

## FORMULATION AND EVALUATION OF RAMIPRIL MOUTH DISSOLVING FILMS

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Received: 08 Jan 2019, Revised and Accepted: 18 Mar 2019

### ABSTRACT

**Objective:** The present investigation was aimed at preparation and evaluation of mouth dissolving films (MDFs) of Ramipril to enhance patient convenience, compliance and to improve bioavailability.

**Methods:** MDFs with 0.5% w/w Ramipril were prepared by a solvent casting method using a wet film applicator. The effects of film formers, wetting/solubilizing, saliva stimulating agents and film modifiers on the physicochemical and *in vitro* Ramipril release from MDFs were evaluated.

**Results:** The MDFs prepared were transparent, smooth and showed no re-crystallization upon storage. MDFs casted with hydroxypropyl methylcellulose (HPMC) E3 as film former and polyethylene glycol (PEG-400) as plasticizer showed superior Ramipril release rates and good physicochemical properties when compared to MDFs with E5 and E15 as film formers. HPMC E3 MDFs with polyvinyl pyrrolidone K30 (PVP K30) and sodium lauryl sulphate (SLS) gave superior drug release properties than MDFs without PVP K30 and SLS. The HPMC E3 MDFs with citric acid (CA) as saliva stimulating and xylitol as soothing agent gave significantly superior *in vitro* drug release than the MDFs without CA and xylitol. Release kinetics data reveals diffusion as a drug release mechanism.

**Conclusion:** From the obtained results, it can be concluded that the administration of Ramipril as MDF may provide a quick onset of action with enhanced oral bioavailability and therapeutic efficacy.

**Keywords:** Hydroxy propyl methyl cellulose, Mouth dissolving films, Ramipril, Wet film applicator

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DOI: <http://dx.doi.org/10.22159/ijap.2019v11i3.32361>

### INTRODUCTION

Hypertension is a chronic medical condition involving the elevated blood pressure levels. The delayed treatment of hypertension can lead to several other fatal disorders like congestive heart failure, kidney failure, stroke, etc. Moreover, the hypertension can occur in sudden, severe and acute attacks requiring immediate treatment [1]. Most of the anti-hypertensives are available in the oral or parenteral dosage forms, which have certain limitations such as swallowing and choking difficulties, delayed onset of action, first pass metabolism, the requirement of skilled personnel and pain during delivery. These limitations and a need for the quicker onset of action with better patient acceptability has paved the way for the development of mouth dissolving films (MDFs) as an alternative to other dosage forms [2]. The MDFs are a very thin polymeric strip, which get hydrated instantly by saliva when placed on a patient's tongue and then disintegrates and/or dissolves to release the medication within the pre-oral cavity [3]. The oral cavity composed of striated squamous epithelia with very thin membranes and fine capillary network provides 4-4000 times greater absorption than other parts of skin [4]. The drug is directly absorbed into the systemic circulation which by-passes the first pass metabolism, improving the bioavailability of the drug [5].

Ramipril is a new generation anti-hypertensive drug and is an angiotensin-converting enzyme (ACE) inhibitor. Ramipril is a prodrug/precursor which is converted into active metabolite 'Ramiprilat' in liver by carboxylesterase. Ramipril inhibits the actions of ACE lowering the production of angiotensin II [6]. This results in relaxation of arteriole smooth muscle leading to a decrease in total peripheral resistance, reducing blood pressure. Ramipril undergoes first-pass metabolism and has an oral bioavailability of about 28-30% [7]. Presently, Ramipril is marketed in the form of oral disintegrating tablets (ALTACE®) and immediate release tablets (CARDACE®).

Few reports were published on formulation and evaluation of ramipril oral disintegrating, immediate release tablets, buccal patches and films. In most of the works reported so far, MDFs were prepared in petri plates, moulds etc. and the films were dried at 40-

45 °C overnight and this procedure may not result in uniformity of thickness and drug content and thereby, vary the drug release rates [7-12]. Moreover, no works on the influence of formulation variables like film thickness, polymer viscosities, surfactants and saliva stimulating agents were reported. Also, the reported works were not evaluated thoroughly for the drug loading effect on the re-crystallization and characterization using photographic, Fourier-transform infrared spectroscopy (FTIR), etc. By considering all the above facts, the present investigation was aimed to prepare MDFs using wet film applicator, an industrially scalable technique and evaluate them systematically.

### MATERIALS AND METHODS

#### Materials

Ramipril was obtained from Mylan Laboratories, Hyderabad. Hydroxypropyl methyl cellulose (HPMC E3, E5 and E15) samples were obtained from Colorcon Asia Ltd., India. Ethanol, polyvinyl pyrrolidone (PVP) K30, sodium lauryl sulphate (SLS) and citric acid (CA) were purchased from Loba Chemie, Mumbai. Pineapple flavour was obtained from Darwin laboratories, Vijayawada. Xylitol was obtained from Rouquette Laboratories, France. All the ingredients of analytical grade were used.

#### Methods

##### Preparation of artificial saliva

Artificial saliva was prepared by dissolving 0.844 g of sodium chloride, 1.2 g of potassium chloride, 0.193 g of calcium chloride dehydrate, 0.111 g of magnesium chloride hexahydrate and 0.342 g of potassium phosphate dibasic one by one in 500 ml of distilled water and then the final volume was made up to 1000 ml using the distilled water. The pH was adjusted with 0.1N HCl to 5.7 [13].

##### Preparation of ramipril MDFs

Ramipril MDFs were prepared as per the formula is given in table 1 by using the solvent casting method to a batch size of 5 g. Ramipril was dissolved in a mixture of solvents (water and ethanol) in a

beaker and other ingredients were added one by one and finally the polymer was added and mixed thoroughly. The mixture was sonicated for 5 min to remove entrapped air bubbles and casted on a glass plate with wet film applicator set at 30 mil (750  $\mu\text{m}$ ) and the film was dried at 45 °C for 60 min in hot air oven. Then the dried films were peeled off from the glass plate, cut into appropriate sizes and stored in desiccators until use.

#### FTIR studies

Samples were analysed using an Attenuated Total Reflectance (ATR)-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000-500  $\text{cm}^{-1}$  at a resolution of 1.0  $\text{cm}^{-1}$ . The powder or film sample was placed onto the ATR crystal and the sample spectrum was collected.

#### Evaluation parameters for ramipril MDFs

##### Morphological properties

Morphological properties of ramipril MDFs were tested by visual observations for a period of 6 mo. All the MDFs prepared were packed in aluminium foil pouches and stored at room temperature (25 $\pm$ 3 °C) with the relative humidity of approximately 65 $\pm$ 5%. Changes in homogeneity, colour, transparency and surface of MDFs were observed once in a month for 6 mo's duration [17].

##### Thickness

The thickness of the film was measured using a screw gauge with a range of 0-10 mm and revolution 0.001 mm. Anvil of the thickness gauge was turned and the film was inserted after making sure that the pointer was set to zero. The film was held on the anvil and the reading on the dial was noted down. The estimations were carried out in triplicate [18].

##### Drug content

The amount of ramipril in the MDFs was estimated by dissolving 1  $\text{cm}^2$  films in a 10 ml volumetric flask containing 5 ml of artificial saliva and then the final volume was made up with the same [19]. The samples were then suitably diluted with artificial saliva and analysed for ramipril content by UV spectrophotometric method measured at 230 nm (UV Spectrophotometer, UV 1800 SHIMADZU). The estimations were carried out in triplicate.

##### Variation of mass

Mass of 1  $\text{cm}^2$  film from different batches of the formulations was noted on an electronic balance. The estimations were carried out in triplicate [17].

##### In vitro disintegration studies

In vitro disintegration time of MDFs was studied visually using two independent methods namely drop and petri dish methods. For both the methods, only a small amount of medium was required, so that natural conditions are simulated.

##### Drop method

In this method, the films were placed on a glass slide and placed planar on a petridish. One drop of distilled water was dropped by a pipette onto the oral films. The time until the film dissolves and forms a hole in the film was measured. The estimations were carried out in triplicate [18].

##### Petri dish method

In this method, 2 ml of distilled water was placed in a petri-dish and a film of 2x2  $\text{cm}^2$  was placed on the surface of the water and the time required to dissolve the film completely was measured. The estimations were carried out in triplicate [18].

##### Tensile strength

Tensile strength is the maximum stress applied to a point at which the film specimen breaks [14]. It is calculated by the load at rupture divided by the cross-sectional area of the film as given below:

$$\text{Tensile strength} = \frac{\text{Load at Failure} \times 100}{\text{Film Thickness} \times \text{Film Width}}$$

Tensile strength of MDFs was measured using Mini Tech Tensiometer-UTM9051 (Dak Systems Inc., Mumbai, India) fitted with a load cell of 500 N (50 kg) capacity and the data was collected using Test Bench II software [17-19]. Samples of appropriate film thickness with fixed dimensions (LxW-10x2 cm) were fixed between pneumatic grips with a gauge dimension of 3 cm length between grips. All the dimensions were entered into the software to calculate the cross-sectional area. The film was carefully placed in between the pneumatic grips avoiding any loose folds. An instrument was operated at a speed of 5 mm/min until the film breaks. Percent elongation data was also computed from the software for each sample. Whole experiment was carried out in triplicate.

##### Percent elongation

When stress is applied the film sample stretches and is referred to as strain. Strain is basically the deformation of the film divided by the original dimension of the film. Generally, elongation of the film increases as the plasticizer concentration increases [15]. Percentage elongation was calculated by measuring the increase in the length of the film after tensile strength measurement by using the following formula:

$$\text{Percent Elongation} = \frac{(L - L_0) \times 100}{L_0}$$

Where, L = Final length,  $L_0$  = initial length. The estimations were carried out in triplicate.

##### Folding endurance

Folding endurance is determined by repeated folding of the film at the same place till the film breaks. This gives an indication of the brittleness of the film. The number of times the film is folded without breaking is computed as the folding endurance value [16]. The estimations were carried out in triplicate.

##### In vitro drug release studies

The in vitro drug release studies were conducted using 500 ml of artificial saliva as dissolution medium with modified USP Type V dissolution rate testing apparatus. A temperature of 37 °C and 50 rpm were maintained. Each film of appropriate size (3 x 2.6  $\text{cm}^2$ ) equivalent to 5 mg dose was cut and placed on a watch glass covered with nylon wire mesh. The watch glass was then dropped into dissolution flask. 5 ml samples were withdrawn at predetermined time intervals 5, 10, 20, 30, 40, 50, 60, 80, 100, 120, 180, 240, 300, 360 s and every time replaced with 5 ml of fresh dissolution medium. The samples were analysed by measuring absorbance at 230 nm. The drug release experiments were conducted in triplicate [17].

##### Stability studies

Stability studies were carried out on F6 (containing 0.5 % ramipril, 7.5 % HPMC E3, 0.04 % PVP K30, 0.25 % CA and 0.5 % xylitol). MDFs were packed in aluminium pouches, sealed and stored at 40 °C/75 $\pm$ 5% RH for 6 mo. The appearance, weight and drug content properties of the MDFs were examined.

##### Statistical analysis

Results of experimental data were subjected to one-way ANOVA (using Fisher's LSD Post HOC test) using SYSTAT software (SYSTAT Software Inc., San Jose, USA). Results with 'p' value of less than 0.05 ( $P < 0.05$ ) were considered as significant variance.

## RESULTS AND DISCUSSION

### Preparation and physical characterization of RPL MDFs

In the present investigation, the MDFs were prepared using a wet film applicator which is also a commercially scalable technique. Initially placebo MDFs were prepared with different polymers like HPMC (E3, E5, E15), methylcellulose, sodium carboxymethyl cellulose (Na CMC) and sodium alginate using PEG-400 as the plasticizer and observed for film forming capacity and appearance. From the trails made and results obtained, HPMC E3, E5, E15 and Na CMC were selected for further development. However, films prepared with NaCMC were not separable from glass plate upon drug loading. Hence HPMC polymers with different viscosity grades were selected for further studies. Ramipril of 0.5 % w/w (25 mg)

was added to the MDFs and the films were casted at 30 mil thickness. The obtained MDFs were found to be smooth, transparent and showed no re-crystallization upon storage. Different ramipril

MDFs were prepared at 0.5 % w/w ramipril load and all the formulae were given in table 1. A 5 g batch size of formulations gave approximately 96 cm<sup>2</sup> film area.

**Table 1: Composition of different ramipril MDFs**

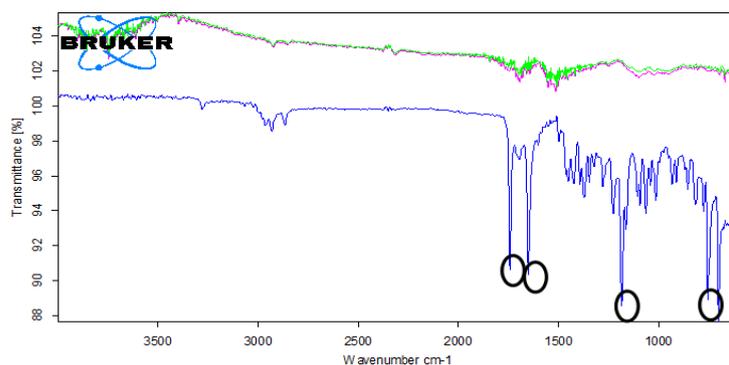
Ingredients(mg)	Formulae (5 g batch size)					
	F1	F2	F3	F4	F5	F6
Ramipril	25	25	25	25	25	25
HPMC E3	375	-	-	375	375	375
HPMC E5	-	375	-	-	-	-
HPMC E15	-	-	375	-	-	-
PEG 400*	25	25	25	25	25	25
PVP K30	-	-	-	2	-	2
SLS	-	-	-	-	2	-
Water*	1785	1785	1785	1785	1785	1785
Ethanol*	2745	2775	2775	2773	2773	2750.5
Citric acid	-	-	-	-	-	12.5
Xylitol	25	25	25	25	25	25
Colouring agent	10	10	10	10	10	10
Flavouring Agent	10	10	10	10	10	10
Total Weight	5000	5000	5000	5000	5000	5000

\*All the amounts were taken based up on their density. [MDFs: Mouth dissolving films, HPMC: Hydroxy propyl methyl cellulose, PEG: Polyethylene glycol, PVP: Polyvinylpyrrolidone, SLS: Sodium Lauryl sulphate]

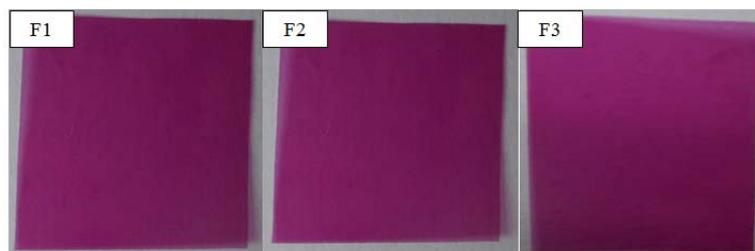
### FTIR analysis

To probe the potential interactions between ramipril and the excipients of MDFs, an FTIR studies were conducted. Four characteristic peaks at 1740.58 cm<sup>-1</sup>(aliphatic C=O stretching),

1648.48 cm<sup>-1</sup>(C=C stretching), 1183.21 cm<sup>-1</sup>(C-N stretching), 778.00 cm<sup>-1</sup>(=C-H bending) were observed. These characteristic peaks of ramipril were all retained in the MDFs. The FTIR spectrum is shown in fig. 1. These results indicate that there is no interaction between ramipril and excipients in MDFs.



**Fig. 1: FTIR spectrum overlay of pure ramipril (—), F4 (—), F6 (—)**



**Fig. 2: Photographs of ramipril MDFs (Mouth dissolving films)**

### Morphological properties

Ramipril MDFs were visually tested for homogeneity, transparency, colour and smoothness. MDFs formulated with 0.5 % w/w ramipril were transparent with no re-crystallization. The photographs were shown in fig. 2.

### Thickness

The thickness was measured with screw gauge at different places of MDFs in order to evaluate the reproducibility of preparation methods [17-19]. Around 90% of wet film thickness was lost during drying. The

results were given in table 2 and good uniformity of thickness was observed. MDFs casted at 30 mil thickness containing PVP and SLS showed higher thickness values compared to the other formulations.

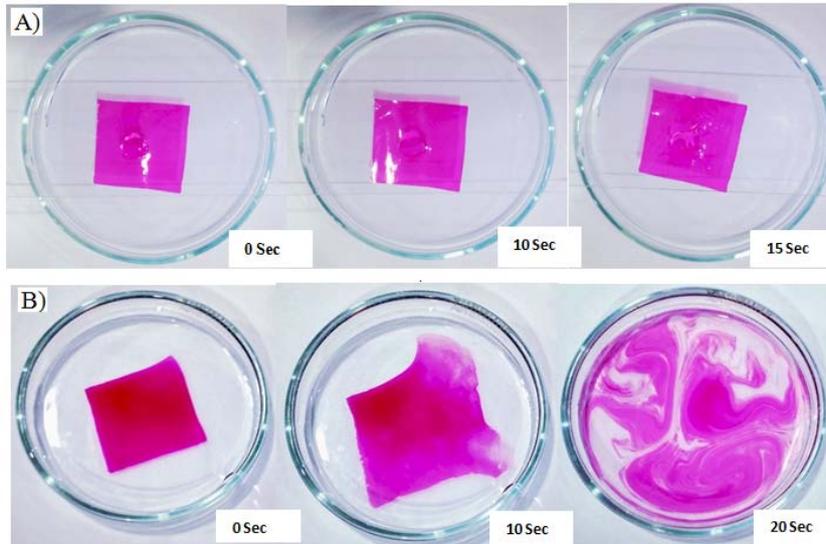
### Drug content

Films of 1 cm<sup>2</sup> were cut from different areas (n=3) of the whole film and ramipril content was estimated. The results were given in table 2. The results indicated a good uniformity of ramipril within the film, overall good solubilization of ramipril in MDFs was observed. MDFs were casted at 30 mil thickness.

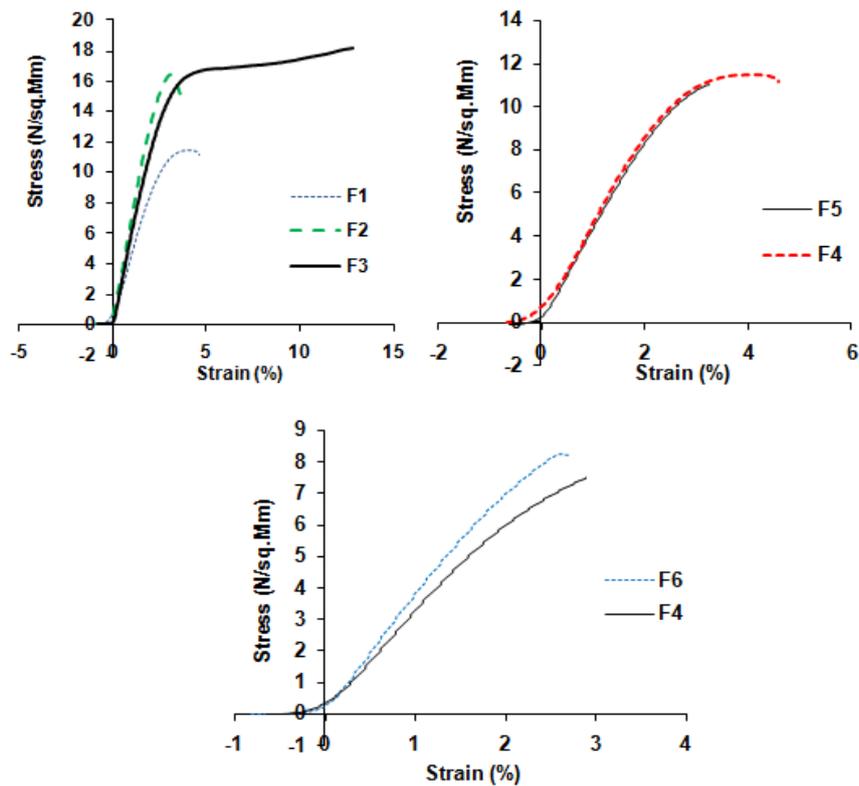
**Table 2: Physicomechanical properties of different ramipril MDFs**

Formulations	Drug content (mg/cm <sup>2</sup> ) <sup>*</sup>	Mass variation (mg) <sup>*</sup>	Thickness (µm) <sup>#</sup>	Disintegration time (sec)	
				Drop method <sup>*</sup>	Petri dish method <sup>*</sup>
F1	0.23±0.019	2.53±0.11	75.00±5.47	21.33±0.58	27.66±0.58
F2	0.31±0.005	2.73±0.05	78.33±4.08	26.67±1.15	34.33±1.15
F3	0.29±0.020	2.96±0.11	86.66±5.16	34.67±1.53	41.00±1.53
F4	0.35±0.011	2.66±0.05	78.33±4.08	18.67±0.58	24.66±0.28
F5	0.38±0.005	2.60±0.10	76.66±5.16	19.33±0.58	25.33±0.58
F6	0.30±0.025	2.76±0.05	78.33±4.08	14.67±0.58	21.00±0.58

All the values are expressed as mean±SD, \* n=3 and # n=6. MDFs: Mouth dissolving films



**Fig. 3: *In vitro* disintegration of ramipril MDFs by A) Drop method B) Petri dish method. MDFs: Mouth dissolving films**



**Fig. 4: Comparative tensile strength profiles of all the ramipril film formulations**

**Table 3: Physicomechanical properties of different ramipril MDFs**

Formulations	% Elongation*	Folding endurance*
F1	5.22±0.09	78±2
F2	5.81±0.02	86±3
F3	7.41±0.13	98±2
F4	5.83±0.04	86±4
F5	5.79±0.07	84±3
F6	5.92±0.23	83±2

\*All the values are expressed as mean±SD (n=3). MDFs: Mouth dissolving films

### Variation of mass

Films of 1 cm<sup>2</sup> were cut from different batches and weighed. The results are given in table 2. Same mass of film was obtained with three batches of films indicating good reproducibility of preparation method and formulation.

### In vitro disintegration studies

The results of the disintegration time are given in table 2. The results indicated that HPMC E3 formulations disintegrated faster than the E5, E15 which is due to low viscosity of E3 polymer compared to E5 and E15. The MDFs with PVP disintegrated faster than the MDFs with and without PVP and SLS. The MDFs with CA disintegrated faster than the other MDF formulations. The images of MDF disintegration by drop and petri dish methods are shown in fig. 3.

### Tensile strength and % elongation

MDFs should possess moderate tensile strength and high % elongation. The results revealed that MDFs containing PVP and SLS showed moderate tensile strength. The results were given in table 3 and shown in fig. 4.

### Folding endurance

MDFs prepared with PVP and SLS showed high folding endurance values compared to other E3 formulations. The results were given in table 3.

### In vitro drug release studies

In the present investigation, *in vitro*, drug release studies of MDFs were carried out using USP Type-V Dissolution Rate Testing Apparatus. 500 ml of artificial saliva was used as dissolution medium in order to mimic the *in vivo* conditions. The *in vitro* drug release profiles of ramipril MDFs are shown in fig. 5.

MDFs of F1, F2 and F3 formulations were prepared with HPMC E3, E5 and E15. The cumulative percent of ramipril released at the end of 5 s is 13.44±9.33, 8.64±1.96 and 3.64±1.75 for F1, F2 and F3 respectively. Complete ramipril release was obtained at 120 s, 240 s and 600 s for F1, F2 and F3 formulations respectively. From the results obtained, it was observed that MDFs with HPMC E3 showed significantly superior ramipril release when compared to MDFs containing E5 and E15. This may be due to the low viscosity of HPMC E3 polymer.

HPMC E3 was selected as the film former in the further studies because of its superior physicomechanical and drug release characteristics. The effect of solubilising and/or wetting agents on ramipril release rates was also studied. PVP K30 and SLS were added to formulations at 0.04 % w/w level. The cumulative percent of ramipril released at the end of 5 s is 18.62±4.99 and 11.64±5.19 for F4 and F5 respectively. A complete ramipril release were obtained at 80 s and 100 s for F4 and F5 formulations respectively.

The formulations containing SLS and PVP K30 gave significantly superior drug release profiles when compared to the formulations without PVP K30 and SLS. MDF formulations with PVP K30 gave superior drug release properties when compared to SLS formulations. The MDF containing PVP K30 i.e. F4 formulation was selected for further studies because of its superior ramipril release profile.

In the further studies, the effect of saliva stimulating and soothing agents on the ramipril release was studied. CA and xylitol were added at 0.25 % and 0.5 % w/w levels respectively to the

formulation. A cumulative percent of 41.53±0.03 was obtained at the end of 5 s and the complete release of ramipril from the formulation was obtained at 60 s. The formulation containing CA and xylitol gave significantly superior drug release when compared to the formulation without CA and xylitol.

Overall, the F6 formulation (0.5 % w/w ramipril load, 7.5 % HPMC E3, 0.04 % PVP K30, 0.25 % CA and 0.5% xylitol) was optimized as the best formulation because of its superior ramipril release profile and physicomechanical properties.

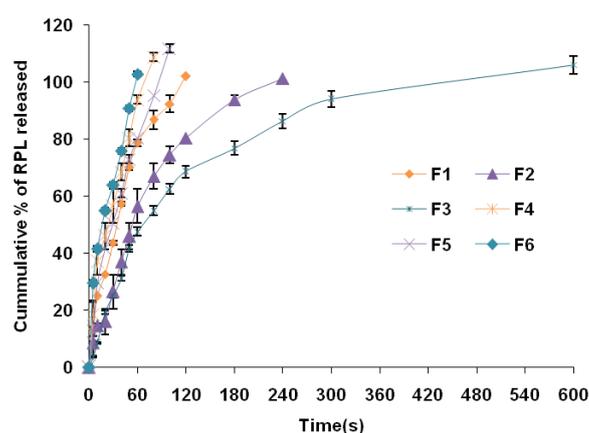
### Drug release kinetics

To better understand the release profiles obtained with ramipril MDFs formulations, the drug release data obtained at different time points was fitted into kinetic models such as First order [20] and Higuchi plots [21]. The first order release rate constant 'k' (sec<sup>-1</sup>) values and correlation coefficient (R<sup>2</sup>) values were calculated from drug release data (0-60 s) for ramipril MDFs.

When compared to F1, the 'k' values were lower for F2 and F3 formulations. A 1.55 and 3.68 fold decrease in 'k' values was observed for F2 and F3 formulations respectively.

When compared to F1, the 'k' values were significantly higher for F4 and F5 formulations containing PVP K30 and SLS respectively. A 1.39 and 1.06 fold increase in 'k' values for F5 and F6 formulations was observed when compared to F1 formulation. Overall, MDFs of ramipril with PVP K30 and SLS gave higher 'k' values when compared to MDFs of ramipril without PVP K30 and SLS.

Among 6 formulations, the 'k' value was significantly (*p*<0.05) higher for F6 when compared to the other formulations. The Higuchi square root model of all MDFs showed higher correlation coefficient values (0.900-0.998) indicating diffusion as release mechanism [21].



**Fig. 5: Comparative *in vitro* ramipril release profiles of MDF formulations (mean±SD; n=3). MDFs: Mouth dissolving films**

### Stability studies

Stability studies were carried out for F6 formulation containing HPMC E3, PVP K30 and CA. MDFs were stored at 40 °C with relative humidity of approximately 75±5 % for 6 mo. The appearance, weight

variation and drug content of the MDFs were examined. The appearance of MDFs remained unchanged throughout the studies and no re-crystallization was observed. There is no statistically significant change observed in the weight of MDFs. F6 formulation showed 94-102% of ramipril content after 6 mo, indicating that the ramipril was stable in MDFs.

### CONCLUSION

From this investigation, it can be concluded that ramipril can be successfully formulated into MDFs. The film properties and drug release rates can be affected by the formulation variables such as polymer viscosities, wetting/solubilizing agents and saliva stimulating agents. The utilization of wet film applicator resulted in batch to batch reproducibility of different physicochemical properties for ramipril MDFs. MDFs formulation F6 was subjected to stability studies and no change in appearance, weight and drug content was observed indicating that the ramipril was stable in the formulations. Formulation F6 containing 7.5 % w/w HPMC E3, 0.5 % w/w PEG-400, 0.04 % w/w PVP K30 and 0.25% CA showed superior physicochemical and ramipril release rate compared to remaining formulations and was optimized as the best formulation. The administration of ramipril as MDFs may provide quick onset of action with enhanced oral bioavailability and therapeutic efficacy when compared to current marketed formulations like immediate release (IR) and orally disintegrating tablets (ODT's) etc.

### ACKNOWLEDGMENT

The authors are thankful to AICTE, New Delhi for supporting the research work, Mylan Laboratories, Hyderabad for providing RPL and to Colorcon India for providing HPMC samples and Siddhartha Academy of General and Technical Education, Vijayawada, for providing necessary facilities to carry out this research work.

### AUTHORS CONTRIBUTIONS

All the authors have contributed equally

### CONFLICTS OF INTERESTS

Declared none

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