ejpmr, 2015,2(5), 1819-1839

SJIF Impact Factor 2.026

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 3294-3211

EJPMR

FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF LABETALOL HYDROCHLORIDE

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Article Received on 18/08/2015 **Article Revised on 10/09/2015** **Article Accepted on 03/10/2015**

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ABSTRACT

The present study was aimed to formulate and evaluate nine prototype formulations (Viz.: F1 to F9) of Labetalol hydrochloride mucoadhesive buccal tablets using various concentrations of mucoadhesive polymers such as HPMC K4M, Locust bean gum and Tara gum, individually and in combination by direct compression method. Objective of the study is to achieve prolonged drug release and improve the bioavailability by avoidance of first-pass hepatic metabolism. Prepared buccal tablets were comparatively evaluated for their physicochemical parameters like weight variation, hardness, friability and drug content. The surface pH, swelling index, bio-adhesive strength are also carried out which has been important aspect for success of mucoadhesive buccal tablets. FTIR studies showed no evidence on interactions between drug and polymers. The swelling of all the formulations was increased as the time proceeds. The in vitro drug release of Labetalol hydrochloride was performed under sink conditions (Phosphate buffer pH 6.8, 37±0.5ºC, 50rpm) using type II dissolution apparatus for 12hrs. Formulation F5 (Combination of HPMC K4M and Tara gum at 25%w/w concentration) is considered as optimized formulation with the best *in vitro* drug release and high bio-adhesive strength i.e. 52.74% and 15g respectively. Mathematical treatment of the *in vitro* drug release data suggests that, all the formulations fitted into first order release kinetics. Drug release from the matrix occurred by combination of two mechanisms, diffusion of drug from tablet matrix and anamolous transport, which was reflected from Higuchi's model and Korsmeyer peppas equation.

KEYWORDS: Labetalol hydrochloride, HPMC K4M, Locust bean gum, Tara gum, Mucoadhesive buccal tablets.

INTRODUCTION

Buccal drug delivery is an alternative route for the oral administration of drugs which undergo degradation in the gastrointestinal track or hepatic first pass metabolism.[1] Buccal delivery is the administration of drugs through the mucosal membrane lining the cheeks. Buccal route provides one of the potential routes for typically large, hydrophilic and unstable proteins, oligonucleotides and polysaccharides as well as conventional small molecules. Buccal mucosa is less permeable and is thus not able to elicit a rapid onset of absorption. After absorption, drug is transported through the deep lingual vein or facial vein which then drains into the general circulation via the jugular vein, bypassing the liver and thereby sparing the drug from first-pass metabolism. Buccal drug delivery offers a safer mode of drug delivery system and the dosage form can be removed in case of toxicity.[2]

Labetalol hydrochloride is a selective α- and nonselective β-adrenergic blocking agent. It is used in management of hypertension, alone or in combination with other classes of antihypertensive agents. The half-life of Labetalol hydrochloride is approximately 4-6 hours. Labetalol hydrochloride has a dosage of 300 mg twice daily initially. For maintenance, manufacturer recommends a usual dosage of 200–400 mg twice daily. When administered such frequently, dose related side effects like nausea, dizziness, somnolence are even more due to fluctuations in the plasma drug concentration levels. Because of high frequency of administration and short biological half-life with low plasma protein binding, Labetalol hydrochloride is an ideal drug for designing a mucoadhesive buccal tablet for buccal delivery. Prolonged release of the drug and increased bioavailability leads to the significant reduction in the dose and hence dose related side effects.

Hence, in the present study an attempt was made to formulate mucoadhesive buccal tablets of labetalol hydrochloride to ensure satisfactory drug release in oral cavity with the use of optimum polymers and thereby to avoid first-pass metabolism and prolong duration of action. So, that it can retain in oral cavity for desired duration and localize the dosage form in a specific region and control the release rate of drug. In the present study, the mucoadhesive buccal tablets of labetalol hydrochloride were formulated using the polymers HPMC K4M, Locust bean gum and Tara gum, individually and in combination. The *in vitro* swelling index, *in vitro* bio-adhesive strength, *in vitro* drug release characteristics and kinetics of the prepared

formulations were studied. The kinetics of the dissolution process was studied by the application of four kinetic models to the dissolution data namely, the zero-order, the first-order, the Higuchi-square root, Korsmeyer-Peppas equation.

MATERIALS AND METHODS

Labetalol hydrochloride was received as a gift sample from Hospira Pharmaceuticals Pvt. Ltd, Visakhapatnam, India. Microcrystalline cellulose was obtained from Indian research products, Chennai. Magnesium stearate and talc were obtained from Sd. fine chemicals Ltd, Mumbai. Locust bean gum was obtained from Lbg. Sicilia Natural gums and Tara gum was obtained from Merck Specialties Pvt. Ltd, Mumbai.

Identification of drug sample

Labetalol hydrochloride was scanned in UV range from 200-400 nm in phosphate buffer pH 6.8 using Elico SL150 UV-Visible Spectrophotometer.

METHOD

An UV-VIS spectrophotometric method was used for the estimation of Labetalol Hydrochloride. A stock solution of Labetalol Hydrochloride was prepared in methanol and the absorbance was measured at 302nm using UV-VIS spectrophotometer. As the dissolution studies were carried out in 6.8pH buffer the calibration curves were constructed in this media.

Preparation of stock solution

10 mg of Labetalol hydrochloride was accurately weighed and transferred in to a 10 mL volumetric flask containing few mL of methanol. The drug was dissolved initially in few mL of methanol and later made up to 10 ml with methanol to prepare mg/mL solution.

Preparation of Buffer solution

0.2M potassium di hydrogen phosphate (250mL) was added with 0.2M sodium hydroxide solution (224ml) and the volume was adjusted to 1000mL.

Development of calibration curve

For the estimation of Labetalol Hydrochloride, the stock solution was subsequently diluted with distilled water to get a series of dilutions containing 5, 10, 15, 20, 25 µg/mL of solution and measured the absorbance at 302 nm (UV-VIS spectrophotometer) against a blank which was phosphate buffer pH 6.8. Standard curve between concentration and absorbance was plotted and intercept (B) and slope (K) values were noted.

Reproducibility of the method

Reproducibility of the method was tested by analyzing six individually weighed samples of Labetalol Hydrochloride. The relative standard deviation (RSD) in the estimated absorbance values was less than 1%. These low RSD values indicated the reproducibility of the analytical method.

Solubility determination

Solubility studies were performed according to the method described by Higuchi and Connors. The solubility of the Labetalol was determined in various solvents (0.1N HCl, 6.8pH and 4.0pH buffers) by adding an excess amount of drug to 10 ml of solvent in 25ml stoppered conical flasks. The flasks were kept at 25± 0.5ºC on a rotary flask shaker for 72 hours to reach equilibrium. The equilibrated samples were removed from the shaker and centrifuged at 4000 rpm for 15 minutes. The supernatant was taken and filtered immediately using a 0.45µ nylon disc filter. The filtered samples were diluted suitably and assayed for drug measuring absorbance at 302 nm using a UV-visible spectrophotometer. Shaking was continued until three constructive estimations were same. The solubility experiments were run in triplicate.

Pre-compression studies

Drug excipient Compatibility study

I.R spectroscopy can be used to investigate and predict any physiochemical interaction between different excipients. Infrared spectra matching approach was used for detection of any possible chemical interaction between the drug and polymer.

Fourier Transform Infrared spectroscopy (FT-IR)

Samples were analyzed using an ATR-FTIR spectrometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000-500 cm^{-1} at a resolution of 1.0 cm^{-1}. The powder or film sample is simply placed onto the ATR crystal and the sample spectrum is collected. The sample is then cleaned from the crystal surface and the accessory is ready to collect additional spectra. ATR analysis is less complicated than using KBr pellets, it is fast and a very small amount of the sample is needed.

Angle of Repose

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement

between particles. This is the maximum angle possible between surface of pile of powder or granules and horizontal plane. The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel (2-4cm) was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. Angle of repose was determined by measuring the height of the cone of powder and radius of the heap of the powder. The angle of repose was calculated using the following equation.

$$\text{Tan } \Theta = h/r$$

$$\Theta = \text{Tan}^{-1} h/r$$

Where, θ = angle of repose,

h = height of the cone,

r = radius.

Bulk density ($D_{b)}$

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/mL and is given by

$$D_t = M/V_0$$

Where, M is the mass of powder,

V_0 is the Bulk volume of the powder.

Tapped density ($D_{t)}$

Tapped density was determined by using graduated cylinder. An accurately weighed sample was carefully added to the graduated cylinder with the aid of funnel. The initial volume was noted and the sample was tapped on a horizontal base. Tapping was continued until no further reduction in sample volume was observed. Volume was noted and tapped density is calculated by using the following formula.

$$D_t = M/V_0$$

Where, M is the mass of powder,

V_0 is the Bulk volume of the powder.

Carr's Index (I)

It indicates the ease with which a material can be induced to flow and powder compressibility. It is expressed in percentage and is given by

$$I= (D_t-D_b/D_t \times 100$$

Where, D_t is the tapped density of the powder

D_b is the bulk density of the powder.

Compressibility Index

In recent years the compressibility index and the closely related Hausner's ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of the bulk density, size, shape, surface area, moisture content and cohesiveness of the materials. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of the powder.

Compressibility Index = $(1-V/V_0) \times 100$

Where, V = volume of powder blend before tap

V_0 = volume of powder blend after 100 tappings.

Hausner's ratio (H)

It is a number that is correlated to the flow ability of a powder. The Hausner's ratio is related to the Carr's Index by the formula

H = 100/ (100-C)

Hausner's ratio also expressed as,

$H = D_t / D_b$ (or) Hausner's ratio = tapped density/ bulk density

Total Porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of the powder blend (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces, V).

Formulation of labetalol hydrochloride mucoadhesive buccal tablets

Mucoadhesive tablets of labetalol hydrochloride were prepared by direct compression technique using different grades of polymer with varying concentrations. Labetalol hydrochloride mucoadhesive buccal tablets were prepared using mucoadhesive polymers such as HPMC K4M, Locust bean gum and Tara gum. Microcrystalline cellulose (MCC) was used as direct compressible vehicle, talc and magnesium stearate as lubricant and glidants respectively. Formulae used for development of labetalol hydrochloride mucoadhesive buccal tablets were shown in Table-1.

Direct compression method

All the ingredients were blended in a closed dry plastic container. The blend of powder was compressed into tablets to a hardness of 4-6 kg/cm^2 using 10mm round punches to round tablets weighing 200mg containing 50 mg drug, on a Cadmach' single punch (10mm) tablet machine. In each case twenty tablets were prepared. The tablets were stored in a tightly closed container and evaluated for following characteristics in triplicate.

Table-1: Formulae used for development of labetalol hydrochloride mucoadhesive buccal tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Labetalol hydrochloride	50	50	50	50	50	50	50	50	50
HPMC K4M	50	-	-	25	25	-	-	37.5	37.5
Locust bean gum	-	50	-	25	-	75	-	37.5	-
Tara gum	-	-	50	-	25	-	75	-	37.5
Micro crystalline cellulose (MCC)	92	92	92	92	92	67	67	67	67
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
Total weight (mg)	200	200	200	200	200	200	200	200	200

Evaluation of labetalol hydrochloride mucoadhesive buccal tablets[3-5]

Weight variation

The tablets were characterized for weight uniformity by weighing 20 tablets of each formulation using an electronic balance, calculating the average weight and comparing the individual tablet weights to the average.

Hardness

The Hardness of the tablets was measured with a Monsanto hardness tester (M/s Campbell Electronics, model EIC-66, India). The results reported were average value with standard deviation of 10 tablets for each formulation.

Friability

For each formulation 10 tabs were weighed, placed in Friabilator (M/S Cambell Electronics, India) and were subjected to 100 rotations in 4 min. The tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Tablets were removed, de-dusted and weighed again. Friability was calculated along with mean and the standard deviation. Following formula was used to calculate the friability.

$$Friability = \frac{W_1 - W_2}{W_1} \times 100$$

Where "W_1" is the initial weight and "W_2" is the final weight of the tablets.

Drug content uniformity

Five tablets were weighed and powdered in a mortar. Accurately weighed tablet powder samples equivalent to 10 mg of labetalol hydrochloride tablets was transferred to a 10ml volumetric flask, and the drug was extracted into 10ml methanol. This solution was filtered through a Whatman No.1 filter paper and collected in to a 10ml volumetric flask. The solution was suitably diluted and the absorbance was measured at 302 nm. The estimations were carried out in triplicate.

In-vitro swelling studies

The swelling index of the buccal tablet was evaluated in phosphate buffer pH 6.8. The initial weight of the tablet was determined (W1) and then tablet was placed in 10 mL phosphate buffer pH 6.8 in a petri dish and then was incubated at 37 ± 1oC. The tablet was removed at different time intervals (1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0 and 12.0 hrs.) from the Petri dish and excess water was removed carefully using the filter paper. The swollen tablet was then reweighed (W2) and the percentage hydration was calculated using the following formula.[6]

Percentage hydration = [(W2-W1)/W1] X100.

Swelling Index =W2-W1/W1

Determination of surface pH of tablets

Buccoadhesive tablets are left to swell for 2hrs on surface of agar plate. The surface pH is measured using pH paper placed on core surface of the swollen Tablet.[7]

Fabrication of apparatus for testing Mucoadhesive/Bio-adhesive strength

Bio-adhesion test apparatus employed for the purpose was a modified simple balance. Two pans of the simple balance were equilibrated in such a way that the left pan was 5 grams heavier than the right pan.[8] A 1000ml glass beaker containing sufficient volume of pH 6.8 phosphate buffer was kept under the right pan of the balance.

Measurement of Bio adhesive strength

Porcine buccal mucosa was used as a model membrane for the measurement of bio adhesive strength. Fresh buccal mucosa was obtained from a local slaughter house and was used within

2h of slaughtering. Fresh mucosal membrane was excised by removing the underlying connective tissue and the surface area of mucosa is 0.001m^2. After washing thoroughly with phosphate buffer p H6.8, mucosa was tethered to the 1000ml glass beaker using a thread such that the underlying mucosa comes in to contact with the pH 6.8 phosphate buffer. Before carrying out the investigation, the two sides of the balance were equilibrated by keeping some weight on the left pan. Tablet is attached to a glass slide and the slide is tethered to the lower surface of the right pan using a thread in such a way that the tablet faces the mucosal membrane. Preload weight from the left pan was removed, that lowered the right pan and the tablet adheres to the mucosal membrane. The assembly was kept undisturbed for 3 min. and weights were slowly added to the left pan till the tablet detached from the membrane surface. The weight required to detach the tablet from the mucosal surface gave the bio-adhesive strength. The experiment was performed in triplicate and average value was calculated. After calculating mucoadhesion strength the force of adhesion and bond strength parameters were calculated from following equations.[8]

Force of Adhesion (N) =Mucoadhesive strength / 100 × 9.81

Bond Strength (N/m^2) = Force of adhesion / Surface area

***In vitro* dissolution studies**

Dissolution study of Labetalol hydrochloride buccal tablets was performed using LABINDIA DISSO 2000 an eight stage dissolution rate testing apparatus with rotating paddle. The dissolution fluid was 900ml of pH 6.8 phosphate buffer solution. The test was prepared at speed of 50 rpm and at a temperature of 37±0.5^{0}c. Samples of 5ml were withdrawn at a specific time intervals (15min, 30min, 45min, 60min, 90min, 2hrs, 3hrs, 4hrs, 6hrs, 8hrs, 10hrs and 12hrs) and the volume was replaced with 5ml fresh medium. The samples obtained were filtered through using 0.45µ nylon filters, and drug release was determined spectrophotometrically at a wave length of 302nm by comparing with the standard calibration curve.

Study of release kinetics and release mechanisms[9-11]

The various release kinetic equations in which the experimental data can be fitted and drug release rate can be predicted as a function of some variable (example time) are mentioned below. The suitability of equation is judged on the basis of best fit to the equation using statistical indicators like r^2 value.

Zero Order Equation

This equation describes the systems where the release rate is independent of the concentration of the dissolved species. The dissolution data are fitted into the zero order equation:

$$X = X_0 - K_0 t$$

Where, X = Amount of drug released at time t

X_0 = Amount of drug released initially

K_0 = Zero order rate constant

A graph of concentration vs. time would yield a straight line with a slope equal to K_0 and the intercept at the origin of the axes. The zero order plots is derived from plotting the cumulative percent drug dissolved vs. time.

First Order Equation

The first order equation describes the release from systems where the dissolution rate is dependent upon the concentration of the dissolving species. Release behavior generally follows the following first order release equation:

$$\ln X = \ln X_0 - K_1 t$$

Where, M is the amount of drug un-dissolved at time t,

M_0 is the amount of drug un-dissolved at t = 0 and

K_1 is the corresponding release rate constant.

A graph of log concentration of drug remaining vs. time yields a straight line with a negative slope.

Higuchi Square Root Law

The Higuchi square root equation describes the release from systems where the solid drug is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion. A form of the Higuchi Square Root Law is given by equation:

$$Q = K_s \sqrt{t}$$

Where, Q = Amount of drug dissolved at time t

K_s = Higuchi rate constant

Korsemeyer Peppas Equation

The Korsemeyer's equation, which derived from, the linear line of log cumulative percentage vs. log time curve, is

$$M_t / M_\infty = Kt^n$$

Where Mt and M∞ are the absolute and the cumulative amount of drug released in time t and infinite time; k is a constant incorporating the structural and geometric characteristics of the device and 'n' is the release exponent which is indicative of the mechanism of release. This is also known as the power law.

Table-2: Exponent 'n' of the power law and drug release mechanism from polymeric controlled delivery systems of different geometry

Exponent, 'n'			Drug release mechanism
Thin Film	Cylinder	Sphere	
0.5	0.45	0.43	Fickian diffusion
0.5<*n*<1.0	0.45<*n*<0.89	0.43<n<0.85	Anomalous transport
1.0	0.89	0.85	Case-II transport (follows zero order)

From the above it is clear that when the exponent 'n' takes a value of 1.0, the drug release rate is independent of time. This case corresponds to zero order release kinetics. For slabs, the mechanism that creates the zero order release is known to polymer scientists as case-II transport. Here the relaxation process of the macromolecules occurring up on water imbibitions in to the system is the rate-controlling step. The value of n=0.5 indicates drug release is Fickian in nature. Thus, equation has two distinct physical meanings in the two special cases of n=0.5 (indicating diffusion-controlled drug release) and n=1 (indicating swelling- controlled drug release). Values of n between 0.5 and 1.0 can be regarded as an indicator for the super position of both phenomena (anomalous transport). It has to be kept in mind that the two extreme values for the exponent n, 0.5 and 1.0 are only valid for slab geometry. Power Law is more comprehensive in describing the drug release as compared to Higuchi.

RESULTS AND DISCUSSION

Solubility studies

The Solubility studies of Labetalol hydrochloride were done using different fluids like 0.1N HCl, 4.0pH, 6.8pH buffers. The obtained results were given in Table-3 and Figure-1. From the obtained results it was clear that solubility of Labetalol was more in 6.8 pH phosphate buffer. The order of solubility of Labetalol hydrochloride was 6.8pH buffer>1.2 pH buffer>4.0 pH buffer. In the present investigation the dissolution studies were carried out in 6.8 pH buffer.

Table-3: Solubility data of Labetalol hydrochloride

S.No	MEDIUM	SOLUBILITY (mg/ml)
1	1.2pH	49.555
2	4.0pH	33.261
3	6.8pH	55.411

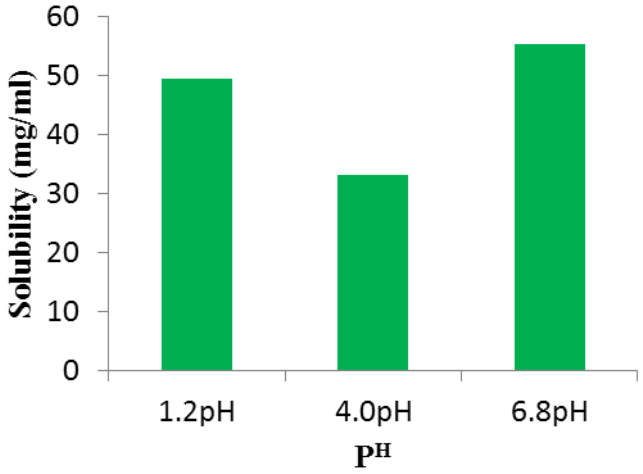


Figure-1: Solubility of Labetalol hydrochloride in different media

Development of calibration curve

Linearity was observed between the range of 5-25µg/ml and λ max was found to be 302nm**.**

FTIR studies

The FTIR studies were done to characterize the drug. To investigate the possibility of chemical interaction between drug and polymer FTIR spectra of pure Labetalol hydrochloride and polymers were analyzed over the range 500-4500 cm $^{-1}$. The IR spectrum of pure Labetalol hydrochloride in Figure-3 showed strong absorption bands at wave numbers as given in Table-4.

Table-4: FTIR spectral wave numbers and functional groups of Labetalol Hydrochloride

S.no	Bond	Functional group	Reference wave number (cm^{-1})	Peak observed at wave number (cm^{-1})
1	N–H stretch	1°, 2° amines, amides	3400–3250	3341.58
2	C=O stretch	esters, saturated aliphatic	1750–1735	1739.48
3	–C=C– stretch	Alkenes	1680–1640	1672.26
4	C–N stretch	aliphatic amines	1250–1020	1208.79
5	C–O stretch	alcohols, carboxylic acids, esters, ethers	1320–1000	1028.63
6	C–H “oop”	Aromatics	900–675	819.06

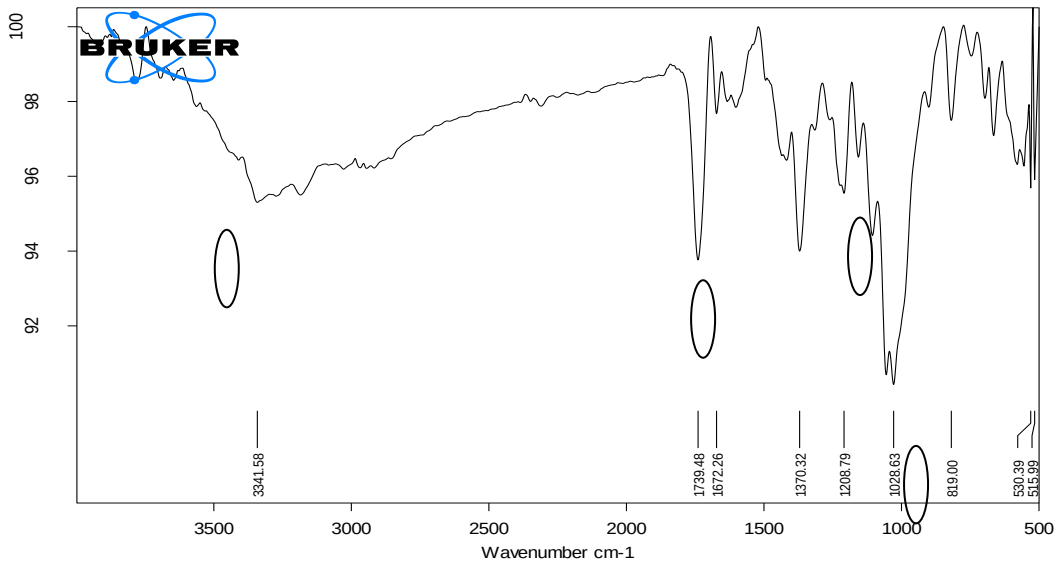


Figure-2: FTIR spectrum of formulation F5 (Drug + HPMC K4M+ Tara gum + Excipients)

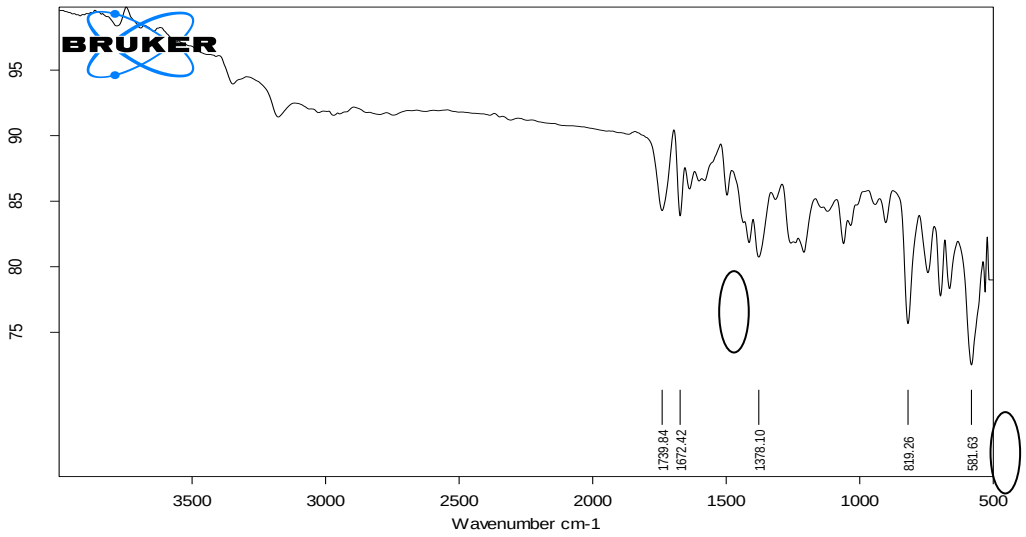


Figure-3: FTIR spectrum of Labetalol hydrochloride

Pre- compression parameters

Formulation blend was taken and their pre-compression parameters like angle of repose, bulk density, tapped density, compressibility index and hausner's ratio are evaluated. Plain Labetalol hydrochloride exhibited angle of repose value of 39.71 ± 0.69° indicating poor flow property. It was further supported by high Carr's index (28.89 ± 0.111) and Hausner's ratio (1.40 ± 0.0022). The micrometric properties of pre-compression mixtures were shown in table-5.

Table-5: Pre compression properties of all formulation

Powder Blend	Angle of Repose (θ)	Bulk density(ρ_b) (g/mL)	Tapped density(ρ_t) (g/mL)	Compressibility index (%)	Hausner's ratio
Pure drug	39.71 ± 0.69	0.39	0.63	28.89±0.111	1.40±0.0022
F1	28.1±0.01	0.57±0.01	0.71±0.04	19.0±0.01	1.24±0.01
F2	26.3±0.02	0.55±0.02	0.67±0.03	16.9±0.02	1.22±0.02
F3	27.6±0.03	0.55±0.01	0.70±0.01	19.9±0.02	1.27±0.03
F4	26.9±0.04	0.54±0.03	0.73±0.03	21.5±0.01	1.35±0.01
F5	26.9±0.05	0.57±0.01	0.67±0.03	20.8±0.02	1.26±0.02
F6	28.0±0.01	0.53±0.04	0.74±0.01	23.1±0.01	1.29±0.01
F7	32.6±0.04	0.56±0.01	0.74±0.02	23.7±0.01	1.30±0.04
F8	27.3±0.05	0.57±0.02	0.73±0.02	22.8±0.01	1.32±0.02
F9	27.9±0.01	0.58±0.03	0.72±0.02	18.7±0.02	1.24±0.01

Post compression parameters

All the prepared muccoadhesive tablets were evaluated for physicochemical parameters such as drug content, weight variation, hardness, friability and the results were given in Table-6.

Table-6: Post compression properties of all formulation

Parameters / Formulations	Hardness (kg/cm^2) ± SD	Percent friability	Weight Variation ± SD	Drug content (mg/tab)±SD
F1	5.5±0.2	0.25±0.01	200±0.02	96.5±0.02
F2	6.0±0.1	0.30±0.06	199±0.04	98.0±0.01
F3	5.5±0.12	0.45±0.04	202±0.02	99.0±0.01
F4	6.0±0.16	0.55±0.02	200±0.06	99.5±0.05
F5	5.5±0.09	0.21±0.03	198±0.07	98.0±0.01
F6	6.0±0.08	0.35±0.03	201±0.03	99.0±0.01
F7	5.5±0.07	0.40±0.02	202±0.04	98.5±0.02
F8	6.0±0.12	0.25±0.03	200±0.02	99.5±0.02
F9	5.5±0.14	0.55±0.01	201±0.04	99.4±0.02

Drug content

The drug content of the tablets was found within100 ± 0.2% of labeled claim and the results were given in Table-6.

Uniformity of weight

The results summarized in Table-6 showed that a good degree of uniformity of weight was achieved for all the batches of tablet formulations prepared. The present deviation did not exceed 5%, indicating excellent uniformity of weight in all batches of tablets.

Mechanical properties

All the batches of tablet formulations prepared, exhibited good mechanical properties with regard to both hardness and friability. The values are given in Table-6. No significant

difference in hardness values within the batches of tablet formulations prepared was observed. The friability values of all the batches of tablet formulations prepared are less than 1%.

In vitro swelling studies

The swelling studies were conducted for all formulations i.e. F1 to F9. All the formulations were hydrated generally by keeping the tablets in contact with phosphate buffer pH 6.8 for 1 to 12th hr. The swelling of all the tablets was increased as the time proceeds because the polymers gradually absorb water due to hydrophilicity of the polymer. The results were shown in table-7and figure-4 and 5.

Table-7: In vitro swelling data of all Labetalol hydrochloride formulations

TIME (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	0.75	3.5	3	1.75	0.9	4	1.95	1	0.7
2	0.85	3.81	2.95	1.82	0.955	4.5	2.075	1.075	0.76
3	0.905	3.99	2.8	1.85	1.05	4.6	2.145	1.13	0.845
4	0.965	4.5	2.75	1.895	1.115	4.75	2.175	1.155	0.9
5	0.99	4.75	2.55	1.91	1.19	4.825	2.24	1.245	0.96
6	1.05	4.75	2.5	1.96	1.245	4.85	2.275	1.35	1.075
7	1.075	4.55	2.3	2.05	1.15	4.8	2.15	1.275	0.9
8	0.975	4	2.2	1.9	1.075	4.725	2.05	1.15	0.855
9	0.905	3.96	2.15	1.86	1	4.66	1.9	1.05	0.795
10	0.85	3.85	2.1	1.75	0.9	4.64	1.825	1.4	0.705
11	0.795	3.75	2.095	1.665	0.875	4.575	1.72	0.825	0.65
12	0.65	3.6	2	1.6	0.8	4.5	1.6	0.75	0.5

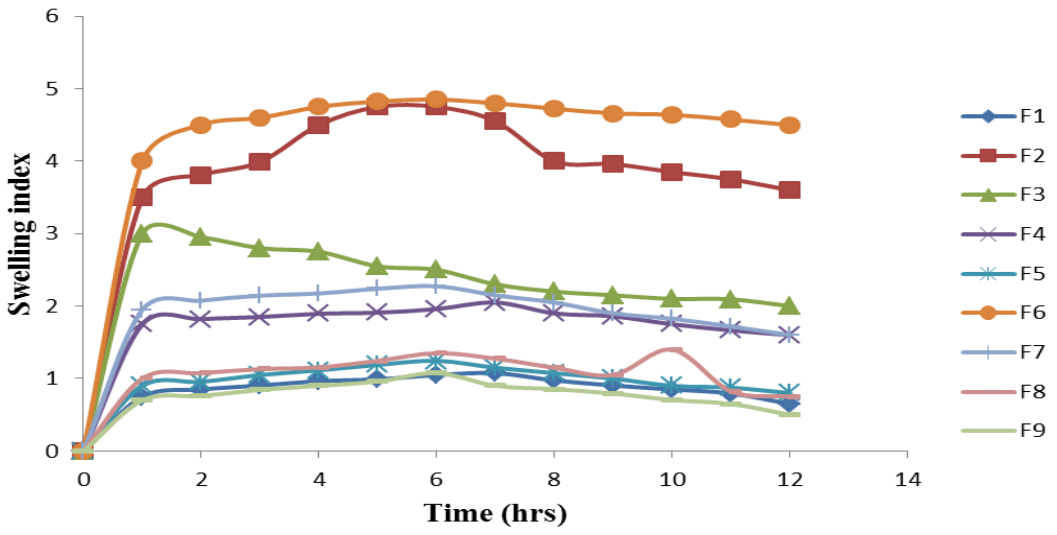


Figure-4: In vitro swelling index of all Labetalol hydrochloride formulations

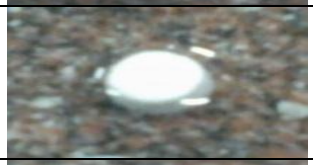
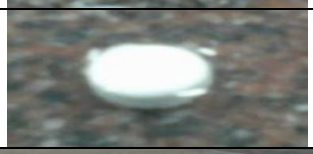
Formulation	Swelling at 1min	Swelling at 12 hrs
F1		
F2		
F3		
F4		
F5		
F6		
F7		
F8		
F9		
		

Figure-5: In vitro swelling studies Determination of surface pH of tablets

The surface pH of the tablets was found to be 6.5 to 6.9 which is well within the limit of acceptable salivary pH range of 5.6 to 7.0. So, it was suggesting that neutral pH of the formulation does not cause any irritation and biocompatible to buccal mucosa.

Determination of In-vitro mucoadhesive strength of tablets

Among the formulations, composition containing HPMCK4M and Tara gum exhibited maximum bio-adhesive strength. The formulation F5 showed highest mucoadhesive strength i.e. 15 gms and force of adhesion i.e. 1.4715. As none of the tablets were dislodged before the end of the study period i.e. 12 hours, the bio-adhesive strength exhibited by all the tablets can be considered satisfactory for maintaining them in the oral cavity for 12 hours. In all the formulations, as the polymer concentration increased, the mucoadhesive strength increased. The higher bio-adhesive strength of the HPMC K4M and Tara gum combination may be due to the formation of secondary bonds with mucin and entanglement and interpenetration of polymeric chain with mucin. The results were shown in Table-8 and Figure-6, 7.

Table-8: In-vitro mucoadhesive strength data

Formulation	Mucoadhesive strength(gms)	Force of adhesion (N)	Bond strength (N/m^2)
F1	7	0.6867	686.7
F2	7.90	0.77499	774.9
F3	9	0.8829	882.9
F4	7.5	0.73575	735.7
F5	15	1.4715	1,471.5
F6	5.5	0.53955	539.5
F7	6.90	0.67689	676.8
F8	7	0.6867	686.7
F9	7.44	0.72986	729.8

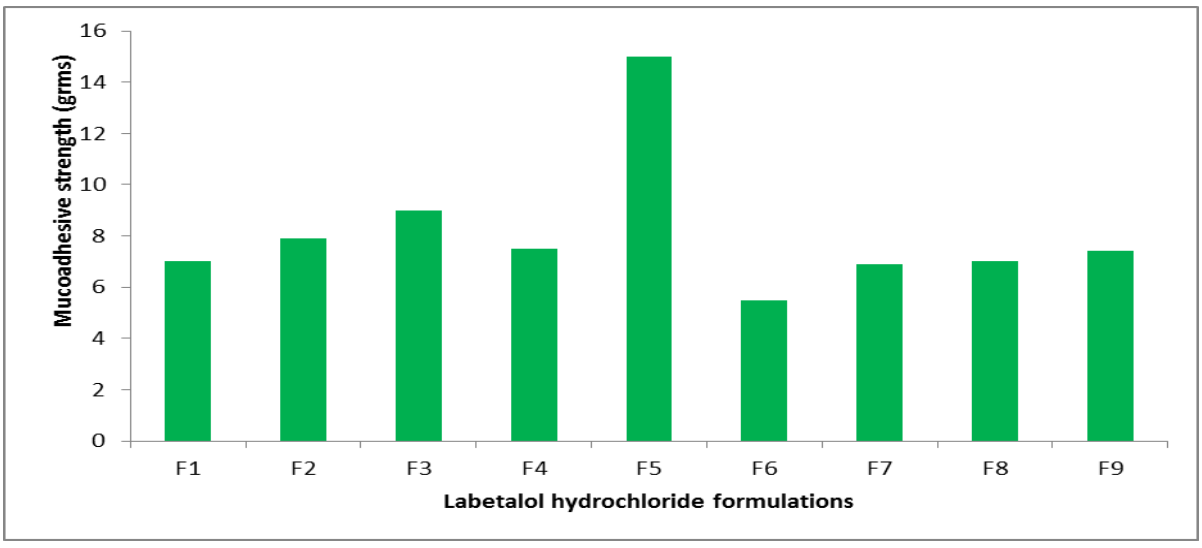


Figure-6: Comparison of In-vitro mucoadhesive strengths of all formulations

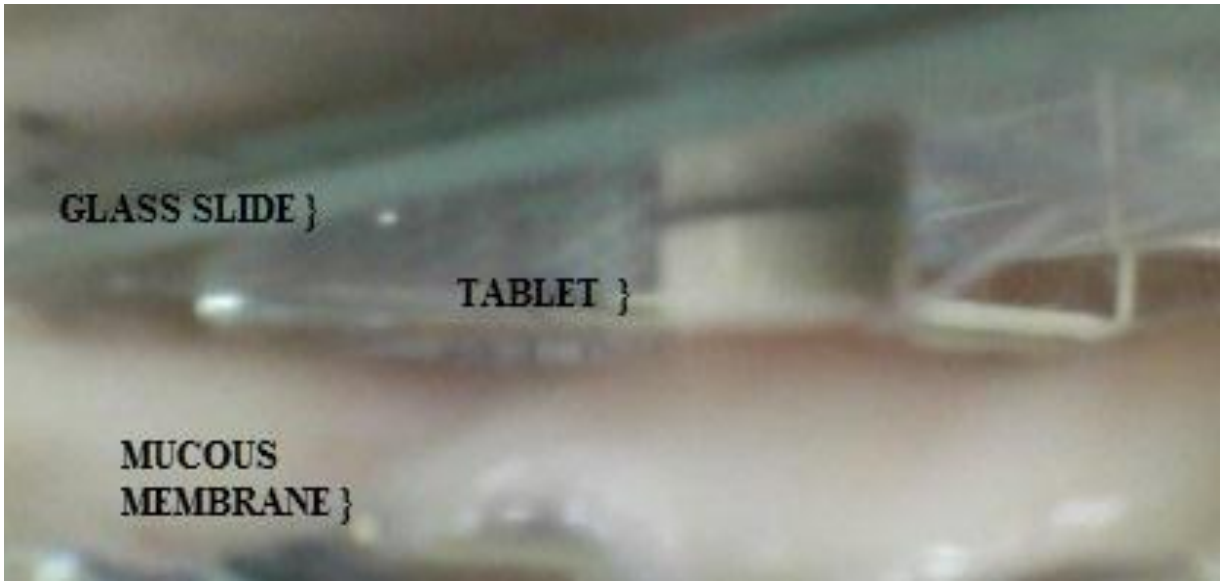


Figure-7: Mucoadhesive strength of Labetalol hydrochloride

In vitro dissolution studies

The *in-vitro* drug release studies of prepared mucoadhesive buccal tablets were carried using 900ml of phosphate buffer of pH with 50rpm at 37°C±0.5°C in USP Type II apparatus. The samples were analyzed spectrophotometrically at 302 nm. The dissolution medium on contact with hydrophilic polymer matrix gradually begins to hydrate from the periphery towards the center, forming a gelatinous swollen mass, which controls the diffusion of drug molecules through the polymeric material into the dissolution medium. The hydrated gel layer thickness determines the diffusional path length of the drug. Release of drug from the buccal mucoadhesive tablets varied according to the concentration of matrix-forming polymer. The drug release was governed by amount of matrix forming polymers. The most important factor affecting the rate of release from buccal tablets is the drug and polymer ratio. Increase in the polymer concentration increases the viscosity of the gel as well as the formation of gel layer with longer diffusional path. This could cause a decrease in the effective diffusion co-efficient of drug and therefore reduction in drug release rate.

The in vitro dissolution studies revealed that the formulations F1, F2 and F3 were formulated using mucoadhesive polymers such as HPMC K4M, Locust bean gum and Tara gum respectively at a concentration of 25%w/w which showed a drug release of 67.15%, 99.59% and 88.26% respectively at the end of 12hrs. Formulations F4 (HPMC K4M and Locust bean gum-25%w/w) and F5 (HPMC K4M and Tara gum-25%w/w) prolonged the drug release until 12thhr, with about 73.064% and 52.744%, respectively. Formulations F6 (Locust bean

gum-37.5%w/w) and F7 (Tara gum-37.5%w/w) prolonged the drug release until 12thhr, with about 98.82% and 61.23% respectively. Formulations F8 (HPMC K4M and Locust bean gum-37.5%w/w) and F9 (HPMC K4M and Tara gum-37.5%w/w) prolonged the drug release until 12thhr, with about 68.18% and 73.33% respectively.

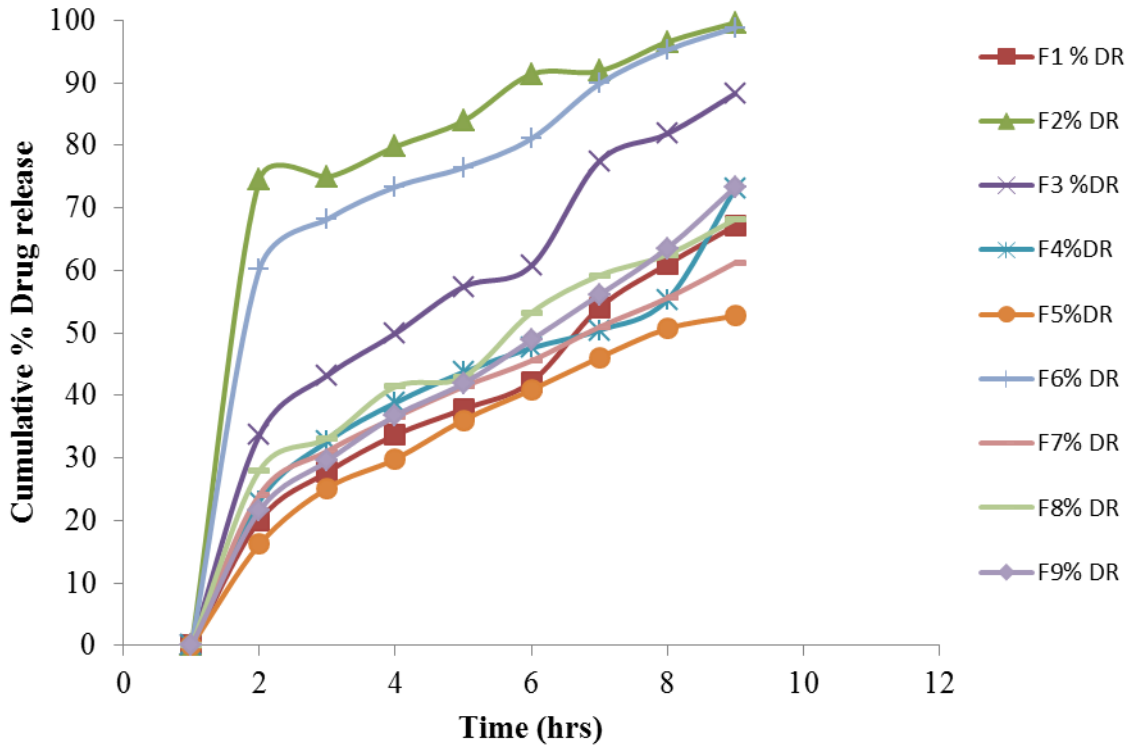


Figure-8: Comparative Dissolution Profiles of Formulations F1-F9

***In vitro* release kinetics**

The dissolution data was fitted into release kinetic profiles to assess the mechanism of drug release. The formulations were found to follow First order release kinetics .Higuchi's plot for F5 showed that the drug release was by diffusion and on extending the dissolution data in peppas plot with ' n ' value 0.677 indicating the drug release was by anomalous transport.

Table-9: The Rate Constant and Regression values for all the formulations of Labetalol hydrochloride

Formulations	Zero order		First order		Higuchi		Peppas	
	K	R^2	K	R^2	KH	R^2	N	R^2
F1	4.8496	0.9363	0.08291	0.9814	18.561	0.9937	0.5779	0.4196
F2	4.2016	0.4483	0.31874	0.8782	18.824	0.652	0.3002	0.0892
F3	5.9653	0.8815	0.15545	0.9775	23.369	0.9802	0.4985	0.280
F4	4.7472	0.8722	0.08429	0.9159	18.573	0.9673	0.5858	0.4155
F5	4.1246	0.8823	0.0608	0.9375	16.205	0.9867	0.6775	0.5507

F6	5.056	0.6305	0.27935	0.9245	21.439	0.8213	0.3582	0.1317
F7	4.0273	0.8523	0.05826	0.9344	16.022	0.9779	0.4899	0.317
F8	4.4993	0.8603	0.08176	0.9513	17.793	0.9747	0.4722	0.282
F9	5.1248	0.9328	0.09396	0.9797	19.652	0.9937	0.5570	0.3814

CONCLUSION

The mucoadhesive buccal tablets of Labetalol hydrochloride were successfully prepared using natural and synthetic polymers and are much preferable when compared to immediate release tablets for better therapy and patient compliance. This study has demonstrated that direct compression technique was suitable for producing mucoadhesive buccal tablets. Lipophilic drug, labetalol hydrochloride can be successfully penetrated through the buccal membrane. Both synthetic and natural gums showed good release retardation effect and mucoadhesive property, but the combination of HPMC K4M and Tara gum (25%w/w) i.e., F5 was having excellent release retardation effect and good mucoadhesive strength.

ACKNOWLEDGEMENT

The authors are thankful to Hospira Pharmaceuticals Pvt. Ltd, Visakhapatnam, India, for providing Labetalol hydrochloride as gift sample for carrying out research work. The authors are also thankful to Management, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, for providing all the facilities required for the completion of the research work successfully.

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