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Formulation and Evaluation of Fast Dissolving Tabletes of Candesartan using Natural Excipients for the Treatment of Hypertension

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ABSTRACT

Candisartan is used commonly for the treatment of hypertantion. Candesartan shows, has a long duration of action. It has half-life of 9 hrs where asT max is 3-4 hr so rapidly achieve desired plasma concentration and stands for long time, so once daily dose is enough for onset of clinical effect, which is also convenient to the patient. Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Provides convenience to whom that has trouble in swallowing tablets. The objective of the present study was to prepare the mouth dissolving tablet of candisartan using different superdisintegrants. .The tablets were evaluated for hardness, friability, weight variation, wetting time, thickness, water absorption ratio, disintegrating time, uniformity of content and in-vitro drug release.

Key words: Sodium Starch Glycolate, Plantago ovata, Superdisintragate, Candisartan

I. INTRODUCTION

A solid dosage form is drug delivery system that includes tablets, capsules, sachets and pills as well as a bulk or unit-dose powders and granules. Among the various dosage forms oral solid dosage forms have greater importance and occupy a prime role in the pharmaceutical market.

The U.S food and drug administration center for drug evaluation and research (CDER) defines an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue. The most desirable formulation for use by the elderly is one that is easy to swallow and easy to handle. Taking these requirements into consideration, attempts have been made to develop a rapid dissolving tablet. Since such a tablet can disintegrate in only a small amount of water in the oral cavity, it is easy to take for any age patient, regardless of time or place. For example, it can be taken anywhere at any time by anyone who do not have easy access to water. It is also easy to dose the aged, bed-ridden patients, or infants who have problems swallowing tablets and capsules. Recently, many companies have researched and developed various types of fast-disintegrating dosage form technologies with the potential to accommodate various physicochemical, pharmacokinetic and pharmacodynamic characteristics of drugs. These dosage forms disintegrate within 30sec with very less quantity of water. This can be achieved by addition of various superdisintegrants like Croscarmellose sodium, Crospovidone, sodium starch glycolate [1, 2].

Some 600 million people worldwide have high blood pressure and nearly 3 million die every year as a direct result. Yet seven out of every 10 people with hypertension are not being treated adequately, according to WHO and the International Society of Hypertension (ISH).

The tablet is the most widely used dosage form because of its convenience in terms of self administration, compactness, and ease in manufacturing. For the past one decade, there has been an enhanced demand for more patient- friendly and compliant dosage forms. As a result, the demand for developing new technologies has

been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost- effective dosage forms[3]

Compare to other ARBs Candesartan shows, has a long duration of action. It has half-life of 9 hrs where asT max is 3-4 hr so rapidly achieve desired plasma concentration and stands for long time, so once daily dose is enough for onset of clinical effect , which is also convenient to the patient. Pharmaceutical products designed for oral delivery and currently available on the prescription and over-the-counter markets are mostly the immediate release type, which are designed for immediate release of drug for rapid absorption. Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. Superdisintegrant improve disintegrant efficiency resulting in decreased use levels when compared to traditional disintegrants.Traditionally, starch has been the disintegrate of choice in tablet formulation, and it is still widely used. For instance, starch generally has to be present at levels greater than 5% to adversely affect compatibility, especially in direct compression. Drug release from a solid dosage form can be enhanced by addition of suitable disintegrants. [4]
anism of Disintegrants:

1) High swellability
2) Capillary action and high swellability
3) Chemical reaction

In this work; an attempt is made to formulate immediate release tablets of Candesartan to increase patient compliance by reducing dosing frequency and to achieve even plasma concentration profile.

II. METHODS AND MATERIAL

Materials

Candesartan was obtained as a gift sample from Ranbaxy Labs Ltd. All solvents were pure analytical grade purchased; Double distilled water was used throughout the experiment.

Methods

Determination of absorption maxima of candesartan cilexetil[5]

Candesartan cilexetil (100mg) was accurately weighed, transferred to 100ml volumetric flask and dissolved in small quantity of ethanol. The volume was made up with ethanol to get a concentration of 1000µg/ml. From this 10 ml was withdrawn and diluted to 100ml in HCl pH1.2/pH 6.8 phosphate buffers to get concentration of 100µg/ml. From this solution, 1 ml was withdrawn and added to the 10 ml volumetric flask. Finally, the standard solution (1µg/ml) of Candesartan cilexetil was scanned between 200-400 nm on UV-visible spectrophotometer to record the wavelength of maximum absorption (λ max). The λ max was found to be 224nm from UV spectrum of candesartan in ethanol; Absorbance was measured at 224nm against ethanol as blank spectrophotometrically. Shown in fig no 1.

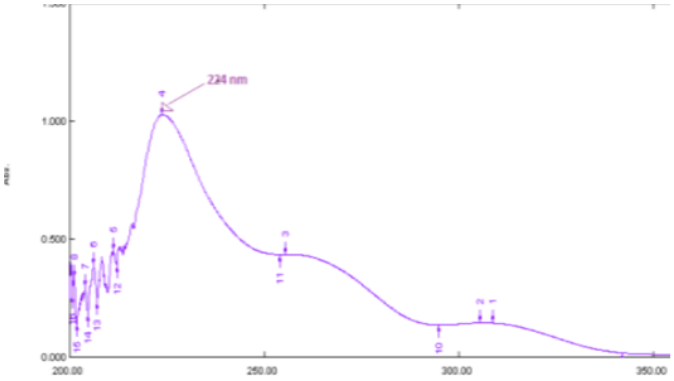


Figure 1: Absorption maxima of candesartan cilexetil in phosphatebuffer pH= 6.8

Calibration curve of Candisartan celexetil [6]

1) Preparation of standard solution:

Candesartan cilexetil (100mg) was accurately weighed into 100ml volumetric flask and dissolved in small quantity of ethanol. The volume was made up with ethanol to get a concentration of 1000µg/ml. From this 10 ml was withdrawn and diluted to 100ml in HCl pH1.2/pH 6.8 phosphate buffers to get concentration of 100µg/ml.

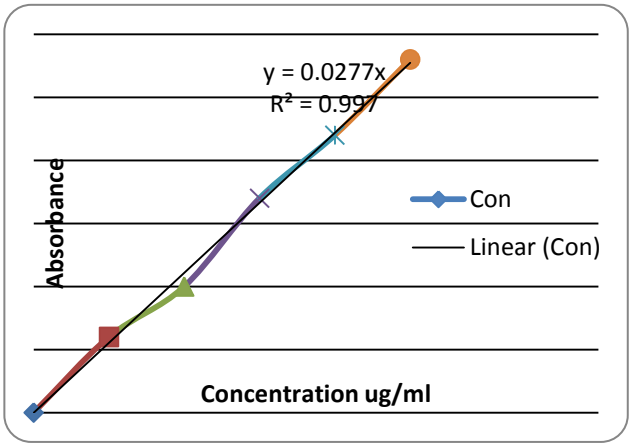
Preparation of working solutions

From the standard stock solution aliquots 2ml, 4ml, 6ml, 8ml and 10ml were pipetted out into 100ml volumetric flask .The volume was made up with phosphate buffer

pH6.8 and HCl pH1.2 to get final concentration of 2 µg/ml, 4 µg/ml,6 µg/ml,8 µg/ml and 10µg/ml respectively .The absorbance of each concentration was measured at 224nm.Absorbance was measured at 224nm against ethanol as blank spectrophotometrically. Shown in table no 1

Table 1: Linearity data of candesartan cilexetil in buffer pH=6.4

1.Calibrationcurve: Concentration (µg/ml)	Average Absorbance
0	0
2	0.06
4	0.10
6	0.17
8	0.22
10	0.28



Physicochemical property of drug[7] [8]:

1. Loose Bulk Density (BD)

25 g of drug was weigh accurately, which was previously passed through 30 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V0). Calculate the apparent bulk density in gm/ml by the following formula

Bulk density = Weight of powder / Bulk volume……..(1)

2. Tapped bulk density (TD)

25 g of drug was weigh accurately, which was previously passed through 30 # sieve and transferred in 100 ml graduated cylinder. Then mechanically tap the cylinder containing the sample by raising the cylinder and allowing it to drop under its own weight using mechanically tapped density tester that provides a fixed drop of 14± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped for 500 times initially and tapped volume (V1) was measured to the nearest graduated units. Tapping was repeated an additional 750 times and the tapped volume (V2) was measured to the nearest graduated units.The tapped bulk density was measured in gm/ml by the following formula

Tapped Density = Weight of powder / Tapped volume (2)

3. Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD)x100]/TD (3)

4. Hausner's Ratio

The hausner's ratio was determined by the following equation

Hausner's Ratio = TD / BD (4)

5. Melting point of drug:

Melting point of the drug was determined as per USP method by DBK prog. Melting point apparatus.Melting point of Candesartan cilexetil was found to be **164°C**, which is in the range as given in literature (158-166°C).Hence the drug can be stated as pure.

6. Solubility profile:

Solubility studies were conducted by placing an excess amount of Candesartan (approximately 200 mg) in a 2 ml microtube containing 1 ml of each buffer. Then, the mixture was vortexed and kept for 3 days at 37oC in a shaking water bath to facilitate the solubilization. The samples were centrifuged at 10,000 rpm for 10 min to remove the undissolved candesartan. The supernatant was taken, diluted with ethanol upto 10 times and filtered through Whatman filter paper for quantification of drug by UV spectroscopy at 224 nm.

Prepration of Candesartan Matrix Tablet

Direct compression was followed to manufacture the gas generating floating tablets of Candesartan. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. Polymers selected with formulation is Shown in table no 2

Evaluation of Candesartan Cilexetil Tablet

1 Description of reference product: The reference product was orange to pink colored, round shaped, uncoated tablets.

2 Physical characterization of reference product: The reference product blopress was physically characterized . Shown in Table no

Table 3: Physical characterization of reference product

Average Weight (mg)	150 ± 3%
Thickness (mm)	2.4 ± 0.03mm-2.8 mm ± 0.03mm
Hardness (Kp)	4-5±0.5kp
Friability (%w/w)	Nil
disintegration time (min.)	17-18 min

3 Acceptance Criteria for Final Product:

Table 4: Acceptance criteria for final product

Test Parameter	**Acceptance Criteria**
Appearance	Orange to pink colour, round shaped
Average weight	150% mg
Uniformity of weight	Average weight 5 %
Hardness	40.5-50.5 kp
Disintegration time	17-18 min
Thickness	2.4± 0.03mm-2.8 mm ± 0.03mm.
Friability	NMT 1%
Dissolution	NLT 85.0 % is dissolved in 15-30 min.
Assay	NLT 99%.& NMT 101% of label claim

Evaluation of Candesartan cilexetil immediate release tablet:

General Appearance: Any variation in tablet thickness within the particular lot of tablets or between manufacturer's lots should not be apparent to unaided eyes for consumer acceptance of the product. In addition thickness and diameter must be controlled to facilitate packaging. Thus thickness and diameter of tablets were important for uniformity of tablet size. Ten tablets were taken and their thickness and diameter were recorded using vernier caliper.

Average weight and weight variation: For weight variation test JP procedure was followed. Twenty tablets were taken and their weight was determined individually and collectively using electronic balance. The average weight of the tablets was determined from collective weight. From the individual tablets weight, the range and percentage standard deviation was calculated. Not more than 2 tablets should deviate from the average weight of tablets and the maximum percentage of deviation allowed. In direct compression of tablet, uniform weight of tablets represents appropriate powder flow and uniform die filling.

Disintegration test

Disintegration time is considered to be one of the important criteria in selecting the best formulation. To achieve correlation between disintegration time in-vitro and in-vivo, several methods were proposed, developed and followed at their convenience. One tablet was placed into each tube and the assembly was suspended into the 1000ml beaker containing water maintained at 37±2oc and operated the apparatus for 15 minutes. The assembly was removed from the liquid and the tablets were observed. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated.

Dissolution test

Dissolution: It is the amount of the solid substance that goes into the solution per unit time under standard conditions of the temperature and pressure.

Method: dissolution media was taken as 6.8pH, 900ml was placed in the vessel and the USP apparatus –II (paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37 + 0.5°C. Tablet was placed in the basket and placed in the vessel; the

apparatus was operated for 15min at 50 rpm. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the fluid was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed using UV

III. RESULT AND DISCUSSION

FTIR studies- Fourier transform infrared (FTIR) spectra of candesartan cilexetil and physical mixture of drug and excipients were recorded using potassium bromide KBr mixing method on FTIR instrument as depicted in Figure 1 and

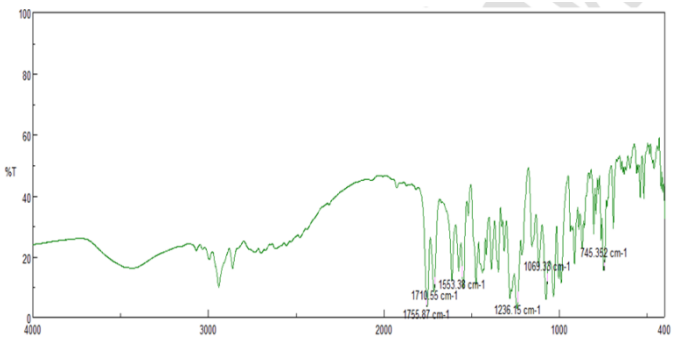


Figure 2: FTIR Study of Candisartan

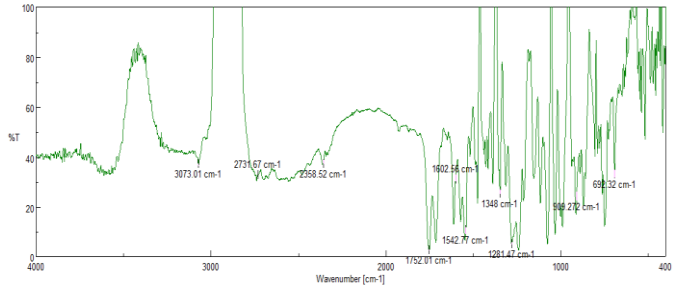


Figure 3: FTIR Study of candisartan and Excipients

FTIR studies revealed that there was no physico-chemical interaction between Candesartan cilexetil and other excipients. The pure drug Candesartan cilexetil showed characteristic absorption at 2731 cm-1, 1752cm-1, 1714cm-1, 1614 cm-1. This absorption peak at 3073 cm-1 was due to stretching of C-H bond, the peaks at 1752cm-1 and 1714cm-1 were due to two CO bonds (carbonyl group) and peak at 1614cm-1 was due to C-N bond. These peaks were present in IR scan of all formulations, so it was conformed that, presence of undisturbed drug in the formulations. Hence there were no drug-excipient interactions. As shown in fig 2.

PRE COMPRESSION PARAMETERS

The physicochemical properties of all the formulation were observed and recorded in the table no.5 and the evaluation of In-process parameters were determined and recorded in table no.5 Tablet was evaluated for hardness, friability, weight variation, thickness, disintegration time, wetting time, water absorption ratio, drug content and stability study. The Pfizer hardness tester and roche friabilator were used to test hardness and friability loss respectively. Results are shown in Table no 5and 6.

Table 5: Precompressional parameters of Candesartan cilexetil

Batch	Bulk density (g/cm3)	Tapped density (g/cm3)	Carr's index (%)	Hausner's ratio	Angle of repose (º)
F01	0.401±0.004	0.510±0.002	21.37	1.27	20.07±1.43
F02	0.420±0.003	0.515±0.002	18.44	1.22	21.32±1.32
F03	0.430±0.002	0.524±0.002	17.73	1.21	22.23±1.22
F04	0.428±0.004	0.543±0.002	21.17	1.26	24.12±1.72

Table 6: Evaluation parameters of Candesartan tablets

Evaluation parameters of Candesartan tablets	Avg. Tab Wt. (mg)	Thickness (mm)	Hardness (Kp)	Friability (%)	D.T. (min)
F01	150 ± 3%	2.5-2.7± 0.03mm	4.4 ±0.05	0.47	16-17
F02	150 ± 3%	2.5 -2.6 ± 0.03mm.	4.54 ±0.05	0.40	16-17
F03	148 ± 3%	2.4 -2.7 ± 0.03mm.	4.57 ±0.05	0.37	16-17
F04	149 ± 3%	2.5 -2.8 ± 0.03mm.	4.78 ±0.05	0.38	15-18

In vitro dissolution test for tablet formulations

In vitro dissolution studies for all batches of tablets were carried out using the USP paddle method in 900 ml of 0.05M phosphate buffer pH 6.5 containing as dissolution media, maintained at 37±0.5 at 50 rpm. 5 ml of aliquots

were withdrawn at 10, 20, 30, 40, 50 and 60 minutes from the basket and replaced by 5 ml of fresh dissolution media. The collected samples were analyzed after suitable dilution at 254 nm using UV- Visible spectrophotometer against the blank. The results of *in vitro* dissolution test is shown in table no 7

Table 7: *In vitro* dissolution tests for tablet (Batch F1-F4)

Time (min)	F01 (%)	F02 (%)	F03 (%)	F04 (%)
0	0	0	0	0
2	13.3±0.3	15.5±0.11	16.1±0.71	25.1±0.55
4	21.3±0.3	18.5±0.11	17.1±0.71	25.1±0.55
6	43.6±0.71	38.2±0.31	35.7±1.34	45±0.42
8	**65.1±1.33**	**52.4±0.42**	**49.8±1.54**	**60.3±1.32**
10	67.9±1.51	65.7±0.32	64.4±1.90	74.1±1.54
12	**71.1±1.8**	**70.5±0.45**	**69.5±1.76**	**75.6±1.9**
15	**72.9±0.64**	**80.3±0.34**	**76.9±1.25**	**78.7±1.97**
17	**74.2±0.70**	**88.89±0.74**	**79.2±1.24**	**80.78±0.54**
20	**77.60±0.64**	**94.14±0.44**	**82±0.74**	**83.87±0.34**

IV. CONCLUSION

Tablet formulation F2 showed a higher rate of dissolution and acceptable stability. Formulation was quick when compare to other formulations. It can be concluded that fast dissolving tablets with improved Candisartan cilexetil dissolution could be prepared by using natural Excipients like Kyran T, Plantago ovata.

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