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FORMULATION DEVELOPMENT AND EVALUATION OF CHITOSAN BASED MUCOADHESIVE BILAYERED BUCCAL PATCHES OF CARVEDILOL

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ABSTRACT: Carvedilol is a non-selective β blocker with α1 blocking activity used in the treatment of congestive heart failure, high blood pressure, and left ventricular dysfunction. Following administration by the oral route, it undergoes extensive first-pass metabolism resulting in low bioavailability of 25-35%. The aim of the present study was to incorporate carvedilol in bilayered chitosan containing mucoadhesive buccal patches to ensure unidirectional drug release. Buccal administration circumvents hepatic first-pass metabolism, as the drug directly enters into the systemic circulation through the buccal mucosa, thereby increasing systemic bioavailability. The patches were prepared using solvent casting method. Chitosan was used as a mucoadhesive polymer as well as the base matrix for the drug. To improve film properties of the patches, PVP was incorporated in all the formulations. An impermeable backing layer of ethylcellulose was used to ensure the unidirectional release of the drug. The compatibility of carvedilol and polymers was confirmed by DSC and FTIR. Bilayered patches were evaluated for various physicochemical parameters like appearance, weight and thickness, folding endurance, tensile strength, surface pH, swelling, drug content uniformity, *in-vitro* drug release, mucoadhesive strength, *ex-vivo* mucoadhesion time and *ex-vivo* permeability studies. The morphology of the patches was studied by SEM. Stability studies of the optimized patches were carried out at 40 ºC / 75% RH for 3 months as well as in natural human saliva. The results indicate that suitable bilayered buccal patches with chitosan as a mucoadhesive polymer can be prepared successfully to ensure satisfactory unidirectional release of Carvedilol with adequate mucoadhesion.

INTRODUCTION: Carvedilol is (2RS)-1-(9H-carbazol-4- yloxy)-3-[2- (2-methoxyphenoxy) ethylamino] propan-2-ol. It is a non-selective β adrenergic antagonist with α1 blocking activity. It is widely used in the treatment of mild to severe congestive heart failure, left ventricular dysfunction following myocardial infarction and hypertension. It has an average molecular weight of 406.482 g/mol, and its half-life ranges from 7-10 h.

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The oral therapeutic dose of carvedilol is low (3.125 – 25 mg). Carvedilol has a poor bioavailability of 25-35% owing to its extensive first-pass metabolism. This justifies a need to develop an effective formulation, which allows the drug to directly enter systemic circulation, thereby bypassing the first-pass metabolism and increasing bioavailability of carvedilol. The buccal route is one such alternative [1, 2].

The buccal route offers numerous advantages like avoidance of presystemic elimination within the GI tract, direct access of the drug to the systemic circulation through the internal jugular vein bypassing the first-pass metabolism leading to high bioavailability. Other advantages offered by buccal route of drug delivery include excellent

accessibility, the suitability of the drugs and excipients that mildly and reversibly damage or irritate the mucosa, painless administration, low enzymatic activity, facility to include an enzyme inhibitor/permeation enhancer or pH modifier in the formulation, versatility in designing a unidirectional or multidirectional system for local or systemic action [3, 4, 5].

Various mucoadhesive formulations have been suggested for buccal drug delivery, including buccal mucoadhesive tablets, buccal patches, mucoadhesive ointments, and gels. Buccal patches are well tolerated by the patients than buccal tablets owing to their high flexibility and comfort. Also, buccal patches ensure more accurate dosing of the drug compared to mucoadhesive ointments and gels, which possess short residence time in the buccal cavity [6, 14]. The present study aimed at the development and optimization of chitosan containing mucoadhesive bilayered buccal patches of carvedilol. The bilayered design of the patch was selected to achieve unidirectional release of the drug, greater surface area of contact, and to administer the bitter drug without taste masking. Chitosan, a mucopolysaccharide of marine origin, has been claimed to act as both a bioadhesive as well as a permeabilizer.

Chitosan was used as a base matrix polymer for the development of mucoadhesive bilayered buccal patches. Polyvinylpyrrolidone (PVP) was incurporated in all the formulations to impart film-forming properties. Ethylcellulose was used as a polymer for the fabrication of the backing layer because of its important properties like hydrophobicity, drug impermeability, moderate flexibility, and low water permeability. The concept of administration of carvedilol *via* buccal route, by formulating it as a bilayered buccal patch formulation has not been explored so far. The present study would also help to study the influence of matrix polymer chitosan on the drug release and on the other physicochemical properties.

MATERIALS AND METHODS:

Materials: Carvedilol, was received as a gift sample from Zydus Cadila Healthcare Ltd., Kundaim-Goa. Chitosan with 87% degree of deacetylation was received as a gift sample from the Central Institute of Fisheries Technology (CIFT), Kochi Kerala. Polyvinylpyrrolidone was obtained from Molychem. Propylene glycol was obtained from Lobachemie Pvt. Ltd. Ethylcellulose was procured from Colorcon, Goa. Dibutyl phthalate was obtained from Lobachemie Pvt. Ltd. All other chemicals employed were of analytical grade.

Methods:

Preparation of Backing Membrane: Initially, a backing membrane of ethyl cellulose was prepared by pouring slowly a solution containing 500 mg of ethylcellulose and 2.5% (v/v) of dibutyl phthalate in 10 ml of acetone to the glass petri plate followed by air drying for 24 h [9].

Preparation of Mucoadhesive Layer Containing Drug: Patches containing different proportions of carvedilol and chitosan were prepared by the solvent casting method. Patches were formulated by dissolving 1, 2, and 3% (m/v) of chitosan in 10 ml of 1.5% glacial acetic acid and was stirred for 1 h.

Polyvinylpyrrolidone was first dissolved in a small volume of distilled water and was added to the polymeric solution. Carvedilol was then added in 2 ml of the solvent system in another beaker and was then added to the polymeric mixture. 5% (v/v) of propylene glycol was added as a plasticizer, and the stirring was continued for another 30 min.

TABLE 1: COMPOSITION OF CHITOSAN BASED BILAYERED BUCCAL PATCHES OF CARVEDILOL

For primary drug layer						
Formula	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Carvedilol	34 mg	34 mg	34 mg	56.67 mg	56.67 mg	56.67 mg
Chitosan (in 1.5% v/v acetic acid)	1%	2%	3%	1%	2%	3%
Polyvinylpyrrolidone (% w/v)	0.05%	0.05%	0.05%	0.05%	0.05%	0.05%
Propylene glycol (% v/v)	5%	5%	5%	5%	5%	5%
For secondary layer						
Ethylcellulose	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg
Dibutylphthalate (% v/v)	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Acetone	10 ml	10 ml	10 ml	10 ml	10 ml	10 ml

The resultant viscous solution was then poured onto the preformed backing layer of ethyl cellulose and allowed to dry undisturbed for 11 h at 40 °C in the vacuum oven. Dried patches were cut into 2 cm^2 dimension so that formulations F1, F2, and F3 consisted of 3 mg of the drug and formulations F4, F5, and F6 contained 5 mg of the drug. The patches were stored in laboratory manufactured aluminum pouches in desiccators to maintain the elasticity and integrity of the patches.

Evaluation of Bilayered Buccal Patches:

Drug-Polymer Compatibility Study: The drug-polymer compatibility study was carried out using the FTIR spectrophotometer (Shimadzu) and Differential scanning calorimetry (DSC) analysis (Mettler Toledo) [7, 8]. The IR spectra of the drug as well as the physical mixture of the drug and polymer in the ratio of 1:1 were recorded. All the spectra were recorded in the range of 400-4000 cm^{-1}.

DSC thermogram of Carvedilol and physical mixture of Carvedilol and polymer in 1:1 ratio were recorded by placing the samples in an aluminum pan sealed hermetically and heated at a constant rate of 10 ºC/min, nitrogen flow rate of 50 ml/min over the temperature range of 40-250 ºC.

General Appearance: The formulated patches were evaluated based on their physical appearance. The patches should ideally be smooth, soft, flexible, and free of bubbles to ensure easy handling for high patient acceptability. Buccal patches were examined visually for clarity, absence of any impurity, precipitation, or crystallization effects of the components involved.

Drug Content Uniformity: The buccal patch was homogenized by shaking in 100 ml of isotonic phosphate buffer pH 6.8. The solution was then sonicated for 30 min and then filtered through a 0.45 µ filter. The drug content was determined by proper dilution at 241 nm using a UV-VIS spectrophotometer (SHIMADZU). The studies were conducted in triplicate, and the average values were then reported [9].

Weight and Thickness of the Patches: Three patches were randomly selected and weighed individually on the analytical weighing balance (Mettler Toledo JB-1603-L-C). The average weight was calculated along with the standard deviation. The thickness of the buccal patches was assessed using a digital Vernier caliper (Mitutoyo) [9].

Surface pH Measurement: Surface pH of the films was determined to check whether the buccal patches cause irritation to the buccal mucosa. Patches were selected randomly, and the measurement of the pH was done using pH meter. The patch was placed in a petri dish that contained 0.5 ml of distilled water and left for 1 h. After complete swelling, the pH probe was placed in close contact with the wetted surface of the patch, and the pH was recorded for each patch [9, 10].

Tensile Strength: The instrument for the measurement of tensile strength was designed in the laboratory as per the literature. The strip (2 × 2 cm) was clamped at the static end and was attached to the movable rod on a railing with the help of a clip. The weights were gradually added to the pan to increase the pull force till the patch was cut. The weight required to break the patch was noted as the brake force. The tensile strength was calculated as follows [11]:

Tensile strength = Force at break g / Initial cross-sectional area cm × cm

FIG. 1: TENSILE STRENGTH TESTER DESIGNED IN THE LABORATORY

Folding Endurance: Folding Endurance of the patch was determined by repeatedly folding one patch at the same place till it broke. The number of times of patch could be folded at the same place without breaking gave the value of the folding endurance. This was done on randomly selected three patches from each batch [9, 10, 19, 20].

Percentage Moisture Loss: The buccal patches were weighed accurately and kept in the desiccators containing fused calcium chloride at

room temperature for 3 days. After 3 days, the films were reweighed, and the percentage moisture content was determined from the below-mentioned formula [11, 13]:

Percentage Moisture Loss = Initial weight - Final weight / Initial weight × 100

Percentage Moisture Absorption: The accurately weighed films were kept in desiccators at room temperature for 3 days containing a saturated solution of potassium chloride in order to maintain 84% RH. After 3 days, the films were reweighed and determine the percentage of moisture uptake from the below mentioned formula [11, 13]:

Percentage Moisture Absorption = Final weight-Initial weight / Initial weight × 100

Swelling Study: Buccal patch was weighed (W1) and was placed in a 2% w/v agar gel plate and was incubated at 37± 1 ºC. At regular 1h time intervals for up to 8 h, the patch was removed from the petri plate, and excess surface water was removed carefully by blotting with a tissue paper. The swollen patch was then reweighed (W_2), and the average swelling index was calculated from the following formula. The experiment was conducted in triplicate, and the average values were then determined [9].

$$\% \text{ Swelling Index} = (W_2 - W_1) / W_1 \times 100$$

***In-vitro* Release Studies:** The release of carvedilol from the formulated buccal patches was studied using the USP dissolution apparatus type II (LAB INDIA) under sink conditions at 37 ± 1 ºC and 50 rpm. The dissolution medium consisted of 500 ml of isotonic phosphate buffer pH 6.8. A patch was applied on a glass slide in such a way that the mucoadhesive layer of the patch was in contact with dissolution media, and the nonadhesive backing layer was fixed onto the slide with the help of clips. Samples (5 ml) were withdrawn at predetermined time intervals and replaced with fresh dissolution medium. The amount of drug released was determined spectrophotometrically using a UV-VIS spectrophotometer (SHIMADZU) at 241 nm after appropriate dilution. The test was performed on three patches of each formulation [9].

***Ex-vivo* Mucoadhesion Time:** The *ex-vivo* mucoadhesion time was evaluated after the application of the patches onto freshly cut sheep buccal mucosa. The mucosa was fixed in the inner side of the beaker, above 2.5 cm from the bottom with cyanoacrylate adhesive. The mucoadhesive side of each patch was wetted with one drop of isotonic phosphate buffer pH 6.8 and affixed to the sheep buccal mucosa by applying a light force with a fingertip for 30 s. The beaker was filled with 500ml of isotonic phosphate buffer pH 6.8 and temperature maintained at 37 ± 1 ºC. After 2 min, a 50 rpm stirring rate was applied to simulate the buccal cavity environment and patch adhesion duration, *i.e.,* the time taken for the patch to detach from the mucosa was recorded as the mucoadhesion time. The tabulated data represents a mean of three determinations [9].

Mucoadhesive Strength: The mucoadhesive strength of the films was measured on a modified physical balance. A lower vial (L) was inverted and fixed in place at the left-hand side of the physical balance. The patch was attached to the lower vial (L). A fresh piece of goat buccal mucosa was used as the model membrane for the study. It was fixed to the rubber closure end of the upper vial (U) with the mucosal surface facing outwards. A string was attached to the other end of the upper vial. This string was attached to the left-hand side of the physical balance. The weight of the vial acted as preload. A plastic container weighing 2.50 g was placed on the right-hand side of the balance.

FIG. 2: MUCOADHESIVE STRENGTH TESTER DESIGNED IN LABORATORY

The balance was then kept in this position for a period of 5 min and then slowly, the water was poured into the plastic container on the right-hand side of the balance till the buccal film detached from the membrane. The weight of the plastic container was then noted. The total weight minus

the weight of the container corresponds to the bioadhesive strength of the film in grams.

Before carrying out the study, the balance was equilibrated. The mucosa was washed thoroughly before use. Fresh mucosa was used for testing of each film [12].

Scanning Electron Microscopy Analysis: The surface morphology of the films was studied using scanning electron microscopy. Samples were mounted on round brass stubs (10 mm diameter) and then sputter-coated under argon atmosphere with gold and palladium and observed under the scanning electron microscope [15, 21].

***Ex-vivo* Permeation Studies of the Optimized formulation:** *Ex-vivo* buccal permeation study of the drug was studied through the goat buccal mucosa using a Franz Diffusion Cell. Freshly obtained goat buccal mucosa was mounted in between the donor and the receptor compartments. The compartments were clamped together. The buccal patch was placed on the mucosa by gentle pressing. The donor compartment was filled with 2 ml of phosphate buffer, pH 6.8. The receptor compartment was filled with 40 ml of phosphate buffer pH 6.8, and the permeation was performed by maintaining the stirring speed of 50 rpm. At predetermined time intervals, 5 ml sample was withdrawn and analyzed using a UV spectro-photometer at 241 nm [11].

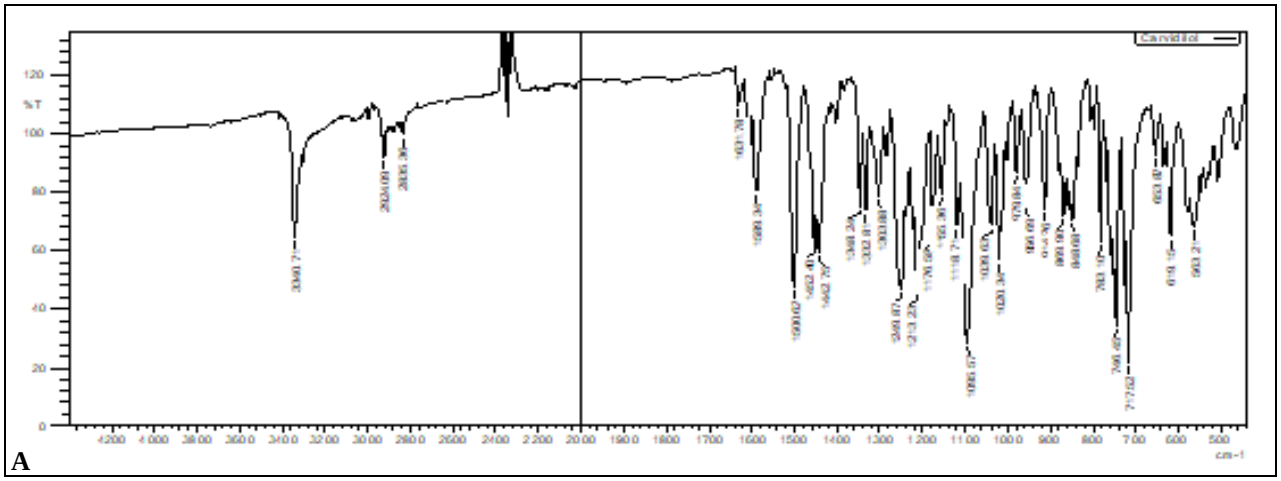
Stability Studies for Optimized Formulations: Stability studies of optimized formulations were carried out by storing the formulations at 40 °C ± 2°C/ 75% RH for 30 and 90 days, respectively. Samples were withdrawn on 30th and 90th day and were analyzed for drug content, thickness, and *in-vitro* release studies [14].

Stability of the Optimized Formulations in Human Saliva: The optimized patches were subjected to the stability studies in natural human saliva, which was collected from humans (aged 22 to 30 years) and filtered. The patches were placed separately in petri plates containing 5 ml of human saliva and kept in a temperature-controlled oven at 37 ± 0.2 ºC for 8 h.

At regular time intervals (0, 0.5, 1, 2, 4, 6 and 8 h), the patches were examined for any change in color and shape, the collapse of the patch and drug content. Drug content was determined by extracting the drug from the patch and diluting appropriately with Phosphate buffer pH 6.8 and analyzed spectrophotometrically at 241 nm [9, 14, 16, 17].

RESULTS AND DISCUSSION: The present investigation was an attempt to develop and evaluate chitosan-based bilayered buccal patches of Carvedilol containing a mucoadhesive layer made up of chitosan as a base matrix and PVP and ethyl cellulose backing layer using the solvent casting method.

FTIR Study: FTIR was performed to detect any sign of interaction, which would be reflected by a change in the position or disappearance of any characteristic peak of carvedilol. IR scans of pure drug carvedilol and 1:1 physical mixtures of carvedilol and ethylcellulose, carvedilol and chitosan, carvedilol, and PVP were taken. From the IR spectra shown in **Fig. 3**, it was observed that there was no interaction of the drug with any of the excipients.



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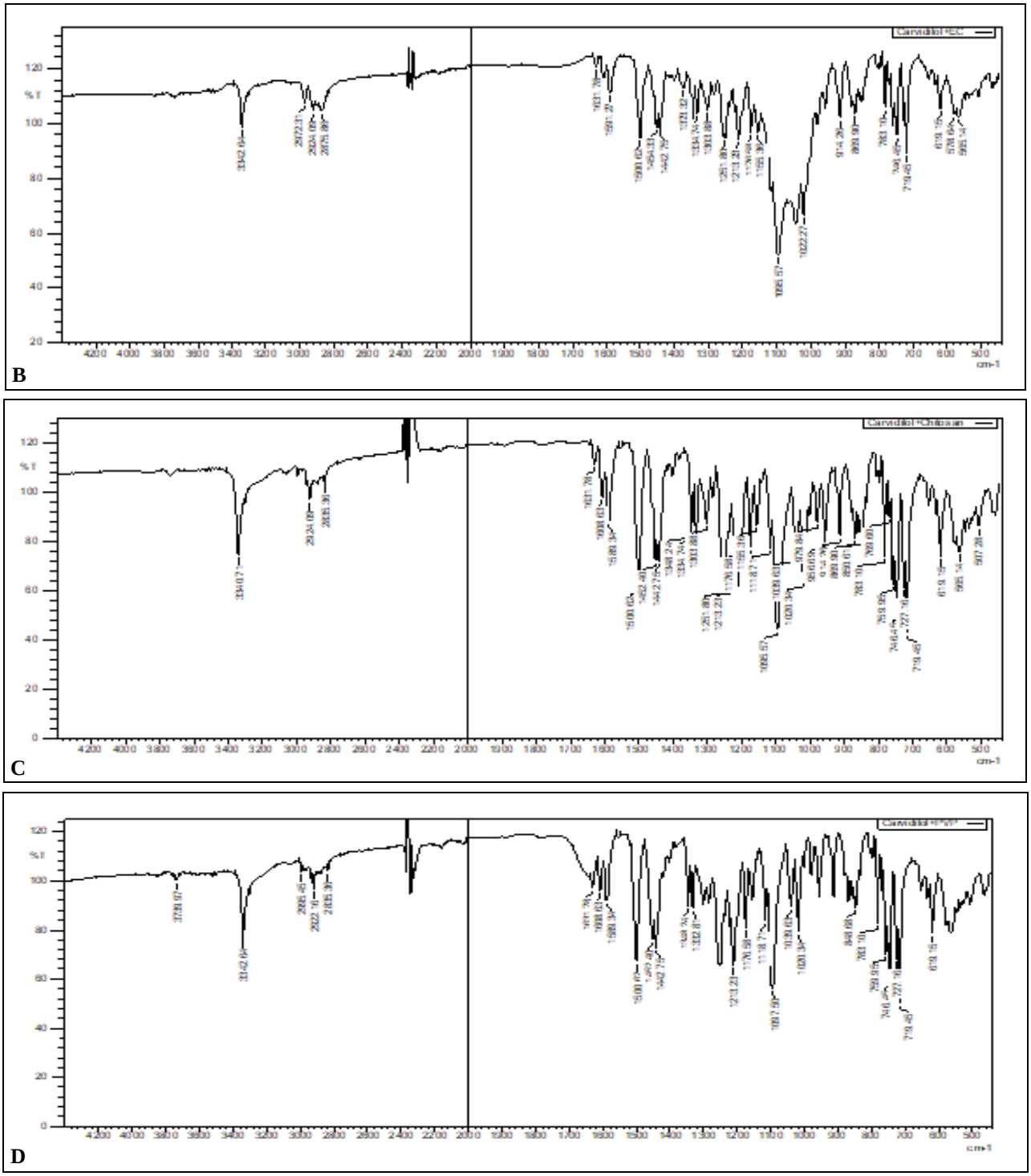

FIG. 3: FTIR SPECTRA OF A) PURE CARVEDILOL B) CARVEDILOL AND ETHYLCELLULOSE 1:1 PHYSICAL MIXTURE C) CARVEDILOL AND CHITOSAN 1:1 PHYSICAL MIXTURE D) CARVEDILOL AND PVP 1:1 PHYSICAL MIXTURE

Differential Scanning Calorimetry (DSC): Differential scanning calorimetry was performed to confirm the identity and purity of the drug and to check for any incompatibility with the excipients. The DSC thermogram of pure Carvedilol exhibited an endothermic peak at 116.63 °C. The physical mixture of Carvedilol with Chitosan, PVP, and Ethylcellulose showed an endothermic peak at 116.35 °C, 121.63 °C, and 116.79 °C respectively, nearly the same temperature as that of pure drug, indicating no interaction between drug and excipients. The DSC thermogram of the drug and its physical mixture are shown in **Fig. 4**.

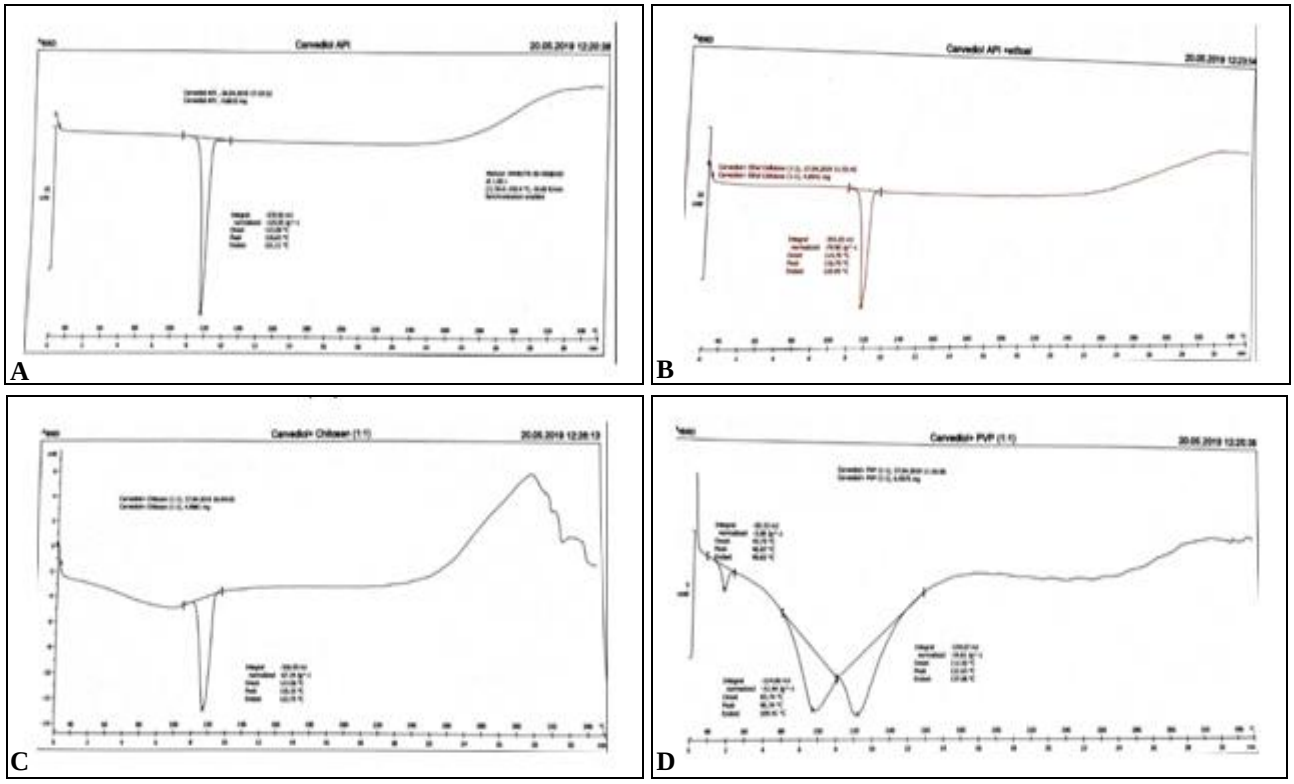

FIG. 4: DSC THERMOGRAM OF A) PURE CARVEDILOL B) 1:1 MIXTURE OF CARVEDILOL AND ETHYLCELLULOSE C) 1:1 MIXTURE OF CARVEDILOL AND CHITOSAN D) 1:1 MIXTURE OF CARVEDILOL AND PVP

General Appearance: The bilayered buccal patches were found to be smooth with flat surfaces, translucent in appearance. Bilayered buccal patches were examined visually and were found to possess a smooth texture and were free from any imperfections or visible non-uniformities.

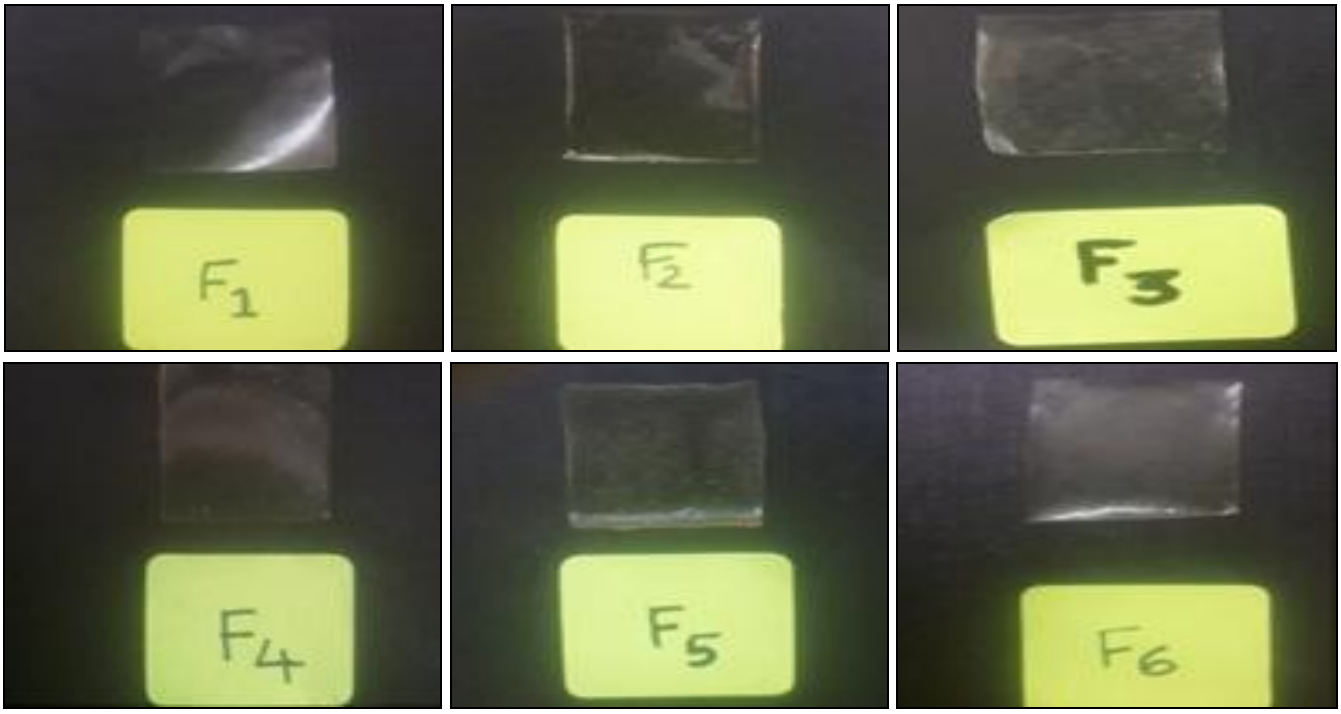

FIG. 5: APPEARANCE OF FORMULATIONS F1-F6

Drug Content Uniformity: Drug content was analyzed for all six formulations in triplicate samples and was found to be between 88.50 ± 0.280% to 94.26 ± 0.300%. The results are tabulated in **Table 2**.

Weight and Thickness: The weight of the patches was recorded using the analytical weighing balance in triplicate and ranged from 53.3 ± 0.152 mg to 160.3 ± 0.15 mg. The patch thickness was measured by using a digital Vernier caliper and ranged from 0.150 ± 0.01 mm to 0.250 ± 0.02 mm.

The weight and thickness of the patches from batch F1 to F6 of size 4 cm^2 is reported in **Table 2**.

Surface pH: The surface pH was determined to check whether the patches cause any damage to the buccal mucosa. The surface pH of the bilayered buccal patches was found to be in the range of 6.03 to 6.78, and hence the patches should not cause any irritation in the buccal cavity. The surface pH of all the formulations is shown in **Table 2**. The values represent the mean of three determinations.

Folding Endurance: Formulated batches were analyzed for folding endurance. Folding endurance of the formulations was determined manually. Data were analyzed using mean and standard deviation. The values for folding endurance are reported in **Table 2**.

Tensile Strength: All sets of formulations were analyzed for their tensile strengths. Results were found to be satisfactory for all the formulations analyzed. Data were analyzed using mean and standard deviation. The values of tensile strength are reported in **Table 2**.

TABLE 2: PHYSICOCHEMICAL PARAMETERS OF CHITOSAN BASED BILAYERED BUCCAL PATCHES OF CARVEDILOL

Formulation Code	% Drug content (X ± S.D)	Weight (mg) (X ± S.D)	Thickness (mm) (X ± S.D)	Surface pH (X ± S.D)	Folding endurance (X ± S.D)	Tensile strength (g/cm²) (X ± S.D)
F1	88.50 ± 0.280	53.3 ± 0.152	0.163 ± 0.020	6.003 ±0.020	249.6 ± 0.577	130.07 ± 0.060
F2	92.77 ± 0.386	101.2 ± 0.015	0.186 ± 0.005	6.18 ± 0.010	198 ± 1.000	112.82 ± 0.430
F3	92.22 ± 0.190	132.4 ± 0.305	0.236 ± 0.015	6.74 ± 0.150	111 ± 1.000	124.00 ± 0.280
F4	91.80 ± 0.500	76.3 ± 0.400	0.150 ± 0.010	6.383 ± 0.280	219.3 ± 0.577	125.99 ± 0.790
F5	94.26 ± 0.300	143.1 ± 0.200	0.190 ± 0.010	6.716 ± 0.060	190 ± 0.000	104.92 ± 0.180
F6	91.46 ± 0.416	160.3 ± 0.150	0.250 ± 0.020	6.78 ± 0.110	100 ± 1.000	111.74 ± 0.390

X- Mean, S.D- Standard deviation

Percentage Moisture Absorption: The percent moisture absorption was found to be between 1.0 to 7.5%. The results for % moisture absorption are given in **Table 3**.

Percentage Moisture Loss: The percent moisture loss was found to be between 1.01 to 8.40%. A small amount of moisture in the buccal patches is necessary in order to keep the film stable and prevent it from being brittle. The results of % moisture loss are given in **Table 3**.

TABLE 3: PERCENTAGE MOISTURE ABSORPTION (% PMA) AND PERCENTAGE MOISTURE LOSS (% PML) OF THE FORMULATIONS

Formulation Code	Percentage Moisture Absorption (% PMA) (X ± S.D)	Percentage Moisture Loss (% PML) (X ± S.D)
F1	2.5 ± 0.420	2.45 ± 0.032
F2	1.02 ± 0.014	1.15 ± 0.030
F3	1.54 ± 0.040	8.40 ± 0.500
F4	2.16 ± 1.430	3.52 ± 1.730
F5	7.5 ± 0.014	1.01 ± 0.014
F6	1.0 ± 0.060	8.26 ± 0.120

Swelling Study: The swelling percentages of the formulations after 8 h was observed. The increasing order of the swelling percentage of the patches is F2> F5> F1> F4> F3> F6> Placebo. The placebo patch showed less swelling index compared to the drug-loaded patches because the presence of the drug would modify the way the water would be bound to or taken up by the polymer. The patches containing 2% Chitosan showed a greater swelling index. The least swelling was shown by the patches containing 3% of chitosan. The swelling property of the patches was also evident during the drug release study. The patches retained their shape and form when kept on the 2% agar gel plate during the study period.

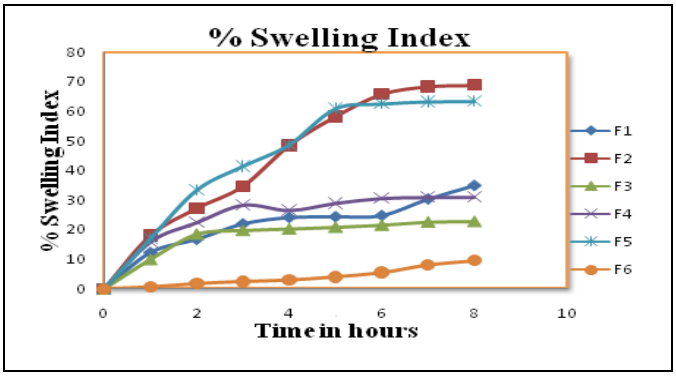

FIG. 6: SWELLING INDICES OF THE BUCCAL PATCHES (F1-F6)

***In-vitro* Release Studies:** The *in-vitro* release study of the chitosan-based bilayered buccal patches of carvedilol was carried out using phosphate buffer pH 6.8. The *in-vitro* release data and profile of the formulated bilayered buccal patches are shown in **Table 4**. The cumulative percentage drug release at the end of 8 h of *in-vitro* release study is shown in the descending order: F2> F5> F1> F4> F3> F6. It was observed that the release of the action was influenced by the amount of the chitosan incorporated into the patches.

Carvedilol is practically insoluble in water, but the rationale behind performing *in-vitro* dissolution testing in Phosphate buffer pH 6.8 was to analyze its release in the salivary fluid. Based on the release profile exhibited by all the formulations, it was evident that formulations F2 and F5 containing 2% chitosan showed the highest release of 95.61% and 92.43%, respectively. The *in-vitro* drug release pattern of Carvedilol from bilayered buccal patches is as shown in **Fig. 7**.

TABLE 4: *IN-VITRO* DRUG RELEASE PROFILE OF DIFFERENT BILAYERED BUCCAL PATCH FORMULATIONS OF CARVEDILOL (F1-F6)

Time (h)	F1 (%CDR)	F2 (%CDR)	F3 (%CDR)	F4 (%CDR)	F5 (%CDR)	F6 (%CDR)
0	0	0	0	0	0	0
1	25.20	35.00	18.50	20.00	32.6	13.00
2	45.17	44.40	22.31	34.5	43.42	19.83
3	55.16	60.13	24.18	41.94	56.00	23.12
4	60.07	73.66	38.17	45.40	72.40	35.95
5	68.49	79.44	48.54	55.00	78.01	46.21
6	75.00	85.66	58.31	56.33	84.60	55.97
7	77.53	93.54	64.71	63.40	89.00	61.42
8	80.60	95.61	66.16	71.00	92.43	64.69

%CDR- % Cumulative Drug Release

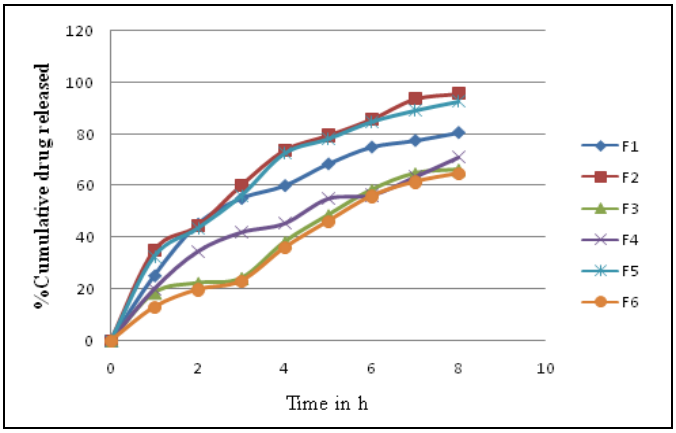

FIG. 7: *IN-VITRO* DRUG RELEASE PROFILE OF FORMULATIONS (F1-F6)

Kinetic Modelling: The Regression coefficient (R2) values for zero-order ranged from 0.896-0.984, and for first-order plots ranged from 0.960-0.997. R2 values were found to be higher for first-order than for zero order. According to the regression coefficients tabulated in **Table 5** for all the formulations, it is evident that all the formulations follow first-order drug release kinetics. Since the Regression coefficient of the Higuchi plot was found to be close to 1 according to the above tabulated data, it also reveals that all the formulations exhibit a diffusion drug release mechanism.

In case of Korsemeyerpeppas plot 'n' values were more than 0.5, which indicates non-fickian drug release kinetics. Hence, from the data obtained from all the models, it was concluded that the drug release through the bilayered buccal patch is diffusion-controlled following first-order kinetics with non-fickian diffusion pattern.

Optimization: From the results of the above tests carried out on all the formulations, it is observed that F2 and F5 having a dose of 3 mg and 5 mg respectively exhibited the highest release, drug content uniformity along with favorable physicochemical properties, confirming them as the optimized formulations.

***Ex-vivo* Mucoadhesion Time:** The *ex-vivo* mucoadhesion time of the patches was studied by using freshly obtained sheep buccal mucosa as a model mucosal membrane. The results of the study are tabulated in **Table 6**.

Mucoadhesive Strength: The mucoadhesive strength of the patches was found out using a modified physical balance. The results of the study were found to be satisfactory and are tabulated in **Table 6**.

TABLE 5: VALUES OF REGRESSION COEFFICIENTS AND RELEASE KINETICS OF FORMULATIONS IN PHOSPHATE BUFFER pH 6.8

Code	Zero-order		First-order		Higuchi		Peppas	
	R^2	K	R^2	K	R^2	K	R^2	n
F1	0.896	10.31	0.986	-0.188	0.973	29.54	0.966	0.540
F2	0.907	10.99	0.968	-0.391	0.985	35.47	0.984	0.516
F3	0.969	8.327	0.960	-0.142	0.934	30.09	0.955	0.346
F4	0.928	7.848	0.976	-0.131	0.967	52.95	0.983	0.571
F5	0.945	8.787	0.992	-0.137	0.981	34.90	0.984	0.532
F6	0.984	8.323	0.997	-0.140	0.896	62	0.968	0.831

TABLE 6: *EX-VIVO* MUCOADHESION TIME AND MUCOADHESIVESTRENGTH

Formulation Code	*Ex-vivo* mucoadhesion time (min)	Mucoadhesive Strength (g)
F1	389 ± 0.000	25 ±0.000
F2	497.33 ± 2.050	20.06 ± 0.094
F3	200.33 ± 0.577	17.16 ± 0.120
F4	390.33 ± 0.577	23.03 ± 0.047
F5	483 ± 1.000	20 ± 0.000
F6	204.66 ± 0.577	18.06 ± 0.094

Scanning Electron Microscopy: Scanning electron microscopy was used to study the surface morphology of the bilayered buccal patches.

***Ex-vivo* Permeation Studies:** The ex-vivo permeation studies were conducted for the optimized formulations F2 and F5 using a goat buccal mucosa. The % drug release obtained for the optimized formulations F2 and F5 at the end of 8h was found to be 66.68% and 65.78%, respectively.

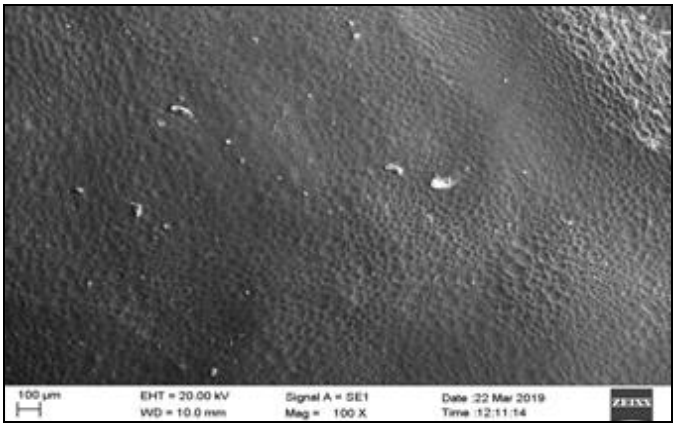

FIG. 8: SEM IMAGE OF MUCOADHESIVE DRUG LAYER OF OPTIMIZED FORMULATION F2

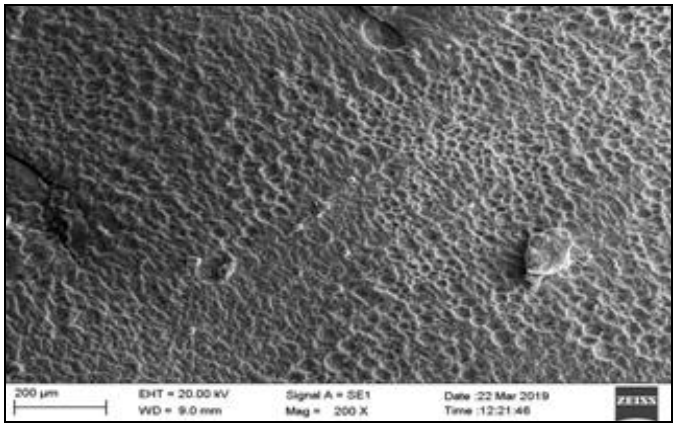

FIG. 9: SEM IMAGE OF MUCOADHESIVE DRUG LAYER OF OPTIMIZED FORMULATION F5

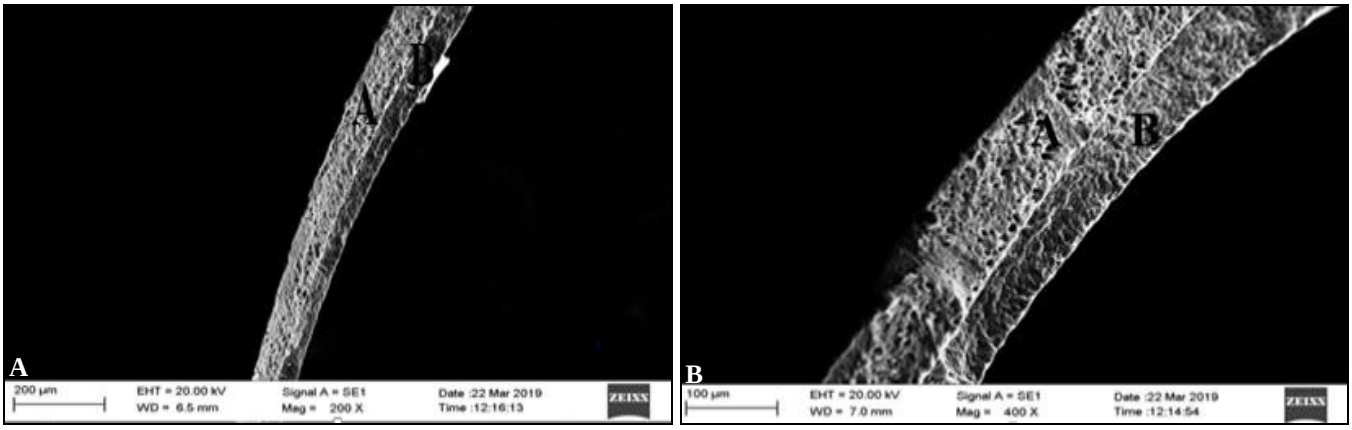

FIG. 10: SEM IMAGES OF CROSS-SECTION OF OPTIMIZED FORMULATION F2 AT DIFFERENT MAGNIFICATIONS (A)BACKING LAYER (B) MUCOADHESIVE DRUG LAYER

Stability Studies for Optimized Formulations: Optimized formulations F2 and F5 were subjected to stability studies at 40° C ± 2 ° C/75 ± 5% RH for 30 and 90 days. Samples were analyzed for thickness, drug content, and *in-vitro* dissolution studies. Results are tabulated in **Table 7**, **Table 8**,

Table 9, and **Table 10** below. No much change was found in the results of stability samples from the previous results of the formulations. This indicates that the formulation is stable at stated conditions and storage period.

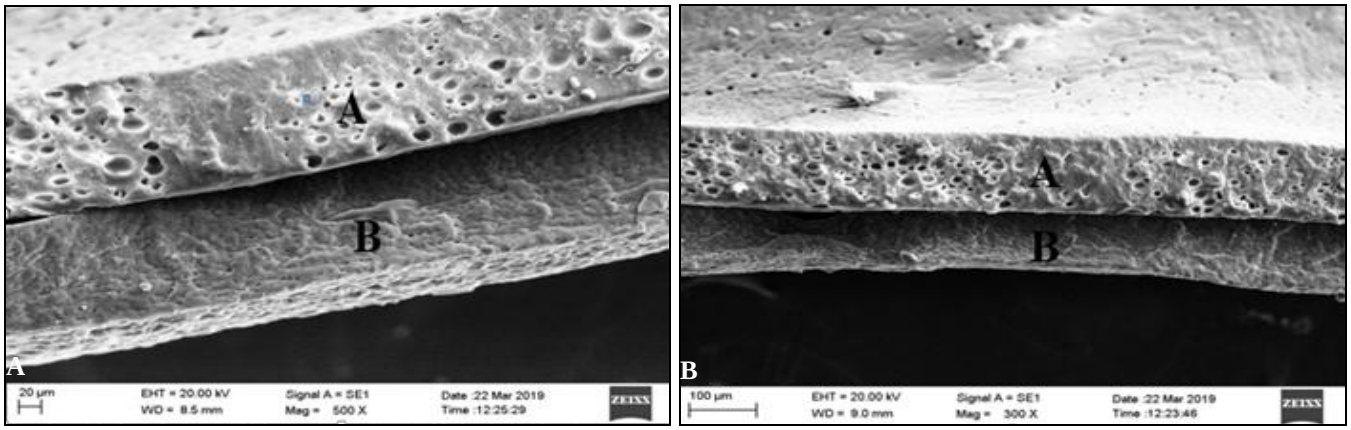

FIG. 11: SEM IMAGES OF CROSS-SECTION OF OPTIMIZED FORMULATION F5 AT DIFFERENT MAGNIFICATIONS (A) BACKING LAYER (B) MUCOADHESIVE DRUG LAYER

TABLE 7: THICKNESS AND % DRUG CONTENT OF STABILITY SAMPLE F2

Stability sample	Stability period (days)	Thickness (mm)	% Drug content
F2	0	0.186 ± 0.006	92.77 ± 0.386
	30	0.20 ± 0.006	92.4 ± 0.430
	90	0.24 ± 0.010	91.44 ± 0.190

TABLE 8: *IN-VITRO* RELEASE STUDY OF STABILITY SAMPLE F2 IN PHOSPHATE BUFFER pH 6.8

Stability sample	Stability period (days)	%CDR at the end of 8 h
F2	0 days	94.95
	30 days	94.57
	90 days	93.13

TABLE 9: THICKNESS AND % DRUG CONTENT OF STABILITY SAMPLE F5

Stability sample	Stability period (days)	Thickness (mm)	% Drug content
F5	0	0.20 ± 0.010	94.26 ± 0.300
	30	0.25 ± 0.015	93.6 ± 0.490
	90	0.39 ± 0.034	92.74 ±0.052

TABLE 10: *IN-VITRO* RELEASE STUDY OF STABILITY SAMPLE F5 IN PHOSPHATE BUFFER PH 6.8

Stability Sample	Stability period (days)	% CDR at the end of 8 h
F5	0 days	91.4
	30 days	90.8
	90 days	90.6

No much variation was observed in the release date of the optimized formulations, *i.e.*, F2 and F5, on completion of the stability period of 30 and 90 days. It is evident from the data that the formulations are stable at the storage period and at stated conditions.

Stability in Human Saliva: Optimized formulations F2 and F5 were subjected to stability study in natural human saliva. Samples were analyzed for physical appearance, thickness, and drug content. The results are tabulated in the tables below. No much change was found in the results of stability samples from the previous results of the formulation. This indicates that the formulation is stable in human saliva. The results are tabulated in **Table 11** below.

TABLE 11: THICKNESS AND % DRUG CONTENT OF STABILITY SAMPLE F2 IN HUMAN SALIVA

Stability Sample	Stability period (h)	Thickness (mm)	% Drug content
F2	0	0.19 ± 0.000	92.41 ± 0.051
	1	0.213 ± 0.010	92.31 ± 0.017
	2	0.24 ± 0.011	92.23 ± 0.088
	4	0.253 ± 0.006	92.20 ± 0.130
	6	0.3066 ± 0.006	91.89 ± 0.057
	8	0.343 ± 0.006	92.23 ± 0.017

TABLE 12: THICKNESS AND % DRUG CONTENT OF STABILITY SAMPLE F5 IN HUMAN SALIVA

Stability sample	Stability period (h)	Thickness (mm)	% Drug content
F5	0	0.20 ± 0.010	94.38 ± 0.120
	1	0.343 ± 0.015	94.38 ± 0.020
	2	0.38 ± 0.006	94.4 ± 0.020
	4	0.39 ± 0.006	94.34 ± 0.009
	6	0.42 ± 0.026	94.08 ± 0.160
	8	0.45 ± 0.010	93.94 ± 0.064

CONCLUSION: A successful attempt was made to develop chitosan-based bilayered buccal patches of carvedilol using the solvent casting method in order to bypass the extensive first-pass metabolism

and increase the systemic bioavailability of the drug. PVP was incorporated in all the formulations to increase the film-forming properties. The formulation of the patches with two different drug loadings was possible. The prepared films evaluated for their physicochemical properties. The DSC and FT-IR data revealed no significant interaction between the drug and the polymers, indicating its compatibility with other ingredients. From the evaluatory tests performed, F2 and F5 were selected as the optimized film formulations as they gave the best results among all others.

The optimized formulations were subjected to *ex-vivo* permeability studies and stability studies. The stability studies were conducted at 40 ºC / 75% RH for 30 and 90 days as well as in natural human saliva, and the patches were found to be fairly stable at the stated conditions of storage.

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CONFLICTS OF INTEREST: Nil

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