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Design and Evaluation of Mucoadhesive Buccal Films of Diltiazem Hydrochloride

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Mucoadhesive buccal films of diltiazem hydrochloride were prepared by solvent casting technique using sodium carboxymethylcellulose, polyvinyl pyrrolidone K-30 and polyvinyl alcohol. Prepared films were evaluated for their weight, thickness, surface pH, swelling index, *in vitro* residence time, folding endurance, *in vitro* release, permeation studies and drug content uniformity. Films exhibited controlled release over more than 6 h. From this study it was concluded that the films containing 20 mg diltiazem hydrochloride in polyvinyl alcohol 10 % and polyvinyl pyrrolidone 1 % w/v (formulation F_5), showed moderate swelling, a convenient residence time and promising drug release, thus can be selected for the development of buccal film for potential therapeutic uses.

Among the various routes of administration tried for novel drug delivery systems, local delivery to tissues of the oral cavity has been investigated for a number of applications, including the treatment of toothaches[1], periodontal disease[2,3], bacterial and fungal infections[4], aphthous and dental stomatitis[5], and in facilitating tooth movement with prostaglandins[6]. Various studies have been conducted on buccal delivery of drugs through mucoadhesive films. Buccal film may be preferred over adhesive tablet in terms of flexibility and comfort. In addition, they can circumvent the relatively short residence time of oral gels on the mucosa, which is easily washed away and removed by saliva. Moreover, the buccal film is able to protect the wound surface, thus reduce pain and also could treat oral diseases more effectively.

Diltiazem hydrochloride is a widely used cardiovascular drug, for the treatment of angina, essential hypertension and atrial flutter. When administered orally[7,8], frequent dosing is needed due to short biological half-life ($t_{1/2}$-4 h). Secondly diltiazem undergoes high hepatic first pass metabolism thus bioavailability is reduced to 40 % only. It has also been reported to cause gastrointestinal discomfort. Buccal route of drug administration may be a promising approach to overcome the above problems. Thus the present work deals with the formulation and characterization of mucoadhesive buccal films of diltiazem hydrochloride using mucoadhesive polymers like sodium carboxymethylcellulose, polyvinyl pyrrolidone and poly vinyl alcohol.

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MATERIALS AND METHODS

Diltiazem hydrochloride was obtained as a gift sample from Dr. Reddy's Laboratories Ltd., Hyderabad. Polyvinyl pyrrolidone K-30 (PVP), polyvinyl alcohol (PVA) and sodium carboxymethylcellulose, 1500-400cps (SCMC) were procured from Central Drug House, Mumbai. Glycerol was procured from E. Merck (P) Ltd, Mumbai. All other reagents used were of analytical grade. The films were prepared by Solvent Casting Method..

Preparation of mucoadhesive buccal films:

Buccal films of diltiazem hydrochloride were prepared by solvent casting technique employing aluminum foil cups (placed on glass surface) as substrate[9]. Composition of a circular cast film of various formulations is mentioned in Table 1. The mucoadhesive films were prepared using ionic polymers SCMC and non-ionic polymers PVA with a water-

TABLE 1: COMPOSITION OF MUCOADHESIVE BUCCAL FILMS

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

soluble hydrophilic additive PVP. PVP was added in 1 and 5 % w/v in the formulations for improving film performance and release characteristics.

For SCMC (3 % w/v), the calculated amount of the polymer was dispersed in three forth volume of water with continuous stirring using mechanical stirrer and the final volume was adjusted with distilled water. In case of PVA films, PVA powder (10 % w/v) was dissolved in hot water at approximately 80–100° with stirring[10]. Two percent w/v diltiazem was incorporated in the polymeric solutions after levigation with 5 % v/v glycerol added as a plasticizer. The medicated gels were left overnight at room temperature to ensure clear, bubble-free gels. The gels were cast into aluminum foil cup (4.5 cm diameter), placed on a glass surface and allowed to dry in a leveled oven maintained at 40°, till a flexible film was formed. The dried films were cut into films of 20 mm diameter, packed in aluminum foil and stored in a desiccator until further use.

Evaluation of mucoadhesive buccal films:

For evaluation of film weight three films of each formulation were taken and weighed individually in digital balance (Fisher Brand PS-200). The average weights were calculated. Three films of each formulation were taken and the film thickness was measured using Micrometer Screw Gauge (Mitutoyo MMO-25DS) at three different places and the mean value was calculated. For determination of 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. 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°. 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: percent swelling (% S)=(Xt–Xo/Xo)×100, where Xt is the weight of the swollen film after time t, Xo is the initial film weight at zero time[11].

***In vitro* residence time:**

The *in vitro* residence time was determined using IP disintegration apparatus. The disintegration medium was composed of 800 ml pH 6.6 phosphate buffer (PB) maintained at 37±2°. The segments of rat intestinal mucosa, 3 cm length, were glued to the surface of a glass slab, vertically attached to the apparatus. Three mucoadhesive films of each formulation 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 (2×2 cm) 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:

Three film units of each formulation were taken in separate 100 ml volumetric flask, added 100 ml of pH 6.6 phosphate buffer and kept for 24 h under constant stirring. The solutions were filtered, diluted suitably and analyzed at 237 nm in a UV spectrophotometer (Thermospectronic UV-1). The average of three films was taken as the content of drug in one film unit.

***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 900 ml pH 6.6 PB. The release study was performed at 37±0.5° with a rotation speed of 50 rpm. The release study was carried out for 6 h. After every one-hour,

samples were withdrawn from each station, filtered, diluted suitably and then analyzed spectrophotometrically at 237 nm. The data presented were the mean of three determinations.

***Ex vivo* permeation studies:**

The *ex vivo* permeation studies of mucoadhesive buccal films of diltiazem hydrochloride through a thick excised layer of porcine buccal mucosa (procured from local slaughter house) was studied using the modified Franz diffusion cell. A 2.0 cm diameter film of each formulation under study was placed in intimate contact with the excised 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 100 ml of pH 7.4 phosphate buffer. The cell contents were stirred with a magnetic stirrer and temperature of 37±1° was maintained throughout the experiment. Samples were withdrawn at every one hour, filtered, diluted suitably and then analyzed using UV- spectrophotometer at 240 nm.

RESULTS AND DISCUSSION

Mucoadhesive buccal films of diltiazem hydrochloride were prepared using mucoadhesive polymers SCMC, PVP and PVA. The drug delivery system was designed as a matrix. The physical characteristics as well as the bioadhesive performance of various films are given in Table2. It was found that film thickness were in the range of 0.49±0.28 mm to 0.99±0.74 mm and weight in the range of 116±1.86 mg to 129±0.77 mg. Surface pH of the films was in the range of 5-6.

The effect of diltiazem hydrochloride on the swelling behaviour and the residence time of the mucoadhesive polymers are observed as given in Table 2. The medicated films showed high swelling values compared to plain films because of the water-soluble drug, which enhanced the water uptake capacity in the finished dosage form. The influence of drug on the swelling properties of polymer matrices is primarily dependent on the substituted groups of the polymer. The hydroxyl group in the molecules played an important role in the matrix integrity of the swollen hydrophilic cellulose matrices. SCMC containing films showed higher percent swelling as compared to PVA films due to presence of more hydroxyl group in the SCMC molecules. The amount and properties of the incorporated drug determine matrix integrity.

The incorporation of the drug induced significant reduction of the residence time of the studied formulae. The enhanced erosion rate observed with the non-ionic polymers PVA may correlate with the increase in swelling behaviour when the drug was added. As the particle swells, the matrix experiences intra-matrix swelling force promoting disintegration and leaching of the drug leaves behind a highly porous matrix. Water influx weakens the network integrity of the polymer, the structural resistance of the swollen matrices is thus greatly influenced and erosion of the lose gel layer is more pronounced[12]. The early dislodgment of the film from the mucosal surface was more distinct with the ionic polymer SCMC. The addition of PVP predominantly decreased the swelling characteristics of the medicated films of PVA. 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[13]. The folding endurance was measured manually, films were folded repeatedly till it broke, and it was considered as the end point. Folding endurance were found to be high (470±5) for F_6 and low (189.96±4.04) for F_3. Drug content in formulations was uniform with a range of 18.94±0.066 (F_2) to 20.08±0.07 (F_1). 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

TABLE 2: PHYSICAL EVALUATION OF MUCOADHESIVE BUCCAL FILMS OF DILTIAZEM HYDROCHLORIDE

Formulation Code	Film weight(mg)	Thickness (mm)	Swelling Index (2h)	*In vitro* Residence time (h)	Folding Endurance	Content Uniformity (mg)
F_1	129±0.771	0.49±0.28	60.14±1.35	2.5±0.559	320.0±7.81	20.08±0.07
F_2	116 ±1.86	0.55±0.13	79.36±1.84	2.5±0.721	279.66±5.5	18.94±0.06
F_3	119±2.63	0.52±0.34	51.85±2.54	3.0±0.908	189.96±4.0	19.14±0.05
F_4	117±1.74	0.98±0.36	28.67±1.42	3.25±0.087	262.33±3.5	19.92±0.01
F_5	126±1.93	0.83±0.54	26.01±1.57	3.75±0.109	209.33±9.0	19.85±0.02
F_6	122±2.04	0.99±0.74	25.41±1.23	1.25±0.192	470.0±5.0	19.59±0.03

performed in pH 6.6 phosphate buffer at 237 nm. Distinguishable difference was obtained in the release pattern of diltiazem 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 diltiazem easily as compared to PVA[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 diffusion 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.2). On the basis of plots it was concluded that the release of diltiazem from the films have obeyed first order kinetics. The correlation coefficient values were found to be -0.9963,

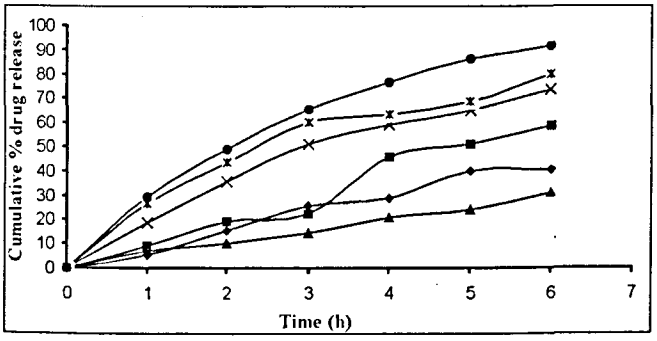

Fig. 1: Cumulative percent drug release in pH 6.6 phosphate buffer

Formulation F_1 (-●-), F_2 (-*-), F_3 (-x-), F_4 (-▲-), F_5 (-■-), F_6 (-◆-)

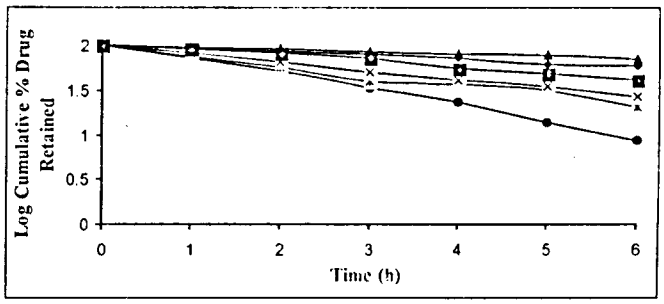

Fig. 2: Log cumulative percent drug retained of different formulations

Formulation F_1 (-●-), F_2 (-*-), F_3 (-x-), F_4 (-▲-), F_5 (-■-), F_6 (-◆-)

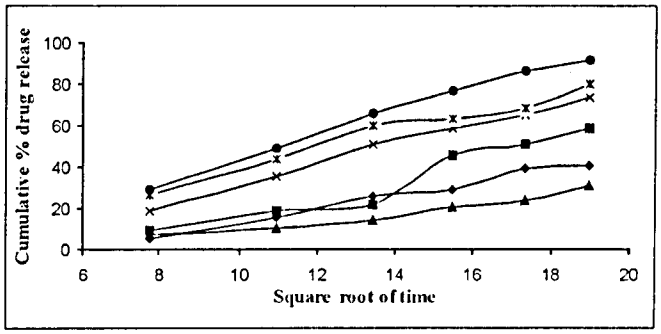

Fig. 3: Higuchi plot of different formulations

Formulation F_1 (-●-), F_2 (-*-), F_3 (-x-), F_4 (-▲-), F_5 (-■-), F_6 (-◆-)

-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. 3 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

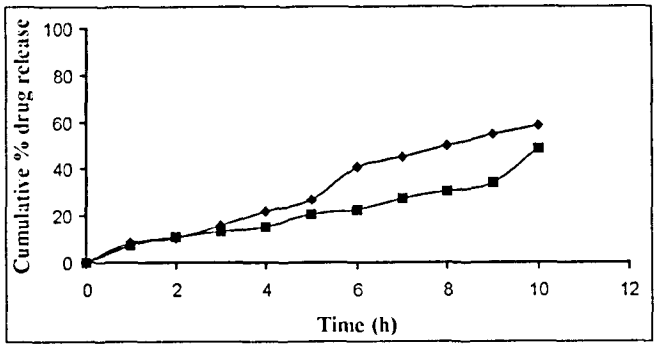

Fig. 4: *Ex vivo* permeation studies of diltiazem hydrochloride

Permeation studies in pH 7.4 phosphate buffer of formulations F_1 (-◆-) containing SCMC 3 % w/v and F_5 (-▪-) containing PVA 10 % and PVP 1 % w/v with 20mg diltiazem in each film.

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 diltiazem 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.

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

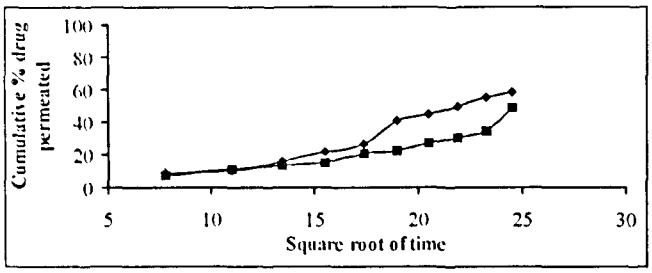

Fig. 5: Higuchi plot for the *ex vivo* studies

Formulations F_1 (-◆-) and F_5 (-▪-)

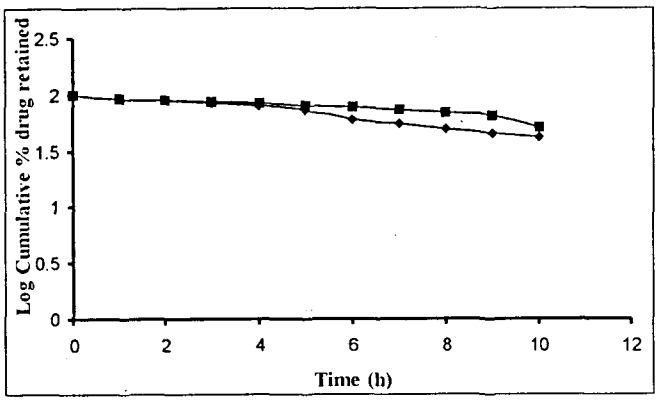

Fig. 6: Log cumulative percent drug retained for the *ex vivo* study

Formulations F_1 (-◆-) and F_5 (-▪-)

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