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SOLUBILITY ENHANCEMENT AND DEVELOPMENT OF DISPERSIBLE TABLET OF CANDESARTAN CILEXITIL

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ABSTRACT: Candesartan Cilexitil is an angiotensin II receptor antagonist used mainly for the treatment of hypertension. Candesartan cilexitil is a BCS class II drug having low solubility and high permeability. Candesartan Cilexitil is a prodrug which is rapidly converted to the active drug, Candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. The bioavailability of Candesartan Cilexitil is approximately 15% after an oral administration. To increase bioavailability of such drug, solubility and dissolution are important parameters. To increase solubility of candesartan cilexitil, spray drying technique was incorporated with use of Fluidised Bed Processor. Also dissolution rate was improved with the use of appropriate superdisintegrants. Superdisintegrants used are Croscarmellose sodium, Crospovidone and Sodium starch glycolate. Dissolution rate of Candesartan Cilexitil from prepared dispersible tablet was compared with marketed formulation. Results have shown that solubility of Candesartan Cilexitil has been increased and dissolution rate was improved significantly. The transformation of Candesartan Cilexitil from crystalline to amorphous state by spray drying and the use of superdisintegrants are considered among the factors which contributed in improvement of Candesartan Cilexitil dissolution.

INTRODUCTION: Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Currently only 8 percent of new drug candidates have both high solubility and permeability. [1]

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Solubility of active pharmaceutical ingredients has always been a concern for formulators, since inadequate aqueous solubility may hamper development and limit bioavailability of oral products. In recent years, the problem has become more acute and more common as pharmaceutical companies cast the drug discovery net ever wider in the anticipation of finding new therapeutic approaches and improving drugs for existing therapeutic areas.

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. [2] In the other words the solubility can also define as the ability of one substance to form a solution with another substance.

Candesartan Cilexitil is an angiotensin II receptor antagonist used mainly for the treatment of hypertension. Candesartan Cilexitil is a prodrug which is rapidly converted to the active drug, Candesartan, by ester hydrolysis during absorption from the gastrointestinal tract. [3] The bioavailability of Candesartan Cilexitil is approximately 15% after an oral administration. [4]

Solubility of low soluble drug can be increased by salt formation, crystal engineering, complex formation and nanosizing. [5] For poorly soluble orally administered drug, rate of absorption is often controlled by rate of dissolution. Rate of dissolution is controlled by rate of disintegration.

Spray drying is a well known technique and is used in food and drug industries. Spray drying has many fields of application in pharmaceutical industry since the early of 1940s. [6] The method is applicable for drying heat-sensitive materials such as amino acids, antibiotics, ascorbic acid, liver extracts, pepsin and similar enzymes. It is applicable for particle formation; spray dried particles are approximately spherical in shape, nearly uniform in size, frequently hollow, and posses good flowability and a rapid rate of solution. Encapsulation of chemicals can be achieved using spray drying equipment. [7] Another application of spray drying process is in tableting and in coating and its application. Frequently, spray drying is more economical than other processes since it produces a dry powder directly from a liquid and it reduces labor, equipment costs, space requirements and possible contamination of the product.

Examples of successfully tested-drugs which improved their dissolution by spray drying technique are indomethacin [8], tolbutamide [9], carbamazepine [10] and ketoprofen. [11]

Fluidised bed dryer is one of the technique which works on the principle of Nanosizing and conversion of crystalline form of drug to amorphous form which leads to increase in solubility. Spray drying is a commonly used method of drying a liquid feed through a hot gas. Typically, this hot gas is air but sensitive materials such as pharmaceuticals and solvents like ethanol require oxygen-free drying and nitrogen gas is used instead. The liquid feed varies depending on the material being dried and is not limited to pharmaceutical products and may be a solution, colloid or a suspension. This process of drying is a one step rapid process and eliminates additional processing. [12] Spray drying of the acid dispersed in acacia solutions resulted in as much as a 50 percent; improvement in the solubility of poorly water soluble salicylic acid. [13]

Due to elevated temperature and high velocity air, porosity of particle is increased which increases solubility. In this case, drug was dissolved in suitable solvent and sprayed on Avicel PH 101 particles, due to high velocity air and elevated temperature, drug gets adsorbed on particles. For rapid dissolution, superdisintegrants were used. A disintegrant is a substance in a tablet formulation that enables the tablet to break up into smaller fragments upon contact with gastrointestinal fluids. The rapid rupture of the tablet matrix increases the surface area of the tablet particles, thereby increasing the rate of dissolution and rate of absorption of the active ingredient and producing the desired therapeutic action. [14]

The disintegrant is routinely integrated into a formulation to speed the process of disintegration. Proposed mechanisms of the action of disintegrants include water uptake through wicking, swelling, deformation (shape) recovery, particle repulsion, and heat of wetting. The swelling of disintegrant particles is perhaps the most widely accepted mechanism for tablet disintegration.

Superdisintegrants are effective at low concentration and have greater disintegrating efficiency and are more effective. Superdisintegrants are generally used at a low level in the solid dosage form, typically 1–10% by weight relative to the total weight of the dosage unit. Examples of superdisintegrants used are Crosscarmelose Sodium, Crospovidone, and Sodium Starch Glycolate, which are crosslinked cellulose, crosslinked polymer, and a crosslinked starch, respectively. [14]

MATERIALS AND METHOD: Candesartan Cilexitil used as a model drug (Ranbaxy Laboratories Limited), crospovidone (Signet

Chemical, Mumbai, India), croscarmellose sodium (FMC Europe, Belgium), sodium starch glycollate (S.D. fine Chemicals, Mumbai, India), Avicel pH 101 (FMC Europe, Belgium), Mannitol (Pearlitol SD 200) (E-Merck, Mumbai, India), Aspartame (Merisant India, Delhi, India), Magnesium Stearate (S.D. Fine Chemicals, Mumbai, India), Potassium Dihydrogen Orthophosphate (S.D. Fine Chemicals, Mumbai, India), Colloidal Silicone Dioxide (Sisco Research Labs, Mumbai, India.)

Fluidized Bed Processor:

Method:

Top spray technique was used for coating of drug solution on Avicel pH 101 under elevated temperature and high air velocity. Drug solution was prepared in 3.5% Ammonia solution.

The instrument parameters were set as follows:

- Temperature set at 65°C
- Fluidized air = 0.45 bar
- Atomized air = 0.25 bar

Evaluation of Coated Particles:

10 mg equivalent powder was weighed accurately in three 15 ml capacity glass bottles and 10 ml of water, 0.1 N HCl and pH 6.8 Phosphate buffer was poured in each respective bottle. These bottles were kept on rotary shaker for 24 hours and then analyzed by U.V. Spectrophotometer.

Blending and Tableting:

Tablets containing 2 mg of Candesartan Cilexitil were prepared by direct compression method and the formulae used in the study are shown in **Table 1**. All the ingredients were passed through # 30 and mixed together (in a poly-bag). The powdered blend was compressed into tablets in Rotary compression machine (Rimek Minipress II) using 8mm concave puch set.

TABLE 1: COMPOSITION OF TRIALS 1, 2, 3, 4, 5, 6, 7, 8 AND 9*

Sr. No.	Ingredients (mg)	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Trial 8	Trial 9
1.	Candesartan Cilexitil	2	2	2	2	2	2	2	2	2
2.	Croscarmellose Sodium	4	8	16	-	-	-	-	-	-
3.	Crospovidone	-	-	-	4	8	16	-	-	-
4.	Sodium Starch Glycollate	-	-	-	-	-	-	4	8	16
5.	Aerosil 200	4	4	4	4	4	4	4	4	4
6.	Mannitol	47	43	35	47	43	35	47	43	35
7.	Magnesium Stearate	1	1	1	1	1	1	1	1	1
8.	Aspartame	1	1	1	1	1	1	1	1	1

Evaluation of Blend: [15]

Blend was evaluated for bulk density, tap density, haushner's ratio and compressibility index.

Apparent bulk density was determined by pouring preserved drug-excipient blend into graduated cylinder and measuring the volume weight "as it is". Tap density was determined by placing a graduated cylinder containing known mass of drug excipients blend, on mechanical tapping apparatus, which was operated for a fixed number of taps using the weight of a blend in a cylinder and this volume, the tapped density was computed. One of the ways of measurement of free flowing powder is compressibility as computed from density of powder. It was calculated by using the formula,

Percentage compressibility = $\rho t - \rho 0 / \rho t \times 100$

ρt –Tapped density;
$\rho 0$ – Bulk density.

Flowability was calculated from compressibility flowability correlation data.

Evaluation of Dispersible Tablets:

Tablets were evaluated for weight variation, hardness, friability, thickness, wicking time and disintegration time. Weight variation test was done by weighing 20 tablets of each formulation using electronic balance (Unibloc, Shimadzu), and their average weight was taken. Tablets were weighed individually and individual weight was compared

with the average weight. Dolphin hardness tester was used to test hardness of tablet. Friability loss of tablet was tested by using Pfizer tester (Model EF-1W, Electrolab, Mumbai, India) Disintegration time was determined using USP tablet disintegration test apparatus (Model ED-2AL, Electrolab, Mumbai, India) using 900 ml of distilled water without disk at room temperature (37 ± 0.5°C). Thickness of tablet was determined by using dial caliper (Mitutoya, Japan).

Dissolution Study:

In vitro release of Candesartan Cilexitil from tablets was monitored by using 900 ml pH 6.5 phosphate buffer + 0.35% Tween 20 at 37 ± 0.5°C and 50 rpm using Dissolution apparatus type II (model TDT-08L, Electrolab, India]. Aliquots were withdrawn at 2 min, 5 min, 10 min, 15 min, 20 min and 30 min time intervals and were replenished immediately with the same volume of fresh buffer medium. Aliquots were assayed spectrophotometrically (UV, Lamada 25, Perkin Elmer) at 257 nm.

RESULTS AND DISCUSSION:

Evaluation of Coated Particles for Solubility Enhancement:

Solubility enhancement was checked in three different medias i.e. Water, 0.1 N HCl and pH 6.8 Phosphate buffer. Comparison of solubility of drug and solubility improved form of drug is shown in **Table 2** and **Fig.1**.

TABLE 2: COMPARISON OF SOLUBILITY

Media	Drug (mcg/ml)	Solubility Improved Form (mcg/ml)
Water	6.43	8.94
0.1 N HCl	7.41	8.72
pH 6.8 Phosphate Buffer	7.38	8.89

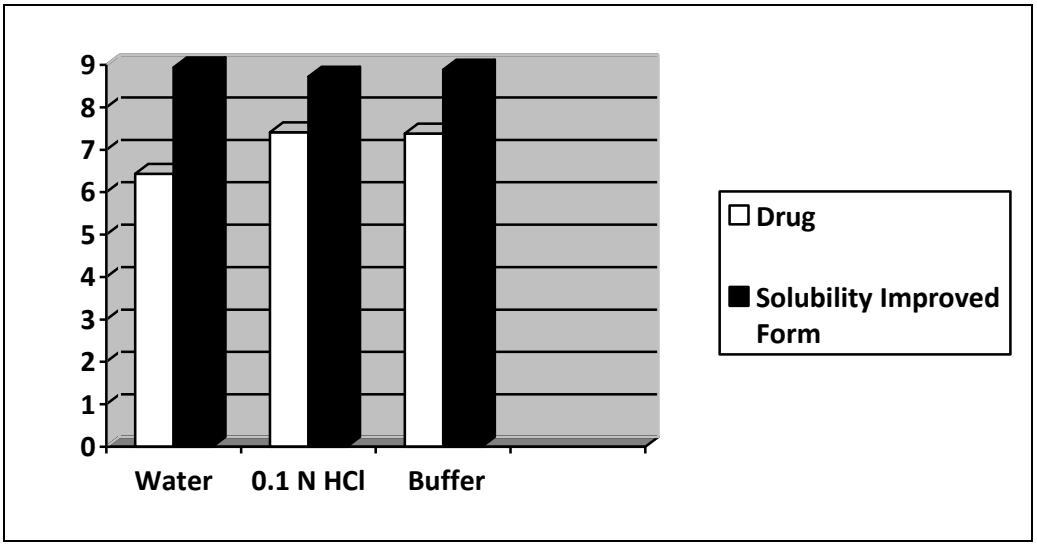

FIG. 1: COMPARISON OF SOLUBILITY BETWEEN DRUG AND SOLUBILITY IMPROVED FORM

Evaluation of blend:

Blend was evaluated for bulk density, tap density, haushner's ratio and compressibility index. Result of evaluation of blend is depicted in **Table 3.**

TABLE 3: EVALUATION OF BLEND

Sr. no.	Physical properties of blend	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Trial 8	Trial 9
1	Bulk Density	0.4	0.3984	0.3968	0.4	0.4016	0.4	0.3968	0.3968	0.3937
2	Tap Density	0.5556	0.5525	0.5495	0.5618	0.5587	0.5565	0.5516	0.5485	0.5495
3	Hausner ratio	1.3889	1.3867	1.3846	1.4045	1.3911	1.3912	1.3900	1.3823	1.3956
4	Compressibility index	28	27.9	27.8	28.8	28.11	28.12	28.06	27.66	28.35

Evaluation of of dispersible tablets:

Candesartan Cilexitil ODT tablets were evaluated for various compression parameters and *in vitro* release and pre compression parameters. Evaluated compression parameters are discussed in **Table 4** and dissolution profile is discussed in **Table 5**.

TABLE 4: COMPRESSION PARAMETERS FOR TRIALS 1, 2, 3, 4, 5, 6, 7, 8 AND 9

Sr. No.	Parameters	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Trial 8	Trial 9
1	Hardness (Kg/cm^2)	2.9	3	2.95	3	3.1	3	2.9	2.95	3.15
2	Thickness (mm)	3.73	3.73	3.71	3.74	3.73	3.71	3.72	3.73	3.72
3	Disintegration Time (Sec)	30	24	34	22	18	17	30	34	36
4	Friability	NMT 1%	NMT 1%	NMT 1%	NMT 1%	NMT 1%	NMT 1%	NMT 1%	NMT 1%	NMT 1%
5	Weight Variation (mg)	199.6	200.3	199.7	200.4	200.8	201.3	199.2	199.9	200.6
6	Assay (%)	102.48	100.37	102.01	103.50	100.64	99.38	97.72	99.20	99.27
7	Wicking Time (Sec)	45	34	38	38	31	32	47	39	39

TABLE 5: DISSOLUTION PROFILE OF TRIALS 1, 2, 3, 4, 5, 6, 7, 8, 9 AND MARKETED FORMULATION

Sr. No.	Time (min)	Mean % dissolution in pH 6.5 Phosphate buffer + 0.35% Tweens 20									
		Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7	Trial 8	Trial 9	Marketed Formulation
1	0	0	0	0	0	0	0	0	0	0	0
2	2	82.55	88.755	83.48	82.395	89.065	91.86	80.375	88.57	85.965	-
3	5	99.48966	100.4241	95.42931	100.2336	99.80517	99.12414	96.56379	101.711	101.65	14.66
4	10	100.326	98.77931	99.9931	100.9509	101.7534	100.875	102.556	101.2692	102.2	72.2
5	15	101.106	100.1664	101.725	102.0405	101.0716	101.1966	100.6519	100.6457	102.5129	95.38
6	20	100.9552	102.9672	101.5793	98.9431	101.9345	102.6026	100.7626	100.7974	101.7388	100.79
7	30	100.644	103.4483	101.2681	99.70172	102.0233	101.9862	100.6428	100.3328	102.6655	101.29
8	45	-	-	-	-	-	-	-	-	-	98.34
9	60	-	-	-	-	-	-	-	-	-	99.48

Comparison of dissolution profile of trials and marketed formulation is shown in **Fig. 2**.

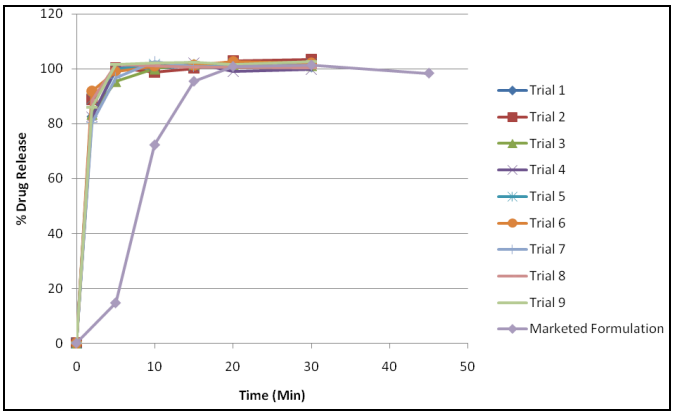

FIG. 2: COMPARISON OF DISSOLUTION PROFILE OF TRIALS 1, 2, 3, 4, 5, 6, 7, 8, 9 AND MARKETED FORMULATION

Candesartan Cilexitil is a low solubility antihypertensive drug with significant low bioavailability (around 15%). Solubility and dissolution are important steps in modifying bioavailability of such type of drugs.

CONCLUSION:

- Spray coating by fluidized bed processor can assist in enhancing the solubility of Candesartan Cilexitil.
- Orally disintegranting tablets using appropriate superdisintegrant promote rapid disintegration of ODT and help in improvement of dissolution rate as compared to marketed formulation.

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