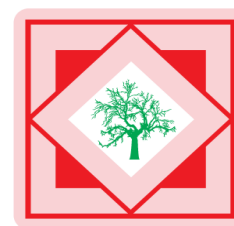




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Formulation and evaluation of fast dissolving tablet of Ramipril

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ABSTRACT

This research was to formulation and evaluation of fast dissolving tablets of Ramipril using direct compression technique (effervescent) with sodium bicarbonate, mannitol, polyvinylpyrrolidone, citric acid. Eight different formulation of Ramipril were prepared by using different ratio of NAHCO_3 : MANNITOL by direct compression method. The tablet was characterized by hardness, wetting time, weight variation, water Absorption Ratio, In Vitro Drug Release. All batches of fast dissolving tablets were satisfactory in terms of dissolution profile. The hardness, wetting time, water absorption ratio and wetting time were also shows the satisfactory result. The batches of all formulations, FDT4 batch with sodium bicarbonate: mannitol (1:3) showed more release than the other concentration and better results. The FDT4 batch of fast dissolving tablets was found to be 97.56 % drug release in 30 minutes. The FDT4 was the best of all eight formulations of Fast Dissolving Tablets of Ramipril. Bioavailability of Ramipril can be increased by formulating it as a Fast Dissolving Tablet.

Keywords: Ramipril, Fast dissolving tablet, Sodium bicarbonate, Mannitol, citric acid.

INTRODUCTION

Fast dissolving tablets offer great advantages for the patients having difficulty in swallowing[5].Fast dissolving tablets are best alternate to deliver the drug having bitter taste and poor oral bioavailability [3].Ramipril is an angiotensin-converting enzyme (ACE) inhibitor, used to treat hypertension and congestive heart failure.

Ramipril is chemically (2S, 3aS, 6aS)-1- [(2S)-2-[[[(2S)-1-ethoxy-1-oxo-4-phenylbutan-2yl] amino]propanoyl octahydrocyclopenta [b] pyrrole -2-carboxylic acid.

Ramipril lowers the production of angiotensin II, therefore relaxing arterial muscles while at the same time enlarging the arteries, allowing the heart to pump blood more easily, and more blood is pumped into and through larger passageways due to increasing blood flow. Ramipril have a poor bioavailability of 28%-30%, extent of absorption is not affected by the presence of food. However, the rate of absorption is reduced [6].

Ramipril is a prodrug and is converted to the active metabolite ramiprilat by liver esterase enzymes. Ramiprilat is mostly excreted by the kidneys. The half-life of ramiprilat is variable (8–18 hours) [12], and is prolonged by heart and liver failure, as well as kidney failure. It is mainly used for the Hypertension, Congestive heart failure, following myocardial infarction in patients with clinical evidence of heart failure. Susceptible patients over 55 years: prevention of myocardial infarction, stroke, cardiovascular death or need of revascularization procedures, Diabetic nephropathy with microalbuminuria.

The rate and extent of dissolution of the drug from any solid dosage form, determines the rate and extent of absorption of the drug. In the case of poorly water- soluble drugs, dissolution is the rate-limiting step in the process of drug absorption. Potential bioavailability problems are prevalent with highly lipophilic drugs ($\log p$ octanol/water, 3.32) due to erratic or incomplete absorption from GIT [6].

Fast dissolving Tablet formulation has been widely and successfully applied to improve the dissolution, solubility, and consequently the bioavailability of poorly water-soluble drugs. Because of its poor aqueous solubility, Ramipril may pose dissolution related absorption problem. In the present study, an attempt had been made to prepare fast dissolving tablets of Ramipril in the oral cavity with enhanced dissolution rate & hence improved patient compliance using sodium bicarbonate and mannitol.

MATERIALS AND METHODS

Ramipril was received as gift sample from Torrent Pharmaceuticals Limited, Gujarat, India. Sodium bi carbonate, polyvinyl pyrrolidone, citric acid, magnesium Stearate were supplied by Central Drug House (P) Ltd., New Delhi, India and mannitol was supplied by Qualigens Fine Chemicals, Mumbai.

2.1 Calibration Curve of Ramipril in 6.8 Ph Phosphate Buffer:

2.1.1 Preparation of 6.8 pH phosphate buffer [13]:

- Prepare a 0.2 M solution of potassium dihydrogen phosphate by dissolving 27.218 gm of substance in 1000 ml of distilled Water.
- Prepare a 0.2 M solution of sodium hydroxide solution by dissolving 8 gm of substance in 1000 ml of distilled Water.
- Take 50 ml of above prepared potassium dihydrogen phosphate solution & 22.4 ml of above prepared sodium hydroxide solution. Add both the solution & make the volume of the resultant solution 200 ml. Calibrate the solution for using pH meter & adjust the pH 6.8.

2.1.2 Preparation of stock solution:

Dissolve 10 mg of Ramipril in few ml of phosphate buffer by taking 100 ml volumetric flask & make up the volume 100 ml to get a solution of 100 mcg/ml concentration solutions.

2.1.3 Procedure:

Prepare different concentrations from 10 mcg/ml to 60 mcg/ml by diluting stock solution as for first concentration 10 mcg/ml, take 1 ml of stock solution & dilute with 10 ml of buffer solution. Similarly other concentrations are prepared. Absorbance are measured at 231nm for each concentration by using UV spectrophotometer (UV-3000, Lab India). Concentration are plotted against absorbance on a graph paper.

Table no. 1 -Calibration curve in 6.8 pH phosphate buffer

S.No.	Concentration ($\mu\text{g/mL}$)	Absorbance
1	10	0.308
2	20	0.646
3	30	0.987
4	40	1.304
5	50	1.612
6	60	1.954

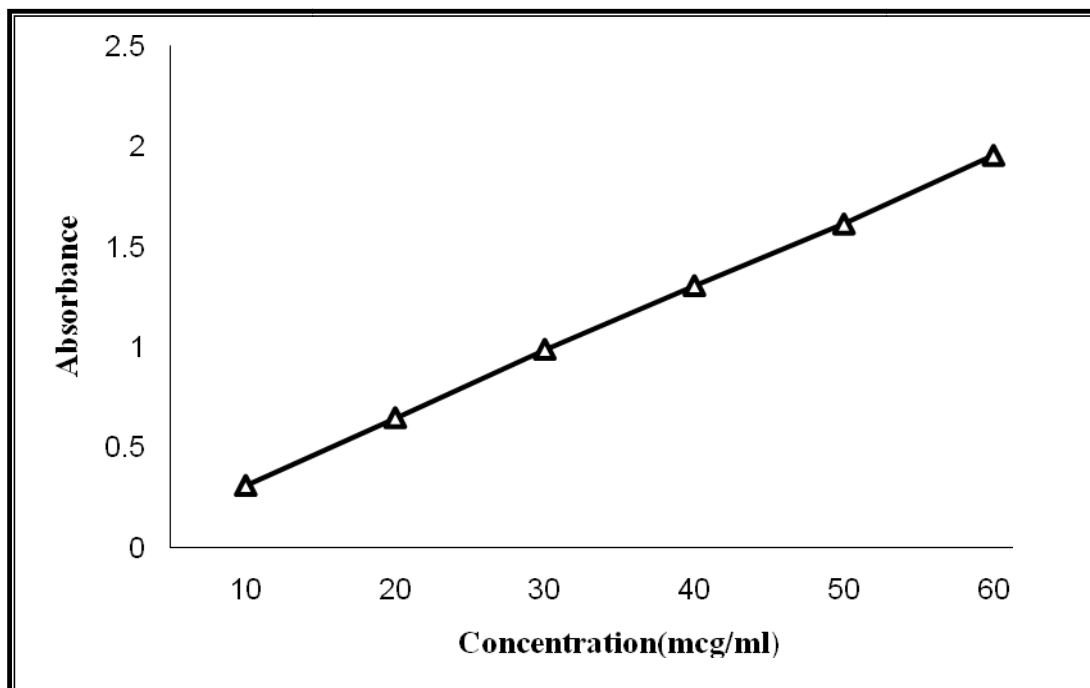


Figure No. 1-(Concentration Vs Absorbance)

Calibration curve for: *Ramipril*
Solvent / Mobile Phase: *Buffer (pH 6.8)*
Wavelength (nm): *231 nm*

2.2 Formulation Development [2, 4]:-

Different batches of tablets prepared by wet granulation method. Eight different batches of tablets were prepared by taking sod. bicarbonate, polymer ratio 1:0, 1:1, 1:2, 1:3 1:4 1:5 5:1 4:2 of each with PVP. Thus total eight batches were prepared (Different combination shown in table 2).

2.2.1 Sieving: Mg. Stereate was sieved through #60 mesh.

2.2.2 Granulation: All the ingredients were mixed in increasing order of weights. The binding solution of PVP in Isopropyl alcohol was used as granulating solvent. The granules were made using #40 mesh. Then granules were dried in oven at 40°C for 15 minutes.

2.2.3 Compression: The tablets were compressed on a single punch tableting machine (Bells India Marketed and Manufactured by Meditron Ing. New Delhi) for 250mg tablet respectively.

Table no. 2- Composition of FDTs of Ramipril (250 mg tablets)

Batches(mg/tablets)	FDT	FDT	FDT	FDT	FDT	FDT	FDT	FDT
Ingredients	1	2	3	4	5	6	7	8
NaHCO ₃ :Mannitol	1:0	1:1	1:2	1:3	1:4	1:5	5:1	4:1
Ramipril	20	20	20	20	20	20	20	20
NaHCO ₃	220	100	66.6	50	40	33.3	166.6	160
Mannitol	0	100	133.3	150	160	166.6	33.3	40
Citric Acid	6	6	6	6	6	6	6	6
PVP	20	20	20	20	20	20	20	20
Talc	2	2	2	2	2	2	2	2
Mg. Stearate	2	2	2	2	2	2	2	2

3. Evaluation of Tablets:-

The tablets were evaluated for appearance, hardness, friability, In-vitro drug release and floating lag time and total floating time.

3.1 Bulk density [9]:

Apparent bulk density (g/ml) was determined by placing pre-sieved bulk powder blend into a graduated cylinder via a large cylinder and measuring the volume and weight “as it is.”

$$P_b = \frac{M}{V_p}$$

Where, p_b = Bulk Density”

M = Weight of sample in gm

V = Final volume of blend in cm³

3.2 Tapped density [9]:

It was determined by placing known mass of powder in a graduated cylinder & tapping it for fixed number of taps (around 250) until the powder bed volume reached a minimum. Using the weight of the powder in the cylinder and this volume, the tapped density was computed. (Table No. 3).

3.3 Angle of repose [9]:

The angle of repose was calculated with the formula $\tan a = H/R$, where ‘a’ is the angle of repose and R is the radius of the conical pile.

$$\tan \theta = h/r$$

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

Where θ = Angle of repose

h = height of the cone

r = Radius of the cone base

Angle of Repose less than 30 ° shows the free flowing of the material

3.4 Compressibility Index [9]:

The compressibility index of the granules was determined by Carr’s compressibility index.

$$\% \text{Carr Index} = (\text{TBD} - \text{LBD}) \times 100 / \text{TBD}$$

Where, TBD= Tapped bulk density
LBD= Lowest bulk density

3.5 Hardness [6, 8]:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. Hardness of tablets was measured using a Monsanto hardness Tester.

3.6 Friability [8, 9]:

It is a measure of mechanical strength of tablets. Roche Friabilator was used to determine the friability by following procedure: Prewighed tablets were placed in the Roche friabilator (Electro lab EFL Friabilator, Mumbai, India) and expressed in the percentage by using this formula.

$$\text{Friability}(\%) = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

3.7 Weight variation study [6, 8, and 10]:

With a tablet designed to contain a specific amount of drug in a specific amount of formula, the weight of a tablet being made is routinely measured to ensure that a tablet contains proper amount of drug. 20 Tablets were taken from each batch. The tablets were weighed and the mean was calculated. The following formula was applied for checking deviation from normal range as per U.S.P. standards.

3.8 Water absorption ratio and wetting time [8]:

A piece of tissue paper folded twice was placed in a Petridish containing 5ml of water. A pre weighed tablet was placed on the paper and the time for complete wetting was measured which is characterized by coloring of tablet. The wetted tablet was then weighed. Water absorption ration R was determined according to the following formula.

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

Where, Wa = weight of tablet after absorption of water
Wb= weight of tablet before absorption of water

3.9 In vitro Dissolution studies [7, 8, and 13]:

In vitro dissolution studies of fast-dissolving tablets were performed by using(type 2 USP dissolution) apparatus as specified in at 50 rpm; and Sorenson's buffer (pH,6.8), 900 ml, was used as dissolution medium , temperature of dissolution medium was maintained at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. Sample of dissolution medium was withdrawn at a specific time interval and was filtered. Absorption of filtered solution was checked by UV spectroscopy (Lab India Uv 3000), and drug

content was determined from standard calibration curve. Dissolution rate was studied for all designed formulation.

RESULTS AND DISCUSSION

Eight formulations of Fast Dissolving Tablets of Ramipril were prepared with varying concentration of Sodium bicarbonate: Mannitol and also Citric acid, PVP were used as diluents (Table. no. 2). For each formulation, blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. The powder blend was compressed using direct compression technique.

Table no. 3- Evaluation data of Micromeritic property of bulk powder blend

Different Batches	FDT 1	FDT 2	FDT 3	FDT 4	FDT 5	FDT 6	FDT 7	FDT 8
Micromeritic properties								
Bulk Density (gm/cm³)	0.96	0.69	0.56	0.50	0.43	0.41	0.82	0.83
Tapped Density (gm/cm³)	1.09	0.79	0.63	0.57	0.50	0.48	0.92	0.95
Angle of Repose (°)	25.34	24.42	26.34	24.24	25.66	25.47	24.98	26.64
Compressibility Index (%)	11.92	12.65	10.93	13.26	12.72	13.30	10.66	12.14

Bulk density, was found in the range of (0.41-0.96 gm/cm³) and the tapped density between (0.48-1.09 g/cm³). The compressibility index was found between (10.66-13.30) which indicates a fairly good flowability of the powder blend. The good flowability of the powder blend was also evidenced with angle of repose in the range of (24.24-26.64) which is below 40(°) indicating good flow properties of the granules (Table no.3)

Table no. 4- Evaluation data of compressed tablets of different formulations

Different Batches	FDT 1	FDT 2	FDT 3	FDT 4	FDT 5	FDT 6	FDT 7	FDT 8
Evaluation data								
Hardness (kg/cm²)	2.3	2.8	3.2	3.8	4.1	4.2	2.5	2.7
Friability (%)	0.51	0.43	0.41	0.42	0.43	0.42	0.43	0.47
Weight variation(mg)	251.2	252.6	250.4	250.0	254.1	253.6	249.5	250.3
Water absorption ratio	102.2	130.5	145.8	156.8	153.9	155.0	150	149.5
Wetting Time (sec)	174	165	159	152	145	143	160	155

Table no. 5:- % Drug release of Different Batches

Batches	% DRUG RELEASE							
	FDT1	FDT2	FDT3	FDT4	FDT5	FDT6	FDT7	FDT8
TIME (min)								
0	0	0	0	0	0	0	0	0
5	52.21	53.67	55.41	60.41	57.87	55.78	58.21	60.15
10	65.34	78.89	85.67	90.23	80.89	78.56	75.34	69.34
15	69.98	80.65	88.56	92.31	87.56	82.34	79.7	74.5
20	75.67	85.67	91.23	96.42	90.87	84.5	83.6	78.6
30	78.34	88.56	95.58	99.91	97.56	95.67	93.67	86.8

Tablets were prepared using direct compression technique. Since the powder material was free flowing, tablets were obtained of uniform weight due of uniform die fill, with acceptable weight variations as per I.P. The average weight of the prepared tablet was found 249 to 254 mg. All the tablets were exhibit in white colour, odourless, smooth surface with zero defects. A tablet requires certain amount of hardness to withstand the mechanical shocks in handling, packaging

and at the time of application. The friability of all the formulation was found to be less than 1.0 %. The hardness of the prepared tablet varied from 2.3 to 4.2 Kg/cm² which have satisfactory strength to withstand the mechanical shocks (Table no.4).

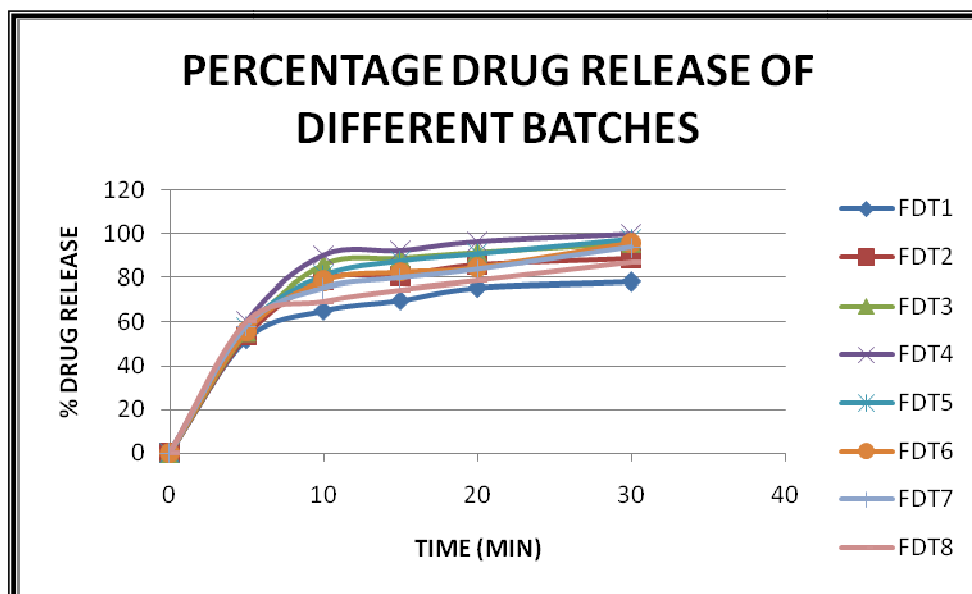


Figure no. 2- % Drug release of Different Batches

The % drug release of different batches with time shown in (Table no.5) and Figure no. 2 shown that the formulations F4 with 99.91 % (mannitol +sodium bicarbonate) show more release than the tablets with only sodium bicarbonate. All the formulations showed no significant variation in all the parameters under the test period.

CONCLUSION

The Fast Dissolving Tablets have potential advantages over conventional dosage forms, with their improved patient compliance; convenience bioavailability and rapid onset of action had drawn the attention of many manufacturers over a decade. The preparation process of direct compression tablets includes co-grinding of all the excipients before compression, resulting the increase in the solubility due to the reduction in the effective particle size of the drug following increase in the wetting of drug particle by the excipients and improved dissolution of drugs. Fast Dissolving Tablet formulation obtained by some of these technologies has sufficient mechanical strength quick disintegration / dissolution in the mouth without water.

In conclusion , overall results suggests that the FDTs containing sodium bicarbonate and mannitol in the ratio of 1:3 (F4) shows best results in terms of percent drug release, compressibility index, hardness and disintegration time. Thus FDTs may be developed for Ramipril, for quick onset of action without need of water for swallowing or administration, however further studies are investigations are needed to confirm the in vivo efficiency and for the development of Fast Dissolving Tablet of Ramipril.

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