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Formulation and Development of Candesartan Cilexetil Fast Dissolving Tablets by Sublimation Technique

Hunashal Sarah Priya[1], Basawaraj S. Patil[1*], Ravindra S. Jeevanagi[2],
1.R.M.E.S's College of Pharmacy, Gulbarga - 585102 – Karnataka
2.Tipu Sultan College of Pharmacy, Gulbarga- 585104 – Karnataka

ABSTRACT

Candesartan cilexetil is a prodrug of candesartan – a compound that inhibits binding of angiotensin II to the AT_1 – receptor. It is mainly used in the treatment of hypertension. In the present work attempts were mase to prepare fast dissolving tablets of candesartan cilexetil by sublimation technique. The prepared formulations were evaluated for pre-compressional and post-compressional parameters. The compatibility of drug with other ingredients was checked by FTIR studies, these 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 less than 1. Drug content was found to be high (≥ 100.27%) and uniform in all the formulations. The tablet thickness was found to be 3.14 – 3.47. 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 decreased significantly with increase in the concentration of subliming agent. The formulations CSC_3, CSM_3, CSA_3, and CSU_3 50 % of drug released in 1.38, 2.55, 4.00 and 3.57 min, and 90 % of drug released in 3.39, 6.04, 7.50 and 7.18 min. The formulation CS (control) released 42.16 % in 60 min. Stability study carried out as per ICH guidelines for three months and results revealed that upon storage disintegration time of tablets decreased significantly ($p<0.05$). The results concluded that by adopting a systemic formulation approach, an optimum point could be reached in the shortest time with minimum efforts. Sublimation technique would be an effective alternative approach compared with the use of more expensive adjuvants in the formulations of fast dissolving tablets.

Keywords: Candesartan cilexetil, Fast dissolving tablets, sublimation technique, Croscarmillose Sodium.

*Corresponding Author Email: bspatilglb17@rediffmail.com
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INTRODUCTION

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[1-7]. 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[8].

The paediatric and geriatric patients are of particular concern. To overcome this, dispersible tablets[9] and fast-disintegrating tablets[10] have been developed. Most commonly used methods to prepare these tablets are; freeze-drying/lyophilization[11] tablet molding[12] and direct-compression methods[13]. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva in to the pores when placed in oral cavity[14]. 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[15]. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets[16].

The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation and solid dispersion)[17]. 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[18].

Candesartan cilexetil is chemically 2-Ethoxy-3-[21-(1H-tetrazol-5-yl) biphenyl-4-ylmethyl] -3Hbenzoimidazole- 4-carboxylic acid 1- cyclohexyloxycarbonyloxy ethyl ester.[19] Candesartan cilexetil is a prodrug of Candesartan – a compound that inhibits binding of angiotensin II to the AT_1 – receptor. Candesartan cilexetil is hydrolyzed to candesartan during absorption from the gastrointestinal tract[20] 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[21].

In the present study, an attempt was made to develop fast dissolving tablets of candesartan cilexetil by sublimation technique to improve its bioavailability.

MATERIALS AND METHOD

Candesartan cilexetil was gift sample from Hetero Labs. Ltd. Medak district. (AP).

crosscarmellose sodium, camphor, urea, ammonium bicarbonate, menthol, mannitol, microcrystalline cellulose talc, magnesium stearate, and all the other chemicals used were of pharmaceutical grade.

Fourier transform infrared (FTIR) spectroscopy

Compatibility studies were carried out to know the possible interactions between Candesartan cilexetil and excipients used in the formulation. Physical mixtures of drug and excipients were prepared to study the compatibility. Drug polymer compatibility studies were carried out using FTIR spectroscopy. IR spectrum of pure drug and excipients was seen in between 500- 4000 cm^{-1} are shown in Figure 1.

Preparation of tablet

Candesartan cilexetil 4 mg was taken and mixed with mannitol, directly compressible microcrystalline cellulose, super disintegrant and camphor (3%, 6%, 9%) in plastic container. Magnesium strearate and talc were passed through sieve No. 60 and blended with initial mixture in the plastic container followed by direct compression of blend (Table 1). After compression 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.

Evaluation of tablets

Tablet was evaluated for hardness, friability, weight variation, thickness, disintegration time, wetting time, water absorption ratio, drug content and stability study. The Pfizer hardness tester and Roche friabilator were used to test hardness and friability loss respectively. In weight variation test, 20 tablets were selected at random and average weight was determined using electronic balance. Tablets were weighed individually and compared with average weight. Disintegration time was determined using USP Tablet disintegration test apparatus using 900 ml distilled water at room temperature. Thickness of tablets was determined by using dial caliper, wetting time study, a piece of tissue paper folded twice was kept in culture dish containing 6 ml of distilled water. A tablet having small amount of amaranth powder on upper surface was kept on tissue paper. A time required to develop a red color on upper surface of tablet was recorded as the wetting time. For drug content analysis, a total 10 tablets were weighed and powdered. The powder equivalent to 4 mg of candesartan cilexetil was taken and dissolved in phosphate buffer 6.8. After that an aliquot of the filtrate was diluted and analyzed spectrophotometrically at 255 nm. Using 900 ml of buffer monitored *in-vitro* dissolution of candesartan cilexetil from tablets at 37 ± 0.5^0C at 50 rpm using programmable dissolution tester. Aliquots were withdrawn at 1 min time intervals. Aliquots, following suitable dilution were assayed spectrophotometrically at 255 nm. The stability study of

the tablets were carried out according to ICH guidelines by storing tablets in stability chamber at 40±2^{0}C/75±5% RH for 3 mouths

RESULTS AND DISCUSSION

Science, the flow properties of the powder mixture are important for the uniformity of mass of tablets, the flow of powder mixture was 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 3and 4. In all the formulations the hardness test indicate good mechanical strength. The hardness of tablet decrease with increase in amount of sublimable component. Friability of all formulation was less than 1%, which indicates the tablets had god mechanical resistance. Drug content was found to be high (≥100.27 %) and uniform in all formulations. The tablet thickness was found to be 3.14 to 3.47. 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 decreased significantly with increase in concentration of subliming agent. The tablets prepared by sublimation technique rapidly exhibit high pores and disintegrate the tablets rapidly. It may be due to their lowest hardness and maximum pours structure was responsible for faster water uptake; hence it facilitates wicking action of crasscarmellose sodium in bringing about faster disintegration. Wetting time of tablets was decreased with increase in the concentration of the subliming agent. Wetting time is closely related to the inner structure of the tablet. The wetting time of all formulations were found to be in the range of 65 t0 148 sec. The dissolution profiles of all formulations are shown in Figure 2 to 5. Out of seven formulations, the formulations prepared by using camphor as subliming agent show faster drug release within 4 to 7 min. in-vitro profile of candesartan cilexetil shown in Figure 6 and in Table 5. The $t_{50\%}$ and $t_{90\%}$ values changed with changing concentration of subliming agent. The formulation CSC_1, CSC_2 and CSC_3 shows faster drug release. The formulations CSC_3, CSM_3, CSA_3, and CSU_3 50 % of drug released in 1.38, 2.55, 4.00 and 3.57 min, and 90 % of drug released in 3.39, 6.04, 7.50 and 7.18 min. The formulation CS (control) released 42.16 % in 60 min.

The stability studies results revealed that, the disintegration time, wetting time was decreased significantly (Table 6). During the sublimation procedure all the formulations were kept in vacuum dryer at 45^{0}C 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.

Conclusion

It may be concluded that by adopting a systemic formulation approach, an optimum point could be reached in the shortest time with minimum efforts. Sublimation technique would be an effective alternative approach compared with the use of more expensive adjuvants in the formulations of fast dissolving tablets.

Table 1: Formulation of Candesartan Cilexetil FDT

Ingredients	**Formulation Code**												
	CS	**CSC_1**	**CSC_2**	**CSC_3**	**CSA_1**	**CSA_2**	**CSA_3**	**CSM_1**	**CSM_2**	**CSM_3**	**CSU_1**	**CSU_2**	**CSU_3**
Candesartan cilexetil	4	4	4	4	4	4	4	4	4	4	4	4	4
Mannitol	94	85	82	79	85	82	79	85	82	79	85	82	79
CCS	--	6	6	6	6	6	6	6	6	6	6	6	6
Camphor	--	3	6	9	--	--	--	--	--	--	--	--	--
Ammonium bicarbonate	--	--	--	--	3	6	9	--	--	--	--	--	--
Menthol	--	--	--	--	--	--	--	3	6	9	--	--	--
Urea	--	--	--	--	--	--	--	--	--	--	3	6	9
Talc	1	1	1	1	1	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1	1
Total wt (mg)	100	100	100	100	100	100	100	100	100	100	100	100	100

Table 2: Precompressional Parameters Of Candesartan Cilexetil FDT

Formulation code	**Angle of repose* (degree) ±SD**	**Bulk density* (g/cc) ± SD**	**Tapped density* (g/cc) ± SD**	**Carr's index* (%) ± SD**	**Hausner's Ratio* ± SD**
CS	32.43 ± 1.37	0.50 ± 0.06	0.61 ± 0.02	18.43 ± 1	1.22 ± 0.02
CSC_1	29.14 ± 1.08	0.49 ± 0.06	0.60 ± 0.01	17.80 ± 1.23	1.21 ± 0.03
CSC_2	30.30 ± 1.17	0.51 ± 0.06	0.61 ± 0.01	17.68 ± 1.02	1.21 ± 0.02
CSC_3	26.37 ± 1.26	0.52 ± 0.06	0.63 ± 0.01	21.05 ± 1.03	1.21 ±0.03
CSM_1	28.50 ± 1.20	0.52 ± 0.06	0.63 ± 0.02	16.87 ± 1.25	1.25 ± 0.03
CSM_2	27.21 ± 1.41	0.52 ± 0.06	0.62 ± 0.01	15.88 ± 1.36	1.18 ± 0.03
CSM_3	29.11 ± 1.45	0.51 ± 0.06	0.62 ± 0.02	16.85 ± 1.29	1.20 ± 0.03
CSA_1	30.19 ± 1.27	0.53 ± 0.06	0.62 ± 0.01	15.08 ± 1.89	1.17 ± 0.03
CSA_2	27.52 ± 1.33	0.48 ± 0.06	0.60 ± 0.02	20.03 ± 1.56	1.25 ± 0.03
CSA_3	28.73 ± 1.23	0.52 ± 0.06	0.63 ± 0.02	17.77 ± 1.57	1.21 ± 0.02
CSU_1	29.86 ± 1.46	0.48 ± 0.06	0.60 ± 0.01	19.86 ± 1.49	1.24 ± 0.03
CSU_2	27.12 ±1.56	0.51 ± 0.06	0.60 ± 0.01	14.80 ± 1.69	1.17 ± 0.03
CSU_3	29.09 ± 1.01	0.50 ± 0.06	0.61 ± 0.01	17.82 ± 1.75	1.21 ± 0.03

* Average of three determinations

Table 3: Post-Compressional Parameters of Candesartan Cilexetil FDT

Formulation Code	Hardness* (Kg/cm^2)± SD	Thickness* (mm)± SD	Friability (%)	Weight variation* (mg) ± SD
CS	2.5 ± 0.42	3.47 ± 0.08	0.48	102 ± 1.81
CSC_1	3.1 ± 0.15	3.33 ± 0.20	0.26	100 ± 1.06
CSC_2	3.0 ± 0.20	3.35 ± 0.28	0.29	97 ± 1.45
CSC_3	2.5 ± 0.05	3.35 ± 0.14	0.31	98 ± 0.67
CSM_1	2.2 ± 0.10	3.23 ± 0.19	0.57	102 ± 1.42
CSM_2	2.1 ± 0.21	3.25 ± 0.09	0.53	98 ± 1.57
CSM_3	2.0 ± 0.15	3.35 ± 0.12	0.41	100 ± 0.78
CSA_1	2.5 ± 0.10	3.43 ± 0.15	0.63	97 ± 1.49
CSA_2	2.1 ± 0.13	3.31 ± 0.17	0.73	98 ± 1.38
CSA_3	2.0 ± 0.12	3.27 ± 0.10	0.77	101 ± 1.22
CSU_1	3.0 ± 0.10	3.32 ± 0.25	0.30	100 ± 0.92
CSU_2	2.5 ± 0.15	3.31 ± 0.15	0.67	101 ± 1.36
CSU_3	2.0 ± 0.21	3.14 ± 0.21	0.65	101 ± 0.29

* Average of three determinations

Table 4: *In Vitro* Disintegration Time, Wetting Time, Water Absorption Ratio and Drug Content Of Candesartan Cilexetil FDT

Formulation Code	*In vitro* disintegration time* (sec) ± SD	Wetting time* (sec) ± SD	Water absorption ratio* ± SD	Drug Content* (%) ± SD
CS	100 ± 1.23	148 ± 1.03	68 ± 1.36	98.96 ± 0.86
CSC_1	30 ± 1.36	70 ± 1.53	82 ± 1.39	99.92 ± 0.45
CSC_2	28 ± 2.36	68 ± 1.37	83 ± 1.53	100.27± 0.53
CSC_3	25 ± 1.56	65 ± 1.25	84 ± 1.20	99.17 ± 1.96
CSM_1	32 ± 1.53	72 ± 1.23	82 ± 1.30	98.18 ± 1.17
CSM_2	29 ± 1.28	69 ± 1.35	83 ± 1.69	99.62 ± 0.97
CSM_3	27 ± 1.59	67 ± 1.54	84 ± 1.98	98.83 ± 1.31
CSA_1	34 ± 1.46	74 ± 2.03	82 ± 1.29	99.15 ± 1.47
CSA_2	32 ± 1.44	72 ± 2.45	83 ± 1.62	98.93 ± 0.64
CSA_3	28 ± 1.29	68 ± 2.09	85 ± 1.93	99.12 ± 1.27
CSU_1	34 ± 1.34	74 ± 2.56	80 ± 1.63	99.03 ± 1.02
CSU_2	31 ± 2.31	71 ± 0.29	82 ± 1.53	99.13 ± 1.90
CSU_3	29 ± 2.04	69 ± 2.26	83 ± 1.49	98.54 ± 1.21

* Average of three determinations

Table 5: Release Profile Of Candesartan Cilexetil Fast Dissolving Tablets Prepared By Sublimation Method

Formulation Code	$t_{50\%}$*	$t_{90\%}$*
CS	--	--
CSC_1	3.57 ± 0.12	6.18 ± 0.29
CSC_2	2.51 ± 0.21	5.15 ± 0.32
CSC_3	1.38 ± 0.39	3.39 ± 0.56

CSM_1	4.31 ± 0.51	8.58 ± 0.18
CSM_2	3.54 ± 0.54	7.24 ± 0.27
CSM_3	2.55 ± 0.45	6.04 ± 0.34
CSA_1	5.30 ± 0.43	9.60 ± 0.54
CSA_2	4.48 ± 0.29	8.24 ± 1.25
CSA_3	4.00 ± 0.43	7.50 ± 0.59
CSU_1	5.34 ± 0.39	9.15 ± 1.03
CSU_2	5.04 ± 0.16	8.40 ± 0.22
CSU_3	3.57 ± 0.38	7.18 ± 0.18

* Average of three determinations

Table 6: Results of Stability Study

Formulation Code	*In vitro* disintegration time*(sec) ± SD	Wetting time* (sec) ± SD	Drug Content* (%) ± SD
CSC_3	22 ±1.03	60 ± 1.65	99.14 ± 0.57
CSM	24 ± 1.49	62 ± 1.72	98.82 ± 0.79
CSU_3	27 ± 0.56	64 ± 1.13	98.52 ± 1.28
CSA_3	26 ± 2.43	63 ± 1.54	99.10 ± 0.81

* Average of three determinations

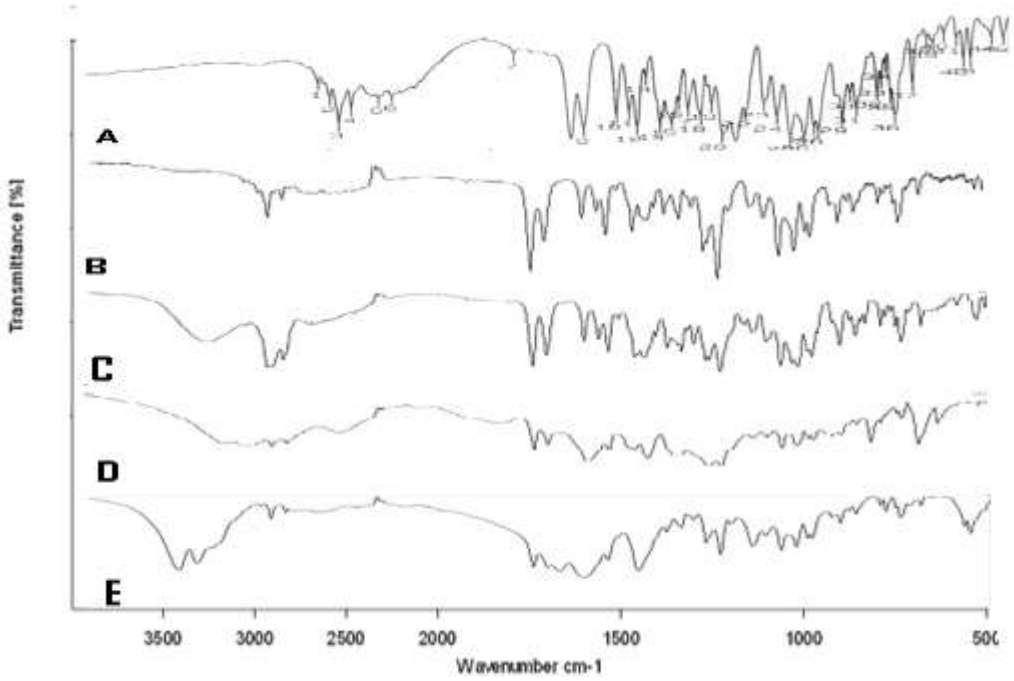

Figure 1: IR spectrum of Candesartan cilexetil

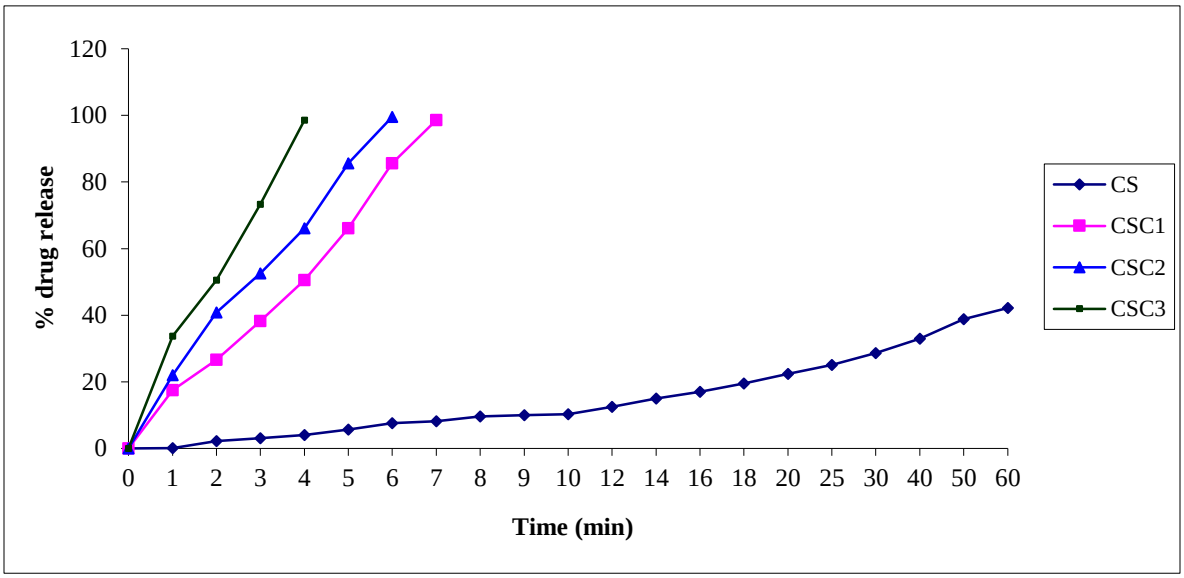

Figure 2: Dissolution profile of formulations CSC_1-CSC_3

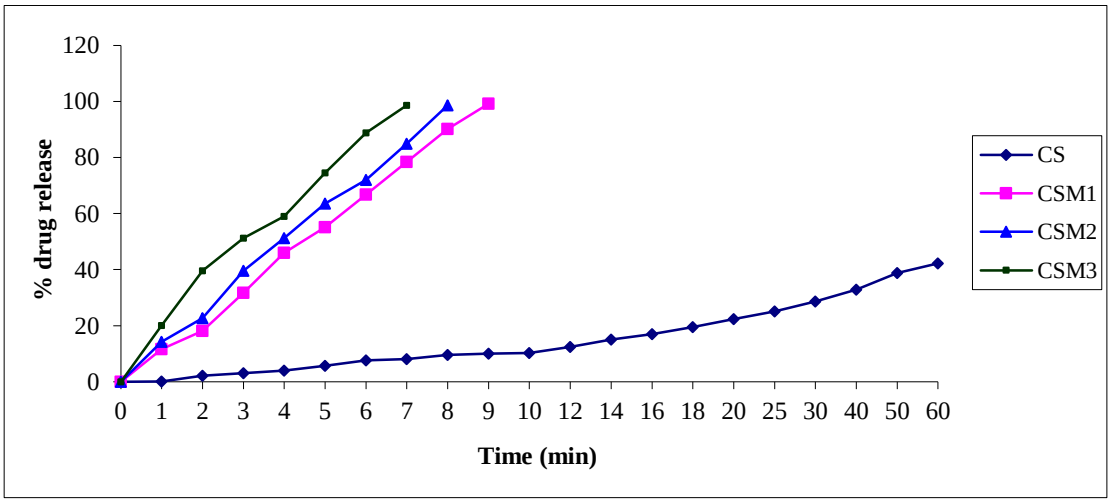

Figure 3: Dissolution profile of formulations CSM_1-CSM_3

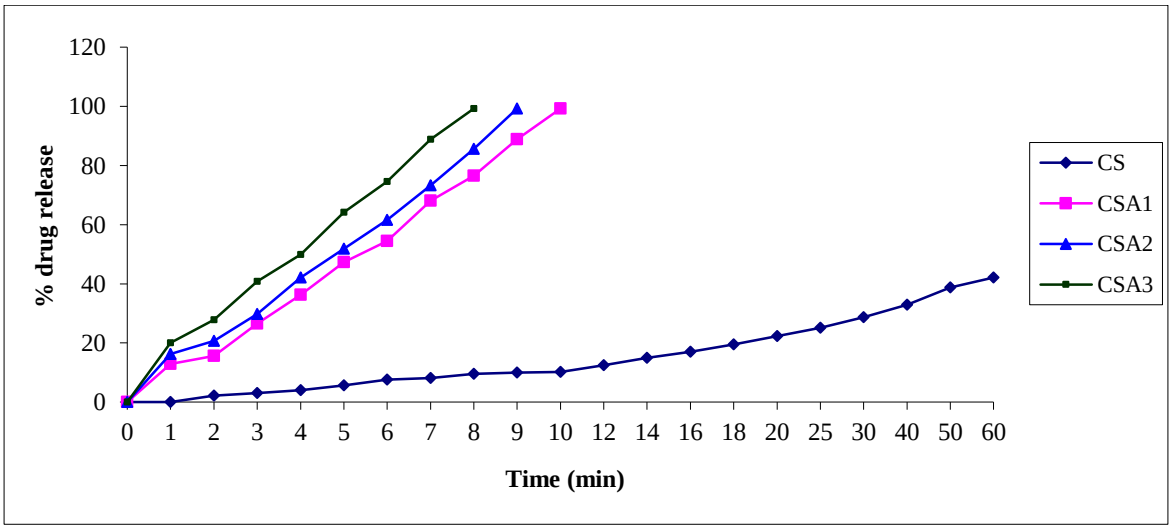

Figure 4: Dissolution profile of formulations CSA_1-CSA_3

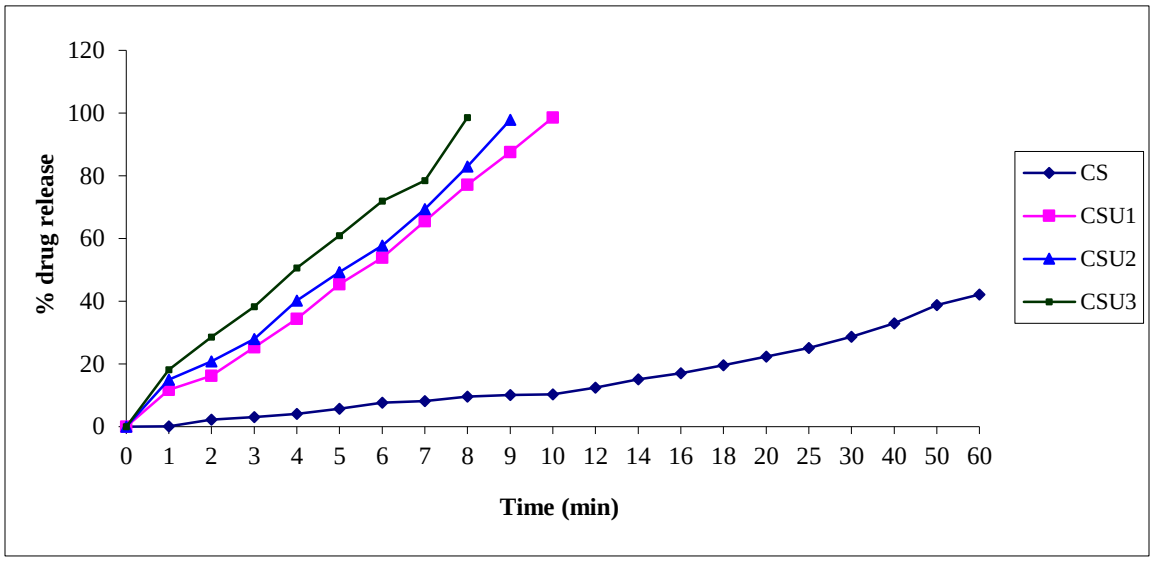

Figure 5: Dissolution profile of formulations CSU_1-CSU_3

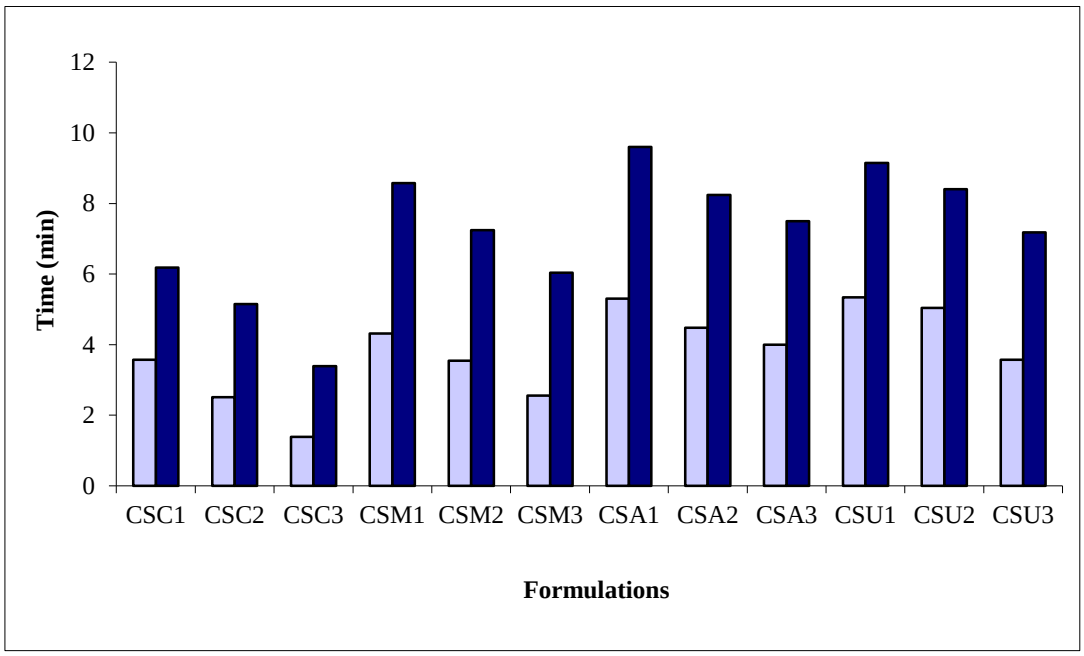

Figure 6: Comparison of release profile ($t_{50\%}$ and $t_{90\%}$)of different formulations

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