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DEVELOPMENT AND ASSESSMENT OF RAPID-DISSOLVING ENALAPRIL MALEATE TABLETS UTILIZING CO-PROCESSED SUPER DISINTEGRANTS

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ABSTRACT

Enalapril maleate, a maleate salt of the amino acid derivative enalapril, functions as an angiotensin-converting enzyme (ACE) inhibitor. This medication effectively lowers blood pressure by diminishing peripheral vascular resistance without significantly impacting cardiac output, heart rate, or contractility. It is particularly beneficial for treating all grades of essential hypertension, especially in patients with diabetes and chronic renal conditions such as glomerulosclerosis. Additionally, enalapril maleate is indicated for managing heart failure. With a half-life of approximately 11 hours, the bioavailability of enalapril maleate tablets is around 55%, and food intake does not significantly influence absorption. To enhance the formulation of fast-dissolving tablets (FDT) of enalapril maleate, a study was conducted using the direct compression technique with co-processed superdisintegrants, specifically Crospovidone and Croscarmellose sodium, in various ratios. The formulated tablets were evaluated for essential pharmaceutical properties, including hardness, friability, weight variation, and drug content, alongside in-vitro dissolution profiles. The findings indicated that employing the direct compression method with co-processed superdisintegrants significantly improved the solubility of enalapril maleate. Characterization through Fourier Transform Infrared Spectroscopy (FTIR) confirmed the integrity of the drug within the formulations. The results for hardness, friability, weight variation, and drug content adhered to the specifications outlined in the Indian Pharmacopoeia (I.P).Tablets containing Crospovidone and Croscarmellose sodium exhibited rapid disintegration and enhanced capillary action, resulting in quick drug release. Notably, formulations SB 3 and CPS 6 achieved 99% drug release within 20 minutes. Stability studies further indicated no significant changes in physical properties, hardness, drug content, or in-vitro dissolution profiles, confirming the stability of the formulations. In summary, the direct compression technique utilizing co-processed superdisintegrants proved effective in enhancing the solubility and overall performance of enalapril maleate tablets.

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

INTRODUCTION

Enalapril maleate is the maleate salt of enalapril, derived from the amino acids L-alanine and L-proline. As an angiotensin-converting enzyme (ACE) inhibitor, it effectively lowers blood pressure by decreasing peripheral vascular resistance without significantly affecting cardiac output, heart rate, or contractility. Enalapril is indicated for all forms of essential hypertension, particularly in patients with diabetes and chronic renal conditions such as glomerulosclerosis, and it is also utilized in treating heart failure. With a half-life of about 11 hours, enalapril maleate has a bioavailability of approximately 55%, and its absorption remains unaffected by food intake[1,2,3].

In light of these characteristics, a new formulation of enalapril maleate tablets was developed using a direct compression method to facilitate a faster onset of action for immediate blood pressure reduction. The emergence of fast-dissolving drug delivery systems (FDDS) is driven by the need for more convenient medication administration. These dosage forms can disintegrate or dissolve in saliva, allowing for quick release of the active ingredient. Fast-dissolving tablets are particularly beneficial for patients such as children, the elderly, bedridden individuals, or those with difficulties in swallowing traditional tablets, thereby enhancing therapeutic efficacy[4,5].

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Many oral pharmaceutical forms require water for swallowing or are intended for chewing, whereas some are designed for absorption in the mouth (e.g., sublingual or buccal tablets). Fast-dissolving tablets have been developed to address the challenges associated with conventional dosage forms, offering advantages in hardness, uniformity, stability, and ease of administration, making them suitable for a wide range of patients, including the elderly and those on the go[6]. Recent advancements in drug delivery systems aim to improve the safety and efficacy of medications by creating user-friendly dosage forms that enhance patient compliance. One such innovation is the formulation of fast-dissolving tablets (FDT). The co-processing of excipients has gained interest as a method to enhance their functionality. This technique involves the interaction of two or more excipients at a sub-particle level to create a synergistic effect that improves their properties and masks undesirable characteristics. Co-processed excipients can result in granules with superior qualities compared to physical mixtures, such as improved flow, compressibility, and uniformity in filling weight[7,8].

Several co-processed superdisintegrants are available commercially, including Ludipress (a blend of lactose monohydrate, polyvinyl pyrrolidone, and Crospovidone), Starlac (lactose and maize starch), and others. Among the commonly used superdisintegrants, Crospovidone (CPS), Croscarmellose sodium (CCS), and sodium starch glycolate (SSG) are notable for their effectiveness. CPS is selected for its high capillary action and pronounced hydration capacity, exhibiting minimal gel formation. Croscarmellose sodium swells significantly within seconds, enhancing its disintegrating capability in both direct compression and wet granulation processes.

Sodium starch glycolate was chosen for its high swelling potential[9,10,11,12,13]. The formulation of fast-dissolving tablets (FDT) of enalapril maleate utilizing co-processed superdisintegrants aims to enhance water uptake and reduce disintegration time, employing the straightforward and cost-effective direct compression technique. The primary benefits of direct compression include lower manufacturing costs and greater mechanical strength of the resulting tablets.

MATERIALS AND METHOD

Materials[14,15,16,17,18,19,20]:

Enalapril Maleate was procured from Aarti Scientific Company Old Puna Naka, Murarji Peth, Solapur (MS). CCS, SSG and CPS were procured as a gift sample from Maruti Chem., Ahmadabad.Mannitol,MCC,aspartame,talcandmagnesiumstearatepu rchasedfromS.D.Finechem.,Mumbai. All other materials were of analytical reagent grade. All other materials used were of pharmaceutical grade.

Drug-excipients compatibility studies:

Fourier Transform Infrared (FT-IR) spectroscopy was employed to assess potential chemical interactions among the components of the optimized formulations. The analysis was conducted using a Shimadzu IR-435 infrared spectrophotometer from Kyoto, Japan. Scanning was performed across a wave number range of 4,000 to 500 cm^{-1}.

Preparation of Co-processed Superdisintegrants:

The co-processed superdisintegrants were synthesized using the solvent evaporation technique. A mixture of Cross povid one and Cross carmellose sodium in varying ratios (1:1, 1:2, and 1:3) was dissolved in 10 ml of ethanol. The contents in a 250 ml beaker were mixed thoroughly, and stirring continued until the majority of the ethanol had evaporated. The resulting wet mass was then granulated using a #44 mesh sieve. Following granulation, the wet granules were dried in a hot air oven at 60ºC for 20 minutes. Once dried, the granules were passed through a #44 mesh sieve again and stored in an airtight container for later use. The tablet compositions are presented in Table 1.

Table 1: Composition of Enalapril Maleate FDT Tablets by Co-Processed Super Disintegrate (weightinmg)

FC	SB1	SB2	SB3	CPS4	CPS5	CPS6
EM	10	10	10	10	10	10
[CCS+CPS]	6	6	6	6	6	6
MCC	40	40	40	40	40	40
Talc	3	3	3	3	3	3
Pineappleflavour	2	2	2	2	2	2
Aspartame	3	3	3	3	3	3
Mgstearate	2	2	2	2	2	2
Mannitol	134	134	134	134	134	134
Total wt (mg)	**200**	**200**	**200**	**200**	**200**	**200**

FC refers to the formulation code, while EM stands for Enalapril Maleate. SB indicates the Single Blendof Crospovidone and Croscarmellose sodium in various ratios (1:1, 1:2, and 1:3). CPS represents the co-processed superdisintegrants composed of Crospovid one and Croscarmellose sodium in those same ratios.

CPS specifically denotes Crospovidone, while CCS refers to Croscarmellose sodium. the formulation of superdisintegrants used in pharmaceutical applications, specifically for enhancing the disintegration of tablets or powders in a dosage form[21,22,23].

CP vs. CCS: CP specifically refers to Crospovidone, while CCS denotes Croscarmellose sodium. These two substances have different mechanisms of action as disintegrants, which means their combination can provide synergistic effects in tablet disintegration[24,25].

Evaluation of Enalapril Maleate tablets[26,27,28,29]:
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[30]:

The prepared tablets underwent a comprehensive evaluation for various parameters, including hardness, weight variation, friability, disintegration time, wetting time, drug content, in-vitro dissolution studies, and stability studies. The hardness of the tablets was assessed using a Pfizer hardness tester, where each tablet was placed between the plungers, and pressure was applied until fracture occurred. The force required for this fracture was recorded.

During the compression process, the thickness and diameter of four tablets (two from each batch) were measured using callipers (Mitutoyo; Japan). The friability of the tablets was determined using a Roche friabilator (Cambel Electronics, Mumbai, India). Two accurately weighed tablets were placed in the friabilator and subjected to 100 revolutions. Afterward, the tablets were dusted off and reweighed. The percentage of friability was calculated using the following formula.

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

Were,

W0 is the weight of the tablets before the test and W is the weight of the tablet after the test.

A total of six tablets were evaluated from each formulation. Generally, friability values below 1% are considered acceptable. For the assessment of drug content uniformity, ten tablets were randomly selected, weighed, and finely powdered. An amount of powder equivalent to one tablet was then dissolved in 100 ml of 0.1N hydrochloric acid in a conical flask. These flasks were placed on a rotary shaker. An aliquot of the solution was centrifuged, and the supernatant was filtered through a 0.22 µm filter. The absorbance of the resulting solution was measured using a UV-visible spectrophotometer at a wavelength of 205 nm, with 0.1N hydrochloric acid as the blank. The concentrations were calculated using a standard calibration curve to determine the total drug content in the formulation.

To assess wetting time, a piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of water. A water-soluble dye, phenolphthalein, was added to the dish to visualize complete wetting of the tablet surface. A tablet was gently placed on the tissue paper, and the time taken for the water to reach the upper surface and fully wet the tablet was recorded. To ensure reproducibility, this measurement was performed in triplicate (n=6), using a stopwatch for accuracy[33].

Disintegration time, a critical parameter for evaluating formulation effectiveness, was determined using a modified disintegration method (n=6). A petri dish with a diameter of 10 cm was filled with 10 ml of 6.8 pH phosphate buffer. The tablet was positioned in the centre, and the time required for it to completely disintegrate into fine particles was noted with a stopwatch. The dissolution rate was examined using a USP type II dissolution apparatus (USP XXIII) operating at 50rSB, with 900 ml of 6.8 pH phosphate buffer as the dissolution medium. The temperature was maintained at 37±0.5°C. Aliquots of the dissolution medium were withdrawn at one-minute intervals, filtered, and the absorbance of the filtered solution was analysed using UV spectrophotometry at 205 nm to quantify the drug concentration based on a standard calibration curve.

Stability studies[34,35]:

The present study, stability studies were carried out as per ICH guideline sat 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 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 Sim vastatin.[Shown in Figure1].

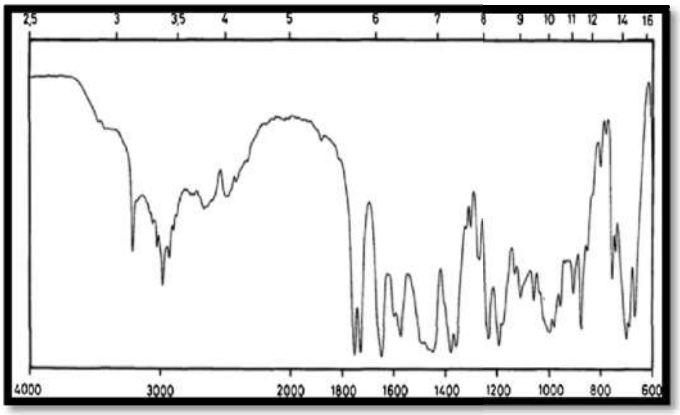

Figure 1: FTIR spectra of Pure drug Enalapril Maleate

Co-processed superdisintegrants were prepared via the solvent evaporation method, utilizing Crospovidone (CPS) with Croscarmellose sodium (CCS) and CPS with Sodium Starch Glycolate (SSG) in various ratios (1:1, 1:2, and 1:3). The co-processed superdisintegrants were assessed for their flow and compression characteristics, comparing them to the physical mixtures of the superdisintegrants. The pre-compression parameters evaluated fell within the acceptable limits, demonstrating favourable flow properties (see Table 2). All post-compression parameters were also evaluated and were found to meet the standards set by the Indian Pharmacopoeia (IP), as presented in Table 3.

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

FC	Bulkdensity(g/cc)	Tapped density(g /cc)	Angle of repose(de gree)	Carr'sinde x(%)	Hausner's Ratio
	±SD,n=3	±SD,n=3	±SD,n=3	±SD,n=3	±SD,n=3
SB1	0.42 ± 0.06	0.512 ± 0.01	23.19 ± 1.27	14.00 ± 1.23	1.28 ± 0.03
SB2	0.39 ± 0.06	0.51 ± 0.01	25.28 ± 1.19	13.95 ± 1.02	1.28 ± 0.02
SB3	0.41± 0.06	0.513 ± 0.01	27.20 ± 1.30	15.82 ± 1.03	1.27 ± 0.03
CP S4	0.38 ± 0.06	0.504 ± 0.02	25.14 ± 1.01	14.21 ± 1.25	1.29 ± 0.03
CP S5	0.40 ± 0.06	0.498 ± 0.01	28.56 ± 1.45	13.25 ± 1.36	1.24 ± 0.03
CP S6	0.44 ± 0.06	0.508 ± 0.02	26.41 ± 1.56	13.21 ± 1.29	1.23 ± 0.03

* FC= Formulation code; Formulation by direct compression method; SB1-SB3 and CPS4-CPS6; Formulations prepared by co-processed super disintegrates method.

Table 3: Post compression parameters of Enalapril Maleate tablets prepared by Single Blended Co-Processed Super Disintegrate:

FC	Hardness (kg/cm$^{2)}$	Friability (%)	Weight variation*	*Invitro* disintegrationtime*	Wettingtime* (sec)	Waterabsorption ratio*±SD	DrugContent* (%)±SD
SB1	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
SB2	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
SB3	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
CPS4	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
CPS5	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
CPS6	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 formulations, the hardness of the tablets produced using the co-processed superdisintegrant method ranged from 3.00 to 3.42 kg/cm². The friability values varied between 0.41% and 0.74%, which is well within the acceptable limit of less than 1%, indicating that the tablets possess good mechanical strength. The weight of the tablets in each formulation ranged from 197.24 mg to 200.14 mg. All tablets met the weight variation criteria, with the average percentage weight variation falling within the pharmacopoeial limit of 7.5%. The overall mean values for hardness, friability, and weight were satisfactory. variation test results are tabulated in table 3.

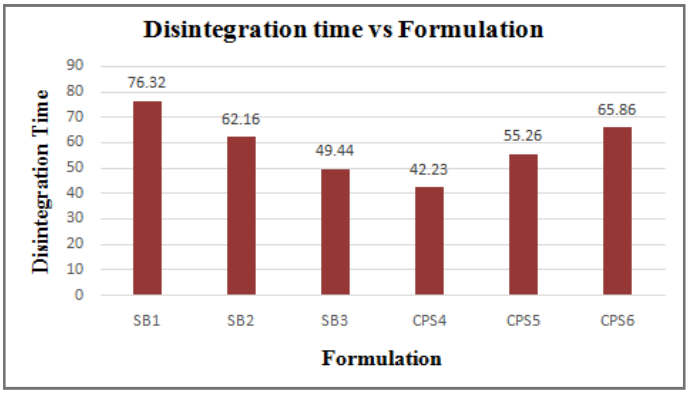

Figure 2: Disintegration time vs. Formulation (SB1-CPS6) Single Blend and Co-Processed Super Disintegrate

The in-vitro disintegration time was assessed by measuring the duration required for uniform disintegration of the tablets. All formulations demonstrated rapid disintegration, occurring within a few minutes. Notably, formulation CPS4 emerged as the most promising, exhibiting a disintegration time of just 42 seconds, and achieving 99% drug release within 20 minutes. The disintegration study indicated that as the concentration of Croscarmellose sodium (CCS) and Crospovidone (CPS) increased, the disintegration time decreased (see Figure 2 and Table 3). However, at certain concentrations, an increase in CCS and CPS led to longer disintegration times.

Wetting time, which is closely related to the internal structure of the tablet, varied among formulations. The wetting time for the Enalapril Maleate tablets prepared using the co-processing method ranged from 54.23 to 98.12 seconds. The water absorption ratio was found to be between 46.32% and 86.62%. Additionally, the drug content of the tablets ranged from 95.26% to 99.28% for Enalapril Maleate, indicating a uniform mixing process. The results for wetting time, water absorption ratios, and drug content are summarized in Table 3.

***In-vitro*d is solution studies:**

The dissolution profiles of Enalapril Maleate from the tablets prepared using co-processing methods are illustrated in Figures 3 and 4. These profiles varied depending on the tablet preparation method. Tablets containing Crospovidone and Croscarmellose sodium exhibited significant capillary activity and enhanced hydration, with minimal gel formation, leading to rapid disintegration. The formulations utilizing co-processed superdisintegrants demonstrated swift drug release rates due to their quick disintegration properties. Notably, formulation CPS4 achieved 99% drug release within 20 minutes and had a disintegration time of just 42 seconds, making it the most promising candidate based on the in-vitro disintegration and dissolution study results.

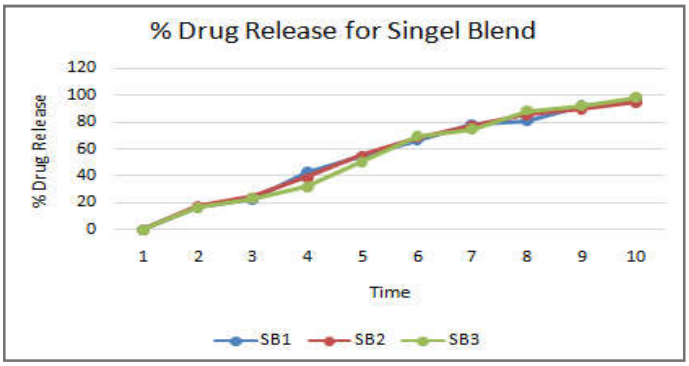

Figure 3: Release profile of formulation Single Blend (SB1-SB3)

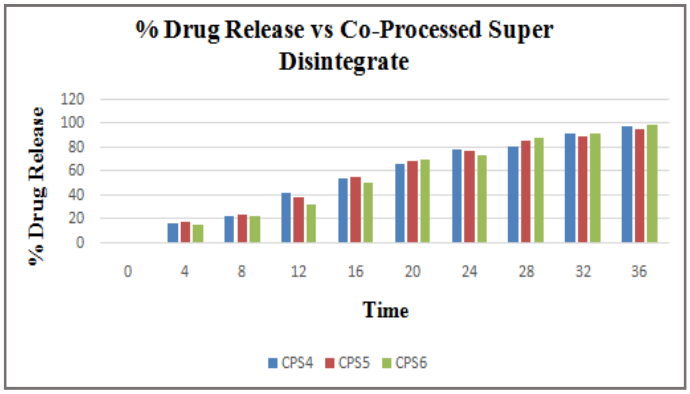

Figure 4: Release profile of formulation Co-processed super disintegrants (CPS4-CPS6)

The most promising formulations were evaluated through a short-term stability study, which involved storing them at 25°C with 65% relative humidity and at 40°C with 75% relative humidity for a period of three months. The optimized formulations selected for this study were SB3 and CPS4. After three months, the tablets were re-evaluated for hardness, friability, drug content uniformity, and disintegration time. An increase in disintegration time was noted for tablets prepared using the direct compression method, likely due to an increase in tablet hardness during storage. However, no significant changes were observed in the hardness and friability of tablets prepared by direct compression, physical mixing, or the co-processing technique.

Table 4: Result for stability study for 3 months.

SL.NO	Formulation code	Month	Hardness Kg/cm²	PercentageFriability	Dispersiontime (sec)
			25°C/60%RH		
1	SB3	1st	3.34	0.74	18.08
		2nd	3.46	0.73	18.22
		3rd	3.58	0.75	18.56
2	CPS4	1st	3.22	0.69	12.06
		2nd	3.42	0.68	12.12
		3s	3.32	0.69	12.54
			40°C/75%RH		
3	SB3	1st	3.34	0.74	18.08
		2nd	3.46	0.73	18.22
		3rd	3.58	0.75	18.56
4	CPS4	1st	3.22	0.69	12.06
		2nd	3.42	0.68	12.12
		3rd	3.42	0.69	12.54

CONCLUSION

Enalapril maleate tablets formulated with co-processed superdisintegrants demonstrate rapid disintegration and enhanced drug dissolution. This study concludes that the combination of Crospovidone and Croscarmellose sodium (CPS+CCS) is superior to the Single Blend of superdisintegrants used in the fast-dissolving tablets of Enalapril maleate. Formulation CPS4 emerged as the most promising, exhibiting a disintegration time of just 42 seconds and achieving 99% drug release within 20 minutes. These results indicate that the direct compression technique, utilizing co-processed superdisintegrants, effectively improves the solubility of Enalapril maleate.

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