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Research Article

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Formulation and evaluation of rapid disintegrating tablet of candesartan cilexetil for the management of hypertension

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ABSTRACT

Candesartan is water insoluble oral antihypertensive agent, with problems of variable bioavailability and bioequivalence related to its water insolubility. Candesartan is a highly potent, long-acting and selective angiotensin II type 1 (AT) receptor blocker. It is administered orally as the inactive prodrug Candesartan Cilexetil which is rapidly and completely converted to Candesartan during gastrointestinal absorption. Candesartan Cilexetil should be administrated orally once or twice daily for a total daily dosage of 4 to 32 mg. In this investigation rapid disintegrating tablet were prepared by using super disintegrating agent crospovidone, croscaremellose sodium, sodium starch glycolate in concentration 8%, 9%, 10%. Sweeteners and flavors were used to enhance the organoleptic properties of tablet. Tablets were prepared by direct compression technique. Prepared tablets were evaluated for thickness, uniformity of weight, hardness, friability, wetting time, in-vitro disintegration time, drug content and in vitro drug release. Disintegration time and drug release were taken as the basis to optimize the rapidly disintegrating tablet. All the formulations were evaluated for the influence of disintegrates and their concentrations on the characteristics of rapid disintegrating tablets mainly in terms of disintegration time and dissolution studies. The disintegration time of all formulation showed less than 37 seconds. Among the three superdisintegrants used, Crospovidone showed less disintegrating time followed by croscarmellose sodium and sodium starch glycolate. The relative efficiency of different superdisintegrants to improve the drug rate of tablets was in order, crospovidone> Croscarmellose sodium >sodium starch glycolate. The optimized formulation was found as F6, which have been made by use of crospovidone as superdisintegrant. And it show less disintegration time, better drug release profile as well as optimize drug content as compared to other excipients formulations.

Key words: Rapid disintegrating tablet, superdisintegratants, Candesartan cilexetil, crospovidone, Croscarmellose sodium, sodium starch glycolate.

INTRODUCTION

Now a day fast dissolving tablets are gaining more importance in the market. Some patient prefers fast dissolving tablets to conventional tablets best of ease of administration, swallowing, pleasant taste and availability in several flavors [1].

The pediatric and geriatric patients are of particular concern. To overcome this dispersible tablets and fast-disintegrating tablets have been developed. Most commonly used methods to prepare these tablets are freeze-drying/lyophillization, tablet molding and direct compression methods [2]. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets [3]. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complication and solid dispersion). The dissolution of drug can also be influenced by disintegration time of the tablet. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution [4].

Candesartan cilexetil is an angiotensin II receptor antagonist used mainly for treatments of hypertension. Candesartan cilexetil show extensive first pass metabolism and less bioavailability [5]. Candesartan cilexetil having low solubility and has half-life of 9 hrs, suggest its suitability for an immediate release formulation [6].

Hence, in the present research work fast dissolving tablets of Effect of Candesartan cilexetil will be prepared by using different super disintegrates. Effect of various super disintegrant on dissolution rate, disintegration time and wetting time will be studied.

Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%) [7].

EXPERIMENTAL SECTION

Materials: Candesartan cilexetil was received as gift sample from Ranbaxy Laboratories Ltd. Dewas M.P. (India). Excipients such as croscarmellose sodium, crospovidone, sodium starch glycolate, Aspartame, mannitol, microcrystalline cellulose, vanilla flavor and Mg stearate were procured from SD Fine Chemicals, Mumbai. All other ingredient were of laboratory grade.

Preparation of standard curve of Candesartan cilexetil:
The samples of different concentration were analyzed at 277 nm using UV-Spectrophotometer against 6.8 pH phosphate buffer as blank.

Fig.1: Calibration curve of Candesartan Cilexetil

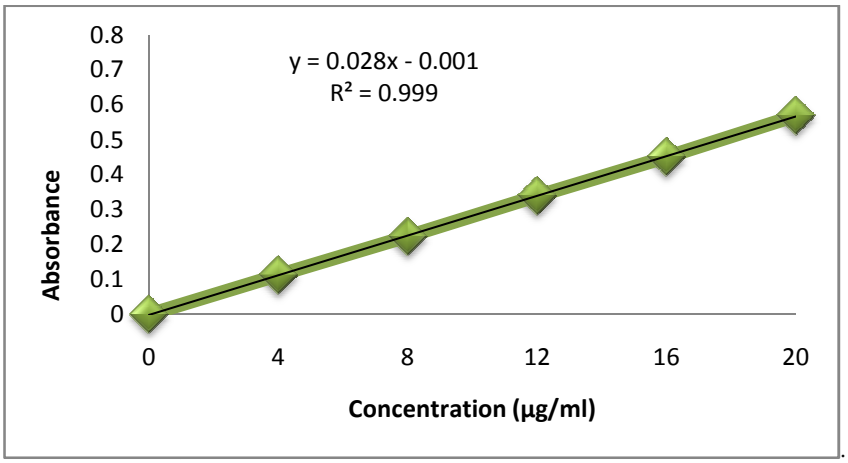
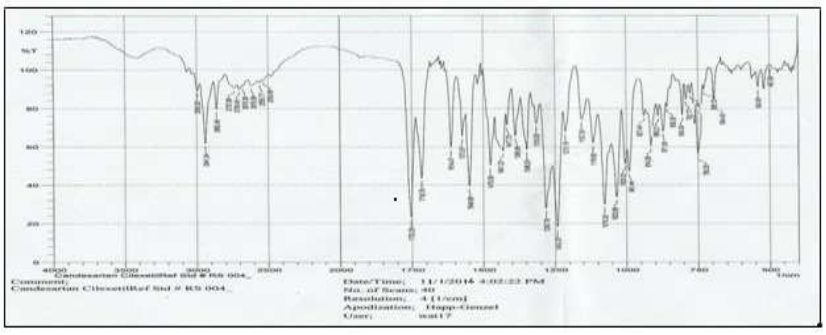


Fig.2: FT-IR of pure drug



DRUG EXCIPIENT COMPATIBILITY STUDIES:
Drug excipient interaction was studies by FTIR spectroscopy. The spectra were recorded for pure Candesartan cilexetil and with excipient mixture. Drug excipient interactions were studied by FTIR spectroscopy. The spectra were recorded for Candesartan cilexetil, physical mixture of excipient and physical mixture of drug with excipient using FTIR-spectrophotometer from KBr pellets. The scanning range was 400-4000cm -1

Fig.3: FT-IR study of Candesartan cilexetil with crospovidone

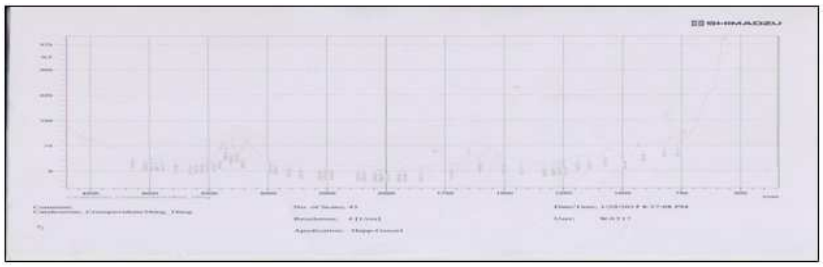


Fig.4: FT-IR study of Candesartan cilexetil with croscarmellose

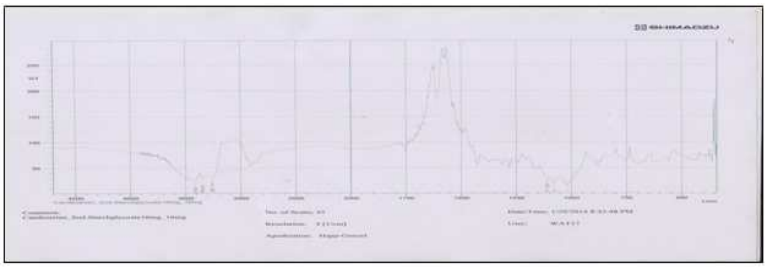
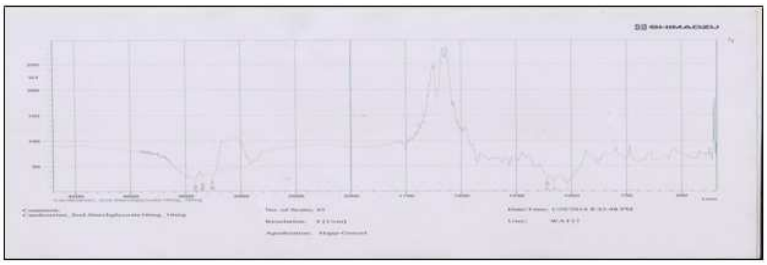


Fig.5: FT-IR study of Candesartan cilexetil with sodium starch glycolate



FORMULATION DEVELOPMENT:

Preparation of RDT by direct compression method: The drug was mixed with proper portion of superdisintegrants. Care should be taken to confirm the proper mixing of drug and superdisintegrants. Then other excipients were added. Then the mixture is passed through sieve No. 44. The mixture is blended with color, lubricating agent (magnesium stearate) and filler. Finally the blend is subjected for compression using 10mm on Clit pilot press 10 Station machine [8].

Table.1: Ingredients require in mg for each tablet containing 8mg of Candesartan cilexetil (200mg each tab)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Candesartan cilexetil	8	8	8	8	8	8	8	8	8
Microcrystalline cellulose	151	149	147	151	149	147	151	149	147
Mannitol	20	20	20	20	20	20	20	20	20
Croscarmellose sodium	16	18	20	-----	-----	-----	-----	-----	------
Crospovidone	-----	-----	-----	16	18	20	-----	-----	------
Sodium starch glycolate	-----	-----	-----	-----	-----	-----	16	18	20
Aspartame	2	2	2	2	2	2	2	2	2
Vanilla flavor	1	1	1	1	1	1	1	1	1
Mg stearate	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200	200

Evaluation of rapid disintegrating tablet of Candesartan cilexetil:

Evaluation was performed to assess the physiochemical properties and release characteristics of developed formulation.

Precompression parameters:

Angle of Repose (θ) [9]:

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

$\tan \theta = h / r$

$\theta = \tan^{-1} (h/r)$

Where, θ is the angle of repose
h is height of pile
r is radius of the base of pile

Different ranges of flow ability in terms of angle of repose are given in table

Table.2: Standard value of powder flow property test

S. No.	Angle of Repose	Powder Flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very Poor

Bulk density [3, 9]:
Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 5 g of powder from each formulation was introduced into a 10 ml measuring cylinder. Initial volume was observed, the cylinder was allowed to tap. The tapping was continued until no further change in volume was noted. Bulk density is calculated by using formula:

Bulk density (ρb) = Bulk volume of the powder/Weight of the powder

Tapped density (ρt) = Tapped volume of the powder/ Weight of the powder

Compressibility Index (Carr's Consolidation Index):
The Carr's index of the powder was determined by using formula:

Carr's index (%) = [(TBD -LBD) × 100]/TBD

Where, LBD = weight of the powder/volume of the packing
TBD = weight of the powder/tapped volume of the packing

Table.3: Grading of the powders for their flow properties according to Carr's Index

S. No.	Carr's index	Type of flow
1	5-15	Excellent
2	12-18	Good
3	18-23	Fair to passable
4	23-35	Poor
5	33-38	Very poor
6	>40	Very very poor

Post compression parameters:
Hardness:
The resistance of tablets to shipping or breakage under the conditions of storage, transportations and handling before usage depends on its hardness. The hardness of tablet was measured by Pfizer hardness tester. The hardness was measured in terms of Kg/cm^2

Friability:
Roche friabilator was used for testing the friability. Ten tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

Friability (f) = (1 - W0/ W) x 100

Where'W0 'is weight of the tablets before the test and
'W' is the weight of the tablet after the test.

Weight variation test [9]:
Twenty tablets from each formulation were selected randomly and weighed individually average weight was determined. Individual tablets weighed were then was compared with average weight.

The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The percentage deviation in weight variation is shown in table

Table.4: Percentage deviation in weight variation according to USP

Average weight of a tablet	Percentage deviation
130 mg or less	±10
More than 130 mg and less than 324 mg	±7.5
324 mg or more	±5

Drug content [10]**:**
Ten tablets were weighed and powdered and 50 mg equivalent weight of Candesartan cilexetil was accurately weighed and transferred into a 100 ml volumetric flask. It was dissolved and made up the volume with 6.8 pH Phosphate buffer. Subsequently the solution in volumetric flask was filtered and suitable dilutions were made and analyzed at 277 nm using UV-Visible spectrophotometer (Shimadzu UV-1800). The drug content of each sample was estimated from standard curve of Candesartan cilexetil using 6.8 pH phosphate buffer.

Wetting time:
The method was applied to measure tablet-wetting time. A piece of tissue paper folded twice was placed in a small Petri dish (i.d. = 6.5 cm) containing 10 ml of pH 6.8 buffer, a tablet was put on the paper, and the time for complete wetting was measured. Three trials from each batch were performed and standard deviation was also determined.

Water absorption ratio
The water absorption ratios of the tablet were carried out in Petri dishes with p^H 6.8 phosphate buffer. Periodically, the tablets were withdrawn from the Petri dishes and weighed on electronic balance after removal of surface water by light blotting with a lab tissue for change of their weight till a constant weight is attained.

In vitro disintegration time [11]:
The process of breakdown of a tablet into smaller particles is called as disintegration. The in-vitro disintegration time of a tablet was determined using disintegration apparatus as per I.P. specifications.

One tablet in each of the 6 tubes of the basket is to be placed and the apparatus subjected to run. The assembly should be raised and lowered between 50 cycles per minute. The time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. Disintegration or more specifically dispersion times were measured in 900 ml pH 6.8 phosphate buffers without using disc at room temperature (25°C ± 2°C)

In vitro dissolution time
In vitro release studies were carried out using tablet USP XXIII dissolution test apparatus. Two objectives in the development of in-vitro dissolution tests was to show that

(i) Release of the drug from the tablet is as close as possible upto 100% and
(ii) Rate of drug release is uniform from batch to batch and is the same as the release rate from those proven to be bioavailable and clinically effective.

Table.5: Summary of general dissolution conditions

S. No.	Parameter	Specifications
1	Dissolution medium	900ml 6.8 pH phosphate buffer
2	Temperature	37°C ±5°C
3	Rotation speed	50 rpm
4	Volume withdrawn	10 ml every minute for 1 minutes & later on after 5 minutes for 30 minutes
5	λmax	277 nm
6	Beer's range	4.44-35.55µg/ml
7	Tablet taken	1 tab (known drug content)

RESULTS AND DISCUSSION

Micromeritic Properties:

Angle of Repose:

The angle of repose was in the range of 27˚.69' to 29˚.81' indicating the good flow properties

Carr's Index:

The compressibility index was found between8.57%-17.9% indicates good flow property.

Table.6: Evaluation of precompression parameters of RDT

Formulation	Angle of repose	Bulk density	Tapped density	Carr's index
F1	28˚.81'	0.318	0.368	13.58
F2	27.75	0.327	0.357	8.57
F3	28.3	0.327	0.368	11.11
F4	28.28	0.338	0.383	11.74
F5	28.92	0.341	0.386	11.76
F6	29.57	0.344	0.374	8.82
F7	29.81	0.32	0.35	8.57
F8	28.21	0.341	0.4	14.72
F9	27.69	0.327	0.393	17.9

Evaluation of Post compression parameters:

Hardness:

Hardness of tablets prepared by direct compression was 3.81±0.6 to 4.215±0.21 kg/cm^2 in formulation F1 to F9

Friability:

Friability of all formulations was within acceptable limits. The friability of the formulations of Candesartan cilexetil formulation F1to F9 respectively was found to be less than 1.0 % and hence the tablets with lower friability may not break during handling on machines and or shipping.

Weight variation:

Weight variation for prepared tablets was found within specifications of USP for formulations of Candesartan cilexetil.

Wetting time:

Wetting time is used as an indicator from the ease of the tablet disintegration in buccal cavity. In formulation of Candesartan cilexetil (F1 to F9) observed that wetting time of tablets was in the range of 36.4 to 46.6 seconds. It was observed that type of the disintegrant affected the wetting of the tablets. On comparing superdisintegrants the formulation containing Sodium starch glycolate take more wetting time than croscarmellose sodium and Crospovidone.

Water absorption ratio:

Water absorption ratio ranged from 56.52-66.77 in formulation containing 8mg of Candesartan cilexetil. Crospovidone and croscarmellose sodium perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling.

Table.7: Evaluation parameters of prepared tablets

Formulation	Hardness (kg/cm2)	Weight variation	Friabiliy %	Wetting Time	Water absorption
F1	4.215±0.21	0.192±1.23	0.4±0.03	38.5±0.4	56.4±0.520
F2	4.125±0.5	0.199±1.09	0.5±0.07	36.43±0.23	57.9±0.008
F3	4.187±0.12	0.201±0.99	0.3±0.06	36.36±2.8	59.72±0.05
F4	4.15±0.1	0.199±1.5	0.9±0.02	38.26±0.69	57.98±0.2
F5	4.25±0.03	0.197±1.9	0.6±0.06	36.56±0.5	60.52±0.53
F6	4.06±0.5	0.201±0.89	0.2±0.04	38.33±0.28	56.52±0.042
F7	3.95±0.2	0.199±1.7	0.4±0.04	44.33±0.2	61.0±1.001
F8	3.81±0.6	0.198±0.34	0.4±0.02	46.66±0.24	62.5±2.107
F9	3.87±0.2	0.201±0.2	0.6±0.06	42.86±1.15	66.77±1.026

Drug content uniformity:

The drug content in different formulation was highly uniform and in the range of 97.23 to 99.24% was seen in the formulation from F1 to F9.

Disintegration time:
Disintegration time is very important for mouth dissolving tablets which is desired to be less than 60 seconds for orally disintegrating tablets. In case of the tablets containing Crospovidone and croscarmellose sodium, an increase in concentration of superdisintegrant resulted in definite decrease in disintegration time. The same result was found for tablets containing Sodium starch glycolate up to 8%. At 9% concentration, it resulted in slight increase in disintegration time from 31 sec. to 34 sec. This delay in disintegration time might have occurred due to probable blockade of capillary pores in tablet mass as result of formation of viscous plug by Sodium starch glycolate, which subsequently, prevented free access of fluid into tablets.

Table.8: In-vitro Disintegration time and Drug content of formulation F1 to F9

Formulation	Disintegrating time (sec)	Drug content uniformity
F1	39.36±0.21	97.23±0.21
F2	38.83±0.2	97.45±0.89
F3	34.3±0.35	98.65±0.56
F4	38.73±0.15	98.23±0.43
F5	34.36±0.5	99.24±0.11
F6	29.3±0.35	99.45±0.66
F7	35.6±0.45	97.35±0.86
F8	31.3±0.95	97.87±0.56
F9	34.4±0.55	99.02±0.24

In-vitro Dissolution Studies: In the formulation of Candesartan cilexetil :Formulations F1, F2 and F3 which contained increasing concentrations of croscarmellose sodium from 8%w/w to 10%w/w, have recorded drug release 81.57%, 86.18% and 90.96% respectively, at the end of 10 minutes. Formulations F4, F5 and F6 which contained increasing concentrations of crospovidone from 8%w/w to 10%w/w, have recorded drug release 85.95%, 94.66% and 98.63% respectively, at the end of 10 minutes. Formulations F7, F8 and F9 which contained increasing concentrations of Sodium starch glycolate from 8%w/w to 10%w/w, have recorded drug release 85.69%, 90.12% and 81.52% respectively, at the end of 10 minutes.

The relative efficiency of different superdisintegrants to improve the dissolution rate of tablets was in order, crospovidone> Croscarmellose sodium >sodium starch glycolate. In comparative study of the formulations F3, F6 and F9 showed 90.96%, 98.63% and 90.12% drug release respectively at the end of 10 minutes.

Table.9: Dissolution Profile of F1 to F9 Formulations

Time(Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	20.3	24.57	28.43	20.31	24.1	28.12	16.07	20.08	24.1
2	24.57	28.7	36.86	28.65	28.43	32.48	24.57	24.36	28.43
3	28.91	37.12	45.39	33.05	36.86	40.95	28.7	32.74	36.86
4	37.33	41.57	54	37.42	49.63	49.52	33.06	37.16	45.39
5	45.86	50.42	62.7	50.02	58.3	58.18	41.52	45.69	50.35
6	54.42	54.92	67.41	54.46	67.03	66.92	50.42	50.42	58.79
7	63.17	63.62	72.21	63.32	75.87	71.68	58.48	59.08	63.45
8	67.89	72.4	77.03	72.08	80.72	80.56	67.68	67.82	72.24
9	72.89	81.28	85.98	80.96	85.63	93.6	76.52	76.66	81.13
10	81.57	86.18	90.96	85.95	94.66	98.63	85.43	81.52	90.12

CONCLUSION

From the studies the following conclusions have been drawn.

- Candesartan cilexetil an angiotension II receptor antagonist can be used to develop the rapid disintegrating tablet successfully, by direct compression techniques using selected superdisintegrants for the better patient's compliance and effective therapy.
- The relative efficiency of these superdisintegrants to improve the disintegration and dissolution rate of tablets was in the order, crospovidone > Croscarmellose sodium > sodium starch glycolate. The disintegration studies revealed that the tablets prepared with crospovidone show faster disintegration as compared to tablets prepared with croscarmellose sodium and sodium starch glycolate.
- It is concluded that crospovidone shows good disintegrating property than croscarmellose, sodium starch glycolate.

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