Research Article

Preparation and Characterization of Candesartan Cilexetil Solid Lipid Nanoparticulate Capsules

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ABSTRACT

The candesartan cilexetil belongs to class II of the biopharmaceutical classification system and bioavailability is 15% due to the poor aqueous solubility. The purpose of the study is to improve aqueous solubility by nano technology of solid lipid nanoparticle by solvent evaporation method. Here glyceryl monosterate (lipid), polaxemor 407, tweeen 80 (co-surfactant and surfactant respectively) and dichloro methane (organic solvent) are used for formulation. The nanoparticles of candesartan cilexetil are formulated to improve the oral bioavailability by preparing particles of nanosize range with good zeta potential. Phase contrast microscopy (PCM) analysis done to confirm the morphology of prepared solid lipid nanoparticles with free clusters. The lyophilizedcandesartan cilexetilsoilid lipid nonoparticles were filled into hard gelatin capsules and it test are complies with IP standards for capsules. *In-vitro* release studies of all the formulations are done to confirm its enhancement of *in-vitro* bioavailability, when compare to pure drug formulation 1.74 folds increase in bioavailability of prepared nanoparticles are noted.

Keywords: Candesartan cilexetil, oral bioavailability, solid lipid nanoparticles, solvent evaporation method

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INTRODUCTION

Candesartan cilexetil is widely used for the treatment of hypertension and heart failure in clinical application. It is a selective AT1 subtype angiotensin II receptor antagonist. After the oral administration it undergoes rapid ester hydrolysis to convert to the active candesartan during absorption in gastrointestinal tract [1,2]. However candesartan cilexetil shows very poor solubility within the physiological pH range, which could result the incomplete intestinal absorption very low systemic exposure after oral administration. Therefore it is necessary to find a new approach to enhance the oral bioavailability of candesartan cilexetil.

Solid lipid nanoparticles are one of the most popular approaches to improve the oral bioavailability of the poorly water soluble drugs. Solid lipid nanoparticles are having size (50-1000 nm) and are composed of lipid components which are in solid state at room temperature. Due to their inherent biodegradability and biocompatibility, lipids are now being extensively investigated as carriers for drugs and proteins. Several polymer-based nanotechnologies are being intended in order to optimize the technological (e.g. solubility, stability, bioavailability, etc.) aspects of drugs [3]. Compounds from BCS class II and class IV are most likely the suitable candidates of choice for preparing solid lipid nanoparticles [4].

Prefomulation studies

Melting point:

A capillary tube was taken and it was filled with the drug was placed in a melting point viewer and degree at which the drug gets melted down was considered as the melting point of the drug.

Solubility study of candesartan cilexetil:

Solubility of the drug is predicted by dissolving 1 gm of the drug in proportions of 1 ml, 10 ml, 30 ml and 100ml of the proposed solvents. So according to the dilution or dissolving property the solubility was predicted by measuring the absorbance by using uv spectrophotometric method.

FT-IR studies:

Infrared spectra of drug and its inclusion complexes were recorded by KBr pellet method. A base line correction was made using dried potassium bromide and then spectra of dried mixtures of drug and inclusion complexes with potassium bromide were recorded at 400 to 4000 cm-1.

Calibration curve of candesartan cilexetil:

A stock solution of 1 mg/ml of cnadesartan cilexetil was prepared by dissolving 100 mg of drug in 100 ml of methanol and bath sonicated for five minutes. The stock solution was serially diluted to get solutions in the range of 1 to 8 mcg / ml and the solution was analyzed in UV –visible spectrophotometer at 212 nm [5].

Preparation of candesartan cilexetil nanoparticulate capsules

The solvent evaporation method is commonly used for the preparation of solid lipid nonoparticles. 10ml of organic solvent was taken in a round bottom flask. To the above required chemicals and drug was weighed and added. The resulting solution was kept overnight for the evaporation of organic solvent leaving behind a thin film. 30ml of water was heated to 50°C and the formed thin film was dissolved in it. It was then subjected to bath sonication followed by probe sonication for 3min. to form SLN [6,7].

Characterization of nanoparticles

Nanoparticles are charecterized in the ways similar to those used for conventional particle such as appearance, color, odor, assay, impurities etc. Nanoparticle should be evaluated for their particle size, zeta potential, *in-vitro* dissolution studies and *in-vivo* studies [8,9].

Particle size and zeta potential:

The particle size and zeta potential analysis of solid lipid nanoparticle was studied by zeta sizer Nano ZS90 (Malvern Instrucments, UK) in double distilled water.

Lyophilization:

The prepared solid lipid nano particles were subjected to lyophilisation by using (Lyodol freeze dryer) and the temperature was maintained at - 40˚ C for 24 hours, the lyophilized nanoparticulate powdered were free flowing, non-sticky and free from aggregates. Powdered nanoparticles were used for tablet formulation.

Charactraization of particle size by using phase contrast microscopy

An aqueous drop of candesartan cilexetil loaded nanoparticle was mounted onto slide and closed with cover slip. And it is observed under phase contrast microscopy to study the shape of nanoparticle.

Drug content in formulation:

A 100mg prepared formulation were weighed and dissolved in 100ml of methanol. From this 1ml was taken and diluted to 25 ml with methanol and absorbance was taken in UV-visible spectrophotometer at 212nm. From the absorbance total drug required for a capsule is calculated.

Evaluation of candesartan cilexetil nanoparticulate capsules:

Weight variation:

20 capsules are weighed individually. Average weight is calculated. The individual weights are compared with the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage deviation in shows in below table and none deviates by more than 10%.

Dissolution study of candesartan cilexetil

Dissolution studies were carried out using USP 24 paddle dissolution instrument.0.35% polysorbate 20 in 0.05M Phosphate buffer (pH 6.5)

containing 1% sodium lauryl sulfate was used as the dissolution medium.

RESULTS AND DISCUSSION

Melting point was found to be 177°C which confirm the identification of drug.

Solubility study

Solubility of candesartan cilexetil in different solvent was done, insoluble in water and freely soluble in methanol and ethanol.

Standard curve of candesartan cilexetil by UV spectroscopy

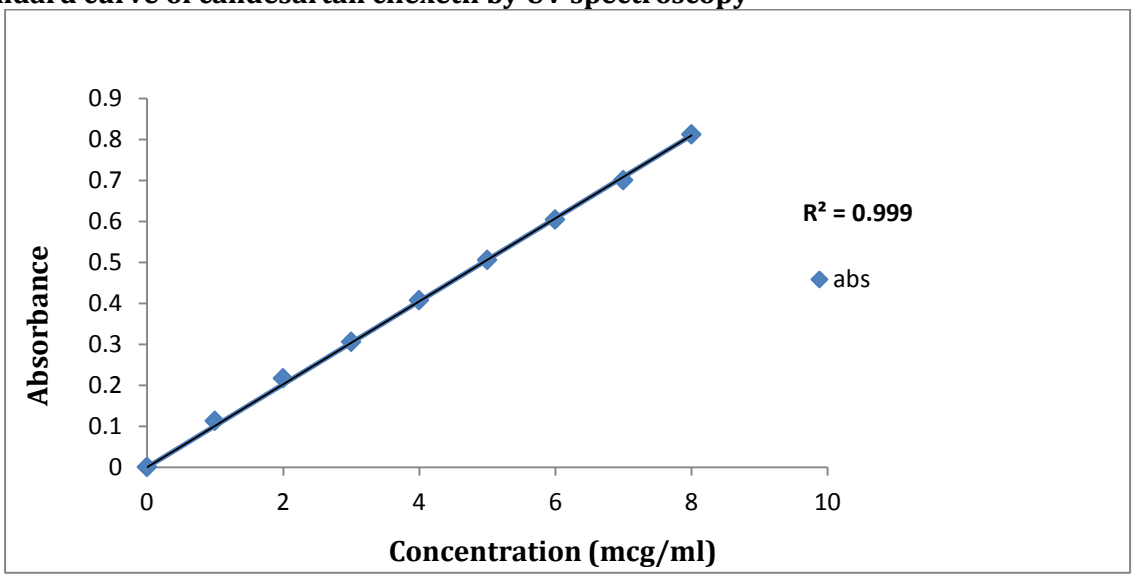

Figure 1: Standard graph of candesartan cilexetil

IR spectra interpretation

The IR spectral interpretation confirms that absence of chemical interaction between the drug and lipid and co-surfactant.

Preparation of candesartan cilexetil solid lipid nanoparticles

A Candesartan cilexetil solid lipid nanoparticle was prepared using glyceryl monosterate as lipid polaxemor 407 and tween 80 as co-surfactant and surfactant respectively dichloro methane as organic solvent and long with water by solvent evaporation method [10].

Particle size analysis, PDI and zeta potential of prepared solid lipid nanoparticle

The candesartan cilexetils solid lipid nanoparticles were analyzed by Malvern Zeta sizer after suitable dilution with water.

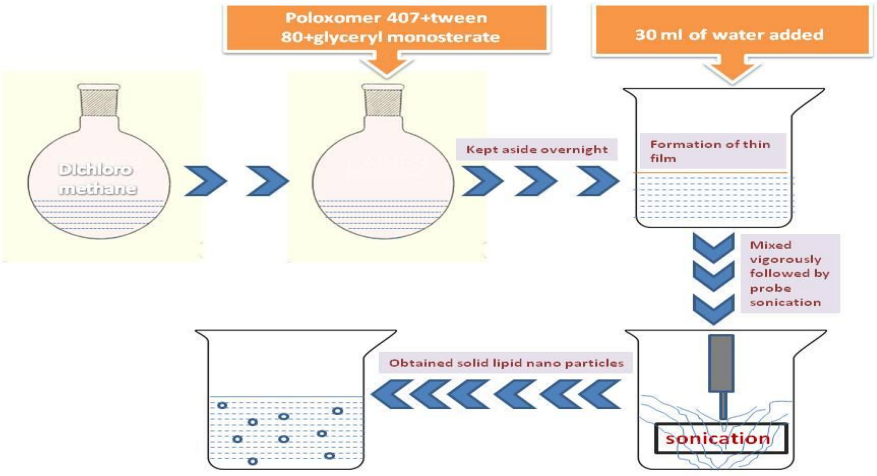

Figure 2: Preparation of candesartan cilexetil SLN by solvent evaporation method

Table1: Particle size and zeta potential of candesartan cilexetil solid lipid nanoparticle formulations

Formulation code	Size	Zeta potential
CLN-1	255.6	-11.1
CLN-2	249.3	- 9.99
CLN-3	559.6	-8.49
CLN-4	503.5	- 7.04
CLN-5	497.9	- 8.09
CLN-6	454.9	-4.03

The particle size was found to be 249.3 nm for CLN-2 and 559.6 nm for CLN-3 formulations respectively; other formulations were between these size ranges. CLN-2 was selected for further studies due to its size of 249.3 nm, and its surface charge of zeta potential was negative (-9.99 mv) for CLN-2 formulation which indicates there was a uniform distribution of particles.

Lyophilization to Convert Solid form of candesartan cilexetil solid lipid Nanoparticle:

The prepared solid lipid nanoparticles of CLN-2 were subjected to lyophilisation by using (Lyodol freeze dryer) and the temperature was maintained at - 40° C for 24 hours, which shows that the lyophilized nanoparticulate powdered were free flowing, non-sticky and free from aggregates while viewing through naked eye, which indicates the process used for formulation was good.

Characterization of particle size by using phase contrast microscopy:

Anaqueous drop of candesartan cilexetil loaded solid lipid nanoparticle was observed under phase contrast microscopy to study the shape of nanoparticle.

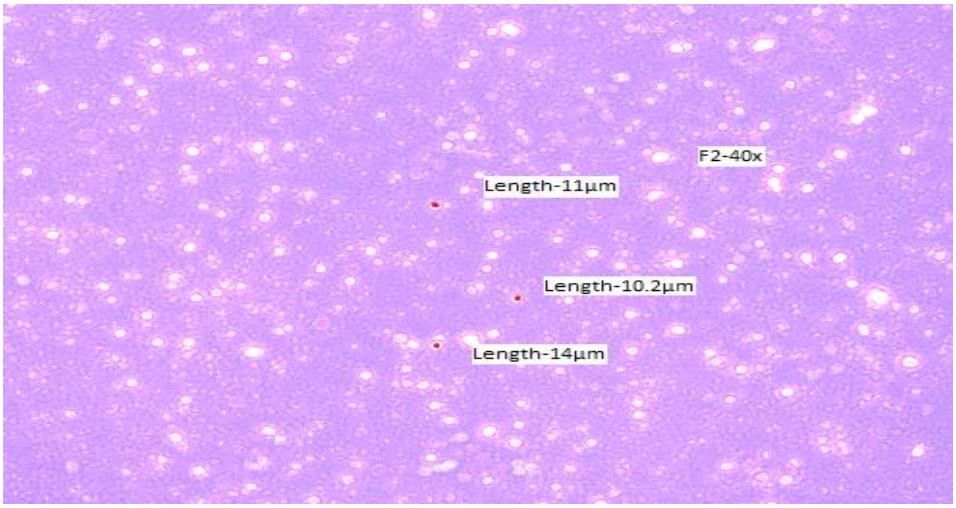

Figure 3: Morphology of candesartan cilexetil SLN by PCM

Drug content:

Lyophilized solid lipid nanoparticles of candesartan cilexetil were prepared as super saturated solution by dissolving excess of solute in methanol as solvent. And filtered using whatmann filter paper, filtrate was analyzed at 212 nm using UV spectroscopy after suitable dilution. The drug content was found to be 10.88 mg in CLN-2 and it was calculated for the equivalent dose of 4mg of candesartan cilexetil. 36.76mg of CLN contains 4mg of candesartan cilexetil.

Capsule filling

Capsules were filled with lyophilized solid lipid nano formulation of candesartan cilexitil CLN-2 with lactose monohydrate as diluent and talc as glident.

Table 2: Formula for CLN-2 capsule

Weight of ingredient	Name of ingredient
36.76 mg	Candesartan cilexetil solid lipid nanoparticulate formulation
209mg	Lactose monohydratd- diluents
5mg	2% Talc-glident

Evalution of candesartan cilexetil solid lipid nanoparticulate capsules

Theprepared lyophilized solid lipid nanoparticulate capsules of candesartan cilexetil CLN-2 were evaluated for weight variation and dissolution. Weight variation of capsules found to be 247.97±0.6. CLN-2 formulation and pure drug formulation (P) were studied for its release character which found to be 95.8% drug release at end of 35 mins for CLN-2 and 86.1% drug release for (P) at end of 60mintes. The release study indicates that the formulation CLN-2 has shown higher amount of drug release when compared to marketed formulation with fast rate of release which shows that 1.74 folds increase in dissolution rate of lyophilized solid lipid nanoparticles of candesartan cilexetil by when compare to pure drug formulation. This confirms the improvement of *in-vitro* bioavailability of candesartan cilexetil by solvent evaporation method for solid lipid nanoparticulate preparation.

Table3: Comparison of *in vitro* release profile of pure drug formulation and Candesartan cilexetil solid lipid nanoparticulate capsules

Time (min)	Pure drug (%)	Formulation CLN-2 (%)
5	15.5±0.1	20.9±1.3
10	27±2.25	47.2±2.2
15	33.7±2.2	64.4±1.2
20	38.2±3.8	79.1±1.7
25	47.2±5.9	87.5±2.2
30	50.9±5.6	92.9±1.3
35	56.2±5.9	95.8±1.4
40	60.7±2.2	95.8±1.4
45	66±2.12	95.8±1.4
50	71.2±2.7	95.8±1.4
55	80.2±4.2	95.8±1.4
60	86.1±1.1	95.8±1.4

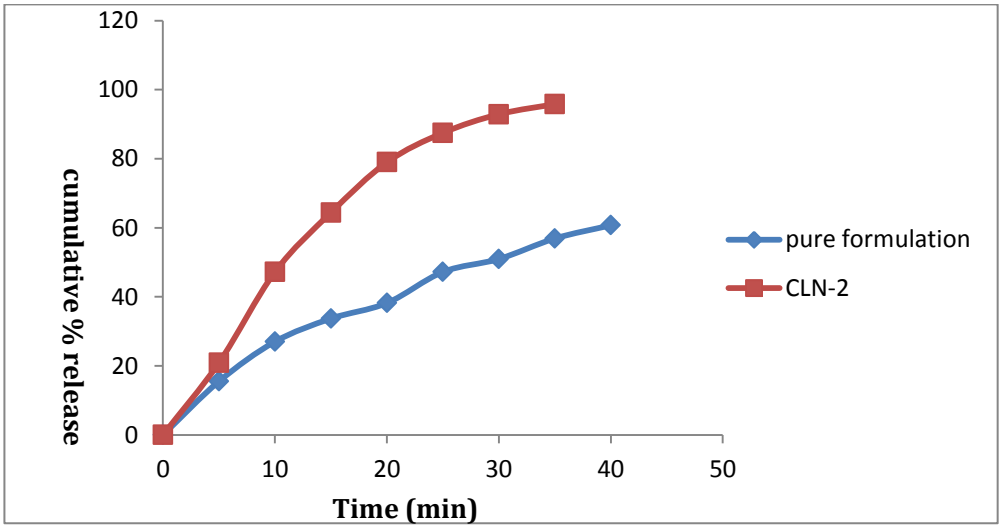

Figure 4: Comparison of *in vitro* release profile

CONCLUSION

Candesartan cilexetil loaded solid lipid nanoparticles was prepared by solvent evaporation method for improve the aqueous solubility and oral bioavailability. In this formulation tween 80, poloxamer 407 were used as surfactant and co-surfactant respectively and glycerylmonostearate was used as lipid. The ratio of drug: surfactant: co-surfactant: lipid were selected 1:4:4:4 and as optimized formulation. Particle sizes of optimized CLN-2 were found to be 249.6 nm.

In-vitro drug release of optimized CLN-2 formulations showed 95.8% at 35 min when compare to pure drug formulation release of 86.1% at 60 min. This confirms increase in the *in-vitro* bioavailability of 1.74 folds.

These optimized CLN formulation can be further evaluated for *in-vivo* bioavailability studies.

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