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Research Article

Formulation and Evaluation of Fast Dissolving Oral Films incorporated with Ramipril and β -Cyclodextrin Complex

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ABSTRACT

Ramipril being angiotensin-converting enzyme (ACE) inhibitor, belongs to biopharmaceutical classification (BCS) class II drug with low solubility and undergoes first-pass metabolism that leads to reduced bioavailability of 28%. The current research is aimed at formulating and evaluating ramipril fast dissolving oral films (FDOF). Solubility enhancement of ramipril was done by formation of inclusion complex with β -cyclodextrin (β -CD) in 3 ratios (1:0.5, 1:1, and 1:2). Based on higher drug content and dissolution values the physical mixture of ramipril with β -cyclodextrin in 1:1 ratio (IC2) was chosen for further studies. Total 12 formulations of ramipril FDOF containing IC2 prepared with various polymers and evaluated for physicochemical properties. The optimized formulation F9 shown better tensile strength (11.6 g/cm²), significant % elongation (9.8), and maximum % drug content of 99.98%. The formulation F9 exhibited minimum disintegration time of 9 seconds that is desirable for immediate onset of action and maximum drug release. The Fourier transform infrared spectroscopy (FTIR) data of F9 assured the compatibility of drug and formulation excipients, found to be stable for 180 days at accelerated conditions. The study confirmed that ramipril FDOF lead to quicker onset of action and enhanced therapeutic efficiency in comparison to marketed product.

INTRODUCTION

Drug delivery by oral route is mostly the favored administration route owing to patient compliance, and convenience in achievement of systemic and local effects. Parenteral, intranasal, transdermal, pulmonary, and buccal apart from oral route can achieve systemic delivery of drugs. In general, there is no ideal absorption route for drug delivery that can match the physiological requirements. But keeping in mind the surface area, contact time, low metabolic activity, high blood supply, lack of variability, accessibility, and permeability relatively oral route can be said to have beneficial characteristics for drug absorption. At present, about 80% of the medications are given by oral route of which tablets, capsules, and granules are most prescribed dosage forms. Thus, a need for advancement of oral drug delivery systems is required

to achieve enhanced therapeutic efficacy and safety of the treatment. Overall, majority of the pharmaceutical market is occupied by oral dosage forms owing to their safety, efficacy, economic, and consumer compliance in comparison to other routes. Also, regulatory restrictions, technical barriers on parenteral, injectables, and inhalation routes again flip the coin towards oral route as they are economic, making their availability to broader range of compounds.^[1]

The requirement of enhanced bioavailability, with quicker onset of action and subject compliance, pave the way for novel oral dosage forms. Of them, FDOF formulated using super disintegrates and hydrophilic ingredients are coming into picture. This system is comprised of a very thin film that placed on tongue or other oral mucosal tissue, followed by hydration with saliva and adherence to the

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site of action. It thereby undergoes quick disintegration releasing the drug that undergoes instant absorption into systemic circulation via buccal mucosa.^[2-4]

Ramipril is a new generation anti-hypertensive drug and is an 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.^[5] This leads to relaxation in arteriole smooth muscle leading to a reduction in total peripheral resistance and blood pressure. The major problems encountered with this drug are poor aqueous solubility, undergoes first-pass metabolism, and poor bioavailability (28–30%) after oral administration. For efficient management of hypertension in geriatric patients, it is advisable to formulate ramipril into fast dissolving oral films for effective drug delivery.^[6]

The current work is aimed at enhancing the solubility and fast action of ramipril by formation of inclusion complex with β -CD, followed by formulation into FDOF.^[7,8]

MATERIALS AND METHODS

Materials

Ramipril obtained from Aurobindo Pharma Ltd., Hyderabad, and marketed product was purchased. β -CD, HPMC E15, chitosan, PEG 400 crospovidone, sodium starch glycolate, and citric acid were procured from MSN Lab, Hyderabad, India.

Methods

Preparation of Ramipril Inclusion Complex with β -CD

Inclusion complex of ramipril prepared by kneading method. The mixture of ramipril: β -CD in varying ratios

of 1:0.5 (IC1), 1:1 (IC2), and 1:2 (IC3) wetted in mortar with carbinol and water (1:1). This wet mass kneaded thoroughly generates paste consistency, followed by drying at room temperature. The dry mass sieved through sieve# 80, stored in a desiccator for future use.^[9]

Formulation of Ramipril FDOF

The ramipril FDOF prepared from IC2 formulation (ramipril 2.5 mg: β -CD 2.5 mg) by adopting solvent casting method with hydroxypropyl methylcellulose (HPMC) 15 cps/chitosan, acting as film-forming polymer. Weighed quantity of polymer mixed with a three-fourth volume of water with continuous stirring, followed by incorporation of inclusion complex containing ramipril. Sodium starch glycolate/ crospovidone (super disintegrants) added to contents and stirred continuously, followed by addition of citric acid and PEG 400, final volume adjusted to 15 mL, using distilled water. The resultant bubble-free viscous solution cast on the Petri dish (area of 63.85 cm²), placed in hot air oven at 40°C for 24 hours (Table 1). The obtained films cut into 2 × 2 cm² pieces, containing 2.5 mg of ramipril, wrapped in aluminum foils, and stored in desiccator.^[10]

Evaluation of Inclusion Complex

Drug content and in vitro drug release of inclusion complex: The inclusion complex comprising 2.5 mg of ramipril taken into 50 mL standard flask, solubilized in carbinol, and diluted suitably using phosphate buffer (pH 6.8). The resultant filtered and filtrate analyzed spectrophotometrically (Shimadzu UV-1201, Japan) at 210 nm.^[11]

The *in vitro* dissolution study conducted in USP dissolution testing apparatus type-II (EDT-08Lx, Electrolab, Mumbai, India). The complex comprising

Table 1: Composition of ramipril FDOF

Formulation code	Ingredients								Distilled water up to (mL)
	Inclusion complex equivalent to 5 mg of drug (mg)	HPMC 15 cps (mg)	Chitosan (mg)	Sodium starch glycolate (mg)	Crospovidone (mg)	Citric acid (mg)	Aspartame (mg)	PEG 400 (mg)	
F1	80	250	-	20	-	30	8	40	10
F2	80	250	-	40	-	30	8	40	10
F3	80	250	-	60	-	30	8	40	10
F4	80	250	-	-	20	30	8	40	10
F5	80	250	-	-	40	30	8	40	10
F6	80	250	-	-	60	30	8	40	10
F7	80	250	250	20	-	30	8	40	10
F8	80	-	250	40	-	30	8	40	10
F9	80	-	250	60	-	30	8	40	10
F10	80	-	250	-	20	30	8	40	10
F11	80	-	250	-	40	30	8	40	10
F12	80	-	250	-	60	30	8	40	10



about 100 mg of ramipril dissolved in 900 mL dissolution medium (phosphate buffer of pH 6.8), maintained at $37 \pm 0.5^\circ\text{C}$ and 50 rpm. 5 mL of resultant sample withdrawn at various time intervals and samples replaced with an equal amount of fresh medium each time. The samples filtered, diluted with dissolution medium, and analyzed spectrophotometrically at 210 nm.^[12]

Evaluation of Ramipril FDOF

FDOFs evaluated for weight variation, moisture content, drug content transparency, thickness of film, disintegration time, folding endurance, tensile strength, surface pH, and percent elongation, as per the procedure given in references.^[13-15]

In vitro Dissolution Study of Ramipril FDOF

The dissolution study was conducted in phosphate buffer pH 6.8 (300 mL), as a dissolution medium, using USP dissolution apparatus XXIV (Electrolab, Mumbai, India) maintained at a temperature of $37 \pm 0.5^\circ\text{C}$, and peddling speed of 50 rpm. 4 cm² of each ramipril FDOF placed on stainless-steel wire mesh with sieve size 700 μm and inundated into dissolution medium. Samples withdrawn at specified time intervals, filtered, and analyzed spectrophotometrically at 210 nm. The sample's actual volume is maintained by adding equal amounts of fresh dissolution medium. The analysis performed in triplicate for all the formulations.^[16]

Drug Excipient Compatibility Study by FTIR

FTIR (Schimadzu IR Affinity 1 spectrophotometer) was used to record the FTIR spectra of pure ramipril and ramipril FDOF in 4,000 to 400 cm⁻¹ range.^[17]

Scanning Electron Microscopy (SEM) Studies

The SEM studies carried out using JEOL JEM 2100 F, USA HITACHI, and S-3700N.^[18]

Stability Studies

Stability testing was conducted in accordance with ICH guidelines for 6 months in stability chamber (Thermo Lab, Mumbai). Samples were withdrawn at predetermined intervals 0, 30, 60, and 90 day's period. The drug content and *in vitro* release data evaluated.^[19]

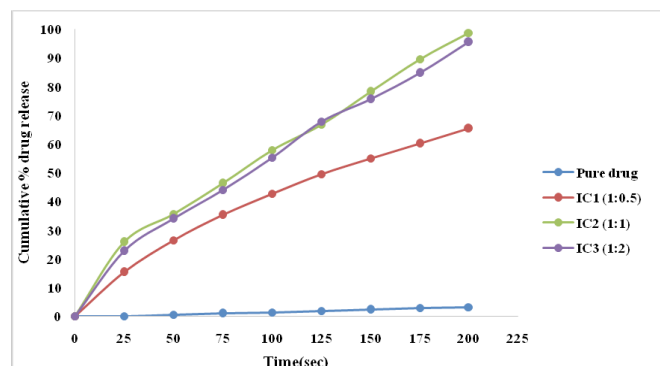


Fig. 1: *In vitro* drug release of ramipril and inclusion complexes

RESULTS

Drug Content and *In vitro* Drug Release of Ramipril Inclusion Complex

The higher drug content of $95.72 \pm 0.63\%$ observed for formulation IC2 that comprises drug and β -CD in 1:1 ratio (Table 2).

In vitro drug release of ramipril and inclusion complexes are displayed in Fig. 1. The maximum dissolution from complex occurred within 200 seconds. The formulation IC2 comprising equimolar drug and β -CD, exhibited a maximum dissolution rate of 98.77% within 180 seconds, while pure drug showed only 3.08% at the end of 200 seconds.

Preparation of Ramipril FDOF

Twelve formulations of ramipril FDOF prepared, as per the ingredients listed in Table 1. All films appeared bubble-free, uniform, and appeared clear (Fig. 2).

Evaluation of Ramipril FDOF

Weight Variation

The data indicate that formulation F1 exhibited least weight variation of 108.1 ± 0.51 mg, and F9 maximum value of 110.6 ± 0.49 mg. All the values are within the pharmacopoeial limit (Table 3).

Transparency

All the ramipril FDOFs were clear in appearance without any air bubbles (Table 3).



Fig. 2: Preparation of ramipril FDOF

Table 2: % drug content of inclusion complex of ramipril with beta-cyclodextrin

Inclusion complex code	% drug content
IC1 (1:0.5)	92.47
IC2 (1:1)	95.72
IC3 (1:2)	93.82

Table 3: Evaluation parameters of ramipril FDOF

Formulation code	Weight variation (mg)	Transparency	Thickness (mm)	DT (sec)
F1	108.1 ± 0.51	Clear	0.22 ± 0.09	15 ± 0.32
F2	109.2 ± 0.59	Clear	0.24 ± 0.04	12 ± 0.38
F3	110.2 ± 0.6	Clear	0.248 ± 0.05	10 ± 0.3
F4	109.2 ± 0.49	Clear	0.22 ± 0.04	14 ± 0.35
F5	108.6 ± 0.51	Clear	0.232 ± 0.05	12 ± 0.3
F6	109.5 ± 0.59	Clear	0.241 ± 0.09	10 ± 0.32
F7	110.3 ± 0.6	Clear	0.237 ± 0.05	11 ± 0.28
F8	108.4 ± 0.59	Clear	0.242 ± 0.09	10 ± 0.3
F9	110.6 ± 0.49	Clear	0.256 ± 0.1	9 ± 0.25
F10	110.2 ± 0.58	Clear	0.219 ± 0.04	13 ± 0.28
F11	109.4 ± 0.59	Clear	0.228 ± 0.05	12 ± 0.29
F12	108.4 ± 0.6	Clear	0.236 ± 0.06	11 ± 0.3

Table 4: Evaluation parameters of ramipril FDOF

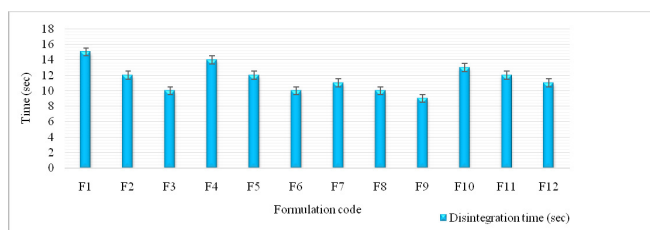
Formulation code	Drug content (%)	Moisture content (%)	Folding endurance (count)	Surface pH
F1	92.18 ± 0.5	3.81 ± 0.09	98 ± 2	6.6 ± 0.5
F2	94.38 ± 0.51	3.9 ± 0.09	96 ± 1	6.79 ± 0.4
F3	96.21 ± 0.52	4.5 ± 0.22	98 ± 1	6.7 ± 0.4
F4	91.18 ± 0.5	4.69 ± 0.22	105 ± 1	6.78 ± 0.2
F5	93.55 ± 0.51	4.98 ± 0.25	100 ± 4	6.88 ± 0.4
F6	95.63 ± 0.52	4.25 ± 0.1	97 ± 1	6.81 ± 0.3
F7	96.48 ± 0.54	4.32 ± 0.15	99 ± 2	6.75 ± 0.6
F8	97.48 ± 0.52	4.34 ± 0.15	104 ± 1	6.8 ± 0.3
F9	99.98 ± 0.69	4.2 ± 0.12	119 ± 2	6.94 ± 0.4
F10	96.12 ± 0.52	3.99 ± 0.09	117 ± 4	6.85 ± 0.5
F11	96.12 ± 0.53	3.99 ± 0.1	117 ± 5	6.87 ± 0.6
F12	97.12 ± 0.54	3.99 ± 0.11	117 ± 6	6.89 ± 0.7

Thickness of Ramipril FDOF

The thickness of all twelve formulations ranged between 0.22 ± 0.04 to 0.25 ± 0.10 mm, with highest thickness observed for F9 with low standard deviation values. Keeping polymer concentration constant in all formulations, the results indicate that low concentration of the super disintegrants lead to thinner film, while higher concentration lead to increase in thickness of the film (Table 3).

Disintegration Time (DT) of Ramipril FDOF

The DT of all ramipril FDOF formulations ranged between 9 to 15 seconds (Table 3). Formulation F9 exhibited minimum DT of 9 seconds, which is sought-after for rapid onset of action. The results indicate that increase in concentration of superdisintegrant decreases the DT (Fig. 3).

**Fig. 3:** Disintegrating time of ramipril FDOF (F1-F12)

% Drug Content

The % drug content for all ramipril FDOF formulations indicated that the drug was distributed uniformly throughout the film and ranged between 91.18 ± 0.5 to 99.98 ± 0.69% with the highest for F9, as given in Table 4.

% Moisture Content

The % moisture content of all ramipril FDOF evaluated and ranged between 3.81 ± 0.09 to 4.98 ± 0.25% (Table 4).



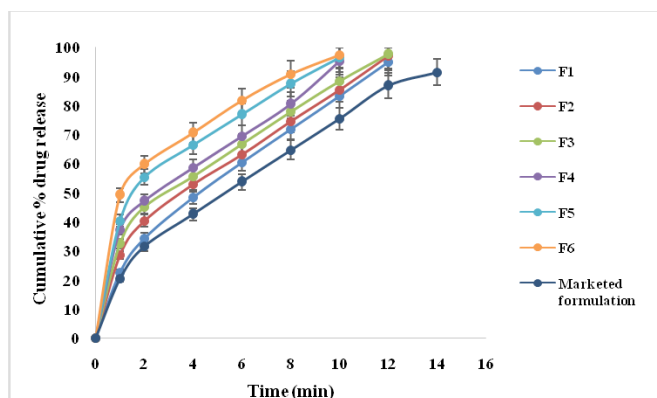


Fig. 4: *In vitro* drug release profile of marketed formulation of ramipril FDOF (F1-F6)

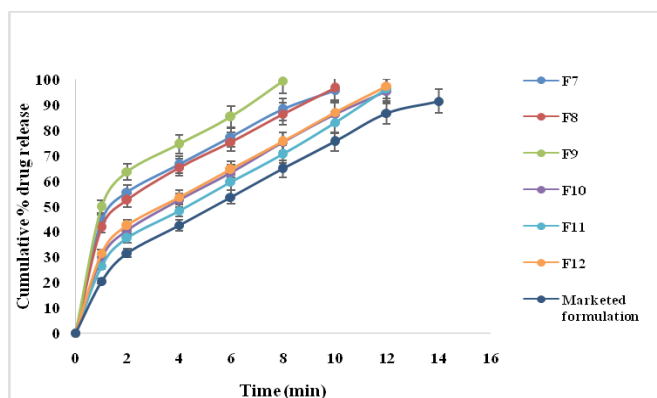


Fig. 5: *In vitro* drug release profile of marketed formulation and ramipril FDOF (F7-F12)

Folding Endurance

The folding endurance of each ramipril FDOF was determined and found within the satisfactory range of 96 ± 1 to 119 ± 2 , and shown in Table 4, with the highest value of 119 for F9.

Surface pH

The surface pH all ramipril FDOF ranged between 6.6 ± 0.5 to 6.94 ± 0.4 , and shown in Table 4, with the highest value of 6.94 exhibited by F9.

Tensile Strength and Percent Elongation

The results demonstrate that optimized ramipril FDOF formulation (F9) exhibited better tensile strength of 11.6 g/cm^2 and modest % elongation of 9.8, which is attributed to film-forming polymers.

In vitro Drug Dissolution Study of Ramipril FDOF

The dissolution data of F1 to F12 is graphically represented in Figs 4 and 5, and all formulations released $> 95\%$ of drug within 12 minutes. The optimized formulation (F9) shows highest drug release of $99.36 \pm 0.52\%$ by the end of 8 minutes. It is very clear from the results that the release profile of film formulation using β -CD has enormously enhanced the solubility of ramipril, and therefore, increased drug release of films, when compared

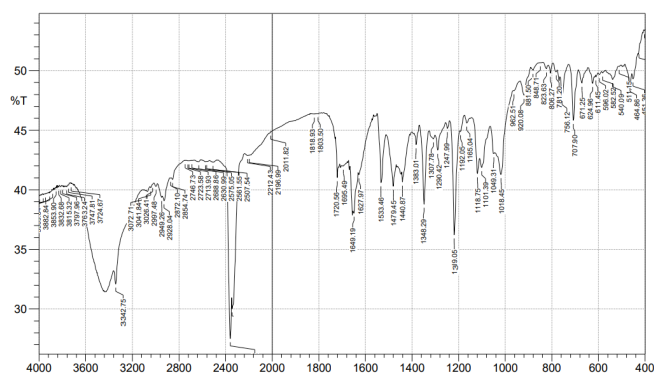


Fig. 6: FTIR of ramipril pure drug

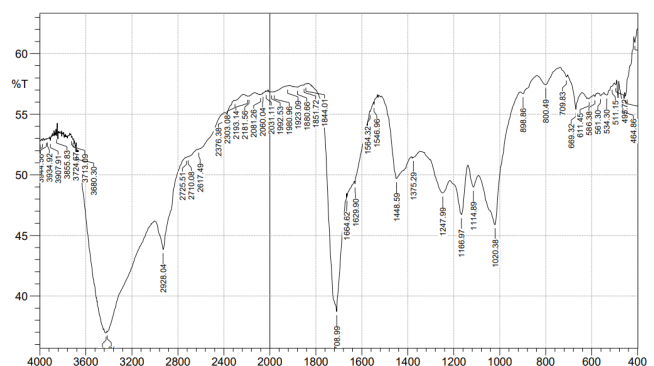


Fig. 7: FTIR of ramipril FDOF (F9)

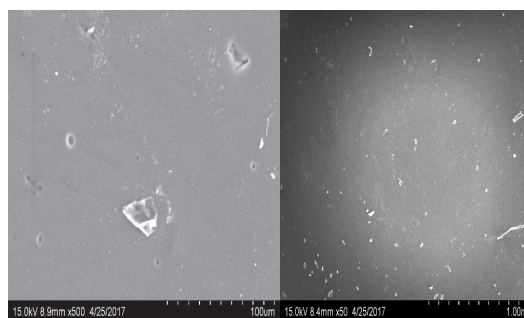


Fig. 8: SEM of ramipril FDOF (F9)

to marketed formulation (91.43% in 15 minutes). As the concentration of the superdisintegrants increased, it resulted in decreasing DT, which in turn enhanced the drug dissolution accordingly.

Drug Excipient Compatibility Study

The existence of characteristic absorption bands of ramipril pure drug (Fig. 6) and ramipril FDOF optimized formulation (F9) (Fig. 7) demonstrate the presence of no interaction amongst drug and excipients.

SEM Studies

SEM of ramipril FDOF confirms that surface is rough, uneven with spherical pits with no particles in it suggesting the existence of drug in dissolved state in the polymer. The data ensures the loss of crystallinity of ramipril during formulation (Fig. 8).

Table 5: Stability studies of optimized formulation (F9) stored at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$

Retest time (days)	Drug content (%)	In vitro drug release profile (%)
0	99.98 $\pm$ 0.69	99.36 $\pm$ 0.52
30	99.38 $\pm$ 0.26	98.85 $\pm$ 0.63
60	98.79 $\pm$ 0.62	98.12 $\pm$ 1.64
90	98.08 $\pm$ 0.39	97.96 $\pm$ 1.59
120	97.79 $\pm$ 0.17	97.75 $\pm$ 2.48
180 days	97.22 $\pm$ 0.53	97.1 $\pm$ 2.43

Stability Study of Optimized Ramipril FDOF (F9)

Optimized formulation subjected to stability study for 6 months, analyzed for drug content, and drug release periodically conclude that F9 is stable, retained its original properties with minute insignificant variations (Table 5).

DISCUSSION

The FDOF of ramipril and β -CD complexes were formulated successfully by solvent casting technique for immediate action and patient compliance. Results obtained showed that introducing β -CD significantly increased solubility of ramipril, and in turn, enhanced the drug release with highest drug release for F9 (99.36 $\pm$ 0.52%) within 8 minutes, compared to marketed formulation. Concentration of the super-disintegrants also showed significant effect on drug release accordingly. An increase in super-disintegrants concentration decreased the DT and increased drug release. All other evaluation parameters were found within satisfactory range for all 12 ramipril FDOFs. Overall preparation was simple, reproducible, cost-effective, and has potential for consideration for ramipril drug delivery with enhanced solubility, drug release, and bypassed first-pass metabolism.

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