. AAPS J 2008; 10:208-12.
6. Löbenberg R, Amidon GL. Modern bioavailability, bioequivalence and Biopharmaceutics classification system. New scientific approaches to international regulatory standards. Eur J Pharm Biopharm 2000; 50:3-12.
7. Ali AA, Gorashi AS. Absorption and dissolution of nitrofurantoin from different experimental formulations. Int J Pharm 1984; 19:297-306.

8. Fawaz F, Bonini F, Guyot M, Bildet J, Maury M, Lagueny AM. Bioavailability of norfloxacin from PEG 6000 solid dispersions and cyclodextrin inclusion complexes in rabbits. Int J Pharm 1996; 132:271-75.
9. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today 2007; 12:1068-75.
10. Craig DQ. The Mechanisms of drug release from solid dispersions in water soluble polymers. Int J Pharm 2002; 231:131-44.
11. Serajuddin AT. Solid dispersion of poorly water soluble drugs: early promises, subsequent problems, and recent brackthroughts. J Pharm Sci 1999; 88:1058-66.
12. Choudhary D, Kumar S, Gupta GD. Enhancement of solubility and dissolution of glipizide by solid dispersion (kneading) technique. Asian J Pharm 2009; 3:245-51.
13. Modi A, Tayade P. Enhancement of dissolution profile by solid dispersion (kneading) technique. AAPS Pharm sci Tech 2006; 7:68.
14. Bhole PG, Patil VR. Enhancement of water solubility of felodipine by preparing solid dispersion using poly-ethylene glycol 6000 and poly-vinyl alcohol. Asian J Pharm 2009; 3:240-4.
15. Polli JE, Rekhi GS, Augsburger LL, Shah VP. Methods to compare dissolution profiles and a rationale for wide dissolution specifications metoprolol tartrate tablets. J Pharm Sci 1997; 86:690-70.
16. Anderson NH, Bauer M, Boussac N, Khan-Malek R, Munden P, Sardaro M. An evaluation of fit factors and dissolution efficiency for the comparison of in vitro dissolution profiles. J Pharm Biomed Anal 1998; 17:811-22.
17. Khan KA. The concept of dissolution efficiency. J Pharm Pharmacol 1975; 27:48-9.
18. Patel MM, Patel DM. Fast dissolving Valdecoxib tablets containing solid dispersion of Valdecoxib. Indian J Pharm Sci 2006; 68:222-6.