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FORMULATION AND EVALUATION OF CANDESARTAN CILEXETIL POROUS TABLETS BY SUBLIMATION TECHNIQUE

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ABSTRACT

The purpose of this investigation was to develop Porous tablets (FDTs) of Candesartan cilexetil by sublimation technique using camphor as subliming agent together with Sodium Starch Glycolate, Croscarmellose Sodium and Crospovidone as superdisintegrants. The prepared formulations were evaluated for pre-compressional and post-compressional parameters. The compatibility of drug with other ingredients was checked by FTIR studies, the results revealed that there was no interaction between dug and other excipients. The values of pre-compressional parameters were within prescribed limits and indicated good free flowing properties. In all the formulations the hardness test indicates good mechanical strength. Friability of all formulations was within the acceptable limits. Drug content was found to be high (≥ 101.02%) and uniform in all the formulations. The tablet thickness was found to be 3.11 to 3.15. The weight variation results revealed that average percentage deviation was less then ± 7.5 %, which provides good uniformity in all formulations. The disintegration time of the tablets found to be in the range of 3 min. The formulations F_6 showed 50 % of drug released in 2 min and 90 % of drug release in 6 min. Stability study carried out as per ICH guidelines for three months and results revealed that upon storage disintegration time of tablets significantly ($p<0.05$) decreased. The release of drug from F_6 formulation was quick when compared to other formulations. It was concluded that porous tablets with improved Candesartan Cilexetil dissolution could be prepared by sublimation of tablets containing suitable subliming agent.

Keywords: Porous tablet, Candesartan cilexetil, subliming agent, super disintegrant, camphor.

INTRODUCTION

From various current methods for treating illness and diseases, chemotherapy (treatment with drugs) is the most frequently used technique. It has the broad range of applications over the greatest variety of disease states and is frequently the preferred treatment method [1]. For many decades, treatment of acute disease or chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols and injectbales as drug carriers [2, 3]. Despite phenomenal advances in the inhalable, injectable, Transdermal, nasal and other routes of administration, the unavoidable truth is that oral drug delivery remains well ahead of the pack as the preferred route. There are of course many applications And large markets for non-oral products and the technologies that deliver them. However, if it is a viable option, oral drug delivery will be chosen in all but the most exceptional circumstances. Moreover, if the oral route is not immediately viable, pharmaceutical companies will often invest resources in making it viable, rather than plumping for an alternative delivery system [4]. Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms and is the most convenient and preferred route for systemic effects due to its ease of dosing administration, pain avoidance, accurate dosage, patient compliance and flexibility in formulation [5, 6]. The oral drug delivery market is the largest segment of the drug delivery market and there's no sign that it is slowing down. With pharmaceutical companies increasingly turning to drug delivery to extend the revenue-earning lifetime of their biggest products, and seeking to tap into the growing elderly population that requires products with a level of ease- of-use and cost benefit, it's no surprise that the oral delivery drug market is a $35 billion industry and expected to grows much as ten percent per year. Oral delivery provides the definitive break down of the

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market for oral delivery drug markets[7]. Amongst drugs that are administered orally; solid oral dosage forms i.e. tablets and capsules, represent the preferred class of products[6, 8]. Out of the two oral solid dosage forms, the tablets are the preferred ones. Tablets have number of advantages over other dosage forms. Recent advances in novel drug-delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being convenient for the administration. Difficulty in swallowing (i.e., dysphagia) is experienced by patients such as paediatrics, geriatric, bedridden, disabled, mentally ill, including motion sickness and sudden episodes of allergic attacks, hence resulting in higher incidence of noncompliance and ineffective therapy[9] In order to solve this problem and improve patient acceptance and compliance, the development of solid dosage forms that disintegrate rapidly or dissolve even when taken orally without water is being undertaken. Oral fast-disintegrating dosage forms (tablet or a capsule) are a relatively novel dosage technology that involves the rapid disintegration or dissolution of the dosage form[10] into a solution or suspension in the mouth without the need for water[11]. The dosage form begins to disintegrate immediately after coming into contact with saliva, with complete disintegration normally occurring within 30–50 s after administration[12]. The solution containing the active ingredients is swallowed, and the active ingredients are then absorbed through the gastrointestinal epithelium to reach the target and produce the desired effect. Tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness, and ease in manufacturing[13]. Orally disintegrating tablets are also called as Orodispersible tablets, quick-disintegrating tablets, mouth-dissolving tablets, fast-disintegrating tablets, fast dissolving tablets, rapid-dissolving tablets, porous tablets, and rapid melts. However, of all the above terms, the United States Pharmacopoeia (USP) approved these dosage forms as Orodispersible tablets (ODTs). Recently, the European Pharmacopoeia has used the term Orodispersible tablets for tablets that disperse readily and within 3 min in the mouth before swallowing. The United States Food and Drug Administration define ODT as "a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute[14]. Other advantages of ODTs that have been investigated are their potential to increase the bioavailability of poorly water soluble drug through enhancing the dissolution profile of the drug[15]. Moreover, pharmaceutical companies also have commercial reasons for formulating ODTs. As a drug reaches the end of its patent, the development and formulation of the drug into new dosage forms allow pharmaceutical companies to extend the patent life and "market exclusivity"[16]. The ODTs could be prepared using various techniques such as tablet moulding, spray drying, sublimation, lyophilization, solid dispersion, or addition of disintegrants[9-13]. The basic approach to the development of ODTs is the use of superdisintegrants such as Croscarmellose sodium and sodium starch glycolate. Another approach used in developing ODTs is maximizing the pore structure of the tablet matrix. Freeze drying and vacuum drying techniques have been tried by researchers to maximize the pore structure of the tablet matrix[14–16]. However, freeze drying is cumbersome and yields a fragile and hygroscopic product. Vacuum drying along with the sublimation of volatilizable ingredient has been employed to increase tablet porosity. While in designing dispersible tablets, it is possible to achieve effective taste masking as well as a pleasant feel in the mouth. The main criterion for ODTs is the ability to disintegrate or dissolve rapidly in saliva of the oral cavity in 15 to 60 s and have a pleasant mouth feel[17].To improve the quality of life and treatment compliance, great efforts have been made to develop fast-disintegrating tablets (FDTs) in the oral cavity, using jelly, water-absorbing, and swelling-gelated materials or water-soluble polymers[18].

Candesartan cilexetil (Fig.1) is chemically 2-Ethoxy-3-[21-(1H-tetrazol-5-yl) biphenyl-4- ylmethyl] -3Hbenzoimidazole- 4-carboxylic acid 1-cyclohexyloxycarbonyloxy ethyl ester.[1] Candesartan Cilexetil is a prodrug of Candesartan – a compound that inhibits binding of angiotensin II to the AT1 – receptor. Candesartan cilexetil is hydrolyzed to Candesartan during absorption from the gastrointestinal tract[19]. It is mainly used in the treatment of hypertension. The typical dose of Candesartan cilexetil is 16 mg per day in patients who are not volume depleted. It may be given once or twice daily with total daily doses ranging from 8 mg to 32mg.[20]. Tablet formulation containing 4 mg and 8 mg Candesartan cilexetil are available in market. The fundamental principle used in the development of the porous tablet is to maximize its pore structure. Researchers have evaluated spray dried materials[21] and plastic materials[22] for development of such tablets.[23-28] Vacuum-drying and freeze- drying[29-32] techniques have been tried by researchers to maximize the pore structure of tablet matrix. Freeze drying is cumbersome and yields a fragile and hygroscopic product. Therefore, a vacuum drying technique was adopted in the present investigation after addition of a subliming agent to increase porosity of the tablets. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly[33-39].In the present study, an attempt was made to develop dissolving tablets of Candesartan Cilexetil and to investigate the effect of subliming agent on the release profile of the drug in the tablets.

Materials and Methods:

Candesartan cilexetil was gift sample from Merck Specialities (Pvt)., Ltd. (AP). Croscarmellose Sodium, Crospovidone, Camphor, Aspartame, Mannitol, Talc, Magnesium Stearate and all the other chemicals used were of pharmaceutical grade.

Drug – Excipient Compatibility Studies:

The Fourier-transform infrared spectra of Candesartan cilexetil and mixture Candesartan cilexetil with other excipients were obtained by using FTIR spectroscopy – 5300 (JASCO Japan). Samples were prepared by KBr pressed pellet technique. The scanning range was 400 - 4600 cm^{-1} and the resolution was 4 cm^{-1}. The spectra are shown in Fig. 1.

Preparation of Candesartan Cilexetil Porous Tablets:

Candesartan Cilexetil 16 mg was taken and mixed with mannitol, directly compressible Microcrystalline Cellulose, superdisintegrant and camphor, (10%) in plastic container and magnesium stearate were passed through sieve No. 60 and blended with initial mixture in the plastic container followed by direct compression of blend (Table-1). After that, above lubricated blend was compressed using 9mm rounding punch at a tablet weight of 300mg. The tablets were collected and vacuum dried at 60^0C until the constant weight is obtained to ensure the complete removal of sublimable component to make a tablet porous.

CHARACTERIZATION OF CANDESARTAN CILEXETIL POROUS TABLETS:

The prepared tablets were evaluated for different Post Compressional properties like weight variation, friability, hardness, thickness, disintegration time, wetting time, Drug Content and In vitro dissolution studies.

Weight variation[39-40]:

20 tablets were selected at a random and then the average weight was determined. All the 20 tablets were weighed individually and compared with the average weight, the tablets meets USP specifications if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Frability[39-40]:

The friability test was performed for all the formulated porous Candesartan Cilexetil tablets. Twenty tablets were taken and their weight was determined. Then they were placed in the Roche friabilator and allowed to make 100 revolutions. The tablets were then de-dusted and reweighed. The percentage weight loss was calculated. Percentage Friability was calculated as follows

Percentage Friability = $(W_1 - W_2) \times 100/W_1$

Where, W1 = Initial weight of the 20 tablets.
W_2 = Final weight of the 20 tablets after testing.
Friability values below 1% are generally acceptable.

Hardness[39-40]:

Monsanto hardness tester was used for measuring the hardness of the formulated porous Candesartan Cilexetil tablets. From each batch five tablets were taken and subjected to test. The mean of the five tablets were calculated. The breaking strength (in kg) of each tablet was tested using a Stokes-Monsanto hardness tester (DT Stokes, Bristol, PA). The formulated as well as the commercial tablets were circular and flat. After the dial on the tester was set to zero, a tablet was placed between the two jaws. The breaking point was determined by gradually increasing the force on the tester. Breaking strength is the force applied (in kg) to break the tablet radially into two halves.

Thickness of tablets [39-40]:

Thickness is measured by using instrument called digital "vernier calipers". Randomly 10 tablets were taken and thickness was measured for each tablet by placing between two anvils and rotating sliding knob until the tablet was tightly fitted and the reading was noted on the digital scale.

Drug content[39-40]:

10 tablets were taken, powdered well and a quantity of powder equivalent to 100mg of Candesartan Cilexetil was accurately weighed and dissolved in 100ml of phosphate buffer pH 6.8 and filtered. The absorbance of the solution was measured at 254nm against blank phosphate buffer pH 6.8. The concentration of the sample was calculated using standard graph.

In-Vitro drug release[39-40]:

In vitro dissolution studies for all the formulated tablets was carried out using USP paddle method at 50 rpm in 500ml of phosphate buffer pH 6.8 as dissolution media, maintained at 37±0.5°C. 5 ml aliquot was withdrawn at the specified time intervals, filtered through Whatmann filter paper and assayed spectrophotometrically at 254nm. An equal volume of fresh medium, which was pre-warmed at 37°C, was replaced into the dissolution media after each sampling to maintain the constant volume throughout the test.

Stability Study [31]:

The Candesartan Cilexetil porous tablets of batch F_6 were wrapped in an aluminum foil and placed in a stability chamber controlled at 40 ± 2^0C/75 ± 5^0C relative humidity for a period of 3 months. At the end of 3rd month the formulation F_6 was evaluated for its Physical Characteristics, Drug Content and Dissolution Properties.

Statistical Analysis:

The results were analyzed by two tailed Student's t-test using the Graph Pad Instat Software (GPIS; Version: 1.13)[32].

RESULTS AND DISCUSSION

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 2941 cm^{-1}, 1752cm^{-1}, 1714cm^{-1}, 1614 cm^{-1}. This absorption peak at 2941 cm^{-1} was due to stretching of C-H bond, the peaks at 1752cm^{-1} and 1714cm^{-1} were due to two C-O bonds (carbonyl group)

and peak at 1614 cm^{-1} was due to C-N bond. Fig – 1 shows IR scan of all formulations, so it was conformed that, presence of undisturbed drug in the formulations. Hence there were no drug-excipient interactions. The flow properties of the powder mixture are important for the uniformity of mass of tablets; the flow of powder mixture was uniform and excellent before compression of tablets. The values of pre-compressional parameters were within prescribed limit as per USP XXVII and indicate good flow properties. The results are shown in table 2. The post compressional parameters results are shown in table 3 and 4. In all the formulations the hardness test indicates good mechanical strength. The hardness of all tablets found between 2.4 to 3.1 kg/cm^2. Friability of all formulation was less than 1%, which indicates the tablets had good mechanical resistance. Drug content was found to be high (≥100.45 %) and uniform in all formulations. The tablet thickness was found to be 3.10 to 3.14 mm. The weight variation results revealed that average percentage deviation of 20 tablets of each formula was less than ± 7.5%, which provide good uniformity in all formulations. The disintegration time of all tablets found to be in the range of 21 to 40 sec. The tablets prepared by vacuum drying technique rapidly exhibit high pores and disintegrate the tablets rapidly. It may be due to their lowest hardness and maximum pore structure was responsible for faster water uptake; hence it facilitates wicking action of superdisintegrants in bringing about faster disintegration. The dissolution profiles of all formulations are shown in Fig. 2 & 3. Out of nine formulations, the formulation F_6 show faster drug release within 3min. *In-vitro* profile of Candesartan cilexetil shown in Fig. 3 and in Table- 3 . The stability studies results revealed that, the disintegration time was decreased significantly. During the sublimation procedure all the formulations were kept in vacuum dryer at 45^0C for 60 min. at this time sum amount of subliming agent may be left in the formulations after vacuum drying. But in case of stability study, the selected formulations were kept at 40^0C for 90 days. This extended expose time may leads to evaporation of subliming agent, which may left after sublimation techniques leads to increased formation of pores in the tablets. So, the disintegration and wetting time of tablets were decreased after stability study.

Table 1: Formulation of Candesartan Cilexetil Porous Tablets

Ingredients	Formulation Code (mg)								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Candesartan Cilexetil	16	16	16	16	16	16	16	16	16
Croscarmellose Sodium	--	--	--	12	15	22.5	--	--	--
Crospovidone	12	15	22.5	--	--	--	--	--	--
Sodium Starch Glycolate	--	--	--	--	--	--	12	15	22.5
MCC	224	221	213.5	224	221	213.5	224	221	213.5
Camphor	45	45	45	45	45	45	45	45	45
Magnesium stearate	3	3	3	3	3	3	3	3	3
Total wt (mg)	300	300	300	300	300	300	300	300	300

Table 2: Precompressional parameters of Porous Candesartan Cilexetil Granules

Formulation Code	Angle of repose* (degree)	Bulk density* (g/cc)	Tapped Density* (g/cc)	Carr's index* (%)	Hausner's Ratio*
F_1	22.25 ± 1.36	0.45 ± 0.02	0.53 ± 0.01	13.13 ± 1.12	1.15 ± 0.01
F_2	26.34 ± 1.10	0.46± 0.01	0.47 ± 0.02	14.59 ± 1.27	1.17 ± 0.04
F_3	26.12 ± 1.17	0.42 ± 0.01	0.49 ± 0.01	15.23 ± 1.37	1.16 ± 0.01
F_4	20.48 ± 1.23	0.48 ± 0.02	0.52 ± 0.01	15.42 ± 1.02	1.15 ± 0.01
F_5	24.33 ± 1.53	0.49 ± 0.01	0.51 ± 0.01	14.25 ± 1.49	1.16 ± 0.01
F_6	20.25 ± 1.29	0.40 ± 0.01	0.42 ± 0.01	14.05 ± 1.03	1.16 ± 0.01
F_7	22.29 ± 1.22	0.41 ± 0.01	0.49 ± 0.01	15.43 ± 1.44	1.15 ± 0.02
F_8	21.36 ± 1.26	0.47 ± 0.02	0.55 ± 0.01	15.18 ± 1.26	1.17 ± 0.03
F_9	20.25 ± 1.09	0.45 ± 0.02	0.51 ± 0.01	14.33 ± 1.27	1.17 ± 0.04

* Average of three determinations

Table 3: Post-compression parameters of Porous Candesartan Cilexetil Tablets

Formulation Code	Weight Variation* (mg)	Thickness* (mm)	Hardness* (Kg/cm²)	Friability (%)
F_1	99 ± 1.10	3.12 ± 0.10	2.4 ± 0.12	0.58
F_2	97 ± 1.02	3.10 ± 0.11	3.1 ± 0.14	0.51
F_3	98 ± 1.15	3.11 ± 0.12	2.6 ± 0.10	0.56
F_4	100 ± 1.09	3.11 ± 0.14	2.5 ± 0.15	0.59
F_5	98 ± 0.64	3.10 ± 0.14	2.6± 0.20	0.69
F_6	99 ± 1.15	3.14 ± 0.15	2.7 ± 0.21	0.51
F_7	101 ± 0.82	3.16 ± 0.05	2.8 ± 0.21	0.74
F_8	97 ± 0.58	3.15 ± 0.13	2.7 ± 0.07	0.53
F_9	96 ± 1.35	3.11 ± 0.12	2.5 ± 0.15	0.51

* Average of three determinations

Table 4: *In-vitro* disintegration Time and drug Porous Candesartan Cilexetil Tablets

Formulation Code	*In-vitro D*isintegration time * (sec)	Drug Content* (%)
F_1	36 ± 1.34	100.45 ± 1.24
F_2	33 ± 1.24	99.78 ± 1.15
F_3	30 ± 1.45	99.17 ± 1.53
F_4	30 ± 1.45	99.48 ± 1.26
F_5	40 ± 1.15	96.02 ± 1.18
F_6	26 ± 1.22	99.06 ± 1.14
F_7	33 ± 1.35	99.58 ± 1.21
F_8	21 ± 1.18	98.47 ± 1.03
F_9	33 ± 1.24	99.48 ± 1.26

* Average of three determinations

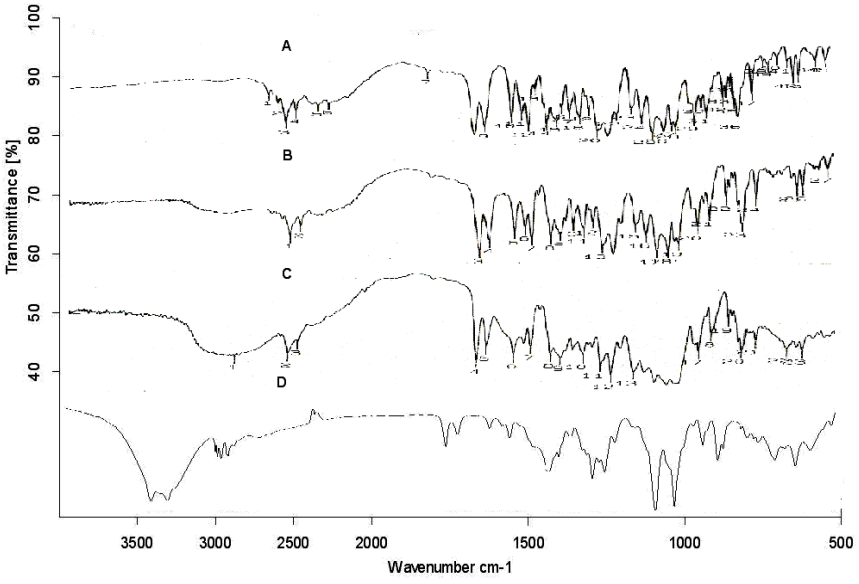

Fig. 1: IR spectrum of Candesartan cilexetil (A), Drug + Croscarmellose (B), Drug + Crospovidone (C), Drug + Camphor (D)

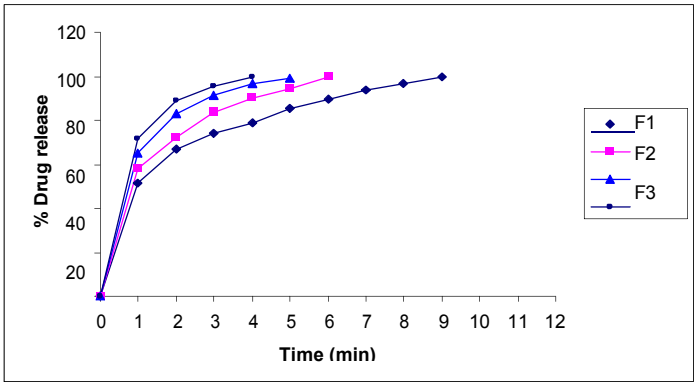

Fig. 2: Dissolution profile of formulations F_1-F_4

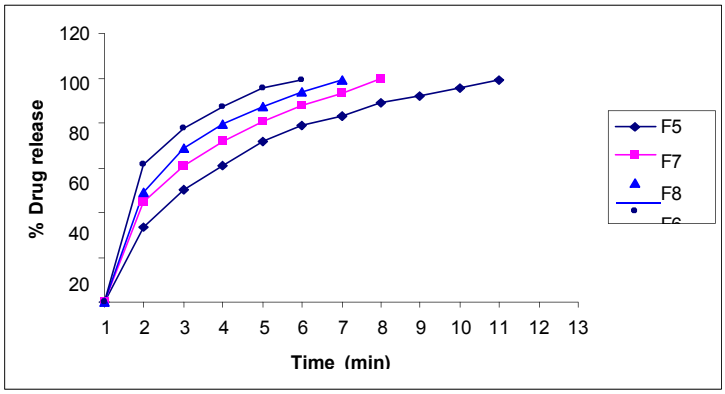

Fig. 3: Dissolution profile of formulations F_5-F_9

CONCLUSION:

The release of drug from the F_6 formulation was quick when compare to other formulations. It can be concluded that fast dissolving tablets with improved Candesartan cilexetil dissolution could be prepared by sublimation of tablets containing suitable subliming agent.

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