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Research Article

ENHANCEMENT OF DISSOLUTION OF CANDESARTAN CILEXETIL

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ABSTRACT

Objective: The main aim of our investigation was to enhance the dissolution of Candesartan Cilexetil (CC), a prodrug of Candesartan, used in the treatment of hypertension. CC bioavailability is dissolution rate limited. The drug was formulated using various excipients such as surfactants, and liquid lipids to improve solubility, dissolution, and hence bioavailability.

Methods: The solubility of CC was determined at 25°C by shake flask method and those showing maximum solubility were selected for the formulation of CC. *In vitro* dissolution studies were done in different media in pH 6.8 phosphate buffer with 1% SLS, tween 20, and 0.1 N HCl with 1% SLS. The surface morphology of LBDDS was studied with scanning electron microscope (SEM) and the crystallinity of the drug and the formulation were studied using X-ray diffraction (XRD).

Results: CC showed maximum solubility in transcutol and labrasol, which, hence, were selected as excipients for the formulation of CC capsules. Drug release was high in 0.1 N HCl with 1% SLS and, hence, was selected as the dissolution medium. The dissolution profile for formulation F5 containing the drug with transcutol and labrasol showed the highest drug release among all formulations, that is, 94.09%. The SEM of the F5 formulation showed that the drug was completely embedded into the lipid matrix and particles were spherical and porous with a size of around 25 µ. XRD of formulation F5 indicated the absence of crystallinity in CC capsules containing transcutol and labrasol.

Conclusion: It was concluded that CC containing transcutol and labrasol significantly increases the solubility and dissolution of the drug.

Keywords: Candesartan cilexetil, Shake flask method, Liquid lipids, *In vitro* dissolution studies.

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INTRODUCTION

Candesartan cilexetil (CC) is a prodrug of candesartan, it is readily and completely bioactivated to an active form of candesartan through hydrolysis throughout absorption from the GIT [1,2].

CC is a non-peptide angiotensin II type 1 receptor antagonist used in the treating hypertension and heart failure [2-5]. Based on its solubility across physiological relevant pH conditions and absorption characteristics, CC is classified in the biopharmaceutics classification system as a class II drug [4]. Low solubility of CC across the physiological pH range results in incomplete absorption from the GI tract and, hence, is reported to have an oral bioavailability of about 15% [3,6]. CC is a highly lipophilic compound and also has good solubility in tri and di-glycerides oil. Thus, a new oral formulation of CC can be developed which results in increased solubility and enhanced permeability across the biological membrane to overcome its poor bioavailability.

Various excipients were studied for the formulation of CC which includes caproyl 90 a water-insoluble surfactant and bioavailability enhancer. Labrafac PG is used as a solubilizer for lipophilic dosage forms. Transcutol is a solvent and powerful solubilizer. Aerosil is used for increasing the viscosity, thixotropy of a wide range of liquid systems [7-9].

MATERIALS AND METHODS

Materials

The active CC was a kind gift sample from Smilax laboratory, Hyderabad, India. Transcutol, labrasol, labrafac PG, and caproyl 90 were gift samples from Gattefosse, Mumbai, India. Methanol was obtained from S.D. Fine chemical Ltd., India.

METHODS

Preformulation studies

Selection of component

Solubility studies: Solubility studies were done to choose the components of the formulation [10]. The components were chosen based on the solubilizing capacity of drug. An excess amount of drug was added to each lipid followed by the sealing of vials. Different lipids and excipients were selected which include transcutol P, caproyl 90, labrafac PG, and labrasol. The vials were shaken on a rotary shaker (Table orbital shaker®) for 72 h. Each vial was centrifuged at 15000 rpm for 10 min using a centrifuge (REMI® Mumbai, India) followed by the removal of an un-dissolved drug by filtering through a Whatman filter paper. Samples were suitably diluted with methanol and analyzed by measuring absorbance in a UV spectrophotometer (Lab India) at 254 nm. The experiment was repeated 3 times. Results were represented as mean values (Mean±SD) [7,11].

Preparation of drug-loaded capsules

- Excipients were accurately weighed and placed into a round bottom flask, heated at 80°C with constant stirring until all the excipients were melted, measured amount of CC was added into the molten mixture at 70°C with stirring to form a homogenous mixture. Aerosil was added to the above-molten mixture until it forms free
- Flowing powder. The powder was filled into a capsule and subjected to further studies [12].

Precompression parameters

Bulk density (g/mL)

Bulk density is the ratio of the mass of powder and its volume determined by measuring the volume of a known mass of the powder sample that has been passed through the screen into graduating cylinder [4].

Bulk density was determined according to USP method I. The powder sample under test was screened through sieve no 180 and 10 g of the pure drug was accurately weighed and filled in a 100 mL graduated cylinder, the powder was leveled, and the unsettled volume (Vo) was noted. Bulk density was calculated in g/mL by the formula [13].

Bulk density = M/V

Where,
M = mass of the powder
Vo = unsettled apparent volume

Tapped density

It is determined by placing a graduated cylinder containing formulation on a mechanical taper apparatus, which is operated for a fixed number of taps (about 1000) until the powder bed volume reached a minimum [4].

Dt = M/Vo

Where,
M = weight of sample powder
Vo =final tapped volume

Angle of repose θ

The angle of repose is a direct measure of the flow property of powders. It is the maximum angle that can be obtained between the surface of a pile of powder and the horizontal plane.

The angle of repose was determined using a funnel to pour the powder on the surface from a fixed height of 2 cm. Circumferences were drawn with a pencil on the graph paper and the radius of the base of a pile was measured at five different points and the average was taken for calculating the angle of repose using the formula [13]:

Angle of Repose (θ) = $\tan^{-1}(h/r)$

Where,
h = height of a pile (2 cm)
r = radius of pile base

Compressibility index and Hausner's ratio

A volume of powder was filled into a graduated glass cylinder and repeatedly tapped for a known duration. The volume of powder after tapping was measured [4].

The free-flowing powder has fewer inter-particulate interactions and the bulk and tapped density difference is close when compared to poorer flowing materials.

Carr's index, that is, % compressibility indicates the flow property and packing ability of the tablet. It was determined by measuring both the bulk and tapped density of a powder [13].

The compressibility index was calculated using the following equation

CI (%) = [(Dt-Db)/Dt] × 100

Hausner's ratio

Hausners ratio was calculated using the formula [4,13]

Hausner Ratio = Dt/Db

- Value <1.25 indicates good flow (=20% Carr)

Evaluation of capsules

In vitro dissolution studies

An *In vitro* dissolution test was carried out using USP type II apparatus (paddle type). The paddle was rotated at 50rpm. Dissolution studies were done in different media which include pH 6.8 phosphate buffer, pH 6.8 phosphate buffer with surfactants (1% SLS, tween 20, and tween 80), 0.1N HCl, and 0.1NHCl with surfactants (1% SLS and tween 80). The temperature of the dissolution medium (900 mL) was maintained at 37±0.5°C. Samples of 5 mL were withdrawn at predetermined time intervals and replaced with 5 mL of fresh dissolution medium to maintain sink conditions. The withdrawn samples were filtered and suitably diluted with dissolution medium and analyzed for determining drug content at 254 nm using UV-visible spectrophotometer (Labindia) [4,14,15].

Table 1: List of ingredients

S. No.	Ingredients	F1	F2	F3	F4	F5
1	Drug	32	32	32	32	32
2	Transcutol	100	-	200	-	100
3	Labrasol	-	100	-	200	100
4	Aerosil	100	100	150	150	150

Characterization of capsules

Scanning electron microscope (SEM)

Surface morphology was studied using a SEM. SEM was carried out for the samples including pure drug CC and drug-loaded capsules. Each sample was mounted on double-sided adhesive tape. The photomicrographs were obtained at the voltage of 0.7 kV and examined at the magnification of 2000× [12,14,16].

X-ray powder diffraction

The crystalline characteristics of candesartan and drug-loaded capsules were determined by X-ray diffraction (XRD)-6000 X-ray powder diffractometry at 40 kV and 40 mA using Cu kα radiation. The scanning angle ranged from 5 to 70° of 2° and the counting rate was 0.4s/step [2,16-18].

RESULTS AND DISCUSSION

Preformulation studies

Solubility studies

The solubility of CC in various lipids was determined using the shake flask method CC exhibited the highest solubility in transcutol (HLB value of 4.2) as compared to other lipids. Hence, it was selected as a lipid for the formulation. CC also showed good solubility in labrasol (HLB value of 8). Hence was selected as a excipient for the formulation of a lipid-based drug delivery system of CC.

Flow properties of formulations F1, F2, F3, and F4 were fair, whereas F5 exhibited good flow properties.

Selection of dissolution media

The selection of dissolution medium was based on the drug substance and formulation characteristics as well as on the interactions among components. Many criteria are taken into consideration while selecting

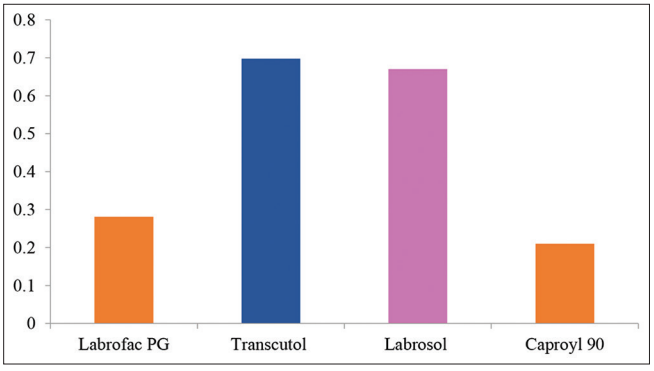

Fig. 1: Solubility of CC in different lipids

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Table 2: Flow properties of formulations

Formulation	Bulk density (g/mL)	Tap density (g/mL)	Compressability index	Hausner's ratio
F1	0.592	0.751	16.5	1.20
F2	0.512	0.733	15.8	1.24
F3	0.654	0.783	18.45	1.22
F4	0.691	0.834	17.1	1.19
F5	0.432	0.625	11.5	1.13

dissolution media. The drug should have adequate solubility in the dissolution media without impacting the sink condition. Surfactants are used in dissolution test medium to improve the solubility and wettability of the drug. Dissolution of CC was carried out in different dissolution media.

Solubility of the drug in various media like 0.1N HCl without surfactants, 0.1N HCl with surfactants (1% SLS, tween 20, and tween 80), pH 6.8 Phosphate buffer without surfactants, and pH 6.8 phosphate buffer with surfactants (1% SLS and tween 20) were studied.

Dissolution studies were carried out using USP type II apparatus which is maintained at 37±0.5°C. Aliquotes of 5 mL were removed at 15, 30, 45, 60, and 75 min time intervals and were analyzed using UV-Spectrophotometer (Labindia) at 254 nm.

In vitro dissolution studies in 0.1N HCl

0.1N HCl with 1% SLS was more discriminating and showed good drug release when compared to other dissolution media. Formulation F5 containing transcutol and labrasol showed the highest drug release rate among all the formulations. % drug release of formulations were show in Fig. 2.

Characterization

SEM

SEM was carried out to determine the surface morphology.

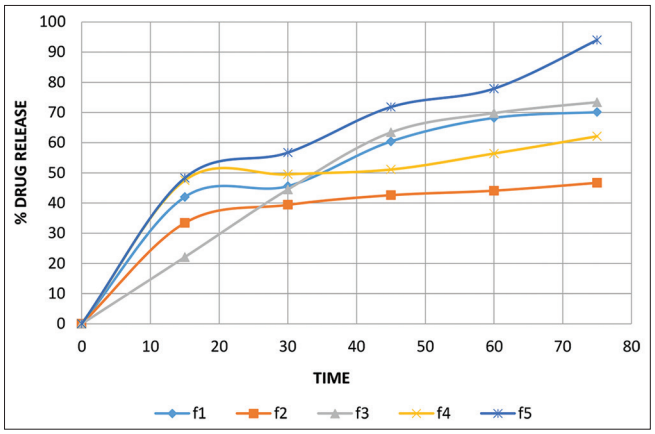

Fig. 2: Percentage drug release of formulations

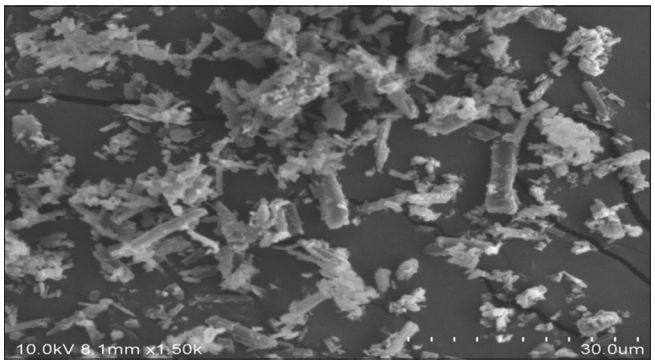

Fig. 3: SEM of pure drug

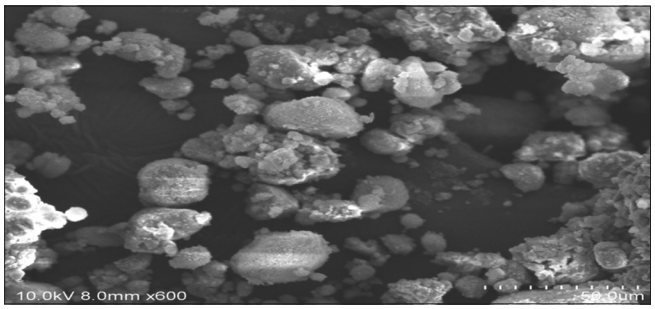

Fig. 4: SEM of formulation F5

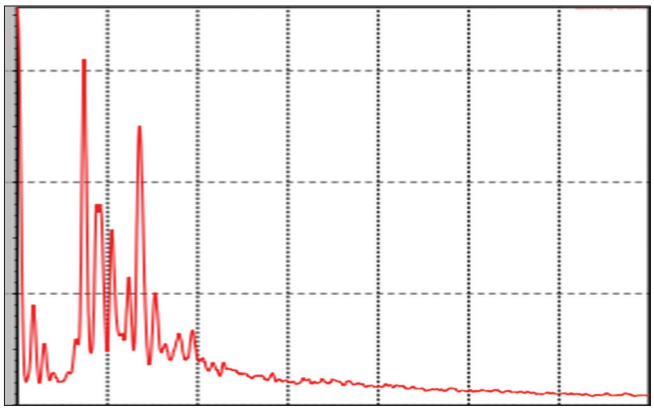

Fig. 5: XRD of pure drug

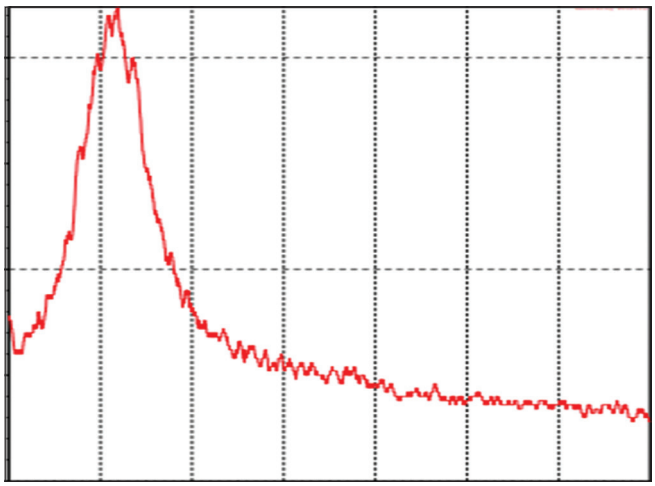

Fig. 6: XRD of formulation F5

The SEM images of a pure drug are shown in Fig. 3. It was observed that the drug particles were long and crystalline.

The SEM of formulation F5 is shown in Fig. 4. It was observed that the drug was completely embedded into a lipid matrix and the particles were spherical and porous with a size around 25 μ.

XRD

XRD is used for the identification of unknown crystalline materials.

XRD of a pure drug is shown in Fig. 5. The diffractogram showed sharp distinct peaks indicating the crystalline nature of the drug.

The XRD of F5 is shown in Fig. 6. It was observed that the formulation indicates the absence of crystallinity in the CC capsules. This could explain the reason for the enhancement of the dissolution of CC capsule.

CONCLUSION

CC is a BCS class II drug with low solubility and high permeability; it is an anti-hypertensive drug with low oral bioavailability of 40%. The XRD and SEM images conclude that the drug is completely embedded into the lipid matrix and the absence of crystallinity could be the reason for high solubility and dissolution of the formulation. Hence, CC prepared using transcutol and labrasol are a good alternative to a conventional oral dosage form which significantly increases the solubility and dissolution.

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AUTHORS' CONTRIBUTIONS

- Anusha contributed to performing the experimental work
- Dr C. Aparna, B. Manisha contributed to the preparation of the final manuscript.

CONFLICTS OF INTEREST

There are no conflicts of interest regarding the publication.

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Author Queries???

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