Formulation and Evaluation of Trandolapril Buccal Patch

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***Abstract*—The buccal area provides a desirable route for systemic medication administration. The present study aims to formulate and evaluate trandolapril buccal Patch to avoid the first-pass hepatic metabolism of the drug and improve bioavailability. Various combinations of mucoadhesive polymers like PVA, HPMC K10, HPMC E15, SCMC, HPMC K100, Eudragit RL-100, and Eudragit-RS 100 were tried. These formulations were evaluated for visual inspection, content uniformity, surface pH, swelling index, thickness variation, assay, *in-vitro* drug release, folding endurance, bio-adhesion time, and Ex-vivo permeation studies. The best-selected formulation showed an *in-vitro* drug release of 97.5% and an *Ex-vivo* drug release of 98.8% in one hour and 30 minutes. Mucoadhesive patches of trandolapril can be developed as release formulations for the treatment of hypertension.**

***Index Terms*—Trandolapril, Buccal patch, PVA, HPMC K10, HPMC E15, SCMC, HPMC K100**

I. INTRODUCTION

Over the last few decades, pharmaceutical scientists throughout the world have been trying to explore transdermal and trans-mucosal routes as an alternative to injections. Among the various trans-mucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms. Because thin mucin film, which exists on the surface of the oral mucosa may provide an opportunity to retain a drug delivery system in contact with the mucosa for prolonged periods if it is designed to be mucoadhesive. The buccal route provides one of the potential routes for typically large, hydrophilic, and unstable proteins, oligonucleotides, and polysaccharides, as well as conventional small drug molecules. Drug delivery via Buccal Lining includes increasing the bioavailability of orally administered drugs that otherwise undergo hepatic first-pass metabolism [1]. The large contact surface of the oral cavity contributes to rapid and extensive drug absorption. Due to the versatility of the manufacturing processes, the release can be oriented either towards the buccal mucosa or
towards the oral cavity [2]. These dosage forms are usually prepared by casting a solution of the polymer, drug, and excipients onto a surface and allowing it to dry.

Trandolapril is a non-sulfhydryl prodrug that belongs to the angiotensin-converting enzyme (ACE) inhibitor class of medications that is orally administered. It is metabolized to its biologically active diacid form, Trandolaprilat, in the liver. The half-life of the drug is 6 hours (trandolapril) & 10 hours (trandolaprilat) and extensive first-pass metabolism results in low bioavailability of 4-14% (Pauly and Safar 1994). Hence, it was thought that it might be beneficial to formulate a buccal drug delivery system for the delivery of Trandolapril. The work aims to formulate and evaluate Trandolapril buccal patch using different polymers like PVA, HPMC K10, HPMC E15[3], SCMC, and HPMC K100 to choose the best formulation among the prepared formulations [4].

II. MATERIALS AND METHODS

Trandolapril drug was purchased from Pharma Train, Kukatpally, Hyderabad. Polyvinyl alcohol (Degree of polymerization 1700-1800) was purchased from Qualikems Fine Chemicals Pvt ltd, Vadodara, India. HPMC K 10, HPMC E15, SCMC, and HPMC K100 chemicals were purchased from SD Fine Chemicals, Mumbai, India.

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

To check the integrity (Compatibility) of the drug in the formulation, FTIR spectra of the formulations along with the drug and other excipients were obtained

and compared using Shimadzu FT-IR 8400 spectrophotometer. The present study employed the Potassium bromide (KBr) pellet method.

Formulation of Trandolapril buccal patch

The buccal patches were prepared by solvent casting method [5]. Glass Petri plates of internal diameter 7 cm were used. Each film with 2cm^2 was chosen as optimum for ease of handling and use. Various polymeric solutions were prepared by dissolving weighed quantities in suitable solvents. The drug was dissolved in methanol and slowly added to the polymer solution, glycerin, PEG 600[6], and PEG 400 were used as plasticizers. This solution was poured onto a glass plate and left overnight for drying at room temperature, the dried patches were peeled, packed properly, and stored in a desiccator till further use [7]

Table I: Formulation of Trandolapril buccal patches (10ml)

Polymer (gm)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug(mg)	38.4	38.4	38.4	38.4	38.4	38.4	38.4	38.4	38.4
PVA	0.3	-	-	0.4	-	-	-	-	0.4
HPMC K100	-	0.3	-	-	-	0.4	-	-	-
HPMC E15	-	-	0.3	-	-	-	-	-	-
HPMC K10	-	-	-	-	0.4	-	-	0.4	-
PVP K30	-	-	-	0.1	0.1	0.1	0.1	-	0.1
Sodium CMC	-	-	-	-	-	-	0.3	-	0.5
Glycerine	1ml	-	-	1ml	1ml	1ml	1ml	-	2ml
PEG 600	-	1ml	1ml	-	-	-	-	2ml	-
PEG 400	-	-	-	-	2ml	2ml	-	-	-

III. EVALUATION OF TRANDOLAPRIL BUCCAL PATCHES

Evaluation was performed to assess the physiochemical properties and release characteristics of the developed formulations.

Thickness, folding endurance, and surface pH

Ten patches were randomly selected for the evaluation tests. The thickness of the patch was measured by a Screw gauge at five different positions of the patch and the average was calculated [8].

Folding Endurance of the patches was determined by repeatedly folding manually, which was considered satisfactory to reveal good patch properties. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance.

The surface pH of the patch was determined to predict the possible irritative effects of the formulation on the buccal mucosa. The patches were allowed to swell at 37 ± 1° C for 2 hrs. in 10 ml phosphate buffer pH 6.8. The surface pH was measured by placing pH meter on the surface of the swollen patch [9].

Swelling studies

Each patch which was individually weighed (W1) were placed in Petri dishes containing 4 ml phosphate buffer pH 6.8 and incubated at 37 °C. At time intervals of 1, 2, 3, 4, 5, 6 hours one petri dish was removed from the incubator, and swollen patches were weighed out (W2). Swelling index (SI) was calculated using the formula

$$SI= (W2-W1) /W1 X 100$$

Drug content uniformity

Ten patches of 4 cm^2 area were randomly sampled and each patch was analyzed separately. A patch was placed carefully in a 100 ml volumetric flask. About 50ml of freshly prepared pH 6.8 PBS was added to dissolve the patch. The solution was made up to 100 ml with pH 6.8 PBS[10]. This solution was allowed to stand for about 1 h and then the absorbance was obtained on a double beam spectrophotometer at 232 nm against carrier blank. The drug content was

calculated by comparison with the standard calibration curve.

Measurement of mucoadhesive time

The mucoadhesive performance of buccal films was evaluated using porcine buccal tissue. The time for the film to detach from porcine buccal tissue in a well-stirred beaker was used to assess the mucoadhesive performance. The fresh-cut porcine buccal tissue was fixed on the side of the beaker with glue. Before the addition of the buffer, the patches were attached to porcine buccal tissue by applying light force with a fingertip for 20 s. the beaker was then filled with 80 ml phosphate buffer and kept at 37℃. A stirring rate of 150 rpm was used to simulate buccal and saliva movement. The attachment of films was monitored until drug release time. The time for the film to detach from the porcine buccal tissue was recorded as muco-adhesion time[11].

In vitro drug release

The dialysis membrane was carefully mounted between the two compartments of a Franz diffusion cell. A 2 cm2 patch under study was placed in intimate contact with the membrane. The cell contents were stirred with a magnetic stirrer, and a temperature of 37±1ºC was maintained throughout the experiment which was carried out in 6.8 pH phosphate buffer. The samples were withdrawn every half an hour to maintain sink conditions. The samples were filtered, diluted suitably, and analyzed using a UV-Vis spectrophotometer [12].

Ex vivo buccal permeation study

This buccal permeation test was planned for the optimized batch. Porcine buccal tissue from domestic pigs was obtained from a local slaughterhouse and tissue was kept in Krebs buffer solution, transported immediately to the laboratory, and used within two hours [13]. The tissue was stored in ringer solution. The epithelium was separated from the underlying connective tissue by surgical method and the delipidized membrane was allowed to equilibrate approximately for one hour in receptor buffer to gain the lost elasticity.

The buccal epithelium was carefully mounted in between the two compartments of a Franz diffusion cell. A 2 cm^2 patch under study was placed in intimate contact with the excised porcine buccal mucosa and the same procedure was followed as *in vitro* drug release.

IV. RESULTS AND DISCUSSION

Drug polymer compatibility studies

The FTIR spectra observed that the characteristic absorption peaks of pure Trandolapril were obtained (Fig. 3).

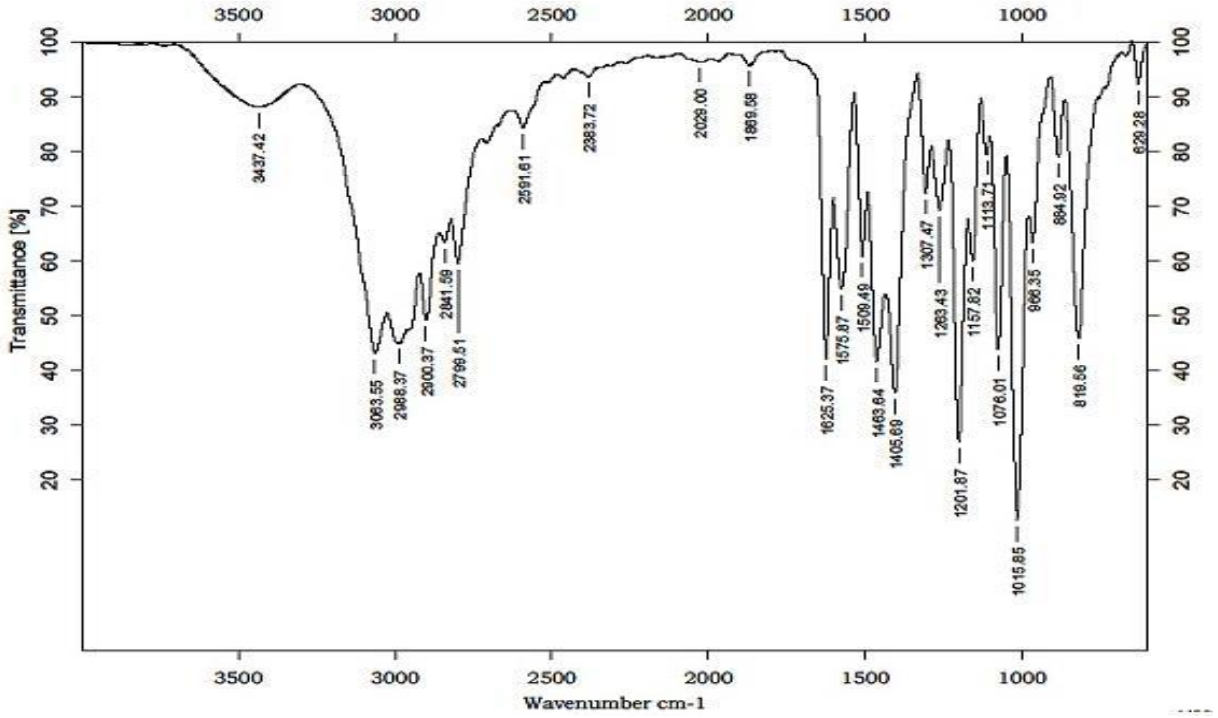


Figure 3: FT-IR spectra of Trandolapril

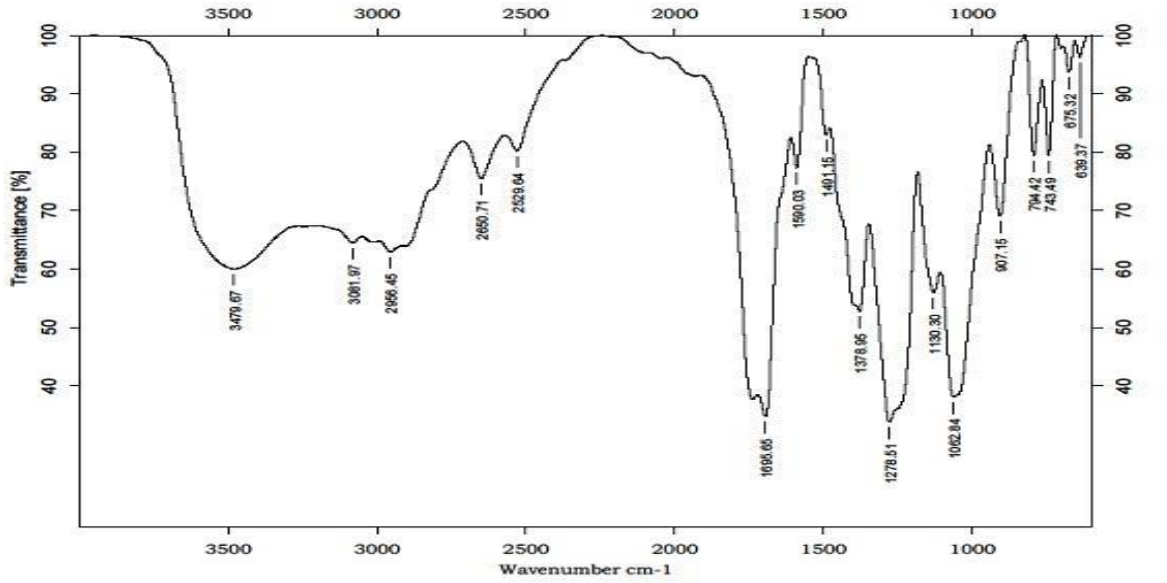


Figure 4: FT-IR spectra of trandolapril optimized formulation

The spectral data suggests that the major peaks for drugs are obtained as nearer value and there were no considerable changes in IR peaks in all physical mixtures of drug and polymers. This indicates that the drugs were molecularly dispersed in the polymers or in drug-loaded formulations thus thereby indicating the absence of any interactions.

Thickness, folding endurance, and surface pH

As mentioned in the previous section the prepared patches were evaluated for all the physicochemical tests to select the optimized formulation and the results are reported in Table II.

Table II: Characterization of buccal patches of Trandolapril

Formulation code	Thickness(mm)	Folding endurance	Surface pH
F1	0.104±0.002	>250	7.95±0.7
F2	0.102±0.002	>250	7.4
F3	0.116±0.002	>250	7.5±0.1
F4	0.146±0.002	>250	7.45±0.15
F5	0.158±0.002	>250	7.2±0.1
F6	0.184±0.002	>250	7.45±0.15
F7	0.102±0.002	>250	7.55±0.05
F8	0.168±0.002	>250	7.6
F9	0.208±0.002	>250	7.5±0.1

The buccal patches exhibit a thickness range of 0.102 mm to 0.208 mm. A patch that is too thick can be uncomfortable or irritating to the buccal mucosa and a patch that is too thin might be fragile. Thickness within this range likely strikes a balance between comfort and structural integrity. Not only that, but the thickness of the patch can also influence the rate at which the drug is released and lead to inconsistencies in drug delivery. A controlled and consistent thickness is therefore very important for predictable drug release.

Folding endurance: In pharmaceutical research, satisfactory folding endurance is often indicated by a value of greater than 200 or 250 folds. This signifies that the patch is flexible enough to withstand the movements within the oral cavity. The folding endurance for all the formulations is satisfactory

Surface pH: Attempts were made to keep the pH of all the patches close to the salivary pH to avoid mucosal irritation. The surface pH of the patches ranged from 7.2 to 7.95, close to the pH of saliva which is 6.2 to 7.6, essentially neutral.

After evaluating the patches for thickness, folding endurance, and pH they were further evaluated for important characteristic tests for buccal patches which

include swelling index, mucoadhesion time, and drug content and reported in Table III.

Table III: Characterization of buccal patches of Trandolapril

Formulation code	Swelling index (%)	Mucoadhesion time (h)	Drug content (%)
F1	33.3	>2	90.1±0.2
F2	42.8	>2	89.2±0.3
F3	64.8	>2	95.11±0.4
F4	51.31	>2	89.31±0.5
F5	55.4	>2	89.41±0.2
F6	34.6	>2	88.12±0.1
F7	50.25	>2	87.21±0.2
F8	62.1	>2	88.23±0.2
F9	65	>2	98.5±0.3

Drug content: The drug content of all the formulations was found to be uniform and was in the range of 87.21 to 98.5 %. This finding suggests that the manufacturing process is reliable and produces consistent formulations, which ensures that the correct drug dose will be delivered, which is a good outcome for the product.

Mucoadhesion time: Mucoadhesion time of all the formulations was greater than 2 h, which is a positive attribute for a buccal patch. Indicating its potential for effective and convenient drug delivery.

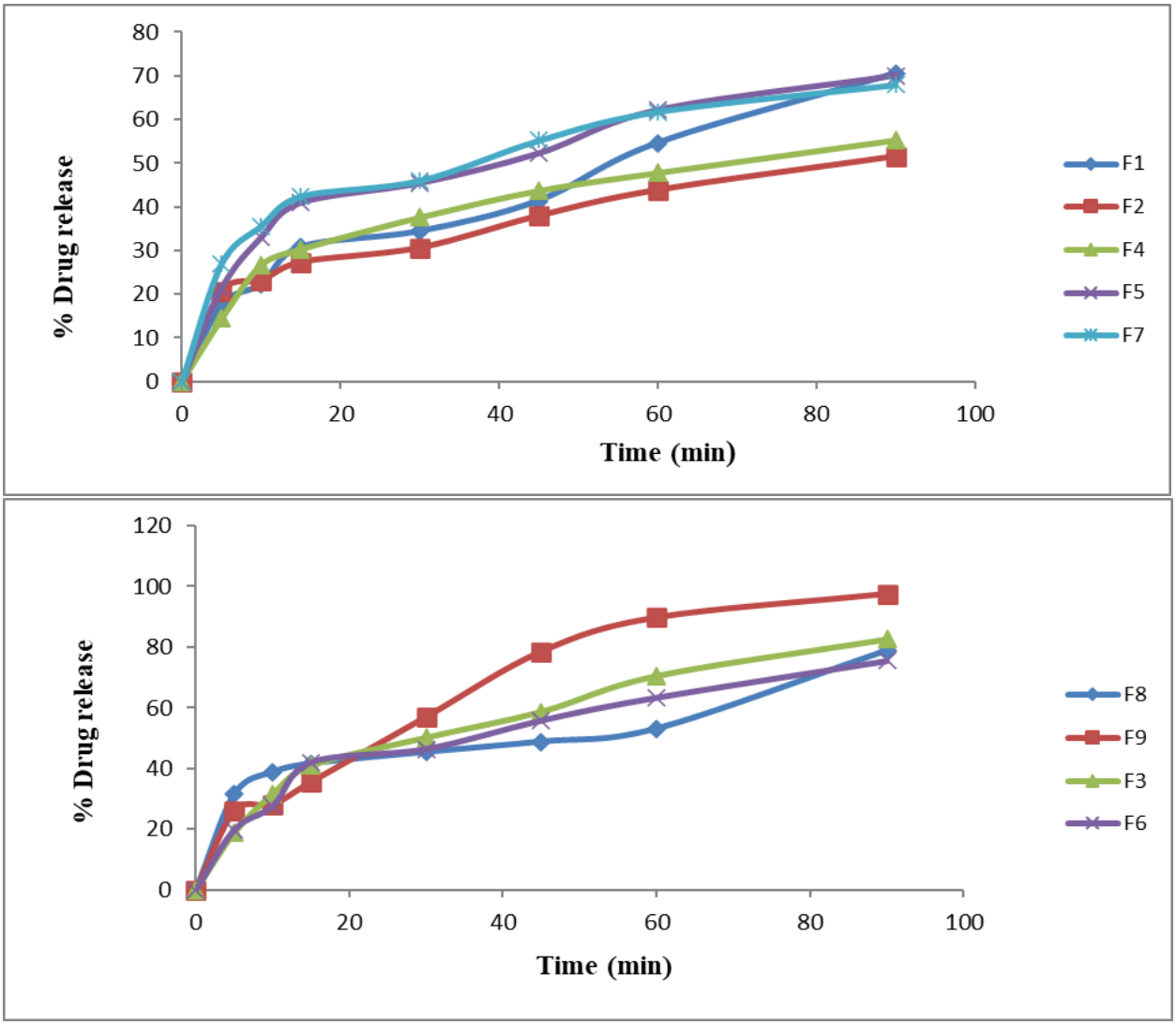
Swelling index: The addition of PVP K30 increases the surface wettability and consequently water penetration within the matrix because of the hydrophilic nature of PVP K30. The optimized patch (F9) showed 65% and (F3) containing HPMC E 15 showed 64.8% swelling index and was further evaluated for other parameters. The swelling index of a buccal patch is a crucial parameter that must be carefully controlled to ensure the optimal performance of buccal patches. Often essential for good mucoadhesion which indicates its ability to absorb fluids, primarily saliva. HPMC K4M, sodium CMC polymers alone or in combination with the other polymers, did not maintain the integrity and hence were rejected.

In vitro release studies

In vitro drug release studies for all the formulations were performed using Franz diffusion cell by taking 6.8 pH phosphate buffer as release medium and reported in Table IV and Figs 5 and 6.

Table IV: *In vitro* drug release studies of formulations F1 to F9

Time (min)			%drug release						
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	17.5±0.1	20.7±0.2	30.6±0.6	14.4±0.5	21.4±0.4	19.8±0.2	27±0.8	31.6±0.8	26±0.12
10	22.3±0.2	23.15±0.8	31.6±0.2	26.7±0.8	33±0.8	27.6±0.1	35.6±0.8	38.8±0.2	28±0.5
15	30.8±0.8	27.3±0.5	41±0.8	30.3±0.9	40.9±0.9	42±0.8	42.4±0.5	41.6±0.8	35.5±0.6
30	34.4±0.6	30.6±0.6	50.2±1.2	37.6±1.2	45.4±1.2	46.4±0.9	46±0.9	45.4±0.9	57±0.9
45	41.4±0.8	37.9±0.2	58.7±1.5	43.7±0.5	52.2±1.8	55.8±0.4	46±0.9	48.8±0.4	78.5±0.5
60	54.6±0.9	43.8±0.1	70.5±1.2	47.8±0.2	62.1±0.2	63.3±0.2	61.8±1.2	53.1±0.8	89.7±0.4
90	70.5±1.2	51.5±0.2	82.6±0.8	55.3±0.8	70±0.8	75.7±0.4	68±0.8	78.8±0.4	97.5±0.5



Figures 5 & 6 *In vitro* release profiles of buccal patches

From the above results, F3 with 82.6±0.8 % and F9 with 97.5±0.5 formulations were selected as optimized formulations and were further evaluated for ex vivo studies.

Ex vivo drug permeation studies through porcine mucosa

As per the *in vitro* drug release studies F3 (HPMC E15 and PEG 600 as plasticizer) and F9 containing PVA, PVP K30, Na CMC and glycerin as plasticizer) which were optimized were subjected to ex vivo permeation studies using porcine mucosa and results were reported in Table V and Fig 7.

Table V: Ex vivo releases profile of F1 and F9 formulations

Time (min)	% Drug release	
	F3 (HPMC E15+PEG 600)	F9 (PVA+ PVP K30 + Na CMC)
5	17.4±0.2	15±1.0
10	31.5±0.4	43±1.2
15	48.2±0.4	56.6±0.8
30	57.9±0.8	71.8±1.5
45	67±0.9	84.6±2.1
60	77.7±0.1	94±2.25
90	92±1.2	98.8±1.8

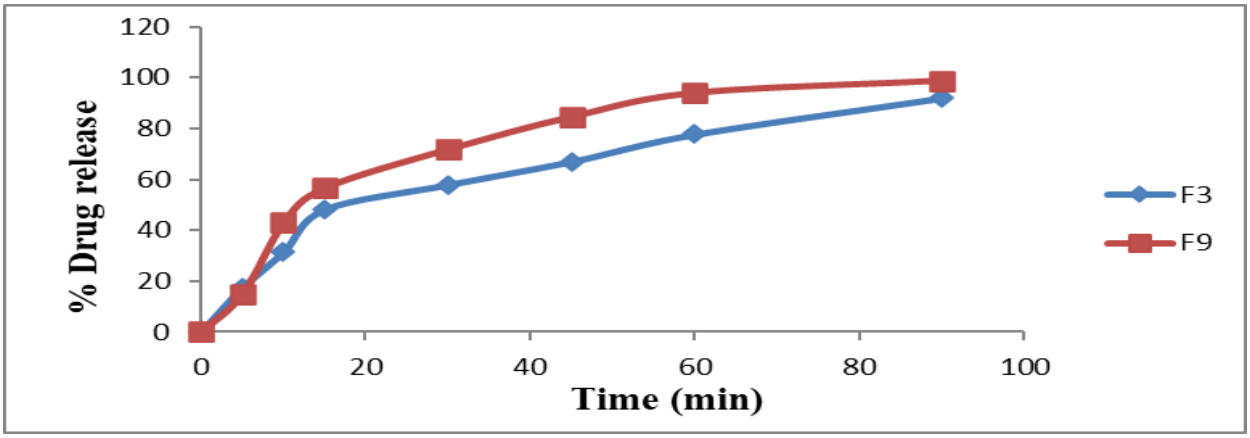


Figure 7: Ex-vivo release profile of F3 and F9 formulations

From the above results, F9 formulation was optimized as the best formulation based on the ex vivo drug release and results shown that therapeutic levels of Trandolapril can be achieved through buccal route.

V. CONCLUSION

The rationale of the present study was to improve the bioavailability of the drug utilizing the buccal drug delivery system like buccal patches. The buccal patches were prepared by solvent casting technique. The drug selected for this is trandolapril. It has a bioavailability of 4-14%, a low half-life of 6 hours, it undergoes extensive hepatic first-pass metabolism. The drug-excipient compatibility indicated that there is no interaction between the drug and excipients. The best-selected formulation F9 (PVA 4%, Na CMC 1%, PVP K30, and drug 4mg) showed in-vitro drug release of 97.5% and ex-vivo release of 98.8 %. From the results of the present studies, it can be concluded that the trandolapril buccal patch showed increased drug release. The present work indicates a good potential for mucoadhesive buccal patches containing trandolapril for systemic delivery with the added advantage of circumventing the hepatic first-pass metabolism.

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