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Development, *in-vitro* and *in-vivo* Evaluation of Bio-Adhesive Buccal Patches of Hydralazine Hydrochloride for Improving the Oral Bioavailability

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Abstract

Background: Conventional routes of drug administration have several disadvantages. The rate and extent of absorption can vary greatly depending on the drug, its formulation, the presence of food, drug interactions, first-pass metabolism, and gastrointestinal pH. Better dosage forms or drug delivery mechanisms could minimize these problems. The pharmaceutical industry has recognized the need for and has developed many new, novel drug delivery systems. Transmucosal drug delivery can result in rapid drug absorption and systemic delivery. Several drugs and drug classes have been studied to determine the feasibility of using buccal dosage forms as a novel route of drug delivery. This study will focus on the systemic delivery of Hydralazine Hydrochloride (HHCl) via a buccal route. **Objective:** This work aims for the preparation of buccal patches of higher absorption and higher bioavailability for rapid control of blood pressure in hypertensive emergencies. The bioavailability of HHCl, when administered buccally, will be compared to the conventional oral route of administration. **Methods:** The present research aimed to develop and evaluate the mucoadhesive buccal patches of Hydralazine hydrochloride by solvent casting technique using HPMC E15 or Eudragit RL 100 and PVP K 30 polymers. **Results:** All the prepared buccal patches were subjected to various evaluation tests and the results of the tests were found to be within the pharmacopeial limits. The swelling study, bioadhesion time, in-vitro and ex-vivo drug permeation studies also appeared good results and the optimized formulation was subjected for bioavailability studies in healthy male rabbits. The pharmacokinetic profile of designed HHCl buccal patches was also showed a maximum plasma concentration (Cmax) and AUC $_{(0-\infty)}$ were found to be 1075.031±255.15 ng/ml and 42874.508±3903.14 ngh/ml. Whereas the administration of an oral solution of HHCl showed a maximum plasma concentration (Cmax) of 614.732±79.274 ng/ml and AUC$_{(0-\infty)}$ were found to be 19408.299±1802.48 ng h/ml. **Conclusion:** This research study demonstrated that developed buccal patches were efficacious could be delivered through the buccal route as it indicates a potential alternative drug delivery system for systemic delivery of HHCl. These results confirm the suitability of the prepared buccal patches to improve the bioavailability by avoiding the hepatic first-pass metabolism and thereby reducing metabolite-dependent adverse drug effects.

Keywords
Hydralazine Hydrochloride (HHCl), buccal drug delivery, first-pass metabolism, bioavailability.

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INTRODUCTION

Recently, muco-adhesive buccal drug delivery has become an essential route of drug administration. Various muco/bio-adhesive dosage forms have been developed, which include adhesive tablets, patches, gels, ointments, and more recently the use of mouth dissolving films for buccal delivery [1]. Hence, the buccal delivery serves as an attractive platform for absorption of medicaments that have poor penetration [2]. Muco/bioadhesive dosage forms may be designed to enable prolonged retention at the site of application, providing a rate of controlled drug release for improved therapeutic effect. Over the last ten years, the market share of muco/bio-adhesive drug delivery systems has extensively increased [3].

Drug delivery employing muco/bio-adhesive buccal route, utilizing adhesive dose forms offers as a novel route of drug administration. Different strategies have been carried out to promote the bioavailability of these drugs, including supplemental modification of enzyme inhibitors, use of absorption or permeation enhancers, innovative formulation techniques, and possible chemical modifications [4, 5]. Based on currently available data of biochemical and physiological aspects of absorption and metabolism, most drugs, cannot be transported effectively via the conventional route, because after administrations that are subjected to cleared extensively in the liver as first-pass clearance, which leads to a lack of significant correlation between mucosal membrane permeability, absorption, and bioavailability [6]. Direct access to the systemic circulation through the internal jugular vein bypasses drugs from the first-pass clearance by hepatic enzyme metabolism leading to higher bioavailability.

Advantages

- The oral mucosa has a rich blood supply.
- Buccal administration, the drug gains direct entry into the systemic circulation thereby bypassing the first-pass effect [7].

Limitations

- This route cannot administer drugs that irritate the mucosa or have a bitter or unpleasant taste or an obnoxious odor.
- The continuous secretion of the saliva (0.5-2 l/day) leads to subsequent dilution of the drug.
- Drugs with large doses are difficult to be administered [8]

Recent reports and its data suggest that the global market share of buccal muco-adhesive drug delivery systems is increasing at a steady growth rate of about 10%. Bioadhesive buccal formulations may prove to be an alternative to conventional medications as they may be freely attached to the buccal membrane retained for an extended period of time. In this system, the delivery of drugs by using matrix tablets, films, discs, microspheres, and gels has been focused on and reported by various researchers [9]. Where prolonged action is required, the dosage form is usually muco or bio-adhesive (tablet or patch) and the drug is slowly absorbed over the buccal mucosa releases for an extended period of time [10, 11].

Hydralazine hydrochloride is a direct-acting vasodilator that is used as an antihypertensive agent. It was chosen as the model medicament for the examination since it has certain qualities that medication is well absorbed from the gastrointestinal tract, but its bioavailability was low. The physicochemical properties of HHCl, its suitable half-life (3-7 h) with low oral bioavailability (26%–50%) and not high molecular weight (196.64), and convenient dose and absence of objectionable odor and taste are suitable for buccal administration. The present research aimed to develop and evaluate the bio-adhesive buccal dosage forms of Hydralazine hydrochloride (HHCl) to improve oral bioavailability [12, 13].

MATERIALS AND METHODS

Hydralazine hydrochloride (HHCl) was obtained as a gift sample from Stride's lab, Bangalore India. Carbopol 934P was obtained from S.D. Fine Chemicals, Mumbai. Hydroxy propyl methyl cellulose (HPM E15), Eudragit RLPO and PVP K30 was obtained from Loba chemicals, Mumbai. Ethyl cellulose obtained from Laksmi chemicals, polyethylene glycol obtained from India glycol Pvt Ltd., Mumbai, India. All other ingredients used in formulations were of analytical grade.

Drug-excipient compatibility studies:

FT-IR spectroscopy was conducted to ascertain the compatibility between the pure drug and selected polymers. The drug and excipients were mixed physically and stored at 40±20C/75±5% RH for a month [14]. After this period of time, IR spectra were recorded to assess the compatibility of the pure drug and its physical mixture. The individual HHCl and HHCl with excipients were scanned separately. Potassium bromide was mixed with drug and polymer in the ratio of 100:1 and pellet was prepared using KBr pellet press and the spectrum was taken using FT-IR. FT-IR spectrum of Hydralazine hydrochloride was compared with the spectrum of

its physical mixture of polymers. The individual HHCl peaks and shifting of a peak in any of the spectra were studied [15].

Preparation of bio-adhesive buccal patches of HHCl by a solvent casting technique:

Weighed quantity of HPMC E15 or Eudragit RL 100 and PVP K 30 was taken in a boiling tube. To this, 25 ml of a solvent mixture of dichloromethane: methanol (1:1) was added and vortexed. Sufficient care was taken to prevent the formation of lumps. The boiling tube was set aside for 4-6 hours to allow the polymer to swell. Then weighed quantity of Hydralazine Hydrochloride (HHCl) was dissolved in 5 ml of the solvent mixture, added to the polymer solution, and mixed well. After swelling, a measured quantity of propylene glycol was added to this mixture and vortexes. It was set aside for some time to exclude any entrapped air and was then transferred into a previously cleaned anumbra Petri plate. Drying of these patches for 8 hrs and it was carried out in oven placed over a flat surface.

The patches formed were removed carefully, placed in a vacuum oven and a vacuum was applied to remove traces of solvent if any. They were stored in desiccators till the evaluation tests were performed. The composition of the patches is given below. Formulated patches were then subjected to the weight variation test, thickness variation test, and content uniformity test (table 1). The secondary polymeric solution was prepared by dissolving ethyl cellulose and propylene glycol in 15 ml of the solvent mixture and poured on the primary layer and allowed for drying at room temperature. The developed patches were removed carefully, cut to size, and stored in desiccators.

Table 1: Formulation Ingredients of HHCl Buccal Patches

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8
Primary layer								
Hydralazine HCl (mg)	200	200	200	200	200	200	200	200
HPMC E15 (mg)	1500	2000	2750	3000	--	--	--	--
Eudragit RLPO	--	--	--	--	1500	2000	2750	3000
PVP K 30 (mg)	150	150	150	150	150	150	150	150
Propylene glycol (ml)	5	5	5	5	5	5	5	5
Secondary layer								
Ethyl Cellulose (mg)	350	350	350	350	350	350	350	350
Propylene glycol (ml)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Evaluation of bio-adhesive buccal patches of HHCl:

Weight uniformity test:

Each formulation was measured in triplicate and patch sizes of 1x1 cm2 were cut. Their weight was measured using Shimadzu digital balance and the weight variation was calculated. The mean ± SD values were calculated for all the formulations [16].

Thickness test:

Three patches of each formulation were set aside for measuring patch thickness using a micrometer screw gauge at three different places. The mean value was then recorded [17].

Surface pH of the patch:

The bioadhesive patch was allowed to swell by keeping it in contact with 1 mL of distilled water for 2 hr on the surface of the agar plate, prepared by dissolving 2% (w/v) agar at room temperature. The pH was measured by bringing the pH-meter electrode, in contact with the surface of the patch and allowing it to equilibrate for 1 min [18].

Content Uniformity:

To determine the drug content uniformity, three patches from each formulation were separately dissolved in 100 mL of pH 6.8 phosphate buffer for 12 hrs under occasional shaking. The solutions were filtered, diluted suitably, and estimated spectrophotometrically at 260 nm. Each formulation was cast in triplicate and the average of drug contents of three patches was taken as final reading [19].

Swelling study:

The polymer used for the formulation of buccal patches is hydrophilic. The swelling or moisture absorption studies indicate the relative swelling capacities of polymers and an idea of whether the formulation maintains its integrity after absorption of moisture. This test was performed according to the modified procedure reported by Varsha Agarwal and Mishra [20].

2-5% w/v agar in distilled water, in hot condition, was transferred into Petri plates and it was allowed to solidify. Three patches of each formulation were selected and weighed. They were placed in a desiccator overnight before the study to remove moisture if any and laminated on one side with a water-impermeable backing membrane. They were placed on the surface of the agar, allowed to swell, and again placed in desiccators. The swollen patches

were removed, weighed again for everyone hour up to 6hrs and an average value was noted. The percentage of swelling (% S) can be calculated using the following equation:

$$\% \text{ Swelling} = \frac{Wt - Wo}{Wo} \times 100$$

Where, Wt is the weight of swollen patch after time t, Wo is the initial weight of the patch.

Folding endurance:

Folding endurance of all the patches was determined by involving repeatedly folding each patch at only one place till it breaks down or folded up to 300times manually, which was now considered as a good satisfactory and to reveal that the best patch properties. The patch can be folded the number of times and an average of at one place without breakdown is considered as the value of the folding endurance. This type of test was done on three patches from each formulation and an average value was noted [21].

Ex-vivo mucoadhesive strength

The force required to detach the attachment of the mucoadhesive patch from the mucosal surface was applied as a measure of the mucoadhesive strength. This study was carried out on a specially fabricated physical balance assembly. Porcine buccal mucosa was glued on a dry Petri dish surface by placing the mucosal surface outward and it was moistened with few drops of simulated saliva (pH 6.2). The right-side pan of the balance was replaced by a glass disc glued with a buccal patch of 3 cm diameter. The balance was adjusted for equal oscillation by keeping sufficient weight on the left pan. A weight of 5 g (W_1) was removed from the left pan, which lowered the pan and the buccal patch was brought in contact with pre-moistened mucosa for 5 min. Then weights were increased gently on the left pan until the attachment breaks (W_2). The difference in weight (W_2-W_1) was taken as mucoadhesive strength [22]. The mucoadhesive force was calculated from the following equation:

Mucoadhesive force (kg/m/s) = (Mucoadhesive strength(g)/1000) * acceleration due to gravity

***In- vitro* HHCl release studies:**

In-vitro, drug release studies were carried out employing dissolution test apparatus type II (USP) paddle method using 500 ml of phosphate buffer (pH 6.8) as the dissolution medium at 50 rpm at 37 ±0.5°C for 6 h. To provide unidirectional release, one side of each patch was attached to a glass disk with the help of cyanoacrylate instant adhesive [23]. An aliquot of 5 ml was withdrawn at suitable time intervals and replaced with fresh phosphate buffer (pH 6.8) maintained at the same temperature. Samples were then analyzed at 260 nm by using a digital UV-Visible spectrometer.

Kinetics modeling of drug release profiles:

The *in-vitro* release data profiles were fit into different kinetic model equations to explain the release kinetics of HHCl from the buccal patches. The *in-vitro* release data of buccal patches were fitted into different kinetic models such as zero-order (Q = kt), first-order (In (1-Q) = -kt), Higuchi (Q=kt1/2), and Korsmeyer – Peppas (Log Q = log k + n log t) models to interpret the HHCl release mechanism from the buccal patches [24, 25, 26].

***Ex-vivo* Permeation Studies:**

The buccal patches of HHCl permeation study were carried by using a Franz-type diffusion cell. Between the two compartments of Franz type diffusion cell, the prepared patches were fixed on the porcine buccal membrane. The porcine buccal mucosa was obtained from a local slaughterhouse. pH 6.8 phosphate buffer was filled in the receiver compartment and the total setup was fixed on a magnetic stirrer along with 37^0C temperature maintenance. Periodically 0.5hr, 1hr, 2hr, 3hr, 4hr, and 6hr intervals samples of 2 ml are withdrawn and immediately replaced by the same phosphate buffer. The HHCl release was analyzed all the samples at 260 nm by using a digital UV-Visible spectrometer and report the results in the results section [27, 28].

Stability study:

Accelerated stability studies were carried out where the optimized formulation product is stored under extreme conditions of temperature at 40±20C/75±5% RH for a duration of three months. After an interval of thirty days, each sample was withdrawn and tested for individual drug content [29].

***In-vivo* Bioavailability Studies**

In-vivo studies in suitable animal models and/or human subjects of designed delivery systems along with *in-vitro* evaluation are a must to predict the therapeutic efficacy of designed formulations. buccal formulations are designed to enhance the bioavailability of drugs linked with poor oral bioavailability due to extensive first-pass effect and/or degradation within the GI tract. The *in-vivo* pharmacokinetic evaluations of buccal drug delivery systems have been reported in a variety of animal models like rabbits, humans, rats, pigs, and dogs [30, 31, 32].

This *in-vivo* study focuses on designing buccal mucoadhesive patches of Hydralazine hydrochloride to improve the oral bioavailability of New Zealand white rabbits weighing 2.0 to 2.5 ± 0.25 kg. Prior approval from Institution Animal Ethics Committee was obtained for carrying out the study (Protocol

approval number: VPC/IAEC/2017/2). Animals were kept on a standard pellet diet and water ab libitum during a period of acclimatization. Animals were kept on fasting 3-4 hrs before the actual start of the experimentation. The rabbits were not provided food and water till 6 hrs after the start of the experiment. A randomized crossover single-dose bioavailability study was performed on two phases with a washout period of 7 days in between, where each rabbit received both treatments of selected buccal formulations and conventional oral solution [33, 34].

For treatment tests, rabbits were anesthetized and positioned in a standard rabbit cage. Using rounded tip stainless tweezers, rabbit's cheeks were carefully holding, and the buccal patch was placed beneath the cheeks and lips. Anesthesia was maintained after drug administration to keep the patch in a buccal position and prevent escaping down through the gastrointestinal tract. For treatment control, equivalent to the calculated animal dose of the oral solution was prepared and given orally to the animal with the aid of gastric gavage after suspension in the minimum volume of water. The entire study was carried out in triplicate [35].

2 ml blood samples were withdrawn from the marginal ear vein of the animals at predetermined time intervals of post dosing using a 24 G needle. Blood sample was also collected before dosing from all the rabbits. The blood was collected in 5 ml centrifuge tubes containing 100 µl of EDTA solution (1.0 mg/ml) and centrifuged at 3500 rpm for 30 min. The plasma supernatant obtained was collected and stored at -20 °C till further processing for analysis.

Sample Processing:

Frozen plasma samples were thawed by keeping the sealed tubes at room temperature (25 ± 2 oC) for at least 60 min. The protein present in the plasma samples was precipitated with acetonitrile. For this, 300 µl of plasma samples were taken and 1 ml of acetonitrile was added to it and vortex mixed. The mixture was then centrifuged for 20 min at 3500-4000 rpm at 4^0C. The supernatant was carefully taken and evaporated to dryness using a vacuum concentrator. The dried residue was further reconstituted with a solvent system containing 1:1 (% v/v) of acetonitrile and acetate buffer (pH 4.5). Finally, the samples were analyzed using the analytical method described earlier. The plasma drug concentration at various time points of the study was thus measured.

Data analysis:

The plasma drug concentration versus time data of HHCl obtained during various sets of studies was subjected to non-compartmental analysis using WinNonlin Standard edition, Version 2.1 (WinNonlin Scientific Consultants, USA) to acquire various pharmacokinetic parameters.

RESULTS AND DISCUSSION

The FTIR spectrum of pure drug exhibits characteristic peaks at 3382.64, 3059.75, 1164.78 and 1554.80, cm^{-1} due to N-H stretch, aromatic C-H, C-N and C=C stretching, respectively. IR spectrum of drug and HPMC E15 formulation showed characteristics peaks shown at 3356.25, 3013.54, 1072.91 and 1528.25 cm^{-1}. The above the peaks confirm that there was no shift in peak position of HHCl in spectra of drug and excipients in figure 1, which proved that drug and excipients were compatible.

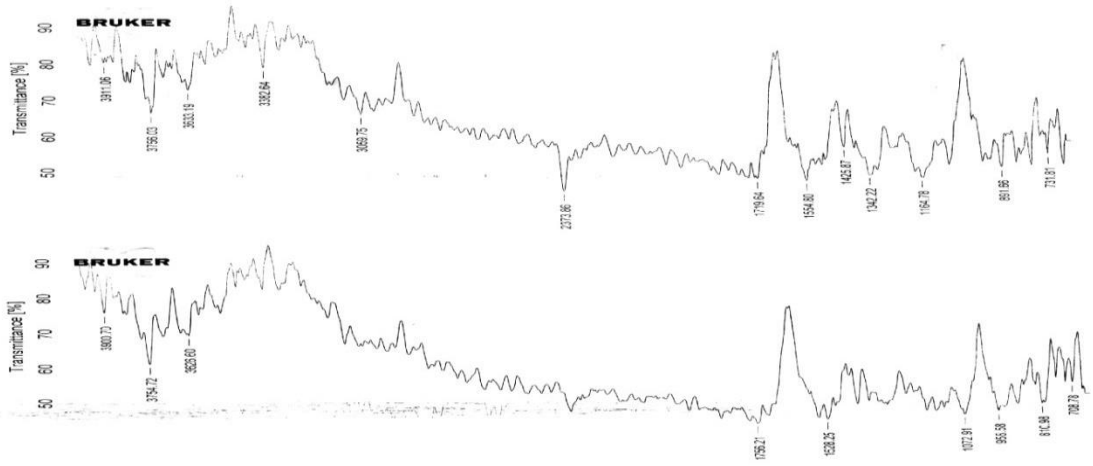

Figure 1: IR spectrum of pure drug and optimized formulation

In the present research, different ratios of polymers were checked in various trials and finally, a total of 8 formulations were prepared and the physiochemical properties of prepared buccal patches are shown in Table 2.

Weight uniformity test:

The weight of the patch varied with polymer concentration. An increase in polymer concentration increased the weight of the patch, but the increase was marginal. Weight variation was found in the range of 137.33±1.12 to 156.13±1.36.

Thickness test:

It was observed that there was no significant difference in the thickness of the patch, which indicated that the patches were uniform. The thickness of the buccal patches is ranged between 0.38±1.66 to 0.42±1.66 mm.

Surface pH of the patch:

The surface pH was found to be in the range of 6.3-6.9, which is close to the neutral pH, which indicated that the patches may have less potential to irritate. Surface pH for all formulations was well within the range of salivary pH and would not irritate the mouth.

Folding endurance:

All the patches prepared were found to be flexible, smooth, non-sticky homogenous, and transparent with no visible particulate matter. The folding endurance measures the ability of the patch to withstand rupture. It was found to be in the range of 275.33±1.08 to 309.67±1.08. The result indicated that the patches would not break and would maintain their integrity with not show any cracks. The folding endurance of Eudragit patches is higher than patches containing hydroxy propyl methyl cellulose.

Table 2: physiochemical properties of HHCl buccal patches:

Formulation	Appearance	Thickness	Weight Variation	Folding endurance	Surface pH
F1	Clear	0.38±1.66	137.33±1.12	275.33±1.08	6.7±0.16
F2	Clear	0.39±1.63	141.67±1.45	291.66±.1.39	6.6±0.13
F3	Clear	0.40±1.75	146.89±1.63	307.15±1.51	6.8±0.11
F4	Clear	0.41±1.89	151.33±2.13	301.67±1.35	6.9±0.14
F5	Clear	0.39±1.33	142.30±1.85	288.58±1.04	6.7±0.13
F6	Clear	0.41±1.56	146.55±1.89	304.36±1.51	6.4±0.17
F7	Clear	0.42±1.41	156.13±1.36	292.33±1.11	6.8±0.18
F8	Clear	0.42±1.66	155.63±2.51	309.67±1.08	6.3±0.21

Content Uniformity:

No significant difference in the drug content among the patches indicated good content uniformity. Estimation of drug content was found to be in the range of 98.84±1.85 to 102.19±1.47 indicating that the drug is uniformly distributed throughout the patches and evidenced by the low values of SD (Table 3).

Table 3: physiochemical properties of HHCl buccal patches:

Formulation	Drug content	%Moisture Absorbed	Muco-adhesive Strength*
F1	100.15±1.68	46.25±1.81	25.46±1.25
F2	99.33±2.74	50.54±1.33	22.89±1.33
F3	99.13±1.63	55.33±2.37	23.35±1.41
F4	98.84±1.85	58.55±1.19	26.66±1.16
F5	99.33±1.25	48.66±1.25	22.63±1.53
F6	102.19±1.47	51.85±2.17	26.54±1.63
F7	100.41±1.83	56.52±2.16	28.66±1.15
F8	99.58±1.39	61.16±1.63	29.33±1.32

Moisture Absorption Studies:

Hydrophilic polymers show considerable swelling, as it increased the surface wet ability, and consequently, water penetration within the matrix varied between 46.25±1.81 to 61.16±1.63%. The difference in swelling of the hydrophilic polymers may be due to the difference in resistance of matrix network structure to the movement of the water molecule. It was observed that patches with HPMC E 15 showed more swelling compared to those with Eudragit, and this may be due to higher water uptake of HPMC E 15 than the Eudragit. The swelling behavior provides an indication of the relative moisture intake capacities of polymers and whether the formulations continue their integrity after absorption of moisture. Optimized formulation considering the fact that the formulation F3 assuming that the swelling of the patches was high.

Ex-vivo mucoadhesive strength:

The ex-vivo mucoadhesive force of formulations was obtained in the range of 22.63±1.53 to 29.33±1.32 Kg/m/s. The highest mucoadhesive force was observed with formulation F8 (Table 18). Increases in swelling behavior, molecular weight, and contact

time with mucin network are directly proportional to the mucoadhesive property of polymers. Mucoadhesive strength in formulations that contain HPMC and eudragit may be related to hydrogen bond formation with mucin. High water uptake of eudragit used patches shows increased mucoadhesion due to increased interpenetration of polymer and mucin chain at the interface.

***In-vitro* release studies of HHCl buccal patches**

From the in-vitro release studies, it was concluded that the patches prepared with HPMC showed maximum release while compared with those patches prepared with eudragit as rate-controlling polymer. The in-vitro release profile of HHCl buccal patches is shown in Figures 2-3. The release of HHCl from HPMC patches was higher when compared to that of eudragit patches. In the first batch, the cumulative release percentage from the formulations F1, F2, F3 and F4, respectively, was 93.33 ±2.12%, 88.78 ±2.13%, 99.62 ±2.89% and 78.95±2.33% in 6 hours, whereas, concerning the second batch, formulations F5, F6, F7 and F8 with eudragit RLPO released 90.34± 2.23%, 95.14±2.78%, 76.12±2.63 and 73.31±1.98% of the drug, respectively, in a time interval of 6 hours.

This was attributed to the high aqueous solubility of polymers HPMC E15 than the eudragit RLPO. Out of the two sustaining polymers, HPMC E15 showed higher drug release due to higher swelling, when compared to eudragit RLPO. The release profile from optimized formulation F3 was much higher than the value for formulation F7 (99.62 ±2.89% and 76.12±2.63%). HPMC E15 is a hydrophilic polymer, which swelled during dissolution, forming a gel layer. The loosely bound polymer molecules were easily eroded, allowing the release of HHCl at a faster rate, when compared to other eudragit derivatives. From the release studies, it was found that the drug followed zero-order release kinetics with a diffusion mechanism (table 4). A relative contribution of erosion and diffusion to the overall release mechanism is observed.

Table 4: *In-vitro* release kinetics of the formulations

Formulation	Zero-order	First-order	Higuchi	Korsmeyer-Peppas
F3	0.958	0.823	0.991	0.995

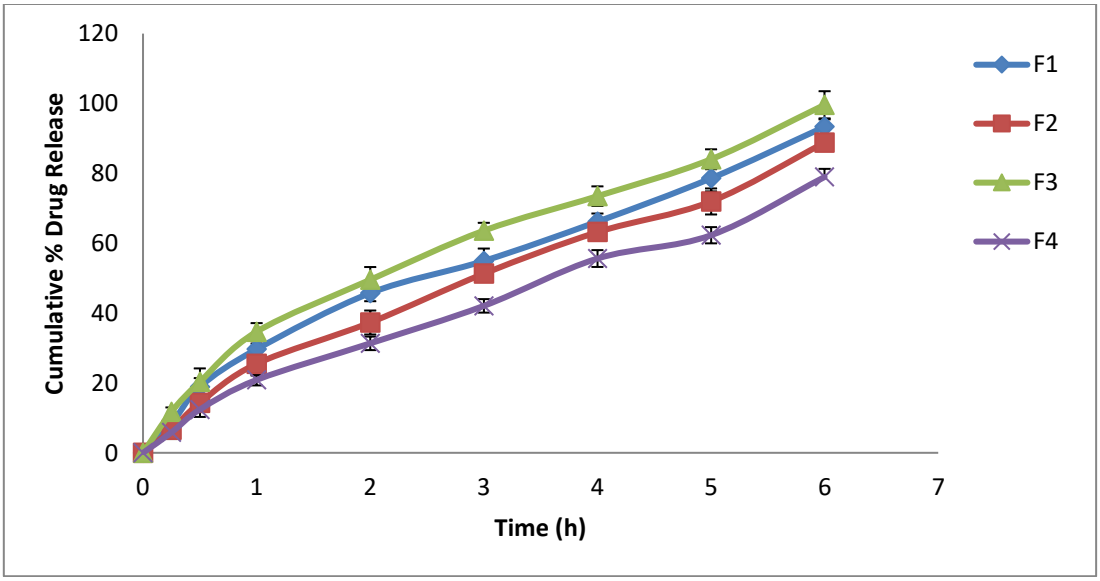

Figure 2: *In-vitro* release profile of HHCl buccal patches

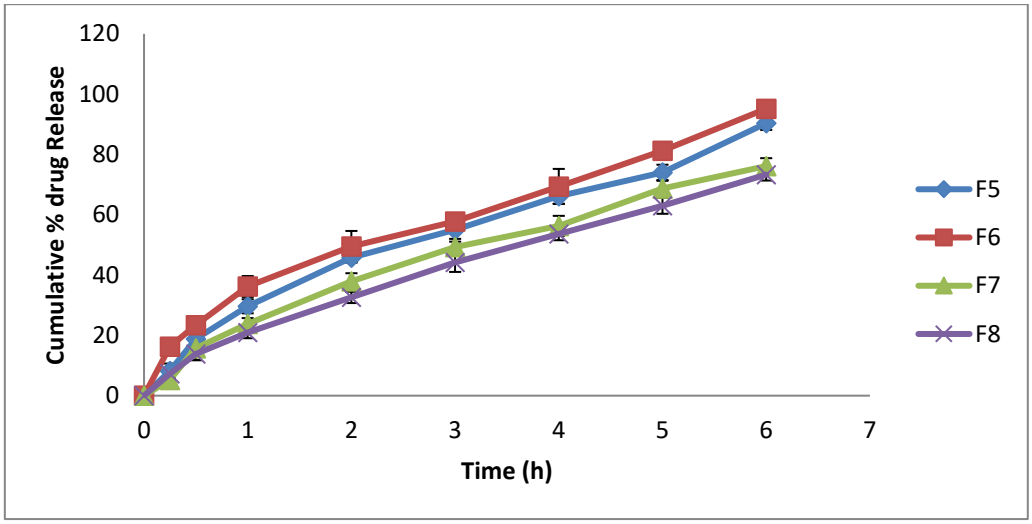

Figure 3: *In-vitro* release profile of HHCl buccal patches

***Ex-vivo* Permeation Studies:**

Based on the drug release profile, *an ex-vivo* study was conducted using F3 formulation with PEG 6000 as permeation enhancer and control (without enhancer). The test drug release has shown 86.52±1.94 as against 63.55±2.33 (figure 4).

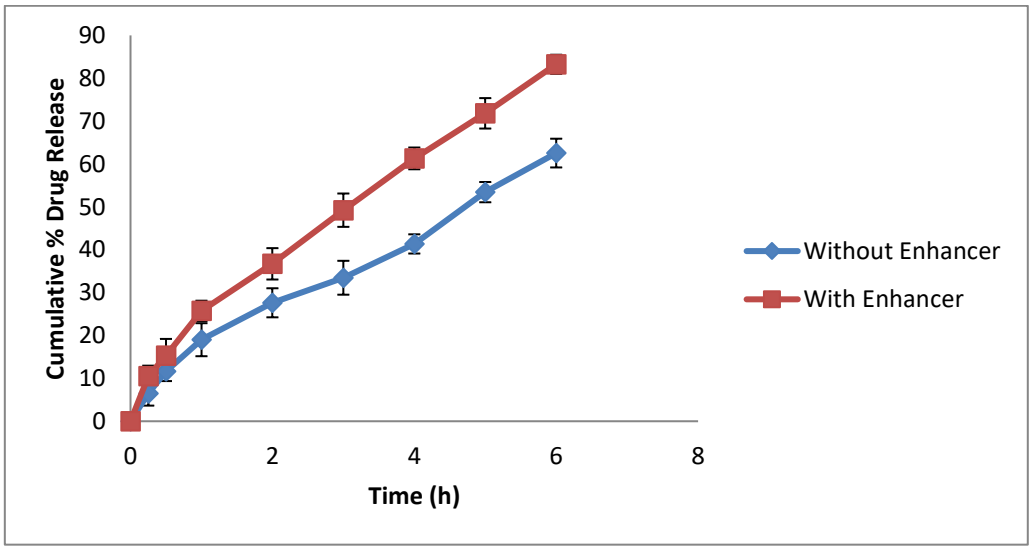

Figure 4: *Ex-vivo* release profile HHCl buccal patches.

Stability studies:

The accelerated stability at 40±20C/75±5% RH studies for the optimized formulation of F3 was conducted and it has given agreeable outcomes in physical appearance and drug content (Table 5).

Table 5: Stability studies of optimized formulations

Properties	30 days	60 days	90 days
Physical Appearance	No alteration	No alteration	No alteration
Assay	99.42±0.36	99.28±0.33	99.33±0.52

Every value was indicated as Mean ± SD

***In-vivo* Bioavailability studies of Hydralazine Hydrochloride (HHCl) buccal patch**

Based on the drug release profile, *the in-vivo* study was conducted on F3 formulation. The pharmacokinetic profile of prepared buccal patches was showed a maximum plasma concentration (Cmax) of 1075.031±255.15 ng/ml, 3.83 hrs post-dosing. AUC(0-∞) and elimination rate constants

were found to be 42874.508±3903.14 ng h/ml and 0.165±0.040 h-1 respectively. Whereas the administration of an oral solution of HHCl showed a maximum plasma concentration (Cmax) of 614.732±79.274 ng/ml, 3.66 hrs post-dosing. AUC (0-∞) was found to be 19408.299±1802.48 ng h/ml. The elimination rate constant was found to be 0.195±0.093 h-1.

These results clearly show that the extent of drug absorption from the buccal route was significantly higher than the conventional oral route as expressed by an increase of both *C*max and AUC. Bioavailability of HHCl from buccal (F(R) Relative bioavailability) was found to be 2.209 times higher concerning that of oral solution (table 6 and figure 5). This enhancement may probably be due to rate controlling absorption, avoid first-pass metabolism, and subsequent permeation of released drug from the buccal patches.

Table 6: The mean pharmacokinetic parameters of HHCl buccal patch

Pharmacokinetic parameter	Oral HHCl	Buccal HHCl
C_{max} (ng/mL)	614.732±79.274	1075.031±255.15
Tmax (hr)	3.666±0.288	3.83±0.288
K_{el} (1/hr)	0.195±0.093	0.165±0.040
$T_{1/2}$ (hr)	4.316±2.472	4.371±01.123
AUC_{0-t} (ng*hr/mL)	2706.040±1003.18	6084.502±4106.15
$AUC_{0-\infty}$ (ng*hr/mL)	19408.299±1802.48	42874.508±3903.14
$F_{(R)}$ (Relative Bioavailability)	--	2.209

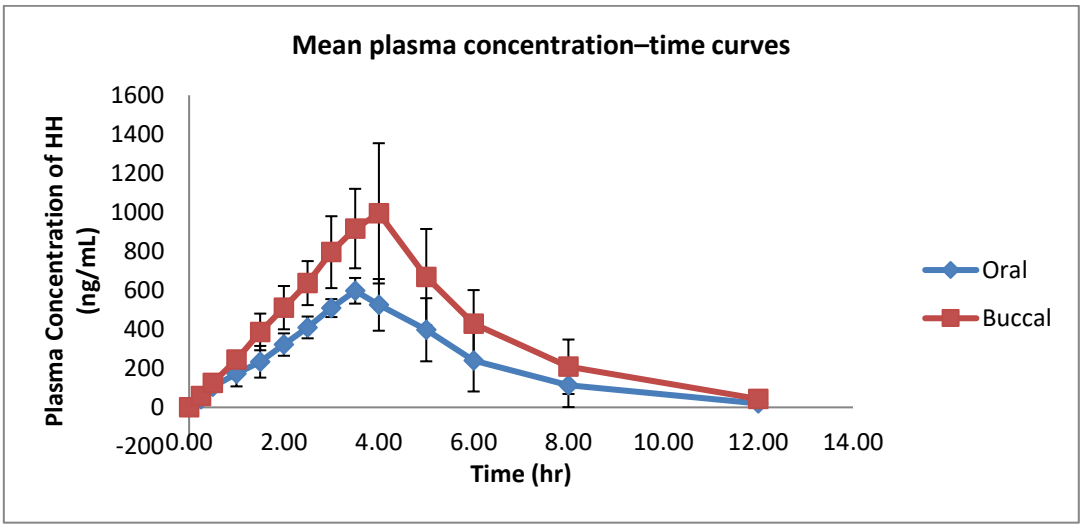

Figure 5: In-vivo profiles of HHCl following administration to rabbits by oral solution and buccal patch (Each value represents mean of 3 independent determinations with standard deviations)**.**

SUMMARY CONCLUSION AND RECOMMENDATIONS

The buccal cavity and its highly permeable mucosal tissues have been taken advantage of for decades as a site of absorption for the delivery of drugs to the systemic circulation. This research study demonstrated that developed buccal patches were efficacious could be delivered through the buccal route as it indicates a potential alternative drug delivery system for systemic delivery of Hydralazine Hydrochloride (HHCl). This covered almost all-important parameters to be considered to understand the drug release mechanism from the formulation. The drug bioavailability from the optimized formula was assessed in comparison to a conventional oral dosage form in rabbits was studied.

The pharmacokinetic profile of designed HHCl buccal patches was also showed a maximum plasma concentration (Cmax) and AUC (0-∞) were found to be 1075.031±255.15 ng/ml and 42874.508±3903.14 ngh/ml. Whereas the administration of an oral solution of HHCl showed a maximum plasma concentration (Cmax) of 614.732±79.274 ng/ml and AUC(0-∞) were found to be 19408.299±1802.48 ng h/ml.

These results confirm the suitability of the prepared buccal dosage forms to improve the bioavailability by avoiding the hepatic first-pass metabolism. It

indicates a potential alternative to the parenteral drug delivery system for systemic delivery of HHCl by an increase of a maximum plasma concentration (Cmax) and area under the curve (AUC(0-∞)). The bioavailability of the optimized HHCl buccal patch was showed higher relative bioavailability (2.209) than the HHCl oral solution. Other delivery systems such as microparticles and nanoparticles can also be explored for the improvement of bioavailability.

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