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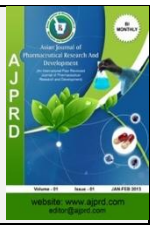

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Research Article

Formulation Development and Evaluation of Mucoadhesive Buccal Tablets of Acebutolol Hydrochloride

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ABSTRACT

A mucoadhesive drug delivery system is an oral dosage form, where the tablet, gel, or patch is attached to the buccal region for direct absorption of the drug into blood circulation. This dosage form has been employed to improve the bioavailability of drugs that undergoes significant hepatic first-pass metabolism. Acebutolol is a beta sympatholytic agent used to treat high blood pressure and irregular heartbeat (arrhythmia). Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. In present investigation, mucoadhesive buccal tablets of acebutolol HCl were prepared using carbopol 940 in varying concentrations with secondary polymer xanthan gum by direct compression method. Nine batches were prepared as per 3^2 factorial designs, to investigate the combined effects of independent variables namely carbopol 940 and xanthan gum on dependant variables namely swelling index, mucoadhesion strength and in-vitro drug release using design expert software version 8.0.7.1. Preformulation studies confirmed the identity and purity of the drug by means of UV spectroscopy, IR spectroscopy, DSC analysis, and melting point determination. The tablets were evaluated for hardness, thickness, weight variation, friability, and drug content concluded that all these parameters were in an acceptable range of pharmacopoeial specification. The buccal tablets were studied for surface pH, swelling index, in vitro drug release study, adhesion force, in vitro mucoadhesive strength, stability, and compatibility study to optimise the formula. Amongst all factorial batches (F1 to F9), batch F5 (30 mg carbopol 940 and 30 mg xanthan gum) showed maximum drug release of 99.96 % after 12 hr of study and also showed better contact with biological membrane. The drug release kinetics of batch F5 was found to be best fitted to zero order kinetic model and exhibited anomalous diffusion release mechanism. The formulation F5 exhibited good correlation (R2=0.992) for in-vitro drug release. All the evaluation parameters give positive results and comply with the standards. Stability studies were carried out on the developed formulations indicating that the formulations were stable during the period of 6 months. In conclusion, the formulation F5 is stable and effective for quick action and seems to be alternative to the conventional tablet.

Keyword: Acebutolol, Mucoadhesive, Buccal, Polymer, Swelling Index

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INTRODUCTION

Mucoadhesive drug delivery gives rapid absorption and good bioavailability due to its considerable surface area and high blood flow. Drug delivery across the mucosa bypasses the first-pass hepatic metabolism and avoiding the degradation of gastrointestinal enzymes. The mucoadhesive ability of a dosage form is dependent upon a variety of factors, including the nature of the mucosal tissue and the physicochemical properties of the polymeric formulation.[1] Buccal mucosa is one of such mucosal site which has a high extent of vascularization and enables direct drain of blood flow into the jugular vein, which helps to

avoid the possible first-pass metabolism and the excessive degradation by the gastrointestinal environment. There are four effective regions for drug administration into the oral cavity: cheek, palate, sublingual and gingival.[2] Buccal administration refers to the release of drugs into or through the buccal mucosa, in which the formulation sits between the cheek and the gum, providing local and/or systemic effects. The buccal delivery thus implies the absorption of medication through the mucosal lining of the buccal cavity. Easier drug administration, the possibility of prompt termination in the condition of unpredicted side effects and emergencies, the possibility of incorporating enzyme inhibitor/permeation enhancer, etc. are other major advantages of this drug delivery system.[3,4]

Various mucoadhesive polymers (natural, semi-synthetic, and synthetic) used in this delivery system become adhesive on hydration[5], therefore can be used for targeting a drug to a particular region of the body. Initially, when the mucoadhesive product is in contact with the mucosal membrane, it swells and spreads, initializing deep contact with the mucosal layer and then mucoadhesive polymers are activated by the presence of moisture and drug releases slowly.[6]

Acebutolol is a cardio selective beta-1 blocker and has intrinsic sympathetic activity. It is most commonly used for the treatment of hypertension, arrhythmias, angina pectoris and acute myocardial infarction in high-risk patients. It is 2-acetyl-4-(butanoyl amino) phenyl ether, slightly soluble in water, methanol and highly permeable. It is characterized as a biopharmaceutical classification system (BCS) class III drug.[7,8] It is low protein-bound (26%) and possesses a short biological half-life of 3 to 4 h. The usual dose of acebutolol is 400 mg per day.[9]The conventional dosage form of acebutolol leads to a lot of inconvenience and fluctuations in therapy, with some adverse effects like gastrointestinal disturbances, hypotension, bradycardia, heart failure and hepatotoxicity. Thus, devising sustained-release medication is a good alternative for reducing its dosing frequency, for prolonged effect with improved bioavailability, while also improving safety and efficacy of the medication.[10,11] This study was designed to formulate the different batches of mucoadhesive acebutolol tablets by using different polymers like carbopol 940 and xanthan gum along with their quality control evaluation.

MATERIALS AND METHODS

Drug and chemicals

Acebutolol hydrochloride was received as a gift sample from Cipla Laboratories Ltd, Goa. Xanthan gum and Carbopol 940 received from Blue Cross Laboratory Pvt Ltd, Nashik. All the other chemicals used throughout the study were of analytical grade, and purchased from S D Fine Chem Ltd, Mumbai (MS, India).

Instruments

IR Spectrophotometer (MIT-Shimadzu, Japan), UV Visible Spectrophotometer V630 (Jasco Analítica, Spain), Dissolution apparatus (Electrolab India Pvt Ltd, Mumbai), Differential Scanning calorimeter (MIT-Shimadzu, Japan), Stability chamber (TI710, TEMPO Instrument Pvt Ltd, Mumbai), Tablet punching machine (Karnavati 10-station rotary machine, Mahesana, Gujarat, India)

Preformulation study

Micrometritics properties like bulk density, tapped density, angle of repose, compressibility index and Hausner'sratio were done to check flow ability of powder blend. Solubility of drug in various solvents like water, ethanol, pH 6.8 phosphate buffer. Identification of drug was carried out by using UV spectroscopy, FTIR and DSC. Drug excipients compatibility studies was done by using FTIR and DSC.

Melting point

The melting point of acebutolol HCl was determined by using melting point apparatus and capillary method. For determination of melting point, drug was taken in a glass capillary whose one end was sealed by flame. The capillary containing drug was dipped in liquid paraffin inside the melting point apparatus (Omega scientific industries India) and temperature was increased gradually.[12] Melting point was noted and reported.

Bulk density

Bulk density is the ratio of total mass of powder to the bulk volume of powder. It was determined by placing the accurately weighed 2g of powder blend placed in a 10ml graduated measuring cylinder and the total volume was noted. This total volume is called as bulk volume. Bulk density was calculated by using following formula.[13]

Bulk Density = Total Weight of powder/Total volume of powder

Average of three bulk densities of powder were taken and tabulated. (n = 3)

Tapped density

Tapped density is the ratio of total mass of powder to the tapped volume. The tapped density was obtained by dividing the mass of powder by the tapped volume in cm3. The powder blend carefully introduced into graduated measuring cylinder. The cylinder was tapped on surface 100 times from a height of 1 inch. After tapping volume was noted. Tapped density was calculated by using following formula[14]

Tapped density = Mass of powder/ Tapped volume of powder

Average of three bulk densities of powder were taken and tabulated. (n = 3)

Compressibility Index

It helps in measuring the force requires to break the friction between the particles and hopper. The flow property of a powder can be easily measured with the help of compressibility. It is expressed in percentage. Compressibility index was determined by placing the powder in a measuring cylinder and the volume (V0) was noted before tapping. After 100 tapings again volume (V) was noticed.

Compressibility Index = (1- V/ V0) x 100

Where,

V_0 = volume of powder before tapping.

V = volume of powder after 100 tapings.

Average of three compressibility index were taken and tabulated. (n = 3)

Hausner'sratio

It is the ratio of tapped density to bulk density. Hausner's ratio is an ease of powder flow; it is calculated by following formula.[15]

Hausner's ratio = Tapped density / Bulk density

Angle of repose (°θ)

Angle of repose is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane. The friction force in a loose powder can be measured by the angle of repose (θ). It is an indicative of the properties of the powder. Angle of repose was determined by measuring the height and radius of the heap of the powder bed. A cut stem funnel was fixed to a stand and bottom of the funnel was fixed at a height of 3 cm from the plane. Powder was placed in the funnel and allowed to flow freely. With the help of Vernier calipers the height and radius of the heap were measured and noted.[16] Average of triplicate reading were noted (n =3).

TAN θ = h/r

Where,

θ = is the angle of repose

h = height of heap of powder/granule blend in cm. r = radius of heap of powder/granule blend in cm.

Ultraviolet Visible spectrophotometric study

Determination of λ_{max} in pH 6.8 phosphate buffer

The UV spectrum of acebutolol HCl was obtained using UV Jasco V630. Acebutolol HCl (100 mg) was accurately weighed and transferred to 100 ml volumetric flask. It was dissolved in 10 ml of ethanol and diluted up to 100 ml with pH 6.8 phosphate buffer. The above made solution was further diluted to obtain concentration ranging from 5-25µg/ml. The resulting solution was scanned from 200-400 nm and the spectrum was recorded to obtain the value of maximum wavelength.

Preparation of calibration curve in pH 6.8 phosphate buffer

Acebutolol HCl (100 mg) was accurately weighed and transferred to 100 ml volumetric flask. It was then dissolved in 10 ml of ethanol and diluted up to 100 ml with pH 6.8 phosphate buffer. The above made solution was further diluted to obtain concentration ranging from 5-25µg/ml. The absorbance of the resulting solutions was recorded at 234 nm using UV-visible spectrophotometer. pH 6.8 phosphate buffer was taken as a blank. Calibration plots were constructed and the linearity was established. Calibration curve was performed in triplicate.[17,18]

Compatibility study

Fourier Transform infrared spectroscopy

Compatibility study was carried out by using Fourier transform infrared spectrophotometer (BRUKER OPUS 7.5). FTIR study was carried on pure drug and physical mixture of drug and polymers. Physical mixtures were prepared and samples kept for 1 month at 40^0C. The infrared absorption spectrum of acebutolol HCl and physical mixture of drug and polymers was recorded with the wave number 4000 to 400 cm^{-1}.[19,20]

Differential scanning calorimetric studies

Thermal analysis was performed using a differential scanning calorimeter equipped with a computerized data station. The sample of pure drug, physical mixture of drug and polymer were weighed and heated at a scanning rate of 10°C/min between 40 and 200°C and 40 ml/min of nitrogen flow. The differential scanning colorimetric analysis gives an idea about the interaction of various materials at different temperatures. It is also allows us to study the possible degradation of the material.[21]

Preparation of mucoadhesive buccal tablet

Mucoadhesive buccal tablets of acebutolol HCl were prepared by direct compression technique using xanthan gum and carbopol 940 polymers with varying concentration. All the ingredients as mention in table 1 were weighed accurately and passed through sieve no.120 and blended thoroughly to obtain uniform mixing. Before tablets preparation, the mixture blends of all the formulations were subjected for compatibility studies (IR and DSC). The blended powder was evaluated for its pre-compression characteristics and then compressed on 10 station pilot press using 8 mm flat faced punches. The machine was adjusted to produce an approximate weight of 200 mg tablet.[22]

Table 1: Composition of formulations

Ingredients	Formulation code								
	F1	F2	F3	F	F5	F6	F7	F8	F9 (mg)
Acebutolol HCl	50	50	50	5	50	50	50	50	50
Xanthan gum	20	30	40	2	30	40	20	30	40
Carbopol 940	20	20	20	3	30	30	40	40	40
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Mannitol	20	20	20	2	20	20	20	20	20
Spray dried lactose	86	76	66	8	76	66	86	76	66
Total	20	20	200	2	200	20	200	200	200

Evaluation of mucoadhesive buccal tablets

Hardness[23]

The tablets were evaluated for their hardness using Pfizer hardness tester. Hardness of tablet is expressed in kg/cm^2. Average of three reading were taken and tabulated. (n = 3)

Thickness[24]

The tablets were evaluated for their thickness using vernier calipers. Average of three readings was taken and the results were tabulated. (n = 3)

Friability

The friability test for tablets was performed to measure the effect of abrasion and shocks. Roche friabilator was used for the tablets. This device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Pre-weighed sample of 6 tablets was placed in the friabilator and where subjected to the 100 revolutions i.e. 4 minutes. Then the tablets were removed and de-dusted and reweighed. The weight loss should not less than 1.0%. Percentage friability (% F) was calculated by using following formula.[25]

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight} \times 100}{\text{Initial weight}}$$

Weight variation test

The weight variation test was performed as per Indian Pharmacopoeia. 20 tablets were taken and weighed individually. Average weight was calculated standard deviation was computed.

Drug content uniformity

From each batch three randomly selected tablets were weighed accurately and powdered in a glass mortar with pestle. Powder equivalent to 10 mg of drug was transferred into 10 ml volumetric flask containing 10 ml of pH 6.8 phosphate buffer and kept aside with constant shaking for 24 h to extract the total drug present in the tablet. Then the solution was filtered and the volume was made with pH 6.8 phosphate buffer and analyzed for drug content at λ_{max} of 250 nm against drug devoid phosphate buffer as blank. Averages of triplicate readings were taken. The content of drug was calculated using standard graph.[25]

Surface pH

Three tablets were allowed to swell for four hour in simulated saliva fluid of pH 6.75. pH was found out by placing the electrode of pH meter just in contact with the surface of the tablets. Average of three readings was computed.[26-28]

Swelling studies

Preparation of simulated saliva solution

Weigh accurately 2.38g of disodium hydrogen phosphate, 0.19g potassium dihydrogen phosphate, 8.00g sodium chloride and dissolve in 1000 ml of distilled water to produce simulated saliva solution; finally adjusted the pH with phosphoric acid to 6.75.

Percentage swelling index [29-31]

Three tablets were weighed individually (W1) and immersed in a petri dishes containing simulated saliva fluid (pH 6.75) for predetermined times (1, 2, up to 12 hr). After immersion tablets were wiped off by the excess surface water by the use of filter paper and weighed (W2). The % swelling index was calculated by:

% Swelling Index = [W2- W1] / W1 x 100

Where, W1 is the initial weight of the tablet and W2 is the weight of the tablet after the particular swelling time interval.

Determination of in-vitro Mucoadhesion Strength of Tablet Formulations

Measurement of adhesion force

In vitro bioadhesion studies were conducted using modified bioadhesion test assembly described by Gupta et al.[32]Goat cheek pouch was obtained commercially; the cheek pouch was collected into a sterile container containing sterile buffer solution of pH 6.75. The cheek pouch brought was stored in a

refrigerator until use. The following procedure was used for all the test formulations using the fabricated equipment. The cheek pouch was removed from refrigerator and allowed to attain equilibrium with ambient conditions in the laboratory. The goat cheek pouch was carefully excised, without removing connective and adipose tissue and washed with simulated saliva solution. The tissue was stored in fresh simulated saliva solution pH 6.75. Immediately afterwards the membrane was placed over the surface of lower Teflon cylinder (B) and secured. This assembly was placed into beaker containing simulated saliva solution pH 6.75 at 37 ± 2°C. From each batch, one tablet at a time was taken and stuck to the lower surface of Teflon cylinder with a standard cyanoacrylate adhesive. The beaker containing mucosal tissue secured upon lower cylinder (B), was manipulated over the base of the balance so that, the mucosal tissue is exactly below the upper cylinder (A). The exposed part of the tablet was wetted with a drop of simulated saliva solution, and then a weight of 20 gm was placed above the expanded cap, left for 10 minutes. After which the tablet binds with mucin. The weight was removed. Then slowly and gradually weights were added on the right side pan till the tablet separates from the mucosal surface/ membrane. The weight required for complete detachment is noted (W1) (W1-5.25gm) gives force required for detachment expressed in weight in grams. Procedure was repeated for two more tablets. Average was computed and recorded. (n=3)[33-36]

In-vitro dissolution studies

The drug release profile was studied using USP dissolution testing apparatus II using a paddle at 50 rpm. 500 ml dissolution fluid, pH 6.8 phosphate buffer, was used and a temperature of 37±0.5°C was maintained. The oral mucoadhesive tablet was attached to glass disk with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. 5ml of aliquots were withdrawn at 0.25, 0.5, 1h, 2h, 3h, 4h, 5h, 6h, 7h, 8h, 9h, 10h, 11h, 12hr respectively and the same volume was replaced with pH 6.8 phosphate buffer. Absorbance was measured at λmax 234 nm and from which percentage of drug release was calculated using calibration curve. The procedure was repeated for three more tablets similarly and average was computed. To analyze the in vitro release data various kinetic models were used to describe the release kinetics.[37] Zero order kinetic model- Cumulative % drug released versus time.[38]First order kinetic model- Log cumulative percent drug remaining versus time.[39]Higuchi's model- Cumulative percent drug released versus square root of time.[40] Korsmeyer equation/Peppa's model- Log cumulative % drug released versus log time.[41]

Stability study

Stability studies were conducted to test the physical and chemical stability of the tablet at different stability conditions. The optimized formulations F5 were subjected to stability studies. These tablets were subjected for a period of three months as per ICH guideline at the 40^0C temperature and relative humidity 75% RH. The samples were withdrawn at 1, 2, 3 and 6 month for given temperature condition. The formulations were evaluated mainly for drug content and percentage drug release at the predetermined intervals.[42]

Compatibility Study

Fourier Transform Infrared Spectroscopy (FTIR) analysis

FT-IR spectroscopy analysis was conducted to investigate any interaction between acebutolol hydrochloride, carbopol 940, xanthan gum, and other tablet excipients. For this purpose, IR spectra of the pure drug, polymers, and tablets were obtained in the range of 4,000–400 cm^{-1} with 4 cm−1 resolutions by using an FT-IR spectrometer equipped with OPUS 7.5 software. The system was operated in transmission mode.[43,44]

Differential Scanning Calorimetric (DSC) analysis

DSC analysis was conducted on acebutolol hydrochloride, carbopol 940, xanthan gum, and buccal tablets by using a differential scanning calorimeter (Mettler Toledo). Valuable information could thus be obtained to have an opinion on the crystal order of RIS and interactions between tablet ingredients. Briefly, 5mg of sample was weighed into the aluminum pan and heated from 40°C to 200°C with a heating rate of 10°C/min under 40 mL/min N2 flow.[45] From the obtained thermograms, onset and melting points of the peaks were detected by the Pyris v11 software (Pelkin Elmer).

RESULT AND DISSCUSION

Preformulation study of drug

Identification and Characterization of the Drug

Organoleptic property

It is white to off-white, crystalline powder complying with the description given in the literature.

Melting point

Melting point of the drug matches with the melting point given in the literature, melting point of acebutolol HCl is shown in the table 2.

Table 2: Melting point of acebutolol HCl against reported value

Parameter	Standard value	Observed value
Melting Point	141-142^{0}C	141-143^{0}C

Solubility

Acebutolol HCl was found to be freely soluble in water, soluble in ethanol and pH 6.8 phosphate buffer

Ultra Violate – Visible spectroscopy study

Determination of λ_{max} of acebutolol HCl in pH 6.8 phosphate buffer

After studying the UV spectra of acebutolol HCl, it was found that drug shows maximum absorbance at 234nm when solution (100 µg/ml) is prepared in methanol: pH 6.8 phosphate buffer (1:9). λ_{max} of acebutolol HCl in pH 6.8 phosphate buffer is shown in Figure no.1. Solutions of acebutolol HCl prepared in pH 6.8 phosphate buffer and scanned between 200-400 nm using UV Spectrometer which showed peak at 234 nm.

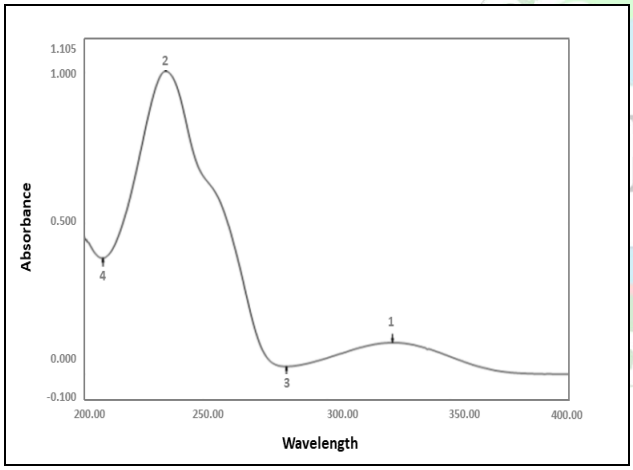

Figure 1: UV-visible spectrum of acebutolol HCl in pH 6.8 phosphate buffer

Calibration curve of acebutolol HCl in pH 6.8 phosphate buffer

The calibration curve (Fig.2) was found to be linear in the concentration range of 5-25 µg/ml (Table 3) having coefficient of regression value R^2 =0.999 and Slope y = 0.034x

Table 3: Absorbance's of different concentration of acebutolol HCl in pH 6.8 phosphate buffer

Sr. No.	Concentration (µg/ml)	Absorbance
1.	5	0.172
2.	10	0.348
3.	15	0.514
4.	20	0.679
5.	25	0.865

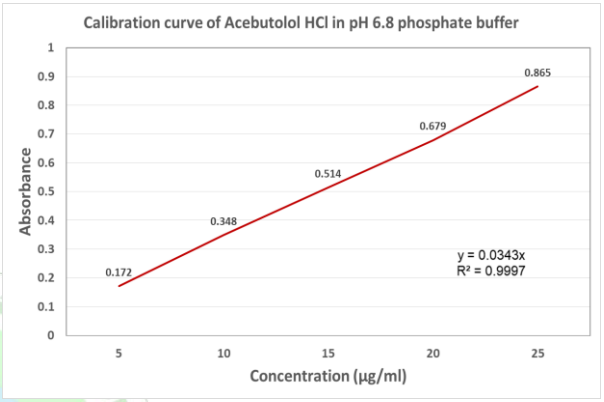

Figure 2: Calibration curve of acebutolol HCl in pH 6.8 phosphate buffer

Evaluation of Pre-compressional characteristics of mucoadhesive tablet formulation

The acebutolol HCl mucoadhesive buccal tablets were prepared by direct compression. Ingredients were accurately weighed, grounded and passed through mesh # 120 and then thoroughly blended with talc and magnesium stearate before compression. The powder blend was studied for rheological characteristics. The uniformly blend of powder was then compressed in a 10 station tablet punching machine using 8 mm flat faced punches. Before compression powder bed of all formulations were studied for various rheological characteristics bulk density, true density, compressibility index, Hausner's ratio and angle of repose. The results of the studies indicated that the powder bed is easily compressible, and hence can be compressed into a compact mass of tablet (table 4). The angle of repose is an indicative parameter of powder flowability from hopper to die cavity. A repose angle between 25^0 to 30^0 indicates excellent flowability of powder bed. In this work, the angle of repose was found to be varying between 27.43º and 29.32º when glidants were incorporated. These studies indicated that, the powder beds of all formulations are easily flowable.

Table 4: Pre-compressional characteristics of all tablet formulations

Formulation code	Angle of repose(θ) Mean± S.D.	Bulk density (gm/cm^3) Mean± S.D.	Tapped density (gm/cm^3) Mean± S.D.	Compressibility index (%) Mean± S.D.	Hausner's ratio Mean± S.D.
F1	29.93±0.668	0.3560±0.0023	0.4160±0.002	14.67±0.50	1.169±0.003
F2	30.52±0.652	0.3654±0.0027	0.4237±0.002	13.74±0.371	1.159±0.01
F3	29.17±0.454	0.3721±0.0016	0.4086±0.009	8.702±0.30	1.096±0.004
F4	25.76±0.538	0.3866±0.0025	0.4366±0.001	11.44±0.163	1.129±0.002
F5	27.95±0.647	0.3810±0.0031	0.4440±0.003	14.11±0.7941	1.163±0.001
F6	26.80±0.527	0.3650±0.0072	0.4322±0.004	12.19±0.633	1.184±0.031
F7	28.12±0.728	0.3790±0.0054	0.4601±0.005	14.20±0.85	1.20±0.010
F8	26.28±0.713	0.3754±0.0021	0.4048±0.003	7.250±0.178	1.058±0.003
F9	28.07±0.731	0.3820±0.0030	0.449±0.005	15.0±0.508	1.178±0.006

Evaluation of mucoadhesive buccal tablet of acebutolol HCl

Hardness of the tablets varied between 3.42 ± 0.02 Kg/cm^2 and 4.81 ± 0.01 Kg/cm^2 indicating good binding and satisfactory strength of tablets to withstand stress during transportation and also may offer good adhesion to mucosa. The thickness of all batches was found to be 2.73 to 2.99 mm. All the tablets showed % friability in the range of 0.403% to 0.719 % which was within the limit. Drug content uniformity ranged from 90.84 ± 0.49 % to 95.88 ± 0.60 %. No variations in weight of tablets as all tablets were found to be within the range limit for weight variation. The surface pH of all the mucoadhesive tablet formulations was found to be uniform, consistent between 6.3 to 6.8 indicating that all the formulations provide an acceptable pH in the range of salivary pH (5.5 to 7.0). All the physical parameters are found in the acceptable limit. The evaluations are depicted in table 5.

Table 5: Physical characteristics of formulation F1 to F9

Formulation code	Hardness(kg/cm^2)	Thickness (mm)	Weight variation (mg)	% Drug content	Surface pH	Friability %
F1	3.73±0.01	2.82±0.01	198.6±1.1	90.84±0.49	6.3±0.2	0.719±0.03
F2	4.30±0.02	2.92±0.02	197±1.5	93.66±0.5	6.5±0.40	0.687±0.02
F3	4.11±0.01	2.95±0.08	196±1.0	92.95±0.60	6.8±0.15	0.517±0.03
F4	3.42±0.02	2.73±0.02	195±1.3	95.06±0.70	6.6±0.14	0.451±0.02
F5	4.69±0.01	2.92±0.01	196±1.5	91.89±0.50	6.6±0.15	0.476±0.03
F6	4.58±0.01	2.89±0.04	198±1.2	94.48±0.61	6.5±0.011	0.403±0.04
F7	4.81±0.01	2.99±0.02	197±1.5	91.19±0.70	6.7±0.058	0.563±0.03
F8	4.21±0.02	2.92±0.04	196±1.5	93.42±0.61	6.8±0.057	0.438±0.03
F9	3.84±0.02	2.81±0.02	198±1.7	95.88±0.60	6.7±0.057	0.441±0.03

(* Mean of three values ± S.D)

Swelling study

The swelling index of mucoadhesive buccal tablets of acebutolol HCl for a period of 12 hr shown in table 6. The water uptake nature of the polymer is one of the important properties that affect the onset of swelling. Swelling has been increases with increase in amount of xanthan gum or carbopol940. Maximum swelling was attained at 12 hr.

Table 6: Swelling study for acebutolol HCl

Time in hours	Formulation code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0.25	18.65	16.65	17.88	18.84	17.45	18.05	15.36	16.36	17.59
0.5	27.62	29.62	28.56	27.96	31.37	30.12	28.87	27.87	30.27
1	32.99	43.99	44.26	38.27	36.77	35.17	32.92	30.92	36.37
2	49.87	58.87	57.6	50.43	50.16	49.48	44.32	43.32	49.05
4	60.41	63.41	65.17	62.99	63.84	65.87	55.84	53.84	62.05
8	70.36	72.36	74.47	76.34	78.34	80.04	68.05	65.05	69.24
12	82.56	83.56	84.89	85.25	89.25	92.85	81.96	84.96	87.23

Mucoadhesive strength

It was found that, all the tablet formulations possess adequate bioadhesion. Xanthan gum and carbopol 940 influences the bioadhesion strength irrespective of the polymer used. Also, bioadhesion is found to be increasing with increase in amount of polymers used. (table 7)

Table 7: Mucoadhesive strength

Sr. No	Formulation code	Mucoadhesive strength (N)
1	F1	0.0673±0.03
2	F2	0.1011±0.010
3	F3	0.1268±0.070
4	F4	0.0699±0.025
5	F5	0.1555±0.020
6	F6	0.1420±0.010
7	F7	0.1188±0.015
8	F8	0.1112±0.025
9	F9	0.1680±0.01

In-vitro drug dissolution study

Present study was aimed to develop buccal tablets of acebutolol HCl with modified release for 12 h in order to maintain steady plasma concentration for longer period of time. Also, release of 10-20% of drug within first hour would help in the maintaining of minimum effective concentration quickly and avoid the use of loading dose in the formulation. The cumulative percentage drug release of the buccal tablets prepared with various polymers was determined and the comparative profiles are presented in Table 8 and Figure 3. Amongst all formulation F5 showed maximum drug release of 99.96 % after 12 h of study and also showed better contact with biological membrane.

Drug release studies clearly observed the identifiable differences in the release behavior of all buccal tablet formulations. With increase in concentration of polymers retardation in drug release takes place, which clearly indicate the release rate controlling behavior of carbopol 940. When tablets containing swellable polymers like xanthan gum and carbopol 940 are exposed to dissolution medium, tablet surface becomes wet and hydrated to form a gel layer. The overall drug release from these tablets was governed by hydration, gel layer formation and drug diffusion into gel layer and to the dissolution medium.

Table 8: *In-vitro* Drug released study formulation of F1 to F9

Time in hr	Cumulative % drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.25	24.17	12.37	10.37	10.37	12.37	4.02	2.42	2.02	2.42
0.5	44.67	16.82	14.82	14.82	17.82	6.02	4.75	4.02	4.75
1	47.20	21.18	18.18	18.18	22.18	7.01	6.01	7.01	6.01
2	55.78	28.02	21.02	21.02	29.02	9.5	8.63	8.15	8.5
3	64.86	34.75	27.75	27.75	38.75	11.25	10.25	11.25	10.25
4	72.73	42.66	32.66	32.66	50.66	16.14	21.14	14.14	14
5	79.13	45.89	36.89	36.89	54.89	21.72	31.72	21.72	19.72
6	84.19	52.38	48.38	48.38	57.38	33.56	37.56	28.56	25.56
7	92.23	55.99	54.99	54.99	64.99	39.06	43.06	36.06	38.06
8	97.82	64.26	62.26	62.26	68.26	45.07	46.07	48.07	46.07
9	99.90	72.82	70.82	70.82	76.82	51.82	49.82	52.82	49.82
10		79.3	74.3	74.3	84.3	57.56	58.56	56.46	54.56
11		86.7	80.87	80.87	94.76	61.79	62.79	61.79	60.79
12		88.68	82.68	82.68	99.96	68.46	76.46	63.46	62.46

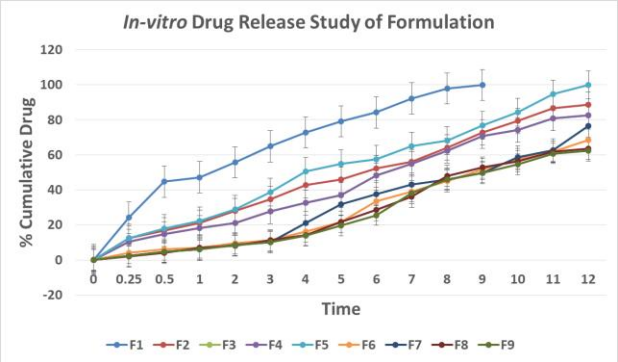

Figure 3: In-vitro drug release of formulations F1 to F9

Kinetics of drug release

In the present study, the drug released was analyzed to study the kinetics of drug released mechanism. The result showed that the factorial design batches followed zero order, first order model kinetics, Higuchi and Connor's model kinetics and Korsemeyer'sPeppas model kinetics.

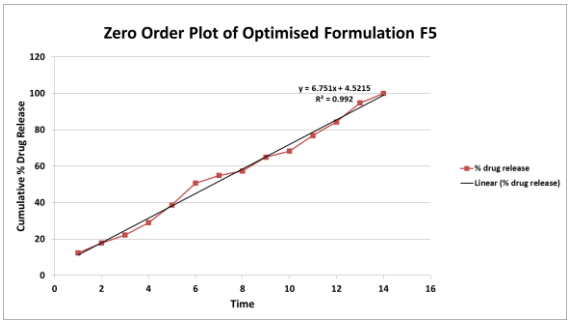

Figure 4: Zero order release kinetics of optimized formulation F5

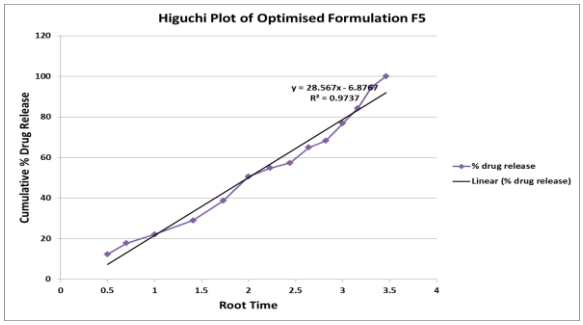

Figure 6: Higuchi model kinetics of optimized formulation F5

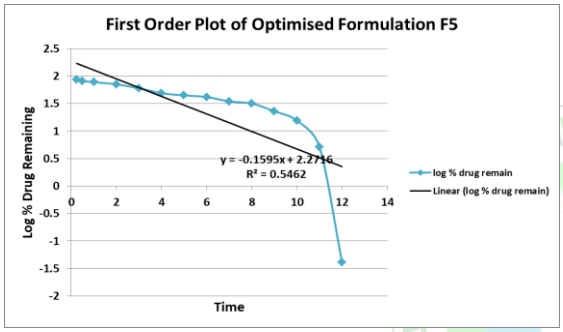

Figure 5: First order model kinetics of optimized formulation F5

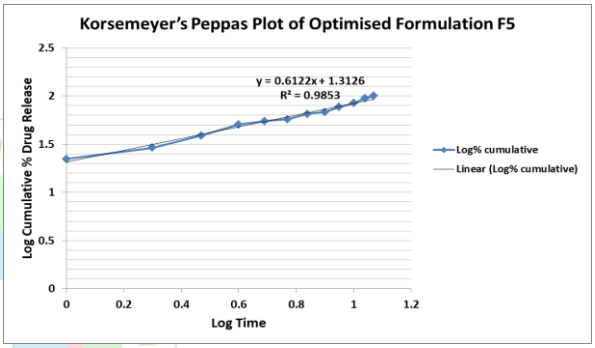

Figure 7: Korsemeyer'sPeppas model kinetics

Table 9: Release kinetics and correlation coefficients (R2) optimized formulation (F5)

Time hr)	% cumulative drug release	log% cumulative drug release	log time	log % drug remaining	Root time
0.25	12.37	1.0923697	-0.6	1.94	0.5
0.5	17.82	1.2509077	-0.3	1.91	0.7
1	22.18	1.345961542	0	1.89	1
2	29.02	1.462697408	0.3	1.85	1.41
3	38.75	1.588271707	0.47	1.78	1.73
4	50.66	1.704665185	0.6	1.69	2
5	54.89	1.739493231	0.69	1.65	2.23
6	57.38	1.758760544	0.77	1.62	2.44
7	64.99	1.812846537	0.84	1.54	2.64
8	68.26	1.834166284	0.9	1.5	2.82
9	76.82	1.885474303	0.95	1.36	3
10	84.3	1.925827575	1	1.19	3.16
11	94.76	1.976625052	1.04	0.71	3.31
12	99.96	1.999826247	1.07	-1.39	3.46

Stability study

The stability study for optimized formulation F5 was conducted at 40^0 C, 75% RH as per ICH guideline as shown in table No.10. From the data obtained it can be inferred that there was no change in physical parameters of the buccal tablets. Also, the tablets did not show any significant loss in their drug content, mucoadhesive strength and percent drug release at 12 hr. Therefore it was ascertained that, the mucoadhesive buccal tablets of acebutolol HCl could be stored for a period of at least 2 years.

Table 10: Stability study for optimized formulation F5 at 400C + 75% RH

Frequency of testing	Drug content (% ± S.D.)	Mucoadhesive strength (gm± S.D.)	% Drug release at 12 h (% ± S.D.)
	Formulation F5		
0	98.68±0.26	26.61±1.02	99.10±1.75
8 days	98.12±0.10	27.12±1.23	98.20±0.99
15 days	99.52±0.25	26.10±1.12	99.74±1.74
1 month	98.25±0.10	27.00±0.98	100.45±1.35
2 months	98.56±0.56	27.10±1.04	99.12±2.15
3 months	99.02±0.45	26.31±1.12	99.46±1.14
6 months	98.12±0.22	26.52±1.00	98.51±2.11

Drug analysis and compatibility study

Fourier Transform Infrared Spectroscopy (FTIR) analysis

The IR spectrum of acebutolol HCl was obtained after scanning in the wavelength 400-4000 cm^{-1} is shown in figure no.8. The IR spectrum of acebutolol HCl shows characteristics peaks. The absorption band show by acebutolol HCl is characteristics of functional group present in its molecular structure above. The presence of absorption band corresponding to the functional group present in the structure of acebutolol HCl conform identification of functional group.

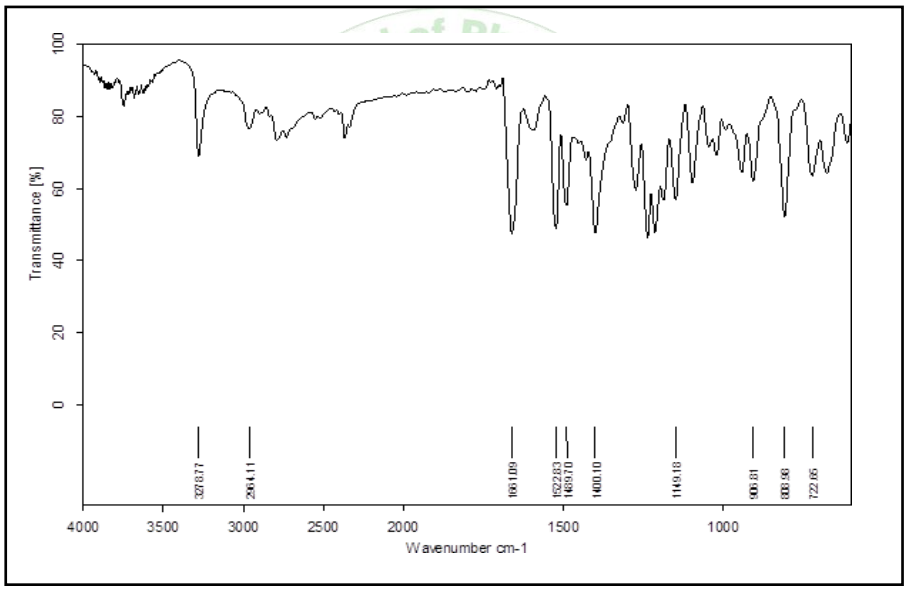

Figure 8: IR spectra of drug acebutolol HCl

Table 11: IR Interpretation of acebutolol HCl

Sr. No.	Functional group	Standard frequency cm-1	Obtained frequency cm-1
1	C-H Stretch	3100-3300	3278.12
2	N-H Stretch	2500-3000	2964.12
3	C=O Stretch	1600-1750	1661.12
4	N-H Bending	1400-1600	1522.23
5	O-H Bending	1400-1550	1489.63

Drug and excipients compatibility study

The characteristic absorption peaks of drug and excipients are correlates with each other. Drug-polymer mixture indicates that there is no prominent chemical reaction between drug and polymer mixture. It indicates that drug was compatible with excipients.

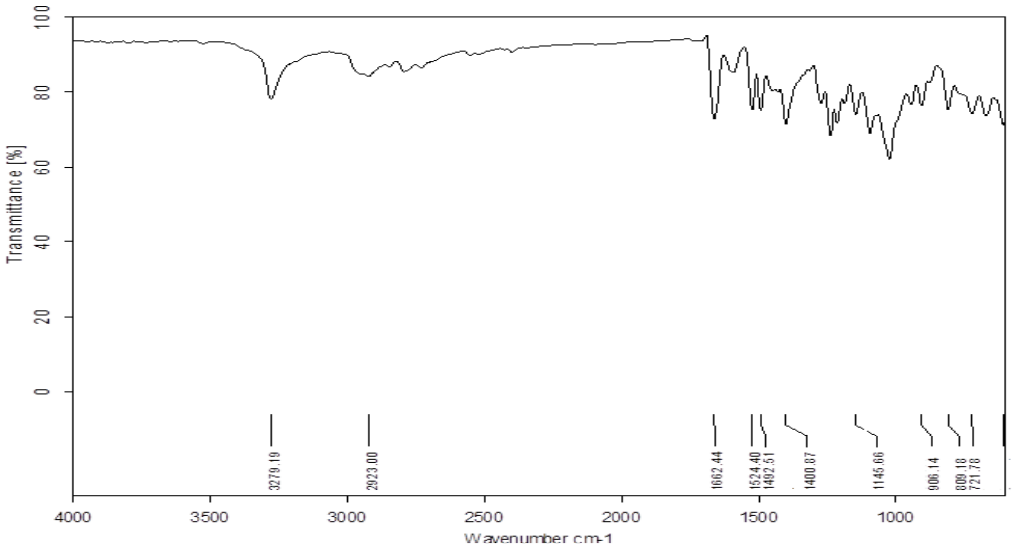

Figure 9: IR spectra of physical mixture of drug and polymers

Table 12: Ranges of functional group present in the IR spectrum of drug and polymer

Sr. No.	Functional group	Standard frequency cm^{-1}	Observed Frequency cm^{-1}	
			Pure Drug	Drug &Polymers Physical mixture
1	C-H Stretch	3100-3300	3278.12	3279.19
2	N-H Stretch	2500-3000	2964.12	2924.52
3	C=O Stretch	1600-1750	1661.12	1662.42
4	N-H Bending	1400-1600	1522.23	1524.56
5	O-H Bending	1400-1550	1489.63	1495.52

Differential Scanning Calorimetry (DSC)Analysis

The thermal behavior of acebutolol HCl was studied using DSC thermogram. The DSC thermogram of acebutolol HCl exhibited an endothermic peak at 139^0C.

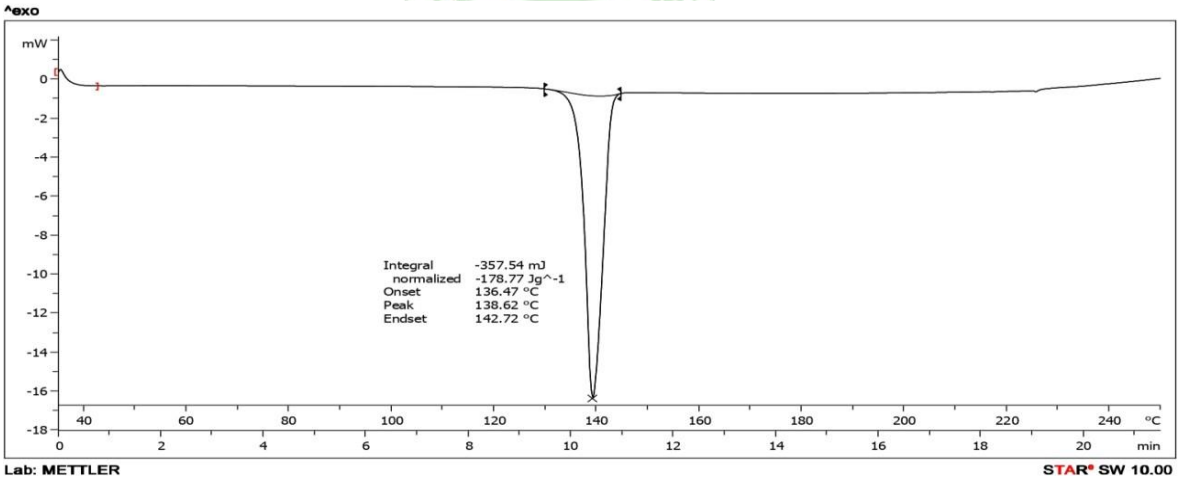

Figure 10: DSC thermogram of acebutolol HCl

Drug and Excipients compatibility study

The DSC thermogram of acebutolol HCl exhibited an endothermic peak at 139^0C and physical mixture exhibited characteristic peak at 141.21^0C. DSC analysis was performed for pure acebutolol HCl and physical mixtures of drug with various excipients. Melting endotherm of drugs was well preserved in most of the cases. For physical mixtures, in all the cases melting endotherm of drug was well preserved with little or no change in enthalpy value of drug indicating compatibility of both drugs with selected excipients in the study. The polymers xanthan gum and Carbopol 940 have been reported to be compatible with a number of drugs.

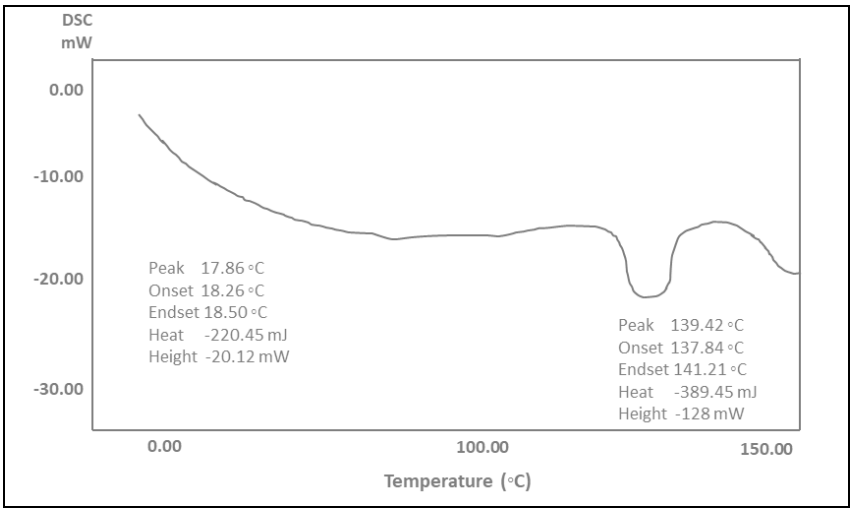

Figure 11: DSC Thermograms of physical mixture of acebutolol HCl and polymers

CONCLUSION

From the present study carried out on of acebutolol HCl mucoadhesive buccal tablet using by direct compression method, the following conclusion can be drawn. The study of rheological characteristics indicated that all the powder beds are free flowing and compressible. Compressional characteristics were uniform for all the formulations. The hardness of all formulation was found in between 4 to 5. Drug content of all the formulations were found to be more than 95% and were fairly uniform, reproducible and consistent. The pH of all mucoadhesive formulation was in between 6 to 7. *In vitro* drug release results of all the formulations were conducted for 12 hr which indicated that, tablet formulations, F1- F9 were found to be diffusion. The formulation F5 was taken as an optimized batch on the basis of *in vitro* dissolution study. Amongst all formulation F5 batch showed maximum drug release of 99.96 % after 12 hr of study and also showed better contact with biological membrane. Stability studies were conducted at 40^0C and 75 % RH showed that there is no decrease in the drug content for the period of 6 months.

Our main aimed developed mucoadhesive buccal tablet of acebutolol HCl to improve the bioavailability of the drug undergoing significant hepatic first-pass metabolism. Cost effective mucoadhesive buccal tablet by direct compression to release the drug in buccalcavity for extended period of time in order to avoid first-pass metabolism for improvement in bioavailability, to reduce the dosing frequency and to improve the patient compliance. Hence it is concluded that formulation F5 is a stable and effective for quick action and it is alternative to the conventional tablet.

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