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Research Article

FORMULATION AND EVALUATION OF RAMIPRIL TRANSDERMAL PATCHES FOR CONTROLLED DRUG DELIVERY IN HYPERTENSION

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ABSTRACT

The present study was undertaken to formulate and evaluate transdermal patches of Ramipril for improved bioavailability and prolonged antihypertensive effect. Ramipril, an ACE inhibitor, undergoes extensive hepatic first-pass metabolism resulting in low oral bioavailability. Transdermal drug delivery offers an alternative route to bypass hepatic metabolism and provide sustained plasma drug levels. Transdermal patches were prepared by solvent casting method using various polymers including HPMC E15, Aloe vera powder, Sodium CMC, and Eudragit RS 100 with suitable plasticizers and permeation enhancers. The prepared formulations were evaluated for thickness, weight uniformity, folding endurance, surface pH, swelling index, drug content, adhesion strength, in vitro diffusion studies, and release kinetics. Among all formulations, F22 (HPMC E15 and Eudragit RS 100 combination) showed optimum adhesion strength (19.6±0.5 g), in vitro residence time (6.0±0.14 hrs), satisfactory surface pH, controlled swelling index, and sustained drug release for 8 hours. Drug release followed diffusion-controlled kinetics. The study concludes that Ramipril transdermal patches can effectively enhance therapeutic efficacy and patient compliance in hypertension management.

Keywords: Ramipril, Transdermal patch, Hypertension, Solvent casting, HPMC E15, Eudragit RS 100.

INTRODUCTION

Transdermal drug delivery systems (TDDS) are polymeric patches that deliver drugs at a controlled rate through intact skin into systemic circulation (Chien, 1992; Guy, 1996). These systems bypass hepatic first-pass metabolism and reduce gastrointestinal side effects. Hypertension is defined as persistent elevation of systolic blood pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg. ACE inhibitors are widely prescribed antihypertensive agents that inhibit the conversion of angiotensin I to angiotensin II, thereby reducing blood pressure. Ramipril is a prodrug converted to ramiprilat, a potent ACE inhibitor. Although well absorbed orally, it undergoes significant first-pass metabolism, leading to low bioavailability (28%). Transdermal delivery can overcome these limitations. Previous studies have reported successful formulation n of Ramipril transdermal patches using polymer combinations (Senthilkumar *et al*., 2011; Dwarakanadha Reddy *et al*., 2010). Similar approaches have been applied for other antihypertensive drugs like Amlodipine and Metoprolol (Nanda *et al*., 2012). Hence, the present study aimed to develop and evaluate Ramipril transdermal patches using suitable polymeric systems.

MATERIALS AND METHODS

Materials

Ramipril (Gift sample, Dr. Reddy's Laboratories), HPMC E15, Aloe vera powder, Sodium CMC, Eudragit RS 100, Propylene glycol, Oleic acid, Ethanol, HP-β-CD.

Analytical Method

Standard calibration curves of Ramipril were prepared in pH 6.8 and 7.4 phosphate buffer. Absorbance was measured at 376 nm using UV spectrophotometer.

Preparation of Transdermal Patches

Transdermal patches were prepared by solvent casting method. Polymers were dissolved in suitable solvents. Plasticizer (propylene glycol) and drug were incorporated.

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The solution was cast onto lubricated Petri plates and dried at room temperature. Dried films were carefully peeled and cut into required size patches.

Evaluation Parameters

Thickness (Screw gauge), Weight variation, Folding endurance, Surface pH, Swelling index, Drug content (UV method at 376 nm), In vitro diffusion (Franz diffusion cell), Release kinetics modeling (Zero order, First order, Higuchi, Korsmeyer–Peppas)

RESULTS AND DISCUSSION

Standard solutions in the range of 0 to 45 µg/ml were prepared and absorption values were recorded at 376 nm against respective buffer blank. From this data, the standard curve of ramipril was obtained.

Table 1. Standard Graph of ramipril in pH 6.8 PBS.

Concentration(µg/ml)	Absorbance
0	0
10	0.176
15	0.265
20	0.363
25	0.471
30	0.541
35	0.646
40	0.735
45	0.841

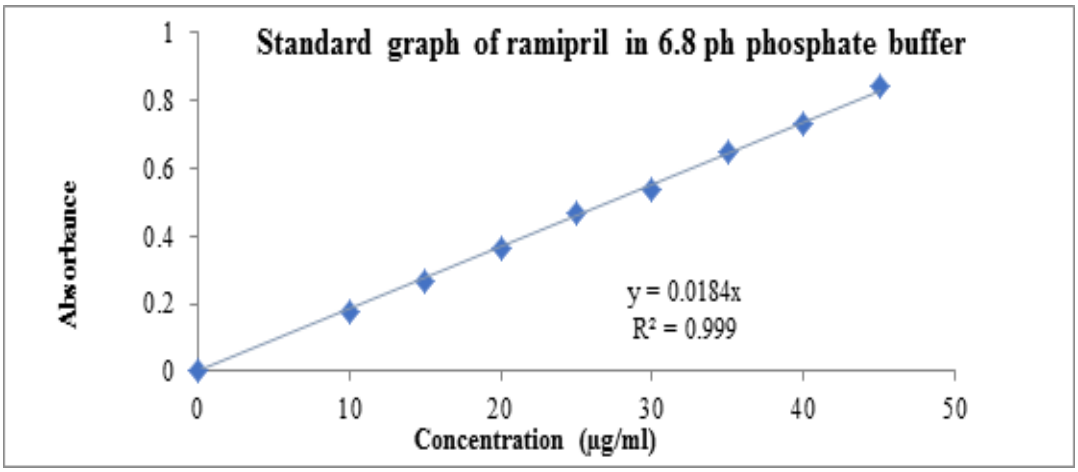

Figure 1. Standard graph of ramipril in 6.8 ph phosphate buffer.

Table 2. Standard Graph of ramipril in pH 7.4 PBS.

Concentration(µg/ml)	Absorbance
0	0
10	0.175
15	0.286
20	0.374
25	0.501
30	0.641
35	0.736
40	0.822
45	0.961

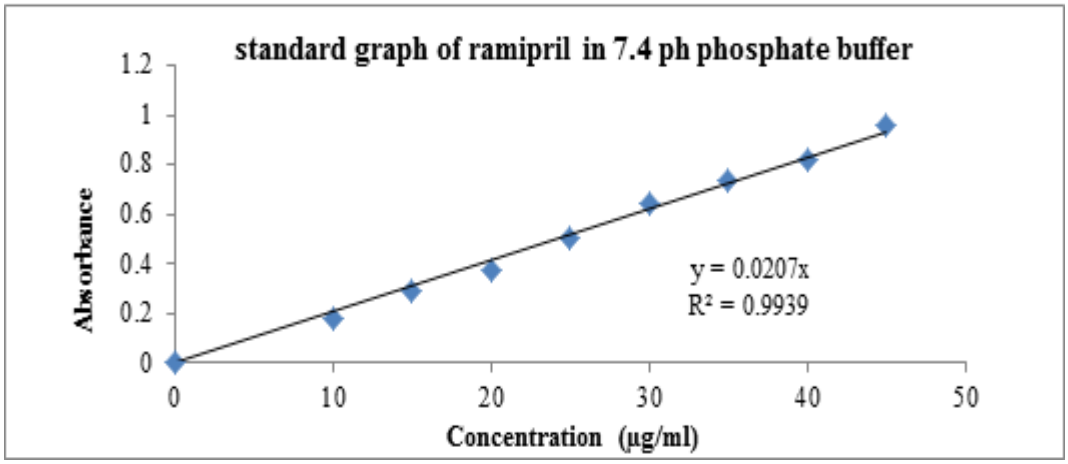

Figure 2. Standard graph of ramipril in 7.4 pH phosphate buffer.

Table 3. Evaluation of physical properties of the patches.

Formulation code	Thickness (mm)	Uniformity of Weight(mg)	Folding endurance	Surface pH	Swelling index
F-1	0.21 ±0.02	11.5±0.09	213±2.0	6.8±0.05	33.12±1.4
F-2	0.21 ±0.07	14.82±0.32	194±1.3	6.7±0.02	35.41±1.6
F-3	0.23 ±0.05	16.62±0.40	190±2.0	7.0±0.06	36.36±2.0
F-4	0.20 ±0.03	11.7±0.26	183±3.6	6.7±0.03	29.54±1.4
F-5	0.21 ±0.06	15.17±0.10	176±1.4	6.6±0.01	31.71±1.3
F-6	0.22 ±0.05	17.22±0.24	171±1.6	6.7±0.05	33.63±1.8
F-7	0.18 ±0.02	10.92±0.17	194±4.0	6.8±0.04	36.5±0.9
F-8	0.20 ±0.04	13.68±0.35	190±2.2	7.1±0.03	37.4±1.1
F-9	0.21 ±0.07	15.73±0.29	187±3.6	6.6±0.06	40.2±1.2
F-10	0.20 ±0.08	16.10±0.16	191±2.0	6.9±0.02	34.7±1.0
F-11	0.30 ±0.03	18.11±0.77	182±2.0	6.8±0.02	35.1±1.3
F-12	0.31 ±0.05	20.41±0.32	180±3.4	6.7±0.05	35.4±0.8
F-13	0.27 ±0.06	17.05±0.16	174±3.2	6.6±0.06	29.3±1.1
F-14	0.27 ±0.02	18.48±0.33	168±1.0	6.7±0.03	32.7±1.5
F-15	0.28 ±0.05	21.27±0.27	159±2.0	6.7±0.01	34.6±1.4
F-16	0.22 ±0.06	16.21±0.21	183±2.6	6.6±0.04	31.4±1.1
F-17	0.24 ±0.04	17.07±0.62	177±3.3	6.5±0.08	33.5±1.3
F-18	0.25 ±0.01	19.34±0.34	173±1.0	6.8±0.01	36.3±1.2
F-19	0.30 ±0.03	21.28±0.41	171±2.0	6.8±0.02	33.4±1.6
F-20	0.28 ±0.02	19.05±0.25	169±3.4	6.7±0.02	31.7±1.0
F-21	0.25 ±0.02	16.81±0.33	176±4.0	7.0±0.06	33.8±1.4
F-22	0.30 ±0.03	20.79±0.21	179±2.0	6.6±0.04	32.4±1.7
F-23	0.28 ±0.01	19.48±0.26	168±3.6	6.5±0.02	30.1±1.5
F-24	0.25 ±0.04	17.03±0.17	177±2.2	6.6±0.05	33.5±1.4

Values are represented as average ± standard deviation of (n=3)

Table 4. Evaluation of Ramipril Patches.

Formulation code	*In vitro* residence time (hrs)	% drug content	adhesion strength (g)
F-1	6.2±0.14	96.0±1.03	18.3±0.8
F-2	6.3±0.11	95.8±0.92	19.2±0.6
F-3	6.6±0.31	95.2±0.81	20.6±0.2
F-4	4.0±0.24	98.5±1.11	16.4±0.4
F-5	4.3±0.19	96.7±1.06	17.1±0.9
F-6	4.4±0.17	96.0±0.72	19.3±0.5
F-7	5.0±0.20	97.2±0.88	21.0±0.5
F-8	5.4±0.16	98.0±1.04	23.6±0.6
F-9	6.0±0.24	96.7±0.75	24.5±0.5
F-10	6.3±0.11	96.3±1.06	18.2±0.7
F-11	6.2±0.31	96.1±0.51	20.5±0.3
F-12	6.0±0.34	95.0±1.22	20.7±0.7
F-13	4.2±0.17	96.5±0.64	17.7±0.8
F-14	4.3±0.18	95.0±0.72	17.0±0.7
F-15	4.0±0.16	94.2±1.06	16.1±0.5
F-16	5.3±0.24	97.6±1.11	22.8±0.6
F-17	4.1±0.27	96.6±0.91	21.3±0.4
F-18	4.8±0.29	96.4±0.67	21.4±0.5
F-19	4.2±0.31	95.3±0.82	19.4±0.9
F-20	5.0±0.16	96.1±1.04	16.1±0.3
F-21	5.6±0.32	96.2±1.12	21.2±0.8
F-22	6.0±0.14	95.4±0.77	19.6±0.5
F-23	4.8±0.16	94.8±0.94	15.8±0.4
F-24	5.4±0.11	96.3±0.65	21.8±0.3

Values are represented as average ± standard deviation of (n=3)

Table 5. *In vitro* Release of Ramipril from formulations F1 to F6.

Time (hrs)	F1 %DR±SD	F2 %DR±SD	F3 %DR±SD	F4 %DR±SD	F5 %DR±SD	F6 %DR±SD
0	0	0	0	0	0	0
½	11.91±1.35	10.22±0.57	8.53±0.65	11.39±0.84	11.09±1.22	10.32±0.63
1	17.91±0.95	11.55±0.73	9.02±0.93	15.38±1.64	14.27±0.85	13.15±0.84
1 .1/2	28.53±0.85	13.37±0.45	11.73±1.38	18.83±1.23	17.63±1.36	15.76±1.36
2	39.33±1.1	14.31±1.21	13.64±0.88	24.95±0.87	23.51±0.96	19.03±0.92
2.1/2	47.06±0.72	17.82±0.96	16.17±1.49	33.49±0.69	30.83±0.82	25.77±1.75
3	56.22±0.63	24.93±1.08	20.35±0.78	40.51±1.32	37.46±0.67	32.07±1.02
3. ½	66.88±1.03	32.31±0.97	26.44±1.29	47.86±0.84	44.3±1.44	37.13±0.86
4	87.64±0.88	37.02±0.84	30.04±1.61	57.71±0.75	52.45±1.72	45.16±1.34
4. ½	89.42±1.16	40.66±1.45	36.53±0.83	67.52±0.81	62.01±0.65	53.51±0.72
5	71.51±0.76	64.88±0.66	60.44±0.76	80±0.93	73.56±0.88	62.84±1.08
5. ½	59.44±0.86	91.55±0.84	75.33±1.44	69.22±0.82	80.16±1.16	69.18±0.64
6	44.27±0.74	78.25±0.82	89.11±1.2	47.63±1.04	69.52±0.84	74.97±0.91

Values are represented as average ± standard deviation of (n=3)

Table 6. *In vitro* Release of ramipril from formulations F7 to F12.

Time (hrs)	F7 %DR±SD	F8 %DR±SD	F9 %DR±SD	F10 %DR±SD	F11 %DR±SD	F12 %DR±SD
0	0	0	0	0	0	0
1/2	18.18±0.62	14.31±0.84	13.95±0.74	10.15±0.64	9.64±0.64	9.27±0.61
1	21.99±0.48	15.28±0.59	18.27±0.61	12.42±0.57	11.78±0.37	11.53±0.3
1. 1/2	29.88±0.73	19.42±0.67	23.03±0.35	16.39±0.81	15.11±0.92	14.48±0.24
2	40.59±0.95	24.45±1.12	28.58±0.44	19.93±0.61	18.72±0.55	17.62±0.48
2. 1/2	45.16±1.04	30±0.88	33.61±0.91	24.31±1.34	22.72±0.57	21.6±0.71
3	52.68±0.66	35.26±0.34	40.46±1.03	28.71±0.47	26.92±0.36	25.78±0.44
3. 1/2	59.89±0.37	41.48±0.51	48.4±0.51	34.34±0.91	31.46±0.61	30.52±0.29
4	69.88±1.01	49.92±0.63	59.1±0.67	40.89±0.64	38.02±0.76	36.31±0.58
4. 1/2	82.83±0.53	57.55±0.75	73.5±0.81	51.19±0.72	48.47±1.05	40.35±0.76
5	70.21 ±0.84	66.48±1.21	80.03±0.37	56.99±0.38	57.13±0.34	43.35±0.36
5. 1/2	61.25±0.77	74.99±0.66	69.23±0.48	67.52±0.68	64.28±0.46	51.13±0.49
6	52.45±1.02	61.52±0.76	57.41±1.03	68.35±0.46	68.78±0.74	56.49±0.81
6. 1/2	44.29±0.84	53.77±0.69	49.22±0.67	72.38±0.77	70.32±1.09	60.73±0.57
7	31.24±0.96	44.21±1.04	36.54±0.94	81.84±1.03	81.97±0.48	70.86±0.64
7. 1/2	28.62±1.06	39.11±0.75	29.33±0.82	90.26±0.44	92.09±0.53	84.73±1.08
8	20.45±0.83	26.43±0.82	21.46±0.76	79.45±1.02	80.26±0.84	91.05±0.84

Values are represented as average ± standard deviation of (n=3)

Table 7. *In vitro* Release of ramipril from formulations F13 to F18.

Time (hrs)	F13 %DR±SD	F14 %DR±SD	F15 %DR±SD	F16 %DR±SD	F17 %DR±SD	F18 %DR±SD
0	0	0	0	0	0	0
1/2	9.66±0.31	9.04±0.64	8.63±0.72	10.27±0.54	9.81±0.43	10.06±0.51
1	12.6±0.51	11.96±0.81	11.6±0.64	14.37±0.27	13.34±0.81	12.71±0.32
1. 1/2	15.92±0.83	14.59±0.37	13.84±0.81	19.29±0.61	17.62±0.64	16.65±0.44
2	17.9±0.46	16.47±0.51	16.8±0.57	23.4±0.48	21.85±0.48	20.55±0.57
2. 1/2	23.79±0.57	22.98±0.64	21.84±0.34	28.08±0.38	26.27±0.51	24.83±0.29
3	28.9±0.81	27.37±0.72	26.36±0.61	33.78±0.91	32.11±0.76	30.36±0.84
3. 1/2	34.21±1.04	33.02±0.64	31.34±0.52	39.82±1.07	37.56±0.91	36.46±0.54
4	40.95±0.65	39.07±0.91	37.73±0.84	46.19±0.84	43.64±0.42	41.26±0.63
4. 1/2	50.27±0.83	47.37±1.01	45.72±0.49	52.99±0.63	50.35±0.38	48.41±0.72
5	58.31±0.67	55.8±0.62	53.3±0.46	61.51±0.53	58.22±0.51	55.8±0.55
5. 1/2	65.46±1.06	63.13±0.87	61.12±0.81	67.27±0.71	64.4±0.72	62.86±0.91
6	72.41±0.64	69.74±0.49	67.75±0.66	75.3±0.48	72.32±0.46	69.67±0.43
6. 1/2	78.48±0.59	75.96±0.37	74.11±0.58	83.43±0.53	78.82±0.34	76.35±0.72
7	83.75±0.81	81.6±0.46	79.37±0.49	70.25±0.64	84±0.47	81.52±0.58
7. 1/2	69.91±1.04	70.88±1.12	84.28±0.72	61.47±1.04	70.15±0.76	68.67±0.74

Values are represented as average ± standard deviation of (n=3)

Table 8. In vitro release of ramipril from formulations F19 to F24 (µg/m^2 /min).

Time (hrs)	F19	F20	F21	F22	F23	F24
1	3.52	3.37	2.98	3.44	3.20	2.91
2	3.02	3.06	2.76	3.18	3.02	2.72
3	2.93	2.91	2.61	3.05	2.87	2.47
4	2.84	2.55	2.52	2.76	2.49	2.34
5	2.56	2.40	2.35	2.68	2.41	2.26
6	2.48	2.23	2.18	2.55	2.28	2.11
7	2.31	2.06	1.91	2.43	2.10	1.90
8	2.15	1.89	1.74	2.20	1.90	1.81

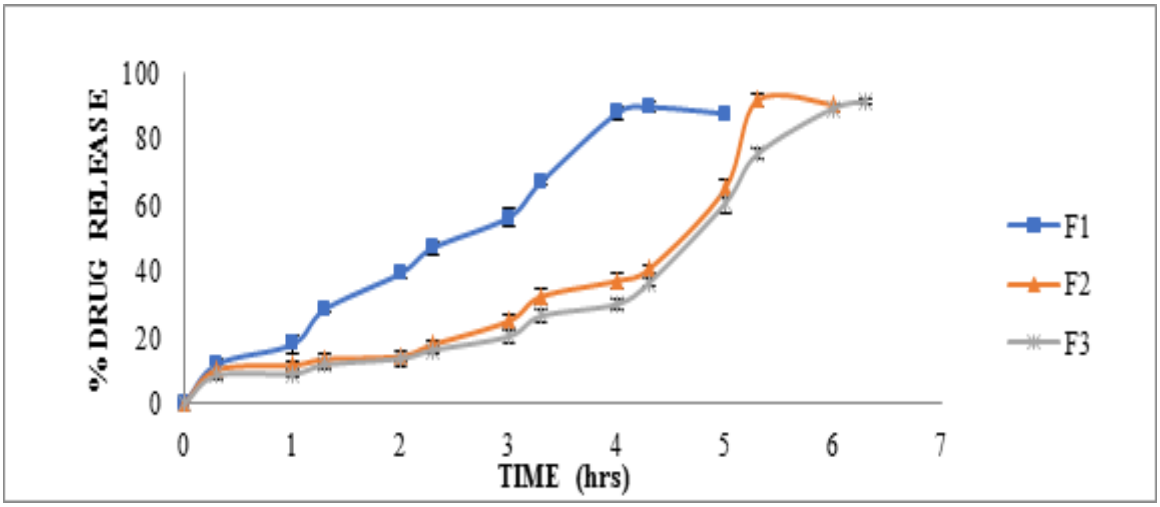

Figure 3. In vitro drug release of ramipril from transdermal patches (F1-F3).

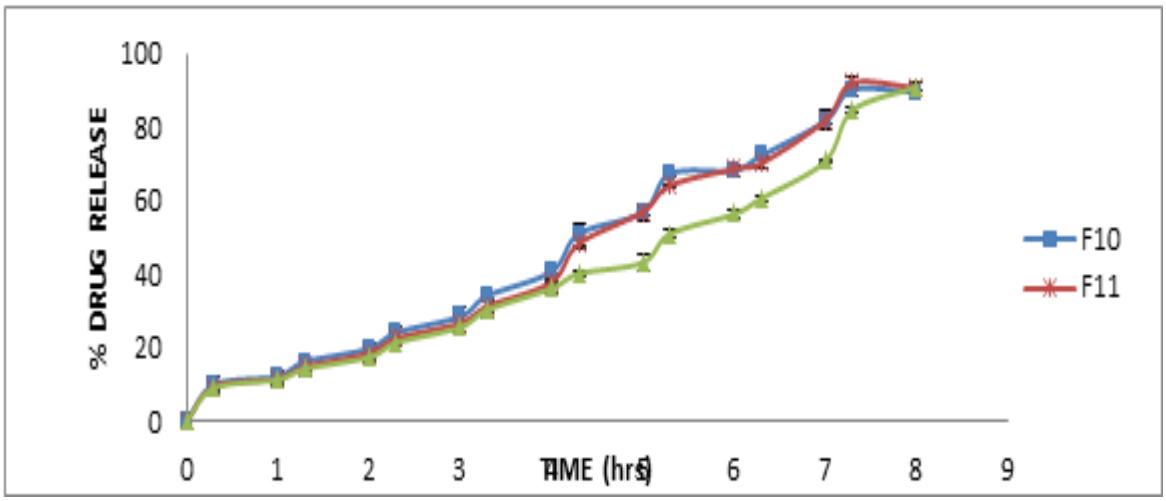

Figure 4. *In vitro* drug release of ramipril from transdermal patches (F4-F6).

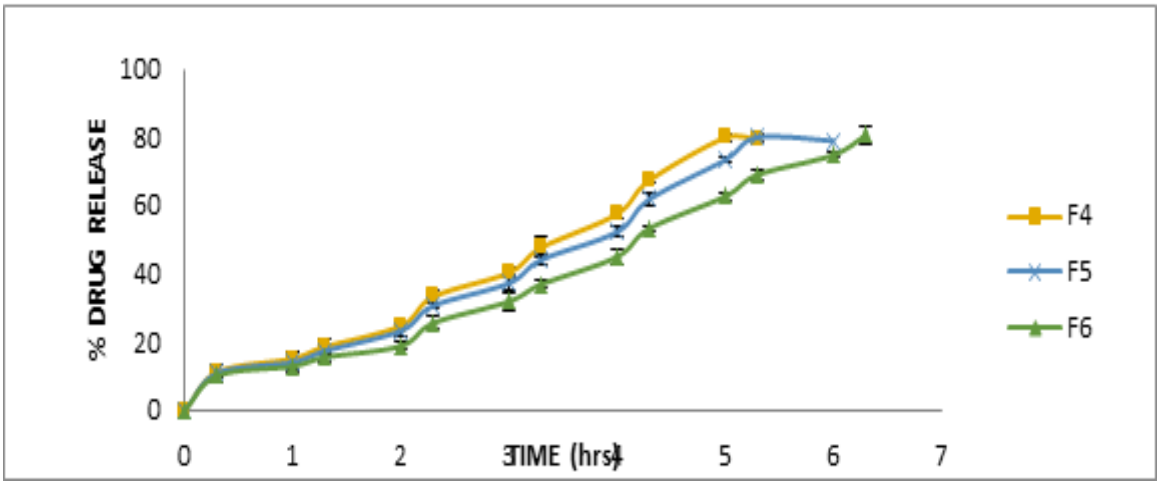

Figure 5. *In vitro* drug release of ramipril from transdermal patches (F7-F9).

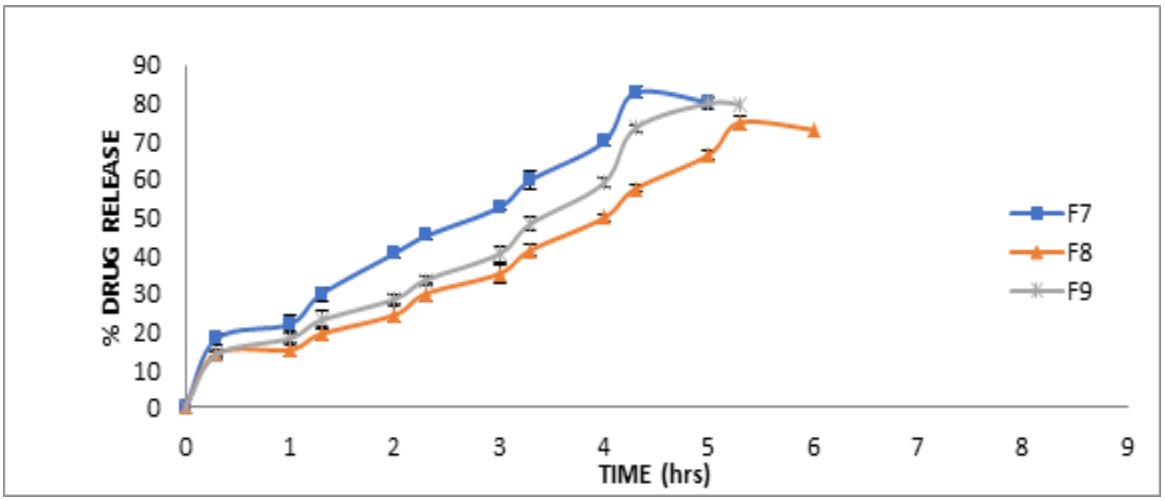

Figure 6. *In vitro* drug release of ramipril from transdermal patches (F10-F12).

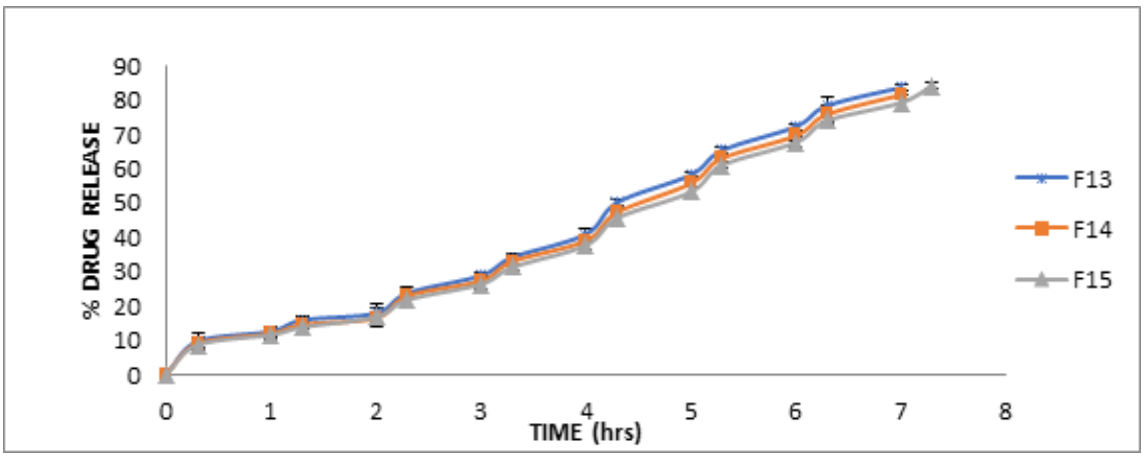

Figure 7. *In vitro* drug release of ramipril from transdermal patches (F13-F15).

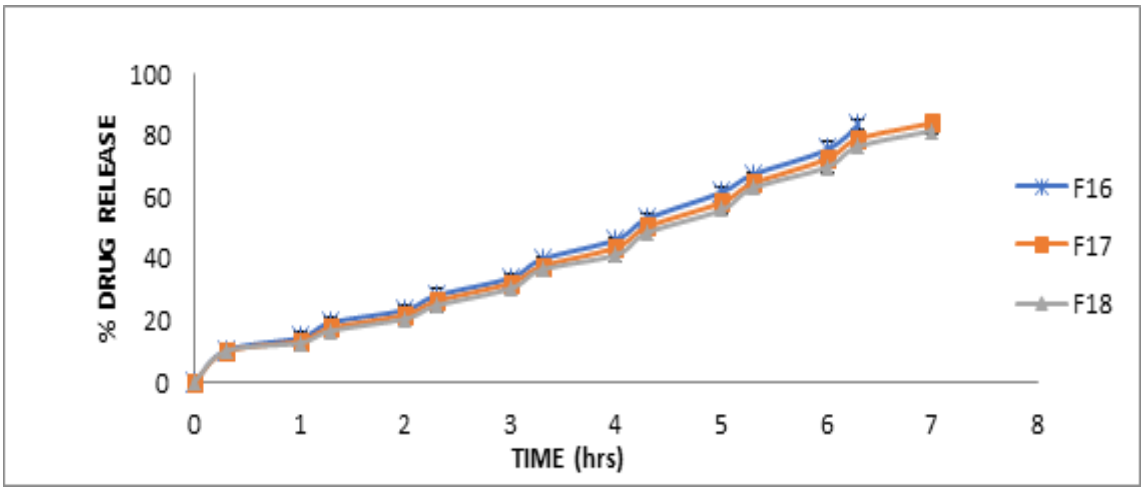

Figure 8. *In vitro* drug release of ramipril from transdermal patches (F16-F18).

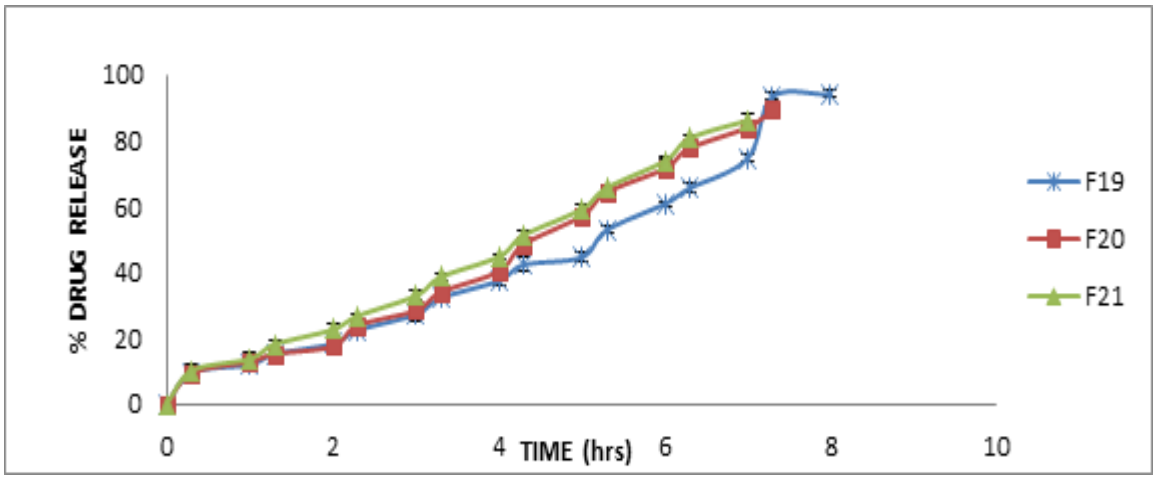

Figure 9. Ex Vivo Permeation of Ramipril from Transdermal Patches (F19-F21).

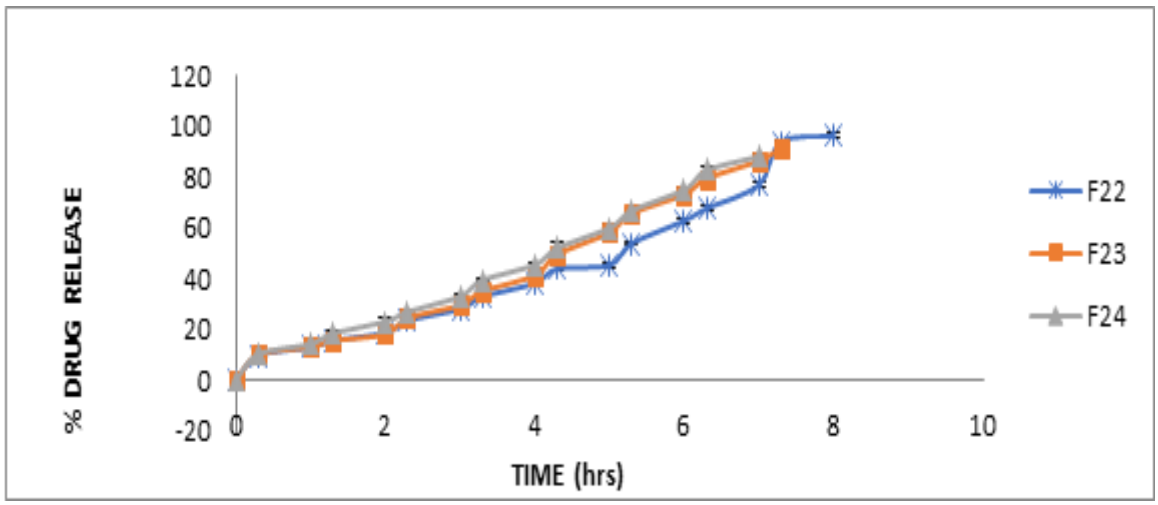

Figure 10. *Ex vivo* permeation of ramipril from transdermal patches (F22-F24).

Standard calibration curves showed linearity in the range of 10–45 µg/ml in both ph 6.8 and 7.4 buffers. All formulations exhibited uniform thickness (0.18–0.31 mm), acceptable weight variation, folding endurance (159–213), and surface ph near neutrality, indicating suitability for skin application. Drug content ranged between 94–98%, showing uniform drug distribution. Adhesion strength varied across formulations, with f22 demonstrating optimal adhesion (19.6±0.5 g). *In vitro* diffusion studies showed sustained drug release up to 8 hours. Polymer combination significantly influenced release rate. Formulations containing hpmc and eudragit rs 100 showed controlled diffusion-mediated release. Release kinetics analysis indicated diffusion-controlled mechanism consistent with higuchi model.

CONCLUSION

The present study successfully developed ramipril transdermal patches using solvent casting technique. All formulations showed satisfactory physicochemical characteristics. Among them, formulation f22 (hpmc e15 and eudragit rs 100 combination) was found to be optimized based on adhesion strength, residence time, controlled swelling, and sustained drug release for 8 hours. Transdermal delivery of ramipril effectively bypasses hepatic first-pass metabolism and improves bioavailability. The developed system may enhance patient compliance and therapeutic efficacy in hypertension management.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

FUNDING

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AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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