FORMULATION AND EVALUATION OF NEBIVOLOL MUCOADHESIVE BUCCAL TABLET

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Summary

The purpose of this study was to design and optimise an oral controlled release Nebivolol mucoadhesive tablet by using HPMC K_4M, HPMC $K_{15}M$ and Carbomer-940 as mucoadhesive polymers, which significantly influence characteristics like swelling index, ex-vivo mucoadhesive strength and *in-vitro* drug release. Tablets were prepared by direct compression and evaluated for mucoadhesive strength and *in-vitro* dissolution parameters. A total of twelve formulations were developed with varying concentration of polymers. The release behaviour was non-fickian controlled by a combination of diffusion and chain relaxation mechanisms and best fitted zero order kinetics. All tablets were acceptable with strength was observed in tablets formulated with HPMC K_4M, HPMC $K_{15}M$ and Carbomer-940. Formulation F_6 showed maximum release 99% in 8 hrs. Formulation F_{11}, F_{12} showed good bioadhesion strength. Formulation F_6 followed zero order drug release pattern. FT-IR studies showed no evidence of interaction between drug and polymers. The results indicate that suitable mucoadhesive buccal tablet with desired property can be prepared.

Key Words: Mucoadhesive, Buccal patch, Nebivolol, HPMC K_4M, HPMC $K_{15}M$ and Carbomer-940.

Introduction

Conventional routes of drug administration such as oral, intramuscular and intravenous have, in many cases, been supplanted by the advent of new, novel drug delivery systems. The systemic delivery of drugs through novel methods of administration is one area in which significant changes and improvements have been made. Consequently, precise control of drug input into the body by a variety of routes is now possible. Controlled and sustained release formulations have been developed and are gaining in popularity and medical acceptance [1]. Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over both injectables and enterable methods [2]. Not all drugs, however, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug.

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of administration problems such as high first pass metabolism, drug degradation in harsh gastro intestinal environment can be circumvented by administering a drug via buccal route [3-5]. More over buccal drug absorption can be terminated promptly in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer the drug to patients who cannot be dosed orally to prevent accidental swallowing. Therefore mucoadhesive dosage forms were suggested for oral drug delivery which includes adhesive tablets [6-8], adhesive gels [9-10] and adhesive patches [11-12].

Nebivolol is a long acting, cardio selective beta blockers, currently licenced for the treatment of hypertension. Nebivolol was selected as a model drug for investigation because of its suitable properties like half-life of 10 hours; molecular weight 44.1 g/mol make it suitable for administration by buccal route [16]. A suitable buccal delivery system should posse's good bioadhisive properties. So that it can retain in oral cavity for desired duration and localise the dosage form in a specific region and control the release rate of drug.

The aim of this study was, design, development and characterization of a buccoadhesive controlled-release tablet of Nebivolol using some selective polymers like carbomer 940 (CP), hydroxypropylmethyl cellulose K4M and K15 M (HPMC).Also the interaction between polymers and drug-polymers, bioadhesion and *in-vitro* release characteristics of Nebivolol from different buccoadhesive matrix tablets was evaluated to assess the suitability of such formulations.

Material and Methods

Nebivolol was provided by Torrent pharmaceutical Ltd (Ahmedabad). Carbomer-940 was obtained as gift sample from Loba Chemie Pvt. Ltd. (Mumbai). Hydroxy propyl methyl cellulose K_4M and $K_{15}M$ was gifted by Apex Pharmaceuticals (Chennai). All other chemicals employed were of analytical grade.

Preparation of Mucoadhesive Tablets

Table 1 enlists the composition of different mucoadhesive formulations prepared using varying amount of polymers. Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100, except lubricant all the ingredients were thoroughly blended in a glass mortar with pestle for 15 min. After sufficient mixing lubricant was added and again mixed for additional 2-3 min. The mixture is compressed using 8 mm flat faced punch on 16 stages rotary tablet compress machine. Composition of the prepared bioadhesive buccal tablet.

Table1a. Composition of formulations containing HPMC K4M in different ratios

Formulation code	F1	F2	F3	F4
Ingredients(mg/tablet)	1:1	1:2	1:3	1:4
Nebivolol	5	5	5	5
HPMC K4M	5	10	15	20
Mannitol	107.00	102.00	97.00	92.00
Magnesium stearate	3	3	3	3
Total weight(mg)	120	120	120	120

Table 1 b Composition of formulations containing HPMC K15M in different ratios

Formulation code	F5	F6	F7	F8
Ingredients(mg/tablet)	1:1	1:2	1:3	1:4
Nebivolol	5	5	5	5
HPMC K15M	5	10	15	20
Mannitol	107.00	102.00	97.00	92.00
Magnesium stearate	3	3	3	3
Total weight(mg)	120	120	120	120

Table 1 c Composition of formulations containing in CARBOMER 940 in different ratios

Formulation code	F9	F10	F11	F12
Ingredients(mg/tablet)	1:0.25	1:0.5	1:0.75	1:1
Nebivolol	5	5	5	5
Carbomer 940	1.25	2.5	3.75	5
Mannitol	110.75	109.50	108.25	107.00
Magnesium stearate	3	3	3	3
Total weight(mg)	120	120	120	120

Evaluation of Formulations

Physical Formulations

Ten tablets from each formulation were evaluated for uniformity in tablet weight and thickness. For each formulation the hardness of five tablets was determined using the monsanto hardness tester (cad mach), 10 tablets from each formulation were examined for friability using the Roche friabilator.

Drug Content Uniformity

Five tablets from each formulation were powdered individually and a quantity equivalent to 100mg of Nebivolol was accurately weighed and extracted with a suitable volume of 0.1 N HCl. Each extract was suitably diluted and analysed spectrophotometrically at 254nm.

Swelling Studies

The tablets of each formulation were weighed individually (W1) and placed separately in Petri-dishes containing 15ml of phosphate buffer (pH 6.8). At regular intervals (1, 2, 4, and 8 hours) the tablets were removed from Petri dishes and excess water removed carefully using filter paper. The swollen tablets were re-weighed (W2); the swelling index of each formulation calculated

by using this formula.

$$\text{Swelling Index (S.I.)} = W1\text{-}W2 / W1$$

W1 = Initial Weight, W2 = Final Weight

In-Vitro Release Studies

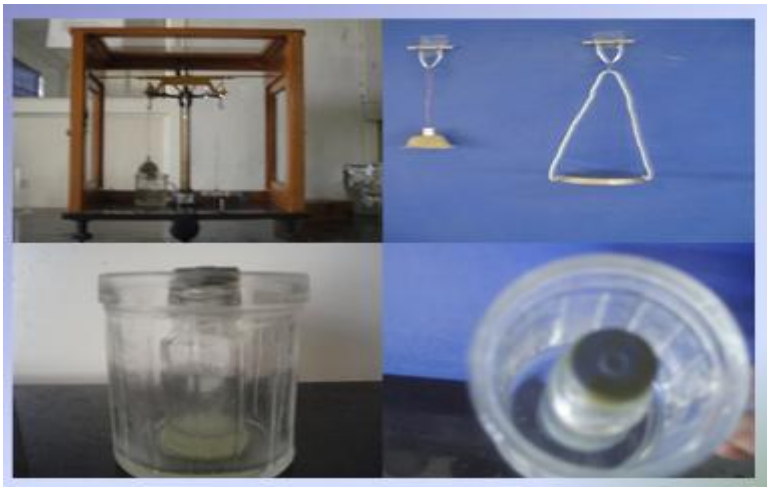
The drug release rate from buccal tablets was studied using the USP (II) dissolution test apparatus (Lab India dissolution test apparatus Disso 2000). The assembly is kept in a jacketed vessel of water maintained at 37±10C. Buccal tablet was made to stick on bottom of the flask (so as to allow one sided release from the tablet). The beaker is filled with 500ml of phosphate buffer pH 6.8. The vessel maintained at 50rpm under stirring conditions by means of paddle fabricated for purpose in dissolution apparatus. At various intervals of time, samples were withdrawn and filtered through whatmann filter paper no.42. It is replaced immediately with equal amount of fresh buffer. The samples are then analyzed U.V. spectrophotometrically at 280 nm up to 10hours.

Ex-Vivo Mucoadhesion Studies

Bioadhesive strength of the tablets was measured on a modified physical balance .The apparatus consisted of a modified double beam physical balance in which a lighter pan had replaced the right pan and the left pan had been replaced by a glass slide (4 cm length and 2.5 cm width) with plastic hang suspended by Teflon rings and copper wire. The left-hand side of the balance was exactly 5 g heavier than the right side .The height of the total set up was adjusted to accommodate a glass container of 6.6cm height. All parts of modified physical balance were shown in Fig 1.

In order to find out the bioadhesion strength first buccal tablet (n=3) was stacked to the glass slide with the help of knob, which was situated at the base of physical balance. Now five grams weight from the right pan was then removed. This lowered the glass slide along with the tablet over the membrane with a weight of 5.0 g. This was kept undisturbed for 5 min. Then the weights on the right-hand side were slowly added in increments of 0.1 g till the tablet just separated from the membrane surface. The excess weight on the right pan, i.e. total weight minus 5g was taken as a measure of the bioadhesive strength.

Figure 1. Bioadhesion strength apparatus.



Ex vivo permeation study of buccal tablets through the porcine buccal mucosa was performed using Franz-type diffusion cell at 37°C ± 0.2°C and 50rpm. This temperature and rpm was maintained by using magnetic stirrer. Porcine buccal mucosa was obtained from a local slaughterhouse and used within 2 hr of slaughter. The tissue was stored in Krebs buffer at 4°C upon collection.

The epithelium was separated from underlying connective tissues with surgical scissors and clamped between donor and receiver chambers of the Franz-type diffusion cell. After the buccal membrane was equilibrated for 30 min with Krebs buffer solution between both the chambers, the receiver chamber was filled with fresh pH 7.4 buffer solution .The buccal tablet was placed in donor chamber and 1mL of buffer solution (pH 6.8) was added. Aliquots (5mL) were collected at predetermined time intervals and filtered through a filter paper, and the amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 280 nm using a UV spectrophotometer. The medium of the same volume (5 mL), which was prewarmed at 37°C, was then replaced into the receiver chamber. The experiments were performed in triplicate (n = 3) and mean value was used to calculate the flux, permeability coefficient.

Drug Release Kinetic Studies

To describe the kinetics of the drug release from the matrix base buccal patch of optimized batch F6, mathematical models such as zero-order, first order, Higuchi, Korsmeyer-Peppas models are where use. The criterion for selecting the most appropriate model was chosen on the basis of the goodness-or fit test.

Drug Excipient Compatibility Study

FTIR Spectroscopic studies were conducted for optimised formulation and Nebivolol pure drug.

Result and Discussion

Physical Evaluation

The weights of all tablets were within ±5% of the average weight, thickness between 2.13 and 3.46mm, and hardness between 4.3 and 5.2 kg/cm^2. Friability ranged between 0.06 and 0.25% thus all the physical parameters of the compressed tablets prepared were practically within the acceptable limits. The assayed content of drug in various formulations varied between 98.17% to 100.38%. The results showed no interference of the formulation excipients, i.e. HPMC K_4M, HPMC $K_{15}M$ and Carbomer-940. The results are shown in (Table No.2).

Swelling Studies

The swelling behavior of a buccal adhesive system is an important property for uniform and prolonged release of drug and bioadhesiveness. The agar plate model used in this study simulates the secreting fluid around the buccal mucosa which is required for adhesion, swelling and release of the drug from tablets. The swelling index of mucoadhesive tablets for a period of 8hours was studied.The value obtained is showed in (fig). It is evident that an increase in the amount of HPMC $K_{15}M$ causes decrease in swelling index and in case of HPMC K_4M, Carbomer-940 there is an increase in swelling index. Among all the formulations F6 swelling index was the highest, giving a value of 2.5.

Table 2. Physico-chemical parameters of formulations

Formulation Code	Thickness (mm)	Weight Variation(mg)	Friability (%)	Hardness (Kg/cm^2)	%Drug content
F1	**2.13±0.010**	**119.6±0.20**	**0.08**	**4.4±0.13**	**98.19**
F2	**2.16±0.020**	**117.0±0.24**	**0.16**	**4.5±0.33**	**99.69**
F3	**2.43±0.035**	**120.9±0.15**	**0.07**	**4.3±0.13**	**99.77**
F4	**2.35±0.010**	**118.2±0.70**	**0.05**	**4.6±0.10**	**100.38**
F5	**2.54±0.040**	**123.0±0.50**	**0.22**	**4.3±0.10**	**99.38**
F6	**2.63±0.030**	**122.3±0.20**	**0.08**	**4.6±0.05**	**99.49**
F7	**2.72±0.010**	**125.9±0.25**	**0.25**	**4.5±0.05**	**98.17**
F8	**2.64±0.030**	**124.3±0.60**	**0.09**	**4.5±0.05**	**98.20**
F9	**2.71±0.042**	**121.9±0.50**	**0.10**	**4.9±0.09**	**98.47**
F10	**3.18±0.057**	**120.9±0.48**	**0.32**	**5.2±0.15**	**99.35**
F11	**3.35±0.023**	**122.4±0.20**	**0.06**	**5.1±0.21**	**99.48**
F12	**3.46±0.010**	**122.1±0.47**	**0.38**	**5.0±0.10**	**100.01**

Each value represents the mean ±SD (*n* =3)

Table 3. Swelling index profile of formulations

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	0.27	0.32	0.39	0.48	0.16	0.24	0.31	0.35	0.11	0.08	0.21	0.32
2	0.84	1.01	1.15	1.45	0.33	0.41	0.51	0.55	0.42	0.37	0.67	0.93
3	1.25	1.57	1.73	1.73	0.56	0.62	0.89	0.96	0.66	0.72	1.01	1.25
4	1.55	2.1	2.08	1.96	0.79	0.85	1.34	1.45	0.95	1.25	1.46	1.51
5	2.11	2.25	2.36	2.15	1.23	1.53	1.89	1.97	1.14	1.44	1.75	1.86
6	2.25	2.32	2.56	2.37	1.54	2.23	2.34	2.45	1.35	1.69	2.12	2.26
7	2.35	2.48	2.61	2.63	2.42	2.38	2.49	2.51	1.58	2.06	2.37	2.59
8	2.41	2.5	2.6	2.67	2.49	2.5	2.63	2.68	2.49	2.52	2.54	2.6

Figure 2a. Swelling index profile of formulations containing HPMC K4M

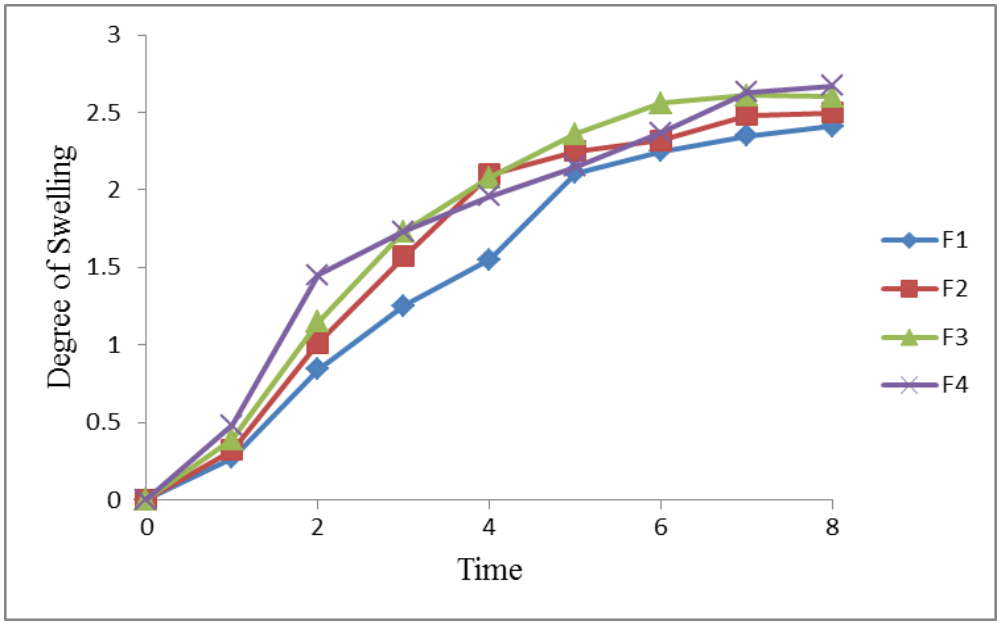


Figure 2 b. Swelling index profile of formulations containing HPMC K15M

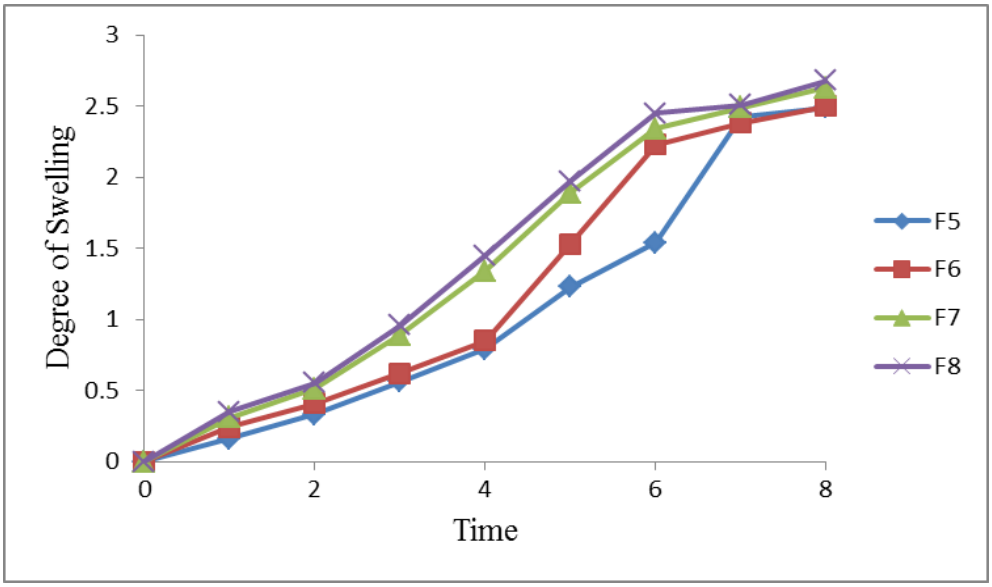
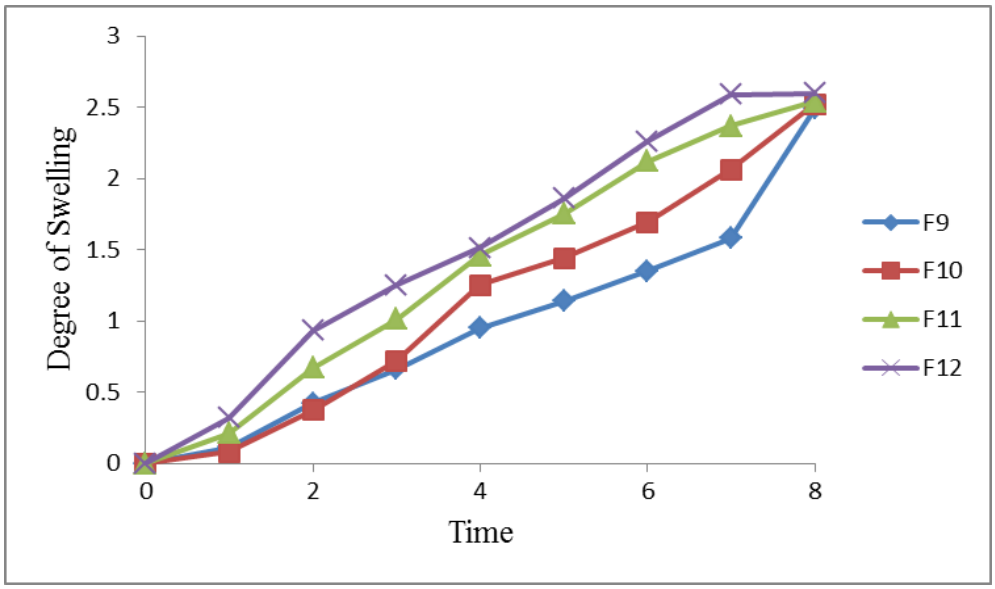


Figure 2 C. Swelling index profile of formulations containing CARBOMER 940



In-Vitro Release Studies

The Release of DTZ from buccal tablets varied according to type and ratio of matrix forming polymers. 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.

As 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 Carbomer-940 is more hydrophilic than HPMC and if it is added in high ratios causes high release rate of Nebivolol as indicated by greater mean dissolution time from the matrices. The release rate of Nebivolol decreased with increasing concentration of HPMC K4M and HPMC K15M in F4 (82.6±0.5%), F8 (94.7±0.7%) respectively. These findings are in compliance with the ability of these cellulose derivatives to form complex matrix network which leads to delay in release of drug from the device. Carbopol is more hydrophilic, it can swell rapidly, and therefore decrease of carbopol content delays the drug release.

Drug release rate was increased with increasing amount of hydrophilic polymer. The maximum cumulative percent release of Nebivolol (99.4±0.5%) from formulation F6 Further, the increase in rate of drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release, of the drug. Moreover, the hydrophilic polymers would reach out and hence, create more pores and channels for the drug to diffuse out of the device.

Table4 a. *In-vitro* cumulative percentage drug release profile of HPMC K4M

Time (hr)	F1	F2	F3	F4
0	0	0	0	0
1	23.6±0.7	19.4±0.8	17.8±0.9	17.3±0.7
2	30±0.3	23.1±0.6	21.5±0.7	20.5±0.8
3	57.8±0.1	55.2±0.7	54.2±0.5	34.2±0.7
4	67.3±0.2	65.2±0.4	63.1±0.4	58.4±0.5
5	72.1±0.2	71.0±0.6	69.4±0.5	68.4±0.7
6	77.8±0.4	74.7±0.5	73.1±0.4	75.7±0.6
7	82.0±0.5	79.4±0.4	77.3±0.8	77.4±0.7
8	86.8±0.6	85.2±0.6	83.6±0.7	82.6±0.5

Figure3 a. *In vitro* cumulative percentage drug release profile of HPMC K4M

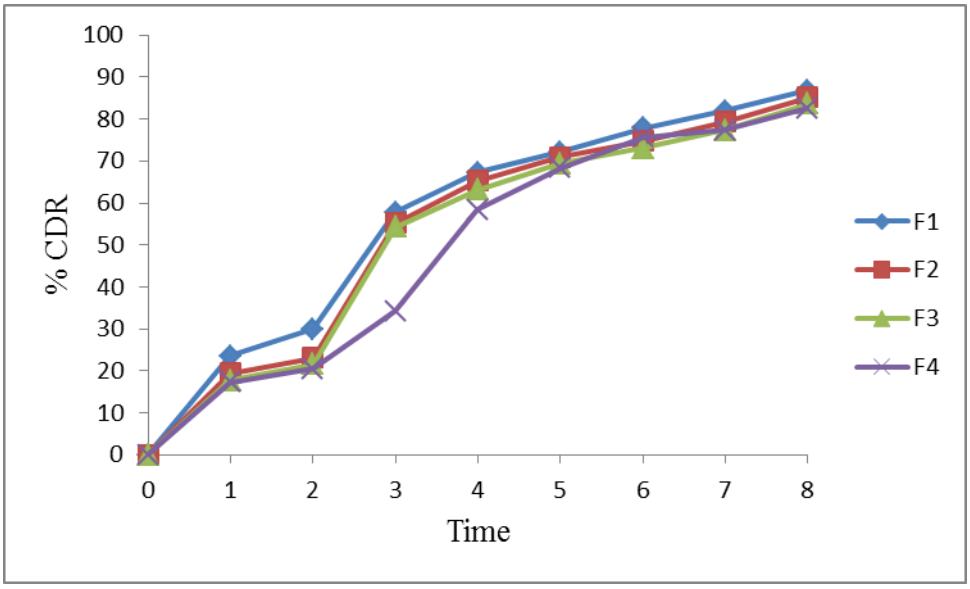


Table4 b *In vitro* cumulative percentage drug release profile of HPMC K15M.

Time (hr)	F5	F6	F7	F8
0	0	0	0	0
1	68.9±0.7	13.1±0.7	12.8±0.5	11.6±0.8
2	82.6±0.6	27.3±0.5	25.1±0.8	23.5±0.5
3	88.4±0.3	45.7±0.6	41.5±0.5	38.7±0.6
4	90.5±0.5	63.1±0.5	60.1±0.6	59.7±0.9
5	98.4±0.4	71.5±0.3	70.1±0.5	68.5±0.7
6	-	84.2±0.5	80.5±0.4	77.8±0.6
7	-	91.1±0.3	89.4±0.9	87.5±0.5
8	-	99.4±0.5	95.7±0.8	94.7±0.7

Figure 3b. *In vitro* cumulative percentage drug release profile of HPMC K15M

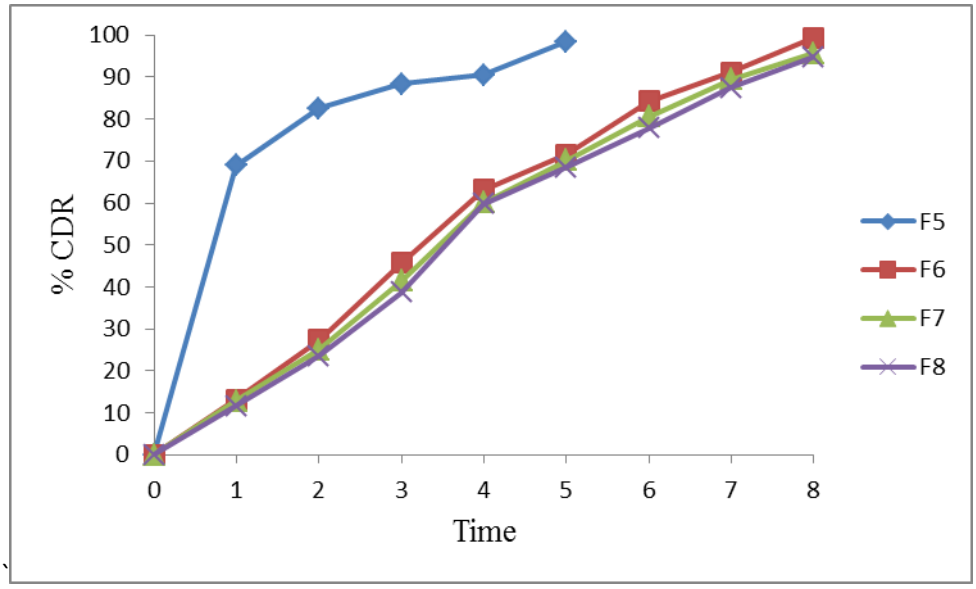
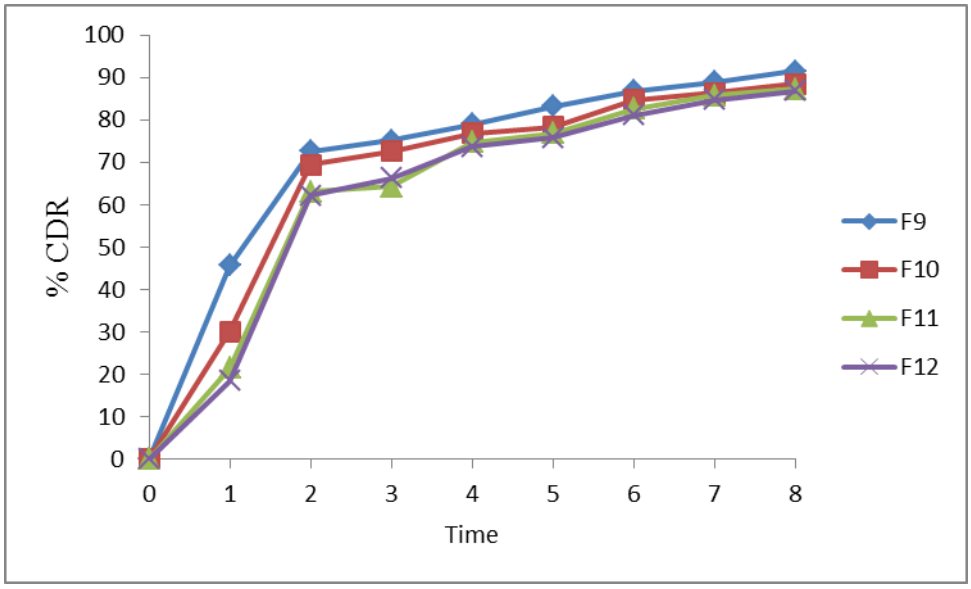


Table 4 c *In vitro* cumulative percentage drug release profile of CARBOMER 940

Time (hr)	F9	F10	F11	F12
0	0	0	0	0
1	45.7±0.8	30±0.9	21.5±0.9	18.4±0.7
2	72.6±0.4	69.4±0.3	63.1±0.5	62.1±0.8
3	75.2±0.6	72.6±0.6	64.2±0.5	66.3±0.7
4	78.9±0.3	76.8±0.5	74.7±0.8	73.6±0.6
5	83.1±0.5	78.4±0.5	76.8±0.6	75.7±0.5
6	86.8±0.4	84.7±0.8	82.6±0.4	81±0.7
7	88.9±0.5	86.3±0.3	85.7±0.5	84.7±0.7
8	91.5±0.6	88.4±0.7	87.3±0.9	86.8±0.5

Figure 3 c.*In vitro* cumulative percentage drug release profile of CARBOMER940.



Ex-Vivo Mucoadhesion Studies

Based on the *in vitro* drug release studies, F6 selected for the *ex vivo* permeation study. The flux, permeation coefficient and cumulative percent drug permeated from formulation F6 were found to be 0.1262mg.hrs^{-1}cm^{-2} and 0.101cm/h respectively. The values of cumulative amount of drug permeated and cumulative percent drug permeated were given in Table 15, the values of flux, permeability coefficient were given in Table 16 and Comparison of cumulative percent drug permeated from drug solution, formulation was given in Figure 8.

Table 5. *Ex vivo* drug permeation profiles of drug solution and optimized formulation

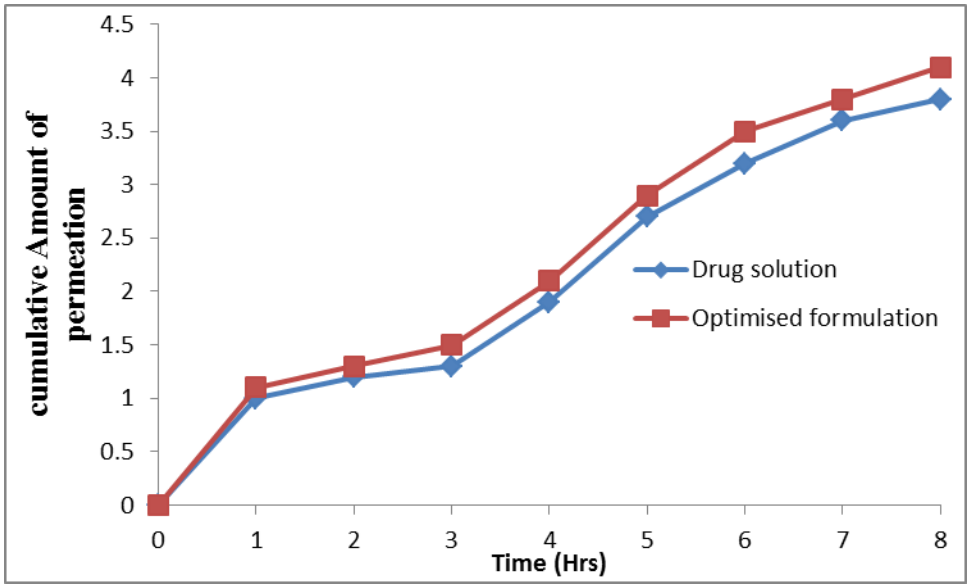
Time (hr)	Drug solution		Optimised formulation	
	Cum amt drug per[a] (mg)	Cum % drug per[b]	Cum amt drug per[a] (mg)	Cum % drug per[b]
0	0	0	0	0
1	1.0±0.2	21.5±0.2	1.1±0.2	22.0±0.2
2	1.2±0.3	24.1±0.5	1.3±0.6	26.0±0.4
3	1.3±0.5	27.6±0.2	1.5±0.7	30.1±0.1
4	1.9±0.6	38.6±0.1	2.1±0.8	42.0±0.7
5	2.7±0.2	54.1±0.8	2.9±0.4	58.1±0.1
6	3.2±0.7	64.4±0.7	3.5±0.2	70.1±0.3
7	3.6±0.2	72.0±0.4	3.8±0.3	76.0±0.1
8	3.8±0.5	77.1±0.3	4.1±0.1	82.0±0.3

Each value represents the mean ±SD (*n* =3).

[a]Cum amt drug per,Cumulative amount of drug permeated.

[b]Cum % drug per, Cumulative percentage drug permeated.

Figure 4. Comparison of cumulative Amount of permeation of drug solution and optimised formulation



Drug Release Kinetic Studies

Release mechanism and kinetics, optimized formulation (F_6) was attempted to fit. The result are shown in (Table 5)

Table 6. Release kinetics and mechanism of optimized formulation

Formulation code	Mathematical models (Kinetics)				
	Zero order	First order	Higuchi	Peppas model	
F6	r^2	r^2	r^2	n	r^2
	0.9756	0.7993	0.9371	1.007	0.9848

Excipients Compatibility Study

FT-IR study revealed that, in pure Nebivolol, gave peaks at respective wave numbers i.e aliphatic sec amine (1493, 1435 cm^{-1}), Carbonyl (1214, 1192 cm^{-1}) and sulphur-oxy group (1074, 1030 cm^{-1}). In optimized formulation also same groups showed peaks very nearer to those wave numbers. From this it was concluded that there was no interaction between drug and excipients.

Figure 5 a. FTIR OF PURE DRUG:

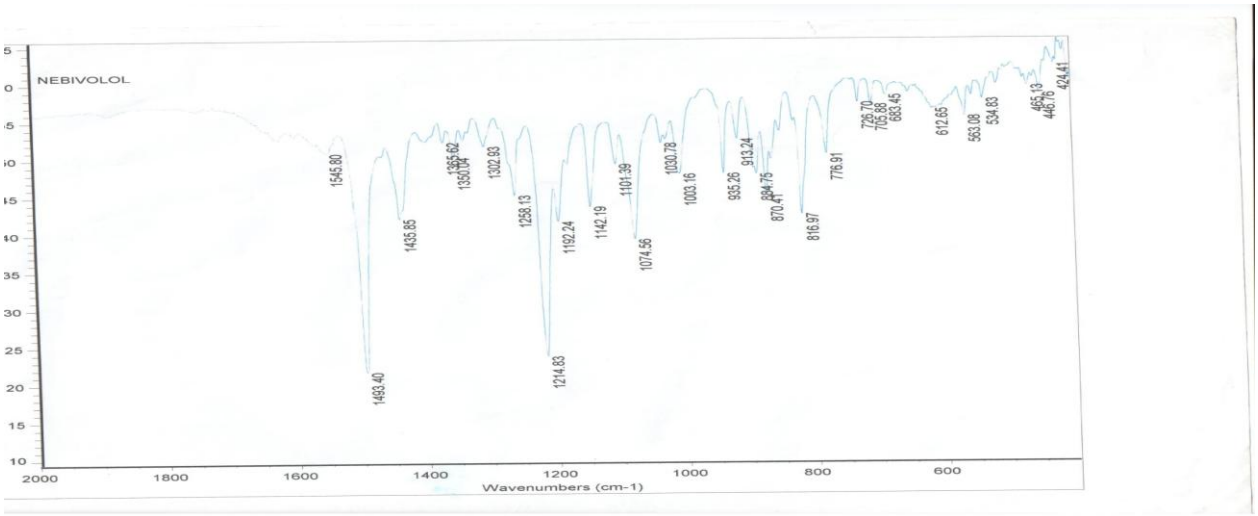
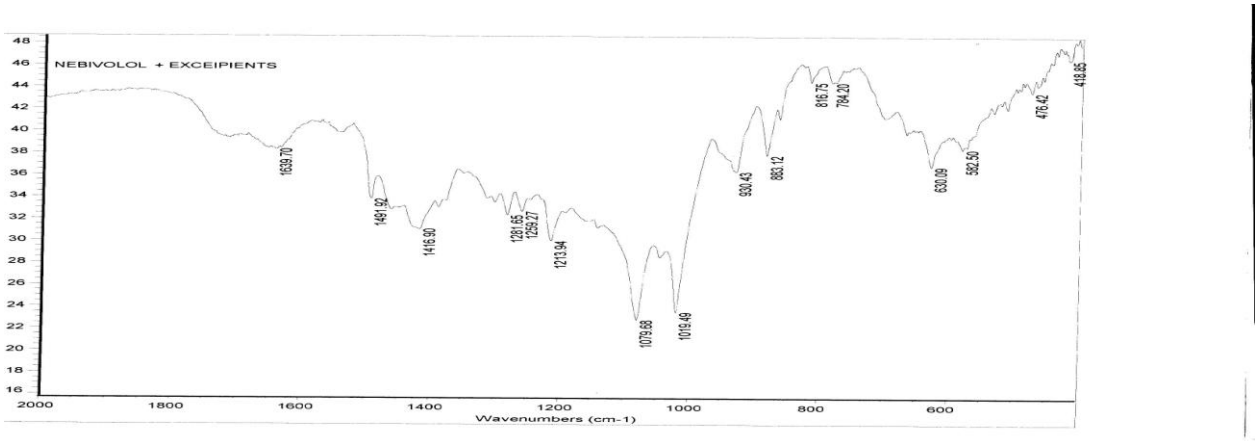


Figure 5 b FTIR OF OPTIMIZED FORMULA:



Conclusion

This study suggests that the polymers HPMC K15M (F6) can produce a controlled pattern of drug release in the prepared Nebivolol tablets. The high mucoadhesive strength of this formulation is likely to increase its residence time in the gastrointestinal tract, which eventually improves the extent of bioavailability. However, an appropriate balance between various levels of the tow polymers is needed to acquire proper release and mucoadhesion. It can be concluded that by formulating mucoadhesive tablets of Nebivolol, its complete release can be ensured prior to absorption window and hence the problem of incomplete drug release and erratic absorption can be solved by increasing the retention time of drug in GIT for a longer duration of time.

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