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FORMULATION DEVELOPMENT OF BUCCAL FILM OF CARVEDILOL PHOSPHATE

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ABSTRACT

Carvedilol phosphate, β- adrenergic antagonist has hepatic first pass effect and low oral bioavailability (25-30%). Hence need arises to develop buccal film of carvedilol phosphate to provide rapid onset of action. Carvedilol phosphate was taste masked by using β- cyclodextrin. Buccal film of taste masked formulation were prepared by solvent casting method based on 3^2 factorial design using polyvinyl pyrrolidone K30 and polyvinyl alcohol. All the films were evaluated for their thickness, weight variations, folding endurance, swelling index, surface pH, disintegration time, drug content, in-vitro drug release, ex-vivo permeation studies and stability study. The FTIR and DSC studies revealed no interaction between drug and polymer. The films were thin, transparent, smooth, flexible and uniform in drug content, weight and thickness. Results showed that F2 containing 4% PVPK30 and 2% polyvinyl alcohol was optimized formulation which showed 98.98% drug release within 21 min. Ex vivo diffusion studies carried out using Franz diffusion cell with goat buccal mucosa and cellophane membrane showed 91.53% and 94.84 of drug release, respectively. From the all evaluation parameter it was concluded that buccal film of carvedilol phosphate is good choice of dosage form for faster action.

KEYWORDS: *Carvedilol phosphate, taste masking, buccal film.*

INTRODUCTION

Buccal drug delivery is a highly effective way to improve bioavailability. This is because the buccal mucosa has rich blood supply which facilitates direct entry of drug molecules into the systemic circulation. Buccal drug delivery is well accepted by patients the buccal cavity is easily accessible for self-medication. In addition, buccal dosage form swallow drug absorption to be rapidly terminated in case of an adverse reaction. Formulation of buccal dosage forms include adhesive tablet, gels, patch & film of which film are preferable in terms of flexibility and comforts. Buccal films were prepared by using polymer. Carvedilol phosphate is β- adrenergic antagonist use in the treatment of hypertension. Its oral bioavilability is 25-35%. Carvedilol was selected because of low molecular weight (406.48) and low oral dose is low (6.25-25mg). for buccal drug delivery system.

Objective of work to mask bitter taste of drug using known concentration of β- cyclodextrin and to prepare evaluate the carvedilol phosphate buccal film by solvent casting method.

MATERIAL AND METHODS

Materials:- Carvedilol was obtained as a gift sample from Mylan Pvt Ltd, Nashik, India. Polyvinyl pyrrolidone K 30 and polyvinyl alcohol were obtained from the Research lab fine chem, India. All other materials used were of analytical grade.

Methods

Taste masking of drug:-Taste masking was carried out by preparation of complex of carvedilol with beta cyclodextrin. A mixture of carvedilol and β-cyclodextrin in 1:2 ratio was grounded in mortar by adding hydroalcoholic solution (ethanol:water =15:85) and kneaded thoroughly with a pestle to obtain a paste which was dried under vacuum at

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room temperature passed through sieve no.60 and stored in a desiccators (Mohd Azharuddin et al 2012).

Preparation of buccal film of carvedilol phosphate by using 3^2 full factorial designs:

Buccal film of carvedilol phosphate was prepared based on the 3^2 factorial design (3level and 2 factor) using design expert 9.0.2 version software. Drug release of (Y) was selected as response parameter as the dependent variable

Buccal film was prepared by solvent casting method using film forming polymers such as PVA and PVPK-30. Aqueous solution (100ml) of polyvinyl alcohol (PVA) and polyvinyl pyrrolidon prepared separately. Then the solution of PVP was added to PVA solution and mixed well to get clear homogeneous solution and labeled as solution (A). Then accurately weighed quantities of taste masked carvedilol-ßCD was dissolved in small quantity of ethanol. PEG200 was added as plasticizer. This solution was labeled as solution (B). The solution B was added to the homogenous aqueous solution A and mixed thoroughly using magnetic stirrer. The obtained solution was casted into a glass petri dish of 9cm diameter (surface area 66.44 sqcm) and allowed to dry for 24h. The film was carefully removed from the petri dish and checked for any imperfection. The resultant film was cut into the dimension of 2cm×2cm in size. The formulation composition of carvedilol phosphate buccal film are given in table1(See Appendix).

Evaluation of carvedilol phosphate buccal film

Taste evaluation:-Taste acceptability of drug and its inclusion complex was measured by a taste panel (n=3). The sample hold in mouth until disintegration, then spat out and the bitterness level was then recorded. Oral cavity was rinsed with sufficiently large amount of distilled water.

Physical appearance and Surface texture:- Physical characterization of film can be carried out by visual inspection for characteristics of transparency and stickiness.

Film weight and film thickness:-All films were weighed on a digital weighing balance and film thickness was measured using vernier callipers from all sides at different position and the average value was noted.

Measurement of pH:-The pH of film formulations was determined by using digital pH meter. Buccal film of size 2x2cm was dissolved in 100 ml of distilled water and kept for 2 h. The measurement of pH of each formulation was done in triplicate and average values were calculated.

Drug content uniformity of the film:-Three films (2×2 cm) of each formulation was taken in separate 100 ml volumetric flask containing pH 6.8 phosphate buffer was added and continuously stirred for 24 h. The solutions were filtered, diluted suitably and analyzed at 248 nm in a UV spectrophotometer (Shimadzu –Japan1800). The average of three films was taken as final reading.

In vitro drug release:-A standard USP dissolution test apparatus (paddle over disk) apparatus was employed to evaluate drug release. A portion of 2x2 cm^2 of film was used. The vessel was filled with phosphate buffer pH 6.8 and maintained at 37˚C while stirring at 50 rpm. The film was submerged into dissolution medium and aliquot of 5ml samples were collected at predetermined time intervals and replaced with an equal volume. The absorbance was noted using spectrophotometer at 248 nm.

Disintegration time:-The time required to disintegrate was measured by disintegration time. The film was placed in the disintegration test apparatus (Scientific Lab, India) containing phosphate buffer having pH 6.8. Instrument was operated until film gets disintegrated. The time required for disintegration was noted.

Swelling index:-The film was weighed and placed on a pre-weighed cover slip. The cover slip was then submerged in a petridish containing 20 ml phosphate buffer (pH 6.8). Increase in weight of the film was determined at regular time intervals until a constant weight was obtained. The hydration ratio of the film was calculated using following formula.

$$\textbf{Swelling index (\%)} = \frac{Wt - W0}{Wo} \times 100$$

Where, W_t was weight of film at time t and W_0 was is the original film weight at zero time.

In vitro diffusion study:-Diffusion studies were carried out for the prepared film by Franz diffusion cell with pH 6.8 phosphate buffer using dialysis membrane for a period of 24h. The donor chamber was exposed to air and receiver chamber contained 6.8 pH phosphate buffer solution with dialysis membrane in between. Two ml of solution from receiver chamber was withdrawn at every 5 min till 30 min. and replaced with the aliquot of 2 ml each time. The withdrawn solution was analyzed by UV at 248 nm.

Folding endurance:-Determination of folding endurance of film was done by folding a small strip of film (2x2cm) at the same place repeatedly until it broke. The number of time the film could be folded at the specific place without breaking given the folding endurance value.

Ex vivo drug permeation study:-Ex vivo drug permeation study was carried out by Franz diffusion cell. Goat buccal mucosa obtained from slaughter house was mounted on a diffusion cell between the donor and receptor compartment. The buccal film was fixed on the buccal mucosa. Phosphate buffer of pH 6.8 was filled in receptor compartment. The fluid was maintained at 37 ± 2°C and stirred continuously at 50 ± 2 rpm. Two ml of solution from receiver

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chamber was withdrawn at every 3min till 21min, and the aliquot of 2ml was replaced. The withdrawn solution was analyzed by UV at 248 nm.

Stability study:-Formulations with requisite for physical appearance, pH, drug content and drug release were selected for stability. For this, film were packed in aluminum foil labelled and stored studies at 25°C/60% relative humidity and 40°C/75% RH for a period of 30 days. Samples were withdrawn at time intervals of 15 days and evaluated for physical appearance, pH, drug content and drug release.

RESULT AND DISCUSSION

Taste evaluation:-Taste masking was evaluated by human panel volunteers. The prepared complex of carvedilol phosphate with β-cyclodextrin was evaluated. The result shows that excellent taste masking are done.

Physical Appearance and texture of film:-The observation revealed that the films are having the smooth surface, transparent and flexible.

Weight uniformity of film:-The weight variations of film in between 100-138 mg of $2cm^2$ film area.

Surface pH of film :-Surface pH of all film prepared by using polymer was found to be in the range of 6.5 to7, which was closed to the neutral pH, which indicated avoidance irritation to the sublingual mucosa, and hence more acceptable by the patient.

Drug content uniformity:-All the film formulation of carvedilol phosphate showed uniform drug content in the range of 91.95 to 98.74%.

Thickness:=-ll the film formulations of different polymer concentration are shown in table 3(See Appendix). Thickness of film was found in the range of-0.14±0.0015 to 0.45±0.03mm. A result of thickness measurement showed that the increase in concentration of polymer increased the thickness of film.

Swelling Index: -Formulation F2 containing 4% PVPK30 and 2% PVA showed the more swelling 14.28%. The swellability of the film was found to increase when the hydrophilic polymer content was increased. (Table no 4 See Appendix)

Disintegration time:-Formulations F1to F9 were found to disintegrate within the range of 2 min to 3.36 min. Formulation F2 containing 4% PVP and 2% PVA showed minimal disintegration time 2min,45sec. Formulation F3 showed the more disintegration time 3.32sec.

Folding endurance:-The concentration of polymer & plasticizer increase the folding endurance. The F2 formulation did not show any crack more than 300 time folding. The folding endurance was found to be optimum and film exhibited good physical and mechanical properties. The average value of all film was given in table 3(See Appendix).

In vitro drug dissolution profile:-The formulation F3 show the drug release up to 99.19% by the end of 35 min. The F2 formulation contain hydrophilic polymer PVP K30 4% and PVA 2% .The concentration of hydrophilic polymer increases the rate of drug release. FormulationF7,F8, F9 shows the slow drug release which contains the 3% PVP K30. Formulation F4, F5, F6 give the 83, 76, 74 % respectively contain 5%PVP K30. Formulation F2 and F3 show the complete drug release contain 4% PVPK30. The result are tabulated in table 4(See Appendix) and graph are depicted in figure no 1(See Appendix).

Contour plots, surface plots were drawn using the drawn using the Design-Expert® (version 9.0.3.1) software. These types of plots are useful in study of effects of two factors on the response at one time.

The regression coefficient of Y_1 (drug release) are as follow:

$$Y_1 = 93.89+7.67\ X_1 -2.33X_2 + 3.25\ X_1X_2 –22.33X_1^2 - 22.33X_2^2$$

Where Y_1 = Drug release, X_1= conc. of PVP K30, X_1= conc. of PVA

Positive sign before a factor in polynomial equations represents that the response increases with the factor. On the other hand, a negative sign means the response and factors have reciprocal relation.

Contour plot:-Analysis of contour plot of formulation F1 to F9 shown in figure3(See Appendix).Straight lines in contour plots predicted nearly linear relationship of factor. In our study contour plots does not show straight line and this indicates that no linear relation between the factor X_1 and X_2. Figure reveals that the contour area was acceptable with % drug release value above 99% containing 4% PVP K30 and 2% PVA show the higher percent drug release.

Response plot: -Three dimensional response figure 4(See Appendix) reveals that factor X_1 (PVP K30) and X_2 (PVA) effect are evaluated. The High level of factor X_1 shows minimal drug release. The percentage drug release was decreased as the concentration of X_1 was increased.

In vitro drug diffusion:-The *in vitro* diffusion study of formulation F1 to F9 was carried out using modified franz diffusion cell across cellophane membrane using pH 6.8 as medium. The diffusion profiles of formulation F2 contain PVP K 30 4% and PVA 2% showed controlled release as compared to other formulation. Diffusion profile for film F1 to F9 were given in table no. 4(See Appendix) and show in figure no 2(See Appendix).

Stability study:-The formulation was found to be stable for one month at accelerated conditions. There was no significant change in the physical appearance, drug content and in vitro drug release profile of film. No growth of microorganism was observed after completion of one month stability study.

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CONCLUSION

Buccal film of carvedilol phosphate prepared by using PVPK 30 and PVA by solvent casting method showed good transparency of film. Bitter taste of carvedilol phosphate was masked using β-CD. Buccal film having 4% PVPK30 and 2% PVA showed faster drug release. The film was found to be stable when exposed for one month stability study. Thus it can be concluded that buccal film of carvedilol phosphate is a very good choice of dosage form for faster onset of action for hypertensive patients.

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APPENDIX

Factor	Level used		
	Low (-1)	Medium (0)	High (+)
X_1-Concentratio of polyvinyl pyrrolidone K30 (gm)	3	4	5
X_2-Concentration of polyvinyl alcohol (gm)	1	2	3

Table no.1 Factorial design parameters

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Carvedilol phosphate	3	3	3	3	3	3	3	3	3
PVP K30 (%)w/v	4	4	4	5	5	5	3	3	3
PVA(%) w/v	3	2	1	3	2	1	3	2	1
Saccharine sodium(mg)	20	20	20	20	20	20	20	20	20
PEG400(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Ethanol (ml)	5	5	5	5	5	5	5	5	5

Table no.2 Composition of different formulation film

Sr.no	Volunteers	Pure drug (Carvedilol)	Complex (carvedilol+βcyclodextrin)
1	V1	+	++
2	V2	+	++++
3	V3	+	++++

+ = Bitter, ++ =Taste masked, ++++ = Excellent taste masking

Table no.3 Taste masking evaluation report

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Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation	128	100	120	138	126	127	132	130	128
Thickness (mm)	0.16	0.23	0.17	0.45	0.20	0.16	0.14	0.15	0.20
Drug content (%)	98.10	98.74	97.1	96.7	96.49	96.02	95.00	95.12	91.95
Disintegration time	2.86	2.75	2.71	3.60	3.16	2.84	3.33	3.00	2.91
Folding endurance	300	>300	300	283	285	300	216	250	242

Table no.4 Evaluation values of prepared films

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Swelling index(%)	10.34	14.28	13.59	14.19	10.40	11.37	8.06	9.61	7.62
Moisture loss (%)	1.36	1.91	2.75	3.43	1.93	2.71	3.90	2.88	2.68
% drug dissolution	80.59	98.98	99.19	83.74	76.46	73.97	60.78	63.70	64.91
% drug diffusion	82.55	91.53	90.23	84.59	77.10	74.38	62.34	57.38	59.38

Table no.5 Evaluation values of prepared films

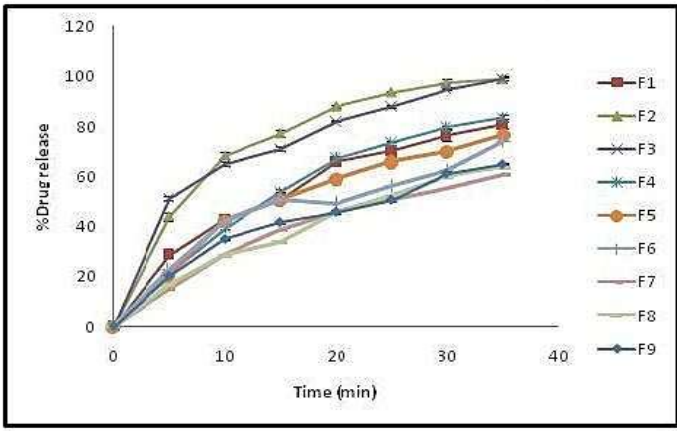

Fig.1 In vitro drug dissolution study

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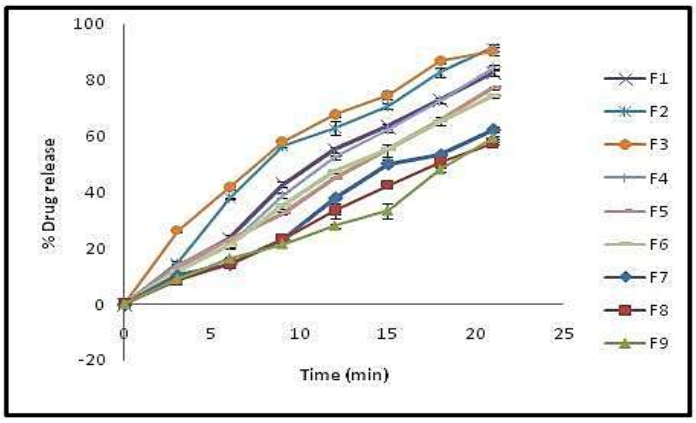

Fig.2 In vitro drug diffusion profile through cellophane membrane

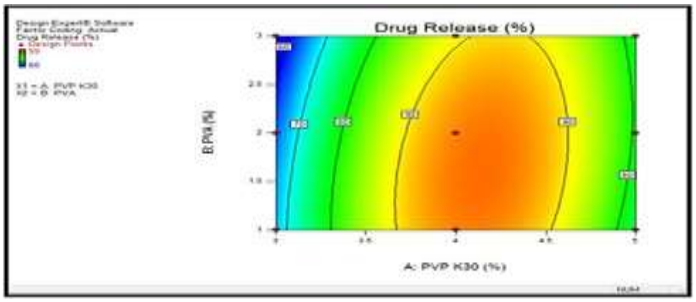

Fig.3 Two-dimensional contour plot

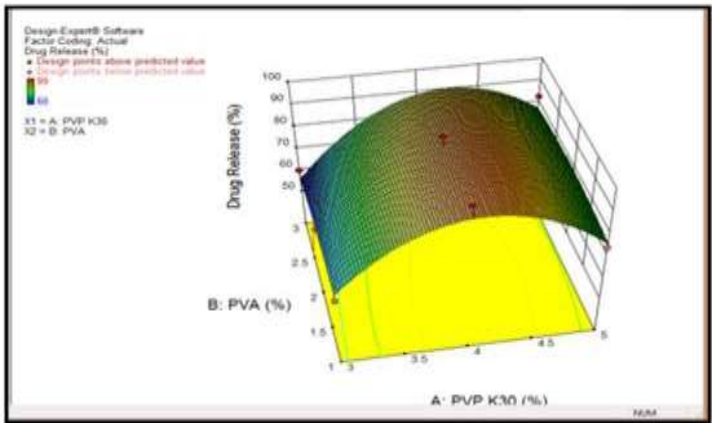

Fig. 4 Three dimensional response surface plots