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DESIGN AND EVALUATION OF DILTIAZEM HYDROCHLORIDE LOADED BUCCAL PATCH

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ABSTRACT: The purpose of this study was to develop and optimise the formulation of mucoadhesive patches of Diltiazem hydrochloride using chitosan as base matrix. The patches were prepared by solvent casting method. PVP (K30) and propylene glycol were introduced into the patches formulae to improve the filming properties. The patches were found to be smooth in appearance, uniform in thickness, weight, and drug content and also showed good mucoadhesive strength and folding endurance and moderate swelling properties. The permeation study of the patches indicated a drug release of 80% in 10 hrs. The data analysis of the release profile using Peppas model indicated a non Fickian type of release profile. It can be concluded that buccal patch of Diltiazem hydrochloride can be an alternate for improving bioavailability with a control release profile.

INTRODUCTION: Conventional formulation for local oral therapy is principally lozenges, mouth paints, oral gels, paste and suspensions. Release of the drugs from this preparation involves an initial burst of activity, whose level rapidly declines to sub therapeutic concentrations. Mucoadhesive drug delivery systems offer benefits over conventional delivery methods in terms of extended residence time of the drug at the site of application, a relatively large permeability of the mucus membranes that allow rapid uptake of a drug into the systemic circulation, and enhanced bioavailability of therapeutic agents resulting from the avoidance of some of the body's natural defence mechanisms [1].

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Mucoadhesion, defined as the ability to adhere to the mucus gel layer, is a key element in the design of these drug delivery systems. Buccal mucosa is an attractive route for systemic delivery of drugs since it is relatively permeable, with rich blood supply.

The problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route and, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity.

Attempts have been made earlier to formulate various buccoadhesive devices, including tablets films, patches, disks, and strip.

However, buccal films and patches are preferable over adhesive tablets in terms of flexibility and comfort. Natural polysaccharides have been widely used as bioadhesive polymer because of their biocompatibility and biodegradability properties [2].

Chitosan [α-(1-4, -2 amino 2- deoxy β-D-glucan) is a linear polyamine with high ratio of glucosamine units. the % of glucosamine is known as degree of deacetylation. Chitosan is gaining increasing importance in pharmaceutical field due to its biocompatibility, non-toxicity and biodegradability. It has excellent film forming properties, and also used as a carrier for sustained drug release [3].

In this study, chitosan (CH) was used as bioadhesive polymers to increase the residence time of the dosage form in buccal cavity. These polymers swell in aqueous media to form a gel through which the drug has to diffuse thus; they can also be used to control the rate of drug release.

Diltiazem hydrochloride is calcium channel blocker widely used in the treatment of angina pectoris, arrhythmias and hypertension. The bioavailability of Diltiazem hydrochloride is about 40-50 %. Its short biological half-life 3-5 hrs which makes it a good candidate for controlled release preparation.

EXPERIMENTAL:

Materials: Chitosan with >85% deacetylation was supplied from CIFL ltd, Cochin. Diltiazem hydrochloride was a gift samples from M/S Micro labs ltd, Bangalore. Other reagents used were of analytical grade from local suppliers.

Preparation of mucoadhesive buccal patches: Patches containing different drug and chitosan proportions were prepared by solvent casting method. One gram of chitosan was dissolved in 100 ml of 1% acetic acid solution with occasional stirring for 48 h, results in resulted in a viscous chitosan solution. To this, hydrophilic additive, PVP K-30 was added in different concentration; followed by propylene glycol as plasticizer, at last the drug was added with constant stirring.

The resultant solution was kept overnight at room temperature to ensure a clear, bubble free solution. The solution was poured into Teflon coated petriplates (7cm diameter) and allowed to dry at ambient temperature till a flexible patch is obtained. The dried patches were removed carefully, checked for any imperfections or air bubbles, cut into patches containing 30 mg of drug/patch. They were stored in air tight containers to maintain the integrity and elasticity. **Table 1** shows the composition of patches.

TABLE 1: COMPOSITION OF CHITOSAN BASED BUCCAL PATCHES OF DILTIAZEM HYDROCHLORIDE

Formulation code	Drug/area of 38.45 cm^2	Chitosan mg	PVP % w/v	Propylene glycol w/w
F1	100	500	1	50
F2	100	500	2	50
F3	100	500	3	50
F4	100	500	4	50
F5	100	500	5	50
F6	100	500	6	50
F7	100	500	7	50
F8	100	500	8	50
F9	100	500	9	50
F10	100	500	10	50

Mass uniformity and Folding endurance: Mass uniformity was tested in 6 different 2 cm^2 patches from each batch. Thickness was measured at 5 different randomly selected points using screw gauge. Folding endurance of the patch was determined by folding repeatedly at same place till it broke.

Swelling studies: Buccal patch was weighed, placed in a 2% agar gel plate and incubated at 37^oC. At regular time intervals of 1 hr, patch was removed from petridish and excess surface water was removed carefully using filter paper. The swollen patch was reweighed and swelling index was calculated. The experiments were carried out in triplicate and average values were reported.

% of hydration was determined by the given formula;

$$\% \text{ hydration} = Xt\text{-}X_0 / X_0 * 100,$$

Where Xt is the weight of swollen film after time t and x_0 is the original film weight at zero time.

Determination of drug content uniformity: The drug content was determined by UV spectroscopically by homogenisation of $1cm^2$ portion of the film in phosphate buffer 6.8 buffer by means of magnetic stirring, filtering through whatman filter paper (0.45µm). The drug content was the determined after proper dilution at 236nm using UV-spectrophotometer (Shimadzu spd - 10AVP Japan). The experiments were carried out in triplicate and average value was calculated.

SEM studies: The surface morphology of the patch was studied by using JSM 840 A, scanning electron microscope, Jeol, Japan. The samples were analysed after they haven gold sputtered using 25nm film thickness

***In vitro* release studies:** *In vitro* release studies were carried out by using USP dissolution test type 2 apparatus. The drug loaded films were placed in basket which was in turn placed in suitable quantity of dissolution medium, which is maintained at temperature of 37^{o}C, at a stirring speed of 50 rpm. At appropriate time intervals the samples were withdrawn from medium and analysed for the drug content at 236 nm spectrophotometrically.

***Ex-vivo* mucoadhesion test:** This study was performed on an optimised bio adhesive patch. A fresh porcine buccal mucosa was fixed in the inner side of the beaker, above 2.5 cm from the bottom, with cyanoacrylate glue. One side of each patch was wetted with one drop of isotonic phosphate buffer 6.8 and pasted buccal mucosa by applying a light force with fingertip for 30 seconds. The beaker was filled with 100 ml of isotonic phosphate buffer pH 6.8 and was kept at 37^{o}C. After two minutes 50 rpm stirring speed was applied to stimulate the buccal cavity environment, and the patch adhesion was monitored. The time required for the patch to detach from the buccal mucosa is recorded.

***Ex-vivo* mucoadhesion strength:** Fresh buccal mucosa was obtained from a local slaughter house and used within 2hrs of slaughter. The mucosal membrane is separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water and isotonic phosphate buffer pH 6.8 at 37^{o}C. Bioadhesive strength of the patch was measured on a modified physical balance using the method.

Fresh buccal mucosa was cut into pieces and washed with isotonic phosphate buffer pH 6.8. The glass vial was tightly fitted in the centre of a glass beaker filled with isotonic phosphate buffer pH 6.8. The patch was stucked to the lower side of the rubber stopper with cyanoacrylate adhesive. The mass in gms, required to detach the patch from the mucosal surface gave a measure of mucoadhesive strength.

***Ex-vivo* permeation studies in cheek pouch**: The *ex vivo* study of diltiazem hydrochloride permeation through porcine buccal mucosa was performed using Franz diffusion cell at 37±0.2^{o}C. The fresh mucosa was mounted between donor and receptor compartments so that smooth surface of the mucosa was faced the donor compartment. The patch was placed on mucosa and compartments were clamped together. To the donor compartment, 1 ml of isotonic phosphate buffer pH 6.8was added. The receptor compartment was filled with isotonic phosphate buffer pH 6.8; hydrodynamics of the receptor compartment is maintained by stirring with a magnetic bead at 100 rpm. 1ml of the sample was withdrawn at predetermined time interval sand analysed for the drug content at 236 nm (**table 2**).

TABLE 2: PARAMETERS FOR CHITOSAN BUCCAL PATCHES

Batch code	Mass mg	Thickness (mm)	Drug content (%)	*Ex-vivo* mucoadhesion Time (min)	Surface pH	Folding endurance	*Ex-vivo* mucoadhesion Strength (g)
F1	24+/-1	0.30+/ 0.08	99.23+/0.11	422+/7	6.67+/0.21	223+/12	25.56+/-1.2
F2	22+/ 1	0.33+/0.05	98.56+/0.12	435+/2	6.12+/0.32	227+/5	25.50+/-2
F3	23+/1	0.35+/0.04	98.36+/0.34	462+/ 3	6.54+/0.45	214+/6	24.65+/-3
F4	23+/0	0.36+/0.05	99.34+/0.24	478+/7	6.23+/0.21	232+/10	23.54+/-2
F5	24+/1	0.34+/0.05	99.16+/0.17	426+/8	6.54+/0.65	221+/12	22.65+/-4
F6	23+/1	0.36+/0.06	98.67+/0.87	488+/5	6.01+/0.54	211+/15	22.33+/-5
F7	22+/1	0.34+/0.06	98.23+/0.54	437+/6	6.56+/0.23	200+/	21.56+/-4
F8	25+/1	0.35+/0.07	99.26+/0.35	483+/3	6.54+/0.21	202+/2	20.54+/-5
F9	24+/ 1	0.35+/0.05	97.99+/0.79	467+/4	5.38+/0.27	208+/10	20.44+/-6
F10	25+/ 1	0.36+/0.06	98.26+/0.96	425+/7	6.13+/0.56	216+/6	19.65+/-3

IR studies: FT IR studies were carried out for both diltiazem hydrochloride and drug loaded patch by using Perkin Elmer FTIR, model spectrum one.

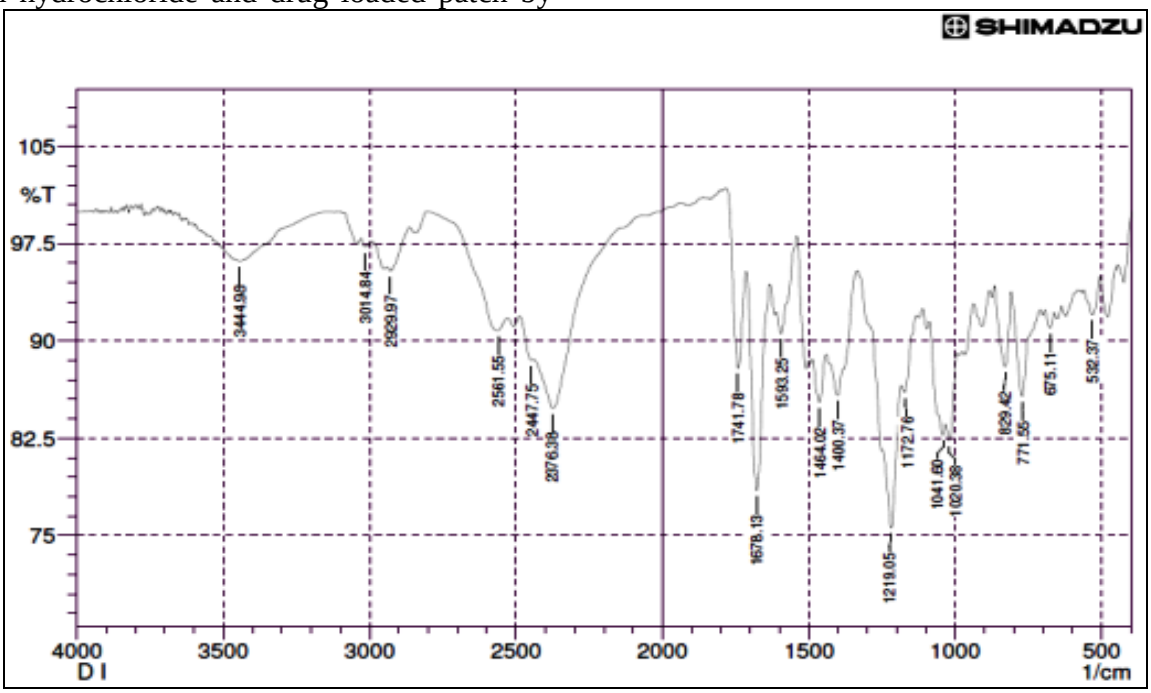

FIGURE 1: FTIR OF DILTIAZEM HYDROCHLORIDE

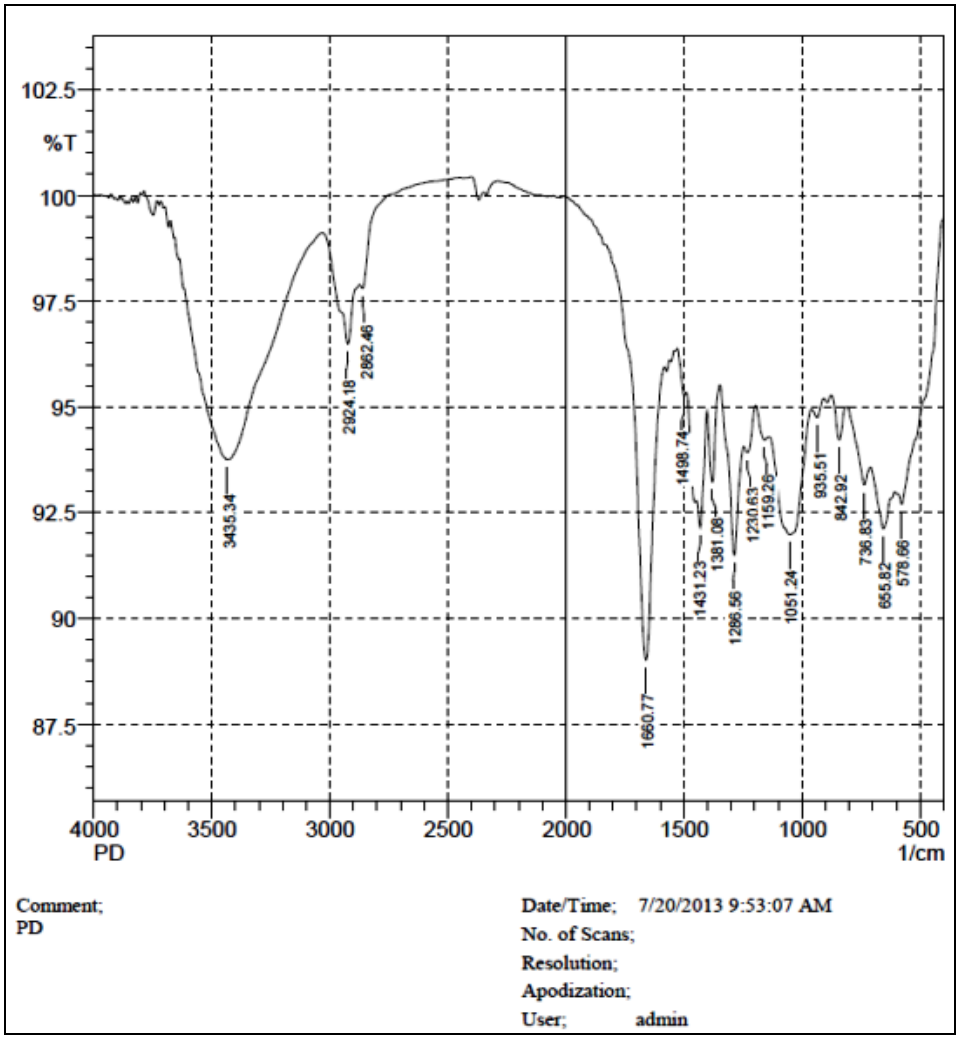

FIGURE 2: FTIR DILTIAZEM HYDROCHLORIDE LOADED

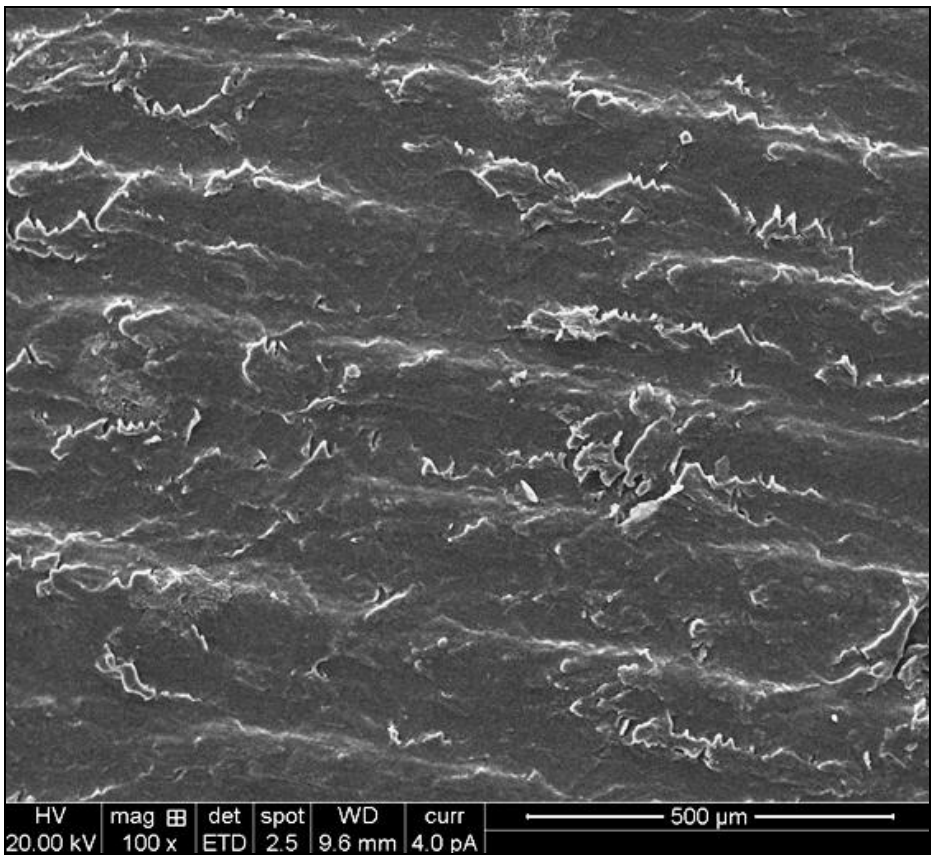

FIGURE 3: SEM PHOTOGRAPH OF OPTIMIZED PATCH

RESULTS AND DISCUSSION: In the present study, buccal patches of diltiazem hydrochloride for controlled drug delivery were prepared by chitosan as base matrix. The patches were prepared using different ratios of chitosan to PVPK-30 to improve the drug release by polymer swelling, elasticity and film forming properties of patches. Propylene glycol 50% was added as plasticizer.

Initially interaction of the drug with polymer was checked by means of IR studies. Existence of the principal peaks indicated that no considerable interaction between the drug and polymer. On the basis of physical properties, F5 was selected for study. Drug incorporated patch was prepared from optimised formula by taking 100 mg of the drug to study the effect of drug concentration in buccal formulations.

The prepared patches were smooth appearance, uniform in thickness, mass, drug content and showed no visible cracks. The patches exhibited good folding endurance (more than 150, table 2). The patch thickness ranged from 0.30+/- 0.08 to -0.36+/- 0.07 and mass ranged from 22 +/- 1 mg to 25+/- mg. The patches had surface pH of 5.38+/0.27to 6.67+/0.21.

The drug content of the patches ranged from 98.23+/0.54 to 99.34+/0.24 %, indicating a favourable drug loading and patches uniformity with respect to drug content. The SEM studies of the mucoadhesive patches indicated an uneven surface which may also responsible for some degree of mucoadhesion.

Appropriate swelling behaviour of buccal adhesive system is essential property for uniform and prolonged release of the drug and effective mucoadhesion. The swelling study indicated that initially patches containing higher concentration of PVP had better swelling index. And also weak aqueous solubility of the cationic polymer limited the swelling of the patches.

The patches did not show any appreciable change in their shape during the swelling studies. The optimised patch showed 36.6% swelling index due to water absorption within 3 hrs. Swelling was seemed as a function of the time. The medicated patches had higher swelling in comparison to plane patches. This may be related to hydrophilic nature of the drug which may add better swelling property to patches.

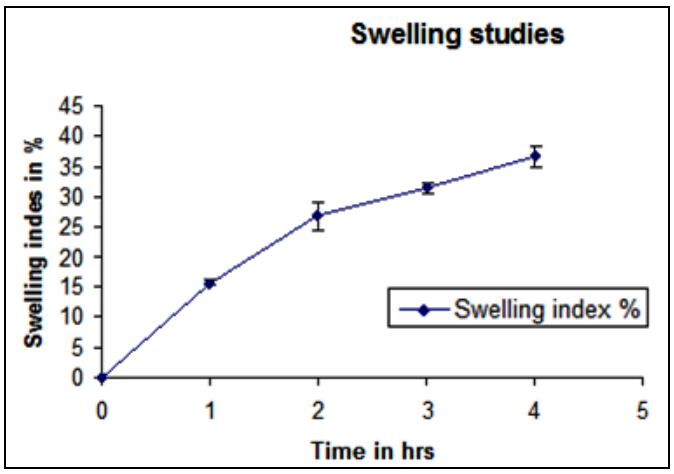

FIGURE 2: SWELLING STUDIES

Mucoadhesion may be defined as adhesion between a polymer and mucus. In general mucoadhesion is considered to occur in 3 stages: wetting, interpenetration, and mechanical interlocking between mucus and polymer. The strength of mucoadhesion is affected by various factors such as molecular mass of polymers, contact time with mucus, swelling rate of polymers and biological membrane used in study. In this study, porcine buccal mucous membrane was used as biological membrane. Plane patches showed higher mucoadhesive strength than medicated patches. The patches containing higher concentration of drug and PVPK30 showed a lesser mucoadhesive strength. Bioadhesive strength of the optimised patch was found to be 22.65+/-4 g. The force of adhesion was found to be 25.56 g. The data is given in **table 2**.

The patches with higher concentration of drug showed a better release profile due to rapid dissolution of drug in the polymer and which resulted in high diffusion of drug (**Table 3**) and also concentration of PVPK30 also affected the drug release. The release data was analysed using Peppas equation.

$Mt/M\alpha = kt^n$, where $Mt/M\alpha$ is the fractional release of the drug, t denotes the release time, k is the kinetic constant, which incorporates structural and geometrical characteristics of the device, n is the diffusional exponent and characterises the type of release mechanism during the dissolution process. For non Fickian release, the value of n falls between 0.5 and 1, while in case of Fickian diffusion n=0.5, for first order release, n=1.

The obtained values K, n, R^2 for the optimised patch formula are presented in **table 4**. The values of n estimated by linear regression of log $Mt/M\alpha$ vs. log t were between 0.5 and 1 indicating the release of the drug was by non Fickian diffusion and kinetics of the study shows a zero order release process.

TABLE 3: COMPARATIVE PERMEATION PROFILE OF SELECTED PATCH FORMULA (F5)

Time in hrs	patch	pure drug
0	0	0
0.5	10.23	3.24
1	14.45	5.76
2	17.56	8.45
3	24.67	10.43
4	31.78	12.78
5	40.87	18.98
6	47.86	25.98
7	58.1	28.89
8	64.87	30.98
9	73.23	33.76
10	80.32	38.87

TABLE 4: KINETIC CONSTANT (K), RELEASE COMPONENT (n) AND DETERMINATION COEFFICIENT (R^2)

Formulation code	K%(h^{-1})	R^2	n
F5	0.1745	0.975	0.9095

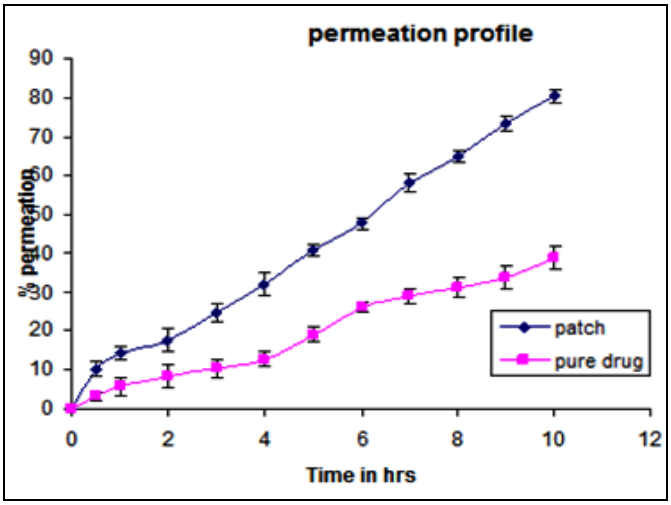

FIGURE 3: PERMEATION PROFILE OF OPTIMISED FORMULA

The surface pH was found to be at neutral range, so that it may not cause any irritation. And also *ex-vivo* mucoadhesion was found to be 19.65+/-3 to25.56+/-1.2minutes. Optimised patches showed a mucoadhesion time of 426 +/- 8 min. The swelling index was found to be moderate. The permeation through was found to be 80.32% in10 hrs.

CONCLUSIONS: From the present study, it may be concluded that bio adhesive patch of diltiazem hydrochloride could meet the ideal requirements of buccal devices, thereby its bioavailability could be increased and also controlled release can be achieved.

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