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FORMULATION, DESIGN AND CHARACTERIZATION OF MUCOADHESIVE BUCCAL FILM OF NEBIVOLOL USING FACTORIAL DESIGN

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Keywords:

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ABSTRACT: The present investigation was to formulation and development of fast dissolving mucoadhesive buccal film of nebivolol by using solvent casting method. Nebivolol is a third-generation cardio selective β1-blocker undergoes extensive metabolism in the liver, gastrointestinal disturbance, abdominal pain after its oral administration and resulting in to a poor (10-12%) bioavailability. In order to improve the bioavailability, efficacy and to minimize the side effects associated with oral administration. Prepared mucoadhesive buccal films using HPMC E15 and PVP as mucoadhesive polymers. Among the two polymers used HPMC E15 showed an increased *in-vitro* residence time due to high mucoadhesive property. Mucoadhesive buccal films were evaluated by weight variation, thickness, folding endurance, pH, *in-vitro* disintegration, *in vitro* dissolution, tensile strength and drug content. In-vitro drug release study showed that more than 98.19 ± 0.02 % drug was released within 40 min. The tensile strength of formulation SW9 was found 50.00 N/mm^2. Folding endurance of formulation SW9 was found 149. The disintegration time for formulation SW1 was found to be 79.37 seconds and SW9 was 70.03 seconds respectively. Thus it can be concluded that the prepared formulation of buccal mucoadhesive film can be a novel treatment for myocardial infarction and angina pectoris.

INTRODUCTION: The buccal mucosa, along with other mucosal tissues, has been investigated as a potential site for controlled delivery of macromolecular therapeutic agents, such as peptides, proteins and polysaccharides because of its accessibility and low enzymatic activity compared to the gastro-intestinal tract [1 - 3]. The potential of the buccal mucosa as an alternative site for the delivery of drugs into the systemic circulation has recently received much attention.

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There are various reasons, why the buccal mucosa might be an attractive site for the delivery of therapeutic agents into the systemic circulation [4 - 6]. Due to the direct drainage of blood from the buccal epithelium into the internal jugular vein, the first-pass metabolism in the liver and intestine may be avoided. This first-pass effect is a major reason for the poor bioavailability of some compounds, when administered orally. Additionally, the mucosal lining the oral cavity is easily accessible, which ensures that a dosage form can be applied to the required site and removed easily in case of emergency.

The film is an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market, is easy to handle and administration, maintains a simple and convenient packaging, alleviates unpleasant taste, and is easy to

manufacture. The film is placed on the top or the floor of the tongue [7, 8]. It is retained at the site of application and rapidly releases the drug for local and systemic absorption [9]. Oral fast dissolving film is one such novel approach to increase consumer acceptance by virtue rapid dissolution, self administration without using water or chewing.

However, the fear of taking solid tablets and the risk of choking for certain patient populations still exist despite their short disintegration/dissolution times. The film overcome the danger/fear of choking[10]. The development of a fast-dissolving film also provides an opportunity for a line extension in the market place; a wide range of drugs (*e.g*., neuroleptics, cardiovascular drugs, analgesics, antihistamines, antiasthmatic and drugs for erectile dysfunction) can be considered suitable candidates for this drug delivery [11]. Drug delivery *via* the oral mucosa is a promising route, to achieve a rapid onset of action or improved bioavailability for drugs with high first-pass metabolism [12].

Thus, there is a growing interest in developing alternative dosage forms, *i.e*. orally fast disintegrating strip, which allow a rapidly dissolving drug to absorb directly into the systemic circulation through the oral mucosa [13]. These kinds of dosage forms are also convenient for children, elderly patients with swallowing difficulties, and in the absence of potable liquids. However, in addition to formulation considerations, the properties of the active compound have to be appropriate in order to achieve drug delivery into systemic circulation after intraoral administration.

Nebivolol is a third-generation β1selective blocker used in the treatment of hypertension, it works by relaxing blood vessels and slowing heart rate to improve blood flow and decrease blood pressure. Nebivolol on oral administration undergoes extensive metabolism in the liver resulting into very poor (10-12%) bioavailability [14, 15]. It can also cause gastrointestinal disturbance and abdominal or stomach pain *etc*.[16] In order to improve its bioavailability, efficacy and to minimize the side effects associated with oral administration, mucoadhesive buccal films of nebivolol using hydroxy propyl methyl cellulose and polyvinyl alcohol were prepared by solvent casting method in the present investigation.

MATERIALS AND METHODS:

Material: Nebivolol hydrochloride drug was procured from East West Pharmaceuticals Pvt. Ltd. Haridwar, Uttrakhand. HPMC E15 was obtained as a gift sample from Colorcon Asia Pvt. Ltd. Goa. Polyvinyl pyrolidone and citric acid was purchased from Molychem Pvt. Ltd. Mumbai, Propylene glycol was purchased from Loba chemie Pvt. Ltd. Mumbai. Tween 80, Mannitol and peppermint oil was purchased from Merck specialities Pvt. Ltd. Mumbai. All other chemicals were of analytical grade.

Methods:

Preparation of Fast Dissolving Film by Solvent Casting Method: Nebivolol mucoadhesive buccal films were prepared by using hydroxyl propyl methyl cellulose (HPMC) and PVP by solvent casting technique [17 - 19]. Water soluble polymers like HPMC E15 and PVP were dissolved in hot water up to 40 ºC to form a homogenous viscous mixture with simultaneous stirring at 1000 rpm.

Cool this viscous solution to room temperature. This was followed by addition of API (Nebivolol hydrochloride), plasticizer (propylene glycol) and other ingredients like mannitol, citric acid and flavour (peppermint oil) were also mixed and sonicated for 15 minutes untill the drug was completely dissolved.

Final film solution casting on a standard petridish for defoaming. It is dried in hot air oven at 40 ºC for 3 h. The film was carefully removed from the petridish, checked for any imperfections and cut into the required size to deliver the equivalent dose (2x2 cm^2) per strip [20, 21]. The samples were stored in desiccators at relative humidity 30-35 % until further analysis. Formulation of mucoadhesive fast dissolving buccal film shown in **Table 1**.

Experimental Design: A 3^2 factorial design was used 2 factors were evaluated, each at 3 levels, experimental batches were performed at all 9 possible combinations. The amount of HPMC E15 (X1) and PVP (X2) were selected as independent variables, whereas tensile strength, cumulative % drug release were selected as dependent variables [22, 23]. The data were subjected to 3-D response surface methodology in PCP Disso 2.08 to determine the effect of types and amount of

polymers on the various dependent variables. Full factorial experimental design layout was shown in **Table 3**. The values of variables in a 3^2 factorial design were indicated in **Table 2**.

TABLE 1: FORMULATION OF MUCOADHESIVE FAST DISSOLVING BUCCAL FILM

Components	SW_1	SW_2	SW_3	SW_4	SW_5	SW_6	SW_7	SW_8	SW_9
Nebivolol (mg)	40	40	40	40	40	40	40	40	40
HPMC E15(mg)	500	500	500	550	550	550	600	600	600
PVP(mg)	300	350	400	300	350	400	300	350	400
Propylene Glycol(ml)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Tween 80(ml)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Citric Acid (mg)	50	50	50	50	50	50	50	50	50
Mannitol(mg)	60	60	60	60	60	60	60	60	60
Peppermint oil	q.s.	q.s.	q.s	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water(ml)	10	10	10	10	10	10	10	10	10

TABLE 2: AMOUNT OF VARIABLES IN A FACTORIAL DESIGN

Variables	Low	Medium	High
HPMC E 15	500	550	600
PVP	300	350	400

TABLE 3: 3^2 FULL FACTORIAL EXPERIMENTAL DESIGN

Batch Code	HPMC E-15	PVP
	X1*	X2*
SW_1	-1 (500)	-1 (300)
SW_2	-1 (500)	0 (350)
SW_3	-1 (500)	+1 (400)
SW_4	0 (550)	-1 (300)
SW_5	0 (550)	0 (350)
SW_6	0 (550)	+1 (400)
SW_7	+1 (600)	-1 (300)
SW_8	+1 (600)	0 (350)
SW_9	+1 (600)	+1 (400)

*X_1 - Amount of HPMC E-15, *X_2 - Amount of PVP,

* -1, 0, +1 – Low, Medium and High amount of HPMC E-15 and PVP

A statistical model incorporating interactive and polynomial terms was used to calculate the responses.

$$Y=b0+b1X1+b2X2+b12X1X2+b11X1X1+b22X2X2+\epsilon \quad \ldots\ldots..1$$

Where, in equation (1), Y is the dependent variable,b0 is the arithmetic mean response of the 9 trials, and bi (b_1,b_2,b_{12},b_{11} and b_{22}) is the estimated coefficient for the corresponding factor Xi (X_1, X_2, X_1X_2, X_{12} and X_{22}, which represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the response changes when 2 factors are simultaneously changed. The polynomial terms (X_1X_1 and X_2X_2) are included to investigate the nonlinearity and ϵ indicates random error.

Characterization of Mucoadhesive Fast Dissolving Buccal Films: The prepared mucoadhesive buccal films characterized by weight variation of film briefly, the weight variation of films were evaluated; three films of every formulation weighed individually average weights were calculated. The thickness of film determined by, three films of each formulation were measured using vernier caliper (Mitutoyo, Japan) at three different places, and the mean value calculated [24]. Folding endurance were determined, three films of each formulation of required size are cut by using sharp blade. Folding endurance was to be determined by repeatedly folding the film ($2\times2cm^2$) at the same place, till it was broken. The number of times, the film could be folded at the same place without breaking gives the value of folding endurance [25]. The surface pH of film was determined by, dissolving one oral film in 10 ml distilled water and measuring the pH of the obtained solution [26].

Tensile strength test for mucoadhesive films was performed by using tensile strength apparatus. The strip of the patch (2×2 cm^2) was cut and holded between these two clamps. Weight was gradually increased on the pan, so as to increase the pulling force till the patch broke. The force required to

break the film was consider as a tensile strength and it was calculated as N/mm^2. Drug content uniformity of film determined by, five film strips (2×2 cm^2) were cut from the four corners and the central part of the molded film. Each film strip was placed in separate conical flask containing 100 ml of distilled water. The flasks were shaken in mechanical shaker for 2 hr. All the solutions were filtered and analyzed at 282 nm by using UV-Visible spectrophotometer. *In-vitro* disintegration test was performed by USP disintegration apparatus (Veego instrument corporation, Mumbai). Film sample (2×2 cm^2) of each batch was placed in 25 ml of simulated saliva. The disintegration time is the time when a film starts to break or disintegrate.

***In-vitro* Dissolution Studies:** The dissolution study was carried out using USP dissolution test apparatus II (paddle apparatus), 500 ml simulated saliva (pH 6.8) kept at 37 ± 0.5 ºC and stirred at 50 rpm. Film was cut into patch of (2×2 cm^2) size and immersed in vessel containing dissolution medium. 5 ml samples were withdrawn at 5, 10, 15, 20 and 40 min. time interval and filtered and analyzed by UV- visible spectrophotometrically at 282 nm.

Fourier Transform Infrared Spectroscopy (FTIR): Infrared spectrum of nebivolol hydrochloride was determined by using Fourier Transform Infrared Spectrophotometer (FTIR-4100, Shimadzu), KBr dispersion method. Infrared spectrums of pure drug and optimized batches were recorded. From the overlay spectrum analysis the compatibility of ingredients in the formulations was found out. Pure, completely dried KBr was used as blank and before running the sample.

Differential Scanning Calorimetry (DSC): Thermograms of physical mixture and optimized formulation were obtained using DSC (Pyris Diamond TG/DTA, Make-Perkin Elmer) equipped with an intracooler. Platinum crucible used with alpha alumina powder as reference to calibrate the DSC temperature and enthalpy scale. The powder samples of 2-10 mg were hermetically kept in the aluminium pan and heated at constant rate per 10 °C.

Stability Studies: For stability study, optimized formulation was kept for 30-90 days in stability chamber and samples were taken after 30 days and 90 days and analyzed for tensile Strength, Drug content and % drug release study for a period of 90 days at 40 °C ± 5 °C and 75 % RH.

RESULT AND DISCUSSION:

Fourier Transform Infrared Spectroscopy Study: FTIR studies revealed that the fundamental peaks of the nebivolol HCl are retained in physical mixture. Results showed that no any chemical interaction between nebivolol HCl and polymers used in the formulation hence; these can be used in the formulation of mucoadhesive fast dissolving film of nebivolol HCl. The FTIR spectrum of HPMC E 15 and PVP, Physical mixture are shown in **Fig. 1**. Fast dissolving mucoadhesive buccal film prepared by solvent casting method and characterized by various parameters.

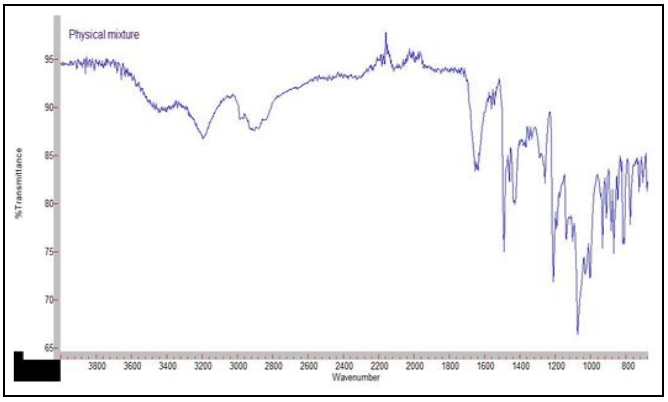

FIG. 1: FTIR SPECTRAL ANALYSIS OF PHYSICAL MIXTURE

Physical Evaluation of Film: The weight of polymer increases the weight of the film also increases. Weight of the films of batches SW1-SW9 was found in the range 92.08 -113.23 mg. The weight of the film was found of the SW1 formulation which was 92.08 mg and 113.23 mg of SW9 formulation shown in **Table 4**. Thickness of film, as polymer concentration increases, the thickness of the film also increases. Film thickness of formulation SW1-SW9 was found in the range 0.18-0.26 mm. Thickness of formulation SW9 was found to be 0.26 mm. The low values for standard deviation indicate physical uniformity of the film. The folding endurance measures the ability of film to withstand rupture. The folding endurance was measured manually and it was found to be as polymer concentration increases the folding endurance of the film also increases. The folding endurance of the film was found between 139-149, the results obtained shown in **Table 4**.

Folding endurance of formulation SW9 was found 149. The folding endurance values of the films were found to be optimum and therefore the films exhibited good physical and mechanical properties. The surface pH of the film was found in the range of 6.9-7.1 for all formulations, the results are shown in **Table 4**. Surface pH of formulation SW9 was found to be 7.0. The surface pH of all the films was within the range of salivary pH. No significant difference was found in surface pH of all formulations. The measured surface pH was found to be close to neutral in all the formulations, which means that they have less potential to irritate the buccal mucosa and therefore they should be fairly comfortable.

Tensile Strength Study: The tensile strength of the film was found between 11.90-50.00 N/mm^2. The tensile strength of formulation SW9 was found 50.00 N/mm^2. The result of tensile strength test is shown in table 4 and response surface plot is shown in **Fig. 2**. From the surface response plot, it is clearly indicates that there was increase in tensile strength with increase the amount of HPMC E15, this may be due to the hydrogen bonding in drug and polymer and also increase in tensile strength with increase in PVP in the polymer blend.

TABLE 4: EVALUATION OF FAST DISSOLVING MUCOADHESIVE BUCCAL FILM OF NEBIVOLOL

Batch code	Weight Variation (mg) *	Thickness (mm) *	Surface pH*	Folding Endurance*	Disintegration Time (sec) *	Drug Content*	Tensile Strength (N/mm^2) *
SW_1	92.08 ± 0.08	0.18 ± 0.05	7.0 ± 0.05	139 ± 0.5	79.37 ± 0.01	99.32 ± 1.42	11.90 ± 0.2
SW_2	93.11 ± 0.02	0.19 ± 0.01	6.9 ± 0.02	140 ± 0.5	78.03 ± 0.04	97.45 ± 0.93	16.06 ± 0.3
SW_3	94.25 ± 0.03	0.20 ±0.01	7.1 ± 0.01	142 ± 1.7	77.02 ± 0.03	99.58 ± 1.55	17.50 ± 0.2
SW_4	94.52 ± 0.03	0.22 ± 0.05	7.0 ± 0.05	144 ± 0.5	75.59 ± 0.005	99.27 ± 1.94	22.91 ± 0.05
SW_5	95.20 ± 0.02	0.23 ± 0.04	7.0 ± 0.02	145 ± 0.5	74.04 ± 0.04	97.59 ± 0.35	26.31 ± 0.05
SW_6	97.09 ± 0.02	0.24 ± 0.05	7.1 ± 0.01	146 ± 1.0	73.04 ± 0.07	99.33 ± 0.84	33.30 ± 0.10
SW_7	98.43 ± 0.01	0.25 ± 0.05	7.0 ± 0.05	147 ± 0.5	72.50 ± 0.01	98.45 ± 1.51	34.21 ± 0.10
SW_8	110.01 ± 0.01	0.25 ± 0.05	6.9 ± 0.01	148 ± 1.1	71.02 ± 0.02	99.12 ± 0.74	36.36 ± 0.20
SW_9	113.23 ± 0.03	0.26 ± 0.08	7.0 ± 0.05	149 ± 0.5	70.03 ± 0.05	99.86 ± 1.64	50.00 ± 0.20

*mean ± S.D. n = 3

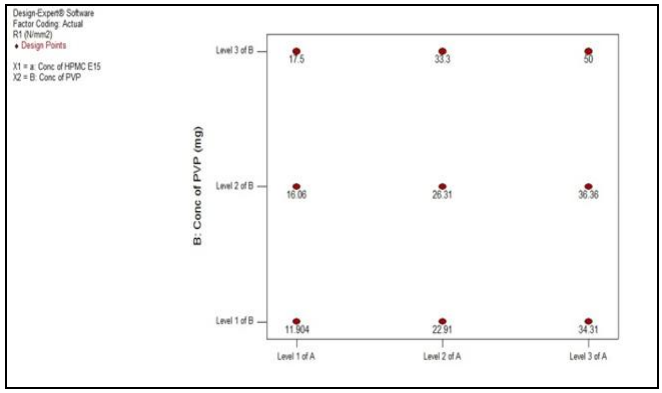

FIG. 2: CONTOUR PLOT OF TENSILE STRENGTH

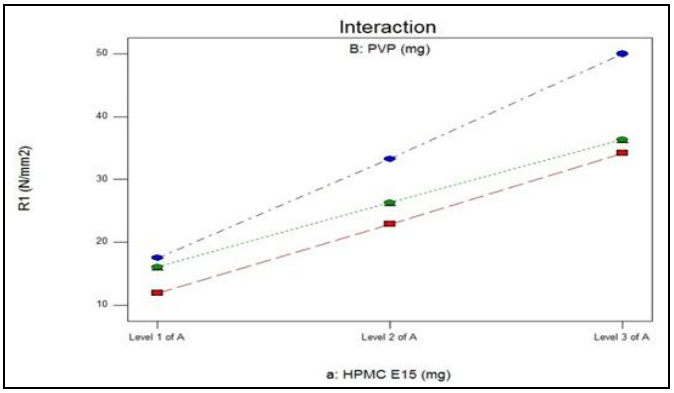

FIG. 3: INTERACTION PLOT OF TENSILE STRENGTH

There are two independent variables plotted against each other. Contour plot of HPMC E 15 and PVP shows that the maximum concentration of HPMC E 15 and PVP increases the tensile strength. In an interaction plot of tensile strength shown in **Fig. 3**, there are dependent variables plotted against independent variables. There are three lines shown these lines represents there is non-significant interaction between HPMC E15 and PVP. It indicates that two independent variables show individual effect on tensile strength. Drug content of all batches were within the range between to be 96.60 to 99.25 %, which shown in **Table 4**. The drug content of formulation SW9 was found to be 99.86 %. It was much closer to 100 % means there is no any loss of drug during the preparation of the film. Disintegration time was found in the range of 70.03 to 79.37 seconds shown in **Table 4**. The disintegration time for formulation SW1 was found to be 79.37 seconds and SW9 was 70.03 seconds respectively.

***In-vitro* Drug Release Studies:** The % cumulative release of drug is shown in **Table 5** and **Fig. 4**. HPMC E15 initially absorbs water and form gel. From the result obtained that % drug release for

first 5 minutes was around approximately 50% (average of SW1-SW9). For formulation SW1-SW3, which contains 500 mg HPMC E15, the drug release in first 5 minutes was found increases from 47.06 % to 49.56 %. The same results obtained for the SW4-SW6 (contains 550 mg HPMC E 15) and SW7-SW9 (contains 600 mg HPMC E 15) with drug release 49.98 % to 50.87 % and 50.98 % to 52.98 %. For the complete release of drug, which was found within 40 min. As these formulations contain increased concentration of HPMC E15 *i.e.* 500 mg, 550 mg and 600 mg for SW1, SW4 and SW7 respectively, drug release was increased. From the results obtained on comparison, as the concentration of HPMC E15 increases the percent drug release increases. Initially there was rapid release of drug from the film as shown in **Fig. 4**. This rapid drug release (burst effect) from mucoadhesive film might be due to rapid dissolution of the surface drug.

TABLE 5: REGRESSION COEFFICIENTS OF SW_1-SW_9 BATCHES

Batch code	Zero order	First order	Matrix	Peppas	Hix. Crowel
SW_1	0.7484	0.9288	0.966	0.9352	0.9308
SW_2	0.7483	0.9273	0.9673	0.9408	0.9316
SW_3	0.7429	0.9189	0.9705	0.9582	0.9296
SW_4	0.7484	0.9118	0.9713	0.9566	0.9301
SW_5	0.7027	0.8549	0.955	0.9366	0.8884
SW_6	0.6991	0.8490	0.9498	0.9295	0.8867
SW_7	0.6998	0.8476	0.9535	0.9308	0.8870
SW_8	0.7305	0.8507	0.9591	0.9314	0.9040
SW_9	0.7304	0.8523	0.9586	0.9285	0.9072

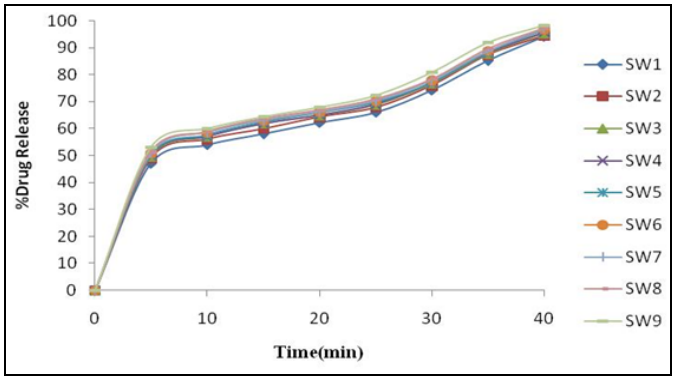

FIG. 4: % CUMULATIVE DRUG RELEASE OF ALL BATCHES

It is well known that the addition of hydrophilic component to an insoluble film former leads to enhance its release rate. This may be due to dissolution of the aqueous soluble fraction of the film, which leads to creation of pores and decrease of mean diffusion path length of the drug molecule to be released. When matrix film comes into contact with a dissolution fluid, the fluid is absorbed into the polymer matrix and this initiates polymer chain dissolution process in the matrix.

In fast dissolving oral films the release kinetics of finest formulations, was best fitted in Higuchi matrix kinetics. It means the drug release follows the linear kinetic process. From the dissolution studies results indicates that, formulation SW9 was showing better drug release than other batch formulations. Hence, formulation SW9 was considered as the optimized formulation, regression coefficients of SW1-SW9 batches shown in **Table 5**.

In contour plot **Fig. 5**, two independent variables plotted against each other. Contour plot of HPMC

E 15 and PVP shows that the maximum concentration of HPMC E 15 and PVP increases the percent drug release. In an interaction plot of percent drug release shown in **Fig. 6**. There are three lines shown these lines represents there is non-significant interaction between HPMC E 15 and PVP. It indicates that two independent variables showing individual effect on percent drug release.

Surface response plot of Tensile strength: The b_0 = 25.74 which is the arithmetic mean of all nine trials batches. The positive X_1 coefficient indicates that as the concentration of X_1 increase there is increase in the tensile strength. The positive X_2 coefficient indicates that as the concentration of X_2 increase, the tensile strength increase. The negative X_1X_1 coefficient indicates that as the concentration of X_1 when multiplied there is negative effect on tensile strength. The positive term X_2X_2 indicates when quantity of X_2 multiplied there is positive effect on tensile strength, which is seen in the response surface plot.

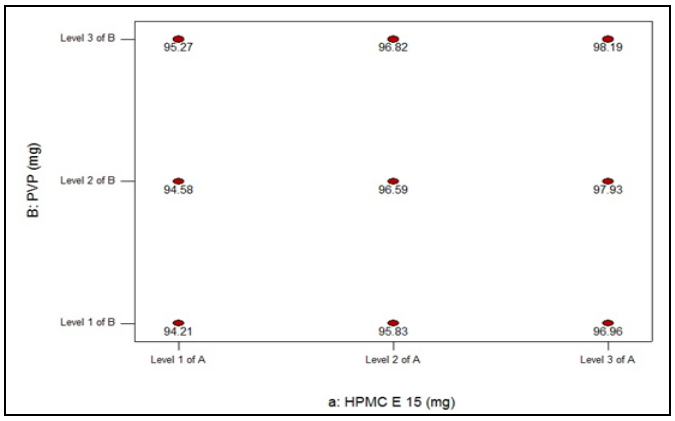

FIG. 5: CONTOUR PLOT OF % DRUG RELEASE

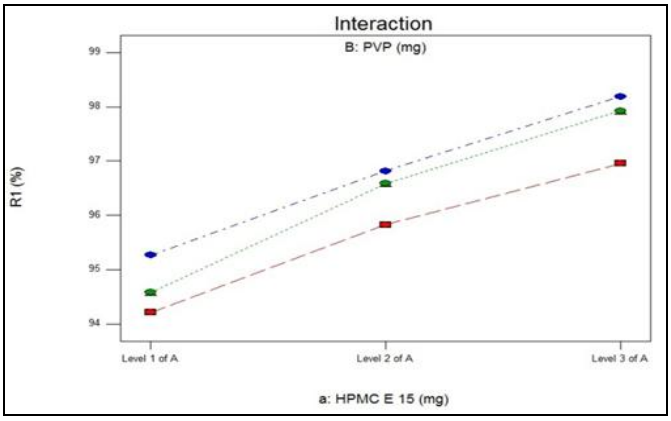

FIG. 6: INTERACTION PLOT OF % DRUG RELEASE

The positive X1X2 coefficient indicates positive effect on tensile strength, which is seen in the response surface plot **Fig. 7**.

$Y_1 = 25.74+12.22X_1+5.29X_2 - 0.124X_1X_1+ 2.64 X_2X_2+1.74X_1X_2$ ...1

Surface Response Plot of % Drug Release: The $b_0 = 96.50$ which is the arithmetic mean of all nine trials batches. The positive X_1 coefficient indicates that as the concentration of X_1 increase there is increase in the percent drug release. The positive X_2 coefficient indicates that as the concentration of X_2 increase, the percent drug release also increase.

The negative X_1X_1 coefficient indicates that as the concentration of X_1 when multiplied there is negative effect on percent drug release. The positive term X_2X_2 indicates when X_2 multiplied positive effect on percent drug release, which is seen in the response surface plot. The positive X_1X_2 coefficient indicates positive effect on percent drug release, which is seen in the response surface plot **Fig. 8**.

$Y_2=96.50+1.49X_1+0.54X_2 - 0.23X_1X_1+ 0.13X_2X_2+ 0.068X_1X_2$ 2

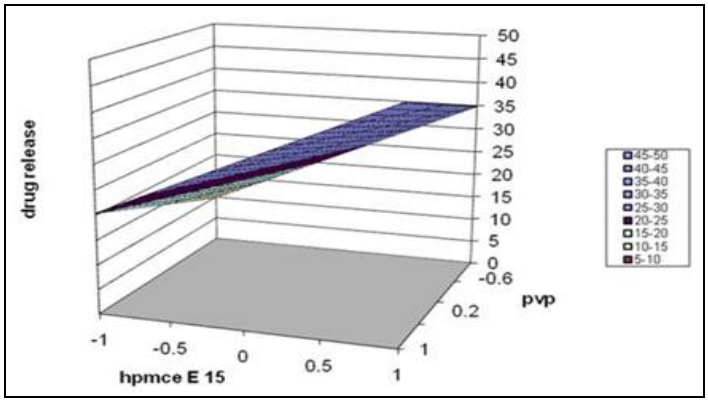

FIG. 7: RESPONSE SURFACE PLOT FOR TENSILE STRENGTH

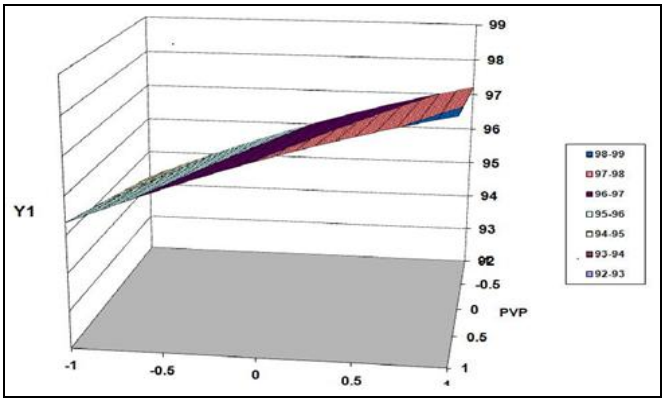

FIG. 8: SURFACE RESPONSE PLOT OF CUMULATIVE DRUG RELEASE

Fourier Transform Infrared Spectroscopy (FTIR): The spectrum of pure nebivolol HCl and optimized batch SW_9 shows characteristic peaks at 1073 cm^{-1} (ether stretch); 3187 cm^{-1}(N-H bend, secondary amines); 1212 cm^{-1} (C-F stretch, aryl fluoride); 1430 cm^{-1} (C=C stretch, aromatic group) and 3138 cm^{-1} (O-H stretch). Principle peaks were found in the range corresponding to functional group. Overlain spectrums of pure drug (Nebivolol HCl) and optimized batch SW_9 were shown in **Fig. 10**. FTIR studies revealed that the fundamental peaks of the nebivolol HCl are retained in physical mixture. The results showed that no chemical interaction between nebivolol HCl and polymers used in the formulation, hence; it can be used in the formulation of fast dissolving film of nebivolol HCl. The spectrum shows all prominent peaks of nebivolol HCl. The FT-IR spectrum of nebivolol HCl is shown in **Fig. 9**.

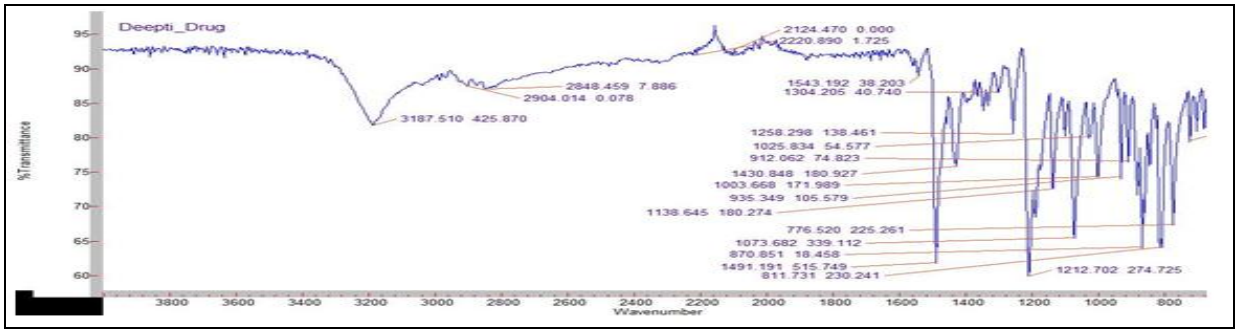

FIG. 9: FTIR SPECTRUM OF NEBIVOLOL

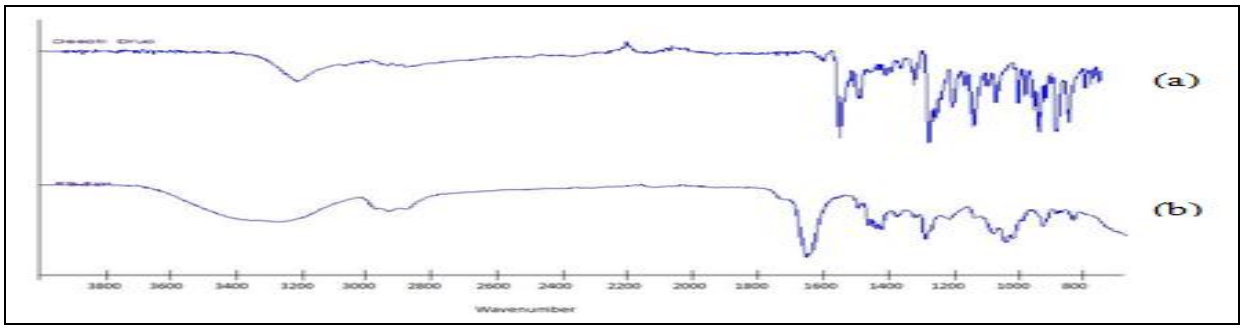

FIG. 10: OVERLAIN OF FTIR OF (a) NEBIVOLOL (b) OPTIMIZED BATCH

Differential Scanning Calorimetry (DSC): From DSC study it was concluded that, the pure drug nebivolol gives rise to a sharp endothermic peak that corresponds to melting at 228 ºC indicating its crystalline nature. In DSC of the formulation, broaden the endothermic peak of 225 ºC was found to be shifted left at 3 ºC. The DSC results revealed that no interaction between the drug and the used polymers occurred as there was only shift, no specific change in the melting endothermic peak. Thermograms of the nebivolol HCl and Optimized Batch (SW9) are shown in the **Fig. 11**.

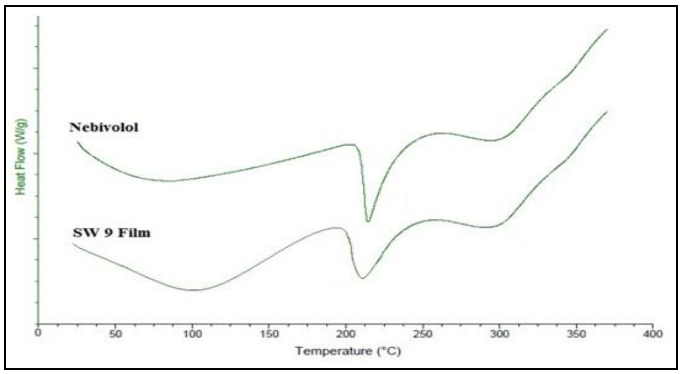

FIG. 11: OVERLAIN OF DSC OF NEBIVOLOL AND OPTIMIZED BATCH

Stability Studies: For stability study, formulation batch SW9 was kept for 30-90 days in stability chamber and samples were taken after 30 days and 90 days and analyzed for tensile strength, drug content and percent drug release after 40 min, which shows slight changes as shown in **Table 6**. The stability studies indicates that the formulation batch SW9 was stable for a period of 90 days at 40°C ± 5 °C and 75 % RH.

TABLE 6: EVALUATION OF OPTIMIZED FORMULATION SW9 FOR STABILITY

Parameters	Time period *		
	Before	After 30 days	After 90 Days
Tensile strength (N/mm^2)	50.00 ± 0.2	50.00 ± 0.1	50.00 ± 0.05
% Drug release	98.19 ± 0.02	98.17 ± 0.02	98.16 ± 0.03
Drug content (%)	98.25 ± 0.02	98.23 ± 0.02	98.23 ± 0.04

*mean ± S.D. n = 3

CONCLUSION: The present work was successfully prepared fast dissolving mucoadhesive buccal film of nebivolol by using solvent casting method. These prepared fast dissolving mucoadhesive buccal film of nebivolol fulfills the need of present work with improve the bioavailability and therapeutic efficacy of drug; avoid first pass effect and side effects associated with high dose of drug. All the formulations possessed the good mucoadhesion, and they were free from irritation and released the drug completely by diffusion mechanism. Thus it can be concluded that the prepared formulation of buccal mucoadhesive film can be a novel treatment for heart diseases such as myocardial infraction and angina pectoris.

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