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Formulation and Evaluation of Fast Dissolving Tablets of Enalapril Maleate Using Co-Processed Superdisintegrants

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ABSTRACT
Enalapril maleate is the maleate salt of enalapril, a derivative of two amino acid, L-alanine and L-proline. Enalapril maleate is angiotensin converting enzyme (ACE) inhibitor. It lowers blood pressure by reducing peripheral vascular resistance without relatively increasing cardiac output, rate or contractility. All grades of essential hypertension especially in patients with diabetes and other chronic renal diseases like glomerulosclerosis can be treated with Enalapril. It is also indicated in the treatment of heart failure. Enalapril maleate is having a half life of 11 hrs. The bioavailability of Enalapril maleate tablets is approximately 55 % and food does not affect absorption. Hence, an attempt was made for preparations of a FDT of enalapril maleate were formulated by direct compression technique using co-processed superdisintegrant like *Crospovidone* and Croscarmellose sodium in different ratios. The prepared were evaluated for various pharmaceutical characteristics viz. hardness, % friability, weight variation, drug content, in-vitro dissolution profiles. Results showed that the direct compression technique by using co-processed superdisintegrants successfully used for enhancing the solubility of Enalapril Maleate. The prepared tablets were characterized using FTIR and finally the prepared tablets were evaluated for various pharmaceutical characteristics such as hardness, % friability, weight variation, drug content all the results were within the I.P Limit. Crosspovidone and CCS containing tablets rapidly exhibit high capillary activity and pronounced hydration with a little tendency to gel formation and disintegrate the tablet rapidly. The formulations prepared by co-processed superdisintegrants showed rapid % drug release due to fast disintegration of tablets. The formulation PM 3 and CP 6 shows 99% drug released within 20 minutes. The results of stability studies revealed no change in physical appearance, hardness, drug content and in vitro dissolution profiles, thus indicating that formulation was stable. Thus Results showed that the direct compression technique by using co-processed superdisintegrants successfully used for enhancing the solubility of Enalapril maleate.

Keywords: Enalapril Maleate, Mannitol, Crospovidone, Croscarmellose, Sodium starch glycolate, direct compression method.

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INTRODUCTION

Enalapril maleate[1-3] is the maleate salt of enalapril, a derivative of two amino acid, L-alanine and L-proline. Enalapril maleate is angiotensin converting enzyme (ACE) inhibitor. It lowers blood pressure by reducing peripheral vascular resistance without relatively increasing cardiac output, rate or contractility. All grades of essential hypertension especially in patients with diabetes and other chronic renal diseases like glomerulosclerosis can be treated with Enalapril. It is also indicated in the treatment of heart failure. Enalapril maleate is having a half life of 11 hrs. The bioavailability of Enalapril maleate tablets is approximately 55 % and food does not affect absorption. Hence, an attempt was made for preparation of a new formulation of Enalapril maleate tablet by direct compression with an aim of providing faster onset of action to reduce the blood pressure immediately.

The concept of fast dissolving drug delivery system emerged from the desired to provide patient with conventional means of taking their medication. Fast dissolving dosage form can be disintegrated, dissolved or suspended by saliva in mouth. The fast dissolving tablets disintegrates instantaneously when placed on tongue and releases the drug dissolve or disperses in saliva[4]. The fast dissolving tablets are useful in patients[5-6], like pediatric, geriatric, bedridden or mentally disabled, who may face difficulty in swallowing conventional tablet or capsule[7] leading to ineffective therapy[8], Most pharmaceutical forms for oral administration are formulated for direct ingestion or for chewing or for prior dispersion/dissolution in water. Some of them are absorbed in mouth (sublingual or buccal tablet) to obviate the problem associated with conventional dosage forms orally fast dissolving tablet have been developed which combine hardness, dosage uniformity, stability and other parameters, since no water is required for swallowing the tablets and they are thus suitable for geriatric, pediatric and traveling patients[9].

Recent advances in novel drug delivery systems aim to enhance safety and efficacy of the drug molecules by formulating convenient dosage form for administration and to achieve better patient's compliance. One such approach is fast dissolving tablets) FDT)[10-13]. New combinations of existing excipients are an interesting option for improving excipients functionality because all formulations contain multiple excipients. One such approach for improving the functionality of excipients is co-processing of two or more excipients. Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual[14]. Co-processing excipients lead to the formulation of excipients granules with superior

properties, compared with physical mixtures of components or individual components, like improved flow properties, improved compressibility, better dilution potential, fill weight uniformity, and reduced lubri-cant sensitivity[15] Several co-processed superdisintegrants are commercially available: Ludipress (lactose monohydrate, polyvinyl pyrrolidone and Crospovidone), Starlac (lactose and maize starch), Starcap 1500 (corn starch and Pregelatinized starch), Ran ExploC (microcrystalline cellulose, silica and crosspovidone), Ran Explo-S (microcrystalline cellulose, silica and sodium starch glycolate), PanExcea MH300G (microcrystalline cellulose, hydroxy propyl methyl cellulose and Crospovidone)[16]. The widely used superdisintegrants are Crospovidone (CP), Croscarmellose sodium (CCS) and sodium starch glycolate (SSG). In the present investigation, the preparation and evaluation of fast dissolving tablets by using co-processed superdisintegrants containing CP and CCS was studied. The reasons for selection of CP are high capillary activity, pronounced hydration capacity and little tendency to form gels. Crospovidone superdisintegrant is effective in wet granulation, dry granulation and direct compression in tablet processing[17]. CCS swells 4-8 folds in 10 sec. The cellulose derivative swells in two dimensions readily[18]. In tablet formulations, it may be used in both direct compression and wet granulation processes. Sodium starch glycolate was chosen because of its high swelling capacity[19]. The concept of formulating fast dissolving tablets (FDT) of Enalapril maleate (used to reduce the blood pressure immediately) using co-processed superdisintegrants helps to increase the water uptake with shortest wetting time and thereby decrease the disintegration time of the tab-lets by simple and cost effective direct compression technique. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets [20-22].

MATERIALS AND METHOD

Materials:

Enalapril Maleate was procured from Aarti Scientific Company Old Puna Naka, Murarji Peth, Solapur (MS). CCS, SSG and CP were procured as a gift sample from Maruti Chem., Ahmadabad. Mannitol, MCC, aspartame, talc and magnesium stearate purchased from S.D. Fine chem., Mumbai. All other materials were of analytical reagent grade. All other materials used were of pharmaceutical grade.

Drug-excipients compatibility studies:

FT-IR spectroscopy was used to investigate the probability of chemical interactions between ingredients of optimized formulae using infrared spectrophotometer: Shimadzu IR- 435, Kyoto, Japan. The scanning was performed within a wave number of 4,000–500 cm^{-1}.

Preparation of Co-processed Superdisintegrants:

The co-processed superdisintegrants were prepared by solvent evaporation method. A blend of Crospovidone and Croscarmellose sodium (in the ratio of 1:1, 1:2 & 1:3) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of ethanol evaporated. The wet coherent mass was granulated through # 44-mesh sieve. The wet granules were dried in a hot air oven at 60º C for 20 min. The dried granules were sifted through # 44-meshsieve and stored in airtight container till further use. The compositions of the tablets were given in Table 1.

Table 1: Composition of Enalapril Maleate FDT Tablets by co-process method (weight in mg)

FC	PM1	PM2	PM3	CP4	CP5	CP6
EM	10	10	10	10	10	10
[CCS+CP]	6	6	6	6	6	6
MCC	40	40	40	40	40	40
Talc	3	3	3	3	3	3
Pine apple flavour	2	2	2	2	2	2
Aspartame	3	3	3	3	3	3
Mg stearate	2	2	2	2	2	2
Mannitol	134	134	134	134	134	134
Total wt(mg)	200	200	200	200	200	200

FC-Formulation code, EM-Enalapril Maleate, PM-Physical Mixture of Crospovidone and Croscarmellose sodium in different ratios (1:1, 1:2, 1:3), CP-Co-processed Superdisintegrants of Crospovidone and Croscarmellose sodium in different ratios (1:1, 1:2, 1:3)CP - Crospovidone, CCS- Croscarmellose sodium.

Evaluation of Enalapril Maleate tablets:

Micromeritic properties of powder blend of tablets before compression: the prepared tablet blends are evaluated for different tests like angle of repose, apparent bulk density, tapped density, percent compressibility and Hausner ratio,

Evaluation of Enalapril Maleate Fast Disintegrating Tablets[23-26]:

The prepared tablets were evaluated for hardness, weight variation, friability, disintegration time, wetting time, drug content, *in-vitro* dissolution studies, and stability studies. Pfizer hardness tester was used for the determination of the hardness of tablets. Tablet was placed in contact between the

plungers, and the handle was pressed, the force of the fracture was recorded. The thickness and diameter of 4 tablets (2 tablets from each batch) were recorded during the process of compression using calipers (Mitotoyo; Japan). The friability of tablets was determined using Roche friabilator (Cambel Electronics, Mumbai, India). Two tablets were accurately weighed and placed in the friabilator and operated for 100 revolutions. The tablets were dedusted and reweighed. Percentage friability was calculated using the following formula.

$F = (1- W0 / W) \times 100$

Where,

W0 is the weight of the tablets before the test and

W is the weight of the tablet after the test.

Six tablets were tested from each formulation. Friability values below 1% are generally acceptable. The drug Content uniformity were performed by selected ten tablets were randomly, weighed and finely powdered and quantity of powder equivalent to one tablet was added to 100 ml 0.1N HCl in a conical flask. Conical flasks were placed on a rotary shaker. An aliquot of solution was centrifuged and supernatant was filtered through a 0.22µ filter. Absorbance of the resulted supernatant solution was measured using U.V Visible spectrophotometer at a wavelength of 205nm against 0.1N HCl as blank. Concentrations were calculated with the help of standard graph and total amount present in the formulation was calculated.

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A water-soluble dye phenolphthalein was added to the petridish. The dye solution is used to identify the complete wetting of the tablet surface (Abdelbary et al, 2009). A tablet was carefully placed on the surface of tissue paper in the petri dish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in replicates (n=6). The wetting time was recorded using a stopwatch. Disintegration time is considered to be one of the important criteria in selecting the best formulation. Disintegration time was also measured using a modified disintegration method (n=6). For this purpose, a petri dish (10 cm diameter) was filled with 10 ml 6.8 pH phosphate buffer. The tablet was carefully put in the center of the petri dish and the time for the tablet to completely disintegrate into fine particles was noted using a stop watch.

Dissolution rate[27] was studied by using USP type-II apparatus (USP XXIII Dissolution Test Apparatus at 50 rpm) using 900ml of 6.8 pH phosphate buffer as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C, aliquot of dissolution medium was withdrawn at every 1 min. interval and filtered. The absorbance of filtered solution

was measured by UV spectrophotometric method at 205nm and concentration of the drug was determined from standard calibration curve.

Stability studies[28-29]:

The present study, stability studies were carried out as per ICH guidelines at 25°C/ 60% and 40±C / 75 % RH for a specific time period up to 3 months for the selected formulations.

RESULTS AND DISCUSSION

Drug-excipients compatibility studies:

The FT-IR spectra of pure drug Enalapril Maleate and Enalapril Maleate with CP and CCS were showed same characteristic absorption bands at or near that of Enalapril Maleate absorption bands values indicating that there was no chemical and physical change in the functional groups present in Simvastatin. [Shown in Figure 1].

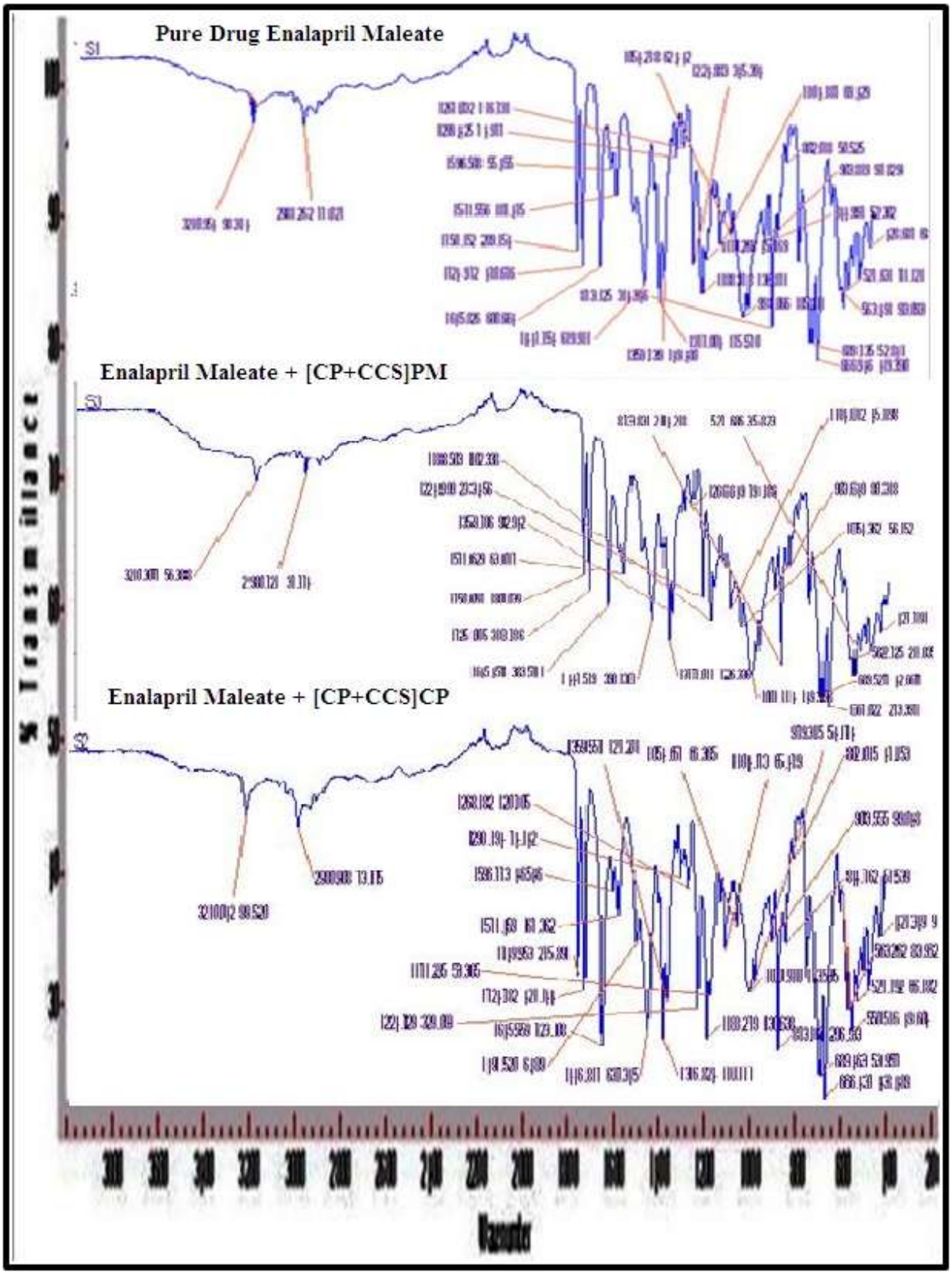

Figure 1: FTIR spectra of Pure drug Enalapril Maleate and Drug+[CP+CCS]PM, Drug+[CP+CCS]CP .

Co-processed superdisintegrants were prepared by solvent evaporation using CP with CCS, and CP with SSG in different ratios (1:1, 1:2, and 1:3). The co-processed superdisintegrants were evaluated for their flow and compression properties in comparison with physical mixture of superdisintegrants. The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property (Table 2). All the post compressional parameter are evaluated were prescribed limits and results were within IP acceptable limits. Results were shown in (Table 3).

Table 2: Pre-compression parameters of Enalapril Maleate FDT by co-processed Superdisintegrant method:

FC	Bulk density(g/cc) ± SD, n=3	Tapped density (g/cc) ± SD, n=3	Angle of repose (degree) ± SD, n=3	Carr's index (%) ± SD, n=3	Hausner's Ratio ± SD, n=3
PM1	0.42 ± 0.06	0.512 ± 0.01	23.19 ± 1.27	14.00 ± 1.23	1.28 ± 0.03
PM2	0.39 ± 0.06	0.51 ± 0.01	25.28 ± 1.19	13.95 ± 1.02	1.28 ± 0.02
PM3	0.41± 0.06	0.513 ± 0.01	27.20 ± 1.30	15.82 ± 1.03	1.27 ± 0.03
CP4	0.38 ± 0.06	0.504 ± 0.02	25.14 ± 1.01	14.21 ± 1.25	1.29 ± 0.03
CP5	0.40 ± 0.06	0.498 ± 0.01	28.56 ± 1.45	13.25 ± 1.36	1.24 ± 0.03
CP6	0.44 ± 0.06	0.508 ± 0.02	26.41 ± 1.56	13.21 ± 1.29	1.23 ± 0.03

*FC= Formulation code; F1-F9= Formulations of direct compression method; PM1-PM3 and CP4-CP6; Formulations prepared by co-processed superdisintegrants method.

Table 3: Post compression parameters of Enalapril Maleate tablets prepared by physical mixture and co-process method:

FC	Hardness ($kg/cm^{2)}$	Friability (%)	Weight variation*	*In vitro* disintegration time*	Wetting time* (sec)	Water absorption ratio* ± SD	Drug Content* (%) ± SD
PM1	3.42 ± 0.17	0.65 ± 0.10	198.12 ± 0.23	76.32 ± 1.2	69.11 ± 1.37	52.1 ± 1.52	97.46± 1.4
PM2	3.34 ± 0.23	0.74± 0.10	197.24 ± 0.56	62.16 ± 1.4	54.23 ±1.53	60.32 ± 1.33	95.26± 1.2
PM3	3.22 ± 0.27	0.69 ± 0.09	199.14 ± 0.45	49.44 ± 1.6	98.12 ±1.54	62.66 ± 1.95	98.48± 0.6
CP4	3.12 ± 0.14	0.41 ± 0.09	200.10 ± 0.55	42.23 ± 0.6	87.15 ±1.35	54.03 ± 1.66	97.76 ± 1.2
CP5	3.00 ± 0.15	0.52 ± 0.06	198.24 ± 0.34	55.26 ± 1.2	76.2 ± 1.23	45.72 ± 1.3	95.24 ± 0.8
CP6	3.12 ± 0.23	0.47 ± 1.2	200.14 ± 0.45	65.86 ± 1.2	84.23 ± 2.09	59.62 ± 1.43	99.28 ± 0.6

In all the formulations, the hardness of all the tablets prepared by co-processed superdisintegrants method ranges from 3.00 to 3.42 kg/cm^2 in co-processed superdisintegrants method. The friability range is 0.41 to 0.74% to be well within the approved range (<1%) indicated that tablet had good mechanical resistance. The weight variation was found in all designed formulations in the range 197.24 to 200.14 mg. All the tablets passed weight variation test as the average percentage weight variation was within 7.5% i.e.in the pharmacopoeia limits. The mean hardness, friability, weight variation test results are tabulated in table 3.

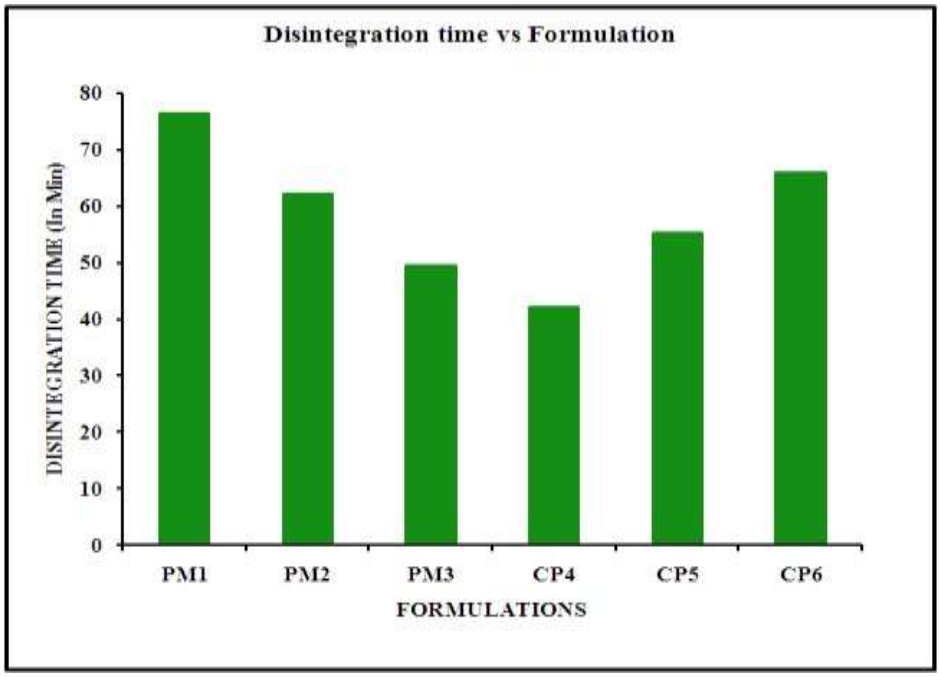

Figure 2: Disintegration time vs Formulation (PM1-CP6) Physical mixture and Co-process Method

The in-vitro disintegration time is measured by the time taken to undergo uniform disintegration. Rapid disintegration within several minutes was observed in all the formulations. Based on the *in-vitro* disintegration time and dissolution studies formulation CP4 was found to be promising and showed a disintegration time of 42 sec. Formulation CP4 shows 99% drug released within 20 min. Disintegrating study showed that the disintegrating times (Figure 2 and Table 3) of the tablets decreased with increase in the concentration of CCS, CP. At particular concentration of CCS and CP increases also increase the disintegration time. Wetting time is closely related to the inner structure of the tablet. The results of wetting time are shown in Table 3. The wetting time of Enalapril Maleate tablets prepared by co-processed method were found to be in the range of 54.23 to 98.12 sec. The water absorption ratio in the range 46.32 to 86.62%. The percentage drugs content of the tablets were found to be between 95.26 to 99.28% of Enalapril Maleate. The results

were within the range and that indicated uniformity of mixing. The wetting time, water absorption ratios and drug content results were tabulated in the Table 3.

***In-vitro* dissolution studies:**

The dissolution of Enalapril Maleate from the tablets is shown in (Figure 3-4) for co-process methods. These values changed with change of method of preparation of tablets. Crosspovidone and CCS containing tablets rapidly exhibit high capillary activity and pronounced hydration with a little tendency to gel formation and disintegrate the tablet rapidly. The formulations prepared by co-processed superdisintegrants showed rapid % drug release due to fast disintegration of tablets. The formulation CP4 shows 99% drug released within 20 min. Based on the *in-vitro* disintegration time and dissolution studies formulation CP4 was found to be promising and showed a disintegration time of 42 sec. Formulation CP4 shows 99% drug released within 20 min.

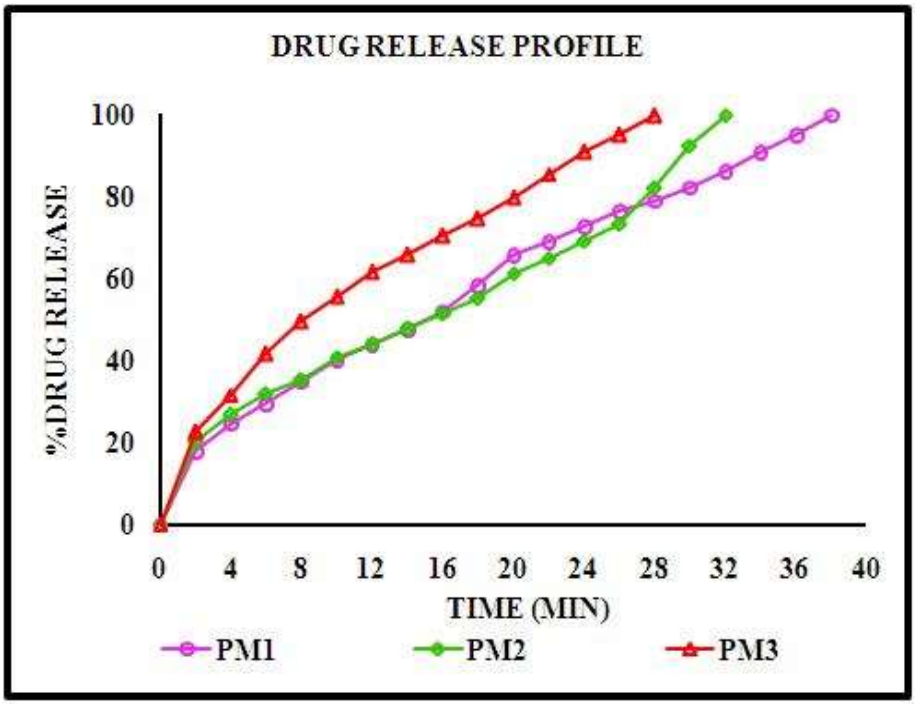

Figure 3: Release profile of formulation containing physical mixture (PM1-PM3)

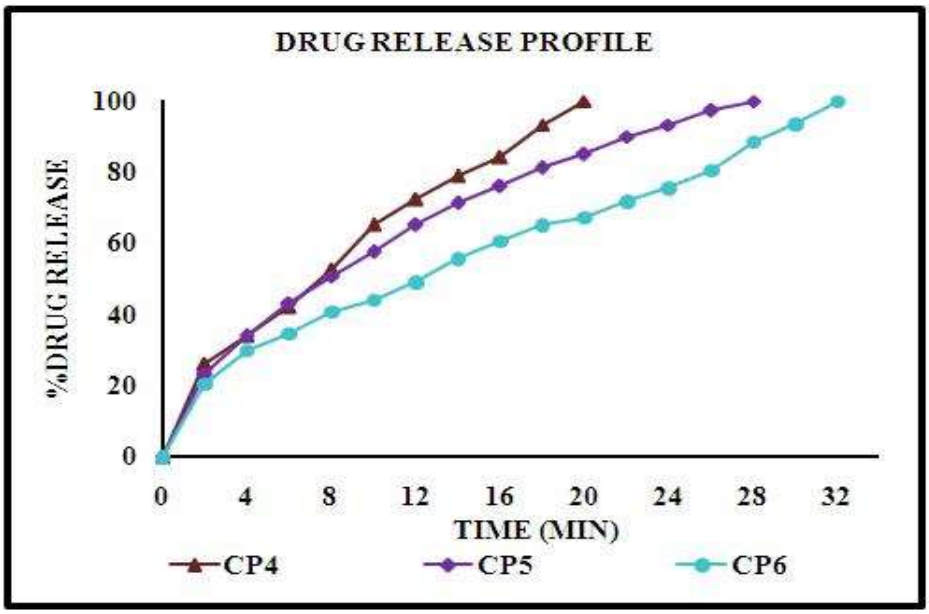

Figure 4: Release profile of formulation containing Co-processed superdisintegrants (CP4-CP6)

The promising formulations were subjected to short term stability study by storing the formulations at 25°C/65% and 40°C/75% RH up to three month. The optimized formulations PM3 and CP4 were selected. After three month the tablets were again analyzed for the hardness, friability, drug content uniformity and disintegration time. The increase in the disintegration time was observed in case of tablets prepared with direct compression method. This may be due to increase in the hardness of the tablets during storage. No change was observed in the hardness, and friability of tablets prepared by direct compression, physical mixture and co-processed technique.

Table 4: Result for stability study for 3 months.

Sl. No.	Formulation code	Month	Hardness Kg/cm²	Percentage Friability	Dispersion time (sec)
25°C/60% RH					
1	**PM3**	**1st**	3.34	0.74	18.08
		2nd	3.46	0.73	18.22
		3rd	3.58	0.75	18.56
2	**CP4**	**1st**	3.22	0.69	12.06
		2nd	3.42	0.68	12.12
		3rd	3.32	0.69	12.54
40°C/75% RH					
3	**PM3**	**1st**	3.34	0.74	18.08
		2nd	3.46	0.73	18.22
		3rd	3.58	0.75	18.56
4	**CP4**	**1st**	3.22	0.69	12.06
		2nd	3.42	0.68	12.12
		3rd	3.32	0.69	12.54

CONCLUSION:

Enalapril maleate tablets containing co-processed superdisintegrants exhibit quick disintegration and improved drug dissolution. It can be concluded from the present work that co-processed superdisintegrants of CP+CCS Superior to Physical mixture of superdisintegrants used in Enalapril maleate fast dissolving tablets. Based on the *in-vitro* disintegration time and dissolution studies formulation CP4 was found to be promising and showed a disintegration time of 42 sec. Formulation CP4 shows 99% drug released within 20 min. Thus Results showed that the direct compression technique by using co-processed superdisintegrants successfully used for enhancing the solubility of Enalapril maleate.

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