
*Leading Article***FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF CANDESARTAN CILEXETIL USING NATURAL AND SYNTHETIC SUPERDISINTEGRANTS****Basawaraj S.Patil^{1*}, N.G.Raghavendra Rao²**¹Research scholar, Singhania University, Pacheri Bari, Dist. Jhunjhunu - Rajasthan, India²Department of Pharmaceutics, Luqman College of Pharmacy, Gulbarga – Karnataka, India**ABSTRACT**

In the present work attempts were made to prepare fast dissolving tablets (FDT) of candesartan cilexetil by direct compression method with a view to enhance patient compliance. The synthetic and natural superdisintegrants used in this study were croscarmellose sodium, and *plantago ovata* mucilage. Tablets having superdisintegrant at different concentration (2.5, 5, 7.5 and 10 mg) level were prepared. The prepared batches of tablets were evaluated for uniformity of weight, thickness, hardness, friability, drug content, wetting time, *in vitro* dispersion time and *in vitro* dissolution study. Swelling index was also investigated with an aim to compare the swelling property of *plantago ovata* mucilage with synthetic superdisintegrant. Compare to croscarmellose sodium, *plantago ovata* mucilage showed the highest swelling index. Hence, the present work revealed that this natural superdisintegrant, *plantago ovata* mucilage showed better disintegrating property than the most widely used synthetic superdisintegrants in the formulation of fast dissolving tablets

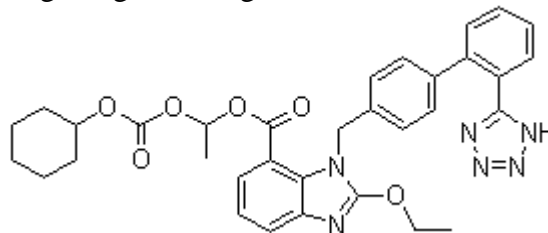
Keywords: Candesartan cilexetil, Fast dissolving tablets, *Plantago ovata* mucilage, Superdisintegrants.

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INTRODUCTION

Candesartan cilexetil 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 [2]. 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 32 mg [3]. Tablet formulation containing 4 mg and 8 mg candesartan cilexetil are available in market.



Structure of Candesartan cilexetil

Now a day fast dissolving tablets are gaining more importance in the market. Currently these tablets are available in the market for treating many disease conditions. More is concerned on hypertension, migraine, dysphasia, nausea and vomiting, Parkinson's disease, schizophrenia, pediatric emergency. [4-10]. These conditions are those, which require the drug to be formulated as fast dissolving tablets. Some patient prefers fast dissolving tablets to conventional tablets best of ease of administration, swallowing, pleasant taste and availability in several flavors [11]. The paediatric and geriatric patients are of particular concern. To overcome this, dispersible tablets[12] and fast-disintegrating tablets[13] have been developed. Most commonly used methods to prepare these tablets are; freeze-drying/lyophilization [14] tablet molding[15] and direct-compression methods[16]. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva in to the pores when placed in oral cavity[17]. The main disadvantages of tablets produced are, in addition to the cost intensive production process, a lack of physical resistance in standard blister packs and their limited ability to incorporate higher concentrations of active drug. Molded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern [18]. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets [19].

In the present study, an attempt was made to develop fast dissolving tablets of candesartan cilexetil using natural and synthetic superdisintegrants to improve its bioavailability.

MATERIALS AND METHODS

Candesartan cilexetil was gift sample from Hetero Labs. Ltd. Medak district. (Andhra Pradesh, India). Seeds of *plantago ovata* were purchased from local market of Gulbarga, Karnataka, India. Croscarmellose sodium, mannitol, microcrystalline cellulose talc, magnesium stearate, and all the other chemicals used were of pharmaceutical grade.

Isolation of Mucilage

The seeds of *plantago ovate* were soaked in distilled water for 48 h and then boiled for few minutes so that mucilage was completely released into water (Washi, 1985). The material collected was squeezed through muslin cloth for filtering and separating out the marc. Then, an equal volume of acetone was added to the filtrate so as to precipitate the mucilage. The

separated mucilage was dried (in oven at temperature less than 60⁰ C), powdered, sieved (# 80) and stored in a desicator until use.

Swelling index

Swelling index (B.P. Vol. II, 1988) is the volume in milliliters that is occupied by 1 gm of drug or any adhering mucilage after it has swollen in an aqueous liquid for 4 h. The method of studying swelling index for *plantago ovata*, croscarmellose sodium were carried out as per BP specifications. Swelling index was calculated from mean readings of three determinations (Table 1).

Table 1: Swelling index for superdisintegrants

Sl. No.	Name of the superdisintegrants	Swelling index (%v/v)*
1	Croscarmellose sodium	75 ± 2.71
2	Plantago ovata mucilage	98 ± 1.24

Preparation of fast dissolving tablets of candesartan cilexetil

Fast dissolving tablets of candesartan cilexetil were prepared by direct compression. All the ingredients (except granular directly compressible excipients) were passed through # 60 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 100 mg using 6 mm round punches on 10-station rotary tablet machine (Rimek Mini Press-1). A batch of 50 tablets of each formulation was prepared for all the designed formulations. Different formulations compositions are given in Table 2.

Table 2: Formulation of Candesartan cilexetil FDT

Ingredients	Formulation Code							
	CCS ₁	CCS ₂	CCS ₃	CCS ₄	CPO ₁	CPO ₂	CPO ₃	CPO ₄
Candesartan cilexetil	4	4	4	4	4	4	4	4
Croscarmellose sodium	2.5	5.0	7.5	10	--	--	--	--
Plantago ovata mucilage	--	--	--	--	2.5	5.0	7.5	10
Microcrystalline cellulose	30	30	30	30	30	30	30	30
Mannitol	58.5	56.0	53.5	51	58.5	56.0	53.5	51
Aspartame	3	3	3	3	3	3	3	3
Magnesium stearate	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1
(Total) mg	100	100	100	100	100	100	100	100

Evaluation of powder blends [20-23]**Bulk density**

Apparent bulk density (ρ_b) was determined by placing pre-sieved drug excipients blend into a graduated cylinder and measuring the volume (V_b) and weight (M) “as it is”.

$$\rho_b = M/V_b$$

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed number of taps. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using following formula.

$$\rho_t = M/V_t$$

Angle of repose

Angle of repose (θ) was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose was calculated.

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

Compressibility index

The simplest way of measurement of free flow property of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by % compressibility, which is calculated as follows:

$$C = (\rho_t - \rho_b) / \rho_t \times 100$$

ρ_t - Tapped density, ρ_b - Untapped bulk density

Hausner's ratio

Hausner's ratio is an index of ease of powder flow; it is calculated by following formula.

$$\text{Hausner's ratio} = \rho_t / \rho_b$$

ρ_t - Tapped density, ρ_b -Untapped bulk density

Evaluation of Sertraline fast dispersible tablets [24-26]**Weight variation test**

Weight variation test was done by weighing 20 tablets individually, by using Shimadzu digital balance (1mg sensitive). Calculating the average weight and comparing the individual tablet weight to the average weight.

Tablet thickness

The thickness was measured by placing tablet between two arms of the Vernier calipers. 5 tablets were taken and their thickness was measured.

Tablet hardness

The tablet hardness, which is the force required to break a tablet in a diametric compression force. The hardness tester used in the study was Monsanto hardness tester, which applies force to the tablet diametrically with the help of an inbuilt spring.

Tablet friability

The friability of the tablets was measured in a Roche friabilator (Camp-bell Electronics, Mumbai). Tablets of a known weight (W_o) or a sample of 20 tablets are dedusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %. Determination was made in triplicate.

$$\% \text{ Friability} = 100 (W_o - W) / W_o$$

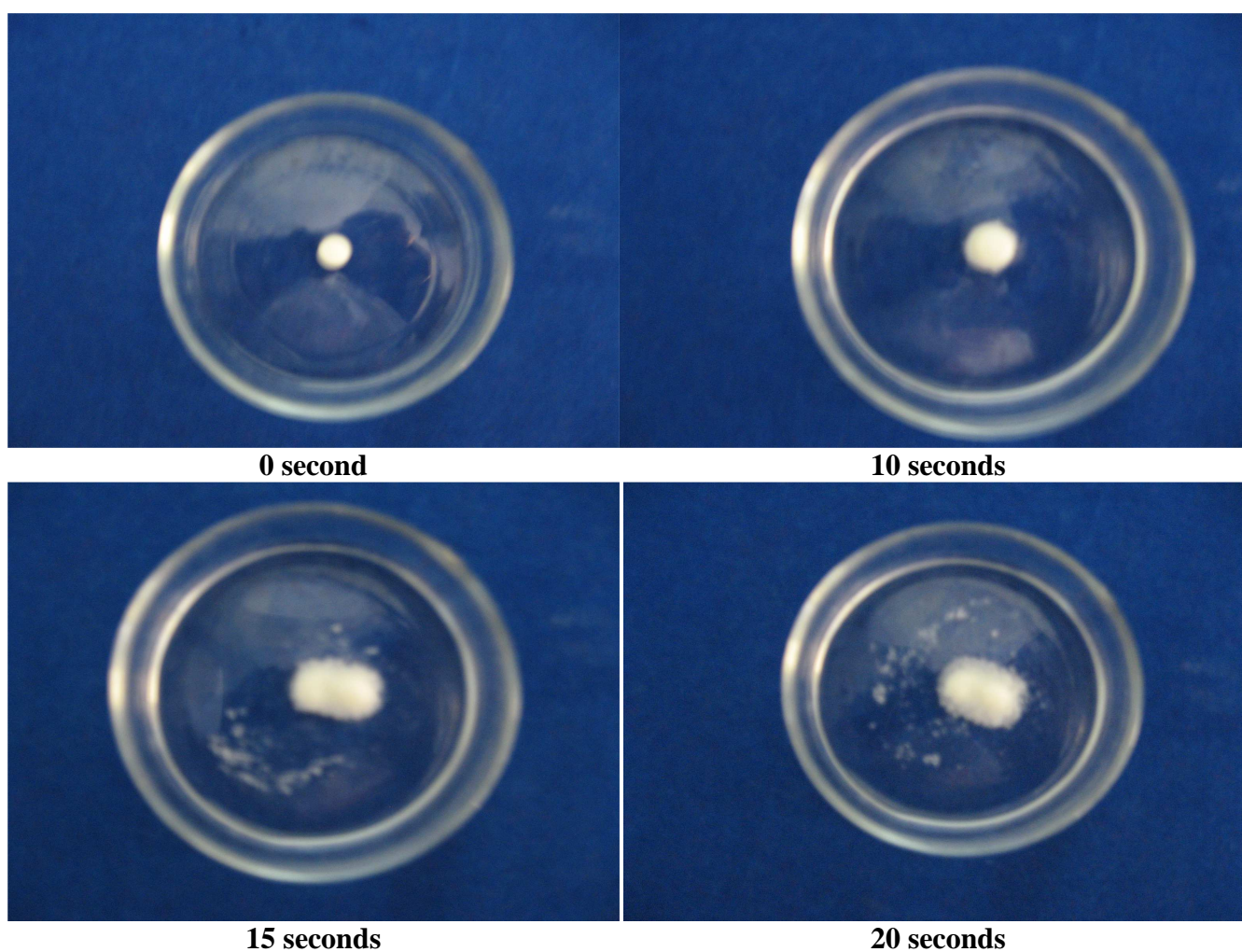


Fig. 1: *In vitro* dispersion of tablets CPO₄ prepared by direct compression method

Drug Content Uniformity

For the content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 4 mg of candesartan cilexetil was extracted into 6.8 pH buffer solution (containing 0.1% polysorbate) and liquid was filtered (0.22 mm membrane filter disc (Millipore Corporation)). The candesartan cilexetil content was determined by measuring the absorbance at 255 nm (PG instrument UV-Visible spectrophotometer T₈₀ model) after appropriate dilution with 6.8 pH buffer solution. The drug content was determined using standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

In vitro dispersion time

Tablet was added to 10 ml of phosphate buffer solution (pH 6.8) at $37 \pm 0.5^{\circ}\text{C}$. Time required for complete dispersion of a tablet was measured. (Fig.1)

Wetting Time and Water Absorption Ratio (R)²⁷

Twice folded tissue paper was placed in a petri dish having an internal diameter of 5 cm containing 6 ml of water. A tablet was carefully placed on the surface of the tissue paper in the Petri dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time. Water absorption ratio (R) was then determined according to the following equation:

$$R = 100 \times (w_a - w_b) / w_b$$

Where w_b and w_a were tablet weights before and after water absorption, respectively.

In vitro dissolution study

The release rate of candesartan cilexetil from fast dissolving tablets was determined using United State Pharmacopoeia (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of phosphate buffer pH 6.8 as a dissolution medium, (containing 0.1% polysorbate 20) at $37 \pm 0.5^{\circ}\text{C}$ and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at different time interval (minutes). The samples were filtered through a 0.45μ membrane filter. Absorbance of these solutions was measured at 255 nm using a PG instrument UV-Visible spectrophotometer T₈₀ model. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

FTIR 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 $400 - 4600 \text{ cm}^{-1}$ and the resolution was 4 cm^{-1} . The spectra are shown in Fig. 2.

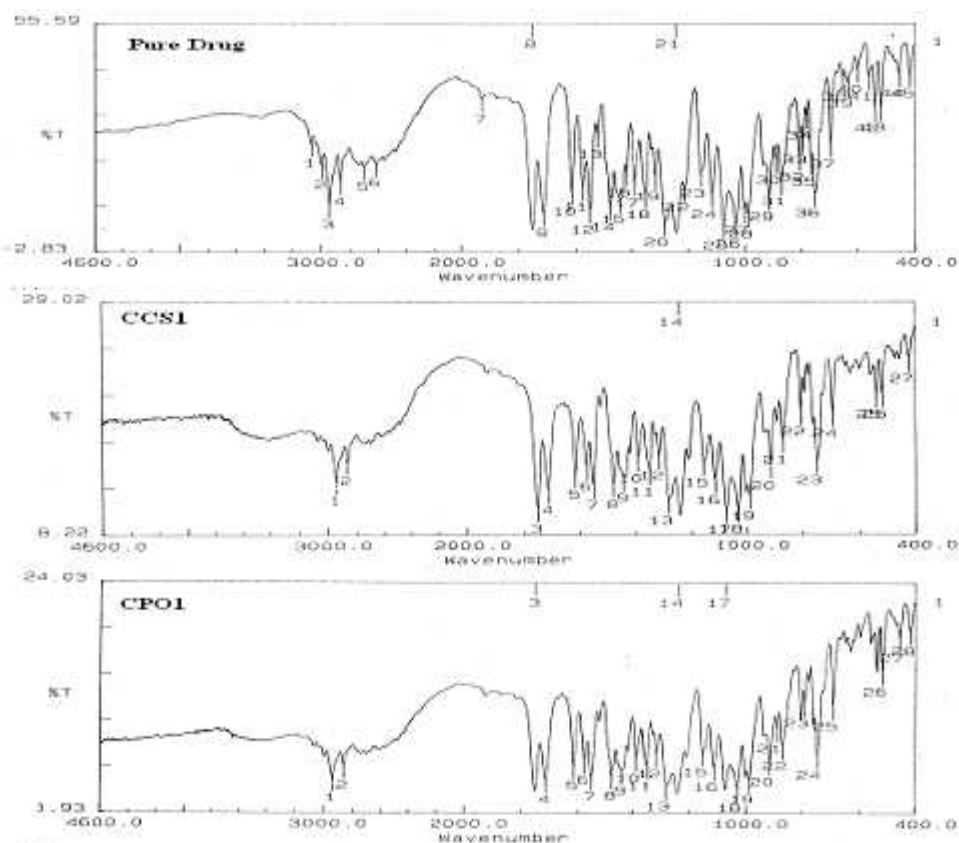


Fig. 2: IR spectrum of Candesartan cilexetil, CCS₁, and COP₁

RESULTS AND DISCUSSION

FTIR studies revealed that there was no physico-chemical interaction between Candesartan cilexetil and other excipients. Swelling index of *plantago ovata* mucilage was more than that of synthetic superdisintegrant croscarmellose sodium. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing properties are given in Table 3. The data obtained from post-compression parameters in all the formulations, friability is less than 1%, indicated that tablets had a good mechanical resistance. Drug content was found to be in the range of 98.48 to 100.27 %, which is within acceptable limits. Hardness of the tablets was found to be in the range of 3.1 to 3.8 kg/cm². *In vitro* dispersion times were found to be in the range of 20 to 62 sec. The water absorption ratio and wetting time, which are important criteria for understanding the capacity of disintegrants to swell in presence of little amount of water, were found to be in the range of 49 to 83 % and 21 to 59 sec respectively are given in Table 4 & 5. The dissolution profiles of formulations are shown in Fig 3 & 4. The dissolution profiles of all formulations are shows the release of drug 99 % within 9 min. The formulations CPO₄ and CCS₄ shows drug release within 4 & 5 min. Compare to croscarmellose sodium formulations, *plantago ovata* formulations shows faster release of drug, this is due to more swelling property of *plantago ovata* mucilage. In case of formulation CPO₄, the 50% and 90% of drug release was found within 0.39 and 1.54 min is shown in Fig. 5.

Table 3: Pre-compressional parameters of Candesartan cilexetil FDT

Formulation Code	Angle of repose (θ) (\pm SD), n=3	Bulk density (gm/ml) (\pm SD), n=3	Tapped density (gm/ml) (\pm SD), n=3	Carr's index (%) (\pm SD), n=3	Hausner's ratio (\pm SD), n=3
CCS ₁	25.02 \pm 1.70	0.55 \pm 0.007	0.63 \pm 0.001	13.19 \pm 1.42	1.15 \pm 0.04
CCS ₂	24.51 \pm 1.39	0.55 \pm 0.002	0.62 \pm 0.002	11.42 \pm 1.16	1.12 \pm 0.03
CCS ₃	25.49 \pm 1.67	0.52 \pm 0.005	0.63 \pm 0.002	17.73 \pm 1.29	1.21 \pm 0.02
CCS ₄	26.52 \pm 1.36	0.52 \pm 0.007	0.62 \pm 0.001	15.61 \pm 1.33	1.18 \pm 0.04
CPO ₁	27.12 \pm 1.41	0.55 \pm 0.002	0.62 \pm 0.001	11.35 \pm 1.53	1.12 \pm 0.03
CPO ₂	28.11 \pm 1.39	0.51 \pm 0.004	0.62 \pm 0.002	13.15 \pm 2.19	1.15 \pm 0.03
CPO ₃	29.10 \pm 1.21	0.52 \pm 0.003	0.63 \pm 0.001	12.60 \pm 1.27	1.14 \pm 0.04
CPO ₄	28.26 \pm 1.50	0.53 \pm 0.007	0.64 \pm 0.002	16.29 \pm 1.48	1.19 \pm 0.04

Table 4: Post-compressional parameters of Candesartan cilexetil FDT

Formulation Code	Weight variation (%) (\pm SD), n=3	Thickness (mm) (\pm SD), n=3	Hardness (kg/cm ²) (\pm SD), n=3	Friability (%)
CCS ₁	103 \pm 1.62	3.25 \pm 0.15	3.3 \pm 0.12	0.36
CCS ₂	98 \pm 1.21	3.21 \pm 0.10	3.2 \pm 0.17	0.22
CCS ₃	101 \pm 1.97	3.30 \pm 0.10	3.1 \pm 0.15	0.38
CCS ₄	102 \pm 0.56	3.35 \pm 0.17	3.8 \pm 0.12	0.67
CPO ₁	100 \pm 1.32	3.42 \pm 0.15	3.1 \pm 0.07	0.57
CPO ₂	99 \pm 1.78	3.65 \pm 0.12	3.1 \pm 0.21	0.51
CPO ₃	100 \pm 0.65	3.61 \pm 0.09	3.3 \pm 0.25	0.48
CPO ₄	101 \pm 1.50	3.37 \pm 0.19	3.2 \pm 0.14	0.66

Table 5: Disintegration, wetting time, water absorption ratio and drug content of candesartan cilexetil FDT

Formulation Code	<i>In vitro</i> dispersion time (sec) (\pm SD), n=3	Wetting time (sec) (\pm SD), n=3	Water absorption ratio (\pm SD), n=3	Drug content (\pm SD), n=3
CCS ₁	60 \pm 1.29	58 \pm 1.41	49 \pm 1.33	98.48 \pm 0.82
CCS ₂	44 \pm 1.35	41 \pm 1.23	54 \pm 1.07	99.31 \pm 0.98
CCS ₃	35 \pm 1.17	32 \pm 1.32	67 \pm 1.18	99.12 \pm 1.58
CCS ₄	25 \pm 1.61	21 \pm 2.12	71 \pm 1.32	100.27 \pm 1.62
CPO ₁	62 \pm 1.01	59 \pm 1.17	57 \pm 1.43	99.56 \pm 1.69
CPO ₂	47 \pm 1.13	43 \pm 1.10	70 \pm 1.59	99.81 \pm 0.25
CPO ₃	31 \pm 2.24	29 \pm 1.29	80 \pm 1.46	99.74 \pm 1.21
CPO ₄	20 \pm 1.52	18 \pm 1.11	83 \pm 1.15	99.25 \pm 1.76

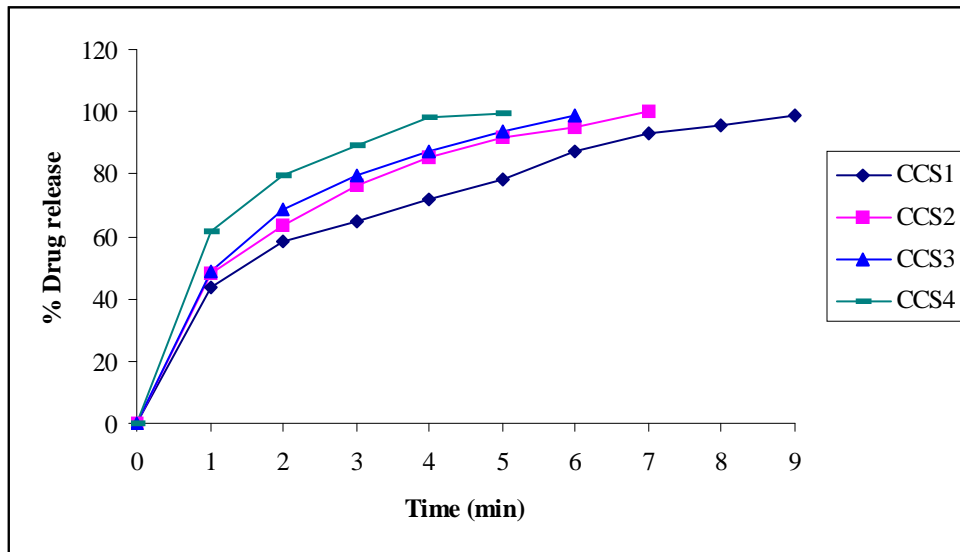


Fig. 3: Dissolution profile of formulations CCS₁-CCS₄

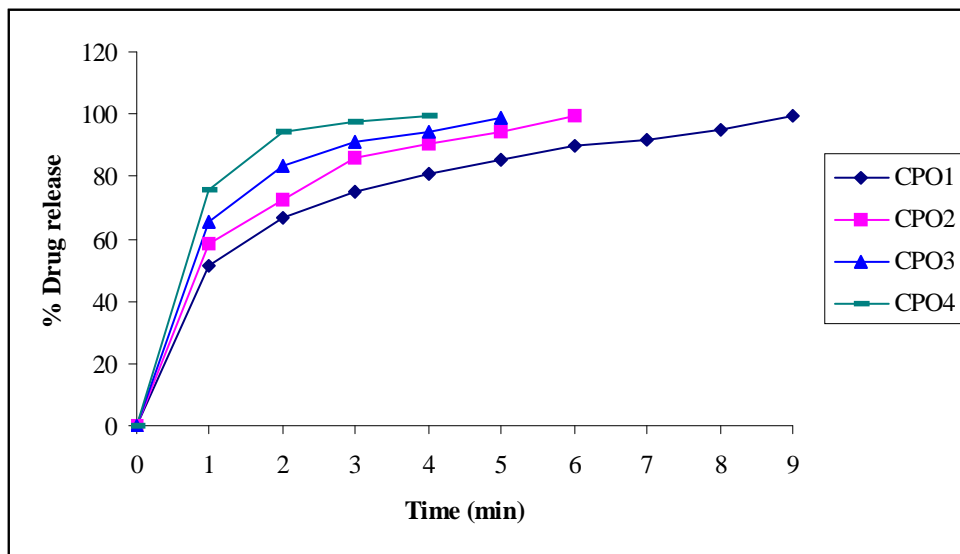


Fig. 4: Dissolution profile of formulations CPO₁-CPO₄

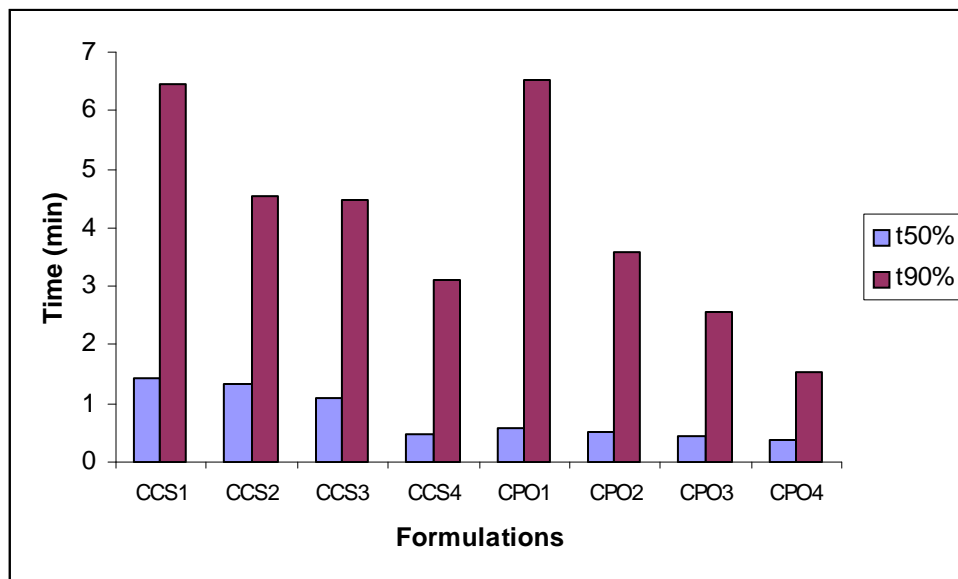


Fig. 5: Comparison of release profile (t_{50%} and t_{90%}) of different formulations

CONCLUSION

The present work revealed that the natural superdisintegrant, *plantago ovata* mucilage showed better disintegrating and dissolution property than the most widely used synthetic superdisintegrants in the formulation of fast dissolving tablets

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