

## “Formulation And Evaluation of Site Specific Buccal Patches of Anti-Hypertensive Drug Pindolol for Management Of Cardio Vascular Disorder”

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### Abstract

The buccal area of the mouth cavity is a desirable location to administer the preferred medication. There are now produced buccal formulations that are becoming more and more well-liked and accepted by doctors. Pindolol is antihypertensive drug with half-life of 3-4 hours. Considering this, the present study aims at formulation development and evaluation of buccal patches of Pindolol. The formulation of patch was performed by solvent casting technique and evaluation was carried out as per protocol mentioned in literature. Results showed that the formulated buccal patches were evaluated for appearance, thickness and weight. All the six formulation were transparent in nature. The thickness varied from  $47\pm 5$  to  $53\pm 4$   $\mu\text{m}$ . The weight of buccal patches varied from  $94\pm 5$  mg to  $115\pm 4$  mg. Further the highest folding endurance was associated with  $189\pm 4$  for F4 formulation. The pH among the formulation ranged from  $6.56\pm 0.14$  to  $6.82\pm 0.25$ . The moisture content spanned from  $2.15\pm 0.32$  to  $2.85\pm 0.23$ . The highest drug content of  $99.45\pm 0.32$  was observed in F4 formulation. The % swelling again maximum for F4 formulation which is 255.8%. The residence time ranged from highest of  $3.14\pm 0.18$  in F4 to lowest of  $2.12\pm 0.25$  in F6 formulation. The % Cumulative Drug Release study indicated that 99.12% drug is released in 6 hour in F4 formulation. The release Kinetics Regression values of formulation F-4 was obtained as 0.817, 0.989, 0.925, 0.961 for Zero order, First order, Higuchi and Korsmeyer-peppas model respectively. From the obtained  $R^2$  value it is clear that release kinetics follows first order kinetics. The inquiry revealed a novel buccal patch formulation made with mucoadhesive polymers for the regulated release of Pindolol. It is possible to conclude that the new buccal patches of Pindolol have great promise for the successful treatment of hypertension over an extended length of time.

Buccal drug delivery, Mucoadhesive

### I. Introduction

A cardiovascular disease (CVD) that raises blood pressure is called hypertension. The Centers for Disease Control and Prevention estimate that 670,000 fatalities in the US in 2020 were related to hypertension. According to WHO estimates, 1.28 billion persons worldwide suffer from hypertension. Compared to high-income countries, low- and middle-income countries have higher rates of hypertension. According to a WHO (Geneva) report from 2008, 51% of fatalities from stroke and 45% of deaths from ischemic coronary disease were attributable to hypertension. When the number of people with hypertension climbed to 1 billion in 2008 from 600 million in 1980, it raised serious concerns about how to treat the condition (Mills *et al.*, 2020; Devi *et al.*, 2013; Dole *et al.*, 2023).

However, the therapy of hypertension now appropriately focuses on the following: The following factors determine the blood pressure level at which antihypertensive medication therapy will be started: 1) the patient's age, absolute 10-year ASCVD risk, known CVD, and comorbidities; and 2) the blood pressure level at which blood pressure should be lowered to the lowest level to offer the best defense against pressure-related CVD events. Seldom can the latter be accomplished with a single pharmaceutical regimen. Most chronic illnesses are treated with long-term pharmaceutical interventions, which have been shown to be effective through numerous thorough clinical trials (Jarraya, 2017; Oparil *et al.*, 2018; Imam *et al.*, 2023).

**Keywords:** Hypertension, Pindolol, Buccal patch,

To make sure that their blood pressure is under control and that any necessary modifications to their treatment plan are made, people with hypertension should lead a healthy lifestyle, manage their stress, and see their doctor frequently. People who have hypertension should also be informed about the possible adverse effects of their drugs and let their healthcare provider know if they have any concerns. Headaches, nausea, fatigue, and dizziness are typical side effects of blood pressure medications (Chobanian, 2017; Angell *et al.*, 2015).

Lately, there has been a lot of research done on the optimal location of a drug delivery system in the body to maximize biological drug availability and reduce dose-dependent side effects. The buccal mucosa is a rich blood supply, generally permeable, and a good site for drug absorption, making it an appealing alternative to other traditional techniques of systemic drug administration for drug delivery. The buccal route of drug delivery allows drug molecules to enter the systemic circulation directly, circumventing the harsh gastrointestinal environment and first pass metabolism that are frequently associated with oral medication administration (Hao and Heng, 2003).

Self-medication via the buccal cavity is safe and well-received by patients since buccal patches are readily applied and removed from the application site, allowing the patient to stop the drug's intake whenever they choose. Drugs are absorbed through the buccal intercellular gaps of the epithelium by passive diffusion of the nonionized species, which is mainly controlled by a concentration gradient. The main mode of transport is the passive movement of non-ionic species over the buccal cavity's lipid membrane. Like many other mucosal membranes, the buccal mucosa has been described as a lipoidal barrier to drug passage; the more lipophilic the drug molecule, the more easily it is absorbed. The relationship (Reddy *et al.*, 2011; Miller and Johnston, 2005).

Buccal patches are matrix-modified release dosage forms that are non-dissolving. They are usually laminated and consist of a nonporous backing layer and a drug-incorporated mucoadhesive layer that adheres to the teeth, gingiva, or oral mucosa. The medication is administered in one way or both, either into the oral cavity, the submucosal layers, or both. One practical and quick screening method to determine the buccal formulation's potential mucoadhesive capacity was the contact angle measurement. The buccal patch was made with different amounts of carbopol 934P and silica elastomer (Jacob *et al.*, 2021). The

INSTRON was used to evaluate the mucoadhesive strength and the ophthalmic shadow scope was used to measure the contact angle. The technique yields sufficient data regarding the patch's adhesive strength when used on recently removed rabbit buccal mucosa. Researchers have looked into the systemic distribution of thyrotropin-releasing hormone, octreotide acetate, buserelin, calcitonin, leu-enkephalin, and RP-56142 (a lauroyl derivative of a tripeptide) from buccal patches. Buccal patches also offer greater flexibility in comparison to other drug administration methods (Veuillez *et al.*, 2001; Kelemen *et al.*, 2020). Nonselective beta blockers like pindolol are recommended for the treatment of hypertension and the prevention of angina. Given that it is taken twice daily, its duration of effect is brief. Additionally, its therapeutic window is broad, with doses ranging from 10 to 60 mg/day. The risk of cardiac failure, unexpected withdrawal from ischemia that exacerbates the condition, nonallergic bronchospasm, disguising hypoglycemia in diabetics, and masking hyperthyroidism should all be discussed with patients (Blier and Bergeron, 1998).

A non-selective beta blocker is pindolol. Blood pressure and heart rate are reduced when beta-1 adrenergic receptors in the heart are blocked. Pindolol suppresses the release of renin, which in turn limits the release of aldosterone and angiotensin II, by inhibiting beta-1 receptors in the juxtaglomerular apparatus. Vasoconstriction is inhibited by reduced angiotensin II, while water retention is inhibited by reduced aldosterone. A similar mechanism is used by beta-2 adrenoceptors found in the kidneys and peripheral blood arteries to activate cAMP-dependant kinase A, which increases smooth muscle contractility.

Vasodilation results from the relaxation of smooth muscle caused by blocking the beta-2 adrenoceptor (Gonasun, 1982; Golightly, 1982). But the half-life of this drug is 3-4 hours. Thus to increase the bioavailability of this drug this study will aim at formulation development and evaluation of buccal patches of antihypertensive drug Pindolol.

#### **Procurement of drug**

Pindolol was obtained as gift sample from pharmaceutical industry.

#### **Materials and Methods**

HPMC-E15, Edudragit RLPO, Eudragit RSPO, Carbopol 934P, PEG, Ethanol were obtained from S. D fine chemicals Pvt Ltd. All chemicals were of

standard laboratory grade.

### Formulation optimization of mucoadhesive buccal patches

Pindolol buccal patches are prepared by solvent casting technique using aluminium foil (placed as substrate on glass mould (5\*15cm). The composition of multiple formulations of a single square cast patches is stated in the table 1. Ethanol was used as a solvent and PEG as a plasticizer in conjunction with Edudragit RLPO, Eudragit RSPO and Carbopol 934P, and Buccal patches were prepared using HPMC-E15 (Semalty *et al.*, 2008).

**Table 1: Preparation of mucoadhesive buccal patches**

Ingredients	F1	F2	F3	F4	F5	F6
Pindolol(mg)	60	60	60	60	60	60
HPMC-E15 (mg)	750	750	750	750	750	750
Edudragit RLPO (mg)	300	-	-	150	-	100
Eudragit RSPO (mg)	-	300	-	150	150	100
Carbopol 934P (mg)	-	-	300	-	150	100
PEG (ml)	0.5	0.5	0.5	0.5	0.5	0.5
Ethanol (ml)	20	20	20	20	20	20

In ethanol, the measured concentrations of polymers were dispersed. After levigation with 0.5ml propylene glycol, which acted as a plasticizer and penetration enhancer, 120mg of Pindolol was introduced into the polymeric solutions. To achieve smooth, bubble-free gels, the medicated gels were left overnight at room temperature. Medicated gels is filled into the vials and securely sealed with rubber seals to avoid alcohol evaporation. To shape a versatile patch, the gels were cast into a glass mold and allowed to dry overnight at room temperature (25°). The dried patches were cut into size of 2.5\*2.5cm, packed in aluminum foil and stored in a desiccator until further use.

#### Dose Calculation

Width of the plate (mould) = 5 cm  
Length of the plate (mould) = 15 cm  
No. of 2.5 x 2.5 cm patch present whole (mould) = 12  
Each patch contains 5 mg of drug.  
12 No. of patches contains mg of drug? = 10×12 = 120mg  
The amount of drug added in each plate was approximately equal to 120 mg.

#### Evaluation of prepared patches Thickness

A vernier caliper was used to determine the thickness of patches in three distinct location (Kashappa, and Desai, 2004).

#### Weight uniformity

Three patches were chosen at random for each formulation. For the weight variance test, 10 patches from each sample were independently weighted on a digital electronic balance, and the average weight was estimated (Nafee, 2003).

#### Percentage of Moisture Content

The patches were measured individually and stored at room temperature for 24 hours in desiccators containing activated silica. Individual patches were measured repeatedly before a consistent weight was reached. The discrepancy between the original and final weight with respect to the final weight was used to measure the percentage of moisture content (Patel and Poddar, 2009).

#### Drug Content Analysis

The patch was dissolved in methanol in a 10 ml volumetric flask, and the amount was filled up of 10 ml methanol. Following that, dilutions were made and UV spectrophotometer at 282nm was used to react them (Thella *et al.*, 2020)

#### Folding Endurance

This was decided by folding one patch in the same spot over and over before it separated. The value of folding endurance was determined by the number of

times the patch could be folded at the same location without splitting or cracking (Vamshi *et al.*, 2007).

### Percent swelling

The samples were allowed to swell on the surface of an agar plate in an incubator held at  $37\pm 0.2^\circ\text{C}$  after the initial patch weight and diameter were determined. After 2 hours, the weight of the patches ( $n = 3$ ) had increased. The following equation was used to measure the percent swelling percent (S) (Mashru *et al.*, 2005):

Percent Swelling (%S) =  $(X_t - X_0/X_0) \times 100$ , where  $X_t$  is the weight of the swollen patch after time  $t$ ,  $X_0$  is the initial patch weight at zero time.

### Surface pH of patches

Three patches of each formulation were allowed to swell for two hours on the surface of an agar plate to determine the surface pH. A pH paper was mounted on the surface of the swollen patch to determine the pH. The composite of three readings was taken (Luana *et al.*, 2004).

### In vitro residence time

The *in vitro* residence time was determined using IP disintegration apparatus (Mashru *et al.*, 2005). The disintegration medium was 800 ml of pH 6.6 phosphate buffer (PB) maintained at  $37\pm 2^\circ$ . Three-centimeter-long segments of rat intestinal mucosa were fused to the surface of a glass slab, which was then vertically connected to the apparatus. Every formulation's three mucoadhesive patches were hydrated on one surface with pH 6.6 PB before being placed in contact with the mucosal membrane. The glass slab was attached to the mechanism vertically and moved up and down. At the lowest point, the patch was totally submerged in the buffer solution, and at the highest point, it was completely out. Table 8.4 shows the time taken for total degradation or detachment of the patch from the mucosal surface ( $n = 3$ ).

### In vitro release study

The USP XXIV six station dissolution apparatus type 1 (Labindia DS-8000) was used throughout the study (Higuchi and Connors, 1965). Using cyanoacrylate adhesive, one patch of each formulation was attached to the central shaft just above the basket. 900 mL of pH 6.6 phosphate buffer acted as the dissolution medium. The release analysis was carried out at a rotating speed of 50 rpm and a temperature of  $37 \pm 0.5^\circ$ . The release analysis lasted six hours. Per hour, 1 ml of sample was taken from each station and substituted (with

the dissolution medium) in the same amount. Each sample was screened, diluted appropriately, and spectrophotometrically analyzed at 282nm. The information given was the average of three tests.

## II. Results and Discussion

A good strategy for improving the poorly bioavailable drug's bioavailability and regulated release is presented in this article. Some medications are widely used in medicine to treat a variety of illnesses, yet occasionally their oral form has no therapeutic benefit due to low bioavailability. Because oral dosage forms have more advantages than parental dose forms—

such as patient compliance, affordability, and less side effects—they are utilized more frequently. The medication that was chosen to be included in the buccal mucoadhesive patch. Despite being the safest method of medication delivery, the primary drawback of the oral route is the drug's pre-systemic metabolism, which leaves the drug partially unavailable in the systemic circulation. Buccal medication delivery is an alternate strategy that offers extended drug release.

The formulated buccal patches were evaluated for appearance, thickness and weight. All the six formulation were transparent in nature. The thickness varied from  $47\pm 5$  to  $53\pm 4$   $\mu\text{m}$ . The weight of buccal patches varied from  $94\pm 5$  mg to  $115\pm 4$  mg.

Further the highest folding endurance was associated with  $189\pm 4$  for F4 formulation. Based on the overall folding endurance data, it was observed that the created buccal patches' folding endurances decreased when isolated HPMC was less frequently included in the buccal patch formula. The flexibility of these freshly manufactured buccal patches containing pindolol was confirmed by the folding endurance tests findings. The pH among the formulation ranged from  $6.56\pm 0.14$  to  $6.82\pm 0.25$ .

The moisture content spanned from  $2.15\pm 0.32$  to  $2.85\pm 0.23$ . The highest drug content of  $99.45\pm 0.32$  was observed in F4 formulation. The % swelling again maximum for F4 formulation which is 255.8%. The residence time ranged from highest of  $3.14\pm 0.18$  in F4 to lowest of  $2.12\pm 0.25$  in F6 formulation. The adhesion between the buccal mucosal surface and mucoadhesive patches is known as buccal patch mucoadhesion. Biological membranes, molecular masses, and the pace at which the polymers in the patch formula swell can all have an impact on how mucoadhesive patches are.

The % Cumulative Drug Release study

indicated that 99.12% drug is released in 6 hour in F4 formulation. The polymer makeup and permeation enhancer concentration have an impact on the medication release from buccal patches. With an increase in permeability enhancer concentration, there was a noticeable increase in drug release from the buccal patches.

It was found that the rate and extent of drug release were faster with a higher Carbopol 934P content. This was brought on by the water soluble polymer Carbopol 934P, which enhanced the wetting and water penetration into the film matrices, increasing the drug's diffusion.

The release Kinetics Regression values of formulation F-4 was obtained as 0.817, 0.989, 0.925, 0.961 for Zero order, First order, Higuchi and Korsmeyer-peppas model respectively. From the obtained R<sup>2</sup> value it is clear that release kinetics follows first order kinetics.

The visual and physiological evaluation of the patches supported the current investigation's conclusion that HPMC and Eudragit, carbapol have good matrix/film forming properties. According to in-vitro and ex-vivo research, hydrophilic polymers, such as chitosan, can be used to successfully create buccal patches of furosemide by the solvent casting approach. Investigation revealed that, although the patches showed less mucoadhesion time, the release rate also increased as the chitosan concentration increased. Conversely, as the chitosan concentration increased, the drug release was found to be controlled, and the patch also reflected a sufficient mucoadhesion time period.

In summary, the available data show that creating pindolol Buccal Patches, which may be utilized to treat a variety of conditions, is confirmably reproducible. One buccal formulation would be preferable to several dosing regimens due to the drug's sustained and prolonged release. Additional research on the in-vivo efficacy following buccal patch application is necessary to validate the therapeutic effectiveness of these systems.

**Table 2: General Appearance, Thickness and weight of buccal patches**

Formulation code	General Appearance	Thickness* (µm)	Weight* (mg)
F1	Transparent	51±5	110±5
F2	Transparent	53±4	115±4
F3	Transparent	49±6	107±7
F4	Transparent	52±3	96±3
F5	Transparent	47±5	99±2
F6	Transparent	45±4	94±5

\*Average of three determination (n=3±SD)

**Table 3: Result of folding endurance, disintegrating time, tensile strength, percentage moisture content and % drug content**

Formulation code	Folding endurance* (Times)	Surface pH*	Percentage of Moisture Content*	% Drug Content*
F1	158±5	6.74±0.15	2.25±0.15	97.85±0.15
F2	165±2	6.82±0.23	2.85±0.23	96.65±0.23
F3	147±3	6.89±0.32	2.45±0.25	98.14±0.20
F4	189±4	6.82±0.25	2.15±0.32	99.45±0.32
F5	165±6	6.56±0.14	2.74±0.14	98.75±0.45
F6	155±5	6.74±0.22	2.32±0.15	97.85±0.25

\*Average of three determinations (n=3)

**Table 4: Results of Percent swelling**

S. No.	Formulation code	Percent Swelling after 2 hrs		
		Final Weight	Initial Weight	% Swelling
1	F1	175	51	243.1
2	F2	165	53	211.3
3	F3	160	49	226.5
4	F4	185	52	255.8
5	F5	132	47	180.9
6	F6	146	45	224.4

**Table 5: Results of *in vitro* residence time**

S. No.	Formulation Code	<i>In vitro</i> Residence time (h)
1	F1	2.45±0.15
2	F2	2.65±0.25
3	F3	2.32±0.32
4	F4	3.14±0.18
5	F5	2.45±0.45
6	F6	2.12±0.25

**Table 6: *In vitro* drug release study of prepared buccal patches**

S. No.	Time (hr)	% Cumulative Drug Release					
		F1	F2	F3	F4	F5	F6
1	0.5	45.52	38.85	35.65	30.25	26.65	22.45
2	1	58.98	43.32	46.65	45.58	35.45	33.12
3	1.5	69.95	62.23	52.23	55.65	42.23	40.65
4	2	86.65	78.85	68.85	68.85	55.96	53.12
5	2.5	96.65	89.98	79.98	79.98	68.87	65.45
6	3	99.12	86.65	89.98	88.85	76.65	73.32
7	4		99.12	98.85	94.45	89.98	78.85
8	6				99.12	92.23	88.85

**Table 7: *In-vitro* drug release data for formulation F-4**

S. No.	Time (hr)	% Cumulative Drug Release
1	0.5	30.25
2	1	45.58
3	1.5	55.65
4	2	68.85
5	2.5	79.98
6	3	88.85
7	4	94.45
8	6	99.12

Time (h)	Square Root of Time(h) <sup>1/2</sup>	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	30.25	1.426	73.35	1.865
1	1.000	0.000	45.58	1.493	68.86	1.838
1.5	1.225	0.176	55.65	1.637	56.68	1.753
2	1.414	0.301	68.85	1.745	44.35	1.647
2.5	1.581	0.398	79.98	1.845	30.02	1.477
3	1.732	0.477	88.85	1.903	20.02	1.301
4	2.000	0.602	94.45	1.954	10.05	1.002
6	2.449	0.778	99.12	1.995	1.15	0.061

**Table 8: Release Kinetics Regression values of formulation F-4**

Formulation code	Zero order	First order	Higuchi	Korsmeyer- peppas
F-4	0.817	0.989	0.925	0.961

### III.

#### IV. Conclusion

Mucoadhesive patches for the oral cavity are a potentially effective drug delivery method for pindolol, it can be inferred. Eudragrit, Carbopol and HPMC, polymers combined, had good mucoadhesive and swelling properties. The buccal cavity was satisfactorily occupied by medicated patches. Therefore, the creation of bioadhesive buccal formulations for pindolol. may be a viable endeavor since it may allow for a reduction in pindolol. dosage and, consequently, a decrease in adverse effects. The inquiry revealed a novel buccal patch formulation made with mucoadhesive polymers for the regulated release of pindolol. Therefore, by avoiding the significant hepatic first pass metabolism, it is possible to conclude that the new buccal patches of pindolol have great promise for the successful treatment of hypertension over an extended length of time.

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