Research Article

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FORMULATION, OPTIMIZATION AND INVITRO EVALUATION OF NEBIVOLOL BUCCAL TABLETS

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Abstract

In this study Nebivolol buccal tablets were prepared and optimized the release of Nebivolol by using Carbopol, Sodium alginate and Sodium carboxy methyl cellulose as polymers. The tablets prepared by direct compression technique and evaluated by physical parameters and invitro dissolution parameters. A total nine formulations were prepared with varying polymer concentrations. All tablets were acceptable with strength was observed in tablets formulated with Carbopol, sodium alginate and Sodium carboxy methyl cellulose. Formulation F_9 showed maximum release 99% in 8 hrs. FT-IR studies showed no evidence of interaction between drug and polymers.

Keywords: Nebivolol, buccal tablets, Carbopol, Sodium alginate, Sodium carboxy methyl cellulose.

Introduction

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. 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 . 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 , adhesive gels and adhesive patches.

Nebivolol is a long acting, cardio selective beta blockers, used for the treatment of hypertension. Nebivolol was selected 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.

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The aim of current study was design, formulation and evaluation of Nebivolol buccal tablets by using Carbopol, sodium alginate and Sodium carboxy methyl cellulose as polymers and evaluated by suitable methods for optimized formulation.

Materials and method

Nebivolol, carbopol, sodium alginate, Sodium carboxy methyl cellulose, magnesium stearate, Citric acid, aspartame, Mannitol all materials are obtained from Spectrum Pharma research lab, Hyderabad. The Nebivolol buccal tablets were prepared by using the Carbopol, sodium alginate and Sodium carboxy methyl cellulose as polymers in different ratios based on the give formula by direct compression method. All the ingredients mixed thoroughly and passed through sieve no. 20.

Evaluation parameters

Pre-compression studies

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve #20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml and is given by

$$D_b = M / Vb$$

Where,
M is the mass of powder
Vb is the bulk volume of the powder.

Tapped density

It is the ratio of the total mass powder to the tapped volume of the powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

$$D_t = M / Vt$$

Where,
M is the mass of powder
Vt is the tapped volume of the powder.

Angle of repose

It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula

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

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

Where,
θ = Angle of repose
h = height of the cone
r = Radius of the cone base.

Compressibility index

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

$$\text{Carr's compressibility index (\%)} = [(D_t - D_b) \times 100] / D_t$$

Where,

D_t is the tapped density
D_b is the bulk density

Hauser's ratio

Hausner's ratio is an indirect index of the ease of powder flow. It is calculated by the following formula.

$$\text{Hausner's ratio} = D_t/D_b$$

Where,
Dt is the tapped density,
Db is the bulk density.

Post compression studies

Tablet thickness test[2]

Randomly 10 tablets were taken from each formulation trial batch and their thickness was measured using a Venire caliperse.

Weight variation test[2]

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Measurement of tablet hardness[2]

The hardness of tablet is an indication of its strength. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Friability test[2]

It is measured of mechanical strength of tablets. Roche Friabilator is used to determine the friability by following procedure. Twenty tablets were weighed and placed in Roche Friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, dedusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability = (loss in weight / Initial weight) X 100

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.

Swelling Index (S.I.) = W1-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.

Drug release kinetic studies

To describe the kinetics of the drug release from the matrix base buccal tablets 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 optimized formulation and Nebivolol pure drug.

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/cm2. 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 %.

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. Drug release rate was increased with increasing amount of hydrophilic polymer. The maximum cumulative percent release of Nebivolol (96.4±0.5%) from formulation $F_{9.}$ 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.

Table No. 01: Composition of different additives with Nebivolol

Ingredients (mg per tablet)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Nebivolol	5	5	5	5	5	5	5	5	5
carbopol	10	-	-	20	-	-	10	10	-
sodium alginate	-	10	-	-	20	-	10	-	10
Sodium carboxy methyl cellulose	-	-	10	-	-	20	-	10	10
magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Citric acid	1	1	1	1	1	1	1	1	1
aspartame	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Mannitol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total tablet weight	100	100	100	100	100	100	100	100	100

Table No. 02: Results of flow properties

S.No	Formulation code	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (I)	Hausner's ratio
1	F1	24.16	0.512	0.647	20.84	1.28
2	F2	23.74	0.549	0.673	19.42	1.25
3	F3	27.70	0.532	0.650	19.15	1.23
4	F4	26.65	0.545	0.651	17.28	1.20
5	F5	24.69	0.541	0.655	17.40	1.21
6	F6	23.89	0.535	0.668	18.91	1.25
7	F7	29.01	0.541	0.682	20.67	1.24
8	F8	29.72	0.532	0.670	19.59	1.25
9	F9	27.54	0.529	0.665	20.45	1.26

Table No. 03: Results of Post compression Studies

Formulation Code	Thickness (mm)	Weight Variation(mg)	Friability (%)	Hardness (Kg/cm2)	%Drug content
F1	2.12±0.010	118.6±0.20	0.09	4.5±0.13	98.19
F2	2.15±0.020	119.0±0.24	0.16	4.4±0.33	99.69
F3	2.40±0.035	120.9±0.15	0.08	4.3±0.13	99.77
F4	2.35±0.010	118.2±0.70	0.04	4.5±0.10	100.38
F5	2.50±0.040	121.0±0.50	0.21	4.3±0.10	99.38
F6	2.62±0.030	122.3±0.20	0.08	4.6±0.05	99.49
F7	2.73±0.010	125.9±0.25	0.24	4.5±0.05	98.17
F8	2.65±0.030	123.3±0.60	0.09	4.6±0.05	98.20
F9	2.73±0.042	121.9±0.50	0.11	4.8±0.09	98.47

Table No. 04: Swelling index profile of formulations

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	0.26	0.32	0.38	0.48	0.15	0.25	0.30	0.35	0.11
2	0.85	1.01	1.15	1.46	0.33	0.41	0.52	0.56	0.42
3	1.23	1.57	1.74	1.73	0.55	0.62	0.89	0.96	0.66
4	1.56	2.1	2.08	1.95	0.78	0.86	1.35	1.46	0.95
5	2.11	2.25	2.36	2.16	1.23	1.53	1.89	1.97	1.14
6	2.24	2.32	2.55	2.37	1.55	2.24	2.35	2.45	1.35
7	2.35	2.48	2.6	2.64	2.42	2.38	2.48	2.55	1.58
8	2.41	2.5	2.61	2.67	2.49	2.55	2.60	2.68	2.49

Table No. 05: In-vitro cumulative percentage drug release

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	51.71	30.16	28.01	36.63	25.85	21.54	21.54	28.01	40.94
2	71.10	36.63	40.94	47.40	32.32	30.16	36.63	38.78	45.25
3	81.88	66.79	71.10	53.86	43.09	38.78	43.09	53.86	51.71
4	94.80	90.5	94.80	60.33	53.86	49.55	64.64	75.41	71.10
5	99.11	96.96	99.11	64.64	62.48	58.17	68.95	79.72	75.41
6				92.65	75.41	68.95	79.72	84.03	88.34
7				96.96	81.88	77.57	86.19	90.5	94.80
8							90.5	92.65	96.96

Table No. 06: Release kinetics and mechanism of optimized formulation

Formulation code	Mathematical models (Kinetics)			
	Zero order	First order	Higuchi	Peppas model
F9	r2	r2	r2	r2
	0.914	0.511	0.980	0.520

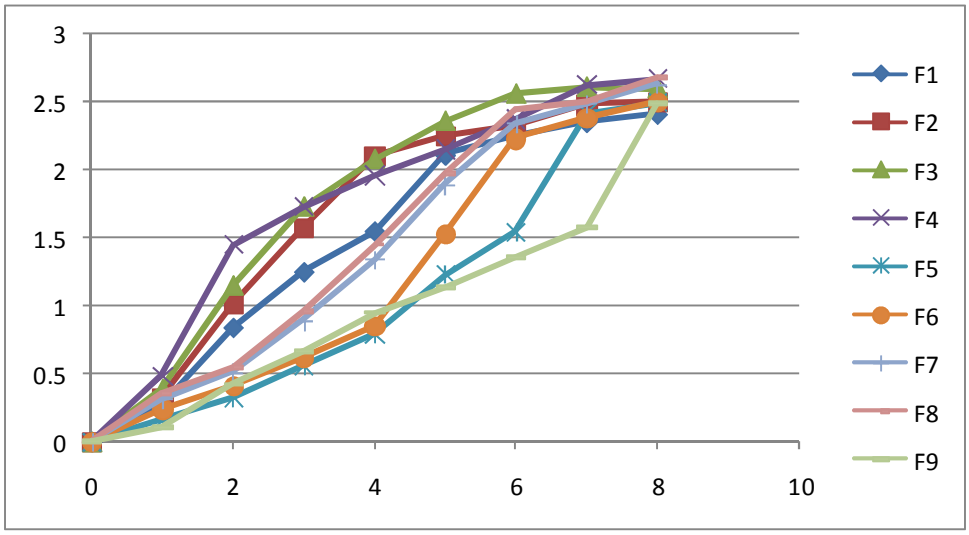

Fig. No. 01: Swelling index profile of formulations

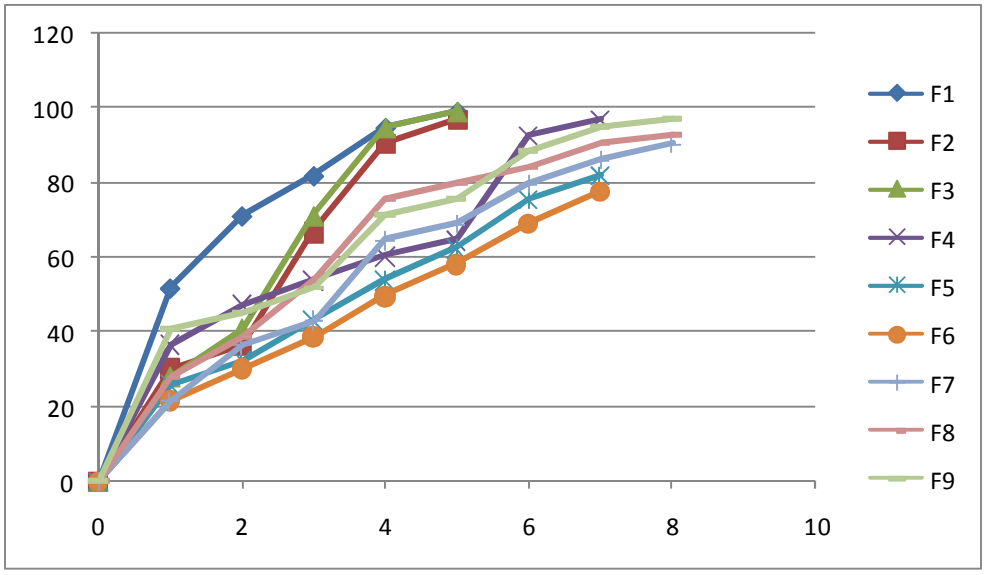

Fig. No. 02: In vitro cumulative percentage drug release profile

Conclusion

This study suggests that formulation 9 (F_9) shows the optimized release in all aspects. The optimized formulation shows required physical and formulation parameters. By using the formulation we can deliver the Nebivolol drug in optimized manner.

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