Original Article

Designing and Evaluation of Mucoadhesive Buccal Films of Propranolol Hydrochloride

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ABSTRACT

Mucoadhesive buccal films of propranolol hydrochloride were prepared by solvent casting technique using hydroxypropyl methylcellulose (HPMC), hydroxy ethyl cellulose (HEC), sodium carboxymethyl cellulose (SCMC), polyvinyl pyrrolidone K-30 (PVP) and polyvinyl alcohol (PVA) in various proportions and combinations. Prepared films were evaluated for their weight, thickness uniformity, surface pH, swelling index, folding endurance, *in-vitro* residence time, *in-vitro* release and drug content uniformity. *Ex-vivo* permeation studies through the porcine buccal mucosa were performed on the selected formulations. Films exhibited sustained release over more than 6 h. The drug release from the films followed the zero order kinetics with matrix diffusion mechanism. From this study it is concluded that the films containing 20 mg propranolol hydrochloride in PVA: PVP (5 % w/v) in a 4:1 ratio (Formulation F_{16}), showed moderate swelling, a convenient residence time and promising drug release.

Key words: Buccal Drug Delivery Systems, Buccal Films, Mucoadhesive

INTRODUCTION

The development of a novel delivery system for existing drug molecules not only improves the drug's performance in terms of efficacy and safety but also improves patient compliance and overall therapeutic benefit to a significant extent.[1]

A method of drug delivery in which a drug is introduced to the body across a mucous membrane which allows for the avoidance of the gastrointestinal tract and first pass liver metabolism and consequently allows the therapeutic to directly enter into circulation. [2] Among the various drug delivery systems, buccal delivery system is found to be the most promising because, buccal mucosa, itself, provides a protective covering for the underlying tissues, acting as a physical barriers against toxins and micro-organisms. [3-4]

Extensive efforts have been focused on the development of new drug delivery systems. Mouth as a structural organ has a wide variety of function and it act as an excellent site for the absorption of drugs. Film type dosage form can be used for transdermal and also for buccal (or) sublingual use. [5] In the discipline of cardiovascular therapy, the buccal drug delivery system may prove valuable in administering drugs to treat hypertension and peripheral vascular diseases.

Propranolol hydrochloride is widely used β blocker, in the treatment of Hypertension, Angina pectoris and Cardiac arrthymia[10]. When administered orally [6-7], frequent dosing is needed due to short biological half-life ($t_{1/2}$-3-5hrs). Secondly drug undergoes high hepatic first pass metabolism thus bioavailability is reduced to 15-23 % only. It has also been reported to cause gastrointestinal discomfort. Buccal route of drug administration may be a promising

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approach to overcome the above problems. Thus the present work deals with the formulation and characterization of mucoadhesive buccal films of propranolol hydrochloride using mucoadhesive polymers. [8-9]

MATERIALS AND METHODS

Propranolol hydrochloride was obtained as a gift sample from Sarabhai Chemicals, Vadodara (Gujarat). Hydroxypropyl Methylcellulose (HPMC) and Polyvinyl Pyrrolidone K-30 (PVP) procured from Otto Kemi Ltd., Mumbai, Polyvinyl Alcohol (PVA) and Sodium Carboxymethyl Cellulose -1500-400cps (SCMC) procured from Central Drug House, Mumbai. (HEC) Glycerol was procured from E. Merck (P) Ltd. All other reagents used were of analytical grade. The films were prepared by Solvent Casting Method.

Preparation of mucoadhesive buccal films:

Buccal films of Propranolol Hydrochloride were prepared by solvent casting technique employing mercury as substrate[9]. Composition of various formulations is mentioned in Table 1.

The mucoadhesive films were prepared using anionic polymer Sodium carboxymethyl cellulose and non-ionic polymers (PVA, HEC, HPMC) polymers. PVP was added in the formulations for improving film performance and release characteristics.

The casting solutions were prepared by dissolving appropriate polymers, plasticizer and penetration enhancer in suitable solvents (distilled water) using a magnetic stirrer. The drug was added slowly to the solution and dissolved by continuous stirring for 30 minutes. The prepared solutions were left overnight at room temperature to ensure clear bubble-free solutions. Mercury was used as the substrate for casting the films. The mercury plates were kept on a platform with smooth horizontal surface. About 5 ml of the casting solution was poured within the glass bangles (5.8 cm diameter) placed on mercury surface in a petridish and allow to dry till a flexible film was formed. The dried films were cut into films of 20 mm diameter, packed on aluminium foil and stored over fused calcium chloride in a dessicator at room temperature for further use.

Evaluation of Mucoadhesive Buccal Films:

Film weight:

Three films of each formulation were taken and weighed individually in digital balance (Fisher Brand PS-200). The average weights were calculated.

Film thickness:

Weight variation test was done by weighing five films individually on a digital balance. The average weight of the film was taken as the weight.

Surface pH:

Three films of each formulation were left to swell for 2 h on the surface of an agar plate. The surface pH was measured by means of a pH paper placed on the surface of the swollen patch. A mean of three readings was recorded.

Swelling study:

After determination of the original film weight and diameter, the samples were allowed to swell on the surface of agar plate kept in an incubator maintained at 37 ^{o}C. Increase in the weight or diameter of the films (n = 3) was determined at preset time intervals (1–5 h). The percent swelling, %S, was calculated using the following equation:

Where *Xt* is the weight of the swollen film after time *t*,

*X*o is the initial film weight at zero time[11].

In-vitro residence time:

The in vitro residence time was determined using a IP disintegration apparatus. The disintegration medium was composed of 800 ml pH 6.6 phosphate buffer (PB) maintained at 37 ± 2°C. The segment of porcine intestinal mucosa, 3 cm length, were glued to the surface of a glass slab, vertically attached to the apparatus. Three mucoadhesive films of each formulations were hydrated from one surface using pH 6.6 PB and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down. The film was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time required for complete erosion or detachment of the film from the mucosal surface were recorded (n=3) as given in Table 2.

Folding endurance:

Three films of each formulation of size (2cm x 2cm) were cut by using sharp blade. Folding Endurance was determined by repeatedly folding a small strip of film at the same place till it broke. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance. The mean value of triplicate and standard deviation were shown in Table 2.

Drug content uniformity:

The uniformity of drug content of the buccal film was determined, based on dry weight of drugs and polymers used by means of a UV Spectrophotometer method. Three film units of each formulation were taken in separate 100ml buffer pH 6.6 and kept for 24 hour under constant stirring. The solutions were filtered, diluted suitably and absorbance read at 290 nm. The average of three films was considered as the drug content in one film unit. [10]

In-vitro release study:

The USP XXIV six station dissolution apparatus type 1 (V Scientific Model No. DA-6DR) was used throughout the study. One Film of each formulation was fixed to the central shaft using a cyanoacrylate adhesive. The dissolution medium consisted of 900ml pH 6.6 PB. The release study was performed at 37 ± 1°C with a rotation speed of 100 RPM. The release study was carried out for 6 h. After every one hour, 5ml samples were withdrawn from each station, filtered, diluted suitably and then analyzed spectrophotometrically at 290 nm. The Cumulative percent Propranolol Hydrochloride were determined. [11]

Ex-vivo permeation studies:

The *ex-vivo* permeation studies of mucoadhesive buccal films of Propranolol hydrochloride through excised porcine buccal mucosa was performed using the modified K-C diffusion cell. A 2.0 cm diameter film of each formulation under study was placed in intimate contact with the porcine buccal mucosa and the topside was covered with aluminum foil as a backing membrane. Teflon bead was placed in the receptor compartment filled with 75 ml of pH 7.4 phosphate buffer. The cell contents were stirred with a magnetic stirrer and temperature of 37 ±1 ^{0}C was maintained with the water jacket throughout the experiment. The amount of drug permeated into the receptor solution was determined by removing 1 ml of sample at hourly

intervals for 10 hrs. The withdrawn volume was replaced with an equal volume of fresh buffer solution. The drug permeated was determined by analyzing the samples at 290 nm.

RESULTS AND DISCUSSION

Mucoadhesive buccal films of Propranolol Hydrochloride were prepared using mucoadhesive polymers HPMC, HEC, SCMC, PVP and PVA. The drug delivery system was designed as a matrix.

The matrices of Propranolol Hydrochloride showed satisfactory physicochemical as well as bioadhesive performance of the formulated films. The physicochemical characteristics are summarized in Table 2.

It was found that film thickness were in the range of 0.323 ± 0.001 mm to 0.616 ± 0.002 mm and the weight of the films varied between 108 ± 1.92 mg to 124± 2.30 mg. The surface pH of all formulations was within 5-6 and hence no mucosal irritation was expected.

The effect of Propranolol hydrochloride on the swelling behaviour and the residence time of the mucoadhesive polymers are observed as given in Table 2.

The folding endurance was measured manually, films were folded repeatedly till it broke, and it was considered as the end point. And it varied between 299 ± 1 and 319 ± 1.

Swelling index of the films was determined using the weighing method. The samples were allowed to swell on surface of agar plate. Increase in the weight was determined at preset time. The percent swelling was calculated. Observation of the result shows that the addition of PVP predominantly decreased the swelling characteristics of the medicated films, except for HEC and Sodium CMC. The water-soluble hydrophilic additive dissolves rapidly introducing porosity. The void volume is thus expected to be occupied by the external solvent diffusing into the film and thereby accelerating the dissolution of the gel. A remarkable increase in swelling properties was observed in the case of Sodium CMC films.

The values of the *in-vitro* residence time are reported in Table 2. All the films, except Sod. CMC remained attached to the mucosal surface until complete erosion, longer duration was recorded for HEC. Upon addition of hydrophilic additive PVP the early dislodgement of the films were reported and it was more distinct with ionic polymer Sodium CMC.

Drug content in formulations was uniform with a range of 19.25 ± 0.25 mg to 20.41 ± 0.38 mg. On the basis of drug content determination it was considered that the drug was dispersed uniformly throughout the film.

In-vitro release studies of various formulations were performed in pH 6.4 phosphate buffer at 237 nm. Distinguishable difference was obtained in the release pattern of Propranolol HCL films containing PVA and SCMC. During dissolution SCMC containing films swelled forming a gel layer on the exposed film surfaces. The loosely bound polymer molecules were easily eroded, allowing the release of Propranolol hydrochloride easily as compared to PVA12,13,14. Both polymers exhibited high swelling, the film weight of these polymers were increased by 25 to 60 % from the initial weight within 2 h (Table 2). Although the marked increase in surface area during swelling can promote drug release, the increase in diffusional path length of the drug may paradoxically delay

the release. In addition, the thick gel layer formed on the swollen film surface is capable of preventing matrix disintegration and controlling additional water penetration[15]. SCMC showed high dissolution rate as compared to PVA. It was found that the drug release from the prepared films varied with respect to the proportion of polymers. Increase in the polymer concentration reduces the diffusion of drug from the matrix. Out of the six formulations, the formulation F_1 showed the good release pattern as compared to others and optimum sustained release profile was obtained in formulation F_5. After 6 h the release was found to be 91.45, 79.89, 73.65, 31.02, 58.76 and 40.45 % in formulation F_1, F_2, F_3, F_4, F_5 and F_6 respectively (Fig. 1). Among the SCMC films, F_1 (SCMC 3%) showed the good release. On the other hand, out of the PVA films, release rate was found to be higher for film containing 1 % w/v PVP.

The plots of log cumulative percent drug retained versus time were found to be linear to the formulations (Fig.3). On the basis of plots it was concluded that the release of Propranolol HCL from the films have obeyed first order kinetics. The correlation coefficient values were found to be -0.9963, -0.9879, -0.9980, -0.9922, -0.9886, -0.9875 for F_1, F_2, F_3, F_4, F_5 and F_6 respectively. It shows that data are in good correlation. Negative values of the correlation coefficient indicate negative slope for the plot.

Mechanism of drug release pattern i.e. diffusion, swelling or erosion was confirmed by Higuchi plots. Fig. 2 shows the graphical representation of cumulative percentage drug release versus square root of time. The Higuchi's Plots were found to be linear with correlation coefficient values of 0.9959, 0.9879, 0.9980, 0.9922, 0.9886, 0.9875 for F_1, F_2, F_3, F_4, F_5 and F_6 respectively. It was concluded that the release of drug from the films followed the diffusion controlled mechanism in all the formulations.

It was also concluded that among the SCMC films formulation F_1 showed the promising release pattern as compared to others. From the PVA films formulation F_5 showed moderate swelling, a convenient residence time as well as adequate drug release. On the basis of release pattern, swelling and residence time F_1 and F_5 formulations were selected for ex-vivo study. In *Ex-vivo* study, drug permeation through the porcine buccal mucosa was observed for formulation F_1 and F_5 (Fig.4). The drug permeation was found to be 58.25 % and 49.01 % in F_1 and F_5 after 10 h.

The Higuchi's Plots of F_1 and F_5 (Fig. 5) were found to be almost linear with correlation coefficient values of 0.9310 and 0.9748 of F_1 and F_5 respectively. It was concluded that the drug permeation followed the matrix diffusion process.

The plots of log cumulative percent drug retained as a function of time were found to be linear for both the formulations (Fig.6). This linearity indicates that the permeation of Propranolol HCL from the films obeyed the first order kinetics. The correlation coefficient values were found to be -0.9877 and -0.9485. It shows that data are in good correlation. Negative values of the correlation coefficient indicate negative slope for the plot.

However SCMC films (F_1) showed good drug release profile compared to the PVA films but they exhibited poor residence time as they dislodged early from the mucosal surface. It is concluded that the films containing 20 mg

Propranolol Hydrochloride in PVA 10 % and PVP 1 % w/v (Formulation F_5), showed moderate swelling, a convenient residence time and promising sustained drug release, thus can be selected for the development of buccal film for potential therapeutic uses.

Table 1: Composition of Mucoadhesive Buccal Films

Ingredients(%w/w)	F_1	F_2	F_3	F_4	F_5	F_6
Propranolol hydrochloride	2	2	2	2	2	2
Sodium carboxymethyl cellulose (1500-400cps)	3	3	3	-	-	-
Polyvinyl alcohol (Hot)	-	-	-	10	10	10
Poly vinyl pyrrolidone K-30	0	1	5	0	1	5
Glycerol (% w/v)	5	5	5	5	5	5

Table 2: Physical Evaluation Of Mucoadhesive Buccal Films Of Propranolol Hydrochloride

Formulation	Film weight(mg)	Thickness (mm)	Swelling Index (2h)	In-vitro residence time (h)	Folding endurance	Content uniformity (mg)
F_1	108±1.92	0.323±0.001	38.17(1.3)	2.5 (0.25)	299 ±1.0	19.25±0.25
F_2	116 ±1.86	0.390±0.001	38.37(1.28)	2.75(0.25)	301 ±1.0	19.39±0.27
F_3	119±2.63	0.423±0.001	35.55(1.27)	3 (0.25)	307 ±0.5	19.45±0.29
F_4	117±1.74	0.510±0.001	35.53(1.65)	2.75 (0.5)	310 ±0.7	19.92±0.30
F_5	122±1.93	0.605±0.001	54.05(0.9)	3.25(0.33)	314 ±1.0	20.15±0.35
F_6	124±2.30	0.616±0.002	55.85(0.9)	3.5 (0.25)	319 ±1.0	20.41±0.38

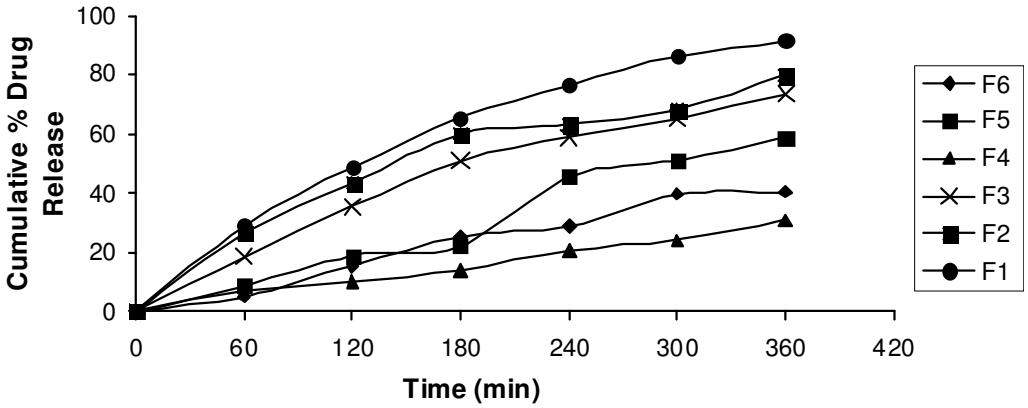

Fig. 1: Cumulative percent Drug Release in pH 6.6 Phosphate Buffer

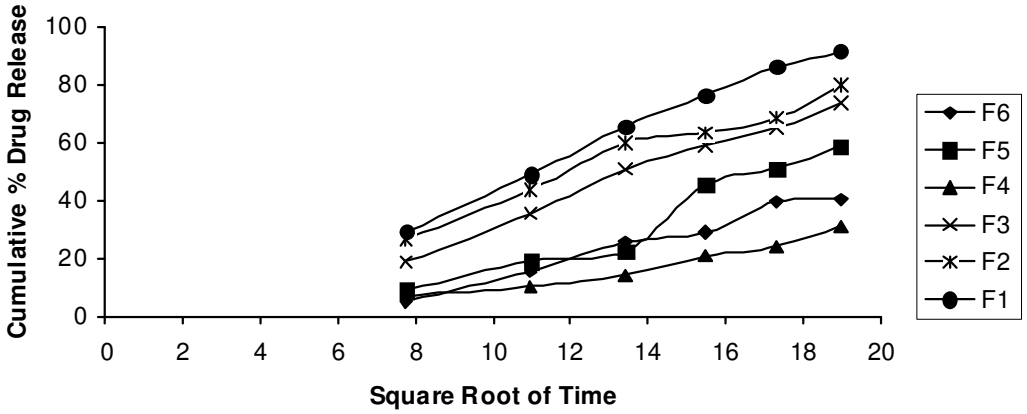

Fig. 2: Higuchi Plot of Different Formulations

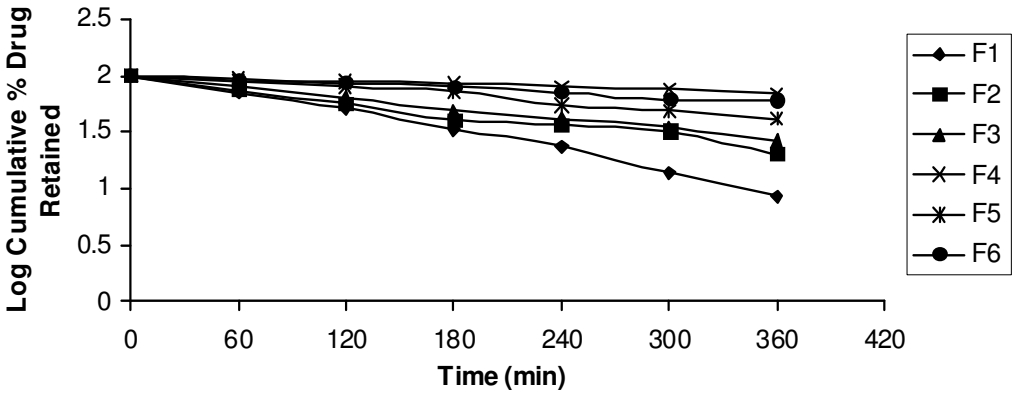

Fig. 3: Log Cumulative percent drug retained of different Formulations

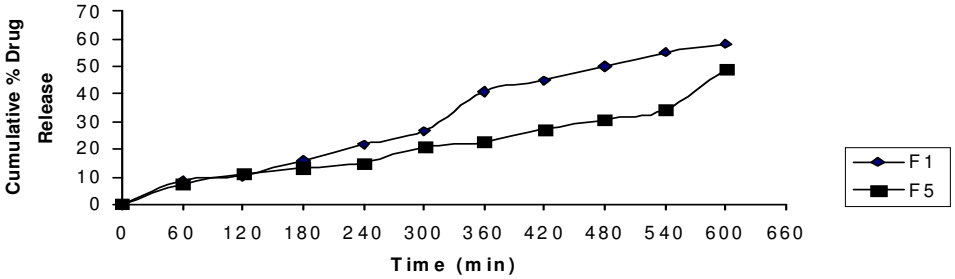

Fig. 4: Ex-Vivo Permeation of Propranolol Hydrochloride in pH 7.4 Phosphate Buffer of selected Formulations

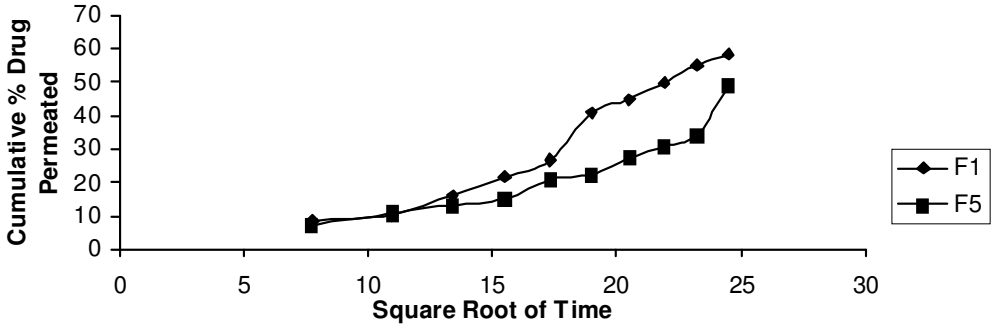

Fig. 5: Higuchi Plot for the Ex-vivo studies of selected formulations

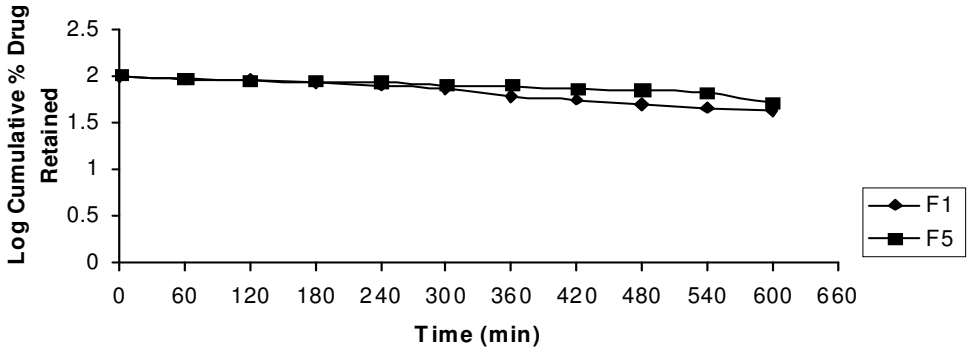

Fig. 6: Log cumulative percent drug retained in selected formulations for Ex-Vivo Studies

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