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FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS ENALAPRIL MALEATE USING DIFFERENT SUPERDISINTEGRANTS

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ABSTRACT

Enalapril maleate is a prodrug that is rapidly metabolized by liver esterases to enalaprilat following oral administration. Enalapril maleate lowers the blood pressure by antagonizing the effect of the RAAS. (Renin angiotensin system). It stimulates the secretion of aldosterone from the adrenal cortex. In the present study work has been made to prepare, formulate and characterize fast dissolving tablets of enalapril maleate. The tablets of enalapril maleate were formulated by direct compression technique using superdisintegrant like Crospovidone, Sodium starch glycolate and Croscarmellose 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 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 IP Limit. 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. The in-vitro disintegration time of Enalapril Maleate fast dissolving tablets prepared by direct compression, was found to be in the range of 46 to 121 sec in using superdisintegrants method fulfilling the official requirements. The in-vitro disintegration time of Enalapril Maleate prepared by direct compression method F6 formulation containing CCS 6% shows around 46 sec. Based on the *in-vitro* disintegration time, formulation F5 and F6 were found to be promising and showed a disintegration time of 46 and 61.26 sec respectively. CCS 6% and 4% containing tablets rapidly exhibit high capillary activity and pronounced hydration with a little tendency to gel formation and disintegrate the tablet rapidly. The in-vitro drug release showed 99.9% within 20min. The results of stability studies revealed no change in physical appearance, and after three month the tablets were again analyzed for the hardness, friability and disintegration time. No change was observed in the hardness, friability and in-vitro dispersion time of tablets prepared by direct compression technique. Thus Results showed that the direct compression technique by using superdisintegrants successfully used for enhancing the solubility of Enalapril maleate.

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

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. 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] The desired criteria for the FDT they should Have a pleasing mouth feel, Leave minimal or no residue in the mouth after oral administration and not require water to swallow, but it should dissolve or disintegrate in the mouth in a matter of seconds.[14-15] Most commonly used methods to prepare these tablets are; freeze-drying/Lyophilization[16] tablet molding[17] and direct-compression methods.[18] Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets.[19] The main objective of the present research work is Enalapril Maleate fast dissolving tablets were prepared by direct compression method using Sodium starch glycolate, Crosspovidone, Crosscarmellose as superdisintegrants.

MATERIALS AND METHODS

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 Enalapril maleate FDT by direct compression method[20-21]: All the ingredients were passed through the sieve no 60. Drug was geometrically mixed with different dry binders until a homogeneous blend was obtained. Final blend was compressed in to tablets on a 10 station rotary tablet machine using 11.9 mm punch.

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[22-25]: 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[26] 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[27]: 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.

RESULT AND DISCUSSION

Drug-excipients compatibility studies: The FT-IR spectra of pure drug Enalapril Maleate and Formulations F5 and F6 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 Fig 1**].

Powder ready for compression containing drug and various excipients were subjected for pre-compression parameters (Micromeritic properties) to study the flow properties of granules, to achieve uniformity of tablet weight. 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).** Formulations containing only 2% of superdisintegrants shows lower water absorption ratio when compared to formulations containing 6% of superdisintegrants, the water absorption ratio also decrease due to less swelling property. It was observed that as concentrations of CCS increases water absorption ratio increases due to CCS is made by cross- linking reaction of MCC. This cross linking greatly reduced water solubility. While permitting material to swell and absorbs water many times of its weight.

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. The *in-vitro* disintegration data is tabulated in the Table 3 and shown in Fig 1 for direct compression method. The *in-vitro* disintegration time of Enalapril Maleate fast dissolving tablets prepared by direct compression, was found to be in the range of 46 to 121 sec in direct compression method fulfilling the official requirements. The *in-vitro* disintegration time of Enalapril Maleate prepared by direct compression method F6 formulation containing CP 6% shows around 46 sec shown in Fig 1. Based on the *in-vitro* disintegration time, formulation F5 and F6 were found to be promising and showed a disintegration time of 61.26 sec and 46.23 respectively.

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 F5 and F6 were selected. After three month the tablets were again analyzed for the hardness, friability and disintegration time. The negligible increase in the disintegration time was observed in case of tablets prepared with direct compression method. No change was observed in the hardness, and friability of tablets prepared by direct compression technique.

Table 1: Composition of 200mg of Enalapril Maleate Fast Dissolving Tablets by direct compression method.

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	10	10	10	10	10	10	10	10	10
Crospovidone	4	8	12	0	0	0	0	0	0
Croscarmellose sodium	0	0	0	4	8	12	0	0	0
sodium starch glycolate	0	0	0	0	0	0	4	8	12
Aspartame	6	6	6	6	6	6	6	6	6
D-mannitol	120	120	120	120	120	120	120	120	120
MCC	50	50	50	50	50	50	50	50	50
MC	5	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3	3
Mg stearate	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200	200

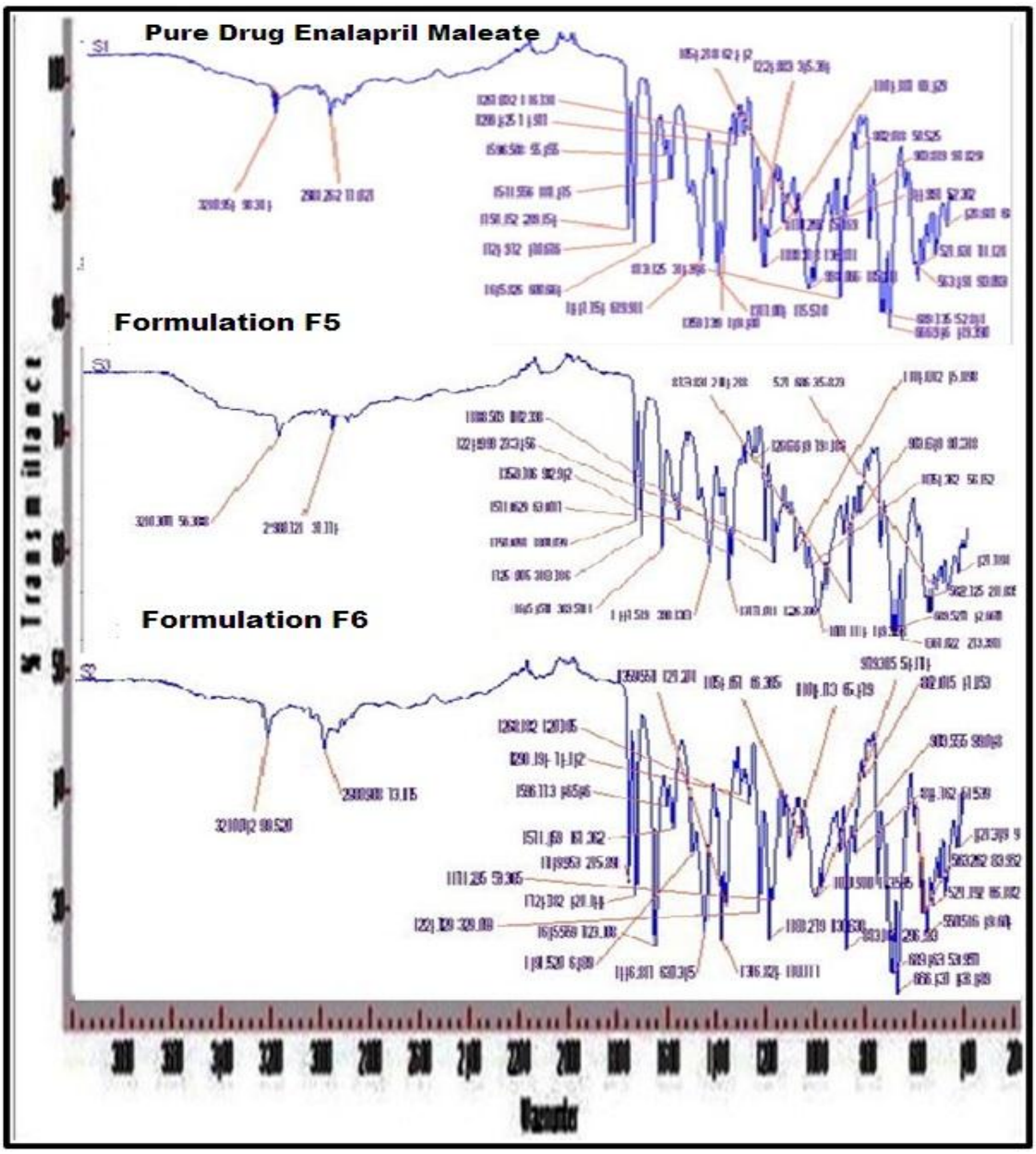

Fig 1: FTIR spectra of Pure drug Enalapril Maleate and Formulation F5 and F6.

Table 2: Pre-compression parameters of Enalapril Maleate fast dissolving tablets by direct compression method 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
F1	0.53 ± 0.03	0.63 ± 0.01	28.19 ± 1.20	15.46 ± 0.25	1.22 ± 0.08
F2	0.52 ± 0.04	0.62 ± 0.02	29.76 ± 0.90	15.24 ± 0.12	1.23 ± 0.10
F3	0.55 ± 0.08	0.64 ± 0.04	28.44 ± 1.10	12.62 ± 0.32	1.13 ± 0.12
F4	0.54 ± 0.02	0.54 ± 0.03	28.84 ± 0.80	14.08 ± 0.14	1.15 ± 0.06
F5	0.51 ± 0.03	0.56 ± 0.02	29.51 ± 0.40	13.73 ± 0.16	1.24 ± 0.06
F6	0.47 ± 0.06	0.59 ± 0.03	28.16 ± 1.30	12.44 ± 0.18	1.23 ± 0.04
F7	0.54 ± 0.04	0.63 ± 0.02	29.66 ± 1.40	15.62 ± 0.14	1.16 ± 0.08
F8	0.45 ± 0.05	0.59 ± 0.03	27.48 ± 0.08	14.48 ± 0.12	1.22 ± 0.02
F9	0.52 ± 0.06	0.58 ± 0.04	26.74 ± 0.12	13.74 ± 0.14	1.26 ± 0.09

***FC= Formulation code;**

Table 3: Post-compression parameters of Enalapril Maleate fast dissolving tablets prepared by direct compression method.

FC	Hardness ($kg/cm^{2)}$ ± SD	Friability (%)	Weight variation* ± SD (mg)	*In vitro* disintegration time* (sec)± SD)	Wetting time* (sec) ± SD	Water absorption ratio* ± S.D	Drug Content* (%) ± SD
F1	3.22 ±0.20	0.59 ±0.10	199.46 ±1.2	90.32 ± 1.2	92.12 ±1.1	52.65 ±1.1	98.46± 1.4
F2	3.34 ±0.06	0.66 ±0.10	198.26 ±1.4	78.16 ± 1.4	91.42±0.8	58.46 ±1.6	97.26± 1.2
F3	3.46 ±0.12	0.68 ±0.09	200.12 ±1.0	63.44 ± 1.6	71.22±0.2	84.41 ±1.2	99.48± 0.6
F4	3.32 ±0.14	0.69 ±0.09	198.68 ±1.2	73.86 ± 1.2	68.31±1.2	86.03 ±0.8	97.76 ±1.2
F5	3.44 ±0.16	0.74 ±0.06	200.32 ±1.4	61.26 ± 1.2	94.42 ±1.4	72.72 ±1.8	98.24 ±0.8
F6	3.32 ±0.14	0.68 ±1.2	197.42 ±0.6	46.23 ± 0.6	86.69 ±1.2	68.62 ±1.4	96.98 ±0.6
F7	3.24 ±0.08	0.58 ±0.10	199.69 ±1.4	121.52 ± 1.4	71.26 ±1.6	56.48 ±1.2	97.68 ±1.2
F8	2.98 ±0.12	0.54 ±0.04	200.44 ±0.6	104.56 ± 1.2	50.32 ±1.0	46.32 ±1.6	99.25 ±1.4
F9	3.32 ±0.14	0.58 ±0.04	200.22 ±1.4	89.42 ± 1.1	92.32 ±1.1	86.62 ±1.2	99.28 ±1.3

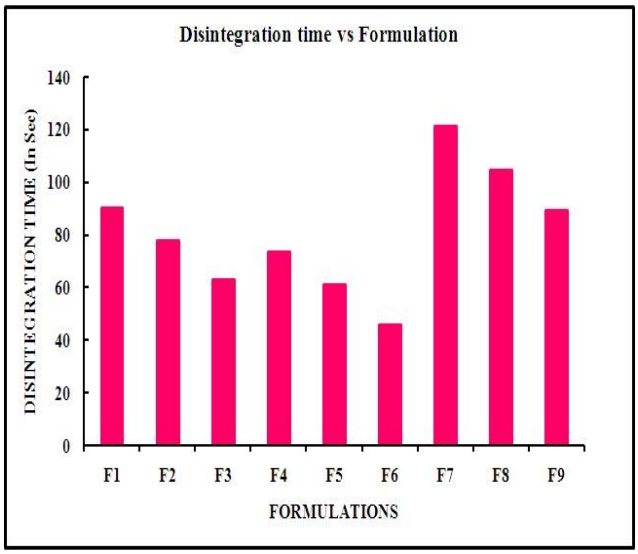

Fig 1: Disintegration time vs Formulation (F1-F9)- Direct Compression Method.

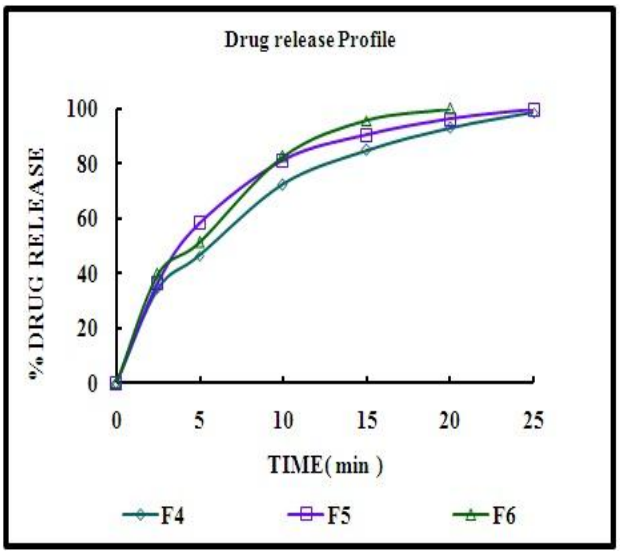

Fig 3: Comparative dissolution profile of Enalapril maleate tablets F4 – F6.

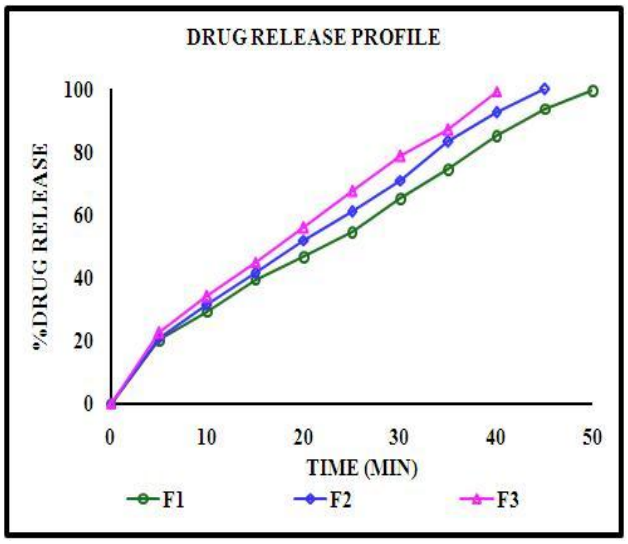

Fig 2: Comparative dissolution profile of Enalapril maleate tablets F1 – F3.

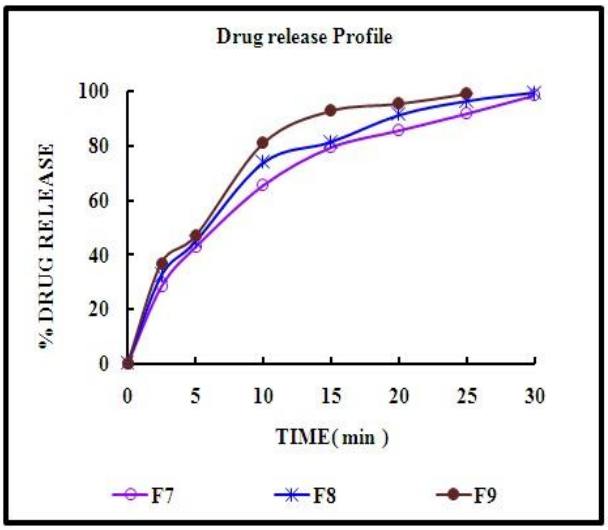

Fig 4: Comparative dissolution profile of Enalapril maleate tablets F7-F9.

Table 4: Result for 25°C/60% RH) and 40°C/75% RH for 3 months.

Sl. No.	Formulation code	Month	Hardness Kg/cm²	Percentage Friability	Dispersion time (sec)
25°C/60% RH					
1	**F5**	**1st**	3.44	0.74	61.26
		2nd	3.52	0.78	61.42
		3rd	3.74	0.82	61.48
2	**F6**	**1st**	3.32	0.68	46.23
		2nd	3.46	0.68	46.14
		3rd	3.68	0.69	46.36
40°C/75% RH					
3	**F5**	**1st**	3.44	0.58	61.26
		2nd	3.62	0.60	61.64
		3rd	3.86	0.59	61.88
4	**F6**	**1st**	3.32	0.68	46.23
		2nd	3.18	0.67	46.56
		3rd	3.24	0.66	46.74

CONCLUSION

Based on the *in-vitro* disintegration time, formulation F5 and F6 were found to be promising and showed a disintegration time of 61.26 sec and 46.23 respectively. Thus Results showed that the direct compression technique by using superdisintegrants successfully used for enhancing the solubility of Enalapril maleate.

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