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Research Article

FORMULATION AND INVITRO EVALUATION OF NEBIVOLOL TABLETS FOR BUCCO ADHESIVE DRUG DELIVERY SYSTEM

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ABSTARCT

In the present study buccal tablets were formulated by using ethyl cellulose as backing membrane. From the foregoing investigation it may be conclude that the release rate of drug from the buccal tablets can be governed by the polymer and concentration of the polymer employed in the preparation of tablets. Regulated drug release in first order manner attained in the current study indicates that the hydrophilic matrix tablets of Nebivolol was prepared using Carbopol 934 and HPMC K100 can successfully be employed as a bucco adhesive controlled released during delivery system. The precompression blend foe all formulations were subjected to various evaluation parameters and the results were found to be within limits. The post compression parameters for all the formulations also found to be within limits. Slow, controlled and complete release of Nebivolol over a period of 9 hours was obtained from matrix tablets formulated employing HPMC K 100 (F5 Formualtion) with 97.62 % drug release.

Keywords: *Buccaltablet, Nebivolol, HPMC, Carbopal.*

INTRODUCTION

The primary objectives of mucoadhesive dosage forms are to provide intimate contact of the dosage form with the absorbing surface and to increase the residence time of the dosage form at the absorbing surface to prolong drug action. Due to mucoadhesion, certain water-soluble polymers become adhesive on hydration and hence can be used for targeting a drug to a particular region of the body including the buccal mucosa, gastrointestinal tract, the urogential tract, the airways, the ear, nose and eye. These represent potential sites for attachment of any mucoadhesive system and hence, the mucoadhesive drug delivery system may includes [1-3],

- Buccal delivery system
- Gastrointestinal delivery system
- Nasal delivery system
- Ocular delivery system
- Vaginal delivery system
- Rectal delivery system

Buccal Delivery System:

The unique environment of the oral cavity offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation, the oral mucosal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extentensively metabolized in the liver (first pass effect).

The total area of the oral cavity is about 100 cm^2. Out of this about one third is the buccal surface, which is lined with an epithelium of about 0.5 mm thickness. The oral mucosal surface is constantly washed by the saliva (daily turn out is about 0.5 to 2 liters). The continuous secretion of saliva results in rapid removal of released drug. Conversely, the thin mucin film, which exists on the surface of the oral mucosa, may provide an opportunity to retain a drug delivery system in contact with the mucosa for prolonged periods if it is designed to be mucoadhesive. Such systems ensure a close contact with absorbing membrane, thus optimizing the drug concentration gradient across the biological membrane and reducing the diffential pathway. Therefore, the buccal (oral) mucosa may be a potential site for controlled or sustained drug delivery [4-7].

Drug delivery via the membranes of the oral cavity is traditionally divided into three categories,

- Buccal delivery, which infers drug administration through the lining of the cheek to the systemic circulation.
- Sublingual delivery, which infers drug administration through the administration of drug via membranes of the floor of the mouth for the systemic circulation.
- Local delivery to mouth, which involves treatment conditions within the oral cavity by administration to the affected mucosal tissues.

These sites for delivery differ in both structure and composition as well as in degree of permeability and therefore, also vary in their ability to retain a delivery for a desired length of time.

Bioadhesive Buccal Tablets:

Bioadhesive tablets are immobilized drug delivery systems. They can be formulated into monolithic, partially coated or multi-layered matrices. Monolithic tablets are easy to manufacture by conventional techniques and provide for the possibility of loading large amount of drug. In case of bi-layered tablets, drug can be incorporated in the adhesive layer, which comes in contact with the mucosal surface. This drug containing mucoadhesive layer is then protected from the oral cavity environment by a super upper inert layer (backing layer), which faces into the oral cavity [8-14].

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MATERIALS AND METHODS

Materials:

Nebivolol, Microcrystalline cellulose, Magnesium stearate, Talc, Ethyl cellulose, Carbopol, HPMC K15M, HPMC K100M.

Preformulation studies:

The goals of the preformulation study are:

- ❖ To establish the necessary physicochemical characteristics of a new drug substance.
- ❖ To determine its kinetic release rate profile.
- ❖ To establish its compatibility with different excipients.

Hence, preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies and flow properties.

Estimation of Nebivolol:

A) Determination of λmax of Nebivolol in phosphate buffer pH 6.8 solution:

Weighed amount of Nebivolol is dissolved in phosphate buffer pH 6.8 to obtain a 1000 mcg/ml solution. This solution was subjected to scanning between 200-400 nm and absorption maximum was determined. The effect of dilution on absorption maxima was studied by diluting the above solution to10 mcg/ml and scanned from 200-400 nm. From the spectra of drug max of Nebivolol 216 nm was selected for the analysis. The calibration curve was prepared in the concentration range of 2-12 µg/ml at 216 nm. By using the calibration curve, the concentration of the sample solution can be determined.

B) Standard calibration curve of Nebivolol in phosphate buffer pH 6.8 solution:

Standard Stock Solution: A stock solution containing 1mg/ml of pure drug was prepared by dissolving 100 mg of Nebivolol in sufficient phosphate buffer pH 6.8 to produce 100 ml solution in a volumetric flask.

Stock solution: From the standard stock solution, 5 ml of the stock solution was further diluted to 50 ml with phosphate buffer pH 6.8 into a 50 ml volumetric flask and diluted up to the mark with phosphate buffer pH 6.8. Aliquots of 0.2, 0.4, 0.6, 0.8, 1 and 1.2 ml of stock solution were pipette out into 10ml volumetric flasks. The volume was made up to the mark with phosphate buffer pH 6.8. These dilutions give 2, 4, 6, 8, 10 and 12 mcg/ml concentration of Nebivolol respectively. The absorbance was measured in the UV-Visible spectrophotometer at 216 nm using distilled water as blank and graph of concentration versus absorbance was plotted. The absorbance data for standard calibration curves are given.

Preformulation parameters:

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$$\tan \theta = h / r \quad \tan \theta = \text{Angle of repose}$$

h = Height of the cone, r = Radius of the cone base

Table No. 1: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample; V_o = apparent volume of powder

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density; M = Weight of sample; V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value.

For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\text{tap} - b) / \text{tap}] \times 100$$

Where, b = Bulk Density; Tap = Tapped Density

Table No. 2: Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Method of Preparation of mucoadhesive tablets:

Mucoadhesive buccal Tablets:

Preparation: Direct compression method has been employed to prepare buccal tablets of Nebivolol using HPMC K15, HPMC K100, and CARBOPOL 934 as polymers.

Procedure: All these ingredients including drug, polymer and excipients were weighed accurately according to the batch formula. All the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend (230 mg) of each formulation was pre-compressed, on multi stationed tablet punching machine at a pressure of 0.5 ton for 30 s to form single layered flat-faced tablet of 9 mm diameter. Then, 50 mg of ethyl cellulose powder was added and final compression was done at a pressure of 3.5 tons for 30 s to get bilayer tablet. Compositions of the designed bilayer tablets are given.

Table No. 3: Formulations of Mucoadhesive buccal tablets of Nebivolol

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
NEBIVOLOL	20	20	20	20	20	20	20	20	20
HPMC K15	20	30	40	----	----	----	----	----	----
HPMC K100	----	----	----	20	30	40	----	----	----
CARBOPOL 934	----	----	----	----	----	----	20	30	40
Magnesium stearate	3	3	3	3	3	3	3	3	3
MCC pH 102	QS	QS	QS	QS	QS	QS	QS	QS	QS
ETHYL CELLULOSE	50	50	50	50	50	50	50	50	50
TOTAL	280	280	280	280	280	280	280	280	280

Characterization of buccal tablets of Nebivolol:

Evaluation of muco adhesive buccal tablets of Nebivolol:

1) Hardness test:

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

2) Thickness:

The thickness of three randomly selected tablets from each formulation was determined in mm using a Screw gauge.

3) Friability test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock orattrition. The friability of tablet was determined by using Roche Friabilator as per IP procedure of friability. It is expressed in percentage (%). Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W_{final}). The percentage friability was then calculated by,

$$F = \frac{W_{inital} - W_{final}\ X100}{W_{initial}}$$

% Friability of tablets less than 1% is considered acceptable.

4) Uniformity of weight:

The weight variation test was performed as per procedure of IP. The weight (mg) of each of 20 individual tablets, selected randomly from each formulation was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation.

5) Uniformity of drug content:

Five tablets were powdered in a glass mortar and the powder equivalent to 50 mg of drug was placed in a stoppered 100 ml conical flask. The drug was extracted with 40 ml distilled water with vigorous shaking on a mechanical gyratory shaker (100 rpm) for 1 hour. Then heated on water bath with occasional shaking for 30 minutes and filtered into 50 ml volumetric flask through cotton wool and filtrate was made up to the mark by passing more distilled water through filter, further appropriate dilution were made and absorbance was measured at 220 nm against blank (distilled water).

6) Swelling Index:

The swelling index of the buccal tablet was evaluated in phosphate buffer pH 6.8 The initial weight of the tablet was determined and then tablet was placed in 6 ml phosphate buffer pH 6.8 in a petridish and then was incubated at 37 ^{o} C. The tablet was removed at different time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 h) blotted with filter paper and reweighed (W_2). The swelling index is calculated by the formula:

$$\text{Swelling index} = 100\ (W_2 - W_1) / W_1$$

Where, W_1 = Initial weight of the tablet; W_2 = Final weight of tablet.

7) In vitro drug release study:

The study was carried out in USP XXIII tablet dissolution test apparatus-II Labindia, Mumbai, India, employing paddle stirrer at 50 rpm and 900 ml of phosphate buffer pH 6.8 as dissolution medium maintained at 37 0.5^{0}C. The tablet was supposed to release drug from one side only hence a one side of tablet was fixed to glass disk with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. At different time interval 5 ml of sample was withdrawn and replaced with fresh medium. The samples were filtered through 0.25 μm membrane filter paper and analyzed for Nebivolol after appropriate dilution at 216 nm using Labindia, Mumbai, India UV-Visible spectrophotometer.

8) Release Kinetics

The analysis of drug release mechanism from a pharmaceutical dosage form is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero-order, first-order, diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation, erosion equation and Peppas-Korsemeyer equation.

Zero Order Release Kinetics:

It defines a linear relationship between the fraction of drug released versus time.

$$Q = k_o t$$

Where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant.

A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First Order Release Kinetics:

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that drug release from most of the slow release tablets could be described adequately by apparent first-order kinetics. The equation that describes first order kinetics is

$$\text{In}\ (1-Q) = -\ K_1 t$$

Where, Q is the fraction of drug released at time t and k_1 is the first order release rate constant.

Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi's equation:

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q=K_2t^{½}$$

Where, K2 is the release rate constant.

A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependant

RESULTS AND DISCUSSION

The main aim of this work was to develop buccoadhesive tablets to release the drug at buccal mucosal site in unidirectional pattern for extended period of time without wash out of drug by saliva. Carbopol 934, HPMC K15, HPMC K 100 was selected as buccoadhesive polymers on the basis of their matrix forming properties and mucoadhesiveness, while ethyl cellulose, being hydrophobic, used as a backing material. Ethyl cellulose has recently been reported to be an excellent backing material, given its low water permeability and moderate flexibility.

Table No. 4: Standard calibration graph of Nebivolol

Concentration (mcg/ml)	Absorbance* (mean±SD)
2	0.08
4	0.158
6	0.237
8	0.318
10	0.397
12	0.485

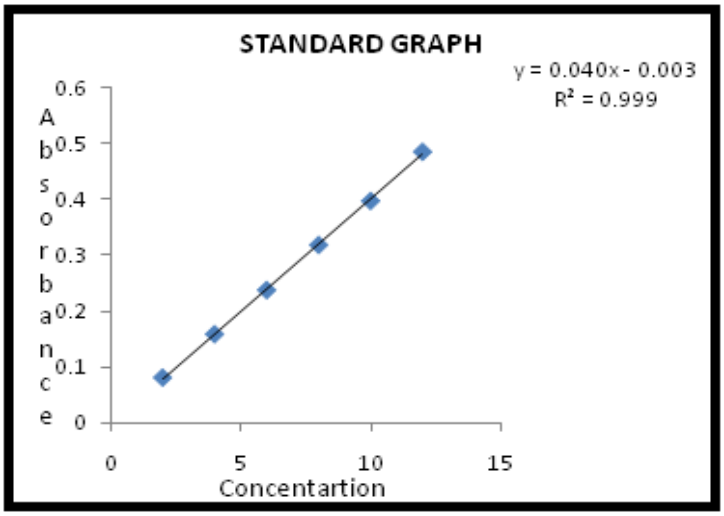

Fig. 1: Calibration curve of Nebivolol

Precompression Evaluation Parameters of Tablets:

Table No. 5: Micromeritic properties of powder blend

Formulation Code	Bulk density	Tapped density	Compressibility Index	Hausner's ratio
F1	0.49±0.07	0.57±0.01	16.21±0.06	0.86±0.06
F2	0.56±0.06	0.62±0.05	16.87±0.05	0.98±0.05
F3	0.52±0.03	0.68±0.07	17.11±0.01	0.64±0.03
F4	0.54±0.04	0.64±0.08	17.67±0.08	1.12±0.04
F5	0.53±0.06	0.67±0.03	16.92±0.04	1.2±0.08
F6	0.56±0.05	0.66±0.06	17.65±0.09	1.06±0.09
F7	0.58±0.06	0.69±0.04	16.43±0.05	0.76±0.03
F8	0.48±0.05	0.57±0.02	17.97±0.02	1.15±0.09
F9	0.54±0.08	0.62±0.03	17.54±0.09	1.17±0.02

Formulations blend of all the formulations were passed the pre compression parameters like angle of repose, bulk density, tapped density and Hausners ratio.

Table No. 6: Evaluation Data of Nebivolol Buccoadhesivetablets

Formulation code	Hardness (kg/cm)	Thickness (mm)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	4.8±0.02	2.80±0.00	279.6±0.99	0.79±0.01	100.09±0.56
F2	4.3±0.05	2.83±0.06	278.8±0.99	0.67±0.01	102.73±0.46
F3	4.3±0.05	2.87±0.06	279.8±0.38	0.57±0.01	98.75±0.88
F4	5.7±0.06	2.86±0.06	280.7±0.99	0.55±0.00	99.70±0.34
F5	5.4±0.03	2.87±0.06	279.8±0.38	0.51±0.01	97.95±0.38
F6	5.0±0.02	2.90±0.00	280.1±0.99	0.87±0.03	98.75±0.88
F7	5.6±0.07	2.97±0.06	279.6±0.17	0.46±0.01	103.36±0.83
F8	5.3±0.05	3.01±0.01	281.0±0.40	0.72±0.01	101.09±4.00
F9	5.1±0.02	2.95±0.00	280.0±0.20	0.56±0.02	99.75±0.38

The assayed drug content in various formulations varied between 98.64% and 100.26% (mean 99.68%). The average weight of the tablet was found to be between 281.4 mg and 283.2 mg (mean 280.2 mg), % friability range between 0.46 and 0.76(mean 0.43 %) and thickness of the tablets for all the formulations was found to be between 2.80 mm and 3.00 mm with average of 2.90 mm.

Buccoadhesive tablets containing Carbopol showed hardness in the range of 5.00 to 5.60 kg/cm ^{2} and it increased when used in combination with HPMC k100. The hardness of the tablets containing HPMC K15 was much lower, ranging from 4.30 to 4.8 kg/cm^2 and increased with increasing amounts of HPMC or Carbopol. The difference in the tablet strengths are reported not to affect the release of the drug from hydrophilic matrices. Drug is released by diffusion through the gel layer and/or erosion of this layer and is therefore independent of the dry state of the tablet.

In-Vitro Drug Release Studies:

Table No. 7: In vitro release data of Nebivolol mucoadhesive tablets (F1, F2 & F3)

Time (h)	F-1	F-2	F-3
0.5	33.91±0.25	25.46±0.54	17.89±0.91
1	55.97±1.56	35.56±1.19	22.28±0.27
2	88.24±0.74	48.51±0.49	29.96±0.47
3	101.52±0.58	60.03±1.21	46.20±0.21
4		71.23±1.77	50.15±0.65
5		86.59±0.62	59.59±0.25
6		94.82±1.17	68.59±1.54
7		102.95±1.54	76.28±0.53
8		---------	88.24±0.11

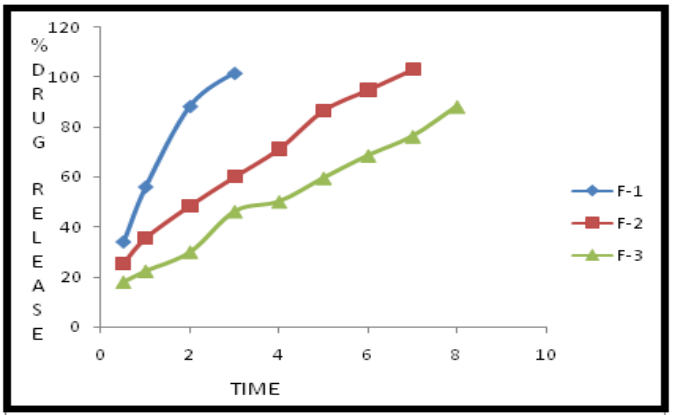

Fig. 2: Invitro dissolution graph of formulations F1-F3

Table No. 8: In vitro release data of Nebivolol mucoadhesive tablets containing HPMC K100 (F4, F5 & F6)

Time (h)	F-4	F-5	F-6
0.5	24.69±0.35	19.86±0.99	17.11±0.08
1	39.73±1.35	27.32±0.25	23.14±1.18
2	48.95±2.36	36.98±1.77	33.20±1.13
3	60.47±2.02	48.40±1.31	43.60±1.10
4	70.35±2.65	57.40±1.95	51.06±0.21
5	82.42±1.95	65.19±0.79	56.02±0.47
6	97.79±0.34	70.46±1.34	60.64±1.65
7	------	78.25±0.38	74.24±1.09
8	------	87.25±0.79	77.75±0.38
9	------	97.62±1.95	83.41±1.31

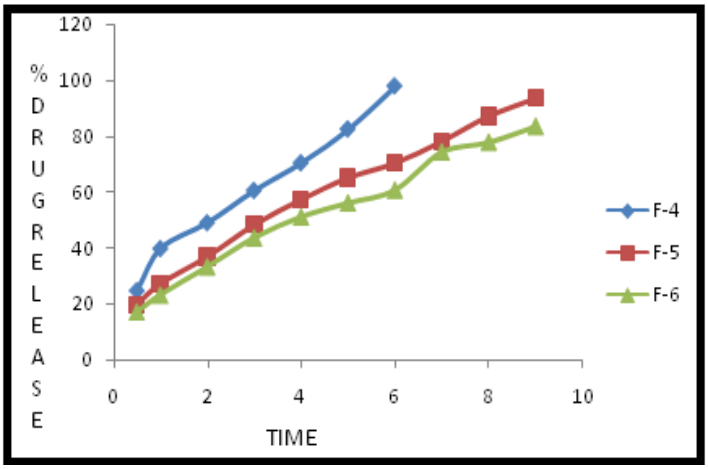

Fig. 3: Invitro dissolution graph of formulations F4-F6

Table No. 9: In vitro release data of Nebivolol containing Carbopol 934 (F7, F8 & F9)

Time (h)	F-7	F-8	F-9
0.5	50.04±0.26	35.56±0.32	21.84±0.44
1	65.63±0.29	40.17±0.18	29.19±0.38
2	68.92±0.72	54.00±0.16	44.02±0.24
3	82.20±2.38	65.96±2.22	58.51±1.59
4	98.89±3.45	74.74±0.33	68.37±0.55
5	------	82.75±0.18	78.36±0.48
6	------	99.43±1.98	87.03±0.82
7	------	------	96.32±1.98

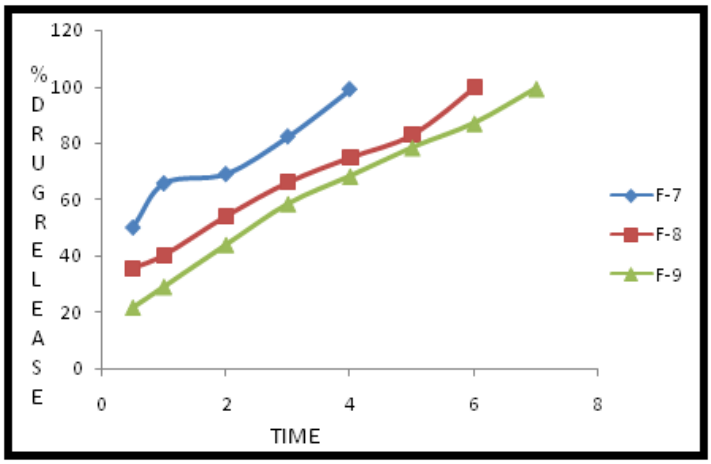

Fig. 4: In Vitro dissolution graphs of formulation (F7, F8 & F9)

In vitro drug release studies revealed that the release of Nebivolol from different formulations varies with characteristics and composition of matrix forming polymers. The release rate of Nebivolol decreased with increasing concentrations of the polymers. The Release rate of the tablets decreased from F1 to F3 when tablets are prepared with HPMC K15 in 1:1, 1:1.5 and 1:2 ratio respectively.

The release rates were similarly studied with increasing concentrations of HPMC K100 and the release rate decreased with increasing concentrations from F4 to F6 respectively. Similarly release rates were studied with Carbopol 934 in increasing concentrations i.e 1:1, 1:1.5, and 1:2 and release rate was found to be decreased with all the three polymers when used in the ratio 1:2.

Among all the formulations Formulation F5 containing HPMC K100 M in the concentration of 1:1.5 was found to be good with better drug release i.e., 93.62% in 9 hours. Several kinetic models describing drug release from immediate and modified released dosage forms. The model that best fits the release data was evaluated by correlation coefficient (r). The correlation coefficient (r) value was used as criteria to choose the best model to describe the drug release from the buccoadhesive tablets. The 'r' values obtained for fitting the drug release data to first order, indicating that the drug release mechanism follows first order kinetics. From higuchi's equation, the high values of correlation coefficient 'r' indicating that the drug release mechanism from these tablets was diffusion controlled. The values of **'n'** in Peppas model indicated the drug release follows non-Fickian diffusion.

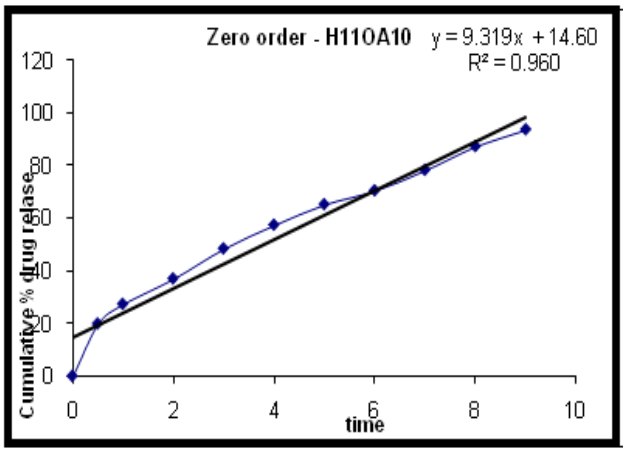

Fig. 5: Zero order release kinetics graph for F5 formulation

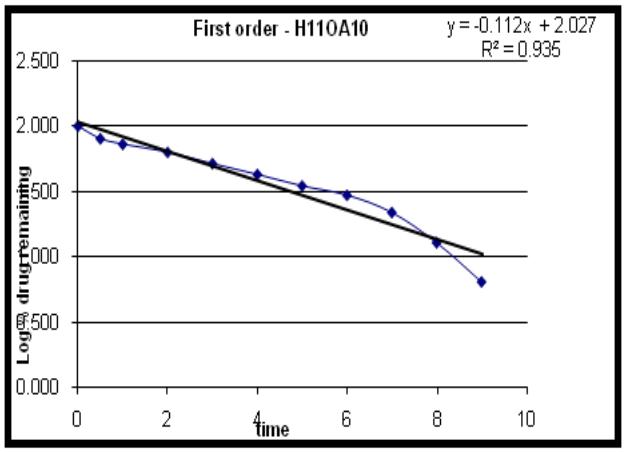

Fig. 6: First order release kinetics graph for F5 formulation

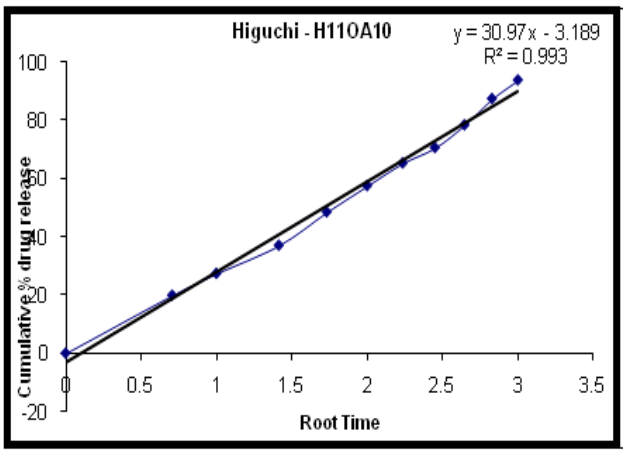

Fig. 7: Higuchi release kinetics graph for F5 formulation

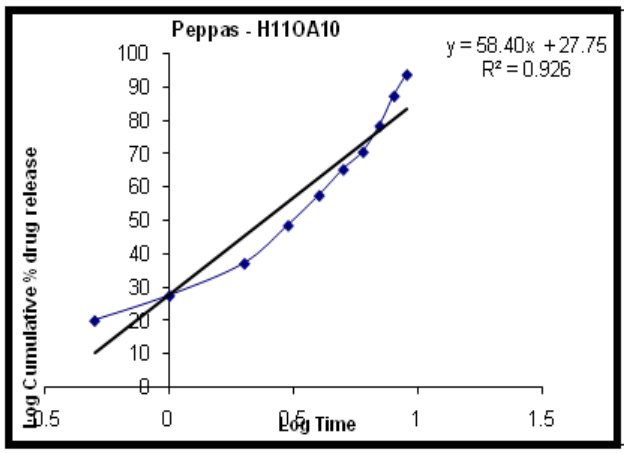

Fig. 8: Korsmayer peppas release kinetics graph for F5 formulation

Table No. 10: Regressional analysis of the in vitro release data according to various release kinetic models

Formulation Code	Ze ro order	First order	Higuchi	Korsmeyer-Peppas
	r^2	r^2	r^2	r^2
F5	0.960	0.935	0.993	0.926

From the above results it is concluded that the drug release from the formulated bucco adhesive tablets of Nebivolol followed Higuchi release kinetics and was diffusion controlled.

CONCLUSION

From the foregoing investigation it may be conclude that the release rate of drug from the buccal tablets can be governed by the polymer and concentration of the polymer employed in the preparation of tablets. Regulated drug release in first order manner attained in the current study indicates that the hydrophilic matrix tablets of Nebivolol was prepared using Carbopol 934 and HPMC K100 can successfully be employed as a buccoadhesive controlled released during delivery system. The precompression blend foe all formulations were subjected to various evaluation parameters and the results were found to be within limits. The post compression parameters for all the formulations also found to be within limits.Slow, controlled and complete release of Nebivolol over a period of 9 hours was obtained from matrix tablets formulated employing HPMC K 100 (F5 Formualtion) with 97.62 % drug release.

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