Research Article

Formulation and Evaluation of Solid Dispersion Tablets of Poorly water soluble drug candesartan cilexetil using poloxamer 407

Dr. A. Seetha Devi[1], Divya Peddinti[1]*, Archana Pinnika[1]
[1]Department of Pharmaceutics, Hindu college of Pharmacy, Guntur, Andhra Pradesh, India.
***Corresponding author's E-mail:** divs2joy@yahoo.co.in

Accepted on: 21-08-2014; **Finalized on:** 31-10-2014.

ABSTRACT

The main objective of the present work was to improve the solubility and dissolution rate of poorly water soluble anti-hypertensive drug Candesartan cilexetil by Solid dispersion technology using hydrophilic polymer poloxamer 407 as carrier. The prepared formulations were evaluated and characterized. All the results of pre-compression parameters were found to be satisfactory and post-compression parameters showed good mechanical strength and good uniformity in all formulations. The solubility of Candesartan cilexetil solid dispersions (K1) showed 6.4 folds of increase when compared with pure drug. From the *in vitro* drug release studies, the formulation CK1 showed 4.4 folds increase in drug release when compared with pure drug of Candesartan cilexetil. Based on solubility studies, disintegration time, *in vitro* drug release studies and other parameters, formulation CK1 was optimized. There was no significant change recorded in the %drug content and disintegration time after stability studies. Thus solid dispersion technology was one of the successfully and promising technology to enhance the solubility and dissolution rate of Candesartan cilexetil.

Keywords: Candesartan cilexetil, *In vitro* drug release, Poloxamer 407, Solid dispersion, Solubility.

INTRODUCTION

Aqueous solubility of a drug can be a critical limitation to its oral absorption. Poorly water soluble drugs are associated with slow drug absorption leading eventually to inadequate and variable bioavailability. Based on their solubility and permeability characteristics, the Biopharmaceutical Classification System (BCS) categories into two major classes, class II and class IV.[1,2] The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Preparation of solid dispersions is a popular approach used to improve the oral bioavailability of poorly water soluble drugs.[3]

Candesartan cilexetil (CC) is an esterified prodrug of candesartan, a non-peptide angiotensin II receptor antagonist indicated for the treatment of hypertension alone or in combination with other antihypertensive agents. Based on its solubility across physiologically relevant pH conditions and absorption characteristics, Candesartan cilexetil is classified in the Biopharmaceutics Classification System (BCS) as a class II drug. The major drawback in the therapeutic application and efficacy of Candesartan cilexetil as an oral dosage form is its low aqueous solubility (0.003mg/ml) and its low oral bioavailability (15%).[4]

Poloxamer is block copolymers used in pharmaceutical formulations for solubilization of poorly water soluble drugs. Owing to their low melting point, they are suitable for the melt technique in solid dispersions. Their ability to self-aggregate, thereby forming micelles and liquid crystalline phases and greater hydrophilicity is another advantage for the solubilization of poorly water soluble drugs.[5]

The aim of the present investigation is to improve the solubility and dissolution rate of poorly water soluble drug Candesartan cilexetil by solid dispersion technique using Poloxamer 407 as a hydrophilic carrier in different ratios (1:1, 1:2, 1:3) by means of kneading method, solvent evaporation method and melting method. Thus obtained solid dispersions of Candesartan cilexetil are formulated into immediate release tablets employing direct compression technique. The formulations are characterized by Differential scanning calorimetry (DSC), Fourier Transform Infrared (FT-IR) and short term stability studies were conducted.

MATERIALS AND METHODS

Candesartan cilexetil and Poloxamer 407 were obtained as gift samples from Hetero labs, Hyderabad. Crospovidone and Sodium starch glycolate were purchased from S.D. Fine Chemicals Ltd. All other chemicals/solvents used were of analytical grade.

Solubility Studies[6, 7]

Solubility study for Candesartan cilexetil

The solubility of Candesartan cilexetil was determined in water and different pH buffers (phosphate buffer of pH 6.5, pH 6.8 and pH 7.4) and buffers containing different amount of solubilizer (0.3%, 0.35%, 0.4%, 0.5% and 0.7% tween20). The solubility study was conducted by taking excess amount of drug in 10ml of solution and the solutions were kept in a rotary shaker for 48hrs. Then the solutions were filtered and diluted with sufficient amount of the same solvent. The absorbances of the solutions were determined at 257nm.

Solubility study for Candesartan cilexetil solid dispersions/physical mixtures

The saturation solubility studies were carried out by taking excess amount of solid dispersion and was added to the screw capped vials containing 5 ml of phosphate buffer of pH 6.5 containing 0.35% tween20, placed in a rotary shaker and agitated at room temperature (37^0C) at 100 rpm for 48 hours. After equilibrium, the solutions were carefully filtered through Whatman filter paper and after appropriate dilution; solutions were analyzed at 257 nm by using UV- visible spectrophotometer.

Compatibility Studies

Fourier-transform infrared (FT IR) spectra of moisture free powdered samples of Candesartan cilexetil and physical mixture of drug and excipients were obtained using a spectrophotometer by Attenuated Total Reflectance method. The scanning range was 500-4000 cm^{-1}.

Determination of Flow Properties[8, 9]

Angle of Repose

A funnel with 10mm inner diameter of stem was fixed at a height (h) of 2 cm over the platform. About 10gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the stream of the funnel. A rough circle was drawn around the pile base and the radius(r) of the powder cone was measured. Angle of repose was calculated from the average radius using the following formula;

$$\theta = \tan^{-1}(h/r)$$

Bulk Density

Apparent bulk density (gm/ml) of the drug was determined by pouring (preserved 40-mesh) gently 25gm of sample through a glass funnel into a 100ml graduated cylinder. After pouring the powder bed was made uniform without disturbing. Then the volume was measured directly from the graduation marks on the cylinder as ml. The volume measure was called as the bulk volume and the bulk density was calculated by the following formula;

Bulk density = Weight of powder/ bulk volume

Tapped density

Tapped density of the drug was determined by pouring gently 25gm of sample through a glass funnel into a 100ml graduated cylinder. The cylinder was tapped from height of 2inches until a constant volume was obtained using bulk density apparatus. Volume occupied by the sample after tapping were recorded and tapped density was calculated.

Tapped density = Weight of powder/Tapped volume

Carr's Compressibility Index

A useful empirical guide is given by the Carr's index or compressibility index calculated from bulk density and tapped density.

Carr's index = (Tapped density – Bulk density / Tapped density) X 100

Hausner's Ratio

Hausner's ratio provides an indication of the degree of densification which could result from vibration of the feed hopper. A lower value of Hausner's ratio indicates better flow and vice versa.

Hausner's Ratio = Tapped density / Bulk density

Preparation of Solid Dispersions[10]

Solid dispersions of Candesartan cilexetil were prepared using Poloxamer 407 as a carrier by different methods like Physical mixing, Melting method and Kneading method and different drug to poloxamer ratios i.e., 1:1, 1:2 and 1:3.

Physical mixing

Physical mixtures were prepared by mixing Candesartan cilexetil and Poloxamer 407 in a glass mortar for 10min. The resulting mixture was passed through sieve no: 60 and then stored in a desiccator at room temperature until use.

Melting method

Solid dispersions were prepared by melting the physical mixture of Candesartan cilexetil and Poloxamer 407 in a china dish. The fusion temperature was controlled between 60-70°C. The molten mixture was immediately cooled and solidified in an ice bath with vigorous stirring. The solid obtained was scrapped, crushed, pulverized and passed through sieve no: 60. The obtained product was stored in a desiccator until used for further studies.

Kneading method

Candesartan cilexetil was dissolved in ethanol and to this solution Poloxamer 407 was added. Then the mixture was triturated in a glass mortar until it forms paste like consistency and allowed to drug. The dried powder was passed through sieve no: 60 and the final product was stored in a desiccator until use.

Preparation of tablets containing Solid dispersions of Candesartan cilexetil[11]

Immediate release tablets of Candesartan cilexetil were prepared by direct compression method. The physical mixtures and solid dispersions equivalent to 16mg of drug Candesartan cilexetil were taken. They are uniformly mixed with directly compressible diluents (Mannitol and MCC), lubricant (Magnesium stearate) and superdisintegrants (Crospovidone and Sodium starch glycolate) in required quantities as per the formulae given in the Table 1. The total weight of the single tablet was

200mg. All the ingredients were passed through sieve no: 60 prior to mixing and blended followed by direct compression of the blend using 10 station compression machine, equipped with 7mm flat faced punches.

Table 1: Composition of Candesartan cilexetil tablets

Formulation Code	Ingredients (mg)						
	Candesartan Cilexetil equivalent to 16mg	Sodium Starch glycolate	Crospovidone	Mannitol	Micro crystalline cellulose	Magnesium stearate	Total weight
SPM1	32	8	-	100	58	2	200
SPM2	48	8	-	100	42	2	200
SPM3	64	8	-	100	26	2	200
SM1	32	8	-	100	58	2	200
SM2	48	8	-	100	42	2	200
SM3	64	8	-	100	26	2	200
SK1	32	8	-	100	58	2	200
SK2	48	8	-	100	42	2	200
SK3	64	8	-	100	26	2	200
CPM1	32	-	8	100	58	2	200
CPM2	48	-	8	100	42	2	200
CPM3	64	-	8	100	26	2	200
CM1	32	-	8	100	58	2	200
CM2	48	-	8	100	42	2	200
CM3	64	-	8	100	26	2	200
CK1	32	-	8	100	58	2	200
CK2	48	-	8	100	42	2	200
CK3	64	-	8	100	26	2	200

Evaluation of Tablets[12]

Hardness

Hardness of the tablets was determined by using Monsanto hardness tester. The tablet was fixed and reading of the indicator adjusted to zero. Then force on the edge of the tablets was gradually increased by moving the screw knob forward until the tablets breaks. The reading was noted from the scale which indicates the pressure required in kg/cm^2 to break the tablet.

Friability

20 Tablets from each batch were selected randomly and weighed. The pre weighed tablets were subjected to friability testing using Roche friabilator for 100 revolutions at 25rpm and dropping a tablet at height of 6inches in each revolution. Tablets were removed, de-dusted and weighted again. Following formula was used to calculate the friability. The acceptable limits of weight loss should not be more than 0.8%.

%F = [loss in weight / initial weight] 100

Weight variation

20 tablets from each batch at random were taken and weighed. The average weight was calculated, then each tablet was weighted individually and weight of each tablet was noted. The weights of individual tablets were then compared with the average weight that was already calculated.

Drug content uniformity[13]

Tablets of Candesartan cilexetil from a batch was taken at random and was crushed to fine powder. The powder material equivalent to 16mg of Candesartan cilexetil was transferred in to a 250ml volumetric flask and 100ml phosphate buffer pH 6.5 containing surfactant was added to it. It was shaken occasionally for about 30 minutes and the volume was made up 250ml by adding same media. The mixture was then filtered and aliquot of filtrate was diluted and then the absorbance was measured at 257nm.

Disintegration time

In the present study disintegration test was carried out on 6 tablets of each batch using the apparatus specified in USP (disintegration apparatus USP). The distilled water at $37^0C \pm 2^0C$ was used as a disintegration media.

***In Vitro* Drug Release / Dissolution Studies**

The tablet samples were subjected to *in vitro* dissolution studies using USP type II dissolution apparatus at 37± 2°C

and 50rpm speed. The dissolution rate was studied using 900ml of phosphate buffer of pH 6.5 containing 0.35% tween20. Samples were withdrawn at regular intervals of 5min, 10min, 15min, 20min, 25min, 30min, 35min, 40min, 45min, 50min, 55min and 60min. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium, to maintain the constant volume of dissolution medium throughout the experiment. Drug content of the each sample was determined by UV spectrophotometer at 257nm after suitable dilution of the samples.

Kinetics and Mechanism of a drug release

The rate and mechanism of release of Candesartan cilexetil from the prepared solid dispersions tablets were analyzed by fitting the dissolution data into Zero- order and First-order release kinetics.

Characterization of solid dispersions[14, 15]

FTIR studies

FT IR studies were carried out for pure drug, physical mixtures and solid dispersions. The IR spectra's were recorded using FT IR spectrophotometer (Bruker) with a scanning range of 500-4000cm^{-1}.

DSC studies

Sample (10.9mg) was heated under nitrogen atmosphere on a platinum pan at a heating rate of 10^{0}C/min over the temperature range of 5 to 300°C.

RESULTS AND DISCUSSION

Solubility Studies

Solubility of Candesartan cilexetil was more in phosphate buffer of pH 6.5 containing 0.35% tween20. So phosphate buffer of pH 6.5 containing 0.35% tween20 was selected as the dissolution medium for further studies.

Table 2: Solubility of Candesartan cilexetil solid dispersions/physical mixtures

Solid dispersions/ physical mixtures	Solubility (mg/ml)	No. of folds increase
CC	0.417	-
PM1	1.579	3.7
PM2	1.115	2.6
PM3	1.054	2.5
M1	2.521	6
M2	2.354	5.6
M3	2.309	5.5
K1	2.699	6.4
K2	2.512	6
K3	2.489	5.9

Table 3: Pre compression evaluation parameters of Candesartan cilexetil Tablets formulation blends

Formulation code	Angle of Repose(^{0})*	Bulk density (gm/cc) *	Tapped density (gm/cc) *	Carr's Index (%)*	Hausner's Ratio*
SPM1	30.5±0.92	0.560±0.015	0.699±0.016	19.88±0.88	1.24±0.023
SPM2	28.9±0.88	0.559±0.022	0.699±0.018	20.02±0.90	1.25±0.028
SPM3	29.7±0.86	0.564±0.016	0.695±0.021	18.84±0.94	1.23±0.025
SM1	27.1±0.97	0.563±0.023	0.696±0.019	19.10±0.97	1.23±0.031
SM2	29.2±0.91	0.571±0.021	0.687±0.016	16.88±0.86	1.20±0.023
SM3	28.5±0.85	0.577±0.018	0.694±0.019	16.85±0.92	1.20±0.032
SK1	25.3±0.93	0.565±0.014	0.690±0.022	18.11±0.89	1.22±0.027
SK2	26.8±0.94	0.567±0.019	0.691±0.017	17.94±0.99	1.21±0.031
SK3	25.1±0.87	0.572±0.015	0.686±0.022	16.61±0.85	1.19±0.028
CPM1	28.2±0.83	0.564±0.023	0.695±0.016	18.84±0.97	1.23±0.025
CPM2	26.3±0.91	0.568±0.014	0.699±0.023	18.74±0.96	1.24±0.030
CPM3	28.1±0.82	0.563±0.015	0.696±0.025	19.10±0.84	1.23±0.027
CM1	26.7±0.94	0.572±0.019	0.693±0.015	17.46±0.88	1.21±0.022
CM2	28.3±0.91	0.562±0.015	0.690±0.017	18.50±0.85	1.22±0.031
CM3	27.1±0.86	0.573±0.022	0.686±0.018	16.47±0.83	1.19±0.033
CK1	24.8±0.87	0.562±0.017	0.681±0.023	17.48±0.91	1.21±0.029
CK2	26.6±0.88	0.578±0.016	0.689±0.018	16.11±0.95	1.20±0.028
CK3	25.4±0.95	0.576±0.023	0.682±0.019	15.54±0.87	1.18±0.035

*All values represent mean± standard deviation (SD), n=3

Table 4: Post compression evaluation parameters of Tablets of Candesartan cilexetil

Formulation code	Weight Variation (mg)*	Hardness (kg/cm^2)*	Friability (%)	Disintegration Time(min)*	Drug content (%) *
SPM1	199.7±0.42	3.5±0.11	0.54	3.45±0.08	99.17±0.36
SPM2	199.2±0.87	3.9±0.15	0.62	5.49±0.06	99.78±0.51
SPM3	200.1±0.52	3.4±0.23	0.57	7.51±0.05	100.45±0.34
SM1	200.8±0.90	3.6±0.26	0.61	0.38±0.09	100.31±0.28
SM2	199.3±0.31	4.0±0.12	0.56	1.32±0.07	99.58±0.54
SM3	199.8±0.71	3.3±0.24	0.73	1.59±0.03	98.21±0.45
SK1	199.4±0.74	3.8±0.15	0.65	0.12±0.04	100.97±0.38
SK2	199.7±0.36	3.7±0.18	0.74	1.08±0.02	98.89±0.42
SK3	200.6±0.58	4.2±0.14	0.58	1.25±0.05	99.32±0.55
CPM1	199.2±0.92	3.8±0.25	0.68	3.11±0.07	99.98±0.43
CPM2	200.7±0.80	4.1±0.17	0.54	5.32±0.03	100.47±0.51
CPM3	198.7±0.44	3.6±0.19	0.75	7.15±0.07	98.34±0.38
CM1	199.1±0.50	3.8±0.11	0.62	0.21±0.04	99.16±0.58
CM2	199.5±0.79	3.5±0.21	0.73	1.14±0.02	100.2±0.42
CM3	200.7±0.65	3.4±0.18	0.55	1.42±0.08	99.11±0.49
CK1	199.6±0.56	3.9±0.22	0.71	0.05±0.04	99.83±0.58
CK2	200.3±0.71	3.6±0.15	0.67	0.58±0.05	99.64±0.49
CK3	199.4±0.57	4.1±0.26	0.68	1.12±0.03	98.55±0.35

*All values represent mean± standard deviation (SD), n=3

For the Candesartan cilexetil physical mixtures the solubility was increased by 2.5 to3.7 folds, for Candesartan cilexetil solid dispersions prepared by melting method the solubility was increased by 5.5 to 6 folds and for Candesartan cilexetil solid dispersions prepared by kneading method the solubility was increased by 5.9 to 6.4 folds, when compared to Candesartan cilexetil pure drug (Table 2).

Compatibility Studies (FTIR Studies)

FT IR studies revealed that there was no physicochemical interaction between Candesartan cilexetil and other excipients. All the peaks were remained unaltered in the IR spectrum of physical mixture of drug and excipients. IR spectra revealed that there was no chemical interaction of drug with other excipients.

Evaluation of Flow Properties

All the prepared powdered blends were evaluated for Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio. The results (Table 3) confirmed that the physical mixture and solid dispersion formulation blends showed improved flow property when compared with pure drug.

Evaluation of tablets

The weight variation was within the range of 199.1mg to 200.8mg for formulations. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than 7.5%, i.e., in the Pharmacopoeial limits, which provide good uniformity in all formulations. The hardness of all the tablets prepared was found to be in the range of $3.3kg/cm^2$ to $4.2kg/cm^2$, this indicates good mechanical strength of tablets. In the friability test, the percentage weight loss of all formulations varied from 0.54% to 0.75%, indicating all the values are within the acceptable limits.

The % drug content of all batches of tablets was determined and it was within the range of 99.11% to 100.97%, indicating good uniformity among different formulation of tablets. The disintegration time of formulations containing solid dispersions was found to be between 5 sec to 1min 59 sec whereas for physical mixtures it was found to be between 3min 11sec to 7min 51sec i.e, solid dispersions releases faster than physical mixtures. All the results were shown in the Table 4.

***In vitro* Dissolution studies**

The % drug released from the Candesartan cilexetil tablets with Crospovidone as superdisintegrant, the formulations containing physical mixtures in different drug to carrier ratios i.e., CPM1, CPM2, CPM3 showed drug release of 98.03% in 40 min, 77.32% in 60min and 73.01% in 60min respectively. The formulations containing solid dispersions prepared by melting method in different drug to carrier ratios i.e., CM1, CM2, CM3 showed drug release of 98.14% in 30 min, 96.01% in 60min and 93.35% in 60min respectively. The formulations containing solid dispersions prepared by kneading method (Figure 1) in different drug to carrier

ratios i.e., CK1, CK2, CK3 showed drug release of 98.2% in 20 min, 98.2% in 60min and 95.81% in 60min respectively.

The % drug released from Candesartan cilexetil tablets with Sodium starch glycolate as superdisintegrant, the formulations containing physical mixtures in different drug to carrier ratios i.e., SPM1, SPM2, SPM3 showed drug release of 95% in 40 min, 75.61% in 60min and 74.57% in 60min respectively. The formulations containing solid dispersions prepared by melting method in different drug to carrier ratios i.e., SM1, SM2, SM3 showed drug release of 96.98% in 30 min, 93.84% in 60min and 91.17% in 60min respectively. The formulations containing solid dispersions prepared by kneading method in different drug to carrier ratios i.e., SK1, SK2, SK3 showed drug release of 97.76% in 20 min, 97.51% in 60min and 96.19% in 60min respectively.

The *in vitro* drug release from Candesartan cilexetil tablets containing different superdisintegrants were found in following ascending order:

Crospovidone > Sodium starch glycolate

The *in vitro* drug release from Candesartan cilexetil tablets containing solid dispersions prepared by different methods and with different drug to polymer ratios were found in following ascending order:

Kneading method > Melting method > Physical mixtures

(Drug: Poloxamer)- 1:1 > 1:2 > 1:3

Tablet formulations containing drug to poloxamer ratio 1:1 showed rapid drug release (5 folds compared to drug in 20min) when compared to tablet formulations containing drug to poloxamer ratio 1:2 and drug to poloxamer ratio 1:3. This might be due to gelling action of poloxamer 407 at high concentrations, which can affect the drug dissolution from solid dispersions.

Release kinetics

In order to elucidate the mode and mechanism of drug release, the *in vitro* data was transformed and interpreted at graphical interface constructed using various kinetic models. When R^2 values of regression plots for First order and Zero order were considered, R^2 values for the First order was found to be more than Zero order. Hence it was confirmed that the drug release from Candesartan cilexetil tablets followed First order release kinetics. Therefore the release rate in formulations dependent on concentration or amount of drug incorporated.

Characterization of Solid dispersions

FTIR Studies

FT IR studies of pure drug Candesartan cilexetil, Poloxamer 407, its physical mixtures and solid dispersions were conducted. FT IR spectra of Candesartan cilexetil showed characteristic peaks at 2932cm^{-1} due to C-H slight bend, 1712cm^{-1} due to C=O stretching, 1115cm^{-1} due to C-O stretching, 1275cm^{-1} due to C-N stretching, 3610cm^{-1} due to N-H bend. FT IR spectra of Poloxamer 407 showed characteristic peaks at 2877cm^{-1} due to C-H bend, 1341cm^{-1} due to O-H stretching and 1098cm^{-1} due to C-O stretching. The IR spectra of physical mixture displayed the superimposition of Candesartan cilexetil and Poloxamer407 peaks with decreased peak intensity. The IR spectra of solid dispersions (Fig 2) showed peak corresponding to C-H of Candesartan cilexetil was shifted from 2932cm^{-1} to 2865cm^{-1} in CK1 , which suggests the presence of hydrogen bonding, resulting increase in solubility. Other peaks related to C=O, C-O, C-N and N-H remained unchanged**.**

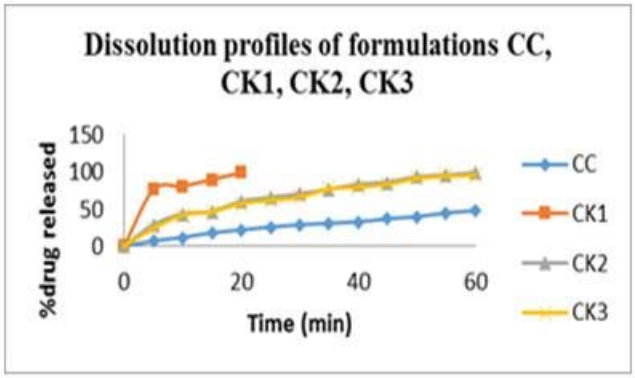

Figure 1: Comparison of dissolution profiles of formulations with Crospovidone containing drug to poloxamer ratio 1:1, 1:2 and 1:3 (Solid dispersions prepared by Kneading method)

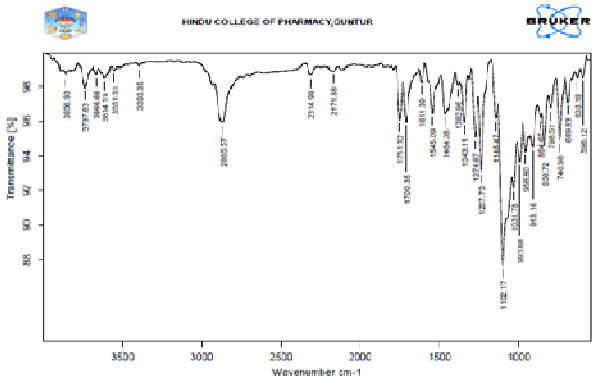

Figure 2: IR spectrum of CK1

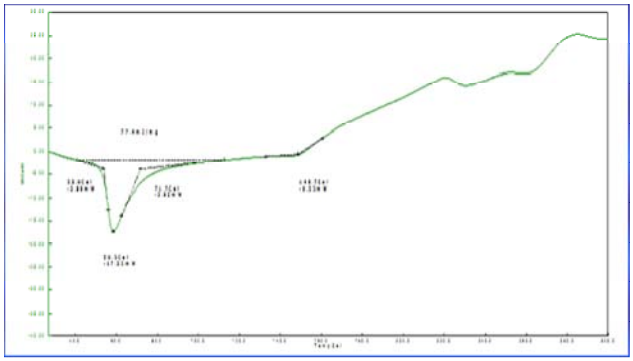

Figure 3: DSC Thermogram of CK1

DSC Studies

The melting point of pure drug Candesartan cilexetil was 178^{0}C whereas polymer Poloxamer 407 was 59.79^{0}C.

Thermogram of optimal formulation containing solid dispersion showed the absence of Candesartan cilexetil melting peak, suggesting that Candesartan cilexetil was completely miscible in the melted carrier. However, the melting peak of Poloxamer 407 in solid dispersion was observed at slightly reduced temperature i.e., 58.5^{0}C (Fig 3) than that of pure Poloxamer 407, indicating the miscibility of drug in carrier.

Short term stability studies

Short term stability studies were conducted for the optimized formulation CK1 of Candesartan cilexetil tablets with Crospovidone as superdisintegrant which contain solid dispersions prepared by kneading method and drug to poloxamer ratio 1:1; at 4^{0}C, at room temperature and 45^{0}C for 3 months. There was no significant change in the %drug content and disintegration time (Table 5).

Table 5: Short term stability studies of optimized formulation CK1

Formulation code	Month	% Drug content*			Disintegration time(sec)*		
		4^{0}C	Room temperature	45^{0}C	4^{0}C	Room temperature	45^{0}C
CK1	1st	99.82±0.45	99.81±0.48	99.82±0.51	08±0.97	06±0.94	08±1.14
	2nd	99.80±0.51	99.80±0.55	99.82±0.48	15±1.21	13±0.97	13±0.91
	3rd	99.80±0.48	99.79±052	99.80±0.54	29±0.99	28±0.92	29±0.98

*All values represent mean± standard deviation (SD), n=3

CONCLUSION

In the present work, an attempt had made to enhance the solubility and dissolution rate of poorly water soluble drug Candesartan cilexetil. All formulations were subjected to phase solubility study, *in vitro* dissolution study, characterization, and short-term stability study and evaluated for pre compression and post compression parameters and the results were found in acceptable range. Among all the formulations CK1 of Candesartan cilexetil tablets with Crospovidone as superdisintegrant which contain solid dispersions prepared by kneading method and drug to poloxamer ratio 1:1 was optimized based on solubility studies, disintegration time, *in vitro* drug release studies and other parameters. Overall, these findings indicate that Solid dispersion technique with poloxamer 407 is a promising approach to enhance the solubility and dissolution rate of poorly water soluble drug Candesartan cilexetil.

REFERENCES

1. Leuner C, Dressman J, Improving Drug Solubility for Oral delivery using Solid dispersions, European Journal of Pharmaceutics and Biopharmaceutics, 50, 2000, 47-60.
2. Swarbrick J, Boylan JC, Encyclopedia of Pharmaceutical Technology, Marcel Dekker. INC. 3, New York, 1991, 315.
3. Chiou WL, Riegelman S, Pharmaceutical Applications of Solid dispersion systems, Journal of Pharmaceutical Sciences, 6(9), 1971, 1281-1302.
4. Asif Husain, Md Sabir Azim, Moloy Mitra, Parminder S. Bhasin, A Review on Candesartan: Pharmacological and pharmaceutical profile, Journal of Applied Pharmaceutical Science, 1(10), 2011, 12-17.
5. Hitesh R. Patel, Rakesh P. Patel, Patel MM, Poloxamers: A pharmaceutical excipients with therapeutic behaviours, International Journal of PharmTech Research, 1(2), 2009, 299-303.
6. Sanjay J. Kshirsagar, Anand Ubhe, Jasmine Malshe, Vidula Sengaokar, A Modified Solvent Method for Preparation of Solid Dispersions, Iranian Journal of Pharmaceutical Sciences, 8(1), 2011, 287-298.
7. Md Sabir Azim, Moloy Mitra, Parimder S. Bhasin, Alam MM, Husain A, Development of Dissolution medium for Candesartan cilexetil by RP HPLC method, American Journal for PharmTech Research, 2(3), 2012, 892-903.
8. Lachman L, Lieberman HA, Kanig JL, The Theory and Practice of Industrial Pharmacy, Varghese Publishing House Bombay, 1987, 182-184.
9. Aulton ME Pharmaceutics, The Science of dosage form design, Churchill living stone, 2nd edition, 2002, 433-435.
10. Prasanthi NL, Manikiran SS, Sowmya S, Anusha B, Rama Rao N, Effect of Poloxamer 188 on In Vitro Dissolution properties of Antipsychotic Solid Dispersions, International Journal of Pharmaceutical Sciences Review and Research, 10(1), 2011, 15-19.
11. Manimaran V, Damodharan N, Mothilal M, Raj Kumar K, Ruby Mamachan Chalackal, Enhancement of Dissolution Rate of Glibenclamide by Solid Dispersion Technology, International Journal of Current Pharmaceutical Research, 2(3), 2011, 14-17.
12. Abba Raju Prasanna Lakshmi, Meka Anand Kumar, Vamshi Krishna M, Annie Vijetha K, Ashwini G, Formulation Development of Irbesartan Immediate release tablets, International Research Journal of Pharmacy, 3(2), 2012, 117-120.
13. Dhrupesh Panchal, Dr. Upendra Patel, Bhavin Bhimani, Formulation and Evaluation of Sustained Release matrix Tablets of Candesartan cilexetil, International Journal of Pharmaceutical Research and Bioscience, 1(4), 2012, 75-101.
14. Monica Rao, Mandage Y, Khole I, Munjapara G, Characterization of Solid Dispersions of Simvastatin with PVP K30 and Poloxamer 188, Indian Journal of Pharmaceutical Education and Research, 45(2), 2011, 145-152.
15. Ebtessam Ahmed Essa, Gehan Fathy Balata, Preparation and Characterization of Domperidone Solid dispersions, Pakistan Journal of Pharmaceutical Sciences, 25(4), 2012, 783-791.

Source of Support: Nil, **Conflict of Interest:** None.