

**FORMULATION AND EVALUATION OF BUCCOADHESIVE FILMS  
OF HYDRALAZINE HYDROCHLORIDE****Gamal M. Mahrous\***

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**ABSTRACT**

The present study was an effort to develop a mucoadhesive buccal delivery system for hydralazine hydrochloride, a hypotensive agent that was formulated onto buccoadhesive films to overcome the limitations in the currently available dosage and routes of administration which in sequence will increase its bioavailability and patients' compliance. Films were cast from aqueous solvents using various bioadhesive polymers namely: sodium carboxymethyl cellulose (CMC), hydroxypropylmethyl cellulose (HPMC) and Carbopol 934. The prepared films were subjected to investigations for their physical and mechanical properties, swelling behaviors, in vitro bioadhesion, in vitro drug release and drug permeation via bovine

buccal mucosa. These properties were found to vary depending on the type of the polymers. Formula number F4 containing carbopol 0.5% and HPMC 0.5% was found to be the best film as it shows good adhesion, acceptable pH, and gives a reasonable drug release (about 86 % at 6 h). The amount permeated through bovine buccal membrane reached about 17% after 6 hours.

**KEYWORDS:** Hydralazine – Buccoadhesive – Swelling – Film casting – Tensile strength – In vitro release- Permeation.

**INTRODUCTION**

Mucoadhesive drug delivery systems offer a promising approach for controlled and site-specific delivery to the GI tract by attaching the devices to the mucus and mucosa of the tract via the process of mucoadhesion. These mucoadhesive systems are also known to provide intimate contact between the dosage form and the absorptive mucosa, resulting in high drug

flux through the absorbing tissue with improved bioavailability.<sup>[1]</sup> Drug delivery via buccal mucosa using bioadhesive dosage form offers such as novel route of drug administration. The route has successfully been tried for the systemic delivery with a number of drug candidates<sup>2</sup>. The buccal mucosa provides excellent opportunities for the delivery of both locally and systemically active drugs. It has potential advantages over other mucosal routes available; it avoids the degradation by the gastrointestinal enzymes and acids, and first-pass metabolism. Because of its excellent accessibility, self-placement of a dosage.<sup>[2]</sup>

The present study was an effort to develop a mucoadhesive buccal delivery system for hydralazine hydrochloride, a hypotensive agent. The drug is well absorbed through the gastrointestinal tract but is subjected to extensive first pass metabolism.<sup>[3]</sup> So, the dose required to produce effective therapeutic serum concentration is relatively high. Oral bio-availability of the drug has been reported to range between 10 and 35 %, depending upon the extent of acetylation. It also has a short biological half-life (2–4 h), high physicochemical stability. The small dose requirement and absence of objectionable taste and odour make it a suitable candidate for buccal administration.<sup>[3]</sup> Previous work was done to formulate hydralazine in to ODT tablets<sup>[4]</sup>, floating tablets<sup>[5]</sup>, and bioadhesivetables.<sup>[6]</sup>

No attempts have been made yet to formulate hydralazine into buccoadhesivefilms which is the aim of this study. In this study, the objective has been to formulate hydralazine hydrochloride in the form of buccoadhesive films using various bioadhesive polymers namely: sodiumcarboxy methyl cellulose,hydroxypropyl methyl cellulose, and carbopol 934, Physico-mechanical properties, swelling behavior, in vitro bioadhesion, in vitro release of the prepared films and have been subjected to investigations. The most promising formula was subjected to permeation study across bovine mucosa.

## Experimental

### 1. MATERIALS

Hydralazine Hydrochloride (HZ) was purchased from MEDEX Co., Naseby, Northants NN6 6DF. Carboxymethyl cellulose Sodium (CMC), high viscosity grade, was purchased from BDH Co., Poole, England. Hydrxypropyl methyl cellulose (HPMC K4M) was purchased from Dow chemical company, Midland, Michigan48674, USA.

Carbopol934P, was supplied from Sorgan Co. Wiedelberg, Germany.Polyvinylpyrrolidene K90 (PVP) was obtained from Serva GmbH & Co., Heidelberg, Germany.

All other chemicals used in this study were of analytical grade and were used without further purification.

## 2. METHODS

### 2.1- Compatibility studies of HZ with the used additives

#### Infrared (IR) Absorption Spectroscopy

To investigate any possible interactions between the drugs and the utilized buccoadhesive materials, the IR spectra of pure HZ and its physical mixtures (1:1) with CP, HPMC, PVP, and CMC were carried out using Shimadzu IR-470 spectrophotometer (Tokyo, Japan). The samples were prepared as KBr disks compressed under a pressure of 6Ton/cm. the wavenumber selected ranged between 250 and 4,500  $\text{cm}^{-1}$ .

### 2-2 – Preparation of HZfilms

#### Preparation of polymeric films containing HZ, cast from hydroalcoholic solvent

Polymeric films composed of HPMC, CMC and carbopal 934(as bioadhesive polymers) and PVP K90 as the film forming polymer in addition to PG as a plasticizer, were prepared. Ten % PVPK90 solution (dissolved in ethanol) was mixed with mucoadhesive polymeric hydrogel that was prepared by dispersing the polymer in deionized water using variable speed mixer, under constant stirring (600 rpm) fitted with four bladed paddle at room temperature. In case of carbopol, the produced gel was neutralized to PH 6.0-6.2 using triethanolamine. The samples were stored for at least 24 hrs in dark at 4-8°C before casting to ensure total hydration of the polymers and to exclude entrapped air. Propylene glycol(PG) was used as plasticizer at concentration of 40% w/w of polymer content, thus protecting the polymeric films from being brittle upon storage. Before pouring on Teflon coated molds (79.7 $\text{cm}^2$ , area), the resulted polymeric gels were brought back to room temp (25°C).The aqueous (hydroalcoholic) polymeric hydro gels were dried at 38±0.5°C in an oven for 48 h and then stored in a desiccator at room temperature after Warping in sealed plastic sheets.

Same procedure was adopted for the medicated films after dissolving HZ and other additives (Saccharin Sodium 0.1%) in the hydroalcoholic solution of PVP. A list of formulations is presented in table (1).

### 2.3- Spectrophotometric Scanning of Hydralazine in presence of the used polymers

A specified concentration of hydralazine in phosphate buffer pH 6.8 was scanned spectrophotometrically at 200-400 nm to determine the wave length of maximum absorption

( $\lambda_{\text{max}}$ ). UV spectrophotometric Scanning of hydralazine solution in presence of polymer solutions in phosphate buffer pH 6.8 was also investigated at the same wave length intervals.

#### **2.4- Construction of hydralazine calibration curve**

Hydralazine was determined spectrophotometrically at  $\lambda$  272 nm. Calibration curve was constructed in the range of 5-40  $\mu\text{g/ml}$  by serial dilutions of stock solution of hydralazine hydrochloride (1  $\text{mg/ml}$ ). Phosphate buffer solution of pH 6.8 was used in preparation of the stock and serial dilutions.

#### **2.5 - Determination of actual hydralazine content in the prepared Films**

Specified weight of the prepared films of was dissolved in 100 ml phosphate buffer (pH6.8). Then an aliquot was withdrawn and filtered through Millipore filter (0.45 $\mu\text{m}$ ). The filtrate was diluted and the concentration of the drug was determined spectrophotometrically at  $\lambda$  272 nm.

#### **2.6-Determination of the physico-mechanical properties of the prepared films**

Dried film sample of (450 $\pm$ 50 $\mu\text{m}$ ) thickness was cut to uniform size 2.5x6 cm using a sharp razor blade. Two pieces of cardboard (1x2.5 cm) were attached to the upper and lower end of the film using cyanoacrylate resin adhesive. Attachment of the film to the cardboard facilitated clamping of the film jaws of the load deformation machine, thus preventing pressure on the film prior to, and slipping during application. The film on the cardboard (exposed area to stress equals (4.0x2.5 cm) was clamped between the two jaws of the machine. The upper jaw was movable and the lower was fixed. The load automatically applied to the film was gradually increased and the corresponding magnitude of elongation was recorded until the break point of the film reached.

Both film breaking load and percentage of elongation were determined. The tensile strength (TS) of the film was calculated from the breaking load and cross sectional area of the film using The following Eq:

The percent of elongation was calculated according to the following equation.

$$\% \text{ of elongation (E/B)} = \frac{L_s - L_o}{L_o} \times 100$$

Where:  $L_o$ =original film length

$L_s$ =film length after elongation

The modulus of elasticity (EM) of the film was calculated according to Equation :  $EM = TS / (L_s / L_o)$

Each experiment was performed in duplicate and the mean value was taken.

### 2.7- Swelling behavior of the prepared Hydralazine polymeric films

The study examined the hydration of the different polymeric films used when placed in contact with artificial saliva. Using a pastry cutter, samples ( $25 \text{ mm}^2$ ) of each polymeric film were cut and then weighed by one scale before and after wetting with artificial saliva. The polymeric film sample was placed in a Petri dish, artificial saliva (0.1 ml) was added onto the surface of the polymeric film using a micropipette, and then incubated in one dissector at room temperature. The wetted film was removed at each observation point at time intervals of (5, 10, 15, 30 and 60 min), where the surface was gently dried using blotting paper and reweighed again. For each observation point, the test was repeated five times. The hydration percentages of the wet polymeric films were calculated according to the following equation.

$$\text{Hydration (\%)} = (WH - WD) / WD \times 100.$$

Where WH and WD represent the weight of the hydrated and dried polymeric films respectively.

### 2.8 -Determination of surface pH of the prepared films

The surface pH of the prepared films was determined after soaking each formula in ( $1 \text{ cm}^2$  of film) in distilled water (1ml) for 15 minutes. After the time of soaking the pH of the wet surface was measured by placing the electrode in contact with the surface of the film.

### 2.9- In-Vitro bioadhesion test of the prepared Films:

In vitro bioadhesion of the formulations was examined adopting previously published method<sup>[7]</sup> using chicken pouch as a model mucosal membrane. The tissue was obtained from chicken after slaughter, removed from its contents and surface fats, and stored frozen in simulated saliva solution (2.38 g  $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$ , 0.19 g  $\text{KH}_2\text{PO}_4$  and 8.0 g  $\text{NaCl/L}$ , pH= 6.75). This membrane was thawed to room temperature before use.

Rectangular piece (Surface area  $4.0 \text{ cm}^2$ ) of the tissue was cut and glued with cyanoacrylate adhesive on the ground surface of the two tissue holders made of Plexiglas. Four  $\text{cm}^2$  of the buccal film was placed between the two tissue surfaces put in contact with each other with

uniform and constant light pressure between fingers for one minute to facilitate adhesion bonding. The upper tissue holder was allowed to hang on an iron stand with the help of an aluminum wire fastened with a hook provided on the backside of the holder. A pre weighed light weight polyethylene bag was attached the hook on the back side of the lower tissue holder with aluminum wire. After a pre-load time of 1.0 minute water was added to the polyethylene bag through an intravenous infusion set at a rate 2.0 drops per second until the lower tissue detached by the heavy weight of water infused. The water collected in the bag was measured and expressed, as weight (gram force) required for the detachment.

### **2.10 In – vitro Release Studies of the prepared Hydralazine Buccal Films.**

The in-vitro release of HZ from the prepared films was investigated using the USP Apparatus 2.

The previously prepared film was removed from the plate, weighed on an analytical balance, and the thickness was measured at both the four corners and the center with a micrometer. The film (2cm<sup>2</sup> contains 20mg HZ) was carefully pressed on and adhered to a plexiglas disk. The temperature of the dissolution medium (500 ml of phosphate buffer pH 6.8) was adjusted to 37±0.5°C. The plexiglas support containing the film was placed in the bottom of the vessel, and then the paddles of the dissolution tester were allowed to rotate at 50 rpm which was the optimum speed to prevent film rupture. It was taken into consideration that the used buffer volume affords sink conditions. Samples (5 ml each) were obtained at time interval while the film completely immersed throughout the release study. The removed sample (5 ml) from the release medium was replaced by an equal volume of buffer. The run was continued for at least 6 hours. All samples were analyzed spectrophotometrically at 272 nm. Blank samples were obtained from the release experiments of patches containing the same components except the drug.

### **Analysis of the release data**

The release data were kinetically analyzed using different Kinetic models (Zero order, first order and Higuchi diffusion model) to determine the mechanism of HZ release from the different Buccal film formulations.

### **2.11 In vitro permeation study**

The permeation of HZ from the prepared buccal film through bovine buccal membrane was carried out using Franz diffusion cell.

### **2.11.1 Tissue Preparation**

Fresh bovine buccal mucosa from cow was obtained at slaughter. Oral mucosa (smooth part) with a fair amount of underlying connective tissue was surgically removed from the oral cavity and placed in cold phosphate isotonic buffer (pH 6.8). The connective tissue was then carefully removed using fine point forceps and surgical scissors. The connective tissue was removed as thoroughly as possible to minimize variation between the tissue specimens. The membrane thickness ranged from 0.3 - 0.4 mm. The membrane was stored in cold (4 °C) phosphate isotonic buffer (pH 6.8) and used within 4 Hours after its removal from the oral cavity of slighted cow.

### **2.11.2. Experimental details of the permeation of HZ from the prepared buccal Films.**

The bovine buccal membrane was mounted in Franz- type diffusion cell, with the epithelial side facing the donor chamber. Fifteen ml of phosphate buffer (pH 6.8) were used as the receiver medium and 1.0 cm<sup>2</sup> of the film was placed on the donor side and 0.5 ml of phosphate buffer was added on the top of the diffusion cell and covered with paraffin film. The diffusion surface area was 3.14 cm<sup>2</sup>. The receptor medium was kept at 37 °C± 0.5 using a circulating water bath and was stirred with a magnetic stirring bar. Aliquots (1 ml) of the receiver medium were withdrawn at specified time intervals (0.5, 1.0, 2.0, 3.0, 4.0, and 6 hours) and replaced immediately with 1 ml of fresh buffer kept at the same temperature. The samples were analyzed by the HPLC

### **2.12- HPLC analytical method for assay of hydralazine permeation samples.**

The method reported in literature<sup>[8]</sup> was used after some modifications as follows.

#### **The chromatographic system used consisted of.**

A waters isocratic liquid chromatography system (Waters, Boston, Mass., USA) consisting of Waters 717 plus autosampler, Waters 1525 binary HPLC pump, Waters 2487 dual absorbance detector. All analyses were conducted at ambient temperature. Separations were performed on symmetry C18, 5 µm, 4.6 X 150 mm waters column. The mobile phases were membrane filtered (Millipore, 0.45 µm pore size) and degassed using Nexul ultrasonic, Kodo technical Co., South Korea. The eluent was monitored at 272 nm. The mobile phase consisted of water: acetonitrile (60 %: 40 %). The pH of the mobile phase was adjusted at 4.5 by glacial acetic acid (0.1%).



**Assay procedure.****a- standard solutions.**

Stock solutions of hydralazine hydrochloride of 0.02 mg/ml were prepared in deionized distilled water. Ketorolac standard solutions were prepared by diluting the 0.02 mg/ml Stock solution with deionized distilled water to 0.5, 1.0, 1.5, 2.0, 2.5, and 5.0 ug/ml. a 30 ul samples were injected, and the obtained peak heights were plotted against hydralazine concentrations.

**c- Samples of permeability study**

A. 0.5 ml of the samples were transferred to microcentrifuge tubes and 0.5 ml of protein precipitant solution (2% Zinc Sulfate in water) were added to precipitate any soluble proteins. The tubes were vortex mixed for 1 minute and centrifuged at 13000 rpm for 10 minutes. 30 micro-liter of the supernatant were then injected into the chromatographic system for determination of their drug content.

**RESULTS AND DISCUSSION****1. Compatibility studies**

The IR spectra revealed that no possible interaction between the drug and the used polymers, as there is no shift in the IR peaks (Fig.1) of the drug. The characteristic peaks of the pure drug<sup>[9]</sup> as N-H stretch ( $3217.1\text{ cm}^{-1}$ ), aromatic C-H stretch ( $3028.1\text{ cm}^{-1}$ ), C=C stretch ( $1591.4\text{ cm}^{-1}$ ) and out of plane bending, adjacent H atoms on an aromatic ring ( $786.6\text{ cm}^{-1}$ ) were present with the peaks obtained in the formulation spectrum. So, it shows the presence of the drug in the formulations and confirms the compatibility of drug with the polymers used.

**2. Spectrophotometric Scanning of Hydralazine in presence of solutions of the polymers used to prepare Films:**

Results of Spectrophotometric Scanning of Ketorolac in phosphate buffer pH 6.8 showed that there is a maximum absorption wavelengths at 272 nm. In the presence of solutions of the polymers used to prepare films, no interference has been detected of the spectrophotometric analysis of the drug at 272 nm.

**3. Calibration curve of hydralazine in phosphate buffer pH 6.8 at 272 nm.**

A linear relationship between the absorbance and the concentration of HZ in phosphate buffer pH 6.8 at 272 nm in concentration range of 5-40ug / ml. The regression equation is  $y = 0.033x + 0.002$  and r value is 0.9998.



**4- Determination of actual Hydralazine content in the prepared Films.**

Actual hydralazine content in the prepared Films was in the range of 95-105% of the claimed content. This indicates the stability of HZ in the used procedure for preparation as well as the even distribution of the drug in the prepared films.

**5- Physico-mechanical properties of the prepared Films.**

An ideal buccal film should be flexible, elastic, soft, adequately strong to withstand breakage due to stress from mouth activities. Moreover it must also possess good bioadhesive strength so that it can be retained in the mouth for a desired duration. Swelling of film should not be too extensive to prevent discomfort. As such, the mechanical, bioadhesive, and swelling properties of buccal film are critical and essential to be evaluated.

**Mechanism of film formation**

For the preparation of polymeric films containing drugs, drugs were dissolved in the polymer solution prior to casting. The concentration of solute is very important in preparation of the polymer matrix. The solution was kept at room temperature for 24 hr. in order to enhance interpenetration of polymer particles. Upon drying, polymer solutions were converted into drug polymer films. Various research groups have studied the mechanism of film formation from polymer dispersions.<sup>[10]</sup> The film formation occurs in three stages.

- (i) Evaporation of casting solvent and subsequent concentration of polymer particles.
- (ii) Deformation and coalescence of polymer particles.
- (iii) Further fusion by interdiffusion of polymeric molecules of adjacent polymer particles

The physical state of the drug in the dried film is dependent on solubility of the drug in the polymer. A prerequisite for the successful preparation of the films was the compatibility of the dissolved drug and the used polymers. All polymers used were found to be compatible with the drug.

**A- Mechanical properties**

The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters tensile strength (TS), elastic modular (EM) and elongation at break (E/B). A soft and weak film is characterized by a low TS, EM and FIB, a hard and brittle film is defined by a moderate TS, high EM and low E/B; a Soft and tough film is characterized by moderate TS, low EM and high EIB, whereas a hard and tough film is characterized by a high

TS, EM and E/B. (Deshpande et al 1997)<sup>10</sup>. Hence it is suggested that a suitable buccoadhesive film should have a relatively moderate TS, E/B and strain but a low EM.

### **I-Non-medicated films**

Several trials were made to reach the required mechanical properties for buccal films (soft and tough), using PVP as a film forming polymer which is widely accepted in preparation of buccal films. Mucoadhesive polymers used were CMC, HPMCK4, and Carbopol. Non plasticized formulae were all hard and brittle. Addition of PG as plasticizer gave good mechanical properties in concentration of 40% in all trials (Table 1).

### **II- Medicated films**

Table (1) shows the composition and the mechanical properties of the prepared HZ films. The inclusion of HZ in the prepared films reduced the EM and TS which could be attributed to the weakening of the polymer intermolecular binding by the presence of the drug allowing the polymer to move more freely resulting in an increase in the flexibility of the medicated films. Addition of PG as plasticizer gave good mechanical properties in concentration of 40%.

### **B- Swelling Studies of the prepared HZ films**

The swelling behavior of the polymer was reported to be crucial for its bioadhesive character. The adhesion occurs shortly after the beginning of swelling but the bond formed is not very strong. The adhesion will increase with the degree of hydration until a point where over hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer tissue interface. The rate and extent of film hydration and swelling will also affect the drug release from the film. Some degrees of hydration appear to be beneficial to bioadhesion.<sup>[11]</sup> An examination of the hydration rates of polymeric films with different bioadhesive characteristics might be helpful to explore the mechanism underlying bioadhesion. Accordingly, shortly after beginning the swelling test (5 min), the prepared polymeric films swelled in the following order namely CMC > HPMC > mix of HMPC and Carbopol > Carbopol; indicating that CMC took the least time for swelling. However, carbopol and HMPC have reached an Equilibrium state of swelling (Table 2); this state of Equilibrium was not reached by CMC. So it could be concluded that carbopol and HMPC may be suitable for buccal polymeric films while in case of CMC, excessive hydration could lead to decrease the formulation consistency and hence in bioadhesive bond. Incorporation of HZ decreased water uptake behavior of the prepared films but not in a significant way that affect the adhesion properties.

### C- In vitro Bioadhesion studies of the prepared HZ films

There are several advantages in having bio/mucoadhesive drug delivery systems. As a result of such adhesion, the formulation stays longer time at the delivery site and this improves the bioavailability of the drug. Also the increased residence time will enhance and prolong the local effect of the drug whenever it is desired. So the bioadhesive force is an important physicochemical parameter for buccoadhesive dosage forms.

**Table (3) shows the results of bioadhesion tests for different polymeric.**

From the results obtained, the following could be concluded:

- The mucoadhesive polymers investigated could be arranged according to their mucoadhesive force as follows.

Carbopol > CMC > HPMC. Increasing polymer concentration leads to an increase in the detachment stress and hence the mucoadhesion.

The anionic polymers give the highest bioadhesive force (carbopol and CMC). However, The combination of carbopol and HPMC (Formula No.F4-F6) showed good adhesion and acceptable pH. Incorporation of hydralazine in the films seems to cause slight decrease in mucoadhesive properties of the investigated film formulations.

### 6- In-vitro release studies the prepared HZ films

The in-vitro release of the drug from buccal Films contain hydralazine Hcl (formulae F1-F6) was studied at 37 °C using phosphate buffer (pH 6.8) as the release medium. The percent released of the drug as function of time is presented in Figure 2. It could be seen from the results that the release of HZ is higher from CMC films. This could be explained on the bases of rapid and high swelling rate of CMC films. The rank order of HZ release from the investigated polymers is as follows. CMC > HPMC > carbopol. Combination of carbopol and HPMC (F4-F6) gave a reasonable HZ release (about 77- 85% at 6 hours ).As concluded before, The formulae contain combination of carbopol and HPMC showed also good adhesion and acceptable pH. Formula F4 which showed good mechanical properties, adhesion, acceptable pH and reasonable release characteristics was chosen for the permeation study.

### Kinetic Assessment of the in-vitro release data of HZ.

In order to determine the release model which best describes the pattern of drug release, the in-vitro release data were fitted to zero order, first order and diffusion controlled release mechanisms according to the simplified Higashi model. The mathematical treatment of the

vitro release data of hydralazine from the prepared buccal films are presented in table 4. n values of these formulation (0.52-0.58) support an anomalous non-fickian release.

#### **7- Permeability Studies of hydralazine from the investigated buccoadhesive Film for mulation through bovine buccal mucosal membrane.**

The oral mucosa represents a barrier to drug permeation and is closer to skin rather than to the gut in its permeability characteristics. The effectiveness of this barrier and whether buccal absorption could provide means for hydralazine administration have been tested in the in-vitro permeability experiments. The in-vitro study in this work employed excised bovine buccal mucosal membrane mounted in a diffusion cell. One compartment of the diffusion cell contains the selected hydralazine film formulation and the other compartment contains the receptor medium (isotonic phosphate buffer of pH 6.8). Table (5) and Fig (3) show the results of the permeation study. The values of the permeation parameters of hydralazine delivered from the investigated formula are presented in Table (6). The obtained results can be explained on the basis of the in-vitro release, i.e., there is a correlation between the in vitro release and the permeation through excised bovine buccal membrane.

In an earlier study, Muthukumaran et al<sup>[6]</sup> studied the release of hydralazine from formulated buccal tablets. They reported that The correlation between in vitro release rate and permeation across porcine membrane was found to be positive with correlation coefficient of 0.9752. The cellular organization of the buccal mucosa suggests that there are two possible routes of drug transport, the Paracellular route and Transcellular route. The Paracellular route would be predominant pathway taken by hydrophilic components, whereas lipophilic compounds would most likely permeate via the Transcellular route (Zhang and Robinson 1996).<sup>[12]</sup>

In this study, the drug, as a weak base is mostly unionized at pH 6.8. That suggests the permeation of HZ via transcellular route. However, the low molecular weight of the drug makes the Transcellular route is possible and cannot be dismissed. It has been demonstrated that most compounds traverse the buccal mucous via the Paracellular route (Squier and Ilesch, 1988).<sup>[13]</sup> The permeability coefficient obtained is in accordance with other data obtained from buccal absorption of drugs with moderate lipophilicity (Nicolazzo et al., 2004, Attia et al., 2004).<sup>[14,15]</sup>

**Table 1: The Physico-Mechanical Properties of non Medicated and HZ Medicated Polymeric films.**

	Polymer type and concentration		PG % Polymer	HZ mg/cm <sup>2</sup>	TS Nmm <sup>-2</sup>	EM N mm <sup>-2</sup>	EIB %mm <sup>-2</sup>	Mechanical observations
	Film forming Polymer	Bioadhesive Polymer						
NM <sub>1</sub>	PVP 10%	HPMC 1%	20					HARD &
NM <sub>2</sub>	PVP 10%	CMC 1%	20					HARD &
NM <sub>3</sub>	PVP 10%	Carbopol 1%	20					HARD &
NM <sub>4</sub>	PVP 10%	Carbopol 0.5% HPMC 0.5%	40		2.47	1.03	239	SOFT & TOUGH
F1	PVP 10%	HPMC 1%	40	10				SOFT & TOUGH
F2	PVP 10%	CMC 1%	40	10				SOFT & TOUGH
F3	PVP 10%	Carbopol 1%	40	10				SOFT & TOUGH
F4	PVP 10%	Carbopol 0.5% HPMC 0.5%	40	10	1.63	0.62	252	SOFT & TOUGH
F5	PVP 10%	Carbopol 0.5% HPMC 1.0%	40	10	0.98	0.41	260	SOFT & TOUGH
F6	PVP 10%	Carbopol 1.0% HPMC 0.5%	40	10				SOFT & TOUGH

**Table (2): Percent Swelling of the non medicated and HZ medicated polymeric films.**

Formula no.	% Swelling at time ( min )				
	5	10	15	30	60
NM1	18.2±20	26±32	55.2±45	98±7.0	120±6
NM2	35.5±31	52.1±4.2	74±7	140±9.1	180±7
NM3	11.2±3.222	18±3.4	30.2±2	46.2±5	61.2±5
NM4	13.5±3.5	20.1±3.5	35.1±34	70±6.1	90.1±6
F1	15.1±3.6	21±4.0	38±3.226	91±6.2	115±7.2
F2	32.2±4	45.2±4.1	71.2±65	135±8.2	160±9.5
F3	8.2±1.2	13.2±1.5	27.4±31	44.2±4.5	66.1±6
F4	10.5±1.5	16.3±1.7	28±3.1	60.2±4.5	86.1±6
F5	11.2±2.5	17.8±2.6	33.0±34	73.0±6.1	90.24.5
F6	12.3±3	18.8±3.1	36.1±32	79.2±5.6	102.4±8.5

**Table (3): Detachment force and surface pH of The Prepared Films**

Formula No.	Detachment force dync/cm <sup>2</sup> x10 <sup>-3</sup>	Surface pH
NM1	19.8 ± 2.8	6.0
NM2	32.2 ± 3.5	6.3
NM3	34.86 ± 4.2	5.8
NM4	28.10 ± 2.8	5.8
F1	19.25 ± 2.2	6.1
F2	31.1 ± 4.3	6.4
F3	33.65 ± 3.8	5.6

F4	$25.66 \pm 2.9$	6.1
F5	$29.0 \pm 2.8$	6.0
F6	$33.92 \pm 2.7$	5.8

**Table (4): Kinetic modeling of drug release form films containing HZ (20mg/2Cm<sup>2</sup>).**

	Release Model	Formula no:-					
		F1	F2	F3	F4	F5	F6
Zero order	r	0.9240	0.9180	0.9317	0.9230	0.9261	0.9277
	K <sub>o</sub> (mg/min)	0.0259	0.0275	0.0252	0.0229	0.0211	0.0193
First order	r	0.9970	0.9780	0.9963	0.9844	0.9900	0.9851
	K1 (min <sup>-1</sup> ) x10 <sup>3</sup>	3.89	7.950	3.31	2.45	2.06	1.68
Higuchi diffusion	r	0.958	0.9810	0.9878	0.9872	0.992	0.9923
	Kh(mg/cm <sup>2</sup> )/min <sup>1/2</sup>	0.561	0.601	0.540	0.499	0.461	0.420
Log Q Vs log t	r	0.961	0.958	0.963	0.959	0.950	0.949
	n	0.575	0.575	0.583	0.558	0.540	0.520
Selected models		Non – Fickidn diffusion					

**Table (5): Hydralazine permeation through bovine buccal mucosa from selected film preparation (F4, 10mg )**

Time(min)	Formula No.F4	±SD
	CummulativeHZ permeated (ug / cm2)	
0	0	0
30	20.2	1.6
60	60.5	3.8
120	140.3	8.2
180	240.4	11.3
240	360.4	12.2
360	550.3	13.4

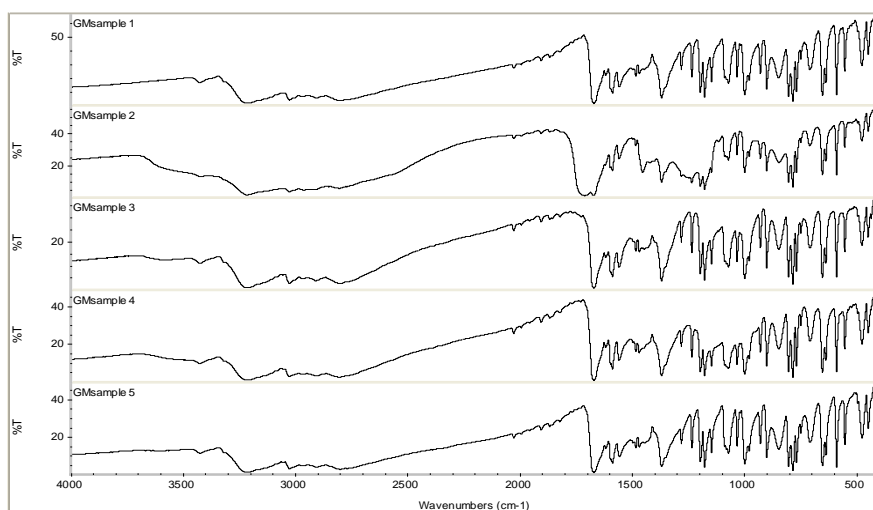
**Table (6): permeation parameters of hydralazine (10 mg) delivered from a selected formulae of the prepared buccoadhesiveFilms through bovine buccal mucosal membrane.**

Formula No	J Ug cm <sup>-2</sup> min	T <sub>L</sub> Min	D X10 <sup>5</sup> Cm <sup>2</sup> .min <sup>-1</sup>	Px10 <sup>4</sup> Cm min <sup>-1</sup>	K	Cumulative % permeated after 6 hours
F4	1.63	40.74	1.66	1.77	0.05	16.7

D= Diffusion coefficient (cm<sup>2</sup>/min)      T<sub>L</sub>= lag time (min)

P= permeability coefficient (cm/min).      K= partition coefficient

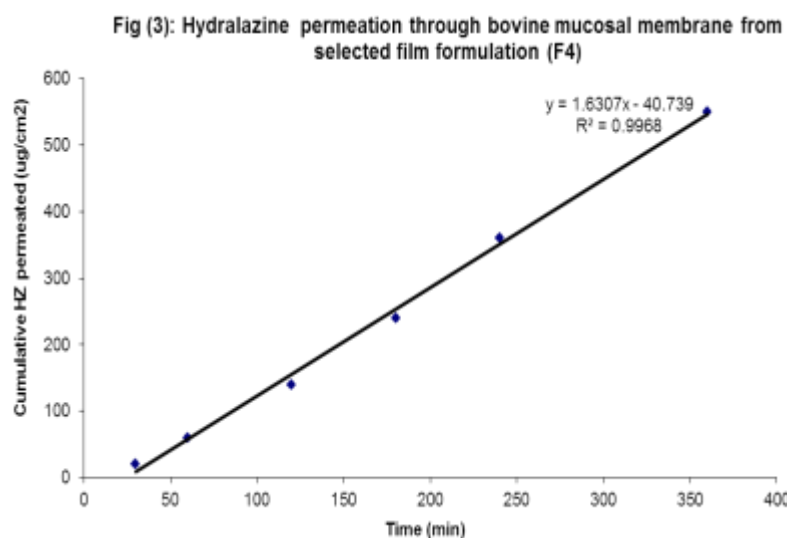
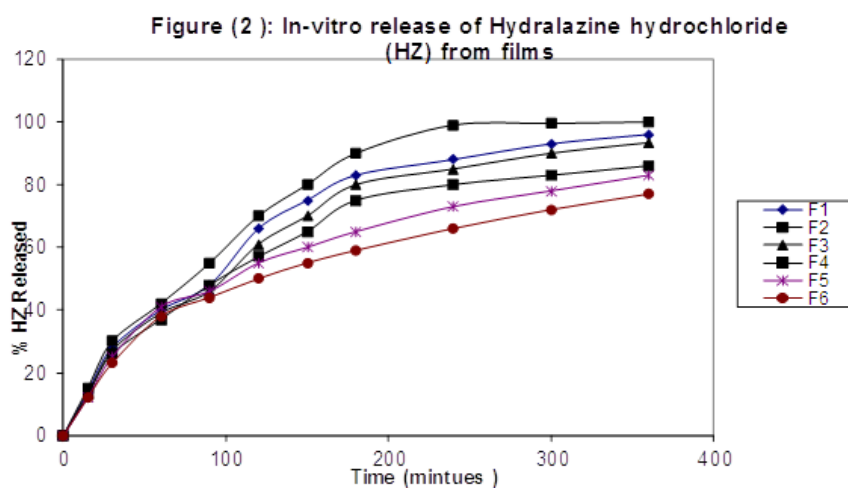
J= flux (ug cm<sup>-2</sup>, min<sup>-1</sup>)



**Figure 1: IR spectra of Hydralazine and its mixtures with the used polymers.**

Key: Sample1: hydralazine hydrochloride (HZ), Sample2: HZ+ CP

Sample3: HZ+CMC, Sample4: HZ+HPMC, Sample5: HZ+PVP





## CONCLUSION

The hydralazine film obtained by solvent casting method showed acceptable mechanical properties with smooth surface without having any drug excipient interaction. The prepared films showed good adhesion properties and satisfactory in vitro release that extended for 6 hours. The formula contains HPMC 0.5% and carbopol 0.5% showed reasonably extension in drug release and permeation through bovine buccal mucosa. So, mucoadhesive films of hydralazine could be promising dosage form as they minimize the dose and could increase the bioavailability. Hydralazine could be a right candidate for sustained drug delivery as buccoadhesive film dosage form.

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