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Original Article

Development and characterization of controlled release polar lipid microparticles of candesartan cilexetil by solid dispersion

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Abstract

Candesartan cilexetil (CC) is a newer class of angiotensin II receptor antagonist used for the treatment of hypertension. The solubility of the CC is very poor and its oral bioavailability is only 15%. The controlled-release polar lipid microparticles of CC (formulations F1, F2, F3 and F4) were prepared using variable erodible lipophilic excipients like hydrogenated castor oil, stearic acid, cetostearyl alcohol and carnauba wax by fusion method. The particle sizes of polar lipid microparticles were less than 50 microns and they were irregular in shape. Drug content ranged between 98.96 ± 2.1 and 101.9 ± 1.6% were present in all the formulations. The formulation F3 showed better drug release throughout the study period in a controlled release manner. Moreover, the *in vitro* release showed that all the formulations were best fitted to Higuchi model. Accelerated stability studies indicated that there was no significant changes in the chemical and physical characteristics of the formulated drug product during initial and at the end of the study period . The FTIR and DSC studies showed that there was no interaction between the drug and lipophilic excipients and no polymorphic transitions in all formulations. The X-ray diffraction peak of solid dispersion indicated that the crystalline nature of CC disappeared and no new peaks could be observed, suggesting the absence of interaction between drug and excipients.

Keywords: Candesartan cilexetil; Diffusion, Higuchi; Korsmeyer-Peppas; Polar lipid microparticles; Solid dispersion

INTRODUCTION

Hypertension is an important public-health challenge worldwide (1) and the drug Candesartan cilexetil (CC) is a newer class of antihypertensive agent comes under angiotensin II receptor antagonist (2). CC is a well tolerated drug and blood pressure lowering to goal levels is achieved in almost 40% of patients (3). The other class of drugs used in the hypertension produces cough, adversely affect lipid profile and rebound hypertension after discontinuation. These adverse effects can be overcome by using angiotensin II receptor antagonists (4). Clinical trials indicates that CC is effective and safe in the treatment of hypertension (4). CC is safe under the dosages of 4 to 32 mg, with these dosages, systolic blood pressure is reduced by 8-12 mmHg and diastolic pressure is reduced by 4-8 mmHg (5). The current commercial formulation of CC is an immediate release and is administered twice daily with a PKa value of 8.15 and log P of 6.85 (6). Once-daily dosing formulation is commercially desirable which would reduce patients dosing regimen and can improve patient's compliance (7). The absolute bioavailability of CC is only 15 % (8) and this can be improved by making lipid formulation using solid dispersion method (9).

Controlled release is usually accomplished by using a membrane or matrix. Matrix type formulations are prepared from either swellable hydrophilic polymers or non-swellable lipophilic excipients like waxes and fats. From the polymer matrices, the drug release rate is controlled by the diffusion of drug molecules in the swollen polymer matrix (10) thus the drug solubility in the matrix material has a marked influence on the release rate. This may

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cause problems when the drug is very hydrophobic, as is often the case with new drug molecules. When lipophilic materials are used as a matrix, this problem relating to poor drug solubility in the matrix can be avoided. When a non-swellable lipophilic excipient is used as a matrix material in controlled-release formulations, the drug substance and the excipients have to be formulated into a solid dispersion.

The term solid dispersions have been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability. Chiou and Riegelman defined these systems as the dispersion of one or more active ingredient in an inert carrier matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method (11). The first solid dispersions created for pharmaceutical applications were prepared by the fusion method. The fusion process is technically the less difficult method of preparing dispersions provided the drug and carrier are miscible in the molten state.

The aim of the present study was to produce controlled release tablets of poorly soluble drug CC using various lipophilic excipients as carriers. CC have been choosed as a model drug substance due to poor aqueous solubility and temperature insensitive properties (8). The lipophilic materials chosen as carriers were all erodible polar lipids and their melting points were between 60-90ºC, which made them suitable to use in the fusion process.

MATERIALS AND METHODS

Materials

CC was obtained as a gift sample from Micro labs, Bangalore, India. Lactose DCL-11, microcrystalline cellulose pH 102, purified talc and magnesium stearate were obtained from Caplin Point Laboratories Limited, Chennai, India. Polysorbate 80 and potassium dihydrogen orthophosphate were purchased from SD Fine chemicals, Bangalore, India. Hydrogenated castor oil, stearic acid, cetostearyl alcohol and carnauba wax were gifted from Malind Labs, Baddi, India. All other reagents used were of analytical grade.

Methods

Formulations of candesartan cilexetil microparticles by fusion method

Polar lipid microparticles of CC were prepared by fusion method. Lipophilic material were melted at the temperature ranged between 60-90°C and CC (2:1 w/w) was incorporated into the above melted solutions. The molten mass was immediately poured in to the tray which was previously coated with high density polyethylene. After the immediate solidification, the mixture was passed through ≤125 micron size mesh. The samples were wrapped with aluminum foil and stored in a desiccator at room temperature for further studies.

Preparation of physical mixtures

For the sake of comparison, physical mixtures having the same composition of the solid dispersions were prepared by simply triturating the drug and lipophilic excipients with other diluents in a porcelain mortar. The mixture was then sieved through less than 125 micron size mesh. The samples were wrapped with aluminum foil and stored in a desiccator at room temperature for further studies.

Formulations of candesartan cilexetil controlled release tablets

The prepared polar lipid microparticles were geometrically mixed with diluents for 15 min and then the sieved lubricants were mixed with the blend (both the diluents microcrystalline cellulose pH 102 and lactose DCL -11, and the lubricants purified talc and magnesium stearate were previously passed through 60 mesh) for 5 min. The mixed blend was compressed by 7.9 mm, flat, beveled edge with centre score punch. 16-station single rotary machine was used to compress the tablets. The theoretical average weight of the tablet for all the formulation was 180 mg and the active content was 8 mg per tablet. The tablets were wrapped with aluminum foil and stored in a desiccator at room temperature. The different ratios of diluents and lubricants used for the formulations are shown in Table 1.

Characterization

FTIR spectral studies

In order to get evidence on the possible interaction of the drug with the excipients,

Table 1. Formulations of controlled-release candesartan cilexetil tablets

S .No.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)
1	CC + Hydrogenated castor oil microparticles	24.00	-	-	-
2	CC + Stearic acid microparticles	-	24.00	-	-
3	CC + Cetostearyl alcohol microparticles	-	-	24.00	-
4	CC + Carnauba wax microparticles	-	-	-	24.00
5	Microcrystalline cellulose pH 102	57.00	57.00	57.00	57.00
6	Lactose DCL-11	92.20	92.20	92.20	92.20
7	Purified talc	2.500	2.500	2.500	2.500
8	Magnesium stearate	2.500	2.500	2.500	2.500
9	Colour ponceau 4 R lake	1.800	-	-	-
10	Colour sunset yellow lake	-	1.800	-	-
11	Colour brilliant blue lake	-	-	1.800	-
12	Colour Erythrosine lake	-	-	-	1.800
	Lipophilic excipients	Hydrogenated castor oil	Stearic acid	Cetostearyl alcohol	Carnauba wax

FTIR analysis was used. Samples were prepared by potassium bromide disc method (2 mg sample in 200 mg of KBR), the scanning range was 400-4000 cm^{-1} and the resolution was 4 cm^{-1}. FTIR spectra of two months storage samples of physical mixture and optimized formulation F3, pure drug, lipophilic excipients were scanned 20 times (12-15).

Differential scanning calorimetry (DSC)

DSC thermogram of two months storage samples of physical mixture and optimized formulation F3, pure drug, lipophilic excipients were recorded. The samples were placed into sealed aluminum pans and scanned at heating rate of $10^{o}C$ min^{-1} over the temperature range of 30-200^{o}C (12-15).

Scanning electron microscopy (SEM)

The surface morphology of the layered sample was examined by using scanning electron microscope (JOEL JSM T330A Scanning microscope, Japanese Electron Optics Laboratory Co. Ltd., Japan). The two-months storage samples of physical mixture and optimized formulation F3, pure drug, binary system with polar lipophilic excipient were manually dispersed onto a carbon tab (double adhesive carbon coated tape) which was adhered to an aluminum stubs. The samples were examined by SEM and photographed under various magnifications with direct data capture of the images onto a computer.

X-ray diffraction (XRD)

X-ray powder diffraction patterns were recorded on Jeol JDX 8030 X-ray diffractometer (Tokyo, Japan) using copper target, a voltage of 40 kV and a current of 30 mA. The scanning was done over 2°θ range of 10-80º. The two months storage samples of physical mixture and optimized formulation F3, pure drug, binary system with polar lipophilic excipient were measured at the temperature of 25°C. The scanning rate employed was 1° min^{-1} over the 10-30° diffraction angle (2θ) range.

Assay

Equal volume of standard and sample preparation of CC was injected separately into the chromatograph of reversed-phase high performance liquid chromatography (Agilent 1200 series, auto sampler with variable wavelength detector, German) and recorded the chromatogram at 215 nm. The stationary phase was C_{18} column (25 cm X 4.6 mm, 5 µm) and maintained at ambient temperature. A mixture of 20% phosphate buffer (pH 2.5) and 80% acetonitrile was used as mobile phase (16). The drug content of CC was determined by calculating the response obtained in the standard and sample chromato-grams. Standard chromatogram of CC is shown in

Fig. 1. The linear plot was drawn with different concentration against mAU for ensuring the linearity and it is shown in Fig. 2.

In vitro dissolution studies

USP II paddle rotating dissolution test apparatus (TDT-08L, USA) was used to study the *in vitro* drug release. 900 ml of 7.2 phosphate buffer with an amount of 0.030% of polysorbate was used as the dissolution medium. Speed of the paddle rotation was 50 rpm and the temperature maintained at 37°C ± 0.5°C throughout the process to preserve sink conditions during dissolution (17). Each tablet was placed in a basket located about 1 cm above the paddle. Samples (10 ml) were withdrawn at pre-determined time intervals (2, 4, 8, 12, 18 and 24 h) and replaced with equal volume of fresh dissolution medium to maintain the constant level. Samples were filtered through a 0.4 µm filter and injected directly into the chromatograph to record the chromatogram at 215 nm.The stationary phase was C_8 column (25 cm X 4.6 mm, 5 µm) and the mobile phase was the mixture of 15% buffer: 85% of acetonitrile. Injection volume was 20 µl and the flow rate was 1 ml per min.

Kinetics release profile

Drug release mechanism was determined by finding the best fit of the release data to Higuchi and Korsmeyer-Peppas plots (18-20).

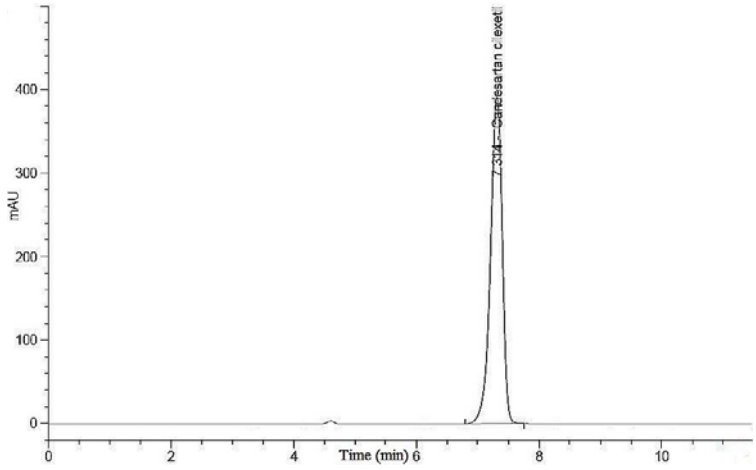

Fig. 1. Standard chromatogram of candesartan cilexetil.

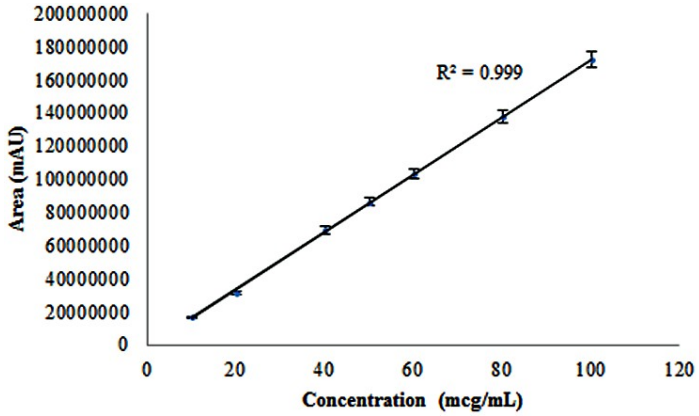

Fig. 2. Linear graph of candesartan cilexetil

Accelerated stability studies

All the formulations were blister packed by polyvinyl dichloride film and these tablets were loaded in stability chamber maintained at 40 ± 5°C and 75 ± 5% RH for 6 months. Changes in the appearance, physical parameter and drug content was closely monitored and analyzed at regular time intervals (1, 2, 3, 4 and 6 months).

RESULTS

FTIR Spectral studies

FTIR spectra of CC and all the formulations are presented in Fig. 3 (a-e). The spectrum of CC showed an important strong band at 2940 cm^{-1} (-C-H Stretching) and the following sharp characteristics peaks. Aromatic C-N stretching at 1350 cm^{-1}, N-H bending at 1615 cm^{-1}, Carbonyl C=O stretching at 1715 cm^{-1}, Strong C=O carbonyl stretch at1753.9 cm^{-1}, Ether stretching (C-O ether stretch) at1076 cm^{-1} and Aromatic C-H bending at 747 cm^{-1}.

All the above characteristic peaks appeared in the spectra of all formulations at same wave number indicated that no modification or interaction between the CC and excipients used in the formulations.

Differential scanning calorimetry (DSC)

Thermal behavior of CC and all the formulations are depicted in Fig. 4 (a-e). The DSC curve of pure drug showed a sharp endothermic peak (Tpeak = 171.91°C) corresponding to its melting, indicating its crystalline nature. However, the characteristic endothermic peak, corresponding to drug melting was broadened and shifted towards lower temperature, with reduced intensity, in both physical mixtures as well as solid dispersions. This could be attributed to uniform distribution of drug in the crust of polymer, resulting in complete miscibility of molten drug in polymer. Moreover, the data also indicated there seems to be no interaction between the drug and lipophilic excipients.

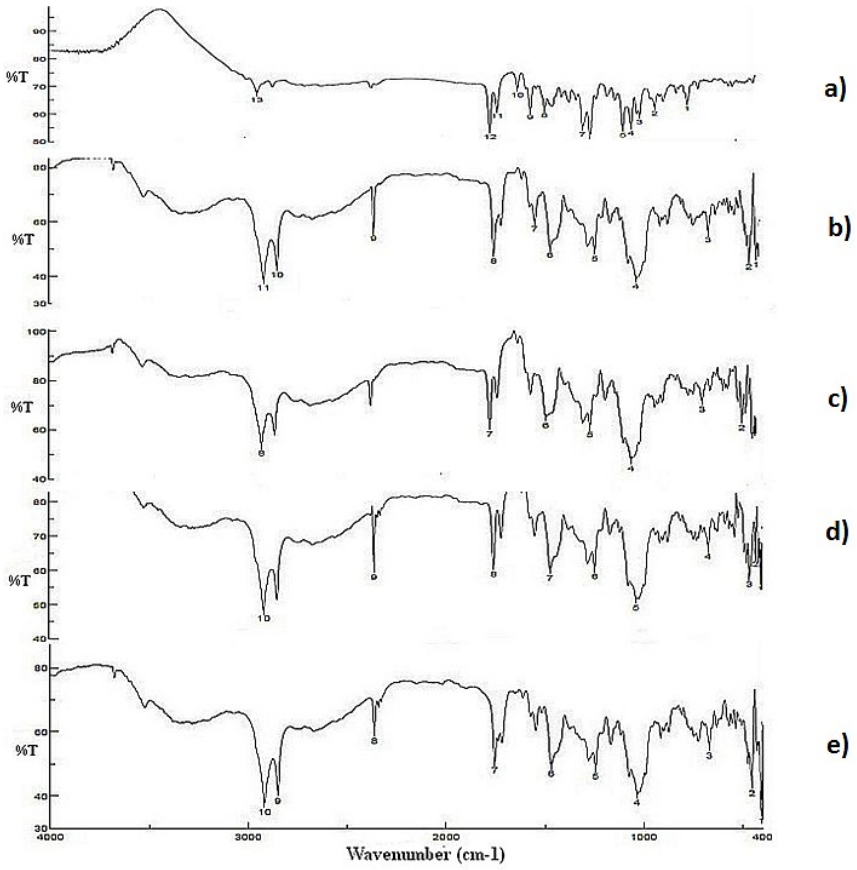

Fig. 3. FTIR Spectrum of candesartan cilexetil and its formulations**,** a) FTIR Spectrum of CC, b) FTIR Spectrum of F1, c) FTIR Spectrum of F2, d) FTIR Spectrum of F3, e) FTIR Spectrum of F4.

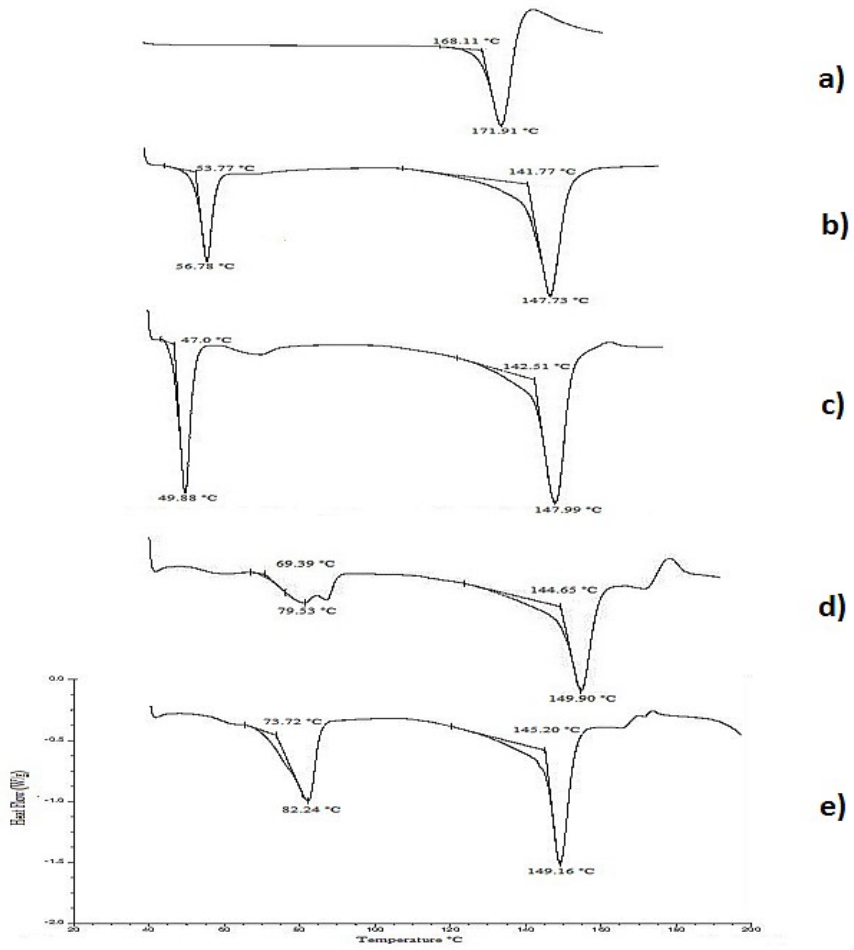

Fig. 4. DSC thermogram of candesartan cilexetil and its formulations**,** a) DSC thermogram of CC, b) DSC thermogram of F1, c) DSC thermogram of F2, d) DSC thermogram of F3, e) DSC thermogram of F4.

X-ray diffraction

X-ray diffractometry spectra of CC, binary system with lipophilic excipients, physical mixture of optimized formulation and solid dispersion of formulation F3 are depicted in Fig. 5 (a-d). The X-ray diffractogram of CC showed sharp peaks at 10.10, 17.44 and 20.47 indicating a typical crystalline pattern. The diffractogram of solid dispersion and physical mixture indicates the changes occurred in the crystal structure. No new peaks could be observed, suggesting the absence of interaction between CC and lipophilic excipients.

Scanning electron microscopy

Fig. 6 shows SEM micrographs of solid dispersions of formulation F3, physical mixture, binary system with lipophilic excipient and pure drug. The surface morphology studies revealed that the solid dispersion was closely compacted into small spherical form. Pure drug was close to 127 µm in size, whereas it was gradually reduced to 62.4, 56 and 42 µm in binary system with lipophilic excipient, physical mixture and solid dispersion respectively. The solid dispersions appeared into the form of spherical particles and the original morphology of components disappeared, which supported DSC and XRD data. These results demonstrated that CC in solid dispersion was homogeneously dispersed into polar lipophilic carriers.

Evaluations of candesartan cilexetil microparticles

The prepared microparticles were subjected to loss on drying, compressibility index, Hausner ratio and angle of repose (Table 2). The formulation F1 showed loss on drying 2.15 ± 1.1%, F2 showed 2.89 ± 1.0%, F3 and

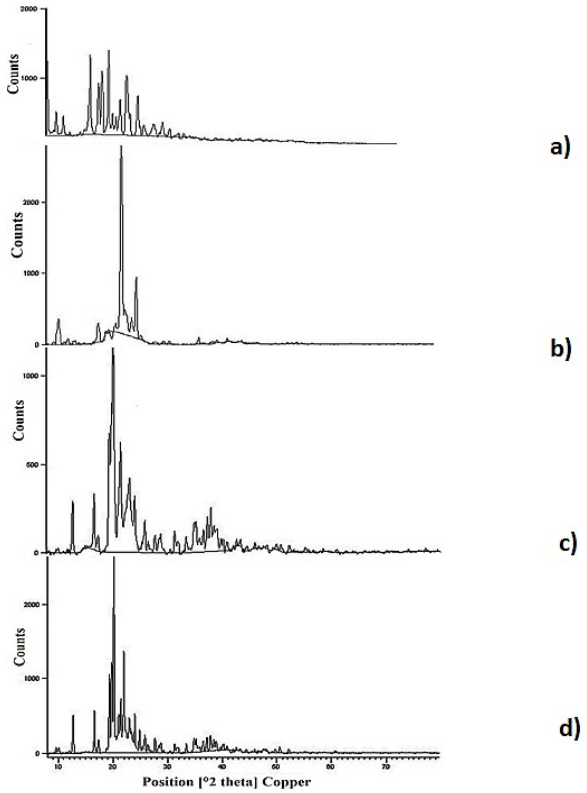

Fig. 5. a) XRD of candesartan cilexetil, b) XRD of binary system with lipophilic excipient, c) XRD of physical mixture of formulation F3, d). XRD of formulation F3

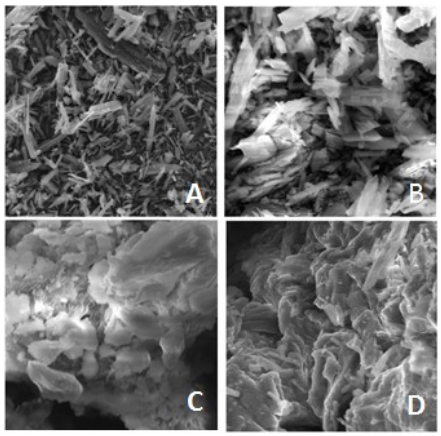

Fig. 6. a) Scanning electron photomicrographs of CC, b) Binary system with lipophilic excipient, c) Formulation F3, d) Physical mixture of formulation F3.

Table 2. Physical properties of formulations blend

Formulation code	Angle of repose (°)*	Bulk density (g/ml)*	Tapped density (g/ml)*	Compressibility index (%)	Hausner ratio	Loss on drying (%)*
F1	31 ± 1.2	0.386 ±0.11	0.434 ±0.86	11.06 ±1.2	1.12 ±1.1	2.15±1.1
F2	34 ±1.0	0.423 ±0.21	0.489 ±0.65	13.49 ±2.4	1.15 ±1.4	2.89±1.0
F3	35 ±0.99	0.424 ±0.42	0.498 ±0.43	14.85 ±2.2	1.17 ±2.1	1.87 ±1.8
F4	32 ±1.1	0.412 ±0.65	0.473 ±0.28	12.89 ±2.4	1.14 ±2.0	1.93 ±1.6

*Average of three determinations

F4 followed 1.87 ± 1.8% and 1.93 ± 1.6% respectively. Loss on drying (LOD) is mainly used to determine the percentage of moisture content and the presence of volatile substances in the granules. All the formulations showed LOD less than 3%, this indicated that all the prepared granules are smooth for tablet compression without having adhesive properties and also less LOD resulted good compressibility, thus leads to release the drug in a controlled manner. The final tablet strength was found to be directly dependent on the tablet LOD result. Higher LOD resulted for poor compressibility which is increased the disintegration time of the tablet. All the used lipophilic excipients showing good stability at varying moisture content levels to well-established safe application. The bulk density of the formulations ranged between 0.386 ± 0.11 and 0.424 ± 0.42 g/ml and tapped density varied between 0.434 ± 0.86 and 0.498 ± 0.43 g/ml. The results of compressibility index and Hausner ratio derived from bulk and tapped density. Compressibility index ranged between 11.06 ± 1.2 and 14.85 ± 2.2% and Hausner ratio varied between 1.12 ± 1.1 and 1.17 ± 2.1. All the four formulations were fallen in good flow character based on the compressibility index and Hausner ratio reports. Angle of repose has been used as indirect methods of quantifying powder flow ability, drug with all lipophilic excipients formulations fallen between 31 ± 1.2 and 35 ± 0.99° and indicated that all the formulations have good flow property thus, provides required hardness to the tablets.

Evaluations of candesartan cilexetil controlled-release tablets

Physico-chemical characteristics like thickness, weight variation, hardness, friability and drug content of all the formulations are shown in Table 3. The thickness of the medicated tablets ranged between 2.80 ± 0.2 and 2.90 ± 0.2 mm and weight varied between 180.7 ± 1.1 and 183.2 ± 2.1 mg. The hardness of the tablets ranged from 3.00 ± 1.5 and 4.00 ± 1.3 kg/cm^2 and it indicated the tablets were mechanically strong and within the limit of not less than 3 kg/cm^2. The friability varied between 0.175 ± 0.19 and 0. 319 ± 0.13 %. Friability test report was clearly stated that the tablets would be physically stable after packing and the result was well within the pharmacopoeial limit of not more than 1%. Drug content of the formulations ranged between 98.96 ± 2.1 and 101.9 ± 1.6 %. Assay parameter is used to ensure that the tablets contains the amount of active substance intended with little variation as per pharmacopoeial limit of ± 5 % and it indicated all the formulations having stated amount of active substance. All these results are allowed that the prepared formulations are suitable for blister packing, with adequate drug efficiency.

In vitro dissolution studies

Formulations F3 and F2 disintegrated within 20 min whereas F4 and F1 showed disintegration after 50 min in water and these results have no influence on the drug release. The faster disintegrated tablets retarded the drug release throughout the period of 24 h but the slower disintegrated tablets released fast while in dissolution.

Formulations F4 showed the drug release maximum of 56.62% after a period of 24 h, F1 and F2 showed around 80% drug release at the end of time period. Moreover, F3 showed maximum drug release of 93.98% after 24 h. In the first three sampling intervals, the drug release was found to be high in formulation F2 whereas the same amount of drug was released at the end of 24 h. F3 showed the better drug release throughout the time intervals in a controlled release manner when compare to F2 and F4. *In vitro* release of CC from different formulations is shown in Fig. 7.

Table 3. Physicochemical parameters of the formulations F1, F2, F3 and F4

Formulation code	Average weight (mg)*	Thickness (mm)*	Hardness (Kg/cm^2)*	Friability (%)*	Assay (%)
F1	181.5 ±1.2	2.90 ± 0.1	3.00 ± 1.5	0.237 ±0.09	99.99 ±1.8
F2	180.7±1.1	2.80 ± 0.2	3.50± 1.4	0. 319 ±0.13	98.96 ±2.1
F3	183.2 ±2.1	2.90 ±0.2	3.00 ±1.0	0.267 ± 0.20	101.9 ± 1.6
F4	182.1 ±1.5	2.80 ±0.2	4.00± 1.3	0.175 ±0.19	101.4 ± 2.0

*Average of six determinations

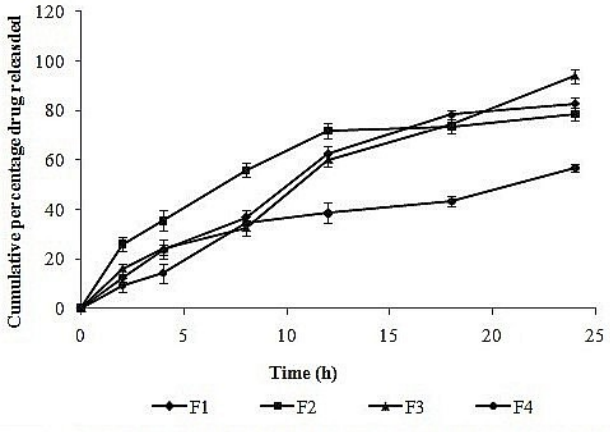

Fig. 7. *In vitro* release of candesartan cilexetil from different formulations

Table 4. Kinetics of drug released by mathematical processing of dissolution data

Formulations	Higuchi		Korsmeyer-Peppas		
	R^2	k	R^2	n	Mechanism of drug-release
F1	0.955	18.25	0.460	0.379	Diffusion
F2	0.956	16.85	0.255	0.399	Diffusion
F3	0.940	19.29	0.498	0.388	Diffusion
F4	0.962	11.52	0.311	0.246	Diffusion

Table 5. Accelerated stability studies of formulation F1, F2, F3 and F4

Evaluation parameter	Formulation code	1st month	2nd month	3rd month	5th month	6th month
Thickness (mm)*	F1	2.80±0.1	2.84±0.2	2.85±0.2	2.94±0.3	2.97±0.3
	F2	2.79±0.3	2.74±0.1	2.78±0.3	2.85±0.3	2.88±0.3
	F3	2.89±0.1	2.88±0.2	2.85±0.2	2.91±0.3	2.90±0.3
	F4	2.89±0.1	2.82±0.2	2.90±0.4	2.86±0.2	2.85±0.3
Weight variation (mg)*	F1	181.3±0.8	181.1±0.3	180.9±0.7	180.5±0.9	180.1±1.1
	F2	180.2±0.3	180.1±0.6	180.0±0.8	179.8±1.2	179.2±0.5
	F3	183.1±0.4	183.0±0.5	182.9±0.3	182.2±0.6	182.0±0.6
	F4	181.9±0.6	181.5±0.6	181.2±0.7	181.0±0.2	179.0±1.5
Hardness (Kg/cm^2)*	F1	3.5±0.5	3.0±0.5	3.0±0.5	3.0±0.5	2.5±0.5
	F2	3.0±0.5	3.00±0.5	2.50±0.5	2.50±0.5	2.50±0.5
	F3	4.0±0.5	3.50±0.5	3.00±0.5	3.50±0.5	3.00±0.5
	F4	3.50±0.5	3.00±0.5	2.50±0.5	3.00±0.5	3.00±0.5
Drug content (mg)*	F1	99.98±0.2	97.90±0.1	98.86±0.5	97.34±0.2	97.51±0.9
	F2	97.91±0.1	96.85±0.3	97.0 ±0.1	98.97 ±0.9	96.43 ±0.2
	F3	101.2±0.4	100.98±0.3	100.2±0.7	98.38±0.4	97.72±0.7
	F4	102.1±0.4	101.0±0.2	98.12±0.4	100.90±0.2	97.09±0.2
In vitro drug release after 24 h (%)*	F1	84.65±1.6	82.11±1.2	83.21±1.6	79.33±1.1	78.11±0.8
	F2	77.17±1.9	74.23±1.7	73.87±1.6	72.64±2.0	71.45±0.8
	F3	95.88±2.1	92.87±0.6	93.65±1.9	91.20±1.4	90.01±1.7
	F4	62.17±1.8	59.34±1.2	62.89±1.3	59.78±1.2	57.40±0.6
Appearance	F1	No change	No change	No change	No change	No change
	F2	No change	No change	No change	No change	No change
	F3	No change	No change	No change	No change	No change
	F4	No change	No change	No change	No change	No change

*Average of three determinations

The R^2, 'k' and 'n' values are shown in Table 4. All the formulations were best fitted to Higuchi model in which the drug release may be controlled by diffusion through the micropores. Accelerated stability study data of the medicated tablets are shown in Table 5.

DISCUSSION

The first solid dispersion created for pharmaceutical applications were prepared by fusion method. In this method drug has to fuse with or dissolve in the rubbery matrix, which is subsequently cooled to vitrify the solid dispersion. Grinding is required to obtain the solid dispersion as powder that is easy to handle (21).

The selected drug candidate is suitable for fusion technique which is not temperature sensitive and poorly soluble in water. All the used lipophilic excipients are erodible polar in nature and having the maximum melting point of 90°C. Moreover the drug and all the lipophilic excipients are compatible and no liquid phases observed in the heated mixture, which results in an homogeneous solid dispersion. Further, the drug and polymers mixture was rapidly cooled, it indicates yielded of amorphous solid dispersion.

The lipophilic polymers dissolve and disintegrate slowly through the gastro intestinal tract (GIT) consequently, the drug will dissolve or penetrate slowly in to the GI fluids and the absorption of drug will take place through paracellular route. This slow rate of absorption can maintain the sustained release of the drug. Furthermore, the lipophilic polymers provide several advantages, ranging from good stability at varying pH and moisture levels to well establish safe application. The fats and waxy materials are potentially erodible and control the release of drug through pore diffusion and erosion (22).

The dispersion of drug in the rubbery matrix and polymer coating around the drug particles are effective factors in obtaining sustained release profile (23). Increasing the polymer ratio in the formulation resulted in a decrease in dissolution rate. The initial formulation made with the drug polymer ratio of 1:1 resulted high dissolution rate. To control the drug release rate, the polymer ratio was increased to 1:3 resulted poor drug release. Based on these formulations, the prototype formulation discovered with the drug polymer ratio of 1:2.

FTIR spectral studies revealed that the drug having strong band at 2940 cm^{-1} remains unchanged in the final formulation, clearly indicates the drug and other excipients used in the formulation were very compatible. The melting point of the pure drug was 171.91°C, the DSC thermogram indicates that the drug changed from an crystalline nature to metastable crystalline form or an amorphous nature after the solid dispersion. X-ray diffractograms also confirmed that the drug was changed from crystalline nature. At 2θ of CC diffractogram shown that the drug was an crystalline nature before solid dispersion and the same has been changed to amorphous states when it dispersed with rubbery matrix. The result of SEM showed the particle size of the drug reduced from 127 to 42 μm after solid dispersion. It clearly indicated that CC in solid dispersion was homogeneously dispersed.

Blend evaluation test results demonstrated that all the formulations having good flow properties. The free flow of blends fallen between excellent and good category as per united state pharmacopoeial limit, it helps to compress the tablets without any defects. The physico-chemical parameters are shown in Table 3, the result was giving assurance that the tablets are mechanically strengthened. All the parameters were well within the desirable limits and it ensure the drug formulation is suitable for controlled drug delivery system. The content of drug in the formulations was checked by high performance liquid chromatographic (HPLC) method. Assay method was developed and validated as per international conference on harmonization (ICH) and USP guidelines. The chromatograms clearly stating that the developed prototype formulation was potential controlled drug delivery of CC.

Furthermore, *in vitro* drug release test was performed by using 900 ml of phosphate buffer with tiny amount of surfactant. The dissolution method was developed and validated as per ICH and USP guidelines. RP-

HPLC method was used to predict the drug release and dissolution sink conditions was maintained.

Hydrogenated castor oil is a white to slightly yellow fine powder obtained by hydrogenation of castor oil using a catalyst. It has been used in the pharmaceutical formulations as a sustained-release coating material and hardening agent (24). Hydrogenated castor oil is extremely hydrophobic in nature with lower wettability, these properties allowed the formulation F1 to release slowly over 24 h time period. Stearic acid is a hard, white or faintly yellow-colored, crystalline solid. Stearic acid is a mixture of stearic acid ($C_{18}H_{36}O_2$) and palmitic acid ($C_{16}H_{32}O_2$). The high percentage of stearic acid showing more hydrophobicity leads to control the drug release due to slower penetration of the dissolution medium in matrices. However, stearic acid acts as a solubilizing agent which imparted higher initial release.

Cetostearyl alcohol is generally a viscosity-increasing agent which is chemically a mixture of solid aliphatic alcohol containing mainly of stearyl [C1aHas0] and cetyl [C1sHs40] alcohols. The proportion of stearyl alcohol varies considerably but usually consists of about 50-70% stearyl and 20-35% cetyl alcohol. The aliphatic portions of the long chain fatty alcohols impart the cetostearyl matrix with sufficient hydrophobicity and impedes wetting of the matrix surface by dissolution fluid (25). Cetostearyl alcohol provides sufficient release in a controlled manner at the end of 24 h with soluble diluent of lactose. Cetostearyl alcohol containing formulation F3 imparted potential drug delivery with adequate drug release in a predetermined time manner. Carnauba wax, on the other hand, composed of alkyl eters of wax acids (80%), chiefly myricyl cerotate, free monohydric alcohols (10%). Less amount of CC was found to be released from this polymer contains formulation. There was no diminution in the tortuosity in formulation contain carnauba wax because of poor wettability and high hydrophobic nature, thus hammered the final drug release in formulation F4. It suggests that carnauba wax imparted the most release controlling capacity.

Lactose caused decrease in the tortuosity of the diffusion path of the drug that resulted in increasing of the drug release. All the formulations dissolution release was enhanced using soluble diluent of lactose. In some cases, it has been reported that the mechanism of release from wax matrices involves the leaching of drug by the eluting medium. Fluid enters through the cracks and pores of the matrix with diffusion of the drug through the matrix being insignificant (26).

From the lipophilic polymers the drug release was based on gradual erosion of the matrix. The obtained chromatograms revealed that formulation F3 (drug + cetostearyl alcohol) showed slow and steady release over the time period of 24 h. In comparison with formulation F2 and F4, formulation F1 showed better drug release at the end of 24 h. The maximum drug release was 82.89% from formulation F1 whereas F3 showed higher drug release of 93.98%, hence the formulation F3 was selected as a prototype formulation for further stability study.

All the formulations were best fitted to Higuchi model and according to this model, the drug release from these formulations may be controlled by diffusion through the micropores (Table 4). During initial and at the end of the accelerated stability study, the tested tablets showed almost similar drug content and release and also showed satisfactory thickness, weight variation and hardness during at the end of the accelerated study period (Table 5).

One of the most problems concerning the use of solid dispersion is their stability. In case the molecular interaction between the lipophilic excipients and drug are not strong enough to hold the drug in an amorphous state, the drug have a tendency to transform back to a stable crystalline form. Preformulation and formulation studies showed that the strong enough bonds between drug and polymer occurred and all the used inactive materials are compatible with drug.

CONCLUSION

The controlled drug delivery system of CC was developed by fusion method to improve the drug bioavailability and overcome the

administration frequency to once daily that would reduce a patients dosing regimen and can improve the patient's compliance.

The *in vitro* studies have shown that this is a potential drug delivery system for CC with considerably good stability and release profile.

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