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Formulation and Evaluation of Polymeric Buccoadhesive Film of Carvedilol.

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Abstract
Mucoadhesive buccal films containing carvedilol were prepared using the solvent casting method. Sodium alginate was used as bioadhesive polymer and different ratios of sodium alginate to PVP K-30 were used. Drug: HPβ-CD complex was incorporated in the buccoadhesive film to improve the dissolution of poorly water soluble drug from the polymeric film. The films were evaluated for their physical characteristics like mass variation, drug content uniformity, folding endurance, *in vitro* mucoadhesion strength, *in vitro* mucoadhesion time, surface pH, *in vitro* drug release, and *in vitro* buccal permeation study. Films exhibited controlled release for a period of 8 h. The release rate from optimized film best fitted Korsemeyer and Peppas (R^2=0.9996), followed by zero order (R^2=0.9963) and the value of n =1.1655 indicated that release from film followed Super Case II transport. The optimized film was subjected to stability study and histopathological examination on porcine buccal mucosa. Also the film was found to be stable in human saliva, no color change was observed. Histopathological studies revealed no effect on the mucosal histology after application of film for 10 hrs. The optimized formulation

Key Words
Mucoadhesion, Carvedilol, Hpβ-CD, Sodium Alginate, PVP K-30.

Introduction
Buccal delivery of drug provides an attractive alternative to the oral route of drug administration. In recent years, delivery of therapeutic agents through various transmucosal routes gained significant attention owing to their presystemic metabolism or instability in the acidic environment associated with oral administration. Buccal delivery provides direct entry into the systemic circulation, thus avoiding the hepatic first-pass effect, ensuring ease of administration, and making it possible to terminate delivery when required. Carvedilol is a non-selective and β-adrenergic antagonist with no intrinsic sympatomimetic activity and is widely used to treat essential hypertension and angina pectoris. Although it is completely absorbed from the gastrointestinal tract, the systemic availability is approximately 25- 35 % because of high first-pass metabolism. Since the buccal route bypasses the hepatic first pass effect, the dose of carvedilol could be reduced. The physicochemical properties of carvedilol, its suitable half life, low molecular weight 406.5, and its low dose (6.25-25 mg) makes it suitable candidate for administration by buccal route. Thus in this study the attempt was taken for preparation of buccoadhesive films by using bioadhesive polymers like sodium alginate and PVP K-30 which will improve oral bioavailability by sparing the drug from first pass metabolism and reduce the dosing frequency. Drug: HPβ-CD complex was incorporated in the buccoadhesive film to improve the dissolution of poorly water soluble drug from the polymeric film.

Materials and Methods
Materials
Carvedilol, Hydroxypropyl-β-Cyclodextrin and Ethocel (20 cps) was obtained from Cipla Ltd., Kurkumbh (Dist.Pune), Roquette Fereres, France and Colorcon Asia Pvt. Ltd., Goa respectively. The other reagents used were of analytical grade.
Method
Preparation of Drug: HPβ-CD complex
Inclusion complex of carvedilol with hydroxypropyl beta cyclodextrin (HPβ-CD) in the ratio 1:1 was prepared by kneading method.

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Formulation and development of buccoadhesive film

Films containing different polymers were prepared by the solvent casting method. First the rate controlling layer of ethyl cellulose (3%) was cast and then drug: HPβ-CD containing polymeric layer was cast over it. The composition of all films is given in Table 1

Evaluation of buccoadhesive film

Film thickness: The thickness of patches was measured at three different places using Tablet Tester (Campbell Electronics, Mumbai, Model CWWTDDH 500N). (Table 2) Film weight: Films of specified area (3.14 cm^2) were cut and were weighed individually using Electronic weighing balance (Model No.AW-220 and BX – 6205, Shimadzu Corporation, Japan). (Table 2)

Drug content: Film of specified area (3.14 cm^2) was dissolved in methanol, and the drug content was found out. (Table 2) Folding endurance: Folding endurance of the film was determined by repeatedly folding one film at the same place till it broke. (Table 2)

Surface pH measurement: Buccal films were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2% (*m/V*) agar in warmed isotonic phosphate buffer of pH 6.8. The surface pH was measured by means of a pH paper placed on the surface of the swollen film. The surface pH of all buccal films was between 6-7. (Table 2)

Swelling study: Buccal film was weighed (W1), placed in a 2% agar gel plate and incubated at 37 ± 1°C. At regular one-hour time intervals (to 2 h), the film was removed from the Petri dish and excess surface water was removed carefully using the filter paper. The swollen films were then reweighed (W2) and the swelling index (SI) were calculated.

SI = (W2- W1) / W1 X 100 (Table 2)

***In vitro* bioadhesion time:**

The *in vitro* mucoadhesion time was performed after application of the films on freshly cut porcine buccal mucosa. The porcine buccal tissues were fixed on the internal side of a beaker with cyano acrylate glue. Each film was divided in portions of 4 cm^2 and cut; a side of each film was wetted with small quantity of simulated saliva fluid and was pasted to the porcine buccal tissue by applying a light force with the finger tip for 20 s. The beaker was filled with 200 ml of the simulated saliva fluid and was kept at 37 °C. After 2 min, it was stirred at 50 rpm; to simulate the buccal cavity environment and film adhesion was monitored over 8 hr.

***In vitro* bioadhesive strength**

Bioadhesive strength of the film was measured on a modified physical balance using the method described by Gupta *et al.*

The following parameters were calculated from the bioadhesive strength.

$$\text{Force of adhesion (N)} = \frac{\text{bioadhesive strength}}{1000} \text{ X } 9.81$$

$$\text{Bond strength (N m-2)} = \frac{\text{force of adhesion}}{\text{Surface area}}$$

***In vitro* drug release**

The drug release was determined using USP dissolution test apparatus Type II thermostated at 37±1°C and stirred at rate of 50 rpm. Each film was fixed on a glass slide with the help of cyano acrylate adhesive so that the drug could be released only from upper face. Slide was immersed in vessel containing simulated salivary solution (pH 6.8). Aliquots were withdrawn at regular intervals and replaced with equal volume of dissolution medium.

***In vitro* permeation studies**

For *in vitro* permeation studies, porcine buccal mucosa was used. The permeation study was carried out by using Keshary-Chein diffusion cell. The method used porcine buccal mucosa as the model mucosal membrane. The membrane was placed between the donor compartment (salivary pH 6.8) and the reservoir compartment (isotonic phosphate buffer pH 7.4, blood pH) to mimic the physiological conditions. The diffusion cell was thermostated at 37±1°C. Aliquots were withdrawn at regular intervals and replaced with equal volume of dissolution medium.

Results and Discussion

The drug content in the prepared complex was found to be 97.08%, and the results of XRD revealed that the drug was present in amorphous state in the complex (Fig 1,2,3,4). The prepared films were smooth in appearance, uniform in thickness, mass and drug content. The films exhibited good folding endurance. Film thickness ranged from 0.52 mm - 1.17 mm and film weight ranged from 37.76 mg-42.56 mg. The surface pH of the prepared buccoadhesive films ranged from 6-7, that indicates no risk of mucosal irritation or damage. The swelling

index of the prepared films was found to be in the order of F7 > F4 > F5 > F6 > F3 > F2 > F1. Water uptake might also be more due to presence of HPβ-CD in the film. The bioadhesive strength of the prepared buccoadhesive film was in the following order: F1 > F2 > F3 > F4 > F5 > F6 > F7.

Sodium alginate has a greater portion of hydroxyl group (OH) than the other polymers, and therefore gets hydrated easily and forms a strong gel that entangles tightly with the mucin molecules. The bioadhesive strength was affected by the proportion of sodium alginate present in the film. PVP K-30 enhanced drug release and swelling index but significantly decreased the bioadhesive strength. The *in vitro* bioadhesion time of the prepared films was found to be dependent on the percentage of sodium alginate in the film. (Table 3)

In vitro drug release

In vitro drug release studies indicated that drug release was dependent on the percentage of polymers used and the swelling of the individual polymer in the combination used. The drug release from sodium alginate film was controlled by the formation of a hydrated viscous layer formed when the film comes in contact with the dissolution medium, which in turn depends on the concentration of polymer used (Table13). This viscous layer act as a barrier to drug release by opposing the penetration of dissolution medium into the matrices and the movement of the dissolved solutes out of the matrices. Cappello B., et al.[49] and Jug M., et al,[50] showed that HPβ-CD act as channeling or wicking agent promoting the dissolution of the poorly water soluble drug inside the polymeric matrix. Although the marked increase in surface area during swelling and presence of HPβ-CD can promote drug release, the increase in diffusional path length of drug may paradoxically delay the release. The drug release increased with addition of PVP K-30 which also depends on the percentage of PVP K-30 in the film. (Table 4)

In vitro permeation

The order of drug permeation from buccoadhesive film was in the following order; F3 > F2 > F1 > F7 > F6 > F5 > F4. (Table 5). Based on swelling, bioadhesion and drug release and drug permeation profile F3 was selected as optimized film which showed appropriate swelling, duration of bioadhesion, drug release and permeation and hence considered for further stability studies.

Kinetic Treatment to dissolution data of F3

The dissolution data of F3 was treated with different kinetic equations to interpret the order of release of carvedilol and the coefficients of determination (R^2). Results indicated that the release rate from film F3 best fitted Korsemeyer and Peppas (R^2=0.9996), followed by zero order (R^2=0.9963) and then square root t kinetics (R^2=0.9075). The value of n =1.1655 indicated that release from film followed Super Case II transport. This mechanism could result from increased plasticization at the relaxing boundary (gel layer).

Stability in human saliva

The stability of carvedilol buccoadhesive film was examined in natural human saliva. Films were placed in separate Petri dishes containing 5 mL of human saliva and kept in a temperature controlled incubator for 8hr at 37 ± 0.2 °C. At regular time intervals (0, 1, 2, 3 and 8hr), the film were examined for changes in color, shape and collapse of the film. (Table 6). Cyclodextrin have been suggested to act as penetration enhancer. They enhance the permeation of the drug by carrying the drug through the aqueous barrier towards the surface of the membrane, where the drug passes from complex into the membrane. Based on swelling, bioadhesion and drug release and drug permeation profile F3 was selected as optimized film which showed appropriate swelling, duration of bioadhesion, drug release and permeation and hence considered for further stability studies.

Histopathological examination on porcine buccal mucosa

Histological analyses were performed to evaluate the pathological changes occurring in cell morphology and tissue organization. Histological studies revealed that the porcine buccal epithelium maintained the integrity even after application of buccoadhesive film for 10hrs.

Stability study of film (F3)

The film F3 was selected as an optimized film and the stability study was carried out at accelerated condition of 40 ± 2^0C/ 75 ± 5% RH conditions for period of three months. After each month film was analyzed for physical characteristics, bioadhesion properties, duration of bioadhesion and the *in vitro* drug release study. The methods adopted were same as described earlier. (Table 7, 8, 9) Study indicates no significant changes in physical characterization of film. From the results of dissolution profile it was concluded that the film F3 was stable for a period of

3months at 40 ± 2°C, 75 ± 5% RH, as there was no significant change in dissolution profile of film over a period of study ($p>0.05$) and as the value of similarity factor *f2* for dissolution profile after l month, 2month and 3month were 99.86, 99.83 and 99.85 respectively. Similarly, no significant difference was observed in bioadhesion study ($p>0.05$)

Conclusion

From the present investigation, it can be concluded that optimized buccoadhesive film of carvedilol with the combination of 70% sodium alginate and 30% PVP K-30 can meet the ideal requirements for buccal devices, which can be a good way to bypass the extensive hepatic first pass metabolism.

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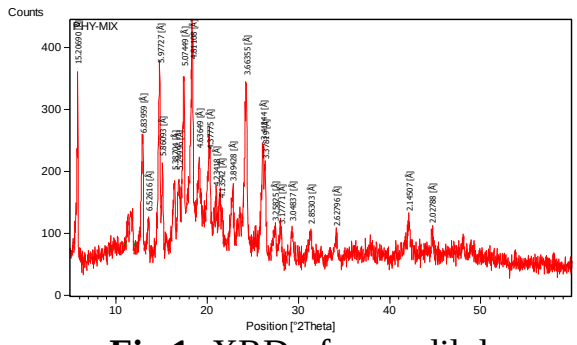

Fig.1: XRD of carvedilol.

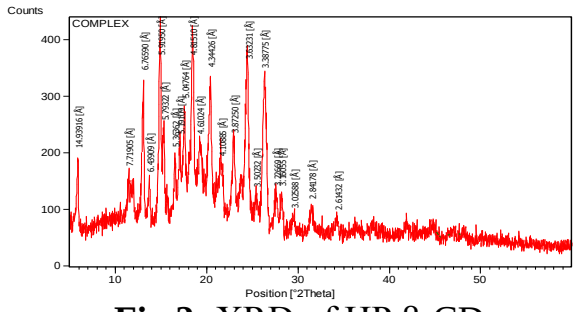

Fig.2: XRD of HP β-CD.

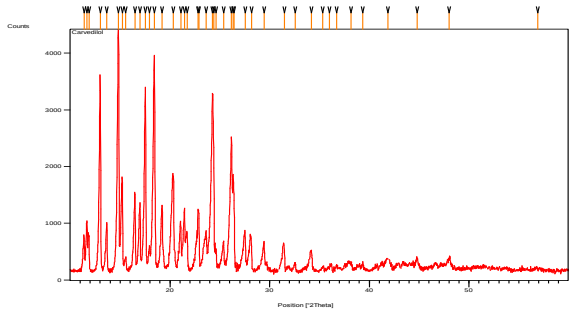

Fig.3: XRD of drug-HPβ-CD physical mixture.

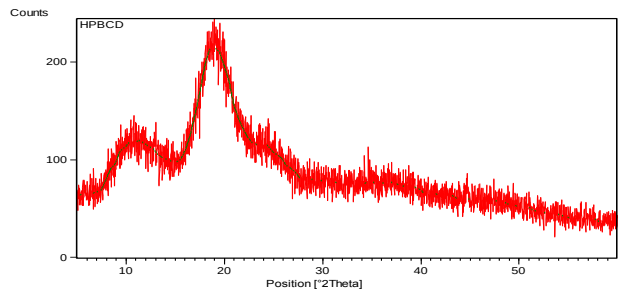

Fig.4: XRD of drug-HPβ-CD complex.

Table 1: Composition of the prepared buccoadhesive films.

Sr No.	Formulation	% of Sodium alginate	% of PVPK-30
1	F1	100	0
2	F2	80	20
3	F3	70	30
4	F4	50	50
5	F5	30	70
6	F6	20	80
7	F7	0	100

Table 2: *In vitro* Bioadhesion study.

Sr No.	Formulation	Film Thickness (mm)*	Film Weight (mg)*	Drug Content (%)*	Folding Endurance*	Surface pH	Swelling index*
1	F1	1.17 ±0.014	42.56 ±0.014	95.02 ± 0.155	188 ± 16	7	48.47 ±0.947
2	F2	0.65 ±0.028	39.87 ±0.007	95.26 ±0.395	176 ± 12	6	49.13 ±1.244
3	F3	0.62 ±0.014	39.53 ±0.014	98.78 ±0.721	172 ± 08	7	50.27 ±1.880
4	F4	0.55 ±0.014	38.57 ±0.014	94.06 ±0.282	161 ± 12	7	54.15 ±0.410
5	F5	0.52 ±0.042	38.83 ±0.007	95.14 ±0.395	159 ± 18	7	53.88 ±0.975
6	F6	0.55 ±0.056	37.88 ±0.028	96.46 ±0.480	155 ± 04	7	53.78 ±0.473
7	F7	0.52 ±0.028	37.76 ±0.007	96.52 ±0.551	142 ± 07	7	54.53 ±1.527

Table 3: Bioadhesive strength and duration of bioadhesion of buccoadhesive films.

Formulation	Bioadhesion time(hr)	Bioadhesive strength(g)*	Force of adhesion(N)*	Bond strength ($N\ m^{-2}$)*
F1	>8	18.2 ± 0.141	0.178 ±0.001	568.60 ±4.41
F2	>8	16.65 ±0.212	0.162 ±0.002	520.17 ±6.62
F3	>8	16.00 ±0.141	0.156 ±0.001	499.86 ±4.41
F4	5	12.9 ±0.141	0.126 ±0.001	403.01 ±4.41
F5	3	11.6 ±0.141	0.113 ±0.001	362.40 ±4.41
F6	3	11.25 ±0.212	0.190 ±0.002	351.46 ±6.62
F7	2	8.45 ±0.212	0.082 ±0.002	263.99 ±6.63

Table 4: *In vitro* drug release from prepared buccoadhesive films.

		% Cumulative Drug Release						
Sr no.	**Time (hr)**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
1	0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
2	1	10.13 ±0.510	8.28 ±0.680	8.55 ±0.64	14.07 ±0.275	13.3 ±0.185	12.63 0.182	21.15 ±1.324
3	2	17.78 ±1.123	16.17 ±0.321	18.46 ±0.324	24.49 ±1.077	38.55 ±0.598	36.77 ±0.860	46.28 ±0.311
4	3	29.47 ±0.923	27.92 ±0.629	31.54 ±0.762	6.79 ±1.153	51.71 ±1.210	50.85 ±1.181	70.81 ±0.681
5	4	36.97 ±0.836	41.98 ±1.136	43.21 ±0.46	60.17 ±0.731	70.21 ±1.053	67.44 ±0.530	94.38 ±0.251
6	5	49.18 ±0.355	57.07 ±0.196	56.92 ±0.810	76.39 ±0.556	84.56 ±1.045	84.41 ±1.428	-
7	6	57.95 ±1.040	68.17 ±0.134	71.44 ±1.156	94.44 ±0.658	92.36 ±0.407	94.17 ±0.642	-
8	7	71.66 ±1.07	79.52 ±0.776	85.74 ±1.033	-	-	-	-
9	8	83.28 ±1.235	85.42 ±0.680	95.84 ±0.112	-	-	-	-
10	9	92.3 ±0.61	93.03 ±0.242	-	-	-	-	-

Table 5: *In vitro* drug permeation from prepared buccoadhesive films.

		Cumulative % drug permeated*						
Sr No.	**Time (hrs)**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
1	0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
2	1	2.65 ±0.24	5.08 ±0.266	4.09 ±0.472	3.72 ±0.288	3.00 ±0.208	2.93 ±0.072	7.88 ±0.286
3	2	7.86 ±0.588	13.95 ±0.196	8.10 ±0.207	8.91 ±0.421	7.3 ±1.201	7.06 ±0.548	12.65 ±0.588
4	3	13.92 ±1.247	22.62 ±1.098	14.35 ±0.719	15.91 ±0.563	11.69 ±0.264	11.77 ±0.628	16.82 ±0.959
5	4	19.03 ±0.192	27.76 ±0.790	18.83 ±1.126	24.42 ±0.236	16.62 ±0.999	16.8 ±0.907	25.26 ±0.104
6	5	27.79 ±0.670	32.45 ±0.108	26.5 ±0.677	34.81 ±0.810	23.3 ±0.516	24.56 ±0.753	29.91 ±0.628
7	6	36.36 ±0.560	39.33 ±1.097	37.00 ±0.242	40.4 ±0.625	31.53 ±0.665	33.1 ±0.497	35.74 ±0.860
8	7	41.04 ±0.998	44.33 ±0.482	44.47 ±1.305	46.18 ±0.593	38.38 ±0.520	38.91 ±0.121	42.66 ±0.502
9	8	47.92 ±0.826	51.49 ±0.681	51.91 ±1.036	51.83 ±0.533	45.88 ±0.73	46.38 ±0.468	48.8 ±0.697
10	9	53.64 ±0.500	57.23 ±0.305	59.16 ±0.423	58.07 ±0.497	52.75 ±0.815	52.91 ±0.785	56.85 ±0.744
11	10	62.07 ±0.21	65.17 ±1.021	67.91 ±1.032	64.19 ±0.754	63.54 ±0.641	64.01 ±0.329	66.03 ±0.448
12	11	69.28 ±0.576	72.49 ±0.346	76.39 ±1.138	69.45 ±0.588	72.08 ±0.642	72.47 ±1.307	74.05 ±0.295
13	12	78.18 ±0.363	80.07 ±0.790	82.94 ±1.008	75.60 ±1.464	77.91 ±0.223	78.37 ±1.124	78.47 ±1.005

Table 6: Stability data of F3 in human saliva.

Sampling time (hour)	Thickness(mm)*	Diameter(mm)*	Color change$	Collapsing
0	**0.62±0.007**	**20.025±0.035**	**No**	**No**
1	**0.64±0.014**	**20.125±0.035**	**No**	**No**
2	**0.66±0.007**	**20.475±0.035**	**No**	**No**
3	**0.76±0.021**	**20.79±0.014**	**No**	**No**
6	**1.07±0.021**	**21.06±0.014**	**No**	**No**
8	**1.19±0.014**	**21.47±0.028**	**No**	**No**

Table 7: Physical characterization of F3 kept for stability study in human saliva.

Parameters	Zero month*	One month*	Two month*	Three month*
Film Thickness(mm)	0.62±0.014	0.62±0.014	0.63±0.007	0.63±0.007
Film Weight(mg)	39.53±0.014	39.53±0.014	39.54±0.007	39.56±0.014
Drug Content (%)	98.78±0.721	98.78±0.721	98.81±0.049	98.83±0.070
Folding Endurance	172±08	172±08	171±05	170±03

Table 8: Bioadhesive measurements of F3 kept for stability study.

Time	Bioadhesive strength(g)*
Zero month	16.00 ± 0.141
One month	15.85 ± 0.070
Two month	15.7 ± 0.141
Three month	15.35 ± 0.212

Table 9: Dissolution data of F3 kept for stability study.

	% Cumulative drug release*			
Time (hr)	**Zero month**	**One month**	**Two month**	**Three month**
0	0±0	0±0	0±0	0±0
1	8.55 ±0.64	8.59 ±0.699	8.62 ±0.651	8.63 ±0.635
2	18.46 ±0.324	18.47 ±0.282	18.54 ±0.226	18.55 ±0.305
3	31.54 ±0.762	31.74 ±1.430	31.76 ±0.429	31.77 ±1.752
4	43.21 ±0.46	43.38 ±0.985	43.39 ±0.738	43.41 ±0.958
5	56.92 ±0.810	56.97 ±1.792	56.97 ±1.673	56.98 ±1.728
6	71.44 ±1.156	71.73 ±1.258	71.75 ±0.995	71.66 ±1.143
7	85.74 ±1.033	85.77 ±1.701	85.77 ±0.501	85.71 ±0.992
8	95.84 ±0.112	95.93 ±0.317	95.94 ±1.625	95.97 ±1.315
f2	Reference	99.86	99.83	99.85

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