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Preformulation Studies of Candesartan Cilexetil: Initial Step towards Development of Mouth Dissolving Tablets

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ABSTRACT:

Introduction: The first stage in creating dosage forms for any pharmacological ingredient is pre-formulation research. It verifies that the compound's development into a commercially available medication is not significantly difficult. **Objective:** The main objective of this research work was to conduct a pre-formulation analysis of Candesartan Cilexetil an angiotensin receptor blocker drug uses as antihypertensive medicine in order to produce a stable, robust including therapeutically effective system. **Methods:** Candesartan Cilexetil was analyzed to determine its physiochemical properties. Solubility was also determined in various pH-varying solvents and its purity was determined by FTIR and absorption maxima. Standard calibration curve was developed to aid in further analytical research studies. At last drug-excipients compatibility studies were performed. **Results:** Organoleptic properties indicated that the drug was almost white in color and odourless. The melting point was recorded at 158.2 ºC. The partition coefficient value log P was found to be 0.59±0.125. The purity of drug was confirmed by infrared spectrum which showed characteristics peaks and by UV spectroscopy which exhibited maxima at 257 nm. The standard curve obtained was linear with correlation coefficient (R2 =0.998) and equation y = 0.033 +0.012. There were no drug excipient interactions which was clear as no visual changes in drug samples were observed with respect to discoloration, liquefaction and odor. **Conclusion:** The powder blend under consideration was pure Candesartan Cilexetil which had good physiochemical property suggesting use of drug to formulation of novel drug such mouth dissolving tablet by various means and it was stable with selected excipient at reported ratio at 40oC / 75 % RH for 4 weeks.

KEY WORDS: Pre-formulation, Candesartan Cilexetil, excipients, flow property, FTIR

INTRODUCTION:

Once a promising novel API has been synthesized and developed, it must be transformed into the proper dose form to demonstrate a better and more desirable effect at the proper site.A unique medication delivery method called the **mouth dissolving tablets** dissolves and disintegrates swiftly to release the drug substance. [1, 2] Superdisintegrants such as carboxy methyl cellulose (Croscarmellose), cross-linked poly-vinyl pyrrolidone or crospovidone (Polyplasdone), sodium starch glycolate (Primogel, Explotab), etc. are the fundamental method utilized in the production of these tablets. [3] The process of developing a new medicine involves extensive, costly, and time-consuming research with a poor success rate. [4] It is crucial to comprehend the physicochemical characteristics of pharmacological content or biological components that are candidates in order to minimize this. [5]

Pre-formulation is the study of the physical and chemical nature of the drug prior to compounding process. Pre-formulation study is the first step in the development of dosage forms of any drug substance. [1, 6] Pre-formulation studies act an important criterion to understand the potential pharmaco-kinetics of a drug substance in humans as well as in animals and the opportunities and limitations for process change as the product is scaled up in production. [6, 7]

These studies are performed after the completion of pre clinical / clinical trial and before starting actual formulation and development of dosage form. These studies designed to determine the effect of physicochemical characteristics of drug substances and excipients on formulation properties of dosage form, method of manufacture and pharmacokinetic–biopharmaceutical properties of the resulting product. [6, 8] Pre-formulation studies utilize to analyze compatibility of drug with all excipients. [9] It helps researcher to choose appropriate form of a drug substance to enhance bioavailability.[10]

Angiotensin-receptor blocker (ARB) **Candesartan** is used either alone or in combination with other medications to treat hypertension. It is taken orally as the prodrug **candesartan cilexetil**, which is quickly absorbed in the gastrointestinal tract and changes into candesartan, its active metabolite.[11] By competing with angiotensin II for binding to the type-1 angiotensin II receptor (AT1) subtype and blocking the blood pressure-raising effects of angiotensin II, candesartan lowers blood pressure by opposing the renin-angiotensin-aldosterone system (RAAS). Angiotensin-converting enzyme (ACE) inhibitors cause dry cough, a side effect that is not experienced by ARBs. Diabetes-related nephropathy, left ventricular hypertrophy, isolated systolic hypertension, and hypertension can all be treated with candesartan. Additionally, it can be utilized as a substitute medication to treat systolic dysfunction, heart failure. .[12, 13]

In order to achieve this objective characterization of candesartan was done by calculate physiochemical parameters. [14] Solubility of drug in various solvents of having different pH was determined. Infrared spectrum was done to determine purity of drug and UV Spectra was developed which will help in further analytical studies. [15] Loss on Drying (LOD) was carried out to calculate assay compensation. Finally drug-excipients compatibility studies were carried out to determine drug – excipient interactions. [16]

Principal Areas of Pre-formulation:

Organoleptic properties: [9, 10]

- **Color:** A small quantity of drug was taken in butter paper and viewed in well-illuminated place.
- **Taste and odour:** Very less quantity of drug was used to get taste with the help of tongue as well as smelled to get the odor

Melting point: Melting point was determined by capillary fusion method. [17]

Partition coefficient ($P_{o/w}$): The partition coefficient of Drug was determined in n-octanol/distilled water at room temperature (25± 2ºC). [18]

$$P_{o/w} = (C_{octanol} / C_{aqueous})$$

Characterization of candesartan: [19, 20]

The drug substance was characterized for following parameters.

Determination of Solubility:

It is an essential and extensively utilized pre-formulation parameter. [22] The solubility of drug Candesartan was determined as per BCS classification system. [23] The solubility was checked in 250 ml different medium and water. The solubility of Candesartan in different solvents like water, 0.1N HCl, and phosphate buffer pH 6.8 was determined by using standard procedure.

Infrared spectrum:

The infrared spectrum of Candesartan pure drug and with excipients was carried out using potassium bromide disk method. The samples were prepared on KBr-press and over wave number range of 4000 to 400cm $^{-1}$ it was scanned.

Differential Scanning Calorimetry: Samples were prepared by placing 5 mg of the drug substance into an aluminium pan, which covered and crimped for analysis. Samples were desiccated over calcium chloride for 24 hours prior to assay in an effort to remove surface absorbed water. Thermograph was analyzed qualitatively by examining both the peak temperature and the endothermic transition contour. The nitrogen flow rate was 20ml/min and the heating rate was 5°C/min over the range of 40 to 2500C.

UV Spectral Analysis: [24]

An accurately weighed amount (10mg) of Candesartan was transferred to 100 ml volumetric flask. The drug was dissolved in methanol and volume was made up to 100 ml with the same solvent (Methanol) to obtain a stock solution of 100mg/ml. From the standard stock solution, 1 ml was taken out in 10 ml volumetric flask and volume was made up to 10 ml with PBS pH 7.5. The resulting solution containing 10mg/ml was scanned over complete UV range (i.e. 200–400 nm)[19] using Shimadzu UV–Visible spectrophotometer for determination of λ_{max} of the Candesartan. This stock solution was diluted with PBS pH 7.5 to give concentrations in the range of 5µg/ml-30µg /ml. Absorbance of these samples at varying concentrations were determined and data was used to plot calibration curve.

Drug Excipients compatibility study:

The study was designed with different ratio for drug and excipients as per their functionality. The weighed amount of API was mixed well with a proposed proportion of individual excipients (Table 5). Blend was filled and sealed in 5 ml glass vials. Vials were subjected to 40°C ± 2°C/75% ± 5% RH and 25°C/60% RH for 4 weeks conditions. The initial samples were analyzed immediately and used as control[25]. The samples were observed for physical changes[26] like discoloration, liquefaction.

RESULTS AND DISCUSSION:

Physiochemical Characterization of Candesartan:

Organoleptic properties indicated that the drug was almost white in color and odourless. The melting point was recorded at 158.2 ºC. The partition coefficient value log P was found to be 0.59±0.125. The observations are recorded in table 1.

Table 1 Results of Physiochemical properties of the Candesartan cilexetil

Characters	Inference
Color	white or almost white powder
Odor	Odorless
Nature	Crystalline powder
Melting Point	158.2 ºC
Partition Coefficient	5.9±0.25
Loss on drying	0.5% w/w (Not more than 1.0%, determined on 1 g by drying in an oven at 1050C)

Solubility Study:

The solubility of **Candesartan cilexetil** in different solvents was determined. The solubility of Candesartan in water is very less or insoluble, in 0.1N HCl, and phosphate buffer pH 6.8 was found to be 3µg/ml and 75µg/ml respectively. The amount of drug (s) dissolved was determined using UV spectrophotometeric method the observations are given in table 2.

Table 2: Results of Solubility of Candesartan Cilexetil in different media

S.No	Solvents	Amount of drug dissolved
1	Water	Insoluble 5×10^{-5} mg/mL
2	0.1N Hcl pH1.2	3 µg/mL
3	Phosphate buffer pH6.8	75 µg/mL

Fourier Transform infrared (FTIR) spectral studies:

While comparing the obtained FTIR spectra with the official spectra given in Indian Pharmacopoeia (2010), no differences were witnessed in the absorption peak pattern, which indicated the purity of the drug.

Among the various bands obtained in the spectra of **Candesartan Cilexetil**, only important ones were identified. An IR band was obtained at 2930.5 which can be assigned to C=C stretch, 3018.4 assigned to stretching of aromatic C-H group, 1715.2 assigned to stretching of aliphatic C=0 Stretching, 2138.4 assigned to N-N Stretching. Table 4

Table 3: Interpretation of FTIR spectra of Candesartan Cilexetil

Stretching type	Spectra range cm^{-1}	Observed peak cm^{-1}
C=C Stretching	3100-2830	2930.5
C=0 Stretching	1725-1700	1715.2
C-H Stretching	3030-2900	3018.4
Aromatic C-N	1450-1200	1350.6
C-O Stretch	1150-1010	1070
N-H Bending	1650-1580	1595.2
N-N Stretching	2145-2120	2138.4

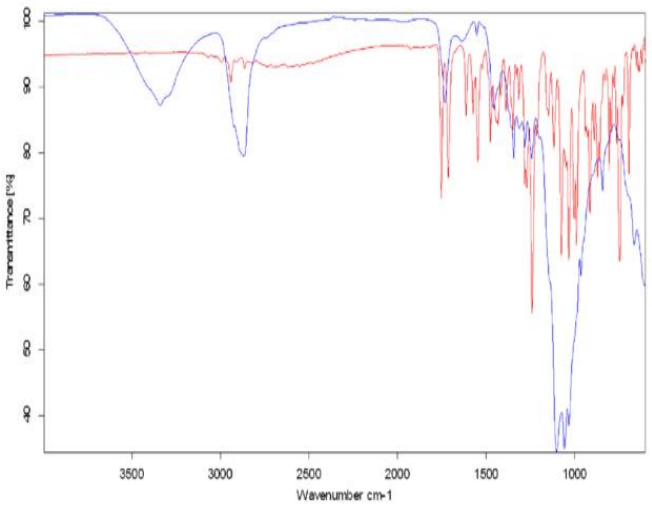

Fig. 1 Official FTIR of Pure Candesartan

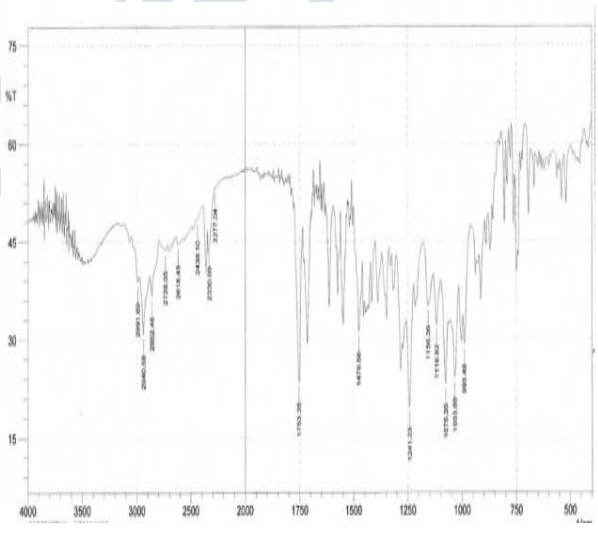

Fig.2 Observed spectra of Candesartan

Differential Scanning Calorimetry:

Differential scanning calorimetry (DSC) curves for DRUG was recorded. Melting point was recorded as 158.2ºC which was almost similar to the value obtained through capillary fusion method. The thermograph is shown in fig.

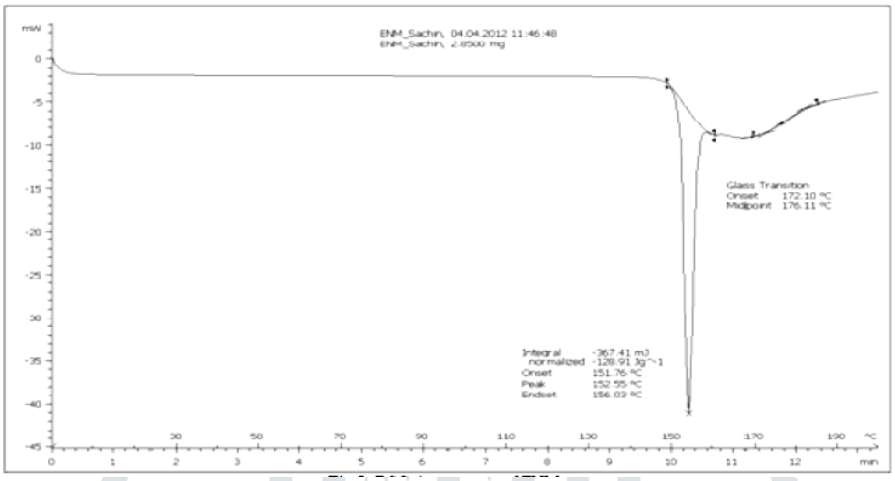

Fig. 3: Thermograph of Pure drug Candesartan Cilexetil

Spectrophotometric Analysis of Candesartan Cilexetil:

Ultraviolet absorption in the range 200 nm to 400 nm of a solution of known concentration in Phosphate Buffer pH 6.8 was measured. The absorption maxima (λ_{max}) of drug in this solution was found to be 257 nm (Fig. 6.4) which is in the close vicinity of maxima (258 nm in Phosphate Buffer pH 6.8) reported in literatures and official monographs[2]. The prepared stock solution was analyzed spectrophotometrically at 257 nm to develop the calibration curve.

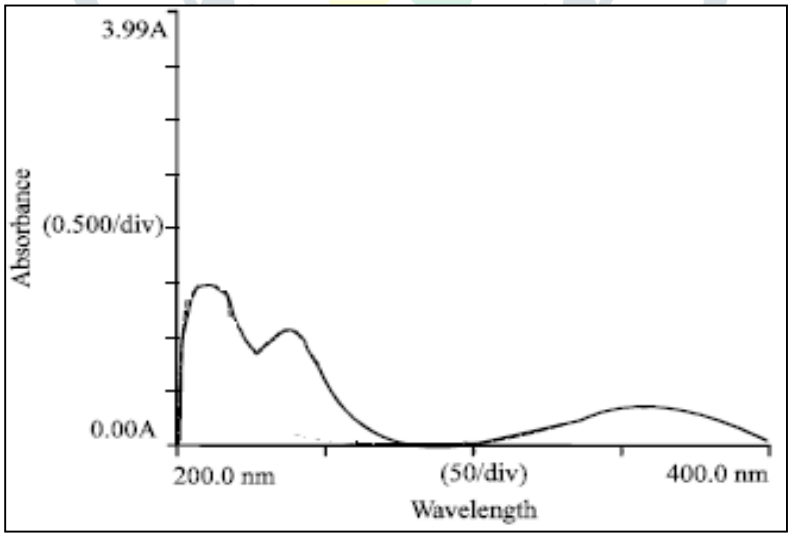

Fig.4: UV scanning of Candesartan cilexetil showing absorption maxima (λ_{max}) at 257nm.

Table 4: Calibration curve data of Candesartan cilexetil in 0.1N HCl pH 1.2 and Phosphate Buffer pH 6.8

Concentration (µg/ml)	Absorbance(257nm) 0.1 N HCl pH 1.2	Concentration (µg/ml)	Absorbance(257nm) Phosphate buffer pH 6.8
5	0.152	10	0.214
10	0.326	20	0.43
15	0.479	30	0.636
20	0.648	40	0.877
25	0.836	50	1.087
30	1.017		

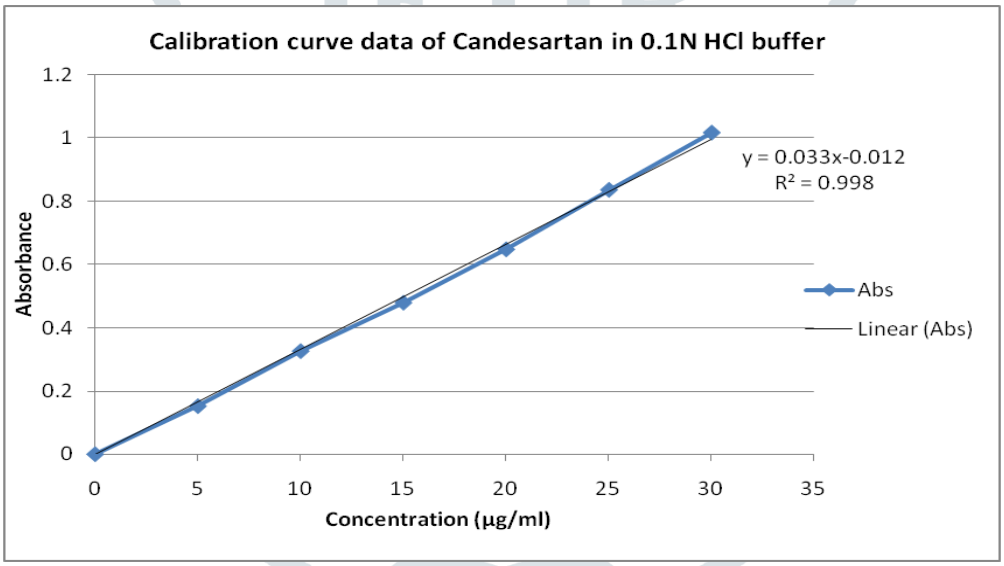

Fig. 5 Calibration curve of Candesartan cilexetil in HCl Buffer pH 1.2

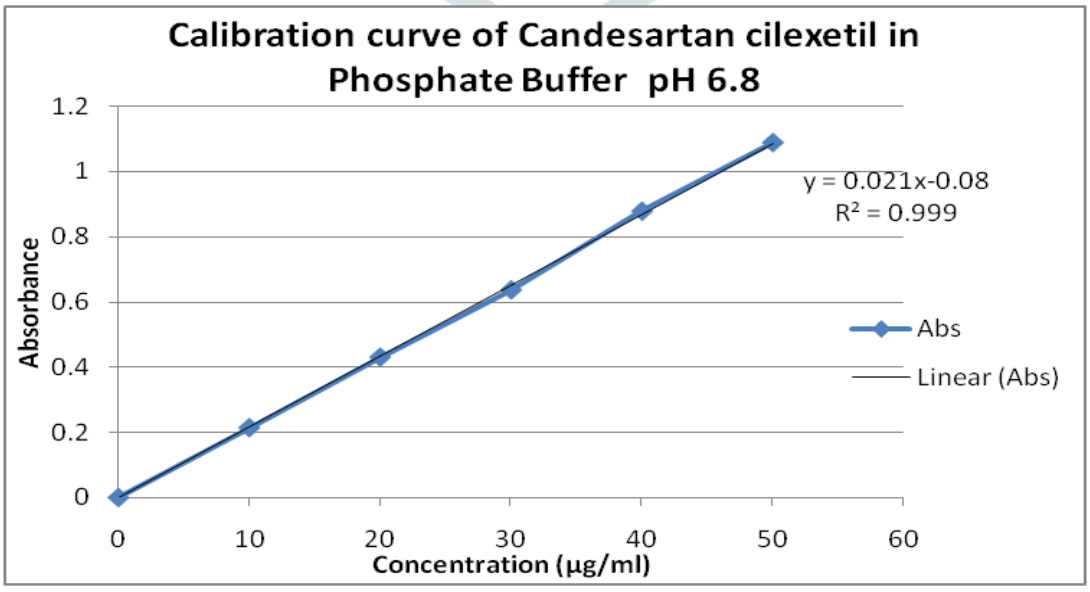

Fig. 6 Calibration curve of Candesartan cilexetil in Phosphate Buffer pH 6.8

Drug-Excipients Compatibility Study:

The different formulation excipients, **Candesartan cilexetil**, and their physical mixtures were found to be stable under selected storage conditions for one month, as there was no change in their physical characteristics.

Table 5: Observations of Drug-Excipient Interaction Studies

S.No	Drug-Excipients Blend	Initial Physical State	Observation at Different Storage Conditions							
			25˚C				40˚C			
			Duration (weeks)							
			1	2	3	4	1	2	3	4
1	CANDESARTAN CILEXETIL	WP*	N	N	N	N	N	N	N	N
2	DRUG +PEG6000	WP	N	N	N	N	N	N	N	N
3	DRUG +PVPK30	WP	N	N	N	N	N	N	N	N
4	DRUG + sodium starch glycolate	WP	N	N	N	N	N	N	N	N
5	DRUG + crospovidone	WP	N	N	N	N	N	N	N	N
6	DRUG +Mannitol +Magnesium Stearate+ Talc+AvicelPH102+ Lact	WP	N	N	N	N	N	N	N	N
7	DRUG +PEG6000+Mannitol+MagnesiumStearate+Talc+AvicelPH102+Lactose	WP	N	N	N	N	N	N	N	N
8	DRUG +PVPK30+Mannitol+MagnesiumStearate+Talc+Avicel PH102+Lactose	WP	N	N	N	N	N	N	N	N

*WP: white powder #N: No change

Conclusion:

In the present work, the preformulation study of antihypertensive drug **Candesartan cilexetil** was done. Pre-formulation analysis is most important phase in developing safe, effective and stable dosage form. Outcomes of these studies have great impact on further development of final dosage form. The organoleptic feature complies with Indian Pharmacopeia. Physical characteristics studies found that drug has good physiochemical properties. Solubility of drug was found to increase with increase in pH. The purity of drug was confirmed by infrared spectrum which showed characteristics peaks and by UV spectroscopy which exhibited maxima at 257 nm. The standard curve obtained was linear with correlation coefficient (R^2 =0.999) and equation y = 0.021x +0.008. The potential excipients Povidone, Sodium Starch Glycolate, Crospovidone, Lactose, Mannitol, Mg Stearate and talc which we are intending to use in formulating mouth dissolving drug delivery system were found to be compatible with drug Candesartan when subjected to different temperature and humidity condition.

This study shows a satisfactory result for all characterization and on the basis of this study we concluded that the drug was suitable for choice of formulation.

CONFLICT OF INTEREST:

No conflicts of interest are mentioned by the researchers. The composition and writing of the document are the sole responsibility of the writer.

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