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Formulation Development and In-Vitro Evaluation of Nebivolol Hydrochloride Buccal Tablets

Nirmala Rangu[1*], M Mounilka Goud[1], A Jaswanth[1]

1.Procadence Institute of Pharmaceutical Sciences, Rimmanaguda, Gajwel, Medak 502312, Telangana, India.

ABSTRACT

The present work aims to develop and evaluate buccal tablets of Nebivolol Hydrochloride. Tablets of Nebivolol Hydrochloride were prepared by direct compression method using bioadhesive polymers like Chitosan, Guargum, Xanthan gum in different ratios. The tablets were evaluated for pre and post compression parameters and found to be within the limits. The tablets were evaluated for *in vitro* release in pH 6.8 phosphate buffer for 8 hr in standard dissolution apparatus. In order to determine the mode of release, the data was subjected to Zero order, first order, Higuchi, Korsmeyer and Peppas diffusion model. The formulation F3 showed maximum drug release (89.06%) in 8 hrs. The optimized formulation F3 showed a surface pH of 6.18 and was following Zero order mechanism with regression value of 0.981. FT-IR studies revealed the absence of any chemical interaction between drug and polymers used.

Keywords: Nebivolol Hydrochloride, Buccal tablets, Chitosan, Guargum, Xanthan gum, *in-vitro* drug release.

INTRODUCTION

Among the various routes of drug delivery, oral route is the most suitable and most widely accepted one by the patients for the delivery of the therapeutically active drugs. But after oral drug administration many drugs are subjected to presystemic clearance in liver, which often leads to a lack of correlation between membrane permeability, absorption and bioavailability.[1-5] Within the oral route, the Buccal cavity is an attractive site for drug delivery due to ease of administration and avoids possible drug degradation in the gastrointesinal tract as well as first pass hepatic metabolism.[6]

Buccal Delivery involves the administration of drug through buccal mucosal membrane (the lining in the oral cavity)[1] Buccal drug delivery is the safer method of drug utilization because drug absorption is terminated in case of toxicity by removing the dosage form from the buccal cavity. The drug directly reaches to the systemic circulation through the internal jugular vein and bypasses the drugs from the hepatic first pass metabolism, which leads to high bioavailability.[7] The other advantages of buccal drug delivery include: low enzymatic activity, suitable for drugs orexcipients that mildly and reversibly damage or irritate the mucosa,painless drug administration, easy drug withdrawal, possible to include the permeation enhancer/enzyme inhibitor or pH modifier in the fo rmulation. A suitable buccal drug delivery system should be flexible and should posses good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration. Bioadhesive formulations have been developed to enhance the bioavailability[(8,9)] of drugs that undergo substantial first pass hepatic effect and to control the drug release to a constant rate.[10]

Nebivolol is a β-1 receptor blocker with nitric oxide-potentiating vasodilatory effect used in treatment of Hypertension and also for left ventricular failure. It is rapidly absorbed from oral route but undergoes first pass metabolism, which resu lts in only 38% oral bioavailability. Nebivolol has half-life about 10 hrs. In hypertension the initial dose of Nebivolol is 5mg once daily and maximum dose is 40mg once daily[11].

Nebivolol is selected as a model drug to avoid first pass hepatic metabolism, to improve bioavailability and to control release rate of drug from tablets by matrix forming polymers, as its half life is low.

MATERIALS AND METHOD

Materials

Nebivolol Hydrochloride was obtained as a gift sample from SURA Laboratories. Chitosan, Guar gum, Xanthan gum were purchased from Sd fine Chem.Ltd. Mumbai. All other chemicals and reagents used were of analytical reagent grade and purchased

from Sd fine Chem.Ltd. Mumbai.

Preparation of Buccal tablets

Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. Chitosan, guar gum and Sodium carboxy methyl cellulose were used as mucoadhesive and biodegradable polymers Nebivolol Hydrochloride was mixed manually in polybags with different ratios of Chitosan, Guar gum and Sodium carboxy methyl cellulose as muco adhesive polymers and Microcrystalline Cellulose (Table 1) as diluent for 10 min. The blend was mixed with talc and magnesium stearate for 3-5 min. The mixed blend was compressed into tablets by the direct compression method using 10mm flat faced punches in a sixteen station LAB PRESS rotary tablet-punching machine. The mass of the tablets was determined using digital balance and thickness with digital vernier calipers.

Table 1: Formulation of Nebivolol Hydrohcloride Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug	5	5	5	5	5	5	5	5	5	5	5	5
Chitosan	10	20	30	40	-	-	-	-	-	-	-	-
Guargum	-	-	-	-	10	20	30	40	-	-	-	-
Xanthan gum	-	-	-	-	-	-	-	-	10	20	30	40
MCC pH 102	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
Mg. Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total Weight (mg)	100	100	100	100	100	100	100	100	100	100	100	100

Evaluation of buccal tablets:

Weight variation[12]:

The weight variation test was done by taking 20 tablets randomly and weighed accurately. The composite weight divided by 20 provides an average weight of tablet. Not more than two of the individual weight deviates from the average weight by 10 % and none should deviate by more than twice that percentage. The weight variation test would be a satisfactory method of determining the drug content uniformity.

The percent deviation was calculated using the following formula:

$$\% \, Deviation = \frac{Individual \, weight - Average \, weight}{Average \, weight} \, x100$$

The average weight of tablets in each formulation was calculated and presented with standard deviation.

Thickness[12]:

The thickness and diameter of the tablets was determined using a Digital Vernier caliper. Ten tablets from each formulation were used and average values were calculated. The average thickness for tablets was calculated and presented with standard deviation.

Hardness[12]:

Six tablets were taken from each formulation and hardness was determined using Monsanto hardness tester and the average was calculated. It is expressed in Kg/cm^2.

Friability[12]:

A sample of preweighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. Percent friability (% F) was calculated as

$$\% \, Friability = \frac{initial \; weight \; of \; tablets - final \; weight \; of \; tablets}{initial \; weight \; of \; tablets} x100$$

Assay:

Six tablets of each formulation were taken and amount of drug present in each tablet was determined. Powder equivalent to one tablet was taken and added in 100ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45μ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using UV-Visible spectrophotometer at 221 nm using pH6.8 phosphate buffer.

In vitro **release studies[13]:**

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500 ml of pH 6.8 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 8 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 221nm. All dissolution studies were performed in triplicate.

In vitro **bioadhesion strength[14]:**

Tissue isolation

Buccal tissue was taken from Pigs slaughter-house. It was collected within 10 minutes after slaughter of pig and tissue was kept in Krebs buffer solution. It was transported immediately to the laboratory and was mounted within 2hrs of isolation of buccal tissue. The tissue was rinsed thoroughly using phosphate buffer saline to remove the adherent material. The buccal membrane from the tissue was isolated using surgical procedure. Buccal membrane was isolated and buccal epithelium was carefully separated from underlying connective tissue. Sufficient care was taken to prevent any damage to the epithelium.

Measurement of bioadhesion strength:

Bioadhesion strength of tablets were evaluated using a microprocessor based on advanced

force gauge equipped with a motorized test stand (Ultra Test Tensile strength tester, Mecmesin, West Sussex, UK) according to method describe as it is fitted with 25kg load cell, in this test porcine membrane was secured tightly to a circular stainless steel adaptor and the buccal tablet to be tested was adhered to another cylindrical stainless steel adaptor similar in diameter using a cyanoacrylate bioadhesive. Mucin 100 µl of 1 %w/v solution was spread over the surface of the buccal mucosa and the tablet immediately brought in contact with the mucosa. At the end of the contact time, upper support was withdrawn at 0.5mm/sec until the tablet was completely detached from the mucosa. The work of adhesion was determined from the area under the force distance curve. The peak detachment force was maximum force to detach the tablet from the mucosa.

$$Force\ of\ adhesion = \frac{Bioadhesion\ Strength}{1000} x9.8$$

$$Bond\ strength = \frac{Force\ of\ adhesion}{Surface\ area}$$

Surface pH[15]:

Weighed tablets were placed in boiling tubes and allowed to swell in contact with pH 6.8 phosphate buffer (12mL). Thereafter, surface pH measurements at predetermined intervals of 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 h were recorded with the aid of a digital pH meter. These measurements were conducted by bringing a pH electrode near the surface of the tablets and allowing it to equilibrate for 1 min prior to recording the readings. Experiments were performed in triplicate (n=3) and a mean of three readings was recorded.

Moisture absorption[16]:

Agar (5% W/V) was dissolved in hot water. It was transferred into Petri dishes and allowed to solidify. Six buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture, if any, and laminated on one side with a water impermeable backing membrane. They were then placed on the surface of the agar and incubated at 37°C for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using following formula:

$$\% \ Moisture\ Absorption = \frac{Final\ Weight - Initial\ Weight}{Initial\ Weight} x100$$

***Ex vivo* residence time[15]:**

The *Ex vivo* residence time is one of the important physical parameter of buccal mucoadhesive tablet. The adhesive tablet was pressed over excised pig mucosa for 30 sec after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing around 500 ml of phosphate buffer, pH 6.8, at 37°C. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm (Figure 1). The time for complete erosion or detachment from the mucosa was recorded.
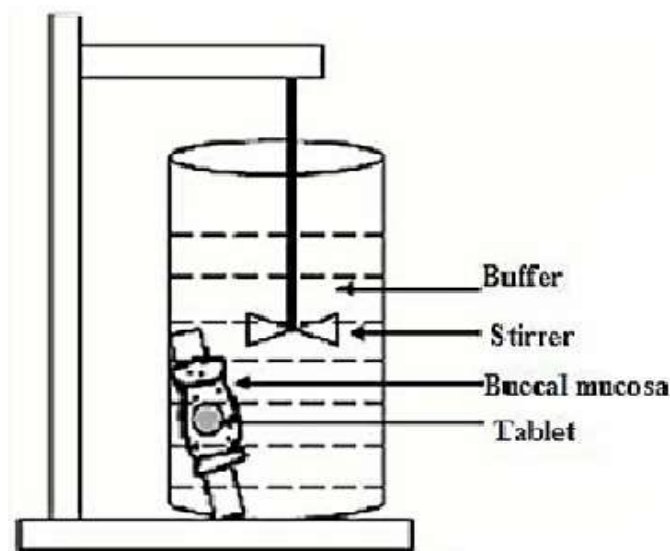
Figure 1: Schematic representation of *Ex-vivo* residence time study

***Ex vivo* permeation studies through porcine buccal mucosa[17]**

The aim of this study was to investigate the permeability of buccal mucosa to Nebivolol. It is based on the generally accepted hypothesis that the epithelium is the rate-limiting barrier in the buccal absorption.*Ex vivo* permeation study of Sodium carboxy methyl cellulose through the porcine buccal mucosa was performed using Franz diffusion cell and membrane assembly, at 37°C ± 0.2°C and 50 rpm. This temperature and rpm was maintained by magnetic stirrer. Porcine buccal mucosa was obtained from a local slaughter house and used within 2 hr of slaughter. The tissue was stored in Krebs buffer at 4°C upon collection. After the buccal membrane was equilibrated for 30 min with the buffer solution between both the chambers, the receiver chamber was filled with fresh buffer solution (pH 6.8), and the donor chamber was charged with 5 mL (1mg/mL) of drug solution. Aliquots (5mL) were collected at predetermined time inter wells up to 8 hr and the amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 221 nm using a UV spectrophotometer. The medium of the same volume (5 mL), which was pre-warmed at 37°C, was then replaced into the receiver chamber.

The experiments were performed in triplicate (n = 3) and mean values were used to calculate flux (J) and permeability coefficient (P).

$$J = \frac{dQ/dt}{A}$$

$$P = \frac{dQ/dt}{\Delta CA}$$

Where,

J is Flux (mg.hrs^{-1}cm^{-2})

P is permeability coefficient (cm/h)

dQ/dt is the slope obtained from the steady state portion of the curve

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ΔC is the concentration difference across the mucosa and

A the area of diffusion (cm^2)

Drug-excipient compatibility studies

The pure drug, Nebivolol Hydrochloride and its mixture with the polymer Chitosan, Guargum and Xanthan gum powders was mixed separately with IR grade KBr and pellets were prepared by applying a pressure of 10 tons in a hydraulic press. The pellets were scanned over a wavelength range of 400 to 4,000 cm-1 using an FTIR 8400S model instrument. Drug-excipient interactions play a vital role in the release of drug from formulations. FTIR techniques have been used to study the physical and chemical interactions between drug and excipients used.

RESULTS AND DISCUSSION

Weight variation, hardness, thickness, friability and content uniformity

The results of the weight variation, hardness, thickness, friability, and drug content of the tablets are given in table 2.All the tablets with different proportion of polymer composition were within the weight range of 96.67 mg to 103 mg with SD values 0-1.52. The tablets thicknesses of the various formulations were observed to be in the range of 2.71mm to 2.96mm with SD values of 0.005-0.015 (Table 2). The mass and thickness of all compressed tablets were within the limit as per USP. The hardness of all the tablets was found to be in the range of 3.5 to 4 kg/cm2. The drug content ranged from 97.4 to 108.1%. The results of content uniformity shows all the formulations comply with that prescribed in the Indian pharmacopeia. The loss in total weight of tablets due to friability was in the range of 0.383 to 0.563%. Friability for all the formulation shown less than 0.90% which is in the acceptable limits which indicates formulations have good mechanical strength.

Table 2: Data of Weight variation, thickness, friability and content uniformity

| Formulation code	Weight variation (mg)$^\text{\textsterling}$	Thickness (mm) $^\text{\textsterling}$	Friability (%)	Content uniformity(%)
F1	101±1	2.75±0.005774	0.430	99.01
F2	103±0	2.73±0.005	0.391	101.02
F3	102.33±1.52	2.71±0.005	0.383	103.1
F4	97.33±0.57	2.8±0.01	0.491	108.01
F5	99±1	2.80±0.005	0.522	98.4
F6	98±1	2.73±0.01	0.563	97.4
F7	99±1	2.75±0.005	0.532	99.3
F8	101±1	2.71±0.005	0.492	98.5
F9	99±1	2.74±0.01	0.482	100.1
F10	101±1	2.96±0.015	0.513	99.5
F11	101.33±1.52	2.74±0.005	0.521	99.3
F12	96.67±1.52	2.78±0.005	0.492	98.4

Mean±SD , $^\text{\textsterling}$ n=10

In vitro **release studies:**

In vitro drug release studies were conducted in phosphate buffer pH 6.8 and the studies revealed that the release of Nebivolol Hydrochloride from different formulations varies with characteristics and composition of matrix forming polymers as shown in graphs (Figure 2-4). From the fig 2 it was evident that Chitosan in the concentration of 40% of polymer of the total tablet weight (F3) showed better release of drug when compared with other three ratios 20%, 30%, 60% of total polymer tablet weight ratios. In case of F1, F2 formulations the polymer quantity was in sufficient to produce the required retarding nature upto 8 hrs, maximum drug release was occurred in 6 hrs only, where as in F4 formulation the quantity of polymer was high hence it showed more drug retardation with less drug release that is 62.56% in 8 hrs.
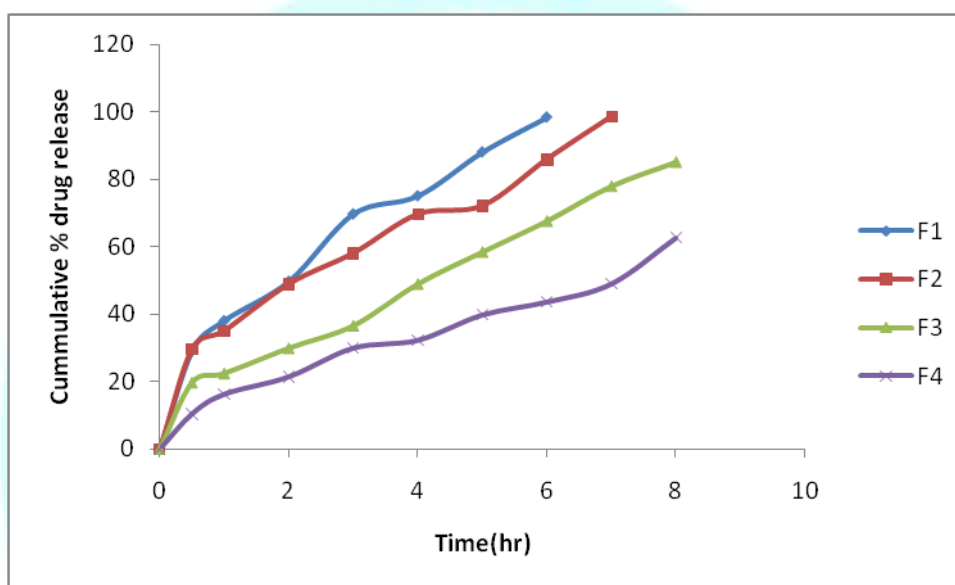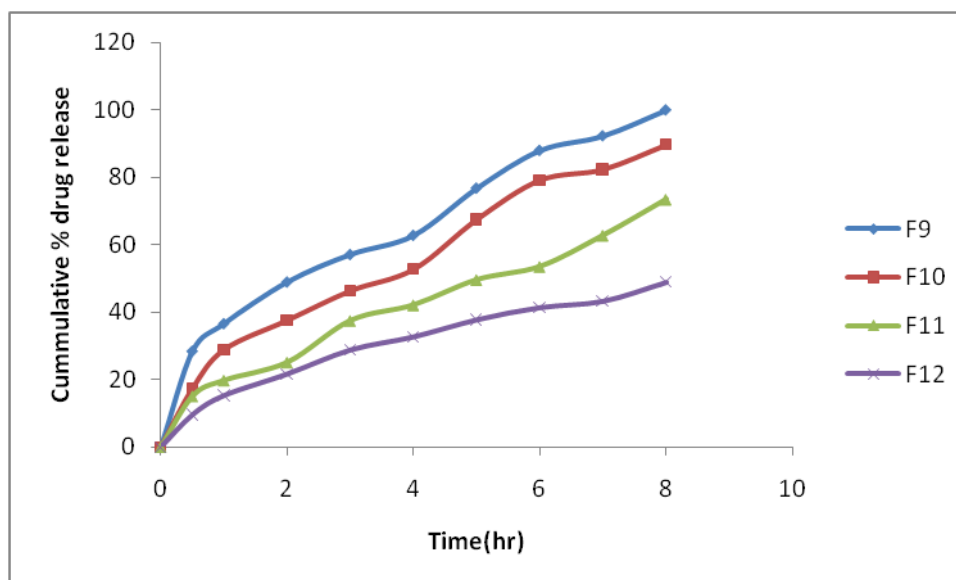

Figure 2 : *In vitro* **dissolution data for formulations F1 - F4by using Chitosan polymer**
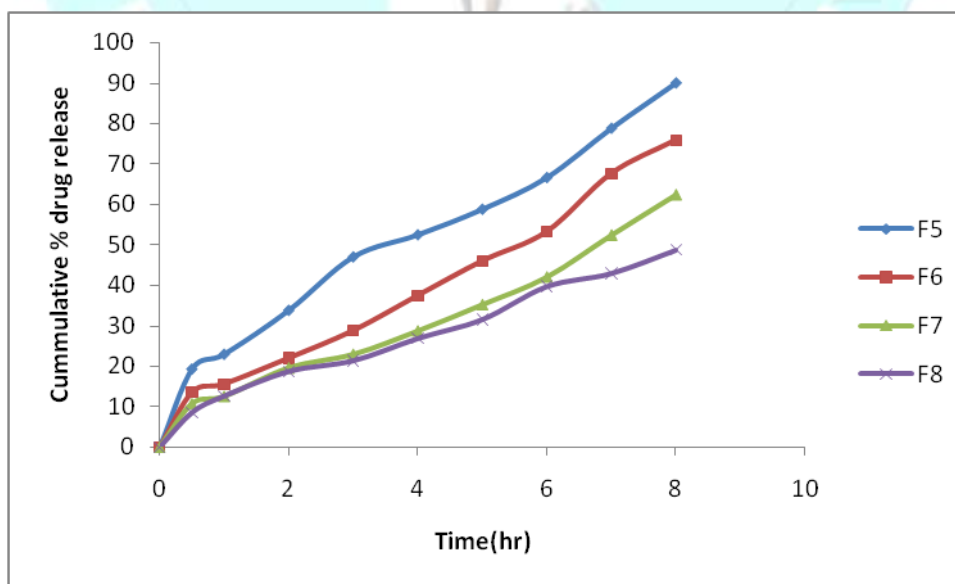
Figure 3 : *In vitro* **dissolution data for formulations F5 - F8 by using Guargum polymer**

Figure 4 : *In vitro* **dissolution data for formulations F9- F12 by using Sodium CMC polymer**

From the figure 3 it was evident that Guargum in the Polymer concentration of 20% of the total tablet (F5) showed better result 89.90% drug release when compared with other three ratios F6, F7 and F8. As the concentration of polymer increases the retarding of drug release also increased. Hence they were not considered.

From the fig 4 it was evident that Sodium CMC in the Polymer concentration 30% of the total tablet weight (F10), showed better result 89.73% drug release when compared with other three formulations. In case of F9 formulation the polymer was to produce required bioadhesion strength and the maximum drug was released in 8 hrs. whereas in F11, F12 formulations the concentration become high and the drug release was retarded more than 8 hrs, hence it was not taken in to consideration.

Ex vivo **residence time, moisture absorption, surface pH, bioadhesion strength values of selected formulations.**

Ex vivo **residence time** is one of the important physical parameter of buccal bioadhesive tablets. The *ex vivo* residence time was determined by specially designed apparatus. Among the selected formulations F3 formulation has shown more residence time when compared with other formulations. **The moisture absorption** studies give important information of the relative moisture absorption capacities of polymers and it also give information regarding whether the formulations maintain the integrity or not. Among the selected formulations F3 formulation shown good moisture absorption. **The surface pH of** the buccal tablets was determined in order to investigate the possibility of any side effects. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The surface pH of the selected formulations was found to be 6.71 to 6.81 and the pH was near to the neutral. These results suggested that the polymeric blend

identified was suitable for oral application and formulations were not irritant to the buccal mucosa. **Bioadhesion strength** was measured for the selected formulations**.** From these two parameters such as peak detachment force (N) and work of adhesion were calculated and they were found to be good for the formulation F3. All these data was tabulated in table 3.

Table 3: Data of selected formulations

Ex vivo residence time, moisture absorption, surface pH, bioadhesion strength

Formulation Code	*Ex vivo* residence time (hrs)	Moisture absorption (%)$^\text{ş}$	Surface pH $^\text{ş}$	Bioadhesion strength	
				Peak detachment force (N)	Work of adhesion (mJ)
F3	7hr 51min	65±2	6.18±1.12	4.5	16.43
F5	7hr 34min	54.6±2.08	6.11±1.4	4.5	15.24
F10	6hr 33min	49.6±1.15	6.14±1.43	4.9	13.43

Mean±SD $^\text{ş}$n=3

***Ex vivo* permeation studies of selected formulations through porcine buccal mucosa**

From the table 4 and fig 5 it was evident that selected formulations were showing good flux and permeability coefficient values. Among the selected formulations F3 formulation was showing maximum flux value of 499.43 ($\mu g.hrs^{-1}cm^{-2}$) and permeability coefficient value was 0.4994 (cm/hrs).

Table 4: Ex vivo permeation studies graph of selected formulations through porcine buccal mucosa

Time (hrs)	F3	F5	F10
0	0	0	0
0.5	19.73	19.28	17.42
1	22.42	22.93	28.89
2	29.90	33.78	37.59
3	36.56	46.97	46.35
4	48.93	52.43	52.75
5	58.40	58.74	67.58
6	67.58	66.56	79.23
7	77.92	78.73	82.42
8	89.06	89.90	89.73
Flux ($\mu g.hrs^{-1}cm^{-2}$)	499.43	469.32	434.38
Permeability coefficient (cm/hr)	0.4994	0.2218	0.1525

Release kinetics:

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Nebivolol release from buccal tablets. The data was fitted into various kinetic models such as zero, first order kinetics, higuchi and korsmeyer peppas mechanisms and the results were shown in table 5 and fig 6-9.

Table 5 : Release kinetics and correlation coefficients (R^2)

Formulation code	Mathematical models (Release kinetics)				
	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	n value
F3	**0.981**	0.910	0.951	0.940	0.612
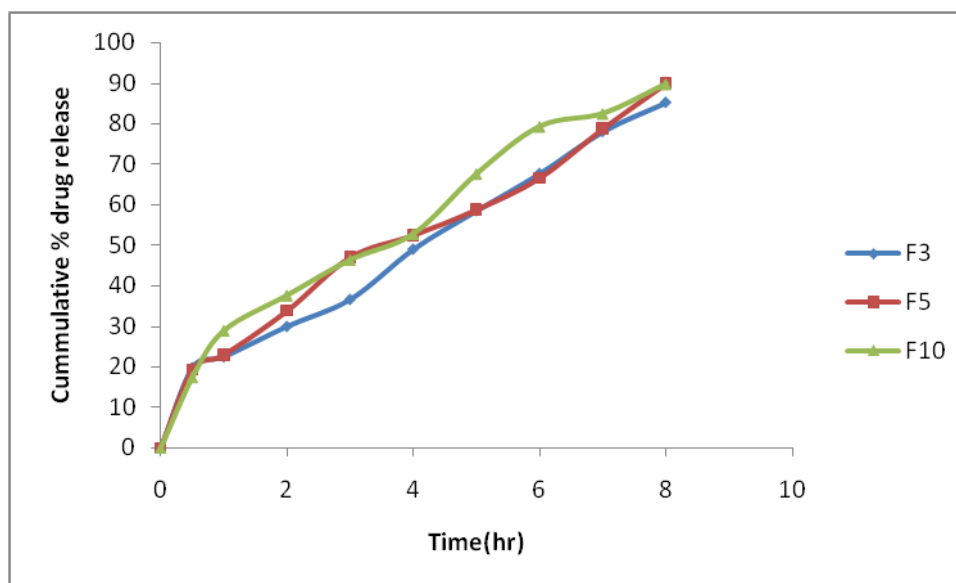
Figure 5: *Ex vivo* **permeation studies of selected formulations through porcine buccal mucosa**
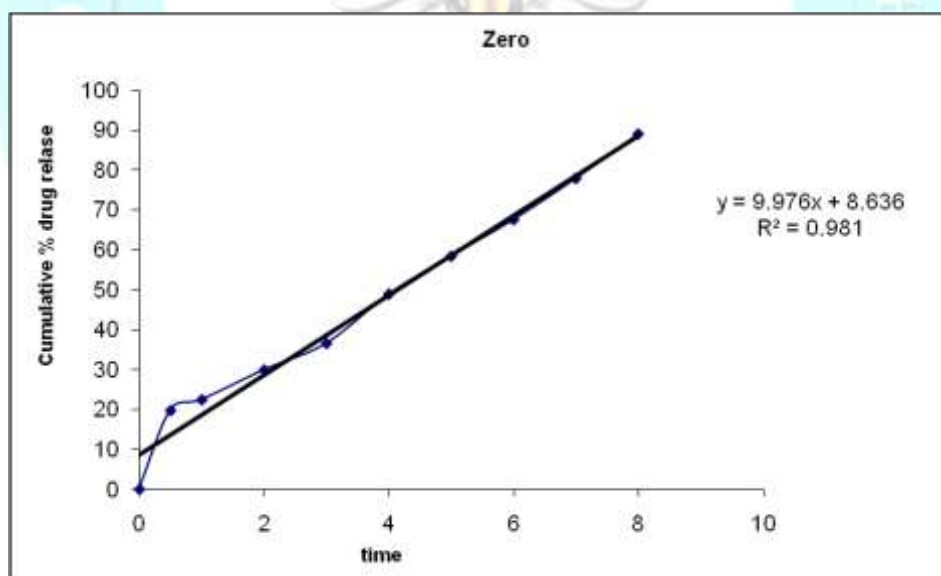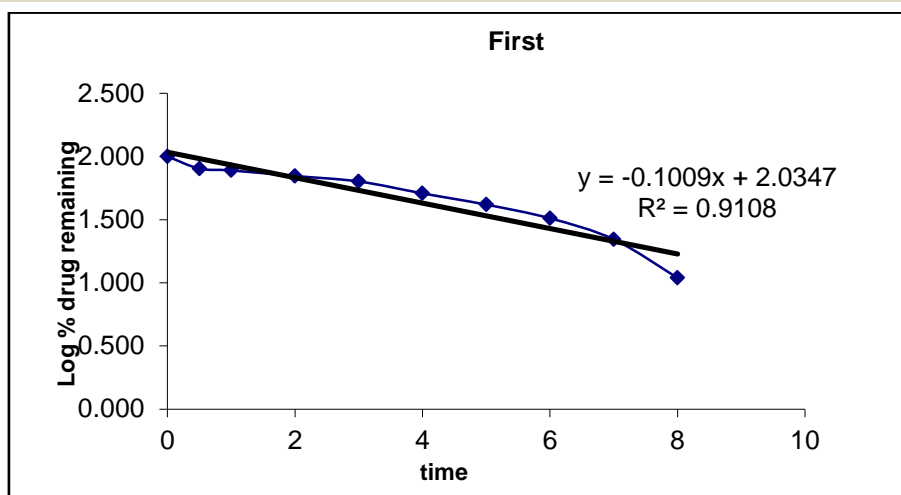

Figure 6 : Zero order plot of optimized formulation

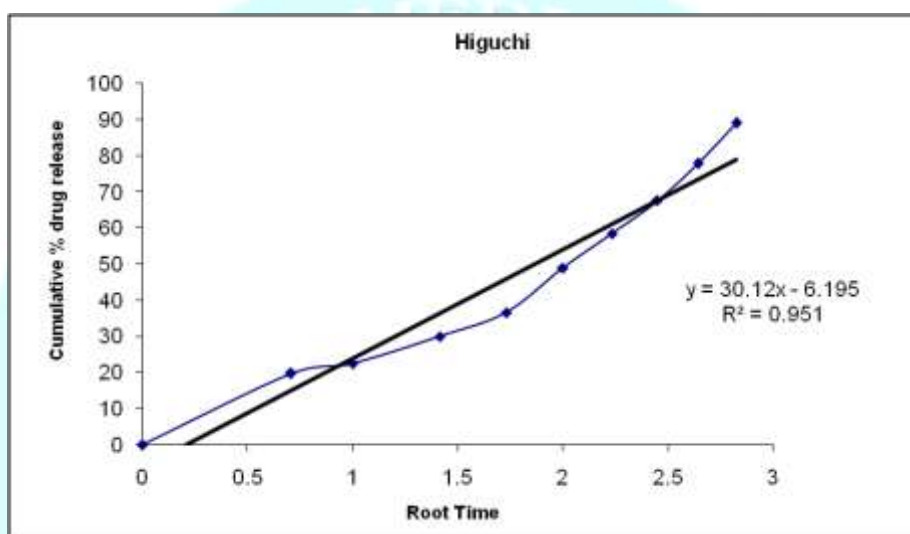**Figure 7: First order plot of optimized formulation**

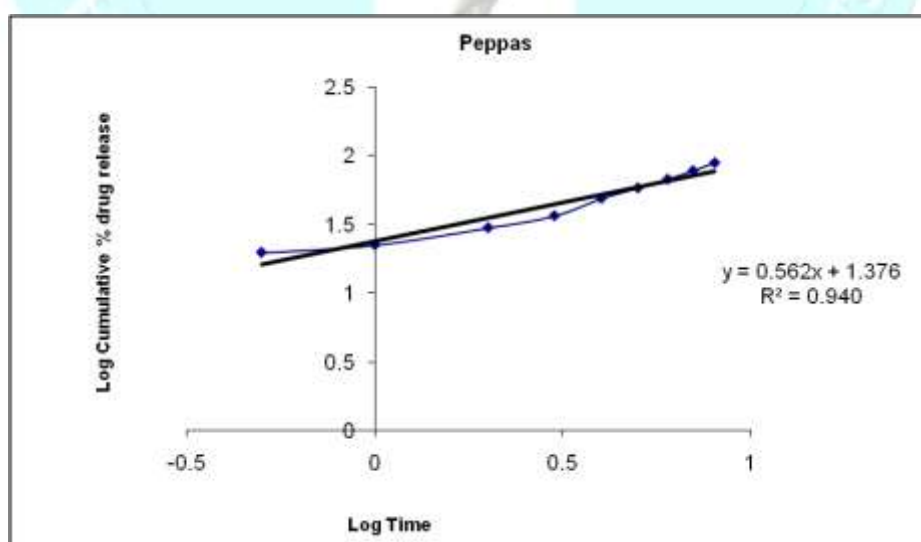**Figure 8: Higuchi plot of optimized formulation**

Figure 9 : Koresmeyer-peppas plot of optimized formulation.

**Drug –excipient compatability studies by physical observation:**

Nebivolol was mixed with various proportions of excipients showed no colour change at the end of two months, proving no drug-excipient interactions.

FTIR

FTIR spectra of the drug and the optimized formulation were recorded. The FTIR spectra of pure Nebivolol drug, drug with polymers (1:1) shown in the below figures respectively. The major peaks which are present in pure drug Nebivolol are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used (Fig 10, 11). This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Figure 10: FTIR Peak of Pure drug Nebivolol

Figure 11: FTIR Peak of Optimized formulation
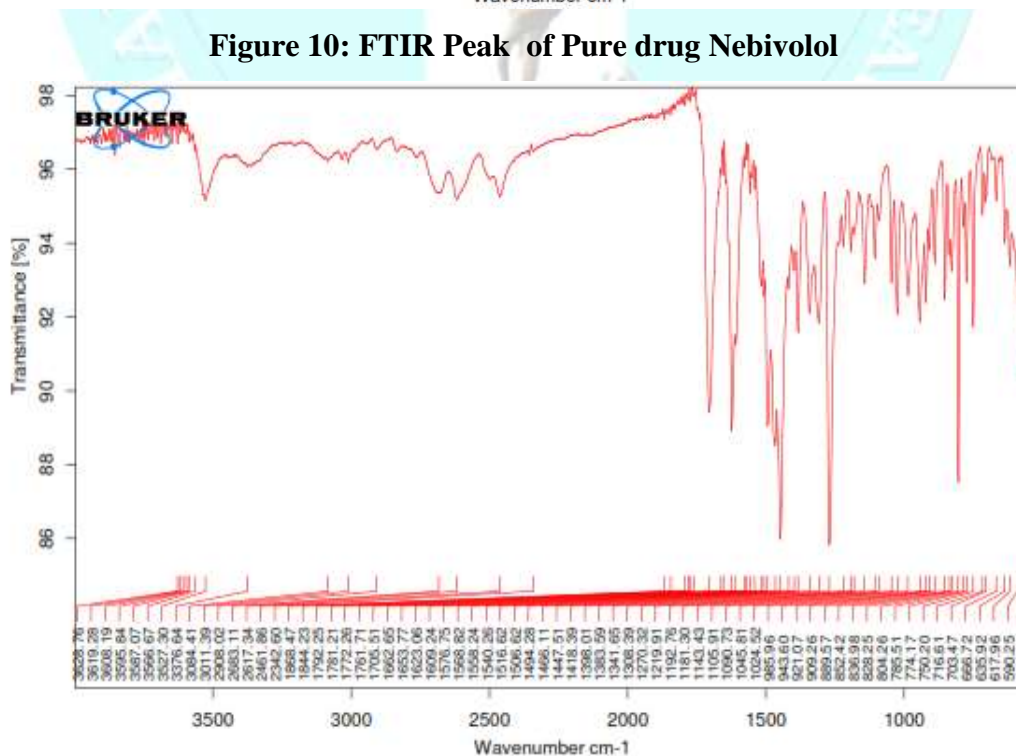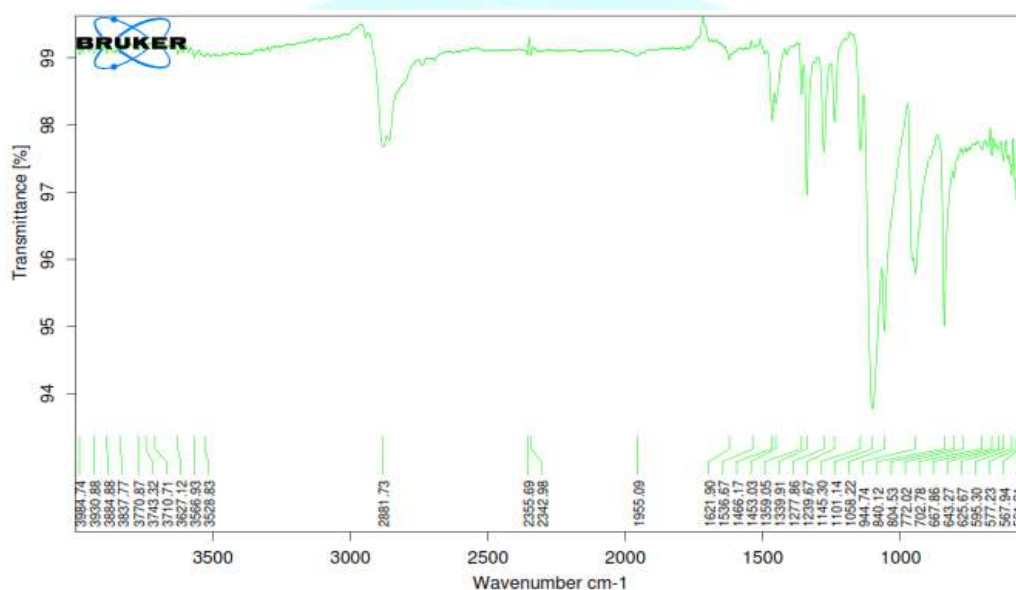
CONCLUSION

Mucoadhesive buccal tablets of Nebivolol Hydrochloride were prepared by direct compression method. It was shown that with the developed formulations, the Nebivolol release and bioadhesion properties of buccal tablets can be controlled by changing the polymer type and concentration. The formulation F3 consists of Nevibolol (5mg), chitosan (30mg), MCC (61mg), magnesium stearate (2mg) and talc (2mg) was selected as optimum formulation. Various physicochemical parameters tested for this formulation showed good results. Bioadhesion of the optimized formulation provided a longer period of residence time, reducing loss of drug by swallowing, which should result in higher bioavailability. It was concluded that development of bioadhesive buccal drug delivery of Nebivolol tablets was one of the alternative routes of administration to avoid first-pass effect and to improve the bioavailability of Nebivolol through buccal mucosa and enhance the release of drug for extended period of time. In addition, these formulations reduce the need of frequent administration and enhance patient compliance. This finding suggested that the Nebivolol tablets have a strong potential for use as a buccal delivery system. However, more studies are necessary to evaluate the in vivo drug delivery and permeation of the final formulation.

ACKNOWLEDGMENT

REFERENCES

1. Naga Raju K, Velmurugan S, Deepika B, Sundar Vinushitha, Formulation and In-vitro Evaluation of Buccal Tablets of Metoprolol Tartrate. International Journal of Pharmacy and Pharmaceutical Sciences, 2011; 3(2): 239-246.

2. El-Samaligy M S, Yahia S A, Basalious E B. Formulation and Evaluation of Diclofenac sodium buccoadhesive discs, International Journal of Pharmaceutics 2004; 286: 27-39.

3. Silvia Rossi, Givseppina Sandri, Carla M.Caramella, Buccal drug delivery Today: Technologies, Drug Delivery or formulation and nanotechnology, 2005; 2(1): 59-65.

4. Prasad B Kadam, Remeth J Dias, Kailas K Mali, Vijay D Havaldar, Niranjan S Mahajan. Formulation and Evaluation of buccoadhesive tablets of Atenolol, J Pharm Res, 2008; 1(2): 193-199.

5. Noha Adel Nafee, Fatma Ahmed Ismail, Nabila A Boraie, Mucoadhesive Delivery Systems I. Evaluation of Mucoadhesive Polymers for Buccal Tablet Formulation, Drug Dev Ind Pharm, 2004; 30(9): 985-993.

6. El Samaligy M S, Afifi N N, Mahmoud E A. Increasing Bioavailability of silymarin using a buccal liposomal delivery system: Preparation and Experimental design investigation, International Journal of Pharmaceutics, 2006; 308: 140-148.

7. Choy Fun Wong, Kah Hey Yuen, Kok Khiang Peh. Formulation and Evaluation of

controlled release Eudragit buccal patches, International Journal of pharmaceutics, 1999; 178: 11-22.

8. Ikinci G, Senel S, Wilson C G. Development of a buccal bioadhesive nicotine tablet formulation for smoking cessation, International Journal of Pharmaceutics, 2004; 27:173-198.

9. Lagoth N, Kahibacher H, Scoffmann G, Schmerold I, Schuh M, Sonja franz, Peter Kurka, Andreas Bernkop-Schnurch, Thiolated Chitosans. Design and In-vivo Evaluation of a Mucoadhesive Buccal Peptide Drug Delivery Systems, Pharmaceutical Research, 2006; 23(3): 573-579.

10. Calum R Park, Dale L. Munday. Development and Evaluation of a biphasic buccal adhesive tablet for nicotine replacement therapy, International Journal of Pharmaceutics, 2002; 237: 215-226.

11. http://www.rxlist.com/drugs/alpha_n.htm#NeNh.

12. Leon Lachman, Herbert A. Liberman. The Theory and Practice of Industrial Pharmacy, Special Indian Edition; 2009: 300-301.

13. Soliman Mohammadi-Samani, Rahim Bahri-Najafi, GolamhoseinYousefi. Formulation and *in vitro* evaluation of prednisolone buccoadhesive tablets, Il Farmaco, 2005; 60: 339–344.

14. Kashappa Goud H. Desai and T.M. Pramod Kumar. Preparation and Evaluation of a Novel Buccal Adhesive System, AAPS PharmSci Tech, 2004; 5 (3): 35, 1-9.

15. Velmurugan S, Deepika B, Nagaraju K, Sundar Vinushitha. Formulation and in-vitro Evaluation of Buccal Tablets of Piroxicam, International Journal of PharmTech Research, 2010; 2 (3): 1958-1968.

16. Bhavin Patel, Piyush Patel, Ashok Bhosale and Shrawaree Hardikar**.** Evaluation of Tamarind Seed Polysaccharide (TSP) as a mucoadhesive and sustained release component of nifedipine buccoadhesive tablet & Comparison with HPMC and Na CMC, International Journal of PharmTech Research, 2009; 1(3): 404-410.

17. Vamshi Vishnu Yamsani, Ramesh Gannu, Chandrasekhar Kolli, M. E. Bhanoji Rao and Madhusudan Rao Y. Development and in vitro evaluation of buccoadhesive carvedilol tablets. Acta Pharm. 2007; 57: 185-197.