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Formulation and evaluation of porous tablets of Ramipril Hydrochloride

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ABSTRACT

Ramipril, sold under the brand name Altace among others, is an angiotensin-converting enzyme (ACE) inhibitor, used to treat high blood pressure (hypertension) and congestive heart failure. By inhibiting an enzyme, ACE inhibitors relax the muscles around small arteries (arterioles). The arterioles expand and allow blood to flow through more easily. This reduces blood pressure. ACE inhibitors inhibit the actions of angiotensin converting enzyme (ACE), thereby lowering the production of angiotensin II and decreasing the breakdown of bradykinin. The decrease in angiotensin II results in relaxation of arteriole smooth muscle leading to a decrease in total peripheral resistance, reducing blood pressure as the blood is pumped through widened vessels. Its effect on bradykinin is responsible for the dry cough side effect. Ramipril, a prodrug or precursor drug is converted to the active metabolite ramiprilat by carboxyl esterase 1. Ramiprilat is mostly excreted by the kidneys. Its half-life is variable (3–16 hours), and is prolonged by heart and liver failure, as well as kidney failure.

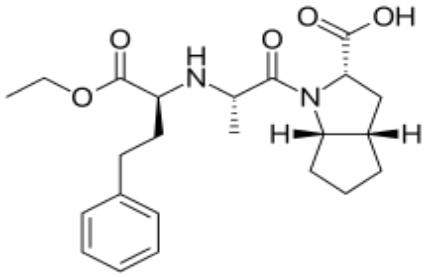
Keywords: Ramipril, Angiotensin-Converting Enzyme (Ace).

INTRODUCTION

Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients [1, 13]. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure [11]. However, some patients, particularly pediatric and geriatric patients, have difficulty in swallowing or chewing solid dosage forms. Many pediatric and geriatric patients are unwilling to make these solid preparations due to fear of choking [2, 15]. Hence orally dissolving tablets have come into existence. Researches have formulated ODT for various categories of drugs, which are used for therapy in which rapid peak plasma concentration is required to achieve desired pharmacological response [12- 14]. These include neuroleptics, CVS agents, analgesics, anti-allergics, and drugs for erectile dysfunction [3].

Drug Profile

Ramipril



AIM AND OBJECTIVES

The main objective of this work is to formulate and evaluate Rimipiril HCl Rapid disintegrating Tablets using different concentrations of superdisintegrants like croscarmellose sodium (CCS), sodium starch glycolate (SSG) and their combinations in different ratios. Tablets were prepared by direct compression method and evaluated for hardness, friability, wetting time disintegration time and percent drug release [4].

Objectives of the study

The present research investigation was panned with the following objectives

1. To optimize the different concentrations of the disintegrants on release of the drug
2. To formulate orally disintegrating tablets of Ramipril by using different concentrations of disintegrants
3. To evaluate the formulations with respect to various physical parameters

Plan of the study

Pre-compression parameters

1. Angle of repose
2. Bulk density
3. Carr's consolidation index
4. Compatibility study

Post-compression parameters

Uniformity of thickness, Hardness test, Friability test, Weight variation test, wetting time, Water absorption ratio. *In-vitro* disintegration time, *In-vitro* dissolution studies [5, 16].

MATERIALS AND METHODOLOGY

Drug and Excipients

The following materials and instruments used in the experiment are of laboratory grade.

Table 1: Details of materials used

Sl. No.	Materials
1	Ramipril hydrochloride
2	Sodium starch glycolate
3	Croscarmellous sodium
4	Magnesium stearate
5	Colloidal silicon di-oxide
6	Lactose monohydrate

Preparation of phosphate buffer pH 6.8

Dissolved 27.22 g of monobasic potassium phosphate in water and diluted to 1000 ml with water. In 50 ml of above solution added 22.4 ml of 0.2 M sodium hydroxide solution and added water to make up 200 ml [6].

Procedure

Oral disintegrating tablets (ODT's) were prepared by direct compression method according to formula given in Table 1. All the ingredients were passed through mesh # 30 except magnesium stearate [10, 17]. Magnesium stearate was passed through mesh # 40. Drug and superdisintegrant were mixed by taking small portion of each in ascending order and blended to get a uniform mixture in a mortar [7, 18]. The other ingredients were weighed and mixed in geometrical order and tablets were compressed using 8mm round flat punches on a Cadmach single punch machine [8].

Tablet punching by direct compression method

Milling of drug and excipients, Mixing of drug and excipients., Tablet compression [9].

Table 2: Formulation chart of Ramipril orally disintegrating tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ramipril	20	20	20	20	20	20	20	20	20
Cross caramellose sodium	4	8	16	-	-	-	-	-	-
Crospovidone	-	-	-	4	8	16	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	4	8	16
Menthol	12	12	12	12	12	12	12	12	12
Sodium saccharine	8	8	8	8	8	8	8	8	8
Talc	2	2	2	2	2	2	2	2	2
Micro crystalline cellulose	150	146	138	150	146	138	150	146	138
Magnesium stearate	4	4	4	4	4	4	4	4	4
Total weight (mg)	200	200	200	200	200	200	200	200	200

RESULTS & DISCUSSION

Determination of λ_{max}:

Ramipril was dissolved in distilled water and further diluted with 0.1N HCI. Then the solution was scanned for maximum absorbance in UV double beam spectrophotometer (Shimadzu 1700) in the range from 200 to 400 nm, using 0.1N HCI as blank. The λ_{max} of the drug was found to be 210 nm.

Table 3: Standard graph of ramipril

Conc. (µg/ml)	Absorbance at 210 nm
0	0
5	0.142
10	0.297
15	0.449
20	0.598
25	0.746
30	0.928

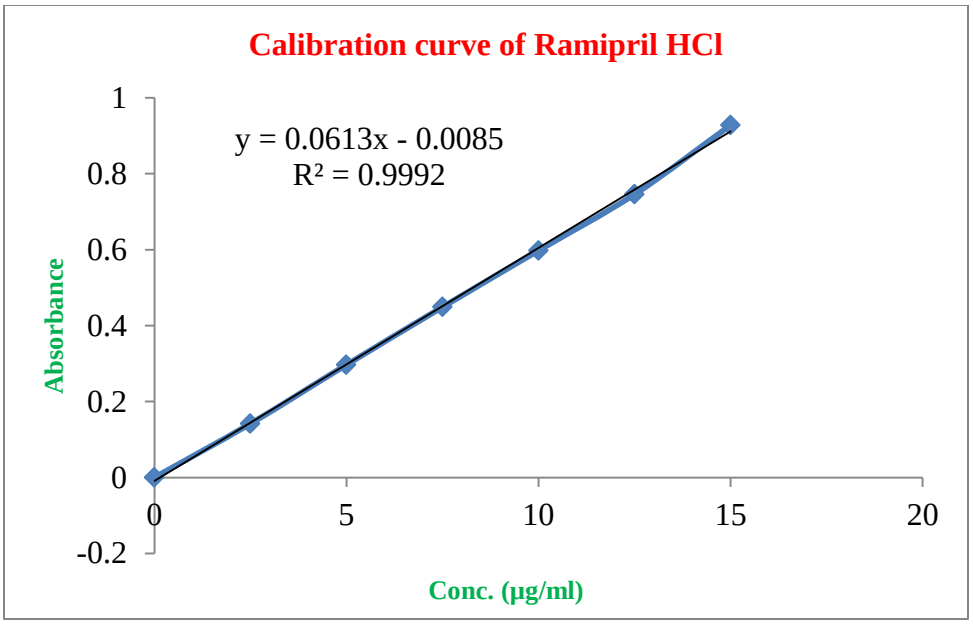


Fig 1: Calibration curve of Ramipril HCl at 210 nm.

Results of pre-compression parameters for Ramipril tablets

Pre-compression parameters

Angle of repose (θ)

The data obtained from angle of repose for all the formulations were found to be in the range of 24.19° and 28.56° which reveals good flow property. All formulations showing angle of repose within 30°, indicates a good flow property of the granules.

Bulk density

Bulk density (BD) and tapped density (TD) for the blend was performed. The loose bulk density and tapped bulk density for the entire formulation blend varied from 0.508 gm/cc to 0.5438 gm/cc and 0.5941 to 0.6408 respectively.

Table 4: Pre-compression parameters for Ramipril tablets

Formulationcode	Bulk density g/cc	Tapped density (g/cc)	Angle of repose	Carr's index (%)
F1	0.5534	0.6241	25.28	12.7755
F2	0.5512	0.6294	26.20	14.1809
F3	0.5537	0.6298	25.14	13.7592
F4	0.5598	0.6298	24.19	14.0050
F5	0.5538	0.6201	26.41	12.044
F6	0.5545	0.6296	28.56	14.296
F7	0.5522	0.6210	26.71	12.5362
F8	0.5542	0.6208	26.38	12.6354
F9	0.5588	0.6241	26.01	12.7578

Results of post-compression parameters

Hardness

The hardness of all the tablets was maintained within the 2.00 kg/cm to 4.00 kg/cm. The mean hardness test results are tabulated in table.

Friability test

The friability was found in all designed formulations in the range 0.42 to 0.74% to be well within the approved range (<1%). The friability study results were tabulated in table.

Weight variation test

All the tablets passed weight variation test as the average percentage weight variation was within 7.5% i.e. in the pharmacopieal limits.

In-vitro disintegration time

The in vitro disintegration time is measured by the time taken to undergo uniform disintegration. Based on the in vitro disintegration time, formulation F 6 found to be promising and showed a disintegration time of 11 sec. Disintegrating study showed that the disintegrating times of the tablets decreased with increasing concentrations of superdisintegrants.

Wetting time

Wetting time closely related to the inner structure of the tablet. The results of wetting time are shown in table. The wetting time were found to be in the range of 11 to 18sec.

Water absorption ratio

Water absorption ratio for all the formulations found in the range 11 to 16%. The results of water absorption ratio for tablets were shown in table.

Table 5: Post-compression parameters of Ramipril Hcl tablets

Formulation	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Weight variation (mg)
F1	3.5	0.69	3.21	200
F2	3.5	0.46	3.30	199
F3	4.0	0.72	3.12	201
F4	4.0	0.72	3.29	202
F5	3.6	0.68	3.34	199
F6	3..5	0.43	3.36	198
F7	4.0	0.42	3.29	199
F8	3.8	0.45	3.36	197
F9	3.7	0.54	3.30	200

Table 6: Post formulation studies of ramipril HCl tablets

Formulation code	In-vitro dispersion time (Sec)	Wetting time (Sec)	Water absorption ratio (%)
F1	41	27	101
F2	30	25	102
F3	26	18	105
F4	20	33	90
F5	17	25	92
F6	**11**	**16**	**102**
F7	38	29	90
F8	26	26	102
F9	20	20	101

Dissolution study

In vitro dissolution studies

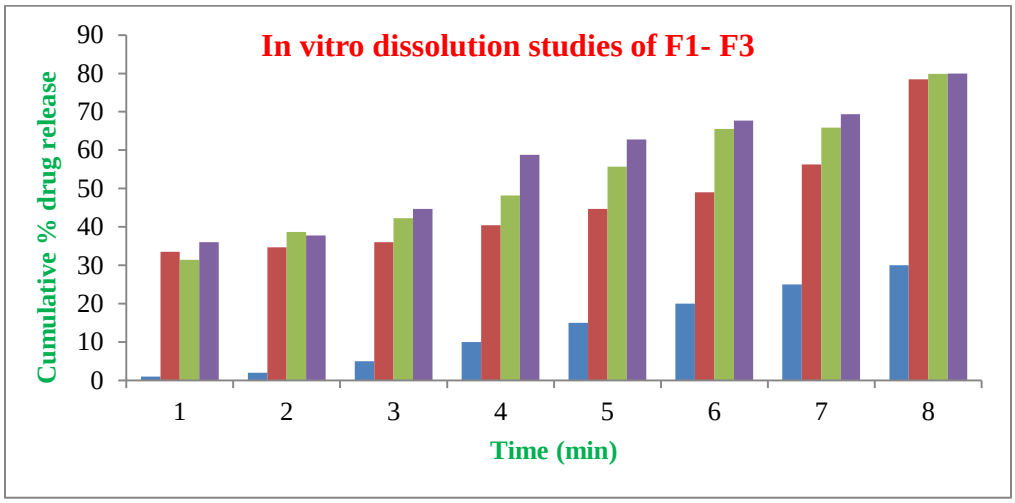


Fig 2: Drug release profile of formulations F1 –F3

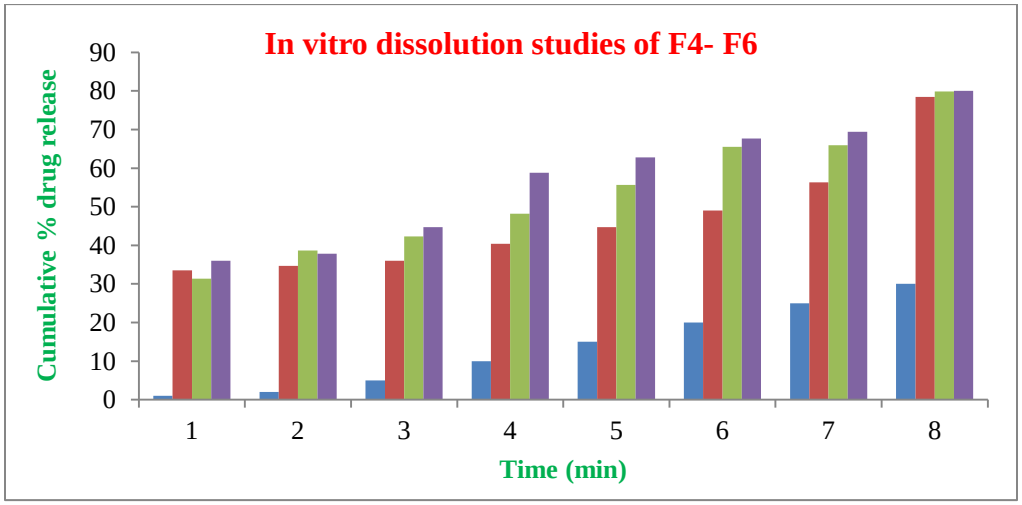


Fig 3: Drug release profile of formulations F4 – F6

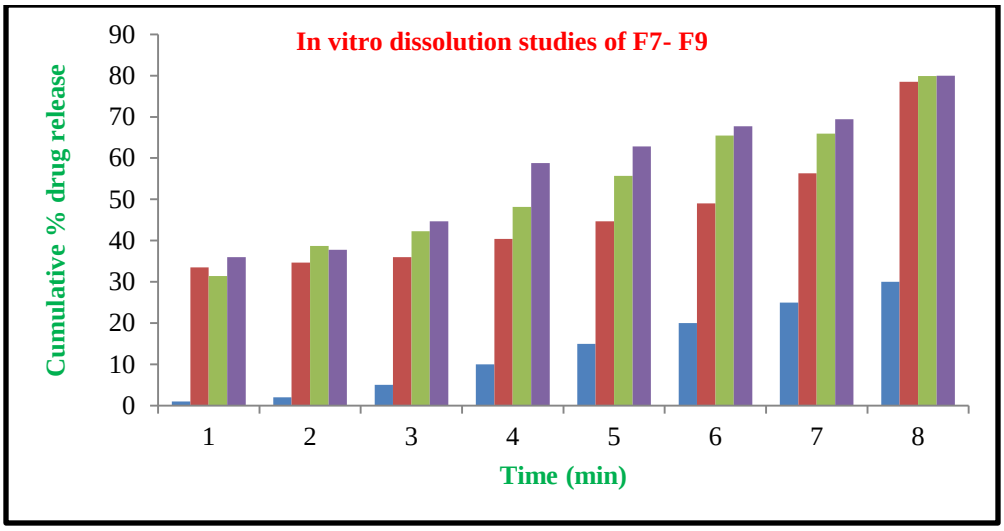


Figure 4: Drug release profile of formulations F7 – F9

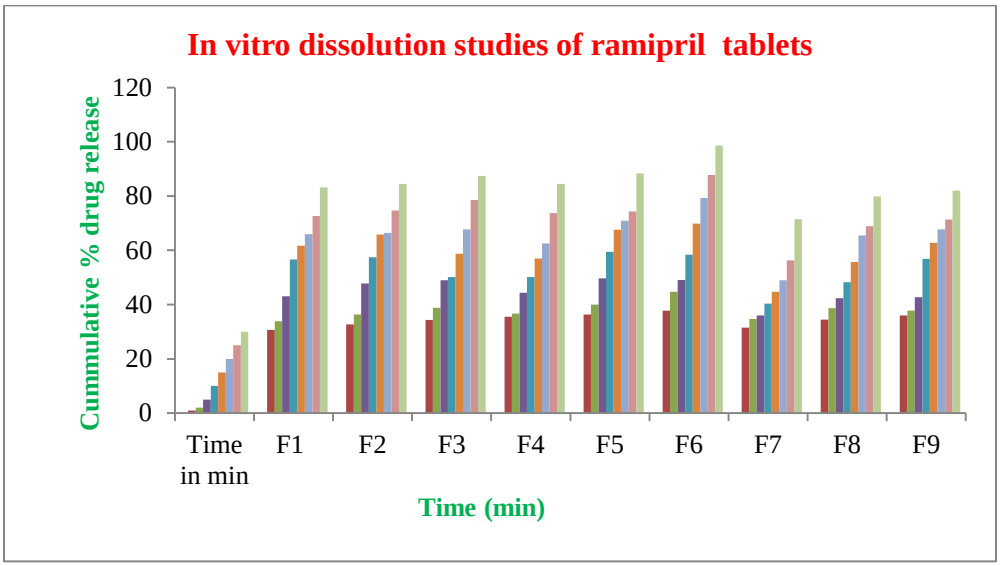


Fig 5: Drug release profile of formulations F1-F9

SUMMARY AND CONCLUSION

In the present work rapid disintegrating tablets of Ramipril by using super disintegrants were prepared by direct compression method. The study demonstrated the effect of three different super disintegrants crospovidone (CP), cros carmellose sodium (CCS), sodium starch glycolate (SSG) on dissolution performance of formulations of oral disintegrating tablets of ramipril hydrochloride. Ramipril HCL 20 mg i.e. tablet weight of 200 mg prepared using different concentration of super disintegrants CCS, CP, SSG in different ratios of 2 %, 4 %, 8% respectively. The dissolution profile of formulations made with disintegrant crospovidone (CP) at 2 %, 4 %, 8 % level were found to be in the order of 84.4 %, 88.5%, 98.6% respectively at the end of 30 minutes. The dissolution profile of formulations made with disintegrant croscarmellose sodium (CCS) at 2 %, 4 %, 8 % level were found to be in the order of 83.1%, 84.5 %, 87.4 % respectively at the end of 30 minutes. The dissolution profile of formulations made with disintegrant sodium starch glycolate (SSG) at 2 %, 4%, 8 % level

were found to be in the order of 71.5%, 79.9 %, 82.0 % respectively at the end of 30 minutes. All the tablets of Ramipril were subjected to weight variation, hardness, friability, in vitro disintegration time, drug content uniformity, water absorption ratio, wetting time, and in vitro drug release. Based on the above studies following conclusions can be drawn. Ramipril Tablets were found to be good and were free from chipping and capping. The low values of weight variation of the prepared tablets indicate weight uniformity within the batches prepared. The hardness of the prepared tablets was found to be in the range of 2 to 4 kg/cm^2.The friability values of the prepared tablets were found to be less than 1%.The in vitro disintegration time of oral disintegrating tablets of Ramipril by using super disintegrants were found to be in the range of 11 to 50 sec fulfilling the official requirements. Based on the in vitro disintegration time, formulation F6 was found to be promising and showed a dispersion time, wetting time of 11 sec and 16 sec respectively, which facilitate the faster dispersion. All the formulations have displayed good water absorption ratio which indicate better and faster swelling ability of the disintegrants in the range of 90 % - 105 % in presence of little amount of water. The drug release from oral disintegrating tablets of Ramipril were found to be in the range of 82.0 % to 98.6 % at the end of 30 minutes. Among all the 9 formulations the best formulation is with 8 % of crospovidone (CP) showed faster disintegration time within 11sec when compared to the other formulations and it showed 98.6 % drug release at the end of 30 mins. Irrespective of disintegrants, increased concentration of disintegrant increases percentage drug release. The dissolution rate and percentage drug release of crospovidone (CP), alone as disintegrant is higher when compared to the tablets with croscarmellose sodium (CCS), sodium starch glycolate (SSG) at initial time points.

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