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BUCCAL MUCOADHESIVE TABLETS OF CARVEDILOL: CHARACTERIZATION AND OPTIMIZATION

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ABSTRACT

The present investigation is concerned with formulation and evaluation of mucoadhesive buccal tablets containing carvedilol to circumvent the first pass effect and to improve its bioavailability with reduction in dosing frequency and also dose related side effects. The tablets were prepared by direct compression method. The mucoadhesive polymers used in formulation were chitosan, HPMC K4M and polyethylene oxide. Tablets were tested for hardness, thickness, friability, drug content, swelling, bioadhesive strength and *in vitro* drug release properties. All tablets were acceptable with regard to hardness, thickness, and friability. F9 showed maximum 101 % drug content and batch F1 showed maximum swelling index of 58.22 % after 6 hr. Batch F4 showed highest bioadhesive strength of 33.12 gm and maximum drug release of 93.51 % in 10 hr. The best mucoadhesive performance and *in vitro* drug release profile were showed by batch F4 and hence it was optimized.

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Key Words

Buccal drug delivery, Swelling index, Carvedilol, Bioadhesive strength, *In vitro* drug release.

INTRODUCTION

Oral mucosal drug delivery is an alternative method of systemic drug delivery that offers several advantages over injectables and enterable methods ^[1, 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]. 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. Carvedilol is a non-selective β -adrenergic antagonist used in the treatment of hypertension and stable angina pectoris. It also possesses antioxidant and antiproliferative effects, which may enhance its ability to combat the deleterious effects of sympathetic nervous system activation in heart failure ^[4, 5]. In the present investigation an attempt has been made to design efficacious and prolonged release mucoadhesive tablets of carvedilol using various polymers to avoid first pass metabolism, to reduce dosing frequency and to improve patient compliance.

MATERIAL AND METHODS

Carvedilol was donated by Medley Pharmaceutical Ltd., Daman, Chitosan by Zydus Cadila, India. HPMC K4M and polyethylene oxide were purchased from Loba chemicals, Mumbai. All other reagents used were of analytical grade.

Formulation of buccoadhesive tablets

Buccoadhesive tablets of carvedilol were prepared by direct compression technique using different grades of polymer with varying concentration. All the ingredients except magnesium stearate were blended in glass mortar uniformly. After the sufficient mixing of drug as well as other components, magnesium stearate was added and further mixed for additional 2-3 min. The

tablets were compressed using 8 mm flat faced punch on a single stroke punching machine (Model: H/416/95, Cadmach Machinery Co. Pvt. Ltd., Ahmedabad).

Evaluation of tablet

Hardness

Tablets require a certain amount of hardness to withstand mechanical shocks of handling in manufacturing, packaging and shipping. Hardness was measured using Pfizer hardness tester ^[6, 7].

Thickness

Three tablets were selected at random from each batch and thickness was measured by using Vernier caliper ^[8, 9].

Friability

Roche type friabilator was used for measuring friability. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of 6 inches with each revolution. After 4 min, the tablets were weighed and the percentage loss was determined ^[10, 11].

Content uniformity

Ten tablets from each formulation were taken, crushed and mixed. From the mixture 10 mg of carvedilol equivalent of mixture was extracted thoroughly with 100 ml of pH 6.8 phosphate buffer. The amount of drug present in each extract was determined using UV spectrophotometer at 285 nm.

Swelling study

Three tablets from each batch were weighed individually (W₁), placed separately in petri dishes containing 4 ml of isotonic phosphate solution (pH 6.8), at regular interval (1, 2, 4 and 6 hr), the tablets were removed from the petri dishes and excess water from surface were removed carefully using filter paper. The swollen tablets were reweighed (W₂). And swelling were calculated using formula,

$$W_2 - W_1$$

$$\% \text{ Swelling Index} = \frac{\text{-----}}{W_1} \times 100$$

$$W_1$$

Bioadhesion study

Bioadhesive strength of prepared carvedilol buccal tablets was measured on a modified physical balance using the method described by Gupta *et al* ^[12, 13].

***In vitro* drug release study**

The *In vitro* dissolution study was conducted as per the United States Pharmacopoeia (USP) XXIV. The rotating paddle method was used to study the drug release from the tablets. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). The release was performed at $37^{\circ}\text{C} \pm 0.5$, at a rotation of speed of 50 rpm. 5 ml samples were withdrawn at predetermined time intervals (1 to 10 hr) and the volume was replaced with fresh medium. The samples were filtered through Whatman filter paper no. 40 and analyzed for carvedilol after appropriate dilution by UV spectrophotometer at 285 nm. The % drug release was calculated using the calibration curve of the drug in phosphate buffer pH 6.8.

RESULT AND DISCUSSION

It was observed that all the prepared tablets fulfill the I.P requirements for physicochemical properties and

results were given in Table 2. The measured hardness of all formulations i.e. F1 to F12 were ranged between 5.4 to 7.1 Kg / cm². The friability test data indicates that it was less than 1% in all formulations ensuring that the tablets were mechanically stable. The thickness of all formulations was found to be in the range of 2.11 to 2.30 mm. All the batches showed drug content above 97%. The highest swelling 58.22 % was observed with the formulation F1 (Table3). The mucoadhesivity of tablets was found to be maximum (33.12gm) in case of formulation F4 (Table 3). It was also found that the batch F4 showed the maximum percentage of drug release i.e. 93.51 % at the end of 10 hr (Table 4). It can be concluded that stable mucoadhesive buccal tablets with desired properties could be prepared by using chitosan and HPMC K4M in proper concentration along with mannitol. Batch F4 was optimized based on good bioadhesive strength and % cumulative drug release.

Table 1: Composition of carvedilol mucoadhesive buccal tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Carvedilol (mg)	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25
Chitosan (mg)	35.75	25.75	15.75	5.75	35.75	25.75	15.75	5.75	----	----	----	---
HPMC K4M (mg)	35	45	55	65	----	---	---	---	35.75	25.75	15.75	5.75
Polyethylene oxide	---	---	---	---	35	45	55	65	35	45	55	65
Mannitol (mg)	18	18	18	18	18	18	18	18	18	18	18	18
Magnesium stearate (%)	2	2	2	2	2	2	2	2	2	2	2	2
Talc (%)	3	3	3	3	3	3	3	3	3	3	3	3
Average weight (mg)	100	100	100	100	100	100	100	100	100	100	100	100

Table 2: Physico-chemical properties of buccoadhesive tablet batches

Batch	Hardness (Kg/cm ²)	Thickness (mm)	Friability (%)	Drug content (%)
F1	6.7	2.15	0.22	99
F2	6.5	2.30	0.18	100
F3	5.7	2.18	0.41	98
F4	5.4	2.25	0.49	99
F5	6.3	2.24	0.39	97
F6	6.3	2.27	0.32	98
F7	5.9	2.29	0.58	100
F8	6.5	2.19	0.31	97
F9	6.8	2.11	0.43	101
F10	7.1	2.30	0.23	97
F11	5.6	2.19	0.34	99
F12	6.7	2.17	0.40	98

Table 3: Bioadhesive strength and swelling studies

Batch	Bioadhesive strength (g)	Swelling index after 6 hr (%)
F1	23.11	58.22
F2	25.21	57.11
F3	25.15	55.27
F4	33.12	53.10
F5	28.18	52.41
F6	25.27	48.32
F7	25.11	50.39
F8	19.61	50.16
F9	21.49	52.77
F10	22.31	55.12
F11	23.43	56.51
F12	25.64	55.32

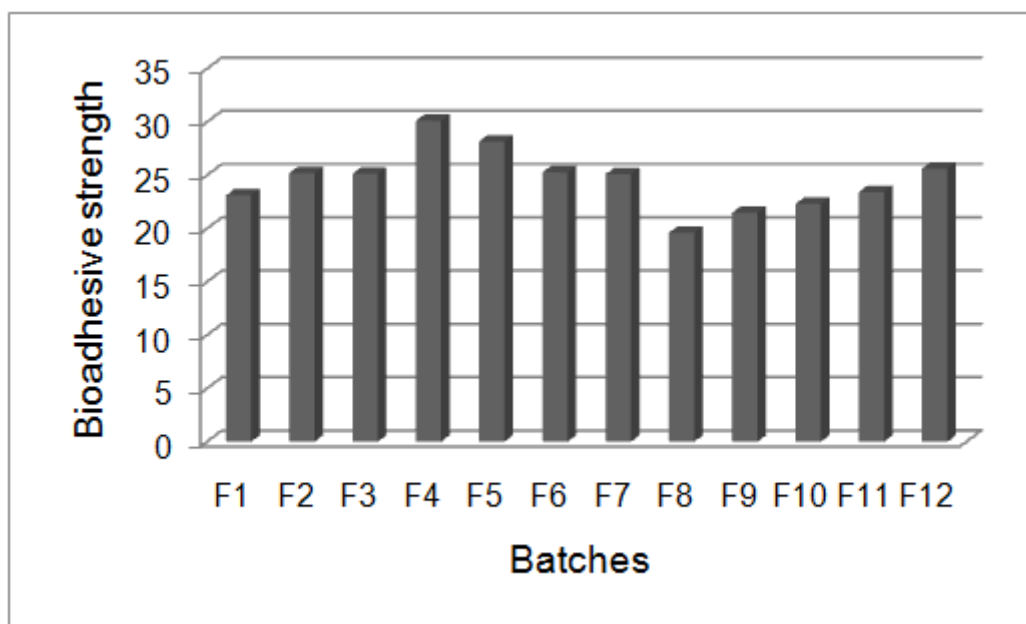


Figure 1: Bioadhesion study

Table 4: *In vitro* cumulative drug release profile of batches

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	0.0	0.0	0.0	0.0	0.0	0.0
1	18.70	18.89	21.52	15.21	17.75	11.17	11.23	06.62	09.18	11.12	05.54	07.53
2	21.33	28.28	28.44	29.86	22.44	17.17	15.16	9.11	15.17	17.12	09.57	13.26
3	28.52	39.11	35.43	37.72	27.51	21.32	22.40	14.22	21.44	21.27	17.24	19.16
4	28.60	48.51	40.22	46.23	34.51	25.54	27.31	19.10	22.16	27.32	21.21	28.11
5	38.40	56.42	51.63	53.54	41.21	27.61	31.13	22.11	37.17	33.38	24.24	34.46
6	45.16	61.59	62.15	58.23	46.26	39.38	34.41	28.26	39.81	37.41	28.17	39.43
7	53.20	67.35	69.54	68.51	52.70	42.39	41.42	35.45	44.23	41.49	35.10	42.44
8	60.44	72.25	75.13	76.11	55.53	47.15	48.15	39.36	56.52	47.39	41.15	48.36
9	66.54	79.16	82.25	82.23	59.29	52.48	50.21	45.21	59.52	57.20	53.30	59.26
10	69.34	85.11	85.41	93.51	63.16	54.71	53.19	49.14	67.17	59.11	55.21	64.21

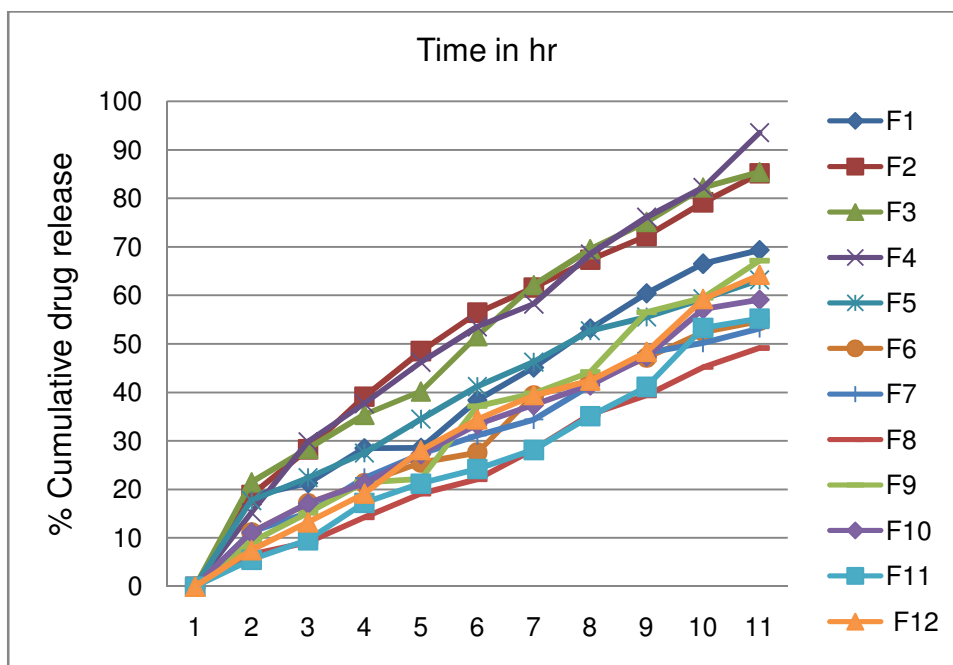


Figure 2: *In vitro* drug release profile of prepared batches

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