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FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLET FOR TREATMENT OF HYPERTENSION

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Abstract

Fast dissolving tablet emerged as an alternative to the conventional oral dosage forms to improve the patient compliance. As the two extreme end age group (pediatrics and geriatric) complain about the swallowing of conventional oral solid dosage forms. fast dissolving tablets are solid dosage form containing medicinal substances or active ingredients which disintegrates rapidly within a few seconds when placed up on tongue. In this article the Enalapril Maleate immediate release tablets were prepared using croscarmellose sodium, sodium starch glycolate and crospovidone as super disintegrant separately and by direct compression method. Enalapril Maleate is the maleate salt form of enalapril, a dicarbocyl containing peptide and angiotensin converting enzyme (ACE) inhibitor with antihypertensive activity. The prepared immediate release tablets were evaluated for various parameters like disintegration time, wetting time, drug content, in-vitro drug release study etc. From the result it was observed that among three super disintegrants used, crospovidone showed better result in disintegration time, in-vitro drug release. The formulation of F4 containing crospovidone showed better result in disintegration time 13 sec. and maximum in-vitro drug release of 98.64±1.217 at the end of 20 minutes. F4 formulation is most complies to marketed product so F4 formulation shows better result.

Keywords: Fast dissolving tablet, Direct Compression, Super disintegrants, Mouth Dissolving, Fast dissolving tablet, Evaluation.

Introduction

The concept of a Fast-dissolving Drug Delivery System emerged from the desire to provide patients with more conventional means of taking their medication. Many people find it challenging to swallow pills and firm gelatin capsules. Hence, they do not comply with a prescription, which ends up during a high incidence of non-compliance and ineffective therapy. In some cases, like motion sickness, sudden episodes of allergic attacks or coughing, and unavailability of water, swallowing conventional tablets could also be difficult. Particularly the problem is experienced by pediatric and geriatric patients. Such problems can be resolved by means of a Fast-Dissolving Tablet. When placed on the tongue, this tablet disintegrates instantaneously, releasing the drug, which dissolves or disperses in the saliva. "A solid dosage form containing medicinal substances, which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue," is how the Center for Drug Evaluation and Research defines an oral drug delivery system (ODT). These tablets are not to be confused with traditional buccal, sublingual, or lozenges, which take longer than a minute to dissolve in the mouth. In the literature these also are called orally disintegrating, Orodisperse, Mouth dissolving, Quick dissolving, Fast-melt and rapidly disintegrating tablets, and freeze-dried wafers.

An oral fast-dissolving drug delivery system is a novel tablet dosage form, that dissolves or disintegrates in the oral cavity with a good taste and flavor increasing the acceptability of various bitter drugs without the need for water or chewing and hence called melt in mouth tablets or rapid melts or porous tablets or oro-dispersible or quick-dissolving or rapid disintegrating tablets. FDT also more useful in emergency condition of any patients to fast relief.

Enalapril Maleate is that the maleates salt sort of enalapril, a dicarbocyl containing peptide and angiotensin converting enzyme (ACE) inhibitor with antihypertensive activity. As a prodrug, enalapril is converted by de-estrification into its active form enalaprilat. Enalaprilat competitively binds to and inhibits ACE thereby blocking the conversion of angiotensin I to angiotensin II and result in vasodilation. [1-8]

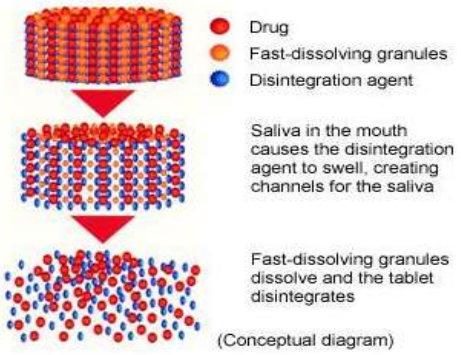

Fig 1: fast dissolving tablets view

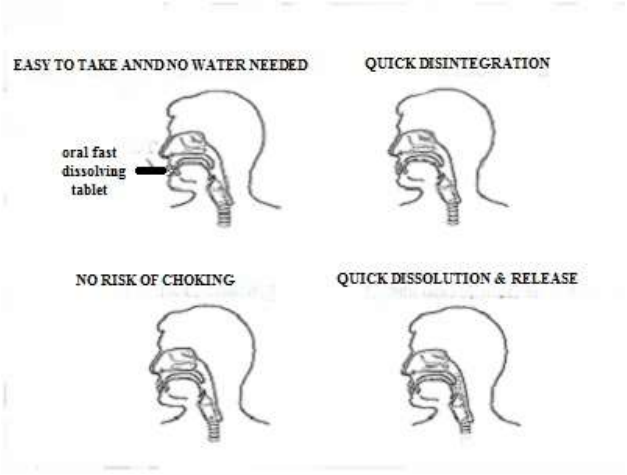

Fig 2: Immediate Release Tablet Overview

Material and Methods:

Materials: Enalapril Maleate was obtained as a gift sample from Kopran Ltd Karjat (Mumbai). Croscarmellose sodium, sodium starch glycolate, Crospovidone and all other ingredients used were of laboratory grade. Crospovidone and Magnesium Sterate were obtained from Pallav chemicals and solvents pvt. Ltd, Tarapur Boisar. Croscarmellose Sodium from Vishal Chem. Mumbai. We bought sodium starch glycolate from Yarrow Chem.Product Mumbai. Microcrystalline Cellulose was from LOBA Chemiepvt. Ltd India. Sodium Saccharin was obtained from Research Lab Mumbai and Talc was from Research Lab POONA.

Formulation of immediate release tablets of enalapril maleate by Direct Compression Method

The fast-dissolving tablet of Enalapril Maleate was prepared by using super disintegrants croscarmellose sodium, sodium starch glycolate, crospovidone at different concentrations by direct compression method as shown in table 1. Enalapril Maleate, super disintegrants, microcrystalline cellulose, magnesium stearate and talc were accurately weighted. All the materials were passed through 60# mesh screen prior to mixing. All the ingredients except magnesium stearate and talc transferred to glass mortar and triturated till uniformly mixed. Then to this mixture talc and magnesium stearate was added. The resulting powder mixture was compressed into tablets by using 8 mm diameter punch on a tablet machine.[9]

Table 1 Formula for fast dissolving Tablet

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Enalapril Maleate	10	10	10	10	10	10	10	10	10
Microcrystalline cellulose	160.8	156.8	152.8	163.8	161.8	159.8	166.8	165.8	164.8

Sodium Starch Glycolate	8	12	16	-	-	-	-	-	-
Crospovidone	-	-	-	5	7	9	-	-	-
Crosscarmellose Sodium	-	-	-	-	-	-	2	3	4
Sodium Saccharin	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2
Magnesium Sterate	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10

Pre-compression evaluation of powder blend:

Angle of repose

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

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

Bulk density

Bulk density was determined by pouring the blend into agraduated cylinder. The bulk volume (V) and weight ofthe powder (M) was determined. The bulk density wascalculated by using the below mentioned formula,

Bulk density = Mass of powder/Bulk Volume of powder

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The tapped density was calculated using the following formula,

Tapped density = Mass of powder / Tapped volume of powder

Compressibility index

The simplest way for measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as follows,

C.I= (Tapped Density-Bulk density/Tapped density) ×100

Hausner's ratio

It is related to interparticle friction and could be used to predict powder flow property.

Hausner's ratio= Tapped density/ Bulk density

Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25). [10-12]

Table 2 Evaluation of Mixed Blend Drug and Excipients

Formulation code	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Angle of repose (θ)	Percentage Compressibility (%)	Hausner's ratio
F1	0.29	0.33	29.30	11.12	1.11
F2	0.29	0.32	28.81	9.37	1.10
F3	0.30	0.33	26.10	9.09	1.10
F4	0.29	0.31	28.81	6.45	1.06
F5	0.30	0.32	27.92	6.20	1.06
F6	0.30	0.33	26.83	9.09	1.10
F7	0.30	0.32	30.46	6.25	1.06
F8	0.29	0.32	29.35	9.15	1.10
F9	0.30	0.32	29.19	6.25	1.06

Evaluation of enalapril maleate fast dissolving tablet:

Weight variation test

Twenty tablets were selected randomly and average weight was determined. Then individual tablets were weighed and was compared with average weight. The comparison variation within the I.P limits, it passes the weight variation test.

Tablet hardness

Tablet crushing strength or hardness, the force required to break a tablet in a diametric compression, was measured using Monsanto tablet hardness tester.

Thickness

The thickness of individual tablets was measured using Vernier caliper, which permits accurate measurements and provides information of the variation between tablets.

Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio indicated with R, which is calculated by using the below mentioned equation.

$$R = 100 \times Wa\text{-}Wb/Wb$$

Wetting time

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper and the time required for complete wetting was measured. The time required for water to reach upper surface of the tablet is noted as a wetting time.

Tablet friability

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W0) or a sample of 20 tablets were 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.

%Friability= Loss in weight/Initial weight×100

***In-Vitro* Disintegration time**

The test was carried out on 3 tablets using tablet disintegration tester ED – 20, Electrolab, distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palable mass remaining in the apparatus was measured in seconds. (fig 3).

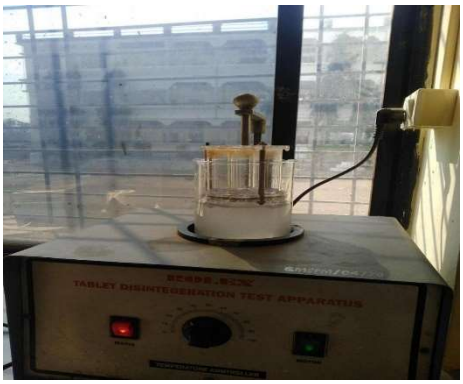

Fig 3: Disintegration test apparatus

Dissolution studies

In Vitro dissolution studies for all the prepared tablets and the marketed available tablets were carried out using USP paddle method at 50 rpm in 900 ml of buffer solution (pH – 6.8) as dissolution media, maintained at 37 ± 0.5º. 5 ml of sample was withdrawn from the dissolution medium at the specified regular intervals, filtered through Whattmann filter paper and assayed spectrophotometrically at 227 nm. An equal volume of pre warmed (37ºC) fresh medium was replaced into the dissolution medium after each sampling, to maintain the constant volume throughout the test. Then the cumulative percentage of drug release was calculated and represent graphically. [13-15]

Table 3 Evaluation of Enalapril Maleate fast dissolving tablets

Formulation code	Average Weight (mg)	Hardness (kg/cm²) ± SD	Thickness (mm) ±SD	Wetting time (Sec) ± SD
F1	199.33±1.154	3.4±0.157	2.7±0.196	45.37±1.172
F2	200.4±1.000	3.5±0.105	2.7±0.185	52.10±1.705

F3	199.3±1.000	3.4±0.101	2.5±0.115	48.12±1.437
F4	200.22±1.537	3.6±0.152	2.7±0.208	41.10±1.427
F5	196.2±1.527	3.6±0.105	2.6±0.152	57.21±0.724
F6	194.45±1.527	3.4±0.110	2.5±0.102	55.20±1.311
F7	198.15±1.723	3.6±0.115	2.7±0.208	53.55±1.225
F8	201.00±1.010	3.5±0.086	2.6±0.102	56.40±0.735
F9	198.17±1.154	3.6±0.057	2.5±0.115	52.60±2.636

Table 4 Evaluation of Enalapril Maleate fast dissolving tablets

Formulation code	Water absorption ratio (%)	Friability (%)	In vitro disintegration time (Sec)	In vitro dissolution time (%)	Drug content uniformity (%)
F1	90.47±0.446	0.69±0.055	25±1.154	92.47±1.062	94.42±1.100
F2	95.56±0.845	0.75±0.026	21.12±1.402	95.53±1.001	95.74±1.112
F3	80.95±0.783	0.50±0.062	18.62±2.823	96.51±0.754	97.32±0.456
F4	100.98±0.258	0.68±0.075	13±3.185	98.64±1.217	98.94±0.321
F5	81.81±0.569	0.47±0.041	15±1.571	93.33±0.472	95.20±1.526
F6	90.98±0.631	0.55±0.051	18±2.968	93.10±0.458	95.58±0.651
F7	100.20±0.473	0.59±0.040	20.77±2.251	98.20±1.046	98.65±0.774
F8	93.35±0.685	0.67±0.005	19.20±2.323	96.96±1.282	98.50±0.661
F9	90.47±0.661	0.49±0.228	16.44±2.401	97.22±0.103	98.39±1.121

Table 5 Evaluation of Marketed product of fast dissolving tablets

Sr. No	Marketed Product	Result
1	Hardness(kg/cm²) ± SD	3.65±0.125

2	Thickness (mm) ±SD	2.7±0.196
3	Average Weight (mg)	200±1.000
4	Wetting time (Sec) ± SD	39±1.172
5	Water absorption ratio (%)	100.90±0.658
6	Friability (%)	0.55±0.051
7	In vitro disintegration time (Sec)	11.47±2.103
8	In vitro dissolution time (%)	98.85±0.152
9	Drug content uniformity (%)	98.97±0.212

Stability Studies

The Fast-dissolving tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for stability studies -40±2°C and RH 75%±5%. The tablets were withdrawn after 15, 30, 45, 60 and 90 days and evaluated hardness, disintegration time, drug content and drug release.

Table 6 Evaluation Parameter of Formulation F4 during Stability Study

Time Interval (In Days)	Hardness (Kg/cm³)	Disintegration Time (Sec)	Wetting Time (Sec)	Drug Content (%)	Drug Release (%)
0	3.60±0.152	13±1.185	41.10±1.42	98.94±0.321	98.64±1.21
15	3.63±0.16	13.11±0.85	41.15±1.56	98.52±0.52	98.25±1.00
30	3.71±0.20	13.61±1.25	42.00±2.32	98.61±0.74	98.12±0.15
45	3.70±0.10	13.54±1.26	43.00±2.32	97.27±1.21	97.77±0.36
60	3.77±0.21	14.21±1.52	43.44±1.25	97.36±1.32	97.34±0.53
90	3.98±0.15	15.30±1.00	45.12±0.61	96.94±1.52	96.56±0.32

RESULT AND DISCUSSION

The powder blend was evaluated for preformulation parameter and results are shown in Table 2. The angle of repose was in the range of 26.10˚-30.46˚indicating the excellent flow properties. Bulk density was found in the range of 0.29-0.30 g/cm³ and the tapped density between 0.31-0.33 g/cm³.Hausners ratios was in the range of 1.062-1.115 indicating excellent flow ability. The Carr's compressibility index was found to be 6.25-12.12%. Hence prepared blend possessed excellent flow properties.

The compressed tablets were evaluated for physical properties and the results are tabulated in Table 3. The hardness of tablets was in the range of 3.43±0.10 to 3.60±0.156 kg/cm². The prepared tablets in all the formulations have good mechanical strength. Mean and standard deviation of thickness was calculated. The thickness of tablets varies in between 2.5±0.10 to 2.7±0.208 mm.

The friability of all formulations was found to be less than 1.0 % and was in the range of 90±0.005 to 95±0.051 % indicating a good mechanical resistance of tablets. Uniformity of weight of prepared tablets was found within specifications of Indian Pharmacopoeia. Uniformity of weight was found to be in the range of 193.66±1.527 to 210.33±1.527 mg. All the batches of immediate release tablets for each formulation were found to disintegrate in less than 25±1.154 sec. F4 and F5 formulation showed minimum disintegration time 13±3.18 and 15±1.57 sec. respectively as compared to other formulations. The wetting time for all the formulated tablets was in the range 41.10±1.42 to 57.21±0.72 sec. F1 and F3 formulation showed minimum wetting time 45.37±1.17 and 48.12±1.43 sec. respectively as compared to other formulations. The water absorption ratio ranged from 80.95±0.783 to100.98±0.258 %. The % drug content of tablets was checked in triplicate by UV spectrophotometer for all formulations. It was found to be between 94.52±1.100 –98.94±0.321 %.

In-vitro drug release of the prepared fast dissolving tablets was performed in pH 6.8 using USP type-II/IP-I dissolution apparatus. In-vitro drug release of all the formulations results were mentioned in the table 6. The results are shows that the increase in proportion of super disintegrants was associated with change in the overall cumulative drug release rate. Release profile of F4 formulation contains crospovidone was found to have maximum release of 98.64±1.217 % at the end of 20 minutes and F7 formulation contains croscarmellose sodium was found to be 98.20±1.046% at the end of 20 minutes. In-vitro drug release of all the formulations were graphically represented by as shown in Figure 8. In-vitro drug release of the F4 and marketed product were graphically represented by as shown in fig 9. The Table 5 shows the marketed product evaluation and the Table 6 shows the parameters of the tablets after stability study.

The best formulations i.e., F4 were subjected to stability study by storing the formulations 40°C/75% RH up to 90 days. After 15, 30, 45, 60 and 90 days the tablets were evaluated for the hardness, disintegration time, wetting time, drug content and drug release. In-vitro drug release of the F4 and marketed product were graphically represented by as shown in fig 9.

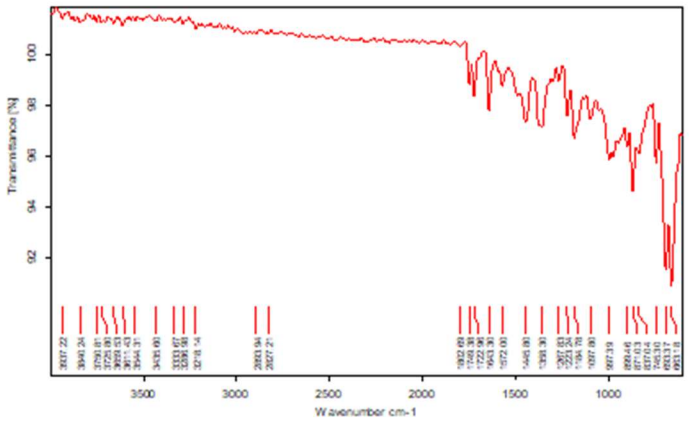

Fig 1: FT-IR Analysis of Pure Drug (Enalapril Maleate)

Fig 4: IR spectra of Drug

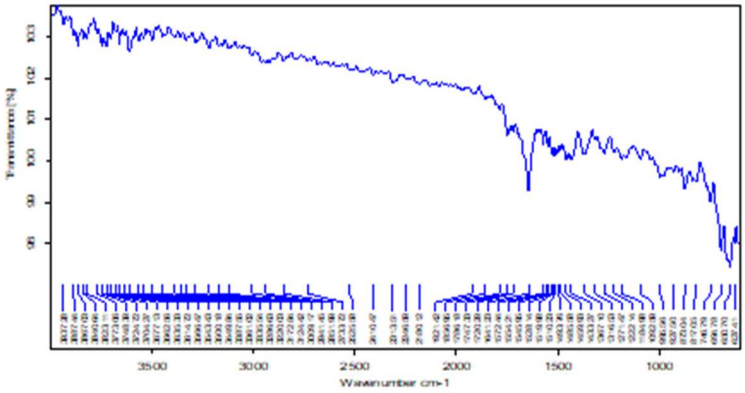

Fig 2: FT-IR Analysis of Drug (Drug+Crospovidone)

Fig 5: IR Spectra of Drug and Crospovidone

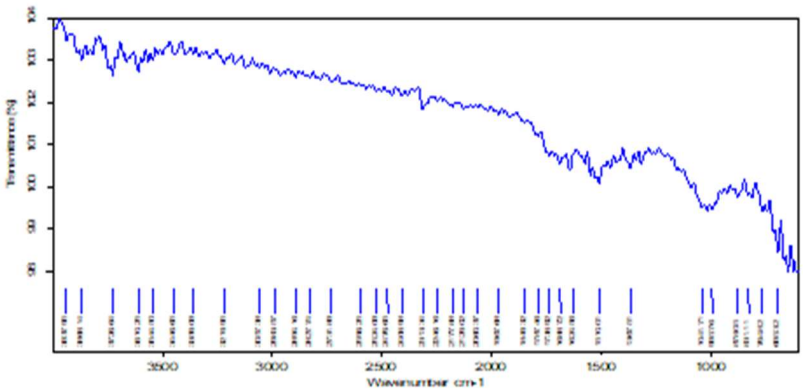

Fig 3: FT-IR Analysis of Drug (Drug+ Croscarmellose Sodium)

Fig 6: IR Spectra of Drug and Croscarmellose Sodium

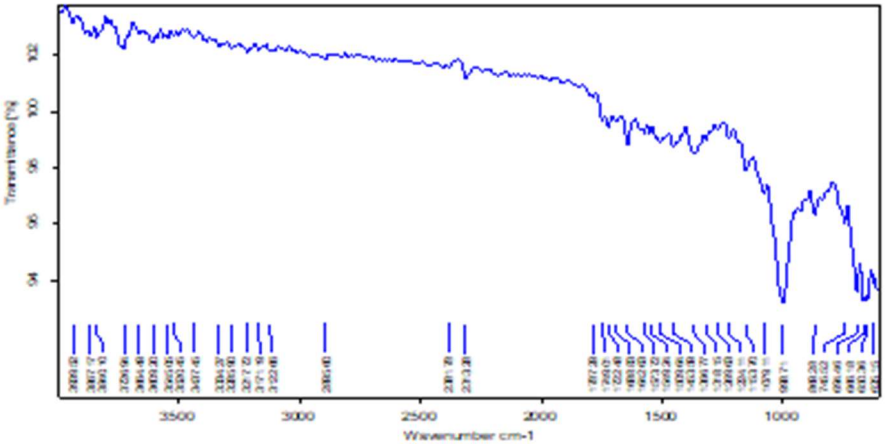

Fig 4: FT-IR Analysis of Drug (Drug+ Sodium Starch Glycolate)

Fig 7: IR Spectra of Drug and Sodium Starch Glycolate

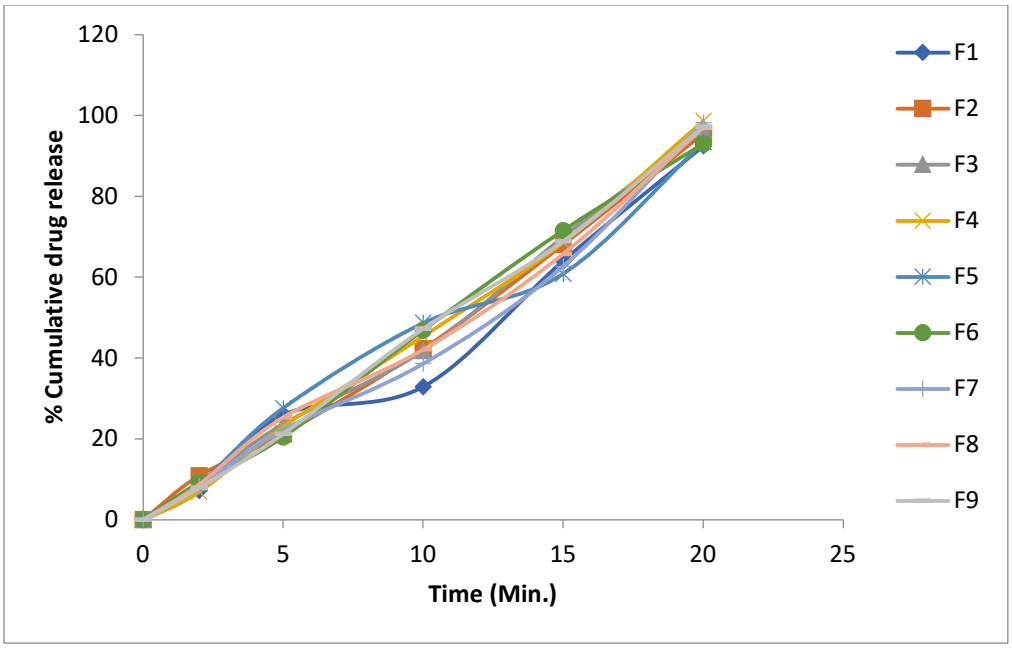

Fig 8: Percentage cumulative drug release of formulations F1-F9

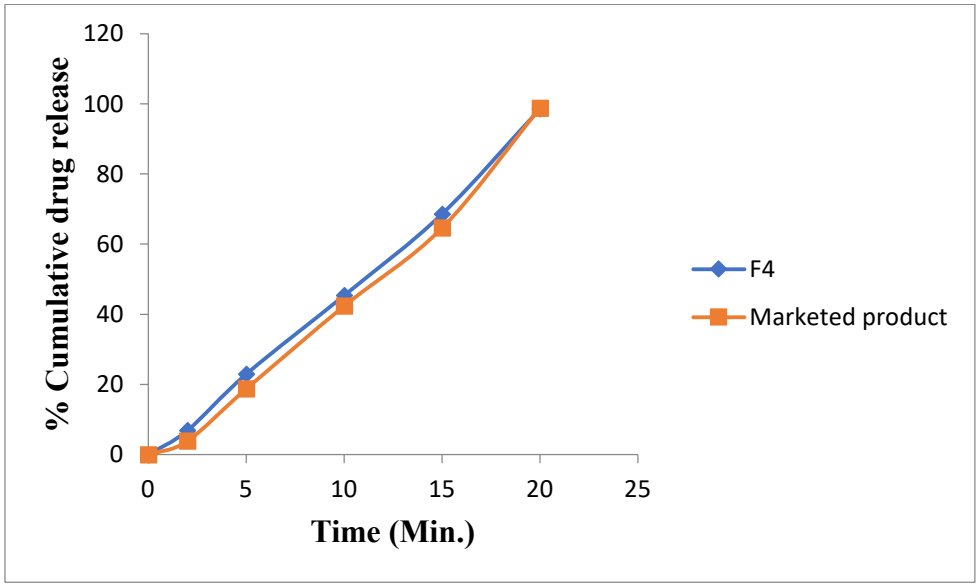

Fig 9: Percentage cumulative drug release of formulations F4 and Marketed Product

Conclusion

The fast-dissolving tablets of Enalapril Maleate were prepared by using superdisintegrants like croscarmellose sodium, crospovidone, sodium starch glycolate at different concentrations. These tablets were prepared by using direct compression method.

Among all the formulations, formulation F4 containing crospovidone as superdisintegrant exhibited excellent in-vitro disintegration time and in vitro cumulative percentage drug release as compared to other formulations. Disintegration time of formulation F4 was found to be 13±3.185 seconds and the drug release was found to be 98.64±1.217% within 20 minutes. And the

disintegration time of marketed product 11.47±2.103 seconds and the drug release were found to be 98.85±0.152% within 20 minutes. Therefore, the formulation F4 was considered as the best formulation because it's almost match with marketed preparation. Based on observation for disintegration time the efficiency of superdisintegrants was found in the following order-

Crospovidone >croscarmellose sodium > sodium starch glycolate.

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