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Original Article

FORMULATION DEVELOPMENT AND EVALUATION OF FAST DISSOLVING TABLET OF RAMIPRIL

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ABSTRACT

Objective: The aim of this study was to prepare fast dissolving tablet of Ramipril by using Sodium starch glycolate, and Crospovidone as superdisintegrants to enhance the dissolution rate and the disintegration rate and evaluated for Pre and Post Compression parameter of the tablet.

Methods: Fast dissolving tablet of Ramipril was prepared by direct compression technique. Fast dissolving tablet was evaluated for Pre compression parameter; bulk density, tapped density, Hausner's ratio, angle of repose and Carr's index and post compression parameter; weight variation, thickness, hardness, friability, wetting time, water absorption ratio, disintegration time and dissolution time. The UV-spectrophotometric method has been used for the quantitation of drug release of Ramipril in the Fast dissolving tablet formulation.

Results: Pre and post compression parameter were evaluated. Five different batches of tablets, F1 to F5 were prepared. Bulk density and tapped density was found in the range of 0.64-0.85 g/cm^3 and 0.68-0.98 g/cm^3 simultaneously. The hardness, friability, wetting time, the water absorption ratio, disintegration and dissolution time were found to be acceptable according to the standard limit and compare to all formulations F4 formulation was selected as the promising formulation. All batches of fast dissolving tablet were satisfactory in term of dissolution. The cumulative percentage of drug release of F4 formulation was 90.12% after 12 min compare to other formulation.

Conclusion: The result suggested that the dissolution and disintegration of Ramipril have improved considerably in batch F4 formulation as compared to rest of the formulation. The dissolution rate and dissolution rate of Ramipril can be enhanced to a great extent by the direct compression technique with the addition of superdisintegrants.

Keywords: Fast dissolving tablet, Ramipril, Sodium starch glycolate, Crospovidone.

INTRODUCTION

Oral routes of drug administration have wide acceptance up to 50-60% of total dosage form. Fast dissolving tablets offer great advantages for the patients having difficulty in swallowing. It has been reported that dysphasia (difficulty in swallowing) is usual among all groups and more specific with pediatric, geriatric population along with patients have nausea, retching, and motion sickness complications [1]. Fast dissolving tablets overcome this problem and provide the advantages for pediatrics, geriatric [2-3],bedridden, disabled patients and also for who may have difficulty in swallowing tablets, capsules and liquid orals. FDT will rapidly disintegrate in the mouth without the need of water [4-5]. Fast dissolving tablet formulation provides sufficient strength, quick disintegration/ dissolution in the mouth without water [6], rapid dissolution and absorption of the drug, which will produce the quick onset of action. Pre gastric absorption of FDT can result in improved bioavailability and as a consequence of reduced dose [7]. In addition, FDT is applicable when local action is desirable, such as oral ulcers, cold sores and teething [8].

Ramipril is (2*S*,3*aS*,6*aS*)-1-[(2*S*)-2-{[(2*S*)-1-ethoxy-1-oxo-4-phenyl butan-2-yl]amino} propanoyl] octahydrocyclopenta [*b*]pyrrole-2-carboxylic acid. Ramipril is a 2-aza-bicyclo[3.3.0]-octane-3-carboxylic acid derivative. Ramiprilat is the active metabolite of Ramipril, competes with angiotensin I for binding at the angiotensin converting enzyme, blocking the conversion of angiotensin I to angiotensin II. Angiotensin II contracts the muscles of most arteries in the body, including the heart, thereby narrowing the arteries and elevating the blood pressure [9]. Ramipril is indicated for the treatment of mild to moderate high blood pressure [10], Congestive heart failure, myocardial infarction in patients with clinical evidence of heart failure [11]. Ramipril, a pro drug, is converted to the active metabolite Ramiprilat by liver esterase enzymes [12]. Even then, it may induce hypotension, cough and other side effects [13]. The aim of the present study is to represent the formulation development of Fast dissolving tablet of Ramipril by using Sodium starch glycolate, and Crospovidone as superdisintegrants to enhance the dissolution rate and the disintegration rate and evaluated for Pre and Post Compression parameter of FDT.

MATERIALS AND METHODS

Chemicals and reagents

Ramipril was a generous gift from Alkam pharmaceutical Ltd. Baddi, (India), Sodium starch glycolate, crospovidone, aspartame, lactose, microcrystalline cellulose (MCC), Magnesium Stearate, methanol and talc was purchased from Himedia Laboratories Pvt. Ltd, Mumbai (India). All other chemicals used were of reagent grade. Triple distilled water was used throughout the study.

Preparation of fast dissolving tablet (FDT) of ramipril

Fast dissolving tablet (FDT) of Ramipril was prepared by direct compression method [14]**.** Five different batches of tablets were prepared by direct compression method. The fast dissolving tablets were prepared by direct compression of Co-processed superdisintegrants likewise Sodium starch glycolate, and Crospovidone with Ramipril [15-16]. FDT prepared by using a physical mixture of superdisintegrants and Co-processed superdisintegrants. In this method drug was mixed with Sodium starch glycolate, Crospovidone, Lactose, MCC, aspartame, talc as gliding & magnesium stearate as the lubricant. All ingredients were passed through #60 mesh, and then the Single punching machine was used to compress tablet containing 20 mg of Ramipril at an average weight of 250 mg/tablet. Different combination of batches was prepared and presented in table 1. Chemical structure, of (a) Ramipril and (b) Cross povidone was shown in fig. 1.

Evaluation of tablets

Fourier transform infrared spectroscopy

FTIR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrometer (1600 series, Perkin Elmer Inc, Norwalk, CT). Sample

was prepared in KBr disk (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1 c m^{-1}. FTIR Spectrum of Ramipril, Crospovidone and combination of Ramipril and Crospovidone both were shown in fig. 2.

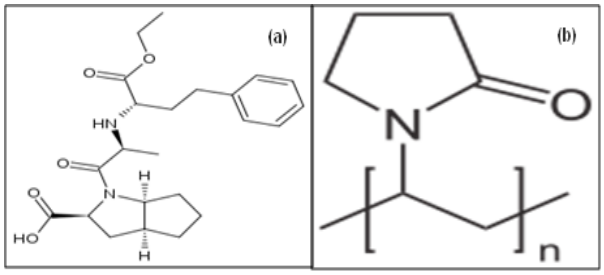

Fig. 1: Chemical structure of (a) Ramipril and (b) Crospovidone

Pre compression parameter

Physical properties of tablets

Pre compression parameter of 5 different formulation batches (F1 to F5) were evaluated for bulk density, tapped density, Hausner's ratio, angle of repose and Carr's index. This Define the Physical properties of the formulation.

Bulk density [17]

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined by transferring the accurate weighed amount of sample in 50 ml measuring cylinder, the granules without any agglomerates and measured the volume of packing and tapped 50 times on a plane surface and tapped volume of packing recorded and LBD and TBD calculated by following formula.

LBD =Mass of powder/Volume of packing

TBD= Mass of powder/Tapped volume of packing.

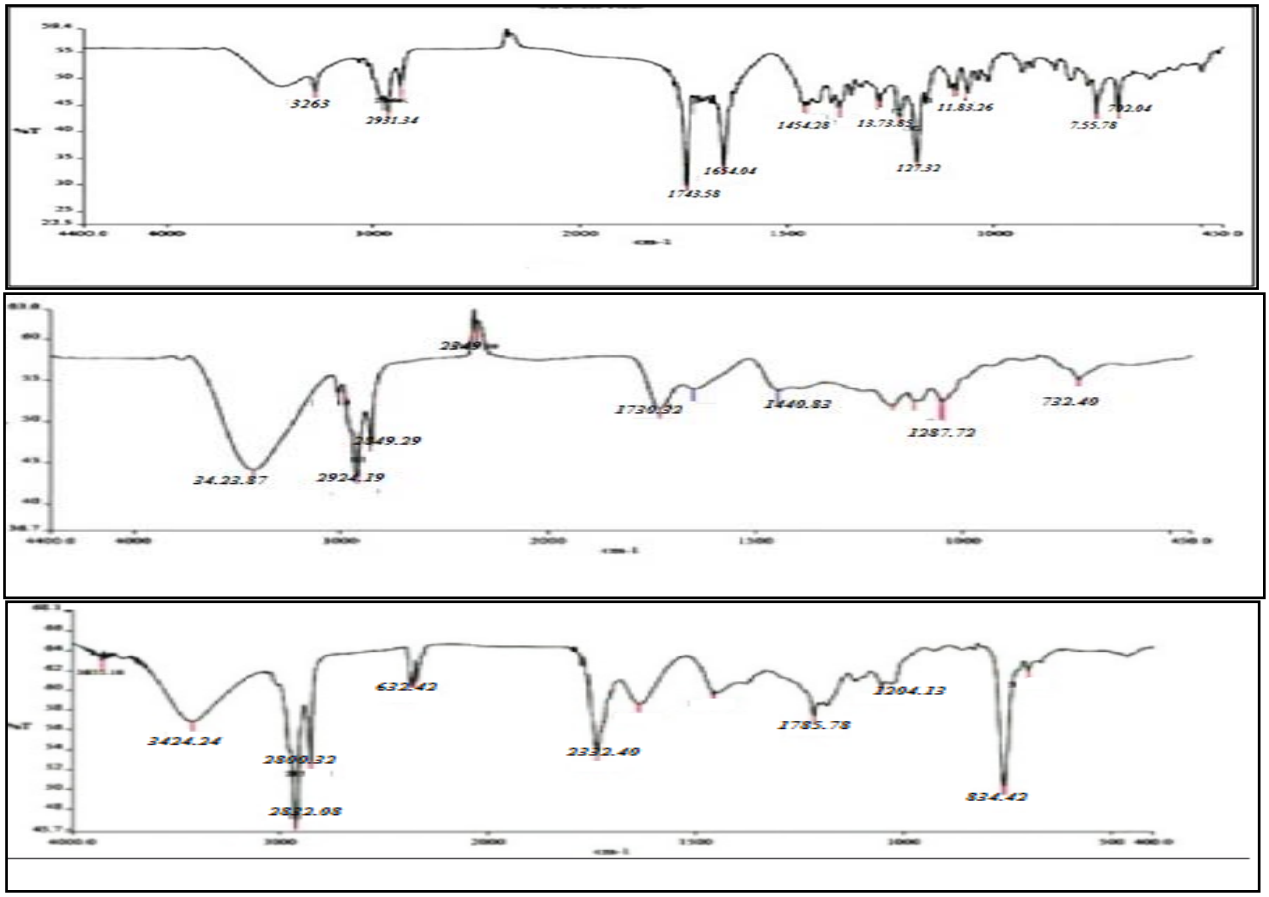

Fig. 2: FT-IR spectra of Ramipril, Crospovidone and combination

Table 1: Different combination of batches (F1-F5) of FDT formulation

Ingredients (mg)	Formulation code				
	F1	F2	F3	F4	F5
Ramipril	20	20	20	20	20
Crospovidone	55	55	55	55	55
Sodium starch glycolate	50	55	60	65	70
Microcrystalline cellulose	90	90	90	90	90
Lactose	30	25	20	15	15
Talc	2.5	2.5	2.5	2.5	2.5
Mg. Stearate	2.5	2.5	2.5	2.5	2.5

*n=3, Average of three determinations; F1-F5= formulation code of Fast dissolving tablet; All the quantities expressed are in mg/tablet. Formulations F4 was selected as the promising and used for further studies.

Hausner's ratio

Hausner's ratio is computed by applying the next equation

Hausner's ratio= Tapped density/Bulk density

Percentage compressibility index [18]

Percentage compressibility of powder mix was determined by Carr's Compressibility Index calculated by the following formula.

% Carr's Index= (TBD-LBD)×100/TBD; Where, TBD= Tapped bulk density; LBD= Loose bulk density.

Angle of repose

The frictional forces in loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a mass of powder or granules and the horizontal plane. Angle of repose is calculated by applying the next equation;

$\tan \theta = h/r$; $\theta = \tan^{-1}(h/r)$, where θ=angle of repose; h=height; r=radius

Post compression parameters

Thickness uniformity[19]

The aim of the present study was to check the uniformity of thickness of the tablet. The thickness of the tablet was measured at 3 different points using a digital caliper and the average thickness of three readings was calculated.

Hardness test[20]

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablet was determined using Monsanto hardness tester and expressed in kg/cm^2.

Friability test

Friability test is performed to assess the effect of friction and shocks, which may often cause the tablet to chip, cap or break. Roche Friabilator was used for the purpose. Pre weight sample of ten tablets was placed in the friabilator, which was then operated for 100 revolutions; after 100 revolutions the tablets were dusted and weighted. Friability was calculated by following formula.

Friability (%) = (Initial weight–Final weight/Initial weight)×100.

Water absorption ratio and wetting time

A piece of tissue paper folded twice was placed in a small Petridish containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was then measured by following formula.

R = Wa-Wb/Wb×100; Where, Wa = weight of the tablet after absorption of water, Wb= weight of the tablet before an absorption of water.

Disintegration studies

In vitro disintegration time was performed by USP disintegration apparatus at 50 rpm. Phosphate buffer (pH 6.8), 600 ml was used as disintegration medium, the temperature was maintained at 37±2°C and one tablet was placed in each of the six basket tubes of the apparatus and one disc was added to each tube. The time taken for the complete disintegration of the tablet (at which, when no mass remaining in the apparatus) was noted.

***In vitro* dissolution studies**

In vitro dissolution studies for all the fabricated tablets was carried out using USP paddle method at 50 rpm in 900 ml of phosphate buffer (pH 6.8) as dissolution media, maintained at 37±0.5 °C temperature. 5 ml aliquot was withdrawn at the specified time intervals, filtered through what man filter paper and assayed spectorphotometrically at 210 nm. An equal volume of fresh medium, which was pre warmed at 37 °C was replaced in the dissolution media after each sampling to maintain the constant volume throughout the test.

Calibration curve of ramipril UV spectroscopy

We have tried various concentrations ranges to find out the optimised concentration range, which obey Beer's Lambert law and find out the optimized concentration in the range of 10-60 µg/ml.

Apparatus

A UV PROB 1700 ultraviolet-visible spectrometer, Shimadzu with 10 mm matched quartz cell was used in the present investigation.

Preparation of stock solution

A stock solution of Ramipril was prepared by dissolution 100 mg accurate weight of standard Ramipril in 100 ml of methanol. Stock solution was suitable diluted to give concentration of 10 µg/ml and this was scanned in UV range the absorption maximum of Ramipril was observed at 210 nm the value was chosen for the preparation of the calibration curve of Ramipril.

Working standard solution

Working standard solution 100 µg/ml was made from the solution by suitable diluted with methanol. Aliquots was prepared by taken 1, 2, 3, 4, 5 & 6 ml from working standard solution and diluted with methanol in 10 ml volumetric flask to give concentration 10,20,30,40,50 & 60 µg/ml the absorption was recorded at 210 nm again a reagent blank and calibration curve was plotted and shown in fig. 3.

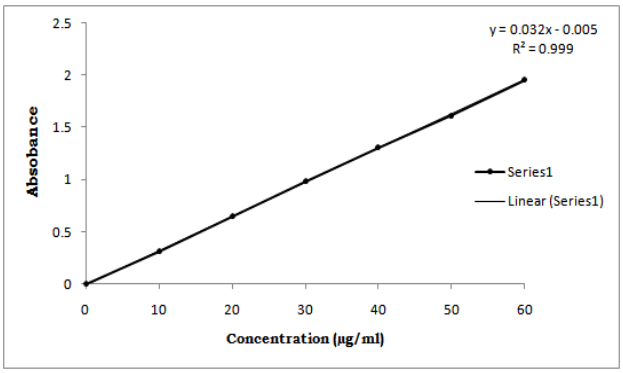

Fig. 3: Calibration curve of ramipril by UV-spectrophotometer (λ_{max}-210 nm)

RESULTS

Pre compression parameter

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Bulk density, was found in the range of 0.64-0.85 g/cm^3 and the tapped density was found between 0.68-0.98 g/cm^3. The results were tabulated and data shown in table 2.

Hausner's ratio

Hausner's ratio was found in the range of 1.06-1.16 g/cm^3. The results were tabulated and data shown in table 2.

Percentage compressibility index

Percentage compressibility of powder mix was determined by the Carr's Compressibility Index. The compressibility index was found between 10.94-13.27 which indicates a good flowbility of the powder blend. The outcomes were tabulated and data demonstrated in table 2.

Angle of repose

The frictional forces in loose powder or granules can be measured by the angle of repose. The good flow ability of the powder blend

was also demonstrated with the angle of repose in the range of (23.23-26.33) which is below 40 (θ°) indicating good flow properties of the granules. The outcomes were tabulated and data demonstrated in table 2.

Table 2: Pre compression parameter of different FDT formulation (F1-F5)

Formulation code	F1	F2	F3	F4	F5
Bulk Density (g/cm^3)*	0.85	0.78	0.69	0.64	0.66
Tapped Density (g/cm^3)*	0.98	0.88	0.75	0.68	0.77
Hausner's ratio*	1.15	1.12	1.08	1.06	1.16
Carr's Compressibility Index %*	11.93	12.64	10.94	13.27	12.76
Angle of Repose (θ°)*	25.33	24.43	26.33	23.23	25.64

*n=3, Average of three determinations; F1-F5= formulation code of Fast dissolving tablet

Post compression parameters

Thickness uniformity

The aim of the present study was to check the uniformity of thickness of the tablet. The outcomes were tabulated and data demonstrated in table 3.

Hardness testing

The hardness of the tablet was determined using a Monsanto hardness tester. The harshness of the prepared tablet varied from 3.4±0.25 to 3.9±0.27 kg/cm2, which have satisfactory strength to resist the mechanical shocks.

The hardness for all the formulations was within 3.5-4.0 kg/cm3, which is a suitable scope of oral disintegration tablets. The outcomes were tabulated and data demonstrated in table 3.

Friability test

Friability test is performed to assess the effect of friction and shocks; Roche Friabilator was used for the purpose. The friability was found between 0.42-0.52.

The friability of all the formulation was found to be less than 1.0% indicating good mechanical strength to packaging operations and transportation. The outcomes were tabulated and data demonstrated in table 3.

Table 3: Post compression parameter of different FDT formulation

Formulation code	F1	F2	F3	F4	F5
Uniformity of weight (n=10)	245±1.18	248.91±2.06	249±1.34	250±1.79	251±1.78
Thickness (mm) (n=3)	2.8±0.03	2.7±0.01	2.7±0.04	2.6±0.02	2.7±0.06
Hardness (n=3) (kg/cm^3)	3.4±0.25	3.9±0.27	3.5±0.26	3.7±0.25	3.8±0.24
Friability (%) (n=10)	0.52	0.46	0.43	0.42	0.44
Water absorption ratio (n=3)	62.00±0.89	64.00±0.24	65.00±0.91	68.00±0.8	67.00±0.32
Wetting Time (s) (n=3)	37±1.09	35±1.07	33±1.23	29±0.30	35±1.94
Disintegrating time (s) (n=3)	32±0.220	31±0.200	31±0.220	29±0.320	29±0.620

*n=3, Average of three determinations for thickness, hardness, Water absorption ratio, wetting time and disintegration time,; n=10, Average of ten determinations for weight uniformity and friability. s denoted time in second.

Water absorption ratio and wetting time

The Water absorption ratio founded between 62.00±0.89-68.00±0.85; the water absorption ratio increased with an increase in the concentration of superdisintegrants. This increased behavior due to the water taking ability of superdisintegrants. The wetting time found between 29±0.30-37±1.09. The outcomes were tabulated and data demonstrated in table 3. It was found that the formulation F4 containing Sodium starch glycolate at concentration 65 mg and crospovidone at the concentration of 55 mg showed less wetting time i.e. 29±0.30s as compared to other formulations.

Disintegration studies

In vitro disintegration time was done by the USP dissolution apparatus. The disintegration rate has a correlation with water absorption capacity of disintegrate and The *In vitro* disintegration time was found between 29±0.320-32±0.220 s. The outcomes were tabulated and data demonstrated in table 3. All the formulation showed disintegration time less than 35 s. It was found that the formulation F4 will show least disintegration time 29s as compare to other formulation. The order for a disintegration time in fast dissolving tablet was found to be F4<F5<F2<F3<F1.

***In vitro* Dissolution studies**

Dissolution rate depends on the wetting time of the disintegrant, among all the formulations F4 has less wetting time and has greater dissolution rate and then this is the other conformance test for correct selection of desirable. *In vitro* dissolution studies of all the formulation were done and depicted in fig. 4. In all formulations F4 formulation was selected as the promising formulation. Containing Sodium starch glycolate, and Crospovidone as superdisintegrants it showed increased *in vitro* drug release. Fig. 4 represent the enhance the dissolution rate of the F4 formulation as compared to the other formulation.

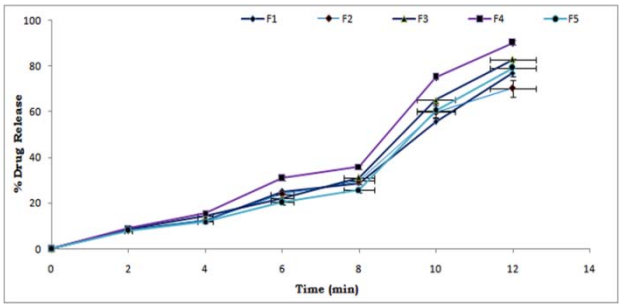

Fig. 4: In-vitro dissolution study of different FDT formulation (F1, F2, F3, F4, F5)

5 Batches of fast dissolving tablets were evaluated. F1-F5 were formulation code for fast dissolving tablet and F4 selected as promising formulation, that provide drug release about 92.5% in 12 minute; USP paddle apparatus was used, 50 rpm and 900 ml of phosphate buffer (pH 6.8) as dissolution media, maintained at

37±0.5 °C temperature and assayed UV-spectorphotometrically at 210 nm.

DISCUSSION

In this work, we have attempted to enhance the dissipation rate and decay rate of the fast dissolving tablet of Ramipril to provide quick onset of action for the patients of High blood pressure. The FDTs were prepared by direct compression method. The powder blend for all formulations containing various concentrations of Sodium starch glycolate (50-70 mg) and crospovidone (55 mg) as superdisintegrants was prepared and then the FTIR studies of Ramipril, crospovidone and combination of both were done that suggest compatibility (Fig.1). This study suggested that the drug and excipient are compatible to each other. The tablets were prepared by direct compression method using a single tablet punching machine. These tablets were evaluated for uniformity of weight, thickness, hardness, friability, the water absorption ratio, wetting time, disintegration time and *In-vitro* dissolution time. The order of uniformity of the thickness of tablet was found to be F4<F2<F3<F5<F1. It was observed that all the tablet passes the test for weight variation as shown in table. 3. Hardness of all tablets was between 3.4±0.25 to 3.9±0.27 kg/cm^{2}while friability was below 1% showed that all tablets have good mechanical strength. The order of hardness of the tablet was found to be F1<F3<F4<F5<F2. In comparing to all formulation tablets F4 batch containing sodium starch glycolate (65 mg), Crospovidone (55 mg), microcrystalline cellulose (90 mg), Lactose (15 mg), Talc (2.5 mg), Mg. Stearate (2.5 mg) showed the highest water absorption ratio. Sodium starch glycolate with Crospovidone inhibited wicking action, increase porously provider pathway for the penetration of fluid into a tablet. The order of friability of the tablet was found to be F4<F3<F5<F2<F1. It was found that as the concentration of crospovidone (55 mg) and sodium starch glycolate (65 mg) fasten the dissolution rate and the disintegration rate. The dissolution studies of formulation batches show good dissolution behavior (Fig.4). The formulation containing sodium starch glycolate (65 mg) batch F4 showed 92.5% drug release within 12 min as compared to other formulation code F1, F2, F3, F5 that release 60-80% (Fig.4). Disintegration time of all tablets was observed within the fraction of time.

CONCLUSION

The use of superdisintegrants for preparation of a fast dissolving tablet is highly effective and commercially feasible. The use of superdisintegrants accelerates the disintegration of the tablet by virtue of their ability to absorb a large number of the water when exposed to an aqueous environment. FDTs may be developed for Ramipril, for quick onset of action without the need of water for swallowing or administration. It was clear that the dissolution and disintegration of Ramipril have improved considerably in batch F4 formulation as compared to rest of the formulation. Batch F4 FDT showed good dissolution efficiency and rapid dissolution. This study was concluded that the dissolution rate of Ramipril can be enhanced to a great extent by the direct compression technique with the addition of superdisintegrants, however further studies are investigations are needed to confirm the *in vivo* efficiency.

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CONFLICT OF INTERESTS

Declared None

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