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ENHANCEMENT OF SOLUBILITY OF CANDESARTAN CILEXETIL BY SOLID DISPERSION METHOD

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ABSTRACT:
Candesartan cilexetil has low bioavailability (16%) and thus presents a challenge in formulating a suitable dosage form. To improve the aqueous solubility, solid dispersion formulation of candesartan cilexetil was prepared by solvent evaporation method utilizing skimmed milk powder as carrier. Five different formulations were prepared with different ratios of drug:carrier and the corresponding physical mixtures were prepared. The formulations were characterized for solubility parameters, drug release studies and drug-polymer interactions by using phase solubility studies, dissolution studies, FTIR spectrum and UV overlay spectra. Pure drug showed around 16.2 % dissolution over a period of 60 minutes. Among all the formulations, F4 [[Candesartan cilexetil : skimmed milk Powder (1:7)] was found to be best of all the trails showing fast drug release up to 87.66 %. These results suggest that solid dispersion of Candesartan cilexetil using skimmed milk as carrier is a promising approach for oral delivery of Candesartan cilexetil.

Key words: Candesartan cilexetil, skimmed milk powder, solvent evaporation method.

INTRODUCTION:

Oral drug delivery is the simplest and easiest way of administering drugs. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that originate an effective and reproducible *in vivo* plasma concentration after oral administration [1]. In drug discovery, about 40% of new drug candidates display low solubility in water, which leads to poor bioavailability, high intrasubject or intersubject variability and lack of dose proportionality[2]. The aqueous solubility is a major indicator for the solubility in the intestinal fluids and its potential contribution to bioavailability issues. There are many approaches to increase solubility, such use of surfactants, complexation, polymorphism, salt formation, size reduction and emulsification[3].

The concept of solid dispersion (SD) is defined the term solid dispersion as "a dispersion of one or more active ingredients in an inert carrier or matrix of solid state prepared by melting (fusion), solvent or melting solvent method"[4]. The concept offers many advantages, such as increased drug wettability, higher degree of porosity, no use of toxic constituents, flexibility of formulation and increased solubility and dissolution rate of the drug[5]. It is particularly advantageous for Bio-pharmaceutical classification system class 2 drugs.

Candesartan cilexetil is a drug used for treating high blood pressure (hypertension).

It is in a class of drugs called angiotensin receptor blockers (ARBs). It has bioavailability of 90% and biological half life 9 hrs[6]. Candesartan cilexetil bioavailability can be improved by developing a method simultaneously reducing the particle size and converting the drug to an amorphous state. Solid dispersion technology utilizes these techniques for improved performance[6]. Ankush Choudhary *et al*., have formulated Solid dispersion of atorvastatin using mannitol, PEG 4000 and PVP-k30[7]. No attempt has been made to using skimmed milk as the carrier in the Candesartan cilexetil formulation. In the present work, solid dispersions of Candesartan cilexetil were prepared using skimmed milk as carrier. The skimmed milk is a colloidal suspension of casein micelles, globular proteins and lipoprotein particles. The principle ingredient casein acts as detergent molecule with surfactant property. The functional properties of skimmed milk powder are emulsifying agent, foaming agent, browning agent and thickening agent[8]. The Candesartan cilexetil SD was evaluated for solubility and dissolution rate. Different ratios of drug and carrier were used in the formulation. Simple physical mixtures(PM) of the drug with hydrophilic polymers increased the solubility of drug to some extent but formulation of solid dispersions by solvent evaporation method further improved the dissolution rate of the drug[9]. Candesartan cilexetil was identified by Infrared (IR) spectroscopy and Ultra violet (UV) spectroscopy determination.

MATERIALS AND METHODS

Materials

Skimmed milk powder was purchased from Mother Diary (Punjab India). All other solvents and reagents were of analytical grade.

Preparation of SD

Different Solid dispersions with different ratios of drug and carrier (skimmed milk powder) (1:1), (1:3), (1:5), (1:7), and (1:9) % w/w were prepared using by following solvent evaporation method, methanol as solvent. Required quantities of drug and polymer were dissolved in methanol to get a clear solution. Solvent was removed by continuous trituration which was carried out until a dry mass was obtained. This was further dried at 50 °c for 4hrs in an oven. The product was powdered in a mortar, sieved through 60 mesh screen[10].

Preparation of PM

Required amounts of Candesartan cilexetil and the carrier (skimmed milk powder) in the ratios of 1:1, 1:3, 1:5, 1:7 and 1:9 % w/w (drug:carrier) were thoroughly mixed in a mortar and pestle in order to obtain a homogenous mixture. The resulting mixture was passed through 60 mesh sieve. The powder was stored in a screw cap vial at room temperature until further use[11].

Estimation of drug content:

The PM and SD equivalent to 10 mg of Candesartan cilexetil were dissolved separately in 10 ml of 0.2N phosphate buffer (pH 6.8). The solution was filtered and further diluted as per requirment. The samples were filtered through a 0.45 μm membrane filter and the drug content was determined spectrophotometrically at 255 nm. The blank formulation was treated in the same manner as the Candesartan cilexetil formulations and used as a blank to minimize the interference of protein in the skimmed milk powder[12].

Saturation solubility studies of pure drug:

Saturation solubility studies were conducted according to the method reported by Hecq *et al*[14]. Pure Candesartan cilexetil, was placed in

a flask with glass stopper containing distilled water, phosphate buffer (pH 6.8) and phosphate buffer (pH 6.5). The samples were placed on a shaker, agitated for 48 hrs at $37\pm0.5°C$ until equilibrium was achieved and the aliquots were filtered through 0.45 μm filter. The filtered samples were diluted and assayed using a UV-visible spectro-photometer against a blank prepared[13,14].

Dissolution studies

The *in-vitro* dissolution study was performed in a USP Type II Dissolution rate test apparatus (Electrolab, India) using 900 ml of 0.2 N phosphate buffer (pH 6.8) at 355 nm , with gentle stirring for 30min. Pure candesartan cilexetil or its equivalent of SD or PM was sprinkled into the dissolution flask. At predetermined time intervals, samples o the dissolution medium were withdrawn, filtered through amillipore membrane of 0.45 μm pore diameter and analysed spectro-photometrically against a blank formulation[15].

Characterization of solid dispersions:

Fourier transform infrared (FTIR) spectroscopy was employed to characterize the possible interactions between the drug and the carrier in the solid state by the conventional KBr pellet method. The spectra were scanned over a frequency range 4000-400 cm^{-1} [16].

RESULTS AND DISCUSSION

Calibration curve: A stock solution of Candesartan cilexetil was prepared by dissolving drug in few ml of methanol and the final volume was made up to the mark using 0.2 N phosphate buffer. A series of standard solutions were prepared from the stock solution whose concentrations ranged from (10-90 mcg/ml). Using a UV-Vis spectro-photometer, calibration curve was obtained by reading corresponding absorbance values at 255 nm.

The linear regression equation obtained was used for calculation of drug concentration in further study. The correlation coefficient was found to be 0.999.
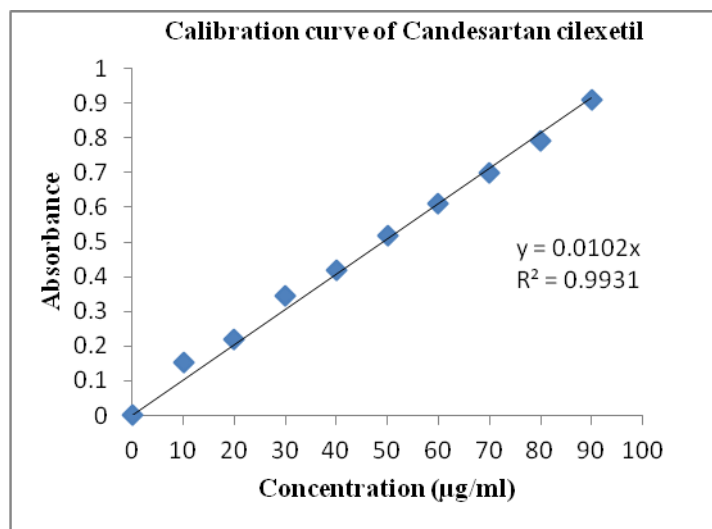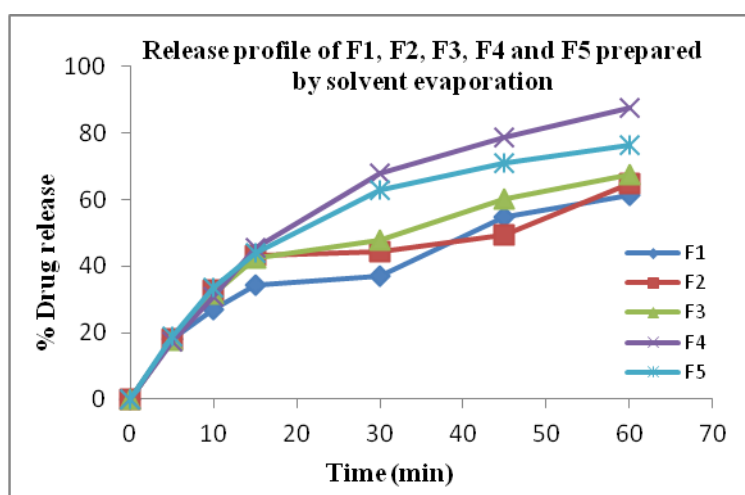

Calibration curve of Candesartan cilexetil

$y = 0.0102x$
$R^2 = 0.9931$

Fig. 1: Calibration curve of Candesartan cilexetil

Table 1: Percent drug release vs time data of pure drug and formulations prepared by solvent evaporation

Time (min)	Percent drug release					
	Drug	SKMP (1:1)	SKMP (1:3)	SKMP (1:5)	SKMP (1:7)	SKMP (1: 9)
5	0.8	17.91	18.18	17.82	17.19	18.99
10	3.6	27.09	32.94	31.50	30.69	33.69
15	5.4	34.20	43.11	42.30	45.54	44.10
30	7.6	36.90	44.37	47.70	67.77	63.09
45	11.7	54.90	49.23	60.30	78.66	71.10
60	16.2	61.20	64.80	67.50	87.66	76.50

Fig. 2: Dissolution profile of Candesartan cilexetil formulations by solvent evaporation

Saturation solubility studies and pH solubility profile of pure drug:

Candesartan cilexetil showed a solubility of 0.142 mg/ml in distilled water, 0.112 mg/ml in 6.5 pH phosphate buffer and 0.142 mg/ml in 6.8 pH phosphate buffer.

In-vitro dissolution studies:

According to the results obtained with dissolution studies, all the solid dispersions exhibited higher rate of dissolution than the pure drug. This might be due to the change in the state of the drug from crystalline to amorphous, reduction of particle size

increase in wettability and prevention of aggregation of the drug particles by carriers. Simple physical mixing of the drug with the hydrophilic polymers increased the solubility of drug to some extent but formulation of solid dispersions by solvent evaporation method further improved the dissolution rate of the drug. Pure drug showed around 16.2 % dissolution over a period of 60 minutes, while its solid dispersions enhanced the dissolution rate up to 87.66 %. Formulation F4 Candesartan cilexetil: skimmed milk powder at a ratio 1:7 prepared by solvent evaporation technique showed highest dissolution rate.

Table 2: Percent drug release vs time data of pure drug and formulations prepared by physical mixing

TIME (min)	Percent drug release					
	Drug	SKMP (1:1)	SKMP (1:3)	SKMP (1:5)	SKMP (1:7)	SKMP (1: 9)
5	0.8	08.55	18.09	18.90	18.72	18.18
10	3.6	10.35	28.44	28.53	34.20	32.76
15	5.4	20.70	31.50	36.90	45.90	38.07
30	7.6	31.50	41.40	45.00	58.50	47.34
45	11.7	47.70	51.36	53.10	67.50	59.04
60	16.2	58.50	63.09	66.60	81.90	72.00
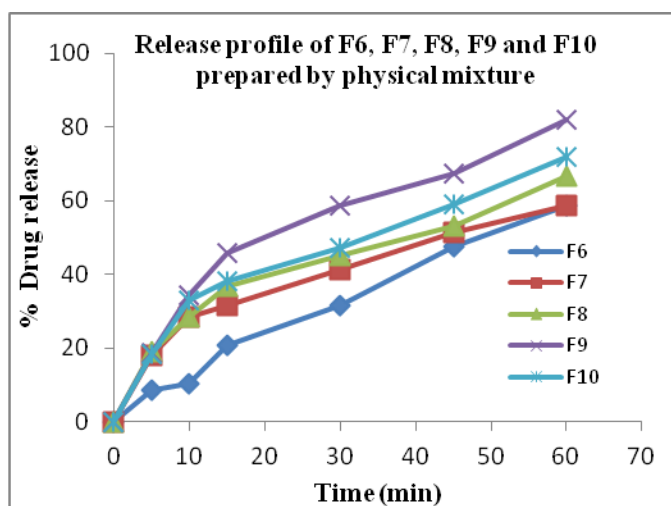
Fig. 3: Dissolution profile of prepared formulations by physical mixing

Drug-polymer compatibility study by Fourier Transform Infrared Spectroscopy

IR spectrum of Candesartan cilexetil was characterized by presence of peaks at 3061.36 cm^{-1} (N-H stretch), 2982.02 cm^{-1} (C-H stretch), 1706.03 cm^{-1} (C=O stretch) and 1611.90 cm^{-1} (C-N stretch). All the solid dispersions showed characteristic peaks of Candesartan cilexetil and the skimmed milk powder. No significant shift in the characteristic peaks for the drug and carrier indicated no significant interaction between them in formulations.
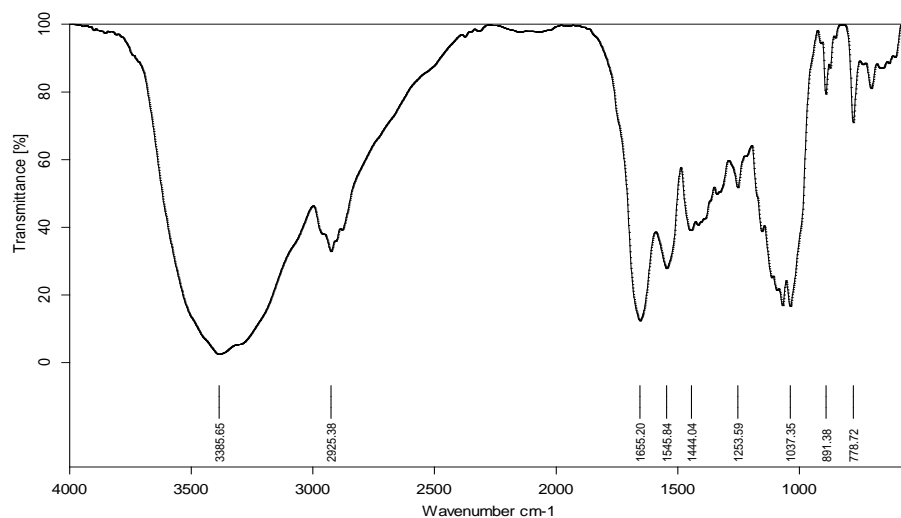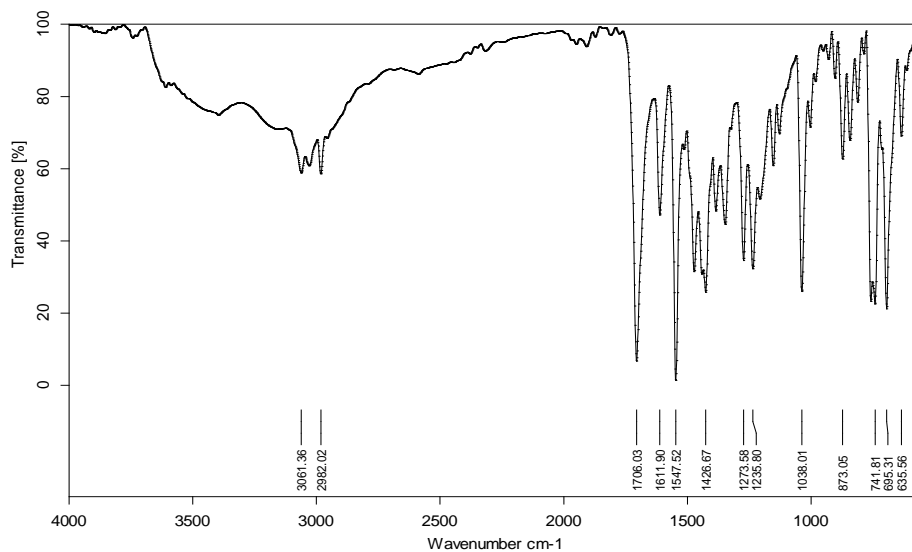
Fig. 4: FTIR spectrum of pure Drug

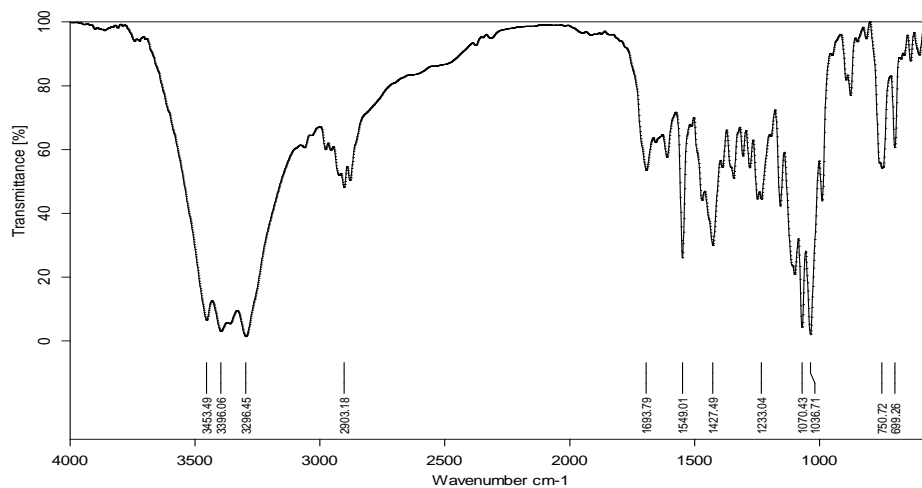**Fig. 5: FTIR spectrum of skimmed milk powder**

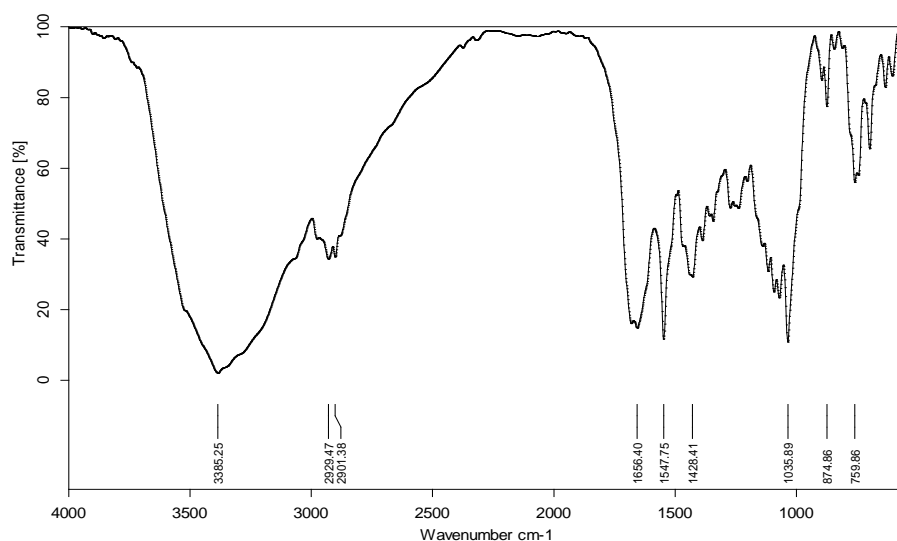**Fig. 6: FTIR spectrum of formulation, F4**

Fig. 6: FTIR spectrum of formulation, F4

CONCLUSION

- The order of drug release of Candesartan cilexetil with skimmed milk powder is as follows: F4> F9> F5> F10> F3> F8> F2> F7> F1> F6.

- All the formulations showed good release of drug. But the formulation F4 (Candesartan cilexetil : skimmed milk powder (1:7)) was found to be best of all the trails showing fast drug release among all the formulations.

- The drug polymer interactions were found to be absent from the results of FT-IR characterization.

- From these results, it was concluded that the solubility and dissolution rate of Candesartan cilexetil can be significantly increased by formulating the solid dispersions with skimmed milk powder with following solvent evaporation method.

- The approach is found to be economical and time saving.

ACKNOWLEDGEMENT

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