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PREFORMULATION STUDY FOR CANDESARTAN CILEXETIL BUCCAL (EFFERVESCENT) TABLET

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Keywords:

Candesartan cilexetil, Preformulation, Drug-excipients interaction, Effervescent

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ABSTRACT: Candesartan cilexetil is a novel, potent, and highly selective non-peptide angiotensin II type 1 receptor blocker. It is a hydrophobic drug that belongs to the BCS Class II drug. For enhancement, the bioavailability and quick systemic action of Candesartan cilexetil a novel formulation of buccal (effervescent) tablet, was designed. Preformulation is an important step in the rational formulation of an active pharmaceutical ingredient (API). Micromeritics properties: Bulk density (du), Tapped density (db), Compressibility Index (% C) and sieve analysis was performed in order to determine the best excipients to be used in the formulation development of Candesartan cilexetil (effervescent) tablets. Results show that Candesartan Cilexetil has a fair flow and compressibility properties (du 0.8 g/mL, db 0.7 g/mL, % C 12.5, and sieve analysis time 4.5 min. HPLC method for estimation of Candesartan cilexetil shows linearity (R^2 = 1) and specific with no interference of excipients. Solubility studies reveal that it soluble at pH 6.8 and 7.5 in phosphate buffer. The ability of a material to absorb water (Hygroscopicity) was found 0.1% after 24 H at 80% Relative Humidity. Melting point range from 161-165 °C. There was no drug excipient interaction observed when analyzed through FTIR and DSC. There was no change in appearance after 15days at 40°C and 75% Relative humidity. These results lead to the better development of Candesartan cilexetil buccal (effervescent) tablet.

INTRODUCTION: Candesartan cilexetil is novel, potent, and highly selective non-peptide angiotensin II type 1 receptor blocker [1]. Its chemical name is (±) - 1-(cyclohexyloxy)carbonyloxyethyl-2-ethoxy-1-2'-(1Htetrazol-5-yl) 1, 1' biphenyl-4-ylmethyl-1Hbenzimidazole-7-Carboxylate as shown in **Fig. 1** and molecular mass is 610.66 g/mol. Its ionization constant is about 6.0, and LogP value is 4.79 [2, 3].

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It is mainly used in the treatment of hypertension. When it is administered orally, it is completely hydrolyzed from candesartan cilexetil to candesartan, an active moiety. It is a hydrophobic drug that belongs to the BCS Class II drug. Its Oral bioavailability is 15-40%; hence it is poorly absorbing from GIT.

For enhancement, the bioavailability and quick systemic action of candesartan cilexetil a novel formulation of the buccal tablet, was designed [4]. Before starting formulation design, we should know the properties of drug substance, its competetiveness to the formulation. A preformulation study is a group of the testing parameter that focus on the

physicochemical parameter of drug substance that could affect the drug performance and development of dosage form. The preformulation study provides information that supports developing effective, bioavailable, safe, stable, and robust formulation [5]. Preformulation study gives information regarding the physicochemical properties of drug substance, its compatibility with other Excipients, solubility, and partition coefficient of drug substance, an analytical method for evaluation of drug substance [6]. The aim of the present work was to perform preformulation studies to inform the development of Candesartan cilexetil buccal (effervescent) tablet for the purpose of determining the physical-chemical characteristics of drug with possible interactions with excipients.

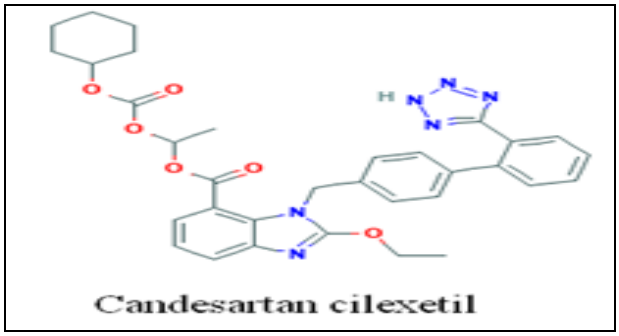


FIG. 1: STRUCTURE OF CANDESARTAN CILEXETIL

MATERIALS AND METHODS:

Chemicals and Reagents: Candesartan was received from Alembic Pharmaceutical Limited, Vadodara, Gujarat, India. Milli-Q water was used during the whole study. Methanol and Acetonitrile were of HPLC grade (Make-Rankem). Potassium dihydrogen phosphate was of AR grade (Make Rankem).

Instruments and Chromatographic Conditions: Shimadzu LC-2010 HT equipped with UV-Visible detector controlled by Lab solution software was used with column Inertsil C8 (150mm × 4.6mm, 5µm) , at 282 nm wavelength. Mobile phase having a mixture of 550 mL Acetonitrile and 450 mL of Milli-Q water and 1mL Ortho Phosphoric Acid (OPA) was used with a flow rate of 1.5 ml/min.

All weighing was done on Sartorius's analytical balance. Thermo Lab made a hot air oven used in the study. The ultrasonic bath of Labman was used. FTIR and DSC were used to Shimadzu Make. Thermo lab-made walk-in stability chamber was used for the study.

Micromeritics Properties of API: Bulk properties for the solid forms such as particle size, bulk density, and surface morphology are also likely to change during process development.

Bulk Density (DU): An accurately weighed sample of granulation was carefully added to the measuring cylinder with the aid of a funnel. Then the volume was noted. The volume of the packing was determined in an apparatus consisting of a graduated cylinder mounted on a mechanical tapping device. Apparent bulk density was determined by the following formula:-

$$DU = M / Vu$$

Where M = Mass of granulation in g Vu = volume of granulation (Initial untapped volume).

Tapped Bulk Density: (DB): The above procedure was followed. The final volume was tapped till no further reduction in volume was noted. Packed bulk density was determined by the following formula.

$$DB = m/Vb$$

Where m = mass of granulation in gm Vb = volume of granulation (Final tapped volume).

Percent Compressibility (%C): It is an important measure that can be obtained from bulk density measurements. The following formula was used to compute the percent compressibility.

$$\%C = (db - du) / db) \times 100$$

Where, DB = Packed bulk density, DU = Apparent bulk density.

Quantitative Assay Method: For linearity of the method, the standard solution was prepared in range 0.5, 1, 3, 5, and 7 mg/mL. Diluent was used as a blank for the specificity of the method.

Solubility Studies by Shake Flask Method: Take 200 ml flask. Add 100 ml solvent (Buffers/ purified water). Shake the flake by a magnetic stirrer. Maintain a temperature of 37 °C. Add drugs until it remains undissolved. Shake the flask for 12hr. Filter the solution with a 0.45 µ filter, analyses filtrate by assay analysis method. Dilute the sample if required. pH-dependent solubility of candesartan cilexetil was done in various pH media at temperature 25 ºC. The media for solubility tests

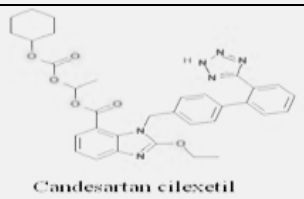
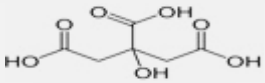
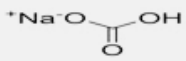
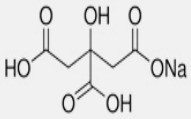
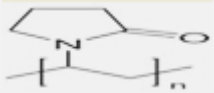
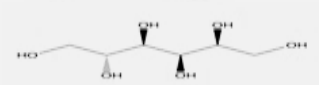
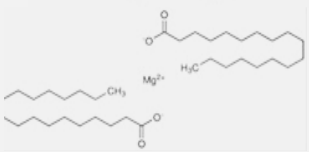
were purified water, phosphate buffer pH 1.2, 4.0, 5.0, 6.8, and 7.5.

Hygroscopicity: Hygroscopicity is the measurement of a material's ability to absorb or release water as a function of humidity (ie water activity). The ideal way of measuring Hygroscopicity would be to create a Moisture sorption isotherm by looking at the change in water content vs. relative humidity at a constant temperature.

Melting Point Determination: Fill a capillary tube with crystals about 3 mm high. Put the capillary tube (open end down) into the crystals and tap it on the bottom of the crystallization dish to get the crystals into the tube. Force the crystals to slide to the bottom of the tube using one of the following methods: tap the tube (open end up) on the lab bench; drop the capillary tube through a 2-3 foot piece of glass tubing, or rub the capillary tube along a piece of wire gauze. Place the capillary tube in the MEL-TEMP melting point apparatus. Set the MEL-TEMP at a high enough level to make a rapid determination of the melting point. Observe the melting process through the magnifying lens. Once a melting point range is determined, prepare another capillary tube (tubes should only be used once and then discarded) and set the MEL-TEMP to the appropriate power level, based on the power level/temperature chart. This time, make sure that the increase in temperature is no more than 2 °C per minute. Again, observe through the lens

Compatibility Study: To ensure physical stability**,** all excipients and active pharmaceutical ingredients were mixed in equal proportion to make a ratio of 1:1, as shown in **Table 1**. The sample shall be kept in the worst condition in a stability chamber. *i.e*. Stress testing condition (40 °C /75% RH) for 15 days. The samples were evaluated for physical observation, by FTIR for change in any functional group peak and by DSC for change in the meting point concerning the initial condition.

TABLE 1: PROPORTION OF ALL EXCIPIENTS FOR COMPATIBILITY STUDY

S. no.	Ingredients	Chemical structure	Specification	Quantity (gm)
1	Candesartan cilexetil	 Candesartan cilexetil	USP	200
2	Citric acid (Anhydrous)		BP	200
3	Sodium bicarbonate (Anhydrous)		BP	200
4	Sodium citrate		BP	200
5	PVP-K 30		USP/BP	200
8	Sorbitol		BP	200
9	Magnesium stearate		IH	200
11	Flavor peppermint	---	IH	200

RESULTS AND DISCUSSION:

Micromeritics Properties: Result of micromeritics properties were as shown in **Table 2**. Bulk density and tapped density was found 0.8 and 0.7 gm/mL, respectively. Compressibility was found good that will minimize the step for compression trials, and

ultimately it will reflect in the cost of the product. Compressibility helps in the selection and determination of the optimal excipients and amount of excipients to be used.

Quantitative Assay Method: The method was found specific, as shown in **Fig. 2** as there was no interference at the interested retention time of candesartan cilexetil. The linearity of the method shows an R2 value of 1.0 that indicates the method follows Beer-Lambert's law, as shown in **Fig. 3, 4,** and area response in **Table 3**.

TABLE 2: MICROMERITICS PROPERTIES OF API

Name of API	Bulk density	Tapped density	% compressibility
Candesartan cilexetil	0.8 gm/ml	0.7 gm/ml	12.5

TABLE 3: LINEARITY DATA FOR CANDESARTAN CILEXETIL

Concentration in mg/mL	Peak Area
0.5	1049112
1.0	2098232
3.0	6399607
5.0	10600983
7.0	14785525

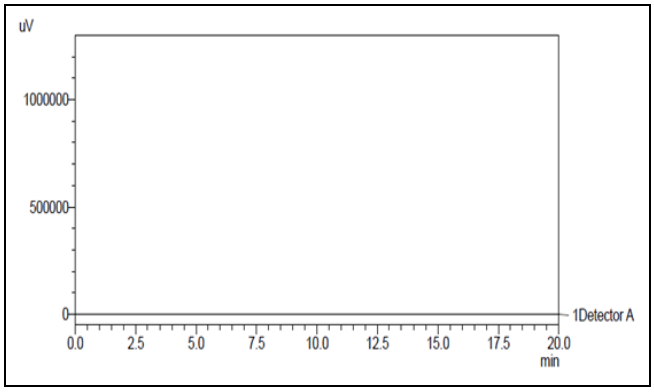


FIG. 2: CHROMATOGRAM OF BLANK OR DILUENT FOR SPECIFICITY

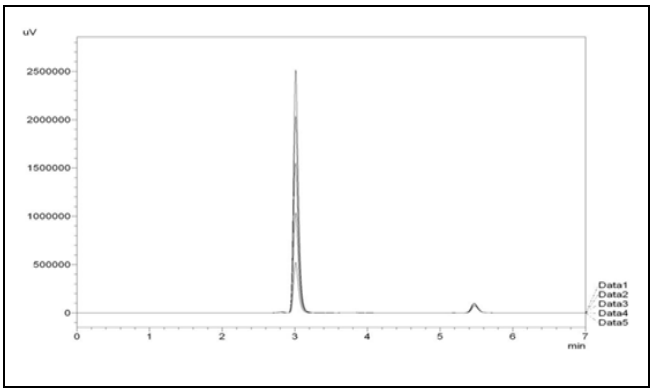


FIG. 3: OVERLAY CHROMATOGRAM OF LINEARITY

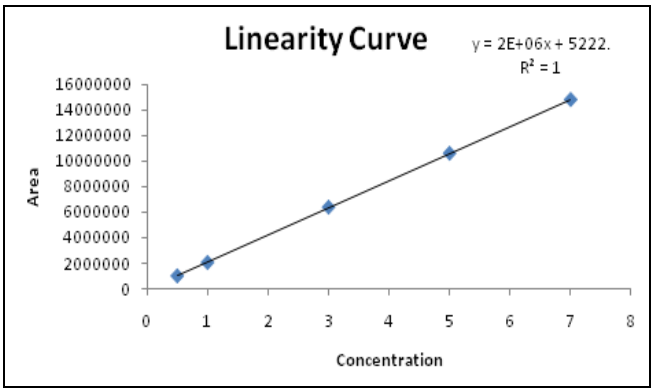


FIG. 4: LINEARITY CURVE FOR CANDESARTAN CILEXETIL

Solubility Study by Shake Flask Method: Solubility of Candesartan cilexetil in different media was found as shown in **Table 4**.

Solubility data helps to predict the dissolution media condition, selection of mobile phase, and diluent for development of the chromatographic method, possible interaction, and stability of the API in particular media.

From the table, it can be said that at lower pH, the API remains insoluble, and its solubility increase as an increase in the pH of media. At pH 6.8 and pH 7.5, the API was found soluble.

Hygroscopicity: The ability of Candesartan cilexetil to absorb moisture was less than 0.1% when it was exposed to 80% Relative Humidity for 24 H. This indicates that the material was non-hygroscopic in nature.

Non-hygroscopic nature will not degrade in higher moisture conditions, but it will also retard the solubility of material.

So, to increase the solubility and thus to make material hygroscopic, the buffering system needs to be develop surrounding the molecule by the concept of effervescent.

TABLE 4: SOLUBILITY OF API IN DIFFERENT MEDIA

Theoretical pH	Individual Concentration at Saturation (Cs) Values mg/mL (Theoritical)	Mean	Amount that can be Dissolved mg/mL (From Assay)	Mean	Results
pH 1.2	0.10	0.09	0.09	0.09	Insoluble
	0.08		0.08		
	0.11		0.10		
pH 4.0	0.95	0.98	0.92	0.97	Very slightly soluble
	0.98		0.97		
	1.0		0.98		
pH 5.0	1.9	2.2	1.85	2.1	Slightly soluble
	2.1		2.0		
	2.5		2.5		
pH 6.8	45	44.3	44.9	44.2	soluble
	46		45.8		
	42		41.8		
pH 7.5	48	49.7	47.8	49.4	soluble
	50		49.9		
	51		50.6		

Melting Point Determination: Determining the melting point of a compound is one way to test if the substance is pure. A pure substance generally has a melting range (the difference between the temperature where the sample starts to melt and the temperature where melting is complete) of one or two degrees. Impurities tend to depress and broaden the melting range, so the purified sample should have a higher and smaller melting range than the original, impure sample. The melting range for Candesartan Cilexetil was found to be 161-165.

Compatibility Study: The results of the compatibility study are summarized in **Table 5**. There was no interaction found between drug and different excipients even after 15 days at 40 °C and 75% Relative Humidity. FTIR spectra remained the same with no change in any functional group peak, as shown in **Fig. 5-6,** and **Table 6**. The endothermic peak in DSC indicates that there was no any impurity generated during the exposure period for drug and excipients, as depicted in **Fig. 7-8.**

TABLE 5: RESULT OF DRUG-EXCIPIENTS COMPATIBILITY STUDY

Test	Acceptance Criteria	Initial Observation	After 15days at 40 °C +75% RH
Appearance	White, odorless, crystalline powder, having a slightly bitter taste	comply Powder was free-flowing and free form lumps. No color change observed	Comply Powder was free-flowing and free form lumps. No color change observed
FTIR	Functional group should remain intact	functional group picks were intake	functional group picks remained intake
DSC	change in melting point NMT ±2%	comply	comply

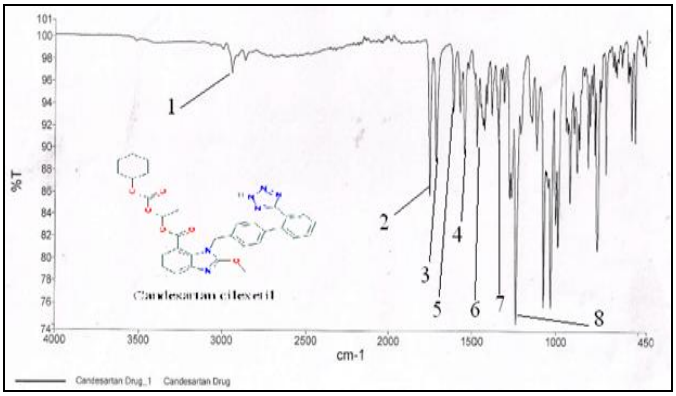


FIG. 5: FTIR SPECTRA OF CANDESARTAN CILEXETIL AT 0 DAYS CILEXETIL

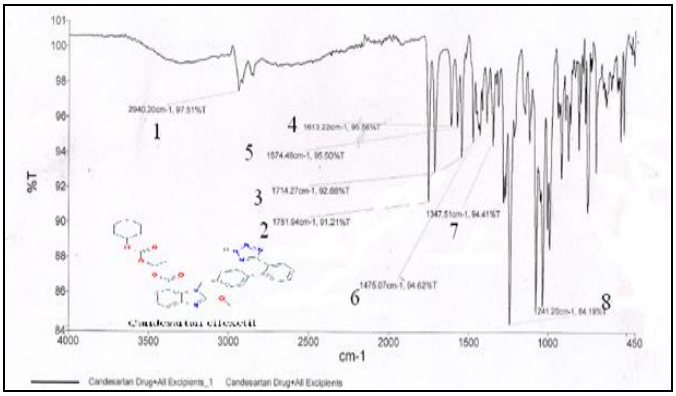


FIG. 6: FTIR SPECTRA OF CANDESARTAN AFTER 15 DAYS AT 40 °C/ 75% RH

TABLE 6: FUNCTIONAL GROUP IDENTIFICATION

Peak Name	Absorption cm^{-1}	Functional Group	Observation
1	2940.58	alkyl C-H stretch	Alkyl group present
2	1751.82	Ester C=O stretch	ester group present
3	1714.22	carboxylic acid stretch	Carboxylic acid group present
4	1612.98	Amide $CONH_2$	$CONH_2$ group present
5	1574.49	N-O stretching	N-O group present
6	1475.1	C-H bending alkane group	Methyl group present
7	1387.82	C-H bending aldehyde group	
8	1240.96	R-C=O -R	ester group present

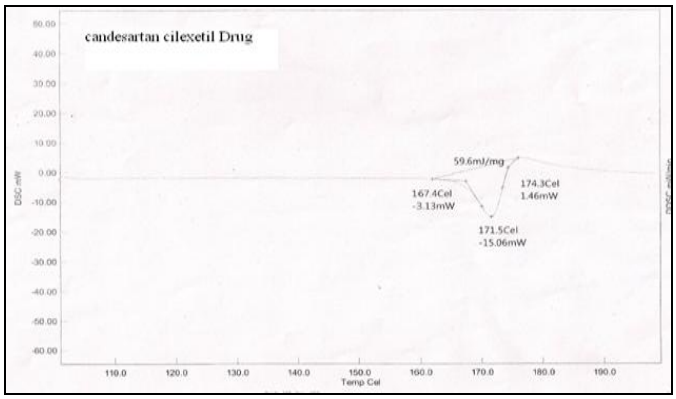


FIG. 7: DSC DATA OF CANDESARTAN CILEXETIL AT 0 DAYS

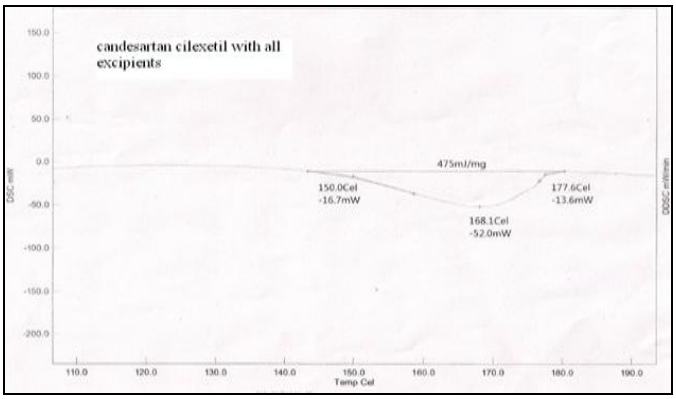


FIG. 8: DSC DATA OF CANDESARTAN CILEXETIL AFTER 15 DAYS AT 40°C/75%RH

CONCLUSION: Preformulation study has a significant part to play in anticipating formulation problems and identifying the logical path for the development of dosage form. The physical characteristics of candesartan cilexetil comply as per the USP requirement. The study of micromeritics properties revealed that the formulation could be prepared by the direct compression method. The chromatographic method with the R^2=1 supports the method for linearity, and the specificity of the method tends to analyze the sample without any interference. Non-hygroscopic nature of drugs will be a single hurdle for formulation development. pH-dependent solubility plays an important role in developing a bioavailable dosage form.

The API soluble at more basic pH can be created by means of effervescence. Results of sold state stability candesartan cilexetil show that it is compatible with Excipients at stressed conditions too. FTIR and DSC interpretation shows that there is no any reaction between Excipients and drug.

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CONFLICTS OF INTEREST: Nil

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