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Research article on formulation and evaluation of ramipril fast mouth dissolving tablet

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Abstract
The aim of present study was to formulate and evaluate fast mouth dissolving tablets of ramipril for the treatment of hypertension. In the present study the fast mouth dissolving tablets were prepared by direct compression by using various proportions of different superdisintegrants. To achieve the desired dissolution profile, sublimating agent like camphor was used. The uncoated tablets were evaluated for hardness, thickness, friability, weight variation, drug content, and disintegration time and *in-vitro* drug release. *In-vitro* drug release was found to be 99.05% from uncoated tablets in 33 min. FT-IR spectra revealed that there is no chemical incompatibility between the drug and other excipients. The results concluded the programmable pulsatile release has been achieved from uncoated tablets after a lag time of 33 min, which is consistent with the demands of the FMDTs drug delivery and increasing bioavailability.

Keywords: ramipril, fast mouth dissolving tablets, superdisintegrants

Introduction

Fast Mouth Dissolving Tablet

The aim of fast dissolving drug delivery system that to improving efficacy and bioavailability of various kinds of drugs and providing benefits of minimizing dosing frequency, decreasing side effect and enhanced patient compliance. Solid dosages forms that can be dissolved or suspended with water in mouth have a large potential among the pediatric and geriatric population. The oral route of drug administration is the mostly used and primary method of drug delivery due to convenience and ease of administration. From a patient's perspective the orally administration drug is more effective as compared with other routes of administration, for example, topical routes [1].

The immediate [2] / fast dissolving dosage forms have the advantages of convenience and accurate dosing as compared to liquids the ACE inhibitors are the first choice of drugs in all grades of essential as well as renovascular Hypertension. Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. The popularity of the oral route is attributed to the patient acceptance, ease of administration, accurate dosing, cost effective manufacturing method, less sterility condition requirement, and flexible design of dosage forms and generally improved shelf-life of the product. Disintegrates that are used in the formulation of MDTs should allow quick release of the drug, resulting in faster dissolution. This includes both the actives and the excipients. Disintegration and solubilization of a direct compressed tablet depend on effects of disintegrates, water-soluble excipients and effervescent agents.

Ramipril [3] 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) that minimize 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.

Ramipril reduces the reabsorption of electrolytes from the renal tubules. This results in increased excretion of water and electrolytes, including sodium, potassium, chloride, and magnesium. It has been used in the treatment of several disorders including edema, hypertension, and hyperparathyroidism. Ramipril is an angiotensin-converting enzyme (ACE) inhibitor, ACE inhibitors lower 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 increasing blood flow due to more blood being pumped into and through bigger passage ways.

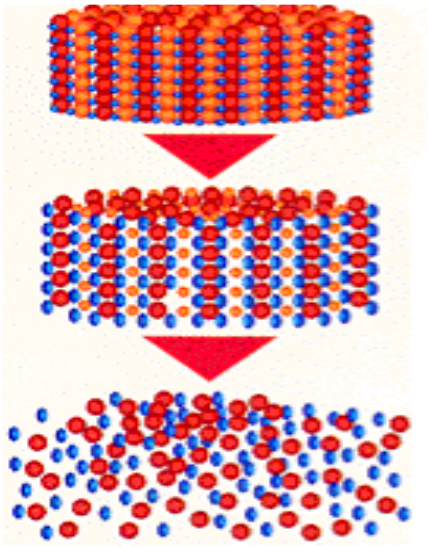

Fig 1: Disintegration of fast dissolving tablets

Red - Drug
Orange - Fast –dissolving granules
Blue - Disintegration agent

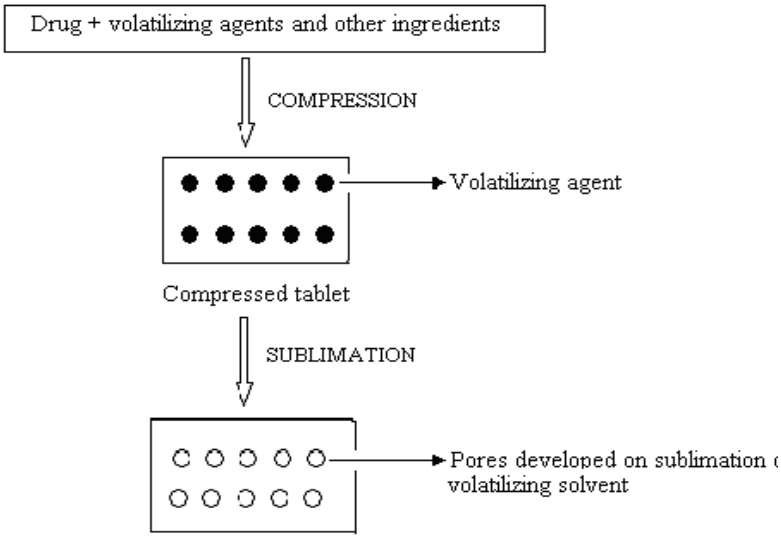

Fig 2: Schematic Diagram of Sublimation Technique for Preparation of MDT

Materials and Methods

Materials: Ramipril was obtained as a Gift sample from Alembic pharma ltd, Mannitol, Sodium starch glycoolate, cross carmellose sodium, cross povidone, magnesium stearate, Camphor, Ammonium bicarbonate, Aerosil, Talc were obtained from H.I.P.R Dehradun. All chemicals and reagents used were of analytical reagent (AR) grade.

Methods

Fourier Transform Infrared Spectroscopy Studies [4]

Electromagnetic radiation ranging between 500cm-1 and 4000cm-1 is passed through a sample and is absorbed by the bonds of the molecules in the sample causing them to stretch or bend. The wave length of the radiation absorbed is characteristic of the bond absorbing it.

Formulation of Ramipril mouth dissolving tablets By Direct Compression Method

Required quantities of the active ingredient, disintegration agents are Weighed and mixed, the above mixture is mixed properly in polyethylene bag for 15mins. Addition of lubricants is done and Compressed into tablets using 6 mm diameter concave shape punch. The formulation is given below in table 1.

Table 1: Formulation of Ramipril mouth dissolving tablets using different ratios of Superdisintegrants

INGRIDIENT	FORMULATION CODE (Mg)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Ramipril	5	5	5	5	5	5	5	5	5	5
Crospovidone	30	30	40	30	20	10	20	20	_	_
Croscarmellose sodium	25	10	5	10	20	30	20	_	20	20
Sodium starch glycolate	10	5	10	20	20	_	_	20	20	25
Camphor	10	20	10	_	_	10	20	10	5	20
Ammonium bicarbonate	_	_	_	10	5	10	10	15	15	10
Aerosil	5	5	10	10	5	10	10	10	10	5
Talc	5	10	5	5	10	10	5	5	10	5
Magnesium stearate	5	10	10	5	10	10	5	10	10	5
Mannitol	5	5	5	5	5	5	5	5	5	5
Total	100	100	100	100	100	100	100	100	100	100

Results and Discussion

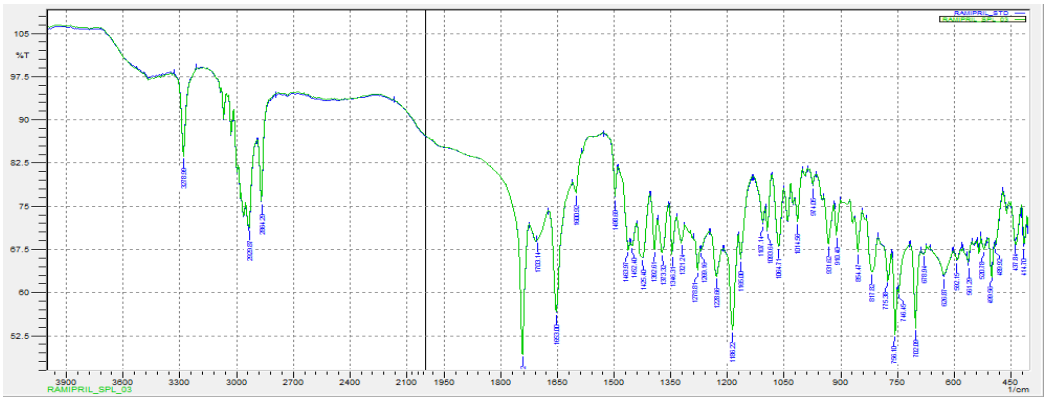

Fig 3: FTIR spectra of Ramipril

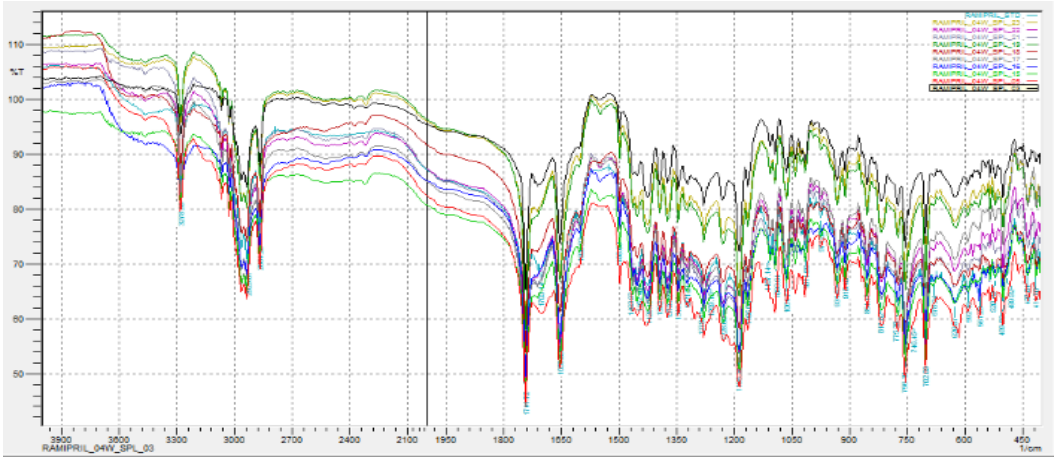

Fig 4: FTIR spectra of Ramipril standard with Ramipril and excipient binary mixtures (1:1)

The above IR graphs show that the peaks that exist in the pure drug of Ramipril are also present in the binary mixtures and hence there is no interaction observed between the drug and other excipients that are present in the formulation. Thus they pass the drug –excipient compatibility study.

Table 2: Data containing Precompression parameters of Ramipril and ingridients mixture

Ingredient	B.D (gm/cm^3)	T.D (gm/cm^3)	% carr's Index	Hausner's Ratio	Angle of repose (θ)
Ramipril	0.60	0.72	16.66	1.20	26.30
Crospovidone	0.38	0.45	15.55	1.34	27.50
Croscarmellose sodium	0.80	0.94	14.89	1.53	28.30
Sodium starch glycolate	0.76	0.86	11.62	1.36	30.32
Camphor	0.83	0.95	12.63	1.33	29.34
Ammonium bicarbonate	0.46	0.64	28.12	1.30	26.74
Aerosil	0.85	1	15	1.22	26.40
Talc	0.67	0.81	17.28	1.46	29.34
Magnesium stearate	0.68	0.76	10.52	1.54	28.43
Mannitol	0.58	0.72	19.44	1.35	34.45

All the pre-compression parameters that were evaluated for the physical mixtures of drug and excipients were found to be within the limits and hence provide good flow properties. Thus the tablets of Ramipril can be formulated by direct compression method by employing microcrystalline cellulose as directly compressible diluent. Bulk density and tapped density are in the range of 0.38-0.85 and 0.45-1 g/cc respectively. Carr's index and angle of repose were in the range of 10.52-28.12 and 26.30-34.45 respectively

Table 3: Result of post-compression parameters of F1 to F5 batches

Parameter	F1	F2	F3	F4	F5
Thickness (mm)	2.0±0.3	2.1±0.3	2.2±0.3	2.1±0.4	2.0±0.3
Hardness (kg/cm^2)	3.1	3.5	3.0	3.5	4.1
Weight variation	103.20±1.2	101.13±1.4	103.25±1.3	103.23±1.5	105.20±1.1
Wetting Time (sec)	29	26	22	24	30
Disintegrating Time (sec)	16	10	20	18	20
Water Absorption Ratio	0.856	0.923	0.845	0.876	0.846
Fitness Dispersion Test	Pass	Pass	Pass	Pass	Pass
Friability (%)	0.75	0.89	0.94	0.67	0.84

Table 4: Result of post-compression parameters of F6 to F10 batches

Parameter	F6	F7	F8	F9	F10
Thickness (mm)	2.5±0.3	2.0±0.5	2.7±0.2	2.3±0.3	2.5±0.4
Hardness (kg/cm^2)	4.7	4.0	3.3	3.9	5.2
Weight variation	105.3±1.5	102.26±2.3	105.23±1.8	101.00±1.2	101.87±1.3
Wetting Time (sec)	20	32	24	25	21
Disintegrating Time (sec)	20	12	8	5	15
Water Absorption Ratio	0.856	0.857	0.958	0.975	0.476
Fitness Dispersion Test	Pass	Pass	Pass	Pass	Pass
Friability (%)	0.98	0.94	0.83	0.65	0.89

All the post compression parameters listed in the above table were found to be within the limits and satisfactory. Hardness, % friability, thickness, disintegration time, weight variation and drug content were found to be in the range of 3.0-5.2kg/cm^2, 0.64-0.98, 2.0-2.7mm, 5-20sec, and 101.00-105.23mg respectively.

Table 5: Data showing the Cumulative % drug release of batches F1 –F5

Time (min.)	% Cumulative Drug Release				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	30.2	25.4	24.13	21.1	20.3
3	40.4	40.1	33.2	29.15	29.4
6	51.23	45.11	39.2	39.3	34.6
9	63.11	53.5	50.6	47.2	44.1
12	72.44	65.4	59.3	54.4	53.2
15	81.2	75.6	67.7	62.6	65.1
18	87.2	83.3	74.2	67.2	68.2
21	94.2	92.2	93.2	75.85	76.6
24	97.4	98.5	98.3	86.5	86.5
27				92.2	90.4
30				93.3	93.6
33				96.6	

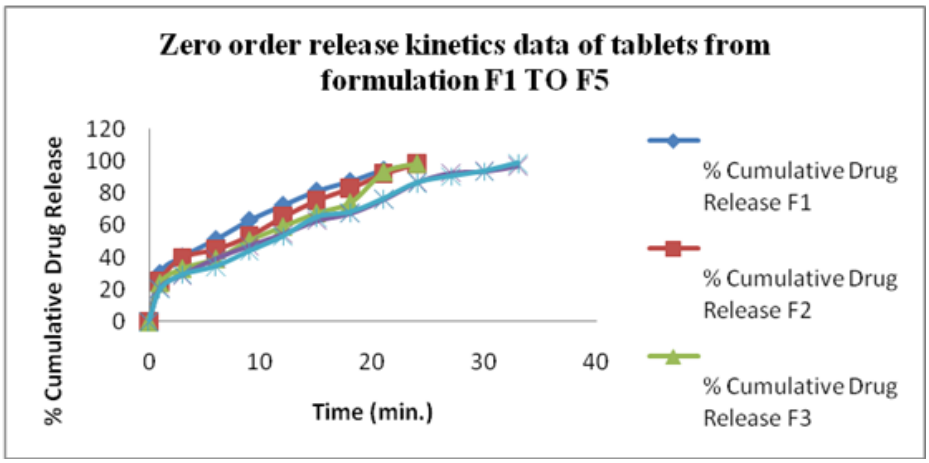

Fig 5: Cumulative % drug release profile of formulation F1 to F5

Table 6: Cumulative % drug release of batches F6 -F10

Time (min.)	% Cumulative Drug Release				
	F6	F7	F8	F9	F10
0	0	0	0	0	0
1	28.1	25.2	24.1	22.1	20.2
3	37.2	31.1	30.2	28.1	26.3
6	46.2	38.2	36.3	38.3	32.5
9	56.2	46.7	44.7	45.5	47.2
12	67.2	56.4	53.3	54.4	54.1
15	72.1	67.2	62.1	64.1	62.2
18	73.2	73.1	76.2	72.2	71.4
21	85.5	83.3	83.2	77.2	83.2
24	98.1	99.7	95.7	84.3	86.3
27				89.2	92.4
30				95.1	93.3
33				98.5	99.05

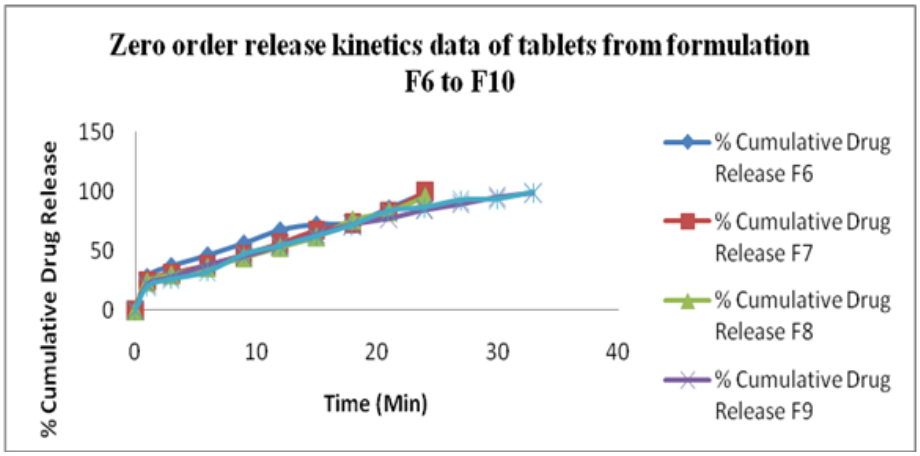

Fig 6: Cumulative % drug release profile of formulation F6 to F10

Conclusion

Fast dissolving or fast disintegrating dosage forms are meant to disintegrate immediately upon contact with the saliva leading to faster release of drug in the oral cavity. By administering the fast disintegrating dosage forms, absorption of the drugs occurs through buccal mucosa and it reduces the first pass metabolism leading to better efficacy of the drug. In this study, overall results suggests that the mouth dissolving tablets containing Croscarmellose sodium, Sodium starch glycolate, Camphor, formulation (F10) shows the best results in terms of percent drug release (99.05%). So it is considered as the better combination of disintegrating agents.

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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