*Asian J. Pharm. Res. Vol 3, Issue 1, 2013, 9-14.*

**e-ISSN 2231 – 363X**
**Print ISSN 2231 – 3621**

**Asian Journal**
**of**
**PHARMACEUTICAL RESEARCH**
**Journal homepage: - www.ajprjournal.com**

# FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF RAMIPRIL

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**ABSTRACT**

The aim of present work was to show the effect of various super disintegrates on the disintegration time and in vitro drug release rate. In this study, an attempt has been made to prepare rapid disintegrating tablets of the drug using different super disintegrants following wet granulation method. The Tablets were formulated by direct compression method, using Mannitol as diluent. Crospovidone (XL-PVP), croscarmellose sodium (Ac-Di-Sol®), Sodium starch glycolate were used as super disintegrants at different concentrations. The Precompression parameters like bulk density, tapped density, Carr's Index and angle of repose were determined. The post compression parameters like the hardness, thickness, friability, weight variation, Disintegration time, in-vitro dissolution, FT-IR studies were carried out to check whether any interaction had occurred, results were promising. The optimized formulation was selected based on the results and stability studies were carried out on the optimized formulation and the percentage drug release was found to be 97.8%.

**Key words:** Mouth dissolving tablets, Ramipril, Mannitol, Super disintegrants, mouth dissolving tablets.

## INTRODUCTION

The easiest and most preferable route by all the age group are the tablet dosage form. Tough several advantages in drug delivery system have evolved during periods the importance and the usage of tablets still stands the first, preferable route. Among the tablets, mouth dissolving tablets have more advantage for pediatrics, geriatric [1,2], bedridden, disabled patients and also for who may have difficulty for swallowing conventional tablets, capsules and liquid orals. In addition, MDT is applicable when local action is desirable such as oral ulcers, cold sores and teething [3].

Bitter drugs can also be formulated as MDT by masking the taste of the drug by different methods. Ramipril is a prodrug which, after absorption from the gastrointestinal tract, is hydrolysed in the liver to form the active moiety, ramiprilat. Ramipril and ramiprilat inhibit angiotensin-converting enzyme (ACE) which is identical to KININASE II. This converting enzyme (ACE) is a peptidyl dipeptidase that catalyses the conversion of angiotensin I to the vasoconstrictor substance, angiotensin II. Angiotensin II also stimulates aldosterone secretion by the adrenal cortex, thus inhibition of ACE results in decreased plasma angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. The latter decrease may result in a small increase in serum potassium.

Ramipril, a prodrug, is converted to the active metabolite ramiprilat by liver esterase enzymes [4]. Ramiprilat is mostly excreted by the kidneys. The half-life of ramiprilat is variable (3–16 hours), and is prolonged by heart and liver failure, as well as kidney failure. Ramipril is an unpleasant drug, so an attempt has been made to mask the taste of the drug and make feel pleasant in the mouth.

## MATERIALS AND METHODS

### Materials

Ramipril was gifted from Ashupi Life Sciences (Prashanthi Nagar), Mannitol (Drugs India, Hyderabad), Microcrystalline cellulose from Scott pharma (richer pharma), Croscarmellose sodium (Drugs India, Hyderabad), Sodium starch glycolate (Drugs India, Hyderabad), crospovidone (Rexer Pharma Drugs India, Hyderabad), Asparmate (Bio leo laboratories, Andhra Pradesh), Micro crystalline cellulose (S.D.Fine Chemicals, Hyderabad). All other chemicals used in the formulation were of analytical grade.

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**Preparation of Ramipril By Direct Compression Method**

The required amount of the active ingredient, disintegration agents are weighed and mixed. This was mixed properly in polyethylene bag for 15mins. To the above mixture add lubricants compressed the tablets in 6mm diameter concave shape punch.

**Physical Properties of Tablets**

Physical properties such as bulk density, tapped density, Hausner's ratio, angle of repose and cars index were determined [5-7].

**Loose Bulk Density (LBD) and Tapped Bulk Density (TBD)**

LBD and TBD were determined by transferring the granules without any agglomerates into a 10ml measuring cylinder and dropping on to a hard surface from 2.5cm height for every 2 seconds interval. The tapping is continued until the volume remains constant. The initial volume occupied by the granules without tapping of cylinder and the final volume occupied by the granules was noted and substituted in the below equation.

**Hausner's ratio**

Hausner's ratio is calculated by using following equation

$$\text{Hausner's ratio} = \frac{Tapped\ density}{Bulk\ density}$$

**Carr's index**

Carr's index is calculated by using below equation.

$$\text{Carr's index (\%)} = \frac{TBD - LBD}{TBD} \text{X}100$$

**In vitro evaluation of bitter taste of mixture**

The drug was accurately weighed and 10ml of phosphate buffer ($p^H$ 6.8) was transformed into 50ml volumetric flask and stirred continuously at 50rpm. The samples were withdrawn at 0, double of 15 time intervals till 120sec. The samples are filtered immediately after withdrawal and filtered through Whattmann filter paper no.41, and the concentration in the filtrate was determined. Time taken for the mixture to obtain drug concentration representing to threshold bitterness in 10ml of phosphate buffer ($p^H$ 6.8) was recorded.

**In vivo evaluation of bitter taste of mixture**

The bitter taste of the mixture was tested by time intensity method by taking 10 healthy human volunteers and collecting the informed consent. DRC equivalent to 100mg was placed on the tongue and at regular time intervals bitterness was tested and rated as 0, 0.5,1,2 and 3 indicate no, threshold, slight, moderate and metallic taste.

**Evaluation of Tablets**

Tablets were evaluated for hardness by using Monsanto hardness tester, friability by Roche Fribilator, weight variation [8], wetting time, water absorption ratio [9], in vitro-in vivo disintegration time, in vivo taste evaluation, sensory evaluation of roughness and dissolution study.

**Wetting time and water absorption ratio**

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. The time required for water to reach upper surface of the tablet is noted as a wetting time. A piece of tissue paper folded double was placed in a Petri plate (internal diameter is 6.5 cm) containing 6ml of water. The tablet was placed on the paper, and the time for complete wetting of the tablet was measured. The method was slightly modified by maintaining water at $37^o$ c. A tablet was placed on the tissue paper, and a small amount of amaranth powder was placed on the upper surface of the tablet. The time required for development of a red color on the upper surface of the tablet was recorded as wetting time [8,9].

The wetted tablet was weighed and water absorption ratio, R, was calculated by using the fallowing equation,

$$R = 100 \times \left( \frac{W_b - W_a}{W_a} \right)$$

Where, $W_a$ is weight of tablet before water absorption.

**In vitro disintegration study**

The In vitro disintegration time was determined using USP disintegration test apparatus with phosphate buffer ($p^H$ 6.8). A tablet was placed in each of the six basket tubes of the apparatus, and one disc was added to each tube. After complete disintegration a time was recorded [9].

**In vivo disintegration time, sensory evaluation of roughness**

The test was performed by taking 6 healthy human volunteers, from whom the informed consent was noted. The tablet was placed on the mouth and the time taken for disintegration was noted. A further 60sec should be remained in the mouth after the disintegration without swallowing, and roughness levels were recorded on a numerical scale ranging from 0-3, where 0,1,2 and 3 indicate no, slight, moderate and high roughness, respectively [10,11].

**In vivo taste evaluation**

The metallic taste of the tablets was tested by time intensity method by taking 10 healthy human volunteers and collecting the informed consent. Tablets containing 5mg of Ramipril was placed in the mouth and at regular time intervals bitterness was tested and rated as 0, 0.5,1,2 and 3 indicate no, threshold, slight, sweet taste [12].

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**Dissolution study**

In vitro dissolution of all formulations was done in 500ml of stimulated gastric fluid by using USP type II (paddle) apparatus by maintaining temperatures at 37±0.5$^0$c and rotation speed at 50rpm. 5ml of sample were withdrawn at regular time interval and replaced with same quantity of fresh dissolution medium. Withdrawn samples were analyzed spectrophotometrically at 205nm [13].

**Stability studies**

Stability studies were conducted for the best formulation at 40 ± 2$^0$C / 75 ± 5% RH for 3months. Samples are withdrawn at initial, 1, 2 and 3 months and evaluated for percentage of drug release, drug and moisture content [14].

**RESULTS AND DISCUSSION**

**Table 1. Formulation of Ramipril MDT's**

| Ingredients (mg) | FR1 | FR2 | FR3 | FR4 | FR5 | FR6 | FR7 | FR8 | FR9 |
|---|---|---|---|---|---|---|---|---|---|
| **Ramipril** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Mannitol** | 111.5 | 108.5 | 105.5 | 111.5 | 108.5 | 105.5 | 111.5 | 108.5 | 105.5 |
| **MCCP 101** | 22.5 | 22.5 | 22.5 | 22.5 | 22.5 | 22.5 | 22.5 | 22.5 | 22.5 |
| **SSG** | 3 | 6 | 9 | - | - | - | - | - | - |
| **CP** | - | - | - | 3 | 6 | 9 | - | - | - |
| **CCS** | - | - | -- | - | - | - | 3 | 6 | 9 |
| **Aerosil** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |

Cp-Crospovidone, SSG-Sodium Starch Glycolate, CCS- Cross Carmellose Sodium,MCCP- Microcrystalline cellulose powder

**Table 2. Blend Evaluation**

| Formulation | Bulk Density (gm/cm$^2$) | Tapped Density ((gm/cm$^2$) | Carr's Index | Hausener's Ratio | Angle of Repose |
|---|---|---|---|---|---|
| **F1** | 0.390 | 0.500 | 22 | 1.28 | 28.1 |
| **F2** | 0.378 | 0.510 | 25.88 | 1.35 | 30.9 |
| **F3** | 0.387 | 0.496 | 22 | 1.28 | 27.2 |
| **F4** | 0.364 | 0.506 | 28.06 | 1.39 | 31.3 |
| **F5** | 0.393 | 0.510 | 22 | 1.32 | 32.6 |
| **F6** | 0.416 | 0.516 | 19.37 | 1.24 | 34.6 |
| **F7** | 0.374 | 0.514 | 27.23 | 1.37 | 28.3 |
| **F8** | 0.388 | 0.526 | 26.23 | 1.36 | 26.7 |
| **F9** | 0.396 | 0.511 | 25.50 | 1.29 | 29.4 |

**Table 3. In Vitro and In Vivo Evaluation of Taste**

| Mixture | In vitro taste evaluation | In vivo taste evaluation | | |
|---|---|---|---|---|
| | | 0 Sec | 30 Sec | 1min |
| Drug alone | <1min | 3 | 3 | 3 |
| 1:1 | <2 min | 0 | 1 | 2 |
| 1:1.5 | >4.5 min | 0 | 0 | 0 |
| 1:2 | >4.5 min | 0 | 0 | 0 |

**Table 4. Evaluation of MDTS**

| Formulation | Hardness (Kg /cm$^2$) | Friability (%) | Thickness (mm) | Disintegration time (sec) | Weight variation (a.w) (mg) |
|---|---|---|---|---|---|
| **F1** | 3.5 | 0.41 | 2.5 | 112 | 132 |
| **F2** | 3.8 | 0.46 | 2.4 | 115 | 130 |
| **F3** | 3.6 | 0.48 | 2.4 | 103 | 131 |
| **F4** | 4.1 | 0.42 | 2.3 | 124 | 132 |
| **F5** | 3.8 | 0.49 | 2.5 | 121 | 133 |
| **F6** | 3.5 | 0.45 | 2.5 | 124 | 131 |
| **F7** | 3.5 | 0.44 | 2.4 | 127 | 130 |
| **F8** | 3.6 | 0.47 | 2.5 | 114 | 127 |
| **F9** | 3.8 | 0.49 | 2.3 | 131 | 132 |

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**Table 5. In Vivo Evaluation of Disintegration, Roughness and Taste**

| Test | Formulation | | | | | |
|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 |
| In vivo disintegration(Sec) | 123±1.13 | 116±1.27 | 97 ± 1.25 | 83 ± 1.16 | 56 ± 1.06 | 41 ± 1.02 |
| Sensory evaluation of roughness | 0 | 0 | 0 | 0 | 0 | 0 |
| In vivo taste evaluation | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 6. Dissolution Table of Formulations in phosphate buffer 6.8**

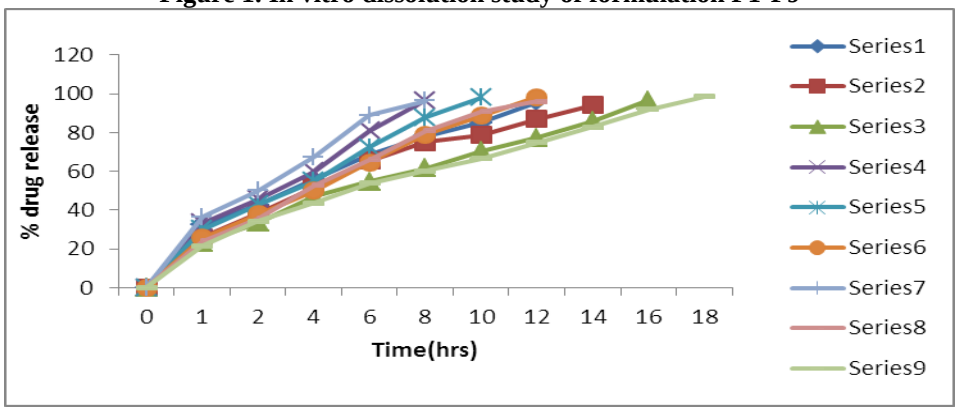
| Time in min | 2min | 4min | 6min | 8min | 10min | 12min |
|---|---|---|---|---|---|---|
| FR1 | 22.23 | 34.61 | 51.48 | 61.34 | 70.32 | 87.54 |
| FR2 | 25.63 | 38.44 | 57.06 | 65.94 | 73.82 | 93.47 |
| FR3 | 26.4 | 42.61 | 58.27 | 68.24 | 82.59 | 96.55 |
| FR4 | 41.18 | 48.52 | 61.56 | 63.31 | 64.84 | 76.89 |
| FR5 | 35.49 | 46.66 | 54.44 | 64.29 | 71.86 | 88.79 |
| FR6 | 28.7 | 43.6 | 53.34 | 60.9 | 70.65 | 91.11 |
| FR7 | 39.87 | 50.16 | 57.28 | 65.39 | 67.03 | 78.97 |
| FR8 | 34.18 | 44.14 | 60.02 | 68.35 | 76.78 | 85.54 |
| FR9 | 27.82 | 42.28 | 57.28 | 66.16 | 75.14 | 90.44 |

**Table 7. Stability Data of Optimized Formulation F6 at 40±20°c / 75±5% RH.**

| S.No | Time in Days | Physical Changes | % age of drug content*±SD | Moisture content | % age of drug release |
|---|---|---|---|---|---|
| 1 | 1st day (initial) | Round, yellow colour uncoated tablets with plain on both side. | 99.51±0.48 | 0.82 | 99.5% |
| 2 | 30th day ($1^{st}$ month) | No changes | 99.35±0.11 | 0.78 | 99.2% |
| 3 | 60th day ($2^{nd}$ month) | No changes | 98.12±0.13 | 0.80 | 99.3% |
| 4 | 90th day ($3^{rd}$ month) | No changes | 97.81±0.28 | 0.78 | 99.2% |

* SD- Standard deviation

**Figure 1. In vitro dissolution study of formulation F1-F9**




## DISCUSSION

The present work is conveyed to mask the bitter taste of Ramipril and to formulate it as an mouth dissolving tablet. Mannitol is used for masking the taste of the drug and the mixture was prepared by co-grinding method. Since Mannitol does not stimulate an increase in blood glucose and is therefore, used as a taste masking agent and also as a sweetener in present formulations. In vitro taste masking evaluation studies revealed that mixture prepared with 1:1 ratio of drug and Mannitol failed to mask the taste of the drug and the bitter taste appeared less than 1min. In addition, 1:1.5 combination

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mixture shown better taste masking capacity and the bitterness was not appeared more than 4.5min, so 1:1.5 combination mixture was selected as the best one and further formulations was done. Furthermore in vivo evaluation studies were also done on granules for finding out the desirable ratio of drug-Mannitol mixture. The results were tabulated in table 1.

Formulations were developed by using 1:1.5 drug-Mannitol mixtures. Super disintegrants like SSG, CCS and crospovidone were added. All the formulations passed preformulation studies like angle of repose, bulk density, tapped density, hausner ratio, carr's index, disintegration time, wetting time, roughness and water absorption capacity. All the formulations were evaluation for weight variation, hardness, friability, thickness, disintegration, wetting time, water absorption capacity and dissolution. The hardness for all the formulations was within 3-3.5kg/cm$^3$, which is desirable range for oral disintegration tablets. An in vitro and in vivo disintegration test was conducted for all the formulations, and the disintegration time for the formulation F3 prepared with SSG was fast when compared to other formulations and it was tabulated in table 5. The disintegration rate has a correlation with water absorption capacity of the disintegrant. SSG has great water absorption capacity of 96.55% so because of high water absorption capacity the tablet may be disintegrated in less time. So among all the formulations F3 was selected as the best because of lesser disintegration time and further stability studies was done. Dissolution rate depends on the wetting time of the disintegrant, among all the formulations F3 has less wetting time and has greater dissolution rate. So this is the other conformation test for correct selection of desirable formulation.

All the formulations passed the roughness test this indicates that all the formulations do not contain any gritty particles and produce fine dispersion during disintegration. In vitro taste evaluation and roughness of all the formulations was shown in the table 6. All the tablets have good palatable taste without any evidence of bitterness.

The formulation F2 shows 93.47% of drug release at 12min, and it was high when compared to F1. In addition, F4 shows a slight difference in the release rate at 12min when compared to F2 but for F6 shown a 70.65% of drug release at 10min and 91.11% at 12min. It is characterized that as the concentration and type of disintegrant has shown a change in the dissolution rate, and the formulation F6 prepared with CCS has greater wetting capacity leading to enormous dissolution compared to F5, so the dissolution rate was high.

The best formulation F3 was subjected for stability studies at 40 ± 2$^0$C / 75 ± 5% RH for 3 months. Parameters like drug content, moisture content and % of drug release were determined at regular time intervals. It is clear from the results that the formulation remained stable without any physical changes (table 7).

## CONCLUSION

In conclusion, overall results suggests that the mouth dissolving tablets containing 9mg of SSG (F3) shows the best results in terms of percent drug release (96.55%). So it is considered as the better disintegrating agent. Thus mouth dissolving tablets can be developed for Ramipril, for quick onset of action without need of water for swallowing or administration.

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