INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com ISSN 2230 – 8407
Research Article

FORMULATION AND EVALUATION OF CANDESARTAN CILEXETIL IMMEDIATE RELEASE TABLETS

Jampani Neeharika*, Bonthu Ravi Kishore, B.Mamatha Reddy
Department of Pharmaceutics, Nayunpalli, Chirala, St.Ann's Group of Institutions, Chirala, Andhra Pradesh, India

Article Received on: 01/04/12 Revised on: 12/05/12 Approved for publication: 30/05/12

*Email: neeharika.pharmacy@gmail.com

ABSTRACT
Candesartan Cilexetil is an esterified prodrug of Candesartan, a non-peptide angiotensin II type-1(AT1) receptor antagonist used in the treatment of hypertension and congestive heart failure. Candesartan meets the requirement of high potency but it is poorly absorbed when administered orally. Therefore, the prodrug Candesartan Cilexetil is developed. It is soluble in methylene chloride, half life is 5.1 to 10.5hrs and bioavailability is 15%. It is marketed as conventional tablets. In this work, it is formulated as immediate release tablets by changing the concentration of ingredients. For many drug substances, conventional immediate-release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with in acceptable level of safety to the patient. The immediate release formulation of Candesartan Cilexetil is prepared by wet granulation method to provide rapid onset of action. In order to optimize the best formulation, ten different trials are developed. The main ingredients used in the formulation are lactose monohydrate, PEG, calcium CMC and MCC. Weight variation, thickness, friability, disintegration time, in-vitro release, pharmaceutical assay are studied as response variables. The formulation containing 38% of MCC is selected as an optimized product in which the different physical properties and in-vitro release profile showed best comparable results with innovator product.

Keywords: Candesartan Cilextil, Wet granulation, Angiotensin receptor antagonist.

INTRODUCTION

Candesartan cilexetil is an esterified prodrug of candesartan, a nonpeptide angiotensin II type 1(AT1) receptor antagonist used in the treatment of hypertension and congestive heart failure. The aim of this project is to develop immediate release formulation of candesartan cilexetil to provide rapid onset of action for the treatment of hypertension and congestive heart failure[5].

AIM

To develop Candesartan Cilexetil immediate release tablets (32mg) comparable to the marketed formulation.

OBJECTIVES:

The medical and pharmaceutical communities are seeing increasing opportunities and benefits for the ability to deliver immediate release dosage forms.

Primary Objective:

1. To formulate and evaluate immediate release Candesartan cilexetil tablets (32mg)

Secondary Objectives:

1. To perform preformulation studies including drug – excipient compatibility study.
2. To develop various formulations with different excipients.
3. To study the effect of excipient concentrations on the tablet characteristics.
4. To establish the invitro release compliance with the established criteria.
5. To achieve immediate release profile for the developed formulation.
6. To establish the stable of the formulation.
7. To improve the therapeutic response.

MATERIALS AND METHODS

Candesartan cilexetil is gift sample from aurobindho pharmaceuticals, Hyderabad. Lactose, pregelatinized starch, polyethylene glycol, calcium CMC, spray dried lactose, magnesium corn starch, ferric oxide from SD fine chemicals Mumbai.

Pre formulation[1,2,3]

Preformulation may be described as a stage of development during which the physicochemical and biopharmaceutical properties of a drug substance are characterized. It is an important part of the drug development process. A wide variety of information must be generated to develop formulations rationally. Characterization of the drug is a very important step at the preformulation phase of product development followed by studying the properties of the excipients and their compatibility.

Objective

The objective is to generate information useful in developing stable and bioavailable dosage form.

Scope

The use of preformulations parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product and at the same time provides the basis for optimizing of the drug product quality.

The API is tested for the following properties

- Organoleptic Properties
- Solubility
- Water Content
- Particle Size determination
- Flow Properties
  - ❖ Angle of Repose
  - ❖ Bulk Density
  - ❖ Tapped Density
  - ❖ Carr's Index
  - ❖ Hausner's Ratio
- Drug – Excipient compatibility study

Organoleptic Properties

The drug sample is viewed visually and viewed under the compound microscope for the determination of its color using the black and white backgrounds and nature of the drug sample. Then the results are compared with the official standards.

Solubility

The solubility of the drug sample is carried out in different solvents (aqueous and organic) according to the United States Pharmacopoeia. The results are then compared with standards.

Water Content

35 to 40ml of a mixture of methanol is transfered to the titration vessel and titrate with Karl fisher reagent to the electrometric end point to consume any moisture that may be present. Use powder from 5 tablets, grind to a fine powder in an atmosphere of temperature and relative humidity known not to influence the results. Accurately weigh and transfer about 300-500mg of the powder in to the titration vessel, mix and titrate with the KF reagent to the electrometric endpoint. Calculate the water content of the specimen in mg taken by the formulae:

Calculation:

$$\text{Water (\%)} = \frac{S \times F \times 100}{W}$$

Where,

S = Volume in ml of reagent consumed in the second titration

F = Water equivalent factor of KF reagent

W = Weight of sample taken in mg

Particle size determination

Size, shape & surface morphology of drug particles affects the flow, formulation homogeneity, dissolution & chemical reactivity of drugs. Particle size of drugs may affect formulation and product efficacy. Certain physical and chemical properties of drug substances are affected by the particle size distribution including:

- Dissolution rate
- Bioavailability
- Content uniformity
- Taste, texture and color
- Stability, flow characteristics and sedimentation rates.

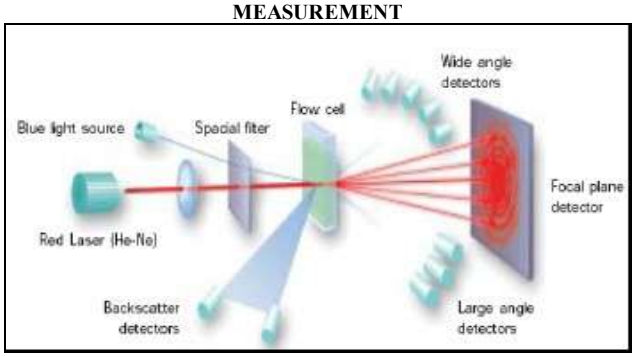
Particle size also has effect on the drug's absorption. Satisfactory content uniformity in solid dosage forms depends to a large degree on particle size and the equal distribution of the active ingredient throughout the formulation.

Particle size analysis is carried out in **"Malvern Particle Size Analyzer"** Model-Mastersizer-2000.

General Principle

The principle of operation consists of measuring the size of particles (powders, suspensions and emulsions) using the diffraction and diffusion of a laser beam. These particles scatter light at an angle that is inversely proportional to their size. The angular intensity of the scattered light is then measured by a series of photosensitive detectors. The map of scattering intensity versus angle is the primary source of information used to calculate the particle size.

SCHEMATIC REPRESENTATION OF THE LASER DIFFRACTION MEASUREMENT



Flow Properties

Angle of repose (θ)

It is a direct measure of flow property of powders. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Procedure

Angle of repose is determined using funnel to pour the powder on the surface from a fixed height of 2cm. Circumference is drawn with a pencil on the graph paper and the radius of base of a pile is measured at 5 different points and average is taken for calculation Angle of repose using following formula:

$$\text{Angle of Repose } (\Theta) = \text{Tan}^{-1} (h/r)$$

Where,

h = height of a pile (2 cm)

r = radius of pile base.

ACCEPTANCE CRITERIA FOR ANGLE OF REPOSE

Range (^{0})	Result
25 – 30	Excellent
31 – 35	Good
36 – 40	Fair
41 - 45	Passable
46 – 55	Poor
56 – 65	Very Poor
> 66	Very Very Poor

Acceptable range for angle of repose is $20^o$to 40^o

Bulk density

It is the ratio of given mass of powder and its bulk volume determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduating cylinder.

Procedure

Bulk density is determined according to USP method I. The powder sample under test is screened through sieve no 18 and 10 mg of pure drug is accurately weighed and filled in a 100ml graduated cylinder and the powder is leveled and the unsettled volume (Vo) is noted. Bulk density (Db) is calculated in g/ml by the formula:

$$(Db) = M/Vo$$

Where,

M = mass of powder taken

Vo= unsettled apparent volume

Limits:

It has been stated that the bulk density values having less than 1.2 g/ml indicates good packing and values greater than 1.5 g/ml indicates poor packing.

Tapped density

Procedure

Tapped density is determined by USP method II. The powder sample under test is screened through sieve no.18 and 10 mg of pure drug is filled in 100ml graduated cylinder of tap density tester (electrolab, ETD 1020). The mechanical tapping of the cylinder is carried out using tapped density tester at a normal rate of 250 drops per minute for 500 times initially and the initial tapped volume (Va) is noted. Tapping is proceeded further for additional 750 times and volume is noted. The difference between two tapping volumes is calculated.

Tapping is continued for additional 1250 tap if the difference is more than 2%. This is continued in increments of 1250 taps until differences between volumes of subsequent tapping is less than 2%. This volume is noted as, the final tapped

volume (Vo). The tapped density (Dt) is calculated in g/ml by the formula:

$$Dt = M/ Vo$$

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

Compressibility Index and Hausner Ratio

Compressibility Index and Hausner Ratio are measures of the propensity of a powder to be compressed. As such they are measures of relative importance of interparticulate interactions. In free flowing powder, such interactions are less significant and bulk & tapped density difference is close. For poorer flowing materials, this difference is greater.

a) Compressibility Index (% Compressibility)

Carr's compressibility index i.e., % compressibility indicates the flow property and packing ability of the tablet. It is determined by measuring both the bulk and tapped density of a powder. When the % compressibility ranges from 5 to 16, the materials have acceptable flow property and packing ability. Compressibility Index is calculated using following equation:

$$CI (\%) = [(Dt - Db)/Dt] \times 100$$

Where,
Dt = tapped density
Db = bulk density

b) Hausner's Ratio

The Hausner ratio indicates the flowability and packing ability of the tablet. When the Hausner ratio is close to 1, materials have acceptable flow and packing ability. Hausner Ratio is calculated using the formula:

$$Hausner\ Ratio = Dt/Db$$

Where,
Dt = tapped density
Db = bulk density

ACCEPTANCE CRITERIA OF FLOW PROPERTIES

Compressibility Index	Flow Character	Hausner Ratio
1 – 10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very Poor	1.46 – 1.59
> 38	Very Very Poor	> 1.60

Drug – Excipient Compatibility Study

Drug is in intimate contact with one or more excipient in all the dosage forms, which Later it could affect the stability of drug. Knowledge of drug excipient interaction is useful in selecting an appropriate excipient.

Procedure

API and excipient are taken in the ratios above mentioned and mixed together in a polybag for 5 min. Each mixture is allotted sample code for identification. 4 sets of sample are allocated where each sample mixture is divided in to 1g in to its corresponding glass vial (USP Type I) at different conditions.

All vials are properly sealed and loaded at respective conditions. The samples are to be checked for its description, related substance and water content by KF.

DRUG – EXCIPIENT RATIO FOR COMPATIBILITY STUDIES

S.No	Drug – Excipient	Ratio
1	Candesartan + Corn starch	1:5
2	Candesartan + PEG 6000	1:5
3	Candesartan + Calcium CMC	1:5
4	Candesartan + Klucel EF	1:5
5	Candesartan + Klucel LF	1:5
6	Candesartan + Ferric oxide red	1:0.1
7	Candesartan + Magnesium stearate	1:0.2
8	Candesartan + Avicel	1:5
9	Candesartan + Lactose	1:5

Sampling schedule

The prepared drug and excipient mixtures are evaluated at various intervals for related substances by HPLC as per the following conditions and time intervals.

SAMPLING SCHEDULE

S.No	Condition	Duration	No. of Sets
1	Initial	0 days	1
2	55°C± 2°C,75% RH±5%RH	14 days	1
3	40°C ± 2°C & 75%RH ± 5% RH	14 days	1
4	40°C ± 2°C & 75%RH ± 5%RH	28 days	1

FORMULATIONS

Formulation trails

10 formulation trails are prepared to get immediate release of Candesartan cilxetil tablets

FORMULATION SELECTION

BATCHES	TRAILS DONE
F1	Using povidone k-30 as binder
F2	Reducing PEG and Ca CMC concentration
F3	Reducing PEG6000 content
F4	With out PEG6000
F5	By incorporating MCC
F6	With out lactose and PEG
F7	With out corn starch
F8	Reducing quantity of corn starch
F9	Direct compression method
F10	By dry granulation(slugging process)

FORMULATION COMPOSITION OF TRIAL BATCHES

No	INGREDIENTS	F1 mg/tab	F2 mg/tab	F3 mg/tab	F4 mg/tab	F5 mg/tb	F6 mg/tb	F7 mg/tb	F8 mg/tb	F9 mg/tb	F10 mg/tab
1.	Candesartan cilexetil	32	32	32	32	32	32	32	32	32	32
2.	Lactose monohydrate	145	164.9	164.9	166.9	52	-	52	52	-	-
3.	Spray dried lactose	-	-	-	-	-	-	-	-	163	310
4.	MCC pH 101	-	-	-	-	100	150	125	120	-	-
5.	PEG 6000	12	6	2	-	12	-	12	12	12	12
6	Ferric oxide red	-	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
7.	Corn starch (PG star	-	40	40	40	25	39	-	5	40	30
8.	Klucel (HPC)EF	-	8	12	12	12	12	12	12	-	-
9.	Purified water	0.5ml	qs	qs	qs	qs	qs	qs	qs	-	-
10.	Ca CMC	-	8	2	8	25	25	25	25	12	14
11.	PVP K-30	7.80	-	-	-	-	-	-	-	-	-
12.	Magnesium sterate	2.60	1	1	1	2	2	2	2	1	2
13.	Sodium lauryl sulphate	10	-	-	-	-	-	-	-	-	-
	Total	260mg	260mg	260Mg	260mg	260mg	260mg	260mg	260mg	260mg	400mg

PROCEDURES

Wet granulation

- Candesartan cilexetil, lactose monohydrate, PEG6000, Avicel, cornstarch and HPC are weighed and passed through 40mesh and then mixed.
- Ferric oxide is weighed and added to above blend and then mixed.
- The above blend is to made as wet mass by using purified water as quantity mentioned in formula.
- That dough mass is passed through 12mesh to get wet granules.
- These granules are dried at 65^{o}C by using fluid bed drier.
- Dried granules are passed through 18mesh and then mixed.
- Ca CMC and magnesium sterate are weighed and passed through 40mesh and added to above blend and then mixed.

Dry granulation (slugging process)

- Candesartan cilexetil, lactose monohydrate, starch 1500 are weighed and passed through 30mesh and then mixed.
- PEG 6000 is taken in mortor to make fine powder by using pestle and added to above blend and then mixed.
- Ferric oxide is added to above.
- That blend is to made as slugs by using 18mm punches. Slugs are milled through 8mm mesh by using multimill.
- Milled granules are passed through 16mesh and then mixed.
- Weigh CaCMC and magnesium stearate are weighed and passed through 30mesh and added to above blend then mixed.

Direct compression

- ✓ Weigh candesartan cilexetil, spray dried lactose, PEG6000, starch1500 are weighed and passed through 40mesh and then mixed.
- ✓ Ferric oxide is added to above blend and then mixed.
- ✓ Ca CMC and magnesium stearate is weighed and passed through 40mesh and added to above blend and then mixed.

INVITRO-CHARACTERIZATION[4,5,6]

Weight variation:

Composite sample of tablets (usually 10) are taken and weighed through out the compression process . The composite weight divided by 10 gives average weight but contains usual problems of averaged values. Within the composite sample that has an acceptable average weight, there could be a tablet excessively over weight or underweight. To alleviate this problem the united states of pharmacopeia provides limits for the permissible variations.

Limits

Average weight of tablets(mg)	Maximum percentage difference allowed(%)
Less than 130	10
130-324	7.5
More than 324	5

Hardness

Tablets require a certain amount of strength or hardness and resistance to friability to withstand mechanical shocks of handling in manufacture packaging and shipping. In addition , tablets should be able to withstand reasonable abuse when in the hands of the consumer. Tablet hardness has been defined as force required to break a tablet in a diametric compression test. To perform this test, a tablet is placed between two anvils, force is applied to the anvils and the crushing strength that just causes the tablet to break is recorded. Hardness is thus sometimes termed the tablet crushing strength.

Several devices operating in this manner have been and continue to be used to test tablet hardness: Monsanto tester, Strong-cobb tester, Pizer tester, Erweka tester and Schleuniger tester.

Limit : Conventional Tablets: 5-15kg/cm^2 , Chewable tablets: 3kg/cm^2, Sustained release tablets: 10-20kg/cm^2

Friability

The laboratory friability tester is the Roche friabilator. It subjects a number of tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 100rpm dropping the tablets a distance of six inches with each revolution. Normally a preweighed tablet sample is placed in the friabilator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Some chewable tablets or most effervescence tablets undergo high friability weight losses, which accounts for the special stack packaging that may be required for these types of tablets. When capping is observed on friability testing, the tablet should not be considered for commercial use, regardless of the percentage of loss seen.

Limit : 1.0%

Disintegration

The drug to be readily available to the body, it must be in solution phase. For most tablets the first important step toward solution is break down of the tablet in to smaller particles or granules, a process known as disintegration. The time that a tablet take to disintegrate is measured in a device as described in the USP/NF. The USP method to test disintegration uses 6 glass tubes that are 3inches long, open at the top, and held against a 10-mesh screen at the bottom end of the basket rack assembly.

Temp: 30^{o}C$\pm$ 2^{o}C

A standard motor device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6cm at a frequency of 28 to 32 cycles per minute.

Limit: uncoated - <15min, Coated -<30min, Enteric coated-within 1hr

Assay: (HPLC)

Instrument : HPLC equipped with UV detector and data handle system

Apparatus : Analytical balance, volumetric flask, pipette, pH meter, filtration unit, 0.45µ membrane filter

Chemicals and reagent:

Candesartan cilexetil
Orthophosphoric acid- HPLC grade
Acetonitrile –HPLC grade
Purified water- milli- Q grade

Chromatographic conditions:

Columm : Hypersil BDS –C8(150*4.6mm)5µm
Wavelength : UV-210nm
Flowrate : 1.5ml/min
Inj.vol : 10µl
Columm oven temp : 40^{o}C
Run time : 25min

Preparation

Mobile phaseA

1ml of orthophosphoric acid is mixed with 1000ml of purified water and filter through 0.45µ membrane filter and degassed.

Mobile phase B

Acetonitrile HPLC grade is filtered through 0.45µ membrane filter

Diluent preparation

The degassed mix of mobile phase A and acetonitrile in ratio of 30:70v/v is prepared

Standard preparation

32mg of Candesartan Cilexetil working standard is weighed and transferred in to 100ml volumetric flask, 60ml of diluent is added and the volume is diluted with diluent. 5ml of above solution is transfered in to volumetric flask and the volume is diluted with diluent.

Sample preparation

5tablets are weighed and transfered into a 100ml volumetric flask. 60ml of diluent is added and sonicated for 30min with occasional shaking. The solution is cooled to room temperature and the volume is diluted with diluent and mixed. Filter, 2ml of above filter solution is transfered into 100ml volumetric flask and the volume is diluted with diluent.

Procedure

Blank standard preparation and sample preparation are injected in to chromatogram and the chromatogram is recorded separately and the peak area responses are measured for analyte peak and then % content of candesartan cilextil is calculated by formula

Calculation

%content of candesartan

TA/SA*SW/100*5/50*100/TW*100/2*P/100*AVG.WT/LA*100

TA- peak area response due to candesartan from sample preparation
SA- peak area response from standard preparation
SW- weigh of candesartan(in mg)
P - purity of candesartan

IN-VITRO DRUG RELEASE

Dissolution

Instrument: HPLC equipped with UV-detector and data handle system

Apparatus: Analytical balance, volumetric flask, PH meter, pipette, 0.45µ membrane filter, syringe, dissolution apparatus.

Chemicals: Candesartan Cilexetil,
potassium dihydrogen phosphosphate monobasic,
Acetonitrile-HPLC grade,
Orthophosphoric acid–HPLC grade,
Purified water-milli-Q grade
Sodium hydroxide –AR grade
Tween 20(polyoxy ethylene sorbiton-AR monolaurate)

Dissolution conditions

MEDIUM : 0.7% tween 20 in 0.05M phosphate buffer pH6.5
VOLUMME : 900ml
TEMP : 37°C± 0.5°C
APPARATUS : USP type-II(paddle)
Rpm : 50
TIME INTERVAL : 10, 20, 30, 45, 60 min

Preparation

0.2M sodium hydroxide solution:

8g of NaoH is dissolved in H_2O and diluted to 100ml with water.

0.2M potassium phosphate monobasic solution:

27.22g of potassium phosphate monobasic is dissolved in water and diluted to 100ml with water

0.05M phosphate buffer Ph 6.5 containing 0.7% tween 20:

250ml of 0.2m potassium dihydrogen orthophosphate is transferred in to 1000ml volumetric flask and 65ml of 0.2M sodium hydroxide is added then diluted to volume with water. If necessary pH of the solution is adjusted to 6.5 with 0.2M sodium hydroxide solution then 7g of tween 20 is added and mixed well.

Chromatographic conditions

column : Hyper sil BDS-C8(150*4.6mm)
wave length : UV-210nm
flow rate : 1.5ml/min
injection volume : 10µl
column over temp : 40°C
run time : 10min

Buffer preparation

1ml of orthophosphoric acid is mixed in 1000ml of purified water. The solution is filtered through 0.45µ membrane filter

Mobile phase preparation

Mixture of buffer and acetonitrile in ratio of 40:60v/v is prepared and filtered.

Standard preparation

35.5 mg of candesartan cilexetil working standard is weighed and transferred into a 200ml volumetric flask. 20ml of acetonitrile is added and sonicated to dissolve. The solution is cooled to room temperature and the volume is diluted with disso medium. 5ml of standard stock preparation is transfered into 25ml volumetric flask and the volume is diluted to with disso medium

Sample preparation

One tablet is placed in each of six disso flask containing 900ml of disso medium, previously maintained at 37°C±0.5°C taking care to exclude air bubbles from the surface of each dosage unit and the apparatus is immediately operated at specified time intervals. After completion of each specified time interval a portion of solution is withdrawn from zone mid way between the surface of the dissolution medium and top of the rotary blade not less than 1cm from the vessel wall and filtered through 0.45µ membrane filter.

Acceptance criteria

- %RSD for replicate injection of peak area response for candesartan cilexetil peak from the standard preparation should be not more than 2.
- Tailing factor for candesartan cilexetil peak should be NMT 2.
- No.of theoretical plates for candesartan cilexetil should not be less than 2000

Procedure :

Blank, standard preparation and sample preparation are injected in to chromatograms separately in equal volumes and chromatographs are recorded and peak area responses are measured for the analyte peak and the %drug dissolved of candesartan is calculated by formula.

Calculation

TA/SA*SW/200*5/25*900/1*P/100*100/32

TA- peak area response due to candesaratan from sample preparation
SA- peak area response from standard preparation
SW- weigh of candesartan(in mg)
P- purity of candesartan

STABILITY STUDIES: (F5)

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives.

RESULTS AND DISCUSSION

Preformulation studies

Preformulation studies like Physical Characterization, Solubility, Moisture Content, Flow properties like Angle of Repose, Bulk Density, Tapped Density, Compressibility Index and Hausner ratio are performed.

a) Physical Characterization of API

RESULTS OF PHYSICAL CHARACTERIZATION OF THE DRUG

S.No:	Description	Result
1.	Appearance	White to off-white powder
2.	Odour	Characteristic odour.
3.	Solubility	Freely soluble in Methylene chloride. Slightly soluble in methanol, Practically insoluble in water.
4.	Water Content	0.07 %

Discussion: The above result shows that physical characterization of the drug candidate (API) complies with the USP specifications.

b)Particle size analysis

RESULTS OF PARTICLE SIZE ANALYSIS

S.No.	Diameter(mm)	Particle Size(µm)
1.	0.1	0.724
2.	0.5	1.490
3.	0.9	2.835

Discussion: Particle size of the API is determined by Malvern Instrument, The above table illustrates the size of the particles.

c)Flow Properties

RESULTS OF FLOW PROPERTIES

S.No.	Flow Properties	Result
1	Bulk density (g/ml)	0.2647
2	Tapped density (g/ml)	0.562
3	Carr's index (%)	52.94
4	Hausner's ratio	2.125
5	Angle of repose	13°

Discussion: From the above results, it is found that the API has **"poor"** flow properties.

d)Compatibility studies results

COMPATIBILITY STUDIES RESULTS

Excipients	% Known impurities			% Unknown impurities			Total impurities		
	I	II	III	I	II	III	I	II	III
Lactose	0.15	0.2	0.3	0.01	0.02	0.04	0.16	0.22	0.34
PEG 6000	0.1	0.15	0.4	0.04	0.05	0.08	0.14	0.2	0.48
PG Starch	0.1	0.12	0.3	0.02	0.05	0.09	0.12	0.17	0.39
HPC	0.2	0.25	0.35	0.02	0.04	0.08	0.22	0.29	0.43
Ca CMC	0.2	0.18	0.28	0.01	0.04	0.05	0.21	0.22	0.33
Mg.Stearate	0.1	0.15	0.18	0.03	0.04	0.05	0.13	0.19	0.23

I = INITIAL
II = LONG TERM (28 DAYS)
III = ACCELERATED (14 DAYS)

PHYSICAL APPEARANCE FOR COMPATABILITY STUDY

INGREDIENTS	INTIAL $25^{o}C\pm2^{o}C$,60%RH±5%RH	14^{TH} DAY $55^{o}C\pm2^{o}C$,75%RH±5%RH	28^{TH}DAY $40^{o}C\pm2^{o}C$,75%RH+5%RH
Candesartan	White powder	White powder	White powder
C.C+ Lactose	White powder	White powder	White powder
C.C +PEG 6000	White crystalline powder	White crystalline powder	White crystalline powder
C.C+ PG starch	White powder	White powder	White powder
C.C+ ferric oxide	Brickred colour	Brick red colour	Brick red colour
C.C+ HPC	White crystalline Powder	White crystalline Powder	White crystallilne Powder
C.C+ Ca CMC	White powder	White powder	White powder
C.C+magnesium sterate	White powder	White powder	White powder

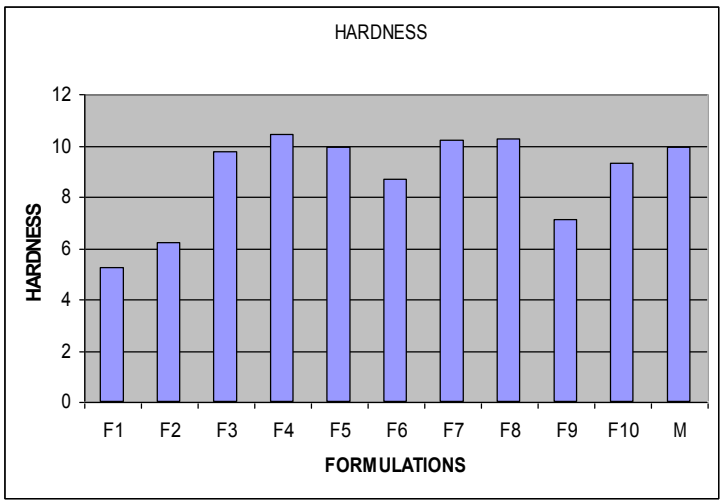
EVALUATION OF GRANULES

BATCH	ANGLE OF REPOSE(^{o})	BULK DENSITY g/ml	TAPPED DENSITY g/ml	COMPRESSIBILITY INDEX (%)	HAUSNER RATIO
F1	34±0.06	0.519±0.03	0.732±0.06	29.09±0.07	1.443±0.03
F2	29±0.04	0.537±0.03	0.761±0.05	30.601±0.03	1.417±0.06
F3	33±0.06	0.510±0.05	0.735±0.04	30.612±0.06	1.417±0.05
F4	39±0.02	0.525±0.04	0.714±0.04	26.47±0.06	1.360±0.07
F5	28±0.04	0.609±0.02	0.781±0.05	19.46±0.05	1.241±0.04
F6	27±0.06	0.510±0.03	0.641±0.03	20.408±0.05	1.250±0.05
F7	39±0.04	0.50 ±0.04	0.735±0.01	32.00±0.07	1.470±0.05
F8	35±0.07	0.520±0.06	0.757±0.03	31.250±0.05	1.454±0.06
F9	44±0.05	0.583±0.07	0.745±0.05	21.74±0.06	1.277±0.07
F10	32±0.04	0.510±0.06	0.727±0.07	29.69±0.03	1.419±0.07

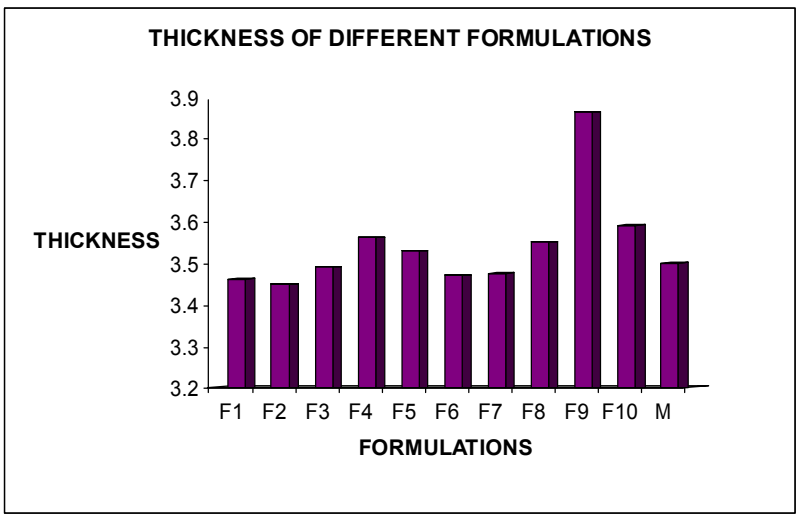
COMPRESSION RESULTS

BATCH NO	WT.VARIATION (mg)	HARDNESS (KP)	THICKNESS (mm)	FRIABILITY (%)	D.T (min.sec)	ASSAY(%)
F1	260.26±0.007	5.26±0.032	3.461±0.0087	0.07	11.23±0.03	96.3
F2	259.5±0.182	6.19±0.22	3.45±0.020	0.214	8.50±0.07	98.4
F3	260.4±0.00	9.75±0.514	3.49±0.025	0.24	14.05±0.06	97.5
F4	260.4±0.08	10.44±0.492	3.56±0.021	0.17	11.33±0.07	99.3
F5	260.3±0.02	9.9±0.472	3.53±0.020	0.00	11±0.03	99.8
F6	258.2±0.03	8.7±0.402	3.47±0.200	0.06	5.30±0.06	99.5
F7	258.5±0.06	10.17±0.305	3.475±0.027	0.13	12.50±0.07	100.9
F8	260.2±0.007	10.28±0.329	3.55±0.013	1.15	10.25±0.05	98.7
F9	260.4±0.130	7.1±0.278	3.862±0.052	1.1	7.20±0.04	96
F10	260.4±0.11	9.29±0.207	3.59±0.021	0.23	8.34±0.05	102.3
M	259.5±0.01	9.9± 0.44	3.50±0.049	0.02	11.17±0.05	99.7

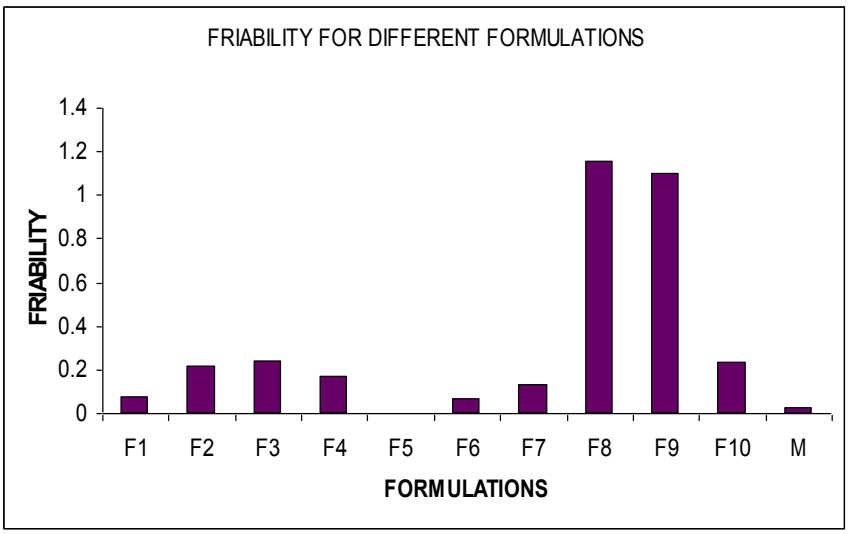
COMPARISION OF HARDNESS FOR DIFFERENT TRIALS



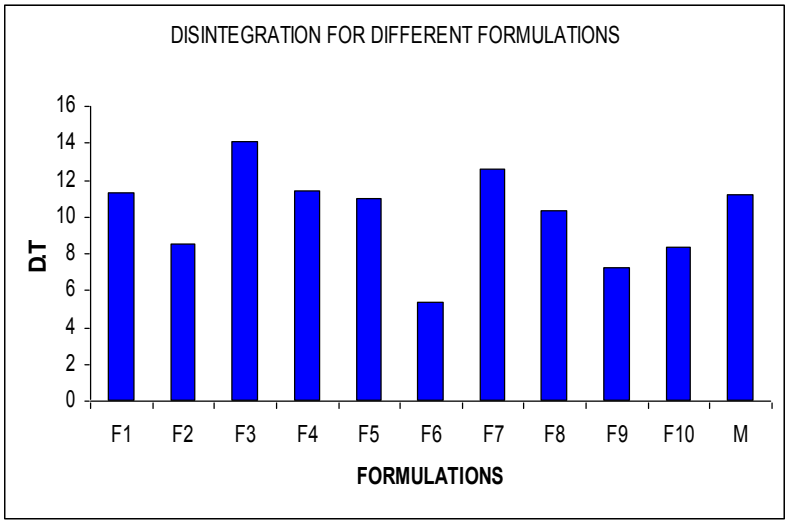
COMPARISION OF THICKNESS FOR DIFFERENT TRIALS



COMPARISION OF FRIABILITY FOR DIFFERENT TRIALS

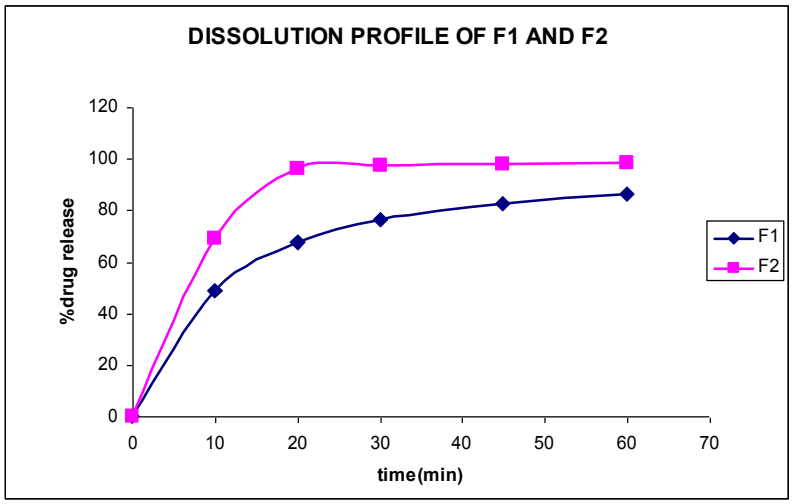


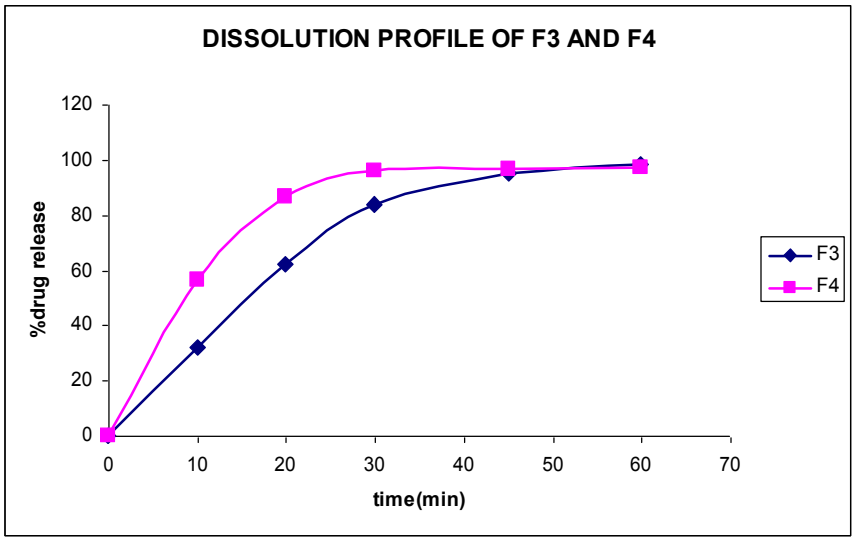
COMPARISION OF DISINTEGRATION FOR DIFFERENT TRIALS

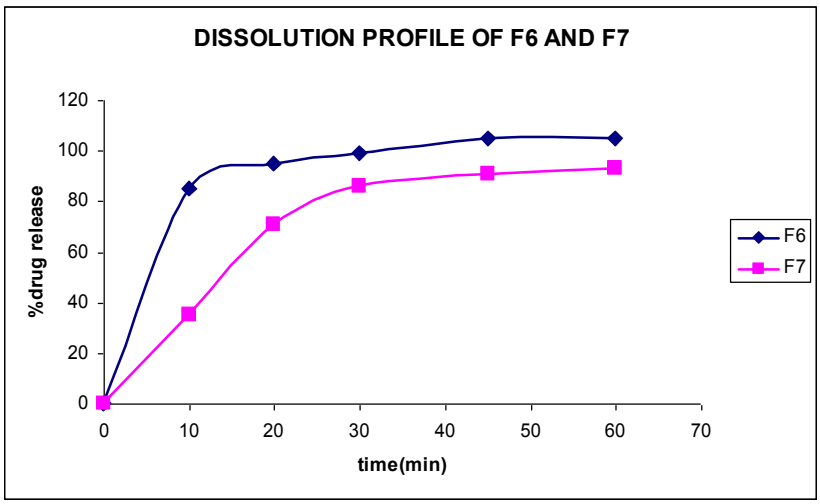


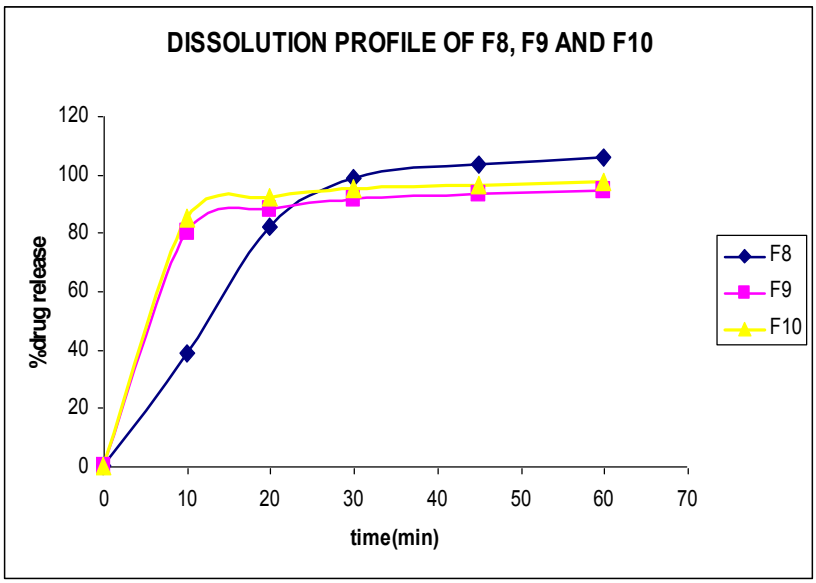
%DRUG RELEASE

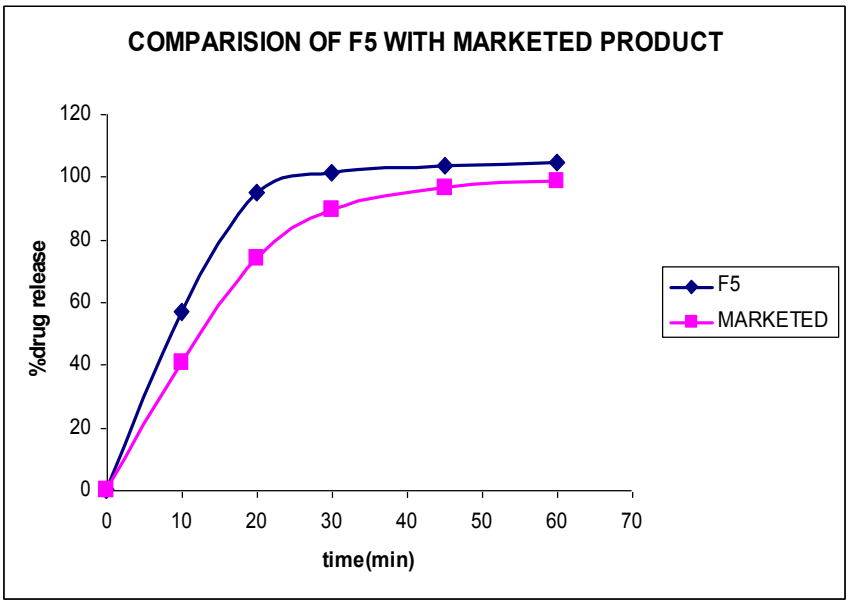
S.O	TIM	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	M
1.	10	48.4±0.9	68.9±1.3	31.6±0.6	56.5±1.1	56.9±1.1	84.7±1.6	34.9±0.6	38.6±0.7	80±1.6	84.8±1.6	40.9±0.8
2.	20	67.6±1.3	96±1.9	61.8±1.2	86.5±1.7	95.0±1.9	94.7±1.8	70.8±1.4	81.8±1.6	87.8±1.7	91.8±1.8	73.9±1.4
3.	30	76.4±1.5	97.6±1.9	84±1.6	96.2±1.9	101.3±2	98.9±1.9	85.8±1.7	98.6±1.9	91.2±1.8	95.1±1.9	89.5±1.7
4.	45	82.3±1.6	97.9±1.9	94.9±1.8	96.4±1.9	103.6±2	104.6±2	90.8±1.8	103.5±2	93.4±1.8	96.5±1.9	96.2±1.9
5.	60	86.4±1.7	98.2±1.9	98.3±1.9	97.1±1.9	104.4±2	104.6±2	93.1±1.8	105.6±2	94.7±1.8	97.7±1.9	98.6±1.9



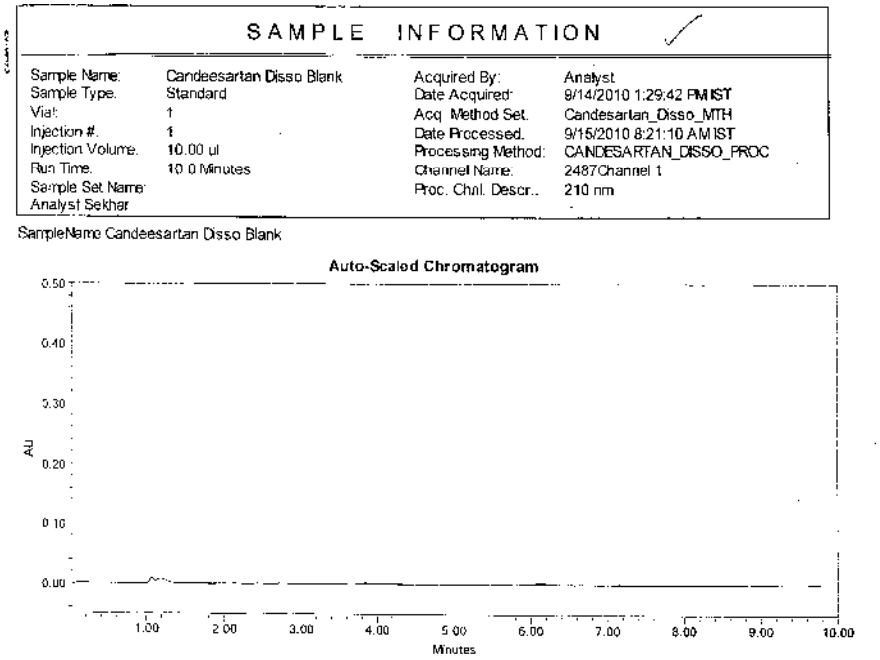

DISSOLUTION PROFILE OF F3 AND F4
%drug release
time(min)
F3
F4


DISSOLUTION PROFILE OF F6 AND F7
%drug release
time(min)
F6
F7

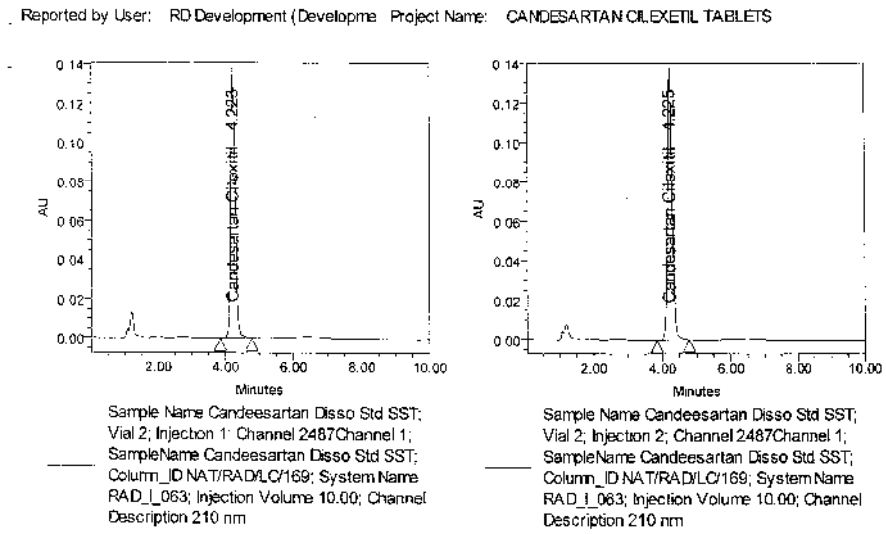

DISSOLUTION PROFILE OF F8, F9 AND F10
%drug release
time(min)
F8
F9
F10

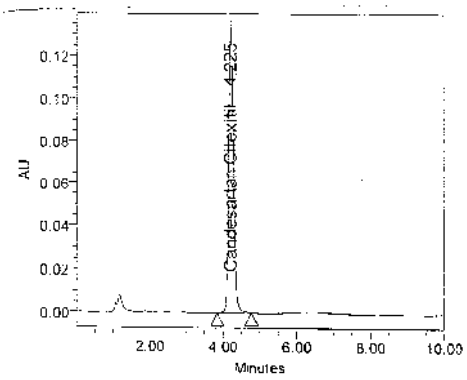


CANDESARATAN DISSOLUTION BLANK

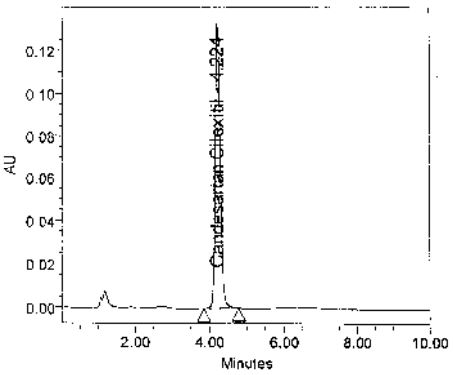


CANDESARTAN STANDARD CURVES



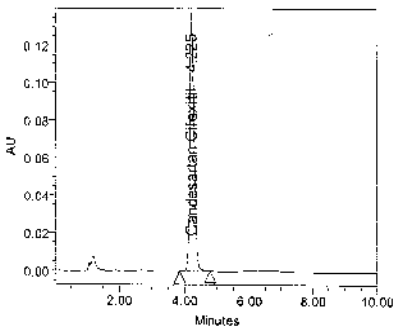


Sample Name Candeesartan Disso Std SST, Vial 2; Injection 3; Channel 2487Channel 1; SampleName Candeesartan Disso Std SST; Column_ID NAT/RAD/LC/169; System Name RAD_I_063; Injection Volume 10.00; Channel Description 210 nm

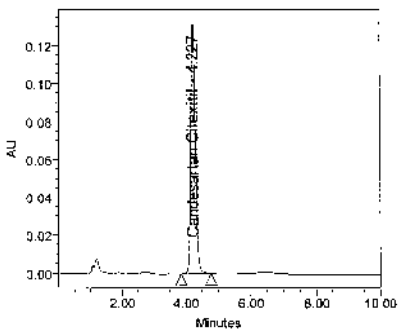


Sample Name Candeesartan Disso Std SST; Vial 2; Injection 4; Channel 2487Channel 1; SampleName Candeesartan Disso Std SST; Column_ID NAT/RAD/LC/169; System Name RAD_I_063; Injection Volume 10.00; Channel Description 210 nm

Reported by User: RD Development (Developme Project Name: CANDESARTAN CILEXETIL TABLETS



Sample Name Candeesartan Disso Std SST; Vial 2; Injection 5; Channel 2487Channel 1; SampleName Candeesartan Disso Std SST; Column_ID NAT/RAD/LC/169; System Name RAD_I_063; Injection Volume 10.00; Channel Description 210 nm



Sample Name Candeesartan Disso Std SST; Vial 2; Injection 6; Channel 2487Channel 1; SampleName Candeesartan Disso Std SST; Column_ID NAT/RAD/LC/169; System Name RAD_I_063; Injection Volume 10.00; Channel Description 210 nm

Component Summary Table
Name: Candesartan Cilexitil

	SampleName	Name	RT	Area	USP Tailing	USP Plate Count
1	Candeesartan Disso Std SST	Candesartan Cilexitil	4.2	1280775	1.2	4566.1
2	Candeesartan Disso Std SST	Candesartan Cilexitil	4.2	1281249	1.2	4545.8
3	Candeesartan Disso Std SST	Candesartan Cilexitil	4.2	1281033	1.2	4521.9
4	Candeesartan Disso Std SST	Candesartan Cilexitil	4.2	1281567	1.2	4515.7
5	Candeesartan Disso Std SST	Candesartan Cilexitil	4.2	1280872	1.2	4504.2
6	Candeesartan Disso Std SST	Candesartan Cilexitil	4.2	1279184	1.2	4467.7
Mean			4.2	1280780	1.15	4520.2
Std. Dev.				831.71		
% RSD				0.06		

STABILITY REPORT
Dissolution

MONTHS	Accelerated stability ($40^{o}C \pm 2^{o}C/75\%RH \pm 5\%RH$)		Long term stability ($25^{o}C \pm 2^{o}C/60\% \pm 5\%RH$RH)	
1st	30min	90.7%	30min	93.8%
	45min	94.8%	45min	95.9%
2nd	30min	80.7%	30min	86.5%
	45min	86.9%	45min	80.3%
3rd	30min	81.1%	30min	77%
	45min	85.2%	45min	85.3%

Assay

MONTHS	Accelerated stability ($40^{o}C \pm 2^{o}C/75\%RH \pm 5\%RH$)	Long term stability ($25^{o}C \pm 2^{o}C/60\%RH \pm 5\%RH$)
1st	98.7%	98.6%
2nd	97.6%	98.2%
3rd	97.5%	97.1%

Water content

MONTHS	Accelerated stability ($40^{o}C \pm 2^{o}C/75\%RH \pm 5\%RH$)	Long term stability ($25^{o}C \pm 2^{o}C/60\%RH \pm 5\%RH$)
1st	3.8%	2.75%
2nd	3.860%	3.198%
3rd	4.422%	3.888%

DISCUSSION

No Characteristic change in the color of the powder and no additional degradation of the product is observed. The increase in impurities at the end of the accelerated condition is not significant. All the excipients are stable and compatible with active ingredient. Hence, it is recommended that the above excipients can be used in further formulation development trials.

The physical appearance and HPLC studies are performed to find out the residual impurities. The residual impurities are candesartan acid, candesartan methyl ester, candesartan ethyl ester, desethyl candesaratan cilexetil, N_2 – ethyl candesartan cilexetil.

F5, F6 gives "EXCELLENT" flow properties where as F1-F4,F10 gives "POOR" flow properties F7,F8 is "VERY POOR" flow and F9 gives "PASSABLE" flow

CONCLUSION

Since the flow properties of the drug candidate are important for the selection of suitable method for granulation of the powder mixture, the flow of the drug is analyzed before the selection of granulation techniques. Hausner's ratio (>1.35), compressability index(>25) and angle of repose (<36) indicates poor flowability of the drug candidate. As the drug candidate, shows poor flowability the wet granulation technique has been selected.

The purpose of carrying out optimization study is to select the best possible formulation. Powders intended for compression into tablets must process good compressibility. Problems in cause variation in die filling and consequently variation in tablet weight and strength.

The important parameter that needs to be optimized in the development of immediate release tablets is the selection of different excipients. In the selection of suitable filler, lactose monohydrate is used. It showed good thickness, friability, and disintegration comparable to reference product.

The selection of suitable binder for the formulation of immediate release tablet is very important because it affects friability, hardness, disintegration and after all in-vitro release of the drug from the formulation. In this study, HPC and MCC is taken into consideration as binder and selection of suitable binder is carried out by evaluating the different physical parameter. The tablet prepared by using HPC and MCC showed similar thickness, friability, disintegration time. The release profiles of the formulations revealed that the incorporation HPC slowed down release rate. Hence, MCC is selected as suitable binder.

During the formulation development of immediate release tablet, the selection of suitable disintegrant is very important. In this experiment, calcium CMC is used. Concentration of calcium CMC is changed in different formulation. Upto 15% concentration is generally recommended in tablets preparation. At 9.6% concentration it gives best results than reference product.

Candesartan cilexetil does not possess good fluidity. The lubricant is added in the formulation because of it, a uniform flow from hopper to die is possible. It prevents adhesion of tablet material to machine parts such as punches and die by reducing inter particulate friction and facilitates the ejection of tablets from the die cavity. In this PEG 6000 and magnesium sterate are taken. Compare to PEG, magnesium sterate is taken in low concentration and it gives best flowability

The optimized batchof Candesartan Cilexetil tablet containing 38% MCC formulation is studied for the different physical parameter and in-vitro release profile. It is observed that the parameters are best comparable with the marketed formulation. It gives the first order kinetics of release. Long term and accelerated stability studies are done for the best formulation.

The optimized batch(F5) gives rapid on set of action when compared to innovator product.

REFERENCES

1. Leonlachman, Herbert.A. liberman lachman, joseph l,kaning, Theory and practice of industrial pharmacy, 2009 ed, pg no: 293-373.
2. Matthew R.Weir, Stanley S.Franklin, The book of hypertension, published in 2005, volume-2, page-13, 225
3. Hiestand, E.N, 2003.Mechanics and physical principles for powders and compacts, SSCI Inc., West Lafayette, USA.
4. A.K Gupta,S.S Bajaj, introduction to pharmaceutics-II, 4th edition, pg no:142
5. Angiotensin II receptor antagonist, wikipedia, [updated april 15th 2012] Available from:http://en.wikipedia.org/wiki/Candesartan
6. Wu Qiaomei, Gao huian, Chen hao, Solid oral pharmaceutical formulations, Us patent 20100267785, oct 10th , 2010 Available from http://www.freepatentsonline.com/y2010/0267785.html

Source of support: Nil, Conflict of interest: None Declared