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Design And In- Vitro Evaluation Of Mucoadhesive Buccal Tablets Of Carvedilol

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Abstract: Mucoadhesive buccal tablets of carvedilolwere prepared by direct compression method. Carbapol 974P, chitosan, were used as a polymers and cross carmalose sodium as a superdisintegrating agent. Tablets were then evaluated for various physicochemical parameters such as drug content (100±0.28%), hardness (5.09±0.55 kg/cm2), weight uniformity (100 ±0.35mg), thickness (2.14±0.10 mm), and friability (0.31%). Prepared formulations were evaluated for the release of drug in phosphate buffer pH 6.8 using USP type-II dissolution apparatus. Optimum formulation consisted of carvedilol(6.25mg),carbapol 974P and chitosan in 3:1 praportion showed a maximum drug release after 8 hrs. Cross Carmalose sodium was used to accelerate the release of drug from polymer matrices. Maximum swelling was attained in 5 hrs. The highest bioadhesive strength i.e. 0.956 N was possessed by optimum formulation. Decreasing the content of carbapol 934P resulted in decreased in adhesion force. The surface pH of tablets of all batches was between 5 and 7. Good correlation was observed betweenin-vitro drug release and drug permeation with a correlation coefficient of 0.9928. Results indicate that the release rate from optimum formulation best fitted zero order rate kinetics. In conclusion, in-vitro release profile indicate that this novel delivery system is useful formulation, which can by-pass the first pass metabolism and enhance the release of drug for extended period of time.

Keywords: Mucoadhesive buccal tablet, swelling index, bioadhesive strength.

INTRODUCTION

Carvedilol is a nonselective β-adrenergic blocking agent with α1-blocking activity, It has vasodilating activity at alpha-1 receptors; at higher doses calcium channel blocking activity may contribute. Carvedilol is used in the management of hypertension and angina pectoris, and as adjunct to standard therapy in symptomatic heart failure. The absolute bioavailibity is about 25% and elimination half-life is about 6 hrs.This is because ofundergoing of drug to first pass metabolism in liver andgut wall[3]. Buccal mucosa is an attractive route for systemic deliveryof many drugs since it is relatively permeable with a rich blood supply [4]. The mucoadhesive buccal drug delivery system offers several advantages as compare to traditional methods of systemic drug administration[5].

In addition to this, drug can be easily applied and localizedto the application site, and can be removed from there if necessary (See Fig. 1). Furthermore, mucoadhesive delivery system via buccal mucosa can by-pass the disadvantages of oral route. Therefore, mucoadhesive delivery system has been considered to be an ideal route for administration of Carvedilol.In earlier research, attempts have made to develop various mucoadhesive formulations of carvedilol. In this research, we have tried to design novel mucoadhesive buccal tablets of carvedilol which will reduce the first pass metabolism and

frequency ofdosage.Firstly, polymers such as carbapol 974P, chitosan, cross carmalose sodium were used in different ratio to examine their effect on the retardation of drug release from tablet matrix. Upon contact with the fluid, Carbopol 974P swells and finally dissolves slowly [9]. The rate of polymer swelling and dissolution as well as corresponding rate of drug release are found to increase with either higher levels of drug loading or with use of lower viscosity grades of carbopol.

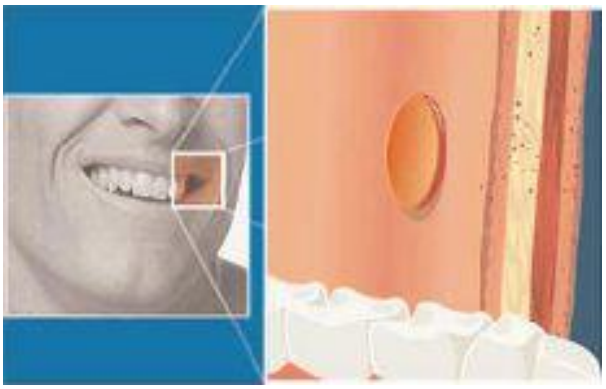


Fig no 1:-site for buccal tablet adhesion.

MATERIALS AND METHODS

Materials

Carvedilolwas a generous gift sample from Zim Laboratories Nagpur. Carbapol 974P from Colorcon Asia Pvt. Ltd., Goa. Chitosan was obtained from Central Institute of Fisheries and Technology,Cochin, India. All other reagents and chemicals used were of analytical reagent grade.

Preparation of Tablets

Polymers like carbapol 974P, chitosan, lactose , magnesium stearate and other ingredients in different ratios were tried to select optimum formulation. The amount of drug was established according to its clinical use and doses usually contained in some brand drug products. Finally, formulation given in Table No. 1 was selected as optimum formulation. Different components in each formula were mixed by trituration in glass pestle and mortar for 30 min. The mixture was then compressed using 6 mm flat-faced punch using a single stroke-punching machine.

Evaluation of Mucoadhesive buccal Tablets[11]

All the prepared mucoadhesive buccal tablets were evaluated for following official and unofficial parameters.

Drug Content

Three tablets from each batch were taken in separate 100 mL volumetric flaks containing 100 ml of pH 6.8phosphate buffer containing 20% methanol and were kept for 24 hrs under constantstirring. The solutions were then filtered, diluted suitablyand analyzed at 241 nm using UV-spectrophotometer.The average of three tablets was taken as the content of drug in one tablet unit.

Hardness

The resistance of tablets to shipping or breaking under the condition of storage, transportation, and handling before the uses depends on its hardness. The hardness of tablets of each batch was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm2.

Weight uniformity, Thickness and Friability

The average weights of the formulated tablets were determined using electronic balance. Thickness was measured using screw gauge at different places and average was calculated. The friability of tablets was determined by using Roche friabilator (See table no.2).

In-Vitro Release[12]

The United state pharmacopoeia (USP) type II dissolution apparatus was used to study the release of drug from buccal tablets. The dissolution medium consisted of 500 mlof phosphate buffer pH 6.8 containing 20% methanol. Therelease was performed at 37 ±0.5°C, at a rotation speed of 50 rpm. Samples (5 mL, at each time) were withdrawn at pre-determined time intervalsand replaced with fresh medium. The samples were filtered through whatman filter paper no. 41 with appropriate dilutions with phosphate buffer pH 6.8 and were assayed spectrophotometrically at 241 nm against phosphate buffer pH 6.8 as blank (See table no.5).

Swelling Study [13]

Swelling study was performed on 1% agar gel plates. Twenty tablets were weighed and average weight of each four tablets was calculated. The tablets were placed on the gel surface in five Petri dishes (each containing four tablets), which were placed in an incubator at 37°C. Four tablets were removed at time intervals of 1, 2, 4 and 6hrs, excess water from the surface was carefully soaked using filter paper, and swollen tablets were weighed (See table no.4).

The swelling index was calculated by using formula,

Swelling index =

$$\frac{\text{wet weight - dry weight}}{\text{wet weight}} \times 100$$

Surface pH [14]

Mucoadhesive buccal tablets were subjected to swell on the surface of agar plate for 2 hrs. The surface pH was measured by using pH paper placed on the surface of the swollen tablets. The mean of two readings was recorded.

In-Vitro Bioadhesive Strength [12]

The term bioadhesion implies attachment of a drug carrier system to a specific biological location.In–vitro bioadhesive strength of tablets was measured using modified physical balance. Porcine buccal mucosa was used as a model membrane and phosphate buffer pH 6.8 was used as moistening fluid. Bioadhesive studies were performed in triplicate and average bioadhesive strength was determined. From the mucoadhesive strength, force of adhesion was calculated.(See table no3.)

Force of adhesion

(N) = (Bioadhesive strength/100) x 9.81

Drug-Excipient Interactions [15]

There is always possibility of drug-excipient interaction in any batch due to their intimate contact. The drug-excipient interaction study was carried out for optimum formulation by using IR-spectroscopic technique, which is one of the most powerful analytical technique that offers possibility of chemical identification. IR-spectra of carvedilol,carbopol974P, chitosan and tablets of optimum batch were obtained by KBr disc method.

Fig no 2:- Modified balance for mucoadhesion study

Table 1 Formulation

Ingredients	**C_1**	**C_2**	**C_3**	**C_4**	**C_5**
Carvedilol (mg)	6.25	6.25	6.25	6.25	6.25
Carbopol 974P	0	2.5	5	7.5	10
Chitosan	10	7.5	5	2.5	0
Cross Camalose Sodium	----	5	----	5	----
Lactose (mg)	80	75	80	75	80
Magnesium Stearate (%)	1.5	1.5	1.5	1.5	1.5
Talc (%)	2	2	2	2	2

Table No 2: - Evaluation of physical parameter of prepared mucoadhesive buccal tablets of carvedilol.

Batch Code	**Evaluation parameter**				
	Uniformity of Wt. (gm) (Mean ± S.D.)	**Drug content (%) (Mean ± S.D.)**	**Friability (%)**	**Hardness (kg/cm^2) (Mean ± S.D.)**	**Thickness (mm) (Mean ± S.D.)**
C_1	101.0 ± 5.13	99.48 ± 0.40	0.19	6.7 ± 0.49	2.61 ± 0.059
C_2	101.38 ± 5.00	99.46 ± 0.35	0.21	6.8 ± 0.14	2.60 ± 0.057
C_3	101.44 ± 4.82	100.05 ± 0.32	0.41	7.2 ± 0.19	2.58 ± 0.054
C_4	101.21 ±1.56	100.12 ± 0.41	0.31	7.6 ± 0.10	2.58 ± 0.051
C_5	101.01 ±0.71	98.92 ± 0.32	0.75	7.4 ± 0.46	2.64 ± 0.091

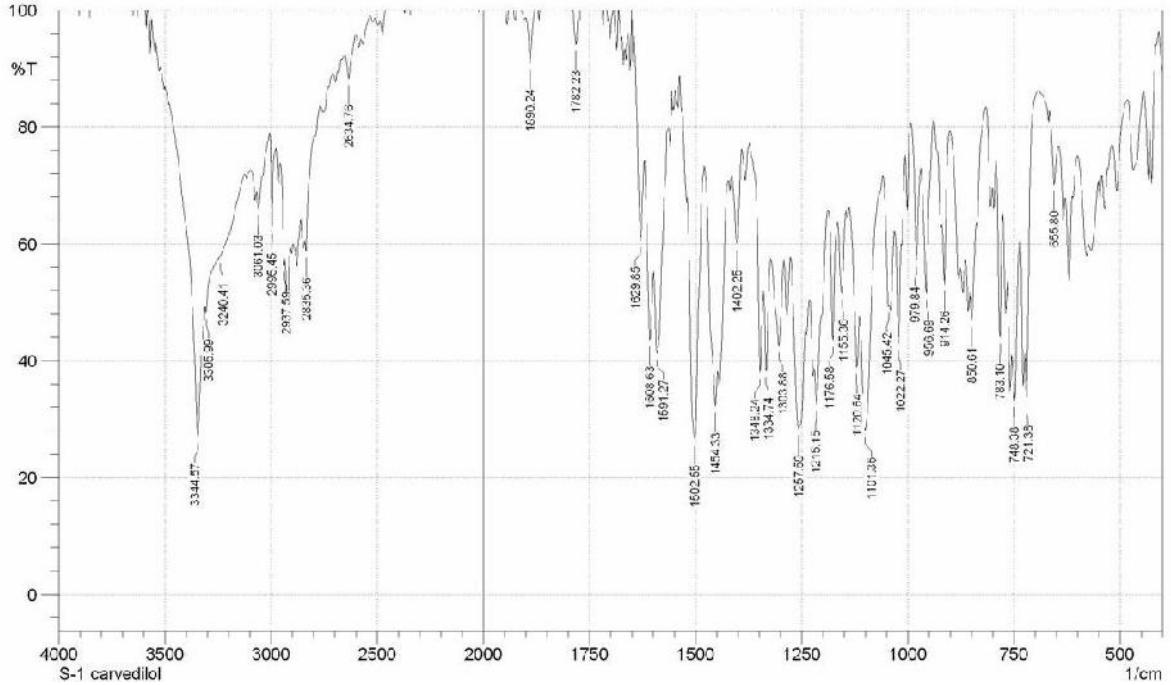


Fig no 3: I.R. Spectra of drug (carvedilol).

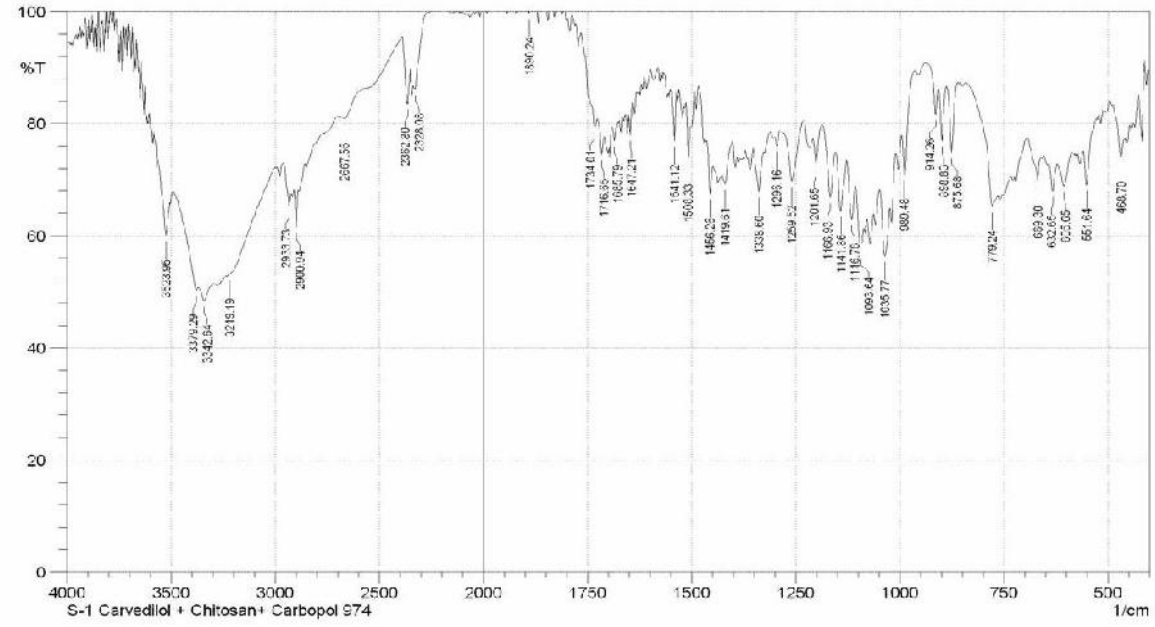


Fig no 4: I.R of final formulation.

Table No. 3: - In-vitro Mucoadhesive strength study of prepared mucoadhesive buccal tablets of carvedilol.

Batch Code	Bioadhesive strength (gm) (Mean ±S. D.)	Force of adhesion (N)
C_1	8.730 ± 0.239	0.856
C_2	8.270 ± 0.147	0.811
C_3	9.220 ±0.152	0.904
C_4	9.750 ± 0.249	0.956
C_5	7.790 ± 0.339	0.764

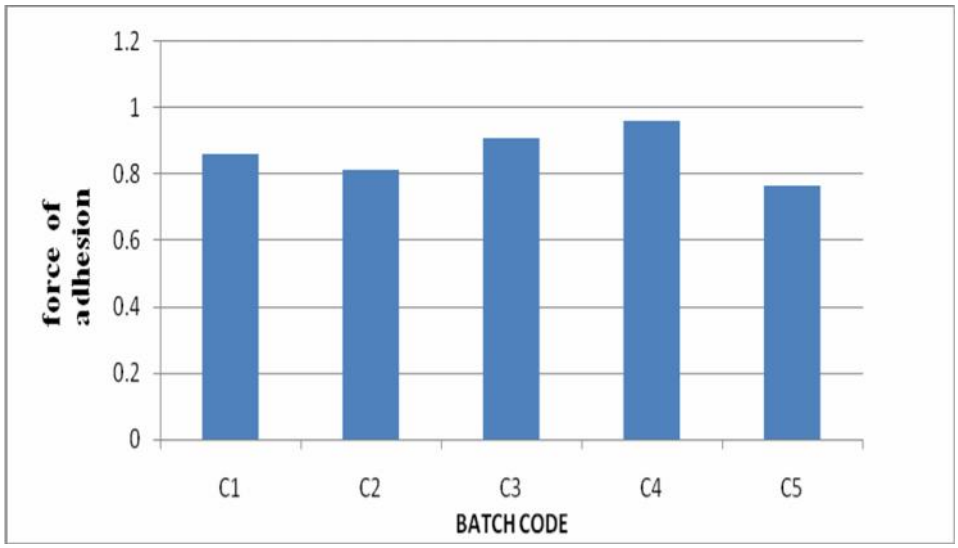


Fig no 5:-graph showing In-vitro Mucoadhesive strength study of prepared mucoadhesive buccal tablets of carvedilol

Table No.4: - In-vitro swelling study of prepared mucoadhesive buccal tablets of carvedilol.

Batch Code	% Swelling Index (Mean ± S. D.)			
	Time (hrs)			
	1	2	4	6
C_1	30.76 ± 0.141	39.23 ± 0.0471	Tablet break	----------
C_2	25.00 ± 0.193	33.42 ± 0.723	42.31 ± 0.210	44.23 ± 0.250
C_3	35.96 ± 0.259	42.11 ± 0.412	54.39 ± 0.439	58.33 ± 0.451
C_4	27.64 ± 0.263	43.49 ± 0.115	54.14 ± 0.141	62.11 ± 0.179
C_5	41.66 ± 0.271	50.71 ± 0.129	53.17±0.471	54.23±0.173

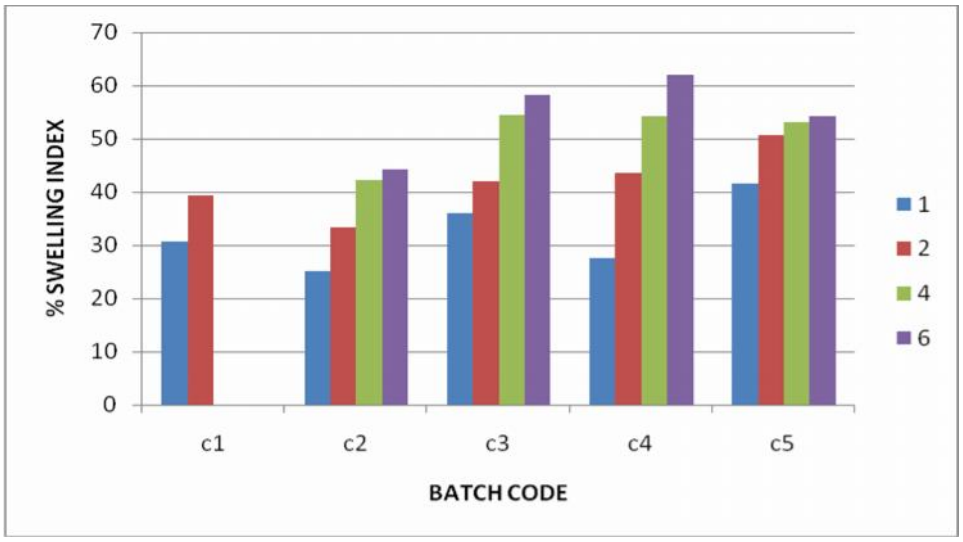
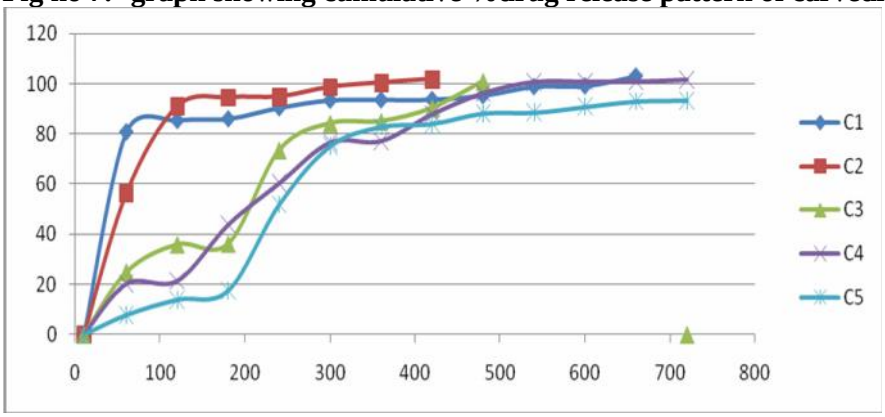


Fig no 6:- graph showingIn-vitro swelling study of prepared mucoadhesive buccal tablets of carvedilol

Table No.5:- cumulative % Drug release

Time	C1	C2	C3	C4	C5
	0	0	0	0	0
10	0	0	0	0	0
60	80.70968	56.51613	25.03226	20.32258	7.870968
120	85.25806	91.03226	35.96774	21.51613	13.96774
180	85.90323	94.51613	36.29032	43.83871	17.64516
240	90.32258	94.83871	73.51613	60.32258	51.93548
300	93.29032	98.67742	84.22581	76.48387	75.09677
360	93.45161	100.4194	85.03226	77.09677	82.74194
420	93.54839	101.8387	90.32258	87.77419	83.96774
480	95.16129	--	100.9355	96.12903	88.09677
540	98.70968	--	--	100.6452	88.3871
600	98.96774	--	--	100.7419	90.67742
660	102.871	--	--	100.8065	92.87097
720	--	--	--	101.5161	93.19355

Fig no 7:- graph showing cumulative %drug release pattern of carvedilol tablets.



RESULTS AND DISCUSSION

An ideal pharmaceutical dosage form for buccal affection treatments would be able to (1) release drug immediately to produce a prompt pharmacological action, (2) remain in oral cavity, and (3) provide a sustained release of enough drug over an extended period of time. Taking into account such requirements, mucoadhesive buccal tablets of carvedilol were prepared, and were evaluated for various physicochemical parameters. The percent drug content for all the formulations was found to be 100.00 ±0.28% w/w. Hardness of the tablets was found to be 5.09±0.55 kg/cm2. Hardness increases with increasing carbapol proportion in the formulation. The average weight of the tablets was found to be 100.00 ±0.35 mg, and the percent deviation was within a specified limit. Hence, all formulations complied with the test for weight uniformity. All the tablets were circular with no visible cracks, andsmooth in appearance with average thickness of 2.14 ±0.10 mm. Further, to strengthen these values, friability test values are also considered. The weight loss less than 1% in friability test is considered as an acceptable value for conventional tablets. It indicates that the tablets can withstand the mechanical shocks reasonably well during their handling. Thus, all the tablets complied with IP standard. Fromin-vitro release study of all batches, formulation (F4) containing carvedilol (6.255mg), carbapol974P and chitosan in3:1 ratio magnesium stearate (1mg) and talc (1mg) was selected asoptimum formulation for further study as it had maximum drug release after 8 hrs and shows good mucoadhesive properties.

The swelling properties of all the formulations were studied, and its results indicate that all the formulations possess good swelling indices. The optimum formulation showed maximum swelling index. Maximum swellingwas attained in 5 hrs after which polymers started eroding slowly in the swelling medium. The swelling index of formulations containingcarbapol 974P and chitosan was increased with increasing the amount of chitosan (See Table No.4).

The surface pH of all the formulations was found to be between 5 and 7. Therefore, it reveals that all formulations provide an acceptable pH in the range of salivary pH (5.5-7.0) and they cannot produce any risk of mucosal damage or irritation.

The bioadhesion characteristics were affected by the types and ratios of bioadhesive polymers. The highest bioadhesive force i.e. 0.956N was possessed by optimum formulation. This is because of polymer carbapol 974P, which swells and becomes adhesive upon hydration (See Fig. 5-6).

In the IR spectral study of optimum formulation (See Fig. 3-4), prominent peaks of carvedilolwere appeared without interference or the shifting of peaks; it reflects that there is no drug-excipient interaction in optimum formulation.

CONCLUSION

Mucoadhesive buccal tablets of carvedilol were prepared by direct compression method. Different polymers and ingredients in different ratios were tried to select optimum formulation. They were selected on the basis of their effect on the retardation of release of drug from tablet matrix. The formulation consist of carvidelol,(6.25mg), carbapol 974P and chitosan in3:1 ratio, Cross camalose sodium, magnesium stearate (1mg) and talc (1mg) was selected as optimum formulation. Various physicochemical parameters tested for this formulation showed good results (See Table No.2). From the release study and mucoadhesive study , it concluded that this novel formulation can by-pass the first pass metabolism and enhance the release of drug for extended period of time.

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