"FORMULATION AND EVALUATION OF MELT-IN-MOUTH TABLETS OF LOSARTAN POTASSIUM AND RAMIPRIL"

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ABSTRACT

The goal of the study was to design and assess melt-in-mouth tablets of Losartan potassium (LP) and Ramipril (RM) utilizing various superdisintegrats to improve drug bioavailability and patient compliance. Melt-in-mouth tablets of LP and RM has been made by direct compression of drugs with diluents and different super disintegrating agents such as sodium starch glycolate and croscarmellose sodium. Weight uniformity, thickness, strength, percent friability, content uniformity, wetting time, water absorption capacity, disintegration time, and *in-vitro* dissolution tests were performed on the powders obtained. All of the parameters' findings are within the acceptable range. According to the findings, formulation F8, which contains 5% w/w sodium starch glycolate, was the best formulation, with the shortest wetting and disintegration time and the highest drug release (94.790.3% LP and 97.980.53%RM) after 20 minutes. Based on outcomes such as drug content, dissolution time, and drug release, melt-in-mouth tablets of LP and RM were found to be appropriate for oral administration.

Key words: Melt-in-mouth tablet, Losartan potassium(LP), Ramipril(RM) sodium starch glycolate and croscarmellose sodium.
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INTRODUCTION

Oral drug delivery is the most extensively used among all the dosage forms and are preferred because of its ease of administration, patient acceptability, convenient, safe, cost-effective and simple manufacturing procedure. Fast dissolving or orally disintegrating tablet dosage form is a superior choice for oral medication to improve the quality of life and treatment compliance of such patients[1]. The concept of a melt-in-mouth or oro-dispersable tablet was devised to meet all of these requirements. These tablets dissolve in saliva without the need for drinking water in 15 to 60 seconds, allowing for rapid absorption and activity. The melt-in-mouth tablets should disperse/disintegrate in less than three minutes, according to European pharmacopoeia[2].

Melt-in-mouth tablets are solid dosage forms that, when placed on the tongue, instantly disintegrate or dissolve, releasing the medicine in a matter of seconds without the use of water. These dose formulations have a quick beginning of effect and are well-accepted by patients. "Oro-dispersable," "Orally disintegrating," "Mouth dissolving tablet's" "Fast dissolving," "Porous," and "rapid dissolving" tablets are all terms used to describe melt-in-mouth tablets and enable for substantial drug loading without the requirement for chewing.[1-4].

Losartan potassium and Ramipril were preferred as model drugs for the proposed study based on the drug information listed below.

Losartan potassium is an antagonist of the angiotensin II receptor. It blocks the rennin-angiotensin system by suppressing the actions of angiotensin II at its receptors. The renin-angiotensin system is critical for blood pressure regulation. Losartan potassium has been shown to be superior to other peptide receptor antagonists and angiotensin converting enzyme (ACE) inhibitors due to its improved specificity, selectivity, and tolerability. In general, losartan potassium is used to treat essential hypertension because it has less side effects, such as cough. It is quickly absorbed and converted to an active metabolite, EXP3174, in the liver via the cytochrome P450 system. Due to first-pass metabolism, it has a limited bioavailability (33 %). It has a half-life of 1.5 to 2 hours.[5-9].

Ramipril is a short-acting prodrug that is converted to its active form ramipril by liver esterase enzymes (3-16 hours). Because it is an unpleasant medicine, it can be made to disguise the bitter taste and make the mouth feel nice. Ramipril reduces angiotensin II production, which relaxes arterial muscles while also widening the arteries. As a result of the increased blood flow, the heart can pump blood more efficiently, and more blood is pumped into and through wider passageways. Ramipril has a low bioavailability of 28-30%, and the amount absorbed is completely unchanged by meal consumption.[10-11].

The goal of this study was to establish a simple, precise, accurate, and repeatable method for simultaneously estimating LP and RM in the formulation, which is a key metric for determining how much of drug concentration is present in a combination. In addition, efforts were made to design and characterize oro-dispersible tablets of LP and RM in order to increase dissolution rate and patient compliance, as well as to develop methods of administration for patients who are unable to swallow ordinary tablets or patients can experience motion sickness. The main concept behind the development of such a dosage form is the use of super disintegrates, such as croscarmellose sodium and sodium starch glycolate, which burst the tablets as soon as they are placed over the tongue, releasing the medication into the saliva. Mannitol was also used as a

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sweetener in the mixture. These technologies could produce superior results by enhancing medication bioavailability.

MATERIALS

Reagents and chemicals: Losartan potassium and Ramipril were obtained from Centaur pharmaceuticals, Goa and Unichem laboratories, Solan, HP. Croscarmellose Sodium and Sodium Starch Glycolate were obtained as a gift sample from Wallace Pharma, Goa. Microcrystalline Cellulose and mannitol were obtained from SD Fine Chemical, Mumbai, India. Talc and Magnesium stearate were obtained as a gift sample from Loba Chemical, Mumbai. All chemicals and reagents were obtained as analytical grade.

Preparation of buffer and Reagents

Sodium hydroxide, 0.2M: Make up a 1000 ml volume with water by dissolving 8.0 g of sodium hydroxide in water

Potassium Dihydrogen ortho-phosphate, 0.2M: Make up to 1000 ml of water by dissolving 27.218 g of potassium dihydrogen phosphate in it.

Preparation of Phosphate Buffer (pH 6.8): In a 100 ml volumetric flask, 50 ml of 0.2 M potassium dihydrogen ortho-phosphate solution was added, followed by 22.4 ml of 0.2 M sodium hydroxide solution. The volume was then increased to the required level with distilled water.

METHODS

I. Preformulation studies: To identify and determine the purity of the materials, relevant procedures such as melting point, IR spectral analysis, compatibility studies and λ_{max}[5].

Melting point determination:

A drug sample's melting point was determined by placing a small amount of the drug in a capillary tube sealed at one end, placing it in a digital melting point apparatus and recording the temperature range at which the drug melts.

FT-IR spectroscopy: The obtained sample's IR spectrum was compared to the standard IR spectrums of LP and RM.

Compatibility studies of pure drugs and polymers by FT-IR spectroscopy: -FT-IR spectra are useful for confirming the identity of a drug and detecting drug-excepient interactions. To test the compatibility of drug and polymers. IR spectroscopy of pure drug, physical mixtures of drug and polymers was performed using a Shimadzu FT-IR spectrometer (00518). The IR spectra of a drug containing polymers were compared to a pure drug's standard IR spectrum. [12-13].

II. Analytical method development for simultaneous estimation of Losartan potassium and Ramipril by simultaneous equation method

a) **Determination of λ_{max}:** The λ_{max} of LM and RM were determined in phosphate buffer of pH 6.8 which was scanned between 200-400 nm in the UV spectrophotometer. The λ_{max} of LM and RM was found to be 224nm and 205nm respectively.

b) **Determination of calibration curves**

- **Calibration curve of Losartan potassium:** 100 mg of LP was precisely weighed and dissolved in 100 mL of phosphate buffer solution at a pH of 6.8. 2 mL of the above-mentioned stock solution was diluted with phosphate buffer solution in a 100mL volumetric flask (pH 6.8). From the stock solution, aliquots of 1.0, 2.0, 3.0, 4.0, and 5.0 ml were obtained and placed in a 10 ml volumetric flask. It was subsequently diluted to reach a volume of 10 ml, providing concentrations of 2, 4, 6, 8, and 10 g/ml. The absorption of each concentration was taken at 224 nm using a Shimadzu UV-1800 UV Visible double beam spectrophotometer.

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- **Calibration curve of Ramipril:** 100 mg of RM was precisely weighed and dissolved in 100 mL of phosphate buffer solution at a pH of 6.8. 2 mL of the above-mentioned stock solution was diluted with phosphate buffer solution in a 100mL volumetric flask (pH 6.8). From the stock solution, aliquots of 1.0, 2.0, 3.0, 4.0, and 5.0 ml were obtained and placed in a 10 ml volumetric flask. It was subsequently diluted to reach a volume of 10 ml, providing concentrations of 2, 4, 6, 8, and 10 g/ml. The absorption of each concentration was taken at 205 nm using a Shimadzu UV-1800 UV Visible double beam spectrophotometer.
- **Simultaneous estimation using simultaneous equation method**
  The method involves measuring absorptivity at its maximum λmax. LM at 224 nm and RM at 205 nm (X and Y) wavelengths were chosen for the development of simultaneous estimation in the formulations. The parameters required are
  (a) The absorptivity value of X at two wavelengths λ_1 and λ_2 are Ax_1 and aX_2 respectively,
  (b) The absorptivity of Y at two wavelengths $\lambda_1$and λ_2 are aY_1 and Ay_2 respectively, and
  (c) diluted sample absorbances at λ_1 and λ_1 are A_1 and A_2 respectively.
  Let Cx and Cy be the concentrations of LM and RM respectively in the diluted sample. Two equations are derived based on the truth that the absorbance of combinations of two drugs is the total of the individual absorbance of LM and RM λ_1 and λ_2.

$$Cx = \frac{(A_2 \times ay_1) - (A_1 \times ay_2)}{(ax_2 \times ay_1) - (ax_1 \times ay_2)}$$

$$Cy = \frac{(A_1 \times ax_2) - (A_2 \times ax_1)}{(ax_2 \times ay_1) - (ax_1 \times ay_2)}$$

Where, A_1 = absorption of sample at 224nm.
A_2 = absorption of sample at 205 nm.
aX_1 = absorptivity of Losartan potassium at 224 nm.
aX_2 = absorptivity of Ramipril at 205 nm.
aY_1 = absorptivity of Losartan potassium at 224 nm.
aY_2 = absorptivity of Ramipril at 205 nm.
Cx and Cy are concentration of Losartan potassium and Ramipril in sample solution[14-15]

III.Preparation of mouth dissolving tablets using Losartan potassium and Ramipril

LP and RM melt-in-mouth tablets were made using a direct compression process. To make melt-in-mouth tablets, different superdisintegrats with varying concentrations were used, and numerous formulations are presented in **Table no 1.** All of the ingredients for the LP and RM melt-in-mouth tablets were weighed and mixed in a mortar with a pestle, then talc and magnesium stearate were added and the material was slightly compressed on an 8mm flat-faced punch using a proton eight station mini press tablet machine. The formulation's total weight was kept at 200mg, and the manufactured tablets were employed for further testing.[16-17].

IV. Pre-compressional evaluations

Angle of repose: The fixed funnel method was used. The powdered mixture was passed through a cut funnel until the highest pile height (h) was reached, at which point the radius of the base pile was evaluated and the angle of repose was calculated by using the equation.

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

Where,
θ = Angle of repose,

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h = Height of pile
r = Radius of the base of the pile.

Bulk density: Bulk density (ρb) was measured using a bulk density apparatus. The volume (Vb) occupied by a given weight of powder (M) was measured, and the bulk density was computed using the formula.

$$\text{Bulk density } (\rho_b) = \frac{M}{Vb}$$

Tapped density: The powder mixture was placed in a measuring cylinder and tapped for a predetermined amount of time. The powder's true volume (Vt) and weight (M) were recorded. The formula was used to calculate the tapped density (ρt).

$$\text{Tapped density } (\rho_t) = \frac{M}{Vt}$$

Hausner's ratio: Hausner's ratio is the ratio of tapped to untapped bulk density. The formula was used to determine it.

$$\text{Hausner's ratio} = \frac{\rho t}{\rho b}$$

Where, ρt is tapped bulk density and ρbis untapped bulk density. The Lower Hausner's ratio (<1.25) indicates better flow properties than the higher ones(>1.25).

Carr's consolidation index: The powdered mix's Carr's consolidation index (CI) (%) was calculated using the formula[18-19].

$$\text{Compressibility index (CI)} = \frac{\text{Tapped density } (\rho t) - \text{Bulk density } (\rho b)}{\text{Tapped density } (\rho t)} \text{x } 100$$

V. Postcompression Parameters

Weight variation test: Twenty tablets were chosen at random, and the weight of each tablet as well as the total weight of all tablets was recorded. The collective weight was divided by the average weight of one tablet, and the percentage weight deviation was calculated.[20].

Thickness: Vernier callipers were used to measure the thickness of ten tablets. It is expressed in millimetres, and the standard deviation has been calculated.

Hardness: Monsanto hardness testers are used to determine tablet hardness. The hardness tester was used to measure the strength required to crush a tablet. It is measured in (kg/cm2).

Friability: The Roche friabilator has been used to calculate the percentage friability. Twenty tablets were chosen at random, and the total weight of all tablets was recorded. These tablets were charged to the friabilitor. The apparatus was allowed to rotate at a rate of 25 rotations per minute for four minutes, for a total of 100 revolutions. The tablets were collected, and their weights noted. The weight difference before and after testing was calculated, and the percent friability was calculated using the formula below.

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

Drug content uniformity: This test was carried out by selecting five tablets at random. These tablets were crushed with a glass mortar and pestle. In a volumetric flask, an accurately weighed tablet was dissolved in 100 ml of pH 6.8 phosphate buffer solution. The resulting solution was clarified, and the content was determined using a UV spectrophotometer at 224nm and 205nm.

Wetting time: In a petridish containing 6 ml of water, double-folded tissue paper was placed. One tablet was placed on this paper, and the time required for complete tablet wetting was recorded.

Water absorption ratio: A petridish containing 6 mL of water was filled with double-folded tissue paper. One tablet was placed on this paper, and the weight of the wetted tablet was recorded. The water absorption ratio, R, was calculated using the formula.

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$$R = \frac{Wa-Wb}{Wb} X\ 100$$

Where, Wa = Weight of tablet before water absorption, Wb = Weight of tablet after water absorption.

Disintegration test: The disintegration period of the tablets was measured using a disintegration test device in distilled water. In each of the basket's six tubes, one tablet was deposited. The basket assembly was placed in a water bath that was kept at 37 ± 2°C. The time in seconds taken for the tablet completely disintegrate and leave no bulk in the instrument was measured.

***In-vitro* Dissolution test:** LM and RM melt-in-mouth tablets were tested *in-vitro* using a USP type – II dissolution apparatus (Electrolab – TDT – 08L). As a dissolution medium, 900 ml of pH 6.8 phosphate buffer solution was used, which was kept at 370±0.5o C with a rotation speed of 50 rpm. At regular intervals, 5 mL aliquots were removed and replaced with the same amount of fresh solution. The materials were filtered and diluted to a sufficient concentration with phosphate buffer solution pH 6.8. The absorbance of the solution was measured at 224 and 205 nm using a UV-Visible spectrophotometer (Shimadzu UV -1800)[21-25].

VI. **Stability Studies**: The prepared melt-in-mouth tablets were packed in appropriate packaging and stored for 3 months under the conditions specified by ICH guidelines. At an interval of 30 days, samples were taken and analyzed for physical characterization such as visual defects, hardness, friability, disintegration time, dissolution rate and drug content[26].

RESULTS AND DISCUSSION

The simultaneous equation approach, which is simple, quick, and accurate for LP and RM, was used among the numerous analytical methods. The obtained medication samples were confirmed to meet the purity standards based on the findings of IR and melting point examinations. The findings of the compatibility study show that medications and excipients do not interact. Indicates that the little faults had no effect on the method. Direct compression method was used to develop LP and RM melt in mouth tablets with superdisintegrats croscarmellose sodium and sodium starch glycolate. As shown in **Table no 2** the results of pre-compression parameters such as powder flow, Hausner's ratio, density measurement and percentage consolidation index revealed that all of the formulations were within the standard limits, indicating that the powder mix of all of the formulations was free flowing. According to the results of post-compression given in **Table no 3 and** in **Table no 4** such as the weight variation test, all batches of tablets were found to be consistent, with the least percent weight fluctuation and to be within the standard range. The order was Croscarmellose sodium SSG, and the disintegration time of prepared melt-in-mouth tablets was in the range of 26.13±0.30 to 99.3±1.115 seconds. This observation is consistent with wetting time results, as SSG swells more with gelling than Croscarmellose sodium, extending disintegration time as a result. The disintegration time decreased as the concentration of superdisintegrats in the formulations also increased. The drug content of the produced tablets ranged from 95.34±0.59 to 99.18±1.11 for LP and 91.99±1.06 to 98.27±0.83 for RM, suggesting that the drug content in the tablets was homogeneous. Using USP dissolving apparatus type 2, an *in-vitro* dissolution investigation of the produced melt-in-mouth tablets was done in phosphate buffer solution at pH 6.8. It was observed that as the concentration of superdisintegrats increased the drug release also increased. With reference to the type of superdisintegrats, the release rate was found to be 78.36±1.84 to 94.79±0.35 for LP and 85.57 ±0.49 to 97.98 ±0.53 RM respectively at the end of 20 min. The better drug release from the F8 tablet could be due to sudden dissolution fluid uptake into the tablet, which causes swelling and bursting of the tablets. These disaggregated particles dissolve quickly in the dissolution medium,

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increasing the drug dissolution rate. According to the findings of the stability study, there was little variation in the physical appearance, drug content, wetting time, and in-vitro release of drugs studies, the results is depicted in **Table no 5.**

CONCLUSION

An attempt has been made to manufacture rapid dissolving tablets containing LP and RM using various superdisintegrats such as croscarmellose sodium and sodium starch glycolate through the use of direct compression method using various superdisintegrats such as croscarmellose sodium and sodium starch glycolate. According to the findings, the tablet containing 10% w/w sodium starch glycolate had the quickest disintegration time, drug content, and in-vitro drug release, so F8 was selected as the best formulation.

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Table no 1. Composition of Losartan potassium and Ramipril mouth dissolving tablets

Ingredients* (mg)	Formulation Code							
	F1	F2	F3	F4	F5	F6	F7	F8
Losartan potassium	50	50	50	50	50	50	50	50
Ramipril	5	5	5	5	5	5	5	5
Croscarmellose Sodium	2	4	6	8	-	-	-	-
Sodium starch glycolate	-	-	-	-	2	4	6	8
MCC	50	50	50	50	50	50	50	50
Mannitol	89	87	85	83	87	85	83	81
Mg stearate	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2
Total-wt(mg)	200	200	200	200	200	200	200	200

Table no 2: An examination of the derived properties of the F1-F8 formulation

Formulation code	Angle of repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Compressibility index (%)
F1	27.44±0.92	0.316±0.005	0.35±0.005	1.12±0.0028	11.20±0.16
F2	27.46±0.90	0.366±0.028	0.42±0.040	1.15±0.017	13.26±1.32
F3	27.46±0.90	0.363±0.032	0.42±0.043	1.15±0.017	13.39±1.30
F4	27.16±0.52	0.336±0.025	0.37±0.034	1.12±0.057	11.66±0.45
F5	27.46±0.90	0.333±0.020	0.38±0.028	1.14±0.025	12.96±1.84
F6	29.67±0.75	0.353±0.045	0.40±0.060	1.14±0.025	12.13±0.63
F7	27.16±0.52	0.370±0.034	0.42±0.046	1.15±0.017	13.16±1.15
F8	29.67±0.75	0.366±0.028	0.43±0.036	1.17±0.03	13.97±1.28

Note: The values indicated are the arithmetic mean SDs of three determinations.

Table no 3: Evaluation of post compression parameters of F1-F8 formulation

Formulation code	Uniformity of weight(mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%))	Wetting time (Sec.)	Water absorption ratio (%))	In-vitro disintegration test (Sec.)
F1	195.33±0.57	3.67±0.025	3.16±1.58	0.10	49.10±0.45	48.16±1.14	99.3±1.15
F2	202.33±1.52	3.76±0.020	3.10±1.55	0.13	38.07±0.52	57.26±1.46	67.66±0.55
F3	198.33±0.57	3.75±0.005	3.53±1.76	0.15	27.06±0.41	69.35±1.21	41.53±1.10
F4	201.33±0.57	3.77±0.023	2.76±1.38	0.17	26.13±0.35	71.47±1.91	29.16±0.35
F5	197.66±1.52	3.69±0.20	3.43±1.71	0.15	45.86±0.41	50.08±0.15	83.01±1.38
F6	201.33±1.15	3.70±0.011	2.92±1.46	0.12	32.80±0.40	58.89±0.67	57.31±1.01
F7	196.66±0.57	3.76±0.011	3.11±1.55	0.12	25.86±0.70	71.77±1.12	35.93±1.53

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F8	**201.66±1.52**	**3.74±0.01**	**3.70±1.85**	**0.13**	**23.90±0.65**	**75.51±1.22**	**26.13±0.30**

Note: The values indicated are the arithmetic mean SDs of three determinations.

Table no 4. Measurement of drug content and percentage cumulative drug release

Formulation code	% Drug content		% Cumulative drug release	
	Losartan potassium	Ramipril	Losartan potassium	Ramipril
F1	98.35±1.20	93.89±0.70	78.36±1.84	85.57±0.49
F2	97.45±0.68	91.99±1.06	83.02±1.12	88.93±2.83
F3	98.01±0.13	94.88±0.81	86.12±1.35	93.35±1.00
F4	97.94±1.32	95.40±0.15	90.52±0.13	94.08±1.84
F5	95.34±0.59	98.19±0.40	81.79±0.98	86.89±1.3
F6	96.06±1.20	94.91±0.79	84.39±1.72	89.45±0.93
F7	98.55±1.37	98.27±0.83	87.85±1.87	94.35±1.55
F8	99.18±1.11	95.02±0.68	94.79±0.35	97.98±0.53

Note: The values indicated are the arithmetic mean SDs of three determinations.

Table no 5: Evaluation of Stability studies of F8 formulation

Parameters	After one month		After two month		After three month	
Formulation (F_8)	Losartan potassium	Ramipril	Losartan potassium	Ramipril	Losartan potassium	Ramipril
Physical appearance	No change		No change		No change	
Wetting time (Sec)	23.2		24.5		23.9	
In-vitro Disintegration time(Sec)	26.5		25.7		26.1	
Drug content (%)	97.88	95.19	99.90	94.25	99.73	95.59
% CDR at 20Min.	94.58	98.28	95.19	97.38	94.58	98.28

Table no 6: Assessment of Mathematical kinetic model for F1-F8 formulations

Formulation Code	Mathematical models (kinetics r- value)				
	Losartan potassium		Ramipril		Best fitted model
	Zero Order	First Order	Zero Order	First Order	
F_1	0.931	0.980	0.932	0.986	First order
F_2	0.943	0.986	0.864	0.984	First order
F_3	0.942	0.968	0.928	0.975	First order
F_4	0.935	0.961	0.900	0.985	First order
F_5	0.921	0.983	0.896	0.984	First order
F_6	0.936	0.984	0.857	0.994	First order
F_7	0.939	0.967	0.917	0.979	First order
F_8	0.929	0.961	0.881	0.978	First order

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