WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 7, 540-553 Research Article ISSN 2278 – 4357

FORMULATION DESIGN AND EVALUATION OF NEBIVOLOL BUCCAL TABLETS

P. Vinod Kumar*[1], Prasanna Kumar Desu[1], K. Nagaraju[1], T. Maheswari[1], E. Shasi[1] and P. Venkateswara Rao[2]

*,[1]Department of Pharmaceutics, St. Mary's Group of Institutions Guntur, Chebrolu (V&M), Guntur, Andhra Pradesh, India – 522212.

[2]Departemnt of Pharmaceutical Chemistry, St. Mary's Group of Institutions Guntur, Chebrolu (V&M), Guntur, Andhra Pradesh, India – 522212.

Article Received on
24 April 2018,

Revised on 14 May 2018,
Accepted on 04 Jun 2018

DOI: 10.20959/wjpps20187-11702

***Corresponding Author**
Dr. P. Vinod Kumar
Department of Pharmaceutics, St. Mary's Group of Institutions Guntur, Chebrolu (V&M), Guntur, Andhra Pradesh, India – 522212.

ABSTRACT

The purpose of this study was to design and optimise an oral controlled release Nebivolol mucoadhesive tablet by using HPMC K4M, CArbopol-940 and Hydroxy Methyl Cellulose as mucoadhesive polymers, which significantly influence characteristics like swelling index, exvivo 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 nine formulations were developed with varying concentration of polymers. Pre-formulation study was carried out for powder blends and it was evaluated to determine the flow characteristics by bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose. The results obtained from these studies indicated that the powder blend had good flow properties. The Mucco adhesive buccal tablets were prepared with different ratios of polymers by direct compression method. The formulated tablets were evaluated for physical characterization like thickness, hardness, friability, weight variation and drug content, swelling index, bio –adhesive strength, Ex-vivo retention time, dissolution. All the physical parameters of prepared Mucco adhesive buccal tablets comply with IP specifications. The formulated tablets were evaluated for drug content and it was found to be in the range of 94% w/w. Thus, all formulation of Nebivolol was found to be within the acceptable range. The optimized formulation (F6) had shown the satisfactory release of drug. The drug polymer

interaction study was carried out by FTIR study. From the report it was concluded that there was no interaction between drug and polymers used in the formulations.

KEYWORDS: Nebivolol, Carbopol, Hydroxy Propyl Methyl Cellulose and and Hydroxy Ethyl Cellulose.

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]

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.[12] 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 carbopol 934, hydroxypropylmethyl cellulose K4M and HEC. 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.

MATERIALS AND METHODS

Nebivolol was obtained as a gift sample from Spectrum labs, Hyderabad. Carbopol, Hydroxy propyl Methyl Cellulsoe and Hydroxy Ethyl Cellulose and Magnesium Stearate were obtained from SVR Labs Hyderabad. All the excipients and solvents used are analytical grade.

Method of Preparation

The buccoadhesive tablets were prepared by direct compression method. All the ingridients were mixed in formulated proportion and lubricants was added and punched using 9 station multi punch tablet compression machine. Each tablet contained 5 mg of Nebvilol the batch size for each formulation was 50 tablets.

Table 1: Composition of Bucccoadhesive Tablets of Nebivolol.

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nebivolol	5	5	5	5	5	5	5	5	5
Lactose	82	72	62	82	72	62	82	72	62
HPMC K4M	10	20	30	-	-	-	-	-	-
Carbopol 934p	-	-	-	10	20	30	-	-	-
Hydroxy ethyl cellulose	-	-	-	-	-	-	10	20	30
Aspertane	1	1	1	1	1	1	1	1	1
SSF (Sodium steryl fumarate)	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Total (mg/tab)	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Evaluation of *Pre-compression parameters*

Angle of repose

Angle is determined using funnel. The accurately weighed powder was taken in a funnel. The height of the funnel is adjusted in such a way the tip of the funnel just touches apex of the head of the blend. The powder is allowed to flow through the funnel freely onto the surface. The diameter of the powder cone is measured, and angle of repose is calculated using the following equation.

tanØ = h\r.

Where h and r the height of the cone and radius cone base respectively.

Bulk density

Apparent bulk density is determined by pouring a weighed quantity of blend into graduated cylinder and measuring the volume and weight. Bulk density is calculated using the following formula:

Bulk density = Weight of powder/bulk volume of powder.

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material.

Hausner's ratio = tapped bulk density/LB.

Compressibility index

The compressibility index is measure of the propensity of the powder to be compressed. As such, they are measures of the relative importance of inter-particulate 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 inter-particulate interactions, and a greater difference between bulk and tapped densities will be observed. These differences are reflected in the compressibility index.

Evaluation of Post Compression Parameters

Dimension (Diameter and Thickness)

The Thickness and diameter permits accurate measurements and provide information on the variation between tablets. The thickness and diameter of the tablets was determined using a Vernier caliper. Three tablets from each type of formulation were used and average values were calculated.

Hardness

There is a certain requirement of hardness in tablets so as to withstand the mechanical shocks during handling, manufacturing, packaging and shipping. For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester. Monsanto hardness tester was used to measure hardness of the tablets. The whole experiment was performed in triplicate. It is expressed in Kg/cm^2.

Friability

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for 4 minutes, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed tablets was placed in Roche friabilator which was then operated for 100 revolutions.

The tablets were then dedusted and reweighed. Generally considered and acceptable limit is loss of less than 1 % in weight. Percent friability (% F) was calculated as

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

Weight variation

The weight variation test is 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 average weight and standard deviation of the tablets were calculated.

Uniformity of Content

The drug content in each formulation was determined by triturating 10 tablets and powder equivalent to 10 mg was 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 Shimadzu-1700 Pharmaspec UV-Visible spectrophotometer at 309 nm using pH 6.8 phosphate buffers.

Surface pH Study

The surface pH of the buccal tablet was determined in order to investigate the possibility of any side effects in an oral cavity. As an acidic or alkaline pH may irritate the buccal mucosa, attempt was made to keep the surface pH close to the buccal pH. The tablets were allowed to swell for 2 h in 1 ml of distilled water. The surface pH was measured by bringing the electrode in contact with the surface of the formulations and allowing it to equilibrate for 1 min.

***In- Vitro* Swelling Study**

Three tablets were used from each formulation for the test. After recording the initial weights the tablets were placed over a 10 cm diameter wet filter paper disc soaked in purified water in a petri dish at room temp. After the time interval of 1, 2, 4, 6 and 8 h., the tablets were removed and weighed individually. The percent water sorption was calculated using following formula:

% Swelling index = $[(w_2-w_1)/w_1] \times 100$

Where, W_2- weight of tablet after particular time interval

W_1- initial weight of tablet

***In- Vitro* Bioadhesion Study[45]**

a) Fabrication of the Test Assembly

For *in-vitro* study, an apparatus designed for the determination of mucoadhesive bond force was used. Bioadhesion test assembly is shown in figure 3. For the designing of the apparatus, two pan weighing balance was used. The pan from the left side was replaced with a glass vial hanged with the thread. Another glass vial inside the glass bottle was placed below this vial in such a way that both (upper and lower) vials just touch each other. The two sides were balanced so that the right side exactly 2 gm heavier than left side by placing appropriate weight in right side pans.

Using this bioadhesion test assembly, the bioadhesion strength expressed in weight (g) required for the detachment of the tablet from the mucosa was determined.

b) Measurement of Adhesion Force

Measurement of adhesion force was determined by using bovine buccal mucosa which was obtained from slaughter house. The underlying tissues were separated and washed thoroughly with phosphate buffer solution (pH 6.8). The membrane was then tied to the bottom of the lower vial using rubber band. The vial was kept in glass bottle which was filled with phosphate buffer solution at 37 ± 1^0C in such way that buffer just reaches the surface of mucosal membrane and kept it moist. The tablet to be tested was stuck on the lower side of the hanging Glass vial by using adhesive tape and the weight (2 gm).

On the right pan was removed. This lowered the left side of the pan along with the tablet over the mucosa. It was kept undisturbed for three minutes and the weights are added on right side

of pan till the tablet just separated from the membrane surface. The excessweight on the right pan i.e. total weight minus 2 gm was taken as measure of bioadhesivestrength. Bioadhesive force was calculated by using following equation.

$$\textbf{Bioadhesive force} = \frac{\textbf{Bioadhesive Strength} \times \textbf{9.81}}{\textbf{100}}$$

***Ex-Vivo* Mucoadhesion Time**

The *ex-vivo* mucoadhesion time was examined after application of the buccal tablet on freshly cut bovine buccal mucosa. The fresh bovine buccal mucosa was tied on the glass slide and a mucoadhesive core side of each tablet was wet with 1 drop of phosphate buffer (pH 6.8) and pasted to the bovine buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer and kept at 37^0C± 1^0C. After 2 minutes, a slow stirring rate was applied to stimulate the buccal cavity environment and tablet adhesion was monitored for 20 hours. The time for the tablet to detach from the bovine buccal mucosa was recorded as the mucoadhesion time.

***In- Vitro* Drug Release Study**

The influence of technologically defined condition and difficulty in simulating *in- vivo* conditions has led to the development of a number of *in- vitro* release methods for buccal formulations, however, no standard method has yet been developed. *In-vitro* release rate of buccoadhesive tablets of Metoclopramide Hydrochloride was carried out using rotating basket apparatus (USP Type I). The dissolution medium consisted of 500 ml of phosphate buffer (pH 6.8). The release study was performed at 37^0C ± 0.5^0C with a rotation speed of 50 rpm. The sample (5 ml) was withdrawn at time interval of 30, 60 and 90 minutes up to 10 h and replaced with 5 ml of dissolution media. The amount of Nebivolol released was determined spectrophotometrically at 262 nm.

RESULTS AND DISCUSSION

Evaluation of Micromeritic Properties of Powder Blend

The Buccoadhesive tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and drug content. Angle of repose was less than 35° and Carr's index values were less than 12 for the raw material of all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

Table 2: Micromeritic Properties of Powder Blend.

Material	Angle of repose (degree)	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility index	Hausners ratio
API	23.92°	0.4526	0.4124	8.88	1.097
F1	25.23°	0.4269	0.4981	14.28	1.166
F2	26.46°	0.3737	0.4983	25.00	1.33
F3	22.36°	0.4250	0.4958	14.28	1.16
F4	22.21°	0.3319	0.3734	11.11	1.12
F5	24.56°	0.3726	0.4258	12.5	1.14
F6	25.62°	0.498	0.598	16.6	1.20
F7	24.35°	0.3775	0.4314	12.50	1.14
F8	26.5°	0.3732	0.4265	12.50	1.14
F9	25.32°	0.3341	0.3758	11.1	1.12

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 99 and 100 mg. The hardness of the tablets ranged from 6.1 to 7.1 Kg/cm^2 and the friability values were less than 1% indicating that the matrix tablets were compact and hard. The thickness the tablets ranged from 2.12 to 2.55 mm. All the formulations satisfied the content of the drug as they contained 90 to 101% of Nebivolol and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practice within control.

Table 3: Evaluation of Postcompressional Parameters of Nebivolol Tablets.

Formulation code	Hard ness (kg/cm^2)	Thickness (mm)	Weight variation	Fraibility (%)	Drug content (%)
F1	6.3±0.60	2.55±0.03	100.74±0.61	0.38	99±0.05
F2	6.8±0.16	2.54±0.02	100.38±0.71	0.15	99±0.01
F3	7.0±0.30	2.51±0.02	100.45±0.64	0.15	98±0.01
F4	6.8±0.16	2.31±0.01	99.91±1.01	0.25	100±0.06
F5	6.3±0.12	2.35±0.03	99.98±0.82	0.15	97±0.12
F6	7.1±0.02	2.12±0.01	100.42±0.61	0.31	98±0.56
F7	6.3±0.17	2.54±0.03	99.98±1.01	0.24	98±0.14
F8	6.8±0.13	2.42±0.01	100.74±0.75	0.43	99±0.25
F9	6.1±0.10	2.51±0.06	100.38±0.71	0.08	99±0.31

Where, All values are mean ±S.D, n=20

The swelling studies were conducted for all formulations i.e. F1 to F9 and the results were shown in Table 4. All the formulations were hydrated generally by keeping the tablets in contact with water for 1 h to 8 h. The highest hydration (swelling) i.e. 86.54% was observed with the formulation F6. This may be due to quick hydration of polymers Carbopol 934p. The

swelling rate of tablets increased in the case of formulation F6 containing Carbopol 934p the ratio of 1:6.

Table 4: Swelling Index of Nebivolol Muco adhesive buccal tablets.

Time (hrs)	Swelling Index (%)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	52.12	36.23	26.35	46.27	35.06	36.55	36.5	33.68	35.21
2	63.52	46.61	35.62	63.51	49.18	45.92	43.1	56.33	49.35
3	71.32	53.24	33.21	76.81	53.34	69.37	62.6	75.92	72.31
4	83.61	63.53	46.41	83.56	66.29	79.11	72.8	83.29	86.35
5	86.15	76.62	56.10	84.17	79.14	86.54	86.3	86.16	78.03
6	66.24	58.8	48.23	60.43	55.55	78.44	72.1	70.13	68.32
7	36.32	34.14	42.11	33.98	46.18	52.15	62.35	56.24	52.42
8	19.25	23.23	36.87	14.26	22.46	32.29	25.6	27.35	24.35

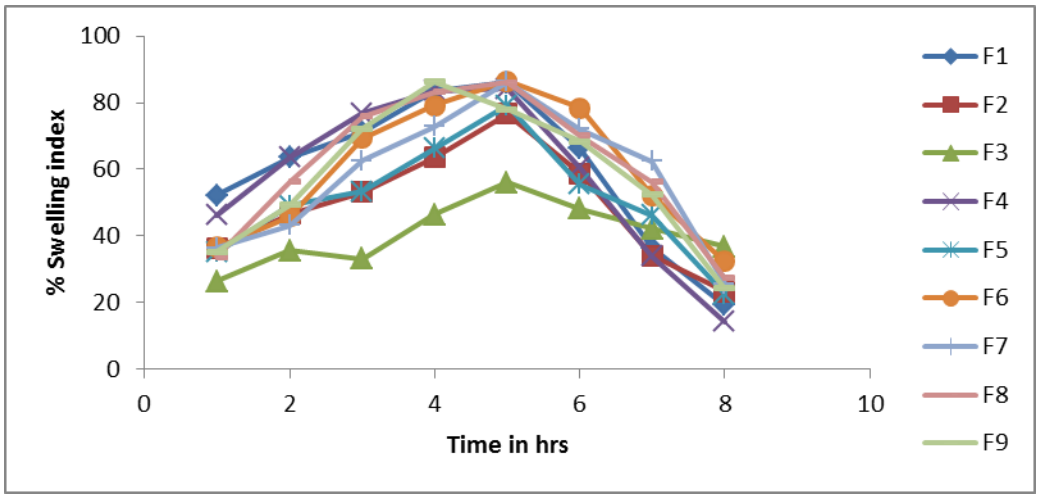

Fig. 1: Swelling index of Nebivolol muccoadhesive buccal tablets.

Surface pH of all the formulations F1 to F9 was found to be 5.7 to 6.82, which is well within the limit of acceptable salivary pH range of 5.69 to 6.34. Hence, it was concluded that all formulations could not produce any local irritation to the mucosal surface. The in vitro bio-adhesive strength study was performed and the results are shown in the Table 5. On the modified physical balance and measure the force (N) required detaching the tablet. The bio-adhesion characteristics were affected by the concentration of the bio-adhesive polymers. Increase in concentration of polymer increases bio-adhesive strength of formulation.

The *Ex vivo* residence time was determined by using specially designed apparatus. Formulations F8 to F9 showed lower residence time when compared to the formulations F1 to F7 Table 5. As the concentration of muco-adhesive material increased, the *ex vivo* residence time also increased. This test reflects the adhesive capacity of polymers used in

formulations. The results revealed that the mixture of carbopol 934 containing formulations showed better residence time than the mixture of and HPMC K4M and Hydroxy ethyl cellulose formulations.

Table 5: Evaluation tests of Nebivolol Mucoadhesive buccal tablets surface pH & Muccoadhesive strength.

Formulation code	Surface PH	Muccoadhesive strength	Ex-vivo residance time
F1	6.82±0.31	18.65±0.36	5hr 15min
F2	6.71±0.2	18.12±0.15	6hr 30min
F3	6.03±0.1	17.95±0.40	7hr 15min
F4	6.82±0.4	16.41±0.37	7hr 45min
F5	6.1±0.2	16.15±0.30	Above 8hrs
F6	6.5±0.21	13.13±0.31	Above 8hrs
F7	6.2±0.35	11.23±0.26	Above 8hrs
F8	6.3±0.3	10.32±0.30	3hr 15min
F9	5.7±0.25	12.41±0.25	4hr 45min

The formulations F1, F2, F3 containing drug, HPMC K4 M polymers in the ratios of 1:2. 1:4, 1:6 respectively. The *in vitro* cumulative drug release profile of formulations F1, F2, F3 and F4 showed 69%, 76%, 81% respectively. Among these four formulations, F3 was found to be highest percentage drug release. During the study it was observed that the tablets were initially swell and no erodible over the period of 8 h.

Similarly the formulations F4, F5, F6 drug, containing Carbopol 934p polymers in the ratios of 1:2, 1:4, 1:6 respectively. The *in vitro* cumulative drug release profile of formulations F4, F5, F6 showed 88%, 90%, 94% respectively. Among these four formulations, F6 was found to be highest percentage drug release. During the study it was observed that the tablets were initially swell and non-erodible over the period of 8 h.

Similarly the formulations F7, F8, F9 drug, containing Hydroxy ethyl cellulose polymers in the ratios of 1:2, 1:4, 1:6 respectively. The *in vitro* cumulative drug release profile of formulations F7, F8, F9 showed 83%, 85%, 87% respectively. Among these four formulations, F9 was found to be highest percentage drug release. During the study it was observed that the tablets were initially swell and non-erodible over the period of 8 h.

It was concluded that by increasing the concentration of Carbopol 934p in the formulation, the drug release rate from the tablets was found to be decreased. But when the concentration of secondary polymers increased, the drug release rate was found to be increased. This may

be due to increased hydration (or) swelling characteristics of polymers with increased concentrations. From the overall data it was found that the formulation F6 showed the maximum percentage of drug release i.e. 94% at the end of 8 h.

Table 6: Invitro Drug Release of Nebivolol Mucoadhesive Buccal Tablets Formulations.

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	22	27	31	28	32	35	24	29	30
2	28	31	38	42	44	46	39	48	50
4	40	46	53	54	58	63	59	63	67
6	50	55	61	73	76	72	66	75	76
7	61	65	71	82	85	81	78	82	85
8	69	76	81	88	90	94	83	85	87

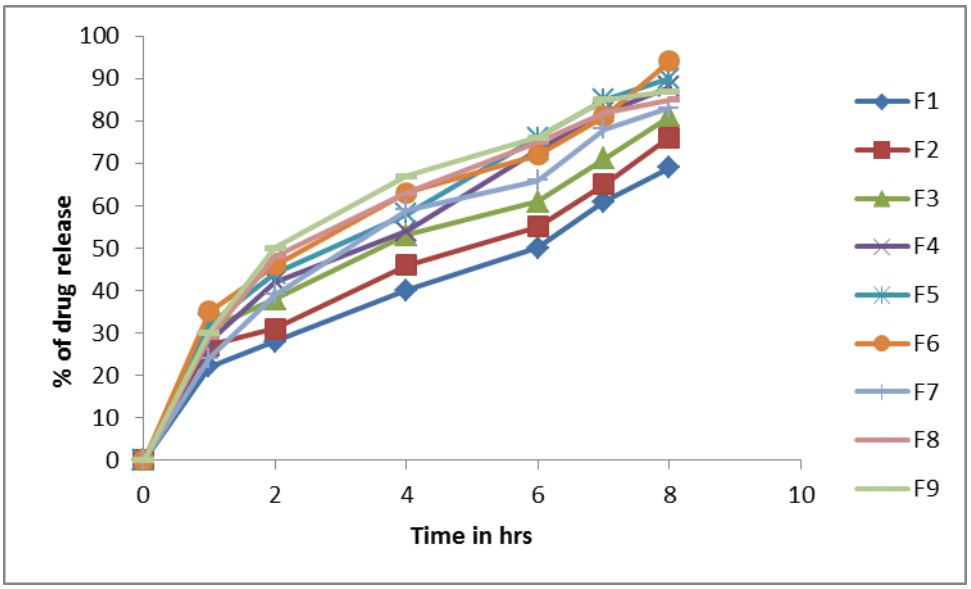

Fig. 2: (%) of drug release in-vitro characterization of Nebivolol Muccoadhesive buccal tablets formulations.

The release rate kinetic data for the F6 is shown in Table 6 As shown in Fig2 drug release data was best explained by zero order equation, as the plots showed the highest linearity (r^2 = 0.912), followed by Higuchi's equation (r^2= 0.974) As the drug release was best fitted in zero order kinetics, indicating that the rate of drug release is concentration in-dependent. Higuchi's kinetics explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases. For the Optimized formulation the Korsmeyer-Peppas equation indicated a good linearity (r^2= 0.984). The diffusion exponent "n" was between 0.45-0.89, which appears to indicating the diffusion mechanism is non-fickian diffusion. And

indicates that the drug release was controlled by more than one process (both diffusion and dissolution).

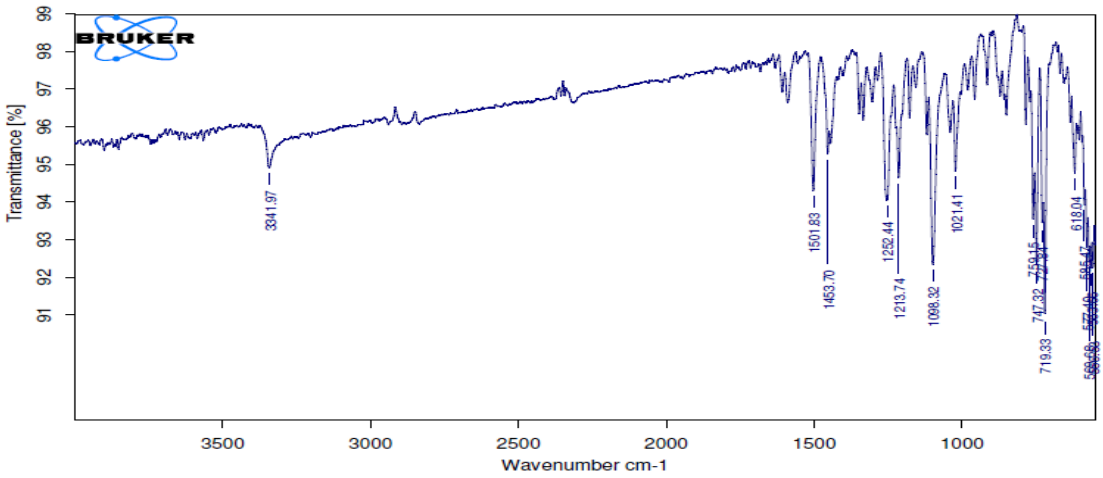

Fig. 3: Pure Nebivolol.

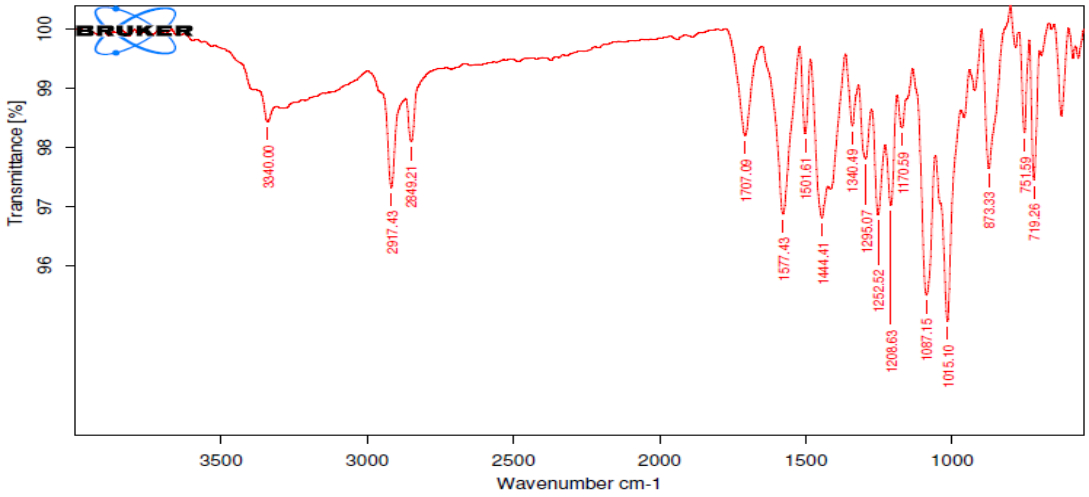

Fig. 4: FTIR Spectra of Optimized Formulation.

CONCLUSION

The overall results indicated that the polymers API and Carbopol 934 in the ratio of 1: 6 showed satisfactory mucoadhesive properties. Among all the formulations, the F6 formulation using these polymers in the above ratio with drug exhibited significant moisture absorption properties with optimum release profile. The optimized formulation F6 also showed satisfactory surface pH and physical parameters, effective *in vitro* permeation, satisfactory stability in human saliva. Hence it can be concluded that the formulation F6 will be useful for buccal administration of Nebivolol. So, the muco-adhesive buccal tablets of Nebivolol may be a good choice to bypass the hepatic first pass metabolism with an

improvement in the bioavailability of Nebivolol through Buccal mucosa Further work is recommended to support its efficacy claims by pharmaco-dynamic and pharmacokinetic studies in human beings.

ACKNOWLEDGEMENT

The authors are Thankful to Rev Dr. K. V. K. Rao and Dr. P. Venkateswara Rao, principal for providing the facilities to carry out this research work in St.Mary's Group of Institutions Guntur.

REFERENCES

1. Chien YW. Novel Drug Delivery Systems. 2nd ed, New York: Marcel Decker Inc, 1992; 1-42.
2. Bouckaert S, Lefebvre RA, Colardyn F, Remon JP. Influence of the application site on bioadhesion and slow-release characteristics of a bioadhesive buccal slow-release tablet of miconazole. Eur J Clin Pharmacol, 1993; 44: 331-335.
3. Harris D, Robinson R. Drug delivery via the mucous membranes of the oral cavity. J Pharm Sci., 1992; 81: 1-10.
4. Senel S, Hincal AA. Drug permeation enhancement via buccal route possibilities limitations. J Control Release, 2001; 72: 133-144.
5. Davis SS, Daly PB, Kennerley JW, Frier M, Wilson CG. The design and evaluation of sustained release formulations for oral and buccal administration. Proceedings of Workshop on Slow Release Nitroglycerin in Buccal and Oral Forms Basle, 1982; 17- 25.
6. Owens TS, Dansereau RJ, Sakr A. Development and evaluation of extended release bioadhesive sodium fluoride tablets. Int J Pharm, 2005; 288: 109-122.
7. Jafar A, Ali N, D Javad F, Massoud A, Mahammad RS. Development and evaluation of buccoadhesive propranolol hydrochloride tablet formulation: effect of fillers. Farmaco, 2004; 59: 155-161.
8. Ishida M, Vambu N, Vagai R. Highly viscous gel ointment containing carbopol for application to the oral mucosa. Chem Pharm Bull, 1983; 31: 4561-4564.
9. Guo JH. Bioadhesive polymer buccal patches for buprenorphine controlled delivery: Formulation in vitro adhesion and release properties. DDrug Dev Ind Pharm, 1994; 20: 2809-2821.
10. Anders R, Merkle HP. Evaluation of laminated mucoadhesive patches for buccal drug delivery. Int J Pharm, 1989; 49: 231-240.

11. Brahmaiah.B, Prasanna Kumar Desu, Sd. Khalillulah, S. Satish Babu, Sreekanth NAma, Formulation and evaluation of extended release mucoadhesive microspheres of simvastatin, International Journal of Pharmaceutical and biomedical Research, ISSN No. 0976-0350, March 2013; 4(1): 57-64.
12. www.drugbank.ca