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PREPARATION AND EVALUATION OF MUCOADHESIVE BUCCAL FILMS OF CARVEDILOL

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ABSTRACT

This research work was carried out to study effect of ionic and non-ionic polymers on buccal films of carvedilol. Solvent casting method was used for preparing mucoadhesive films of carvedilol using carboxymethyl cellulose, polyvinyl pyrrolidone K-30 and polyvinyl alcohol and evaluated for their weight, thickness, surface pH, swelling index, in vitro residence time, folding endurance, in vitro release, permeation studies and drug content uniformity. F1 formulation (prepared from carboxymethyl cellulose) exhibited good controlled release over six hours. Physical characteristics of the studied films showed promising with good bio-adhesion. Performance of ionic polymers was good when compared with non-ionic polymer.

Keywords : Buccal films, carvedilol, ionic polymers, non-ionic polymers etc.

INTRODUCTION

Transmucosal route has gained significant attention to prolong the residence time of the dosage form at the site of application or absorption and to facilitate intimate contact of the dosage form with the underlying absorption surface (1-5). The oral mucosa can be categorized into sublingual, gingival, and buccal mucosa through which oral transmucosal delivery can be achieved and absorption of therapeutic agents from the oral cavity bioavailability, thereby avoiding the first-pass hepatic metabolism and gastrointestinal degradation (6-10). Several studies (11) reported mucoadhesive drug delivery systems in the form of tablets, films, patches, and gels for oral, buccal, nasal, ocular, and topical routes; however, very few reports on mucoadhesive patches are available (12-15).

The objective of this study was to develop, characterize, and evaluate mucoadhesive patches of carvedilol employing various mucoadhesive polymers for prolonged gastrointestinal absorption. Carvedilol, an effective antihypertensive that requires controlled release owing to its short biological half-life, was used chosen as a model drug candidate. The mucoadhesive films were evaluated by in vitro and in vivo methods for controlled release.

MATERIALS AND METHODS

Carvedilol was obtained as a gift sample from Shri Chemicals, Indore.

Preparation of mucoadhesive buccal films

Solvent casting technique was used to prepare the buccal films of carvedilol using aluminum foil cups as substrate. Composition of a circular cast film of various formulations is mentioned in table 1. The mucoadhesive films were prepared using ionic polymers Sodium carboxy methyl cellulose (SCMC) and non-ionic polymers Poly vinyl alcohol (PVA) with a water-soluble hydrophilic additive Poly vinyl pyrrolidone (PVP) in 1 and 5 % w/v 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 0 C with stirring. Two percent w/v carvedilol was incorporated in the polymeric solution 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 (45. cm diameter), placed on a glass surface and allowed to dry in leveled oven maintained at 40^0 C, 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.

Physical Characteristics of Buccal films

The prepared films were weighed individually and the

average weights were calculated. The thickness of three films from each formulation was measured using micrometer Screw Gauge 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 swollen patch. A mean of three reading was recorded.

Percent swelling (% S) = (Xt-Xo/Xo) x 100, were Xt is the weight of the swollen film after time t; Xo is the initial film weight at zero time.

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^{0}c 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 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 table2.

Folding endurance

Three films of each formulation of size (2x2 cm) were cut 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 242 nm in a UV spectrophotometer. 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 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^{0}C with a rotation speed of 50 rpm. The release study was carried out for 6h. After every one-hour sample were withdrawn from each station, filtered, diluted suitably and then analyzed spectrophotometrically at 242 nm. The data were the mean of three determinations.

Ex vivo permeation studies

The ex vivo permeation studies of mucoadhesive buccal films of carvedilol 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 backing membrane. Teflon bead was placed in the receptor compartment filled with 100 ml of pH 7.4-phosphate buffer. The contents were stirred with a magnetic stirrer and temperature of 37±1^{0}C was maintained throughout the study. Sample were withdrawn at every one hour, filtered, diluted suitably and then analyzed using UV-Spectrophotometer at 242 nm.

RESULTS AND DISCUSSION

Mucoadhesive buccal films of carvedilol were prepared using mucoadhesive polymers SCMC, PVP and PVA. The physical characteristics as well as the bioadhesive performance of various films are given in table 2. It was found that film thickness was in range of 0.35±0.3mm to 0.80±0.30 and weight in range of 0.1587?0.031 and0.1862 ±0.027 mg. Surface pH of film was in range of 5-6.

Formulations F1 and F2 showed high swelling values compared to plain films because of presence of more hydroxyl group in the SCMC molecules. The incorporation of the drug induced significant reduction of the residence time of the studied formulae. The enhanced erosion is observed with the non- ionic polymers PVA may correlate with increase in swelling behavior when drug was added. As the particle swells, the matrix experiences intra-matrix swelling force promoting disintegration and leaching of drug leaves behind a highly porous matrix. Water influx weakens the network integrity of the polymer, the structural resistance of swollen

matrices is thus greatly influenced and erosion the lose gel layer is more pronounced. The early dislodgement of the film from the mucous surface was more distinct with the ionic polymer SCMC. The addition of PVP predominantly decreased the swelling characteristics of the medicated films of PVA.

Marked variation was observed in the release pattern of carvedilol containing PVA and SCMC. Swelling of SCMC allowed polymer molecules easily erode and so release observed was comparatively high. It was found that the drug release from the prepared film 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, formulation F1 showed the good release pattern as compared to the others and optimum sustained release profile was obtained in formulation F5. After 6h the release was found to be 96.25, 82.35, 76.56, 35.02, 62.76 and 42.27 % in formulation F1, F2, F3, F4, F5, and F6 respectively (fig1). Among the SCMC films, F1 (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.

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 for F1, F2, F3, F4, F5, and F6 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 film formulation F1 showed the promising release as compared to others. From the PVA films formulation F6 showed moderate swelling, a convenient residence time as well as adequate drug release. On the basis of the release pattern, swelling and residence time F1 and F5 formulations were selected for ex vivo study. In ex vivo study permeation through the porcine buccal mucosa was observed for formulation F1 and F5 (fig. 3). The drug permeation was found to be 62.54% and 51.56 % in F1and F5 after 10 h.

However SCMC films (F1) 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 carvedilol in PVA 10 % and PVP 1 % w/v (F5), 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.

Table 1: Composition of mucoadhesive buccal films

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6
Carvedilol	0.5	0.5	0.5	0.5	0.5	0.5
Sodium CMC (1500-4000cps)	3	3	3	-	-	-
Poly vinyl 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

Table 2: Evaluation parameters of carvedilol mucoadhesive buccal film

Formulation code	Film weight (mg)	Thickness (mm)	Swelling Index (1hr)	In vitro resi dence Time (hr)	Folding endurance	Content uniformity(mg)	
F1	0.1865±0.027	0.35±0.03	52.71±1.53	2.4±0.1	846.67±7.63	11.20±0.20	
F2	0.1587±0.031	0.39±0.01	46.43±1.75	2.43±0.057	735.67±5.69	10.93±0.11	
F3	0.1656±0.031	0.39±0.03	41.56±0.573	3.2±0.10	561.67±4.72	11.03±0.15	
F4	0.1813±0.032	0.78±0.02	36.51±1.67	3.6±0.361	758.33±4.72	11.13±0.15	
F5	0.1811±0.028	0.73±0.05	34.23±1.85	3.75±0.25	691.22±9.85	11.10±0.26	
F6	01792±0.028	0.80±0.03	33.55±2.16	1.53±0.451	665.35±6.24	11.03±0.57	

Table 3: In vitro drug **release (%)**

S.No.	Time (hr)	F1	F2	F3	F4	F5	F6
1	1	25.13±0.11	21.45±0.21	19.56±0.08	5.25±0.38	11.25±0.78	5.36±0.07
2	2	40.52±0.24	32.02±0.34	26.23±0.35	8.56±0.56	19.25±0.68	8.95±0.11
3	3	58.32±0.31	46.25±0.56	38.25±0.34	15.24±0.47	25.69±0.23	17.58±0.21
4	4	68.25±0.36	59.65±0.42	48.55±0.22	19.25±0.53	39.56±0.36	26.53±0.32
5	5	82.36±0.56	76.25±0.27	65.23±0.62	26.21±0.32	51.25±0.21	33.45±0.38
6	6	96.25±0.43	82.35±0.53	76.56±0.51	35.02±0.32	62.76±0.56	42.27±0.45

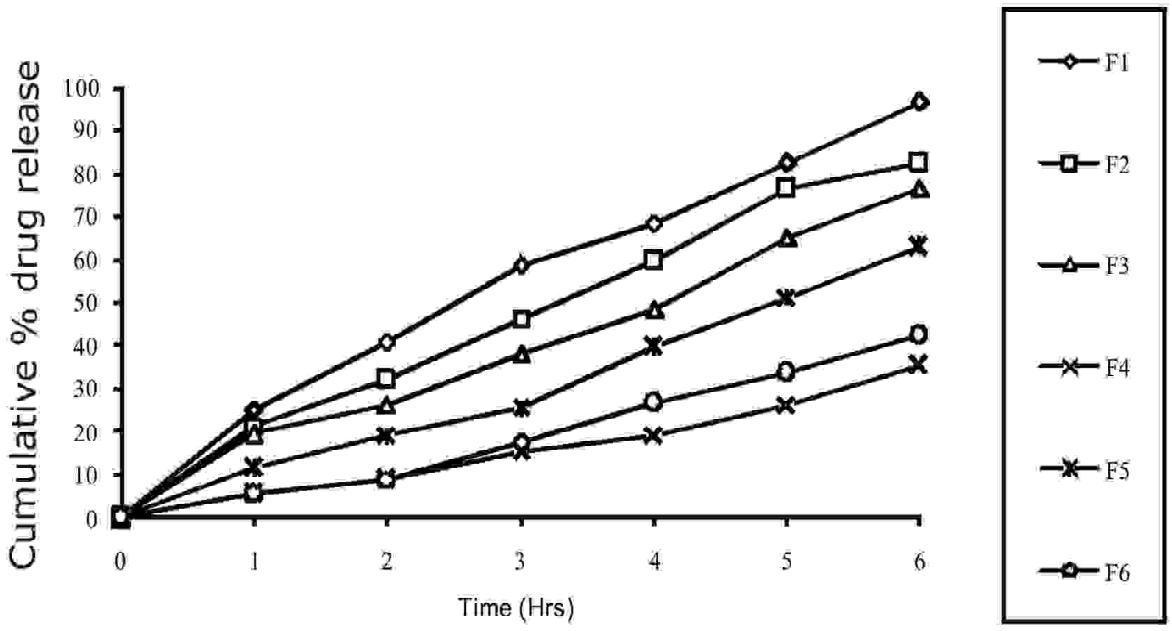

Figure 1: Cumulative percent drug release in pH 6.6-phosphate buffer

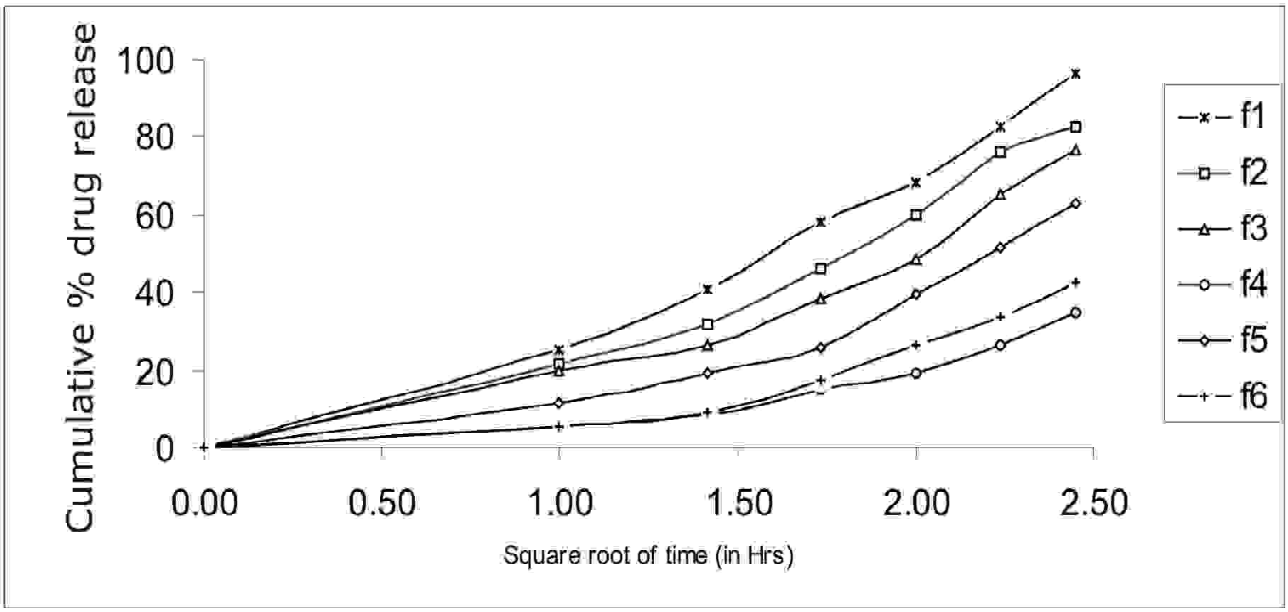

Figure 2: Higuchi plots of different formulations

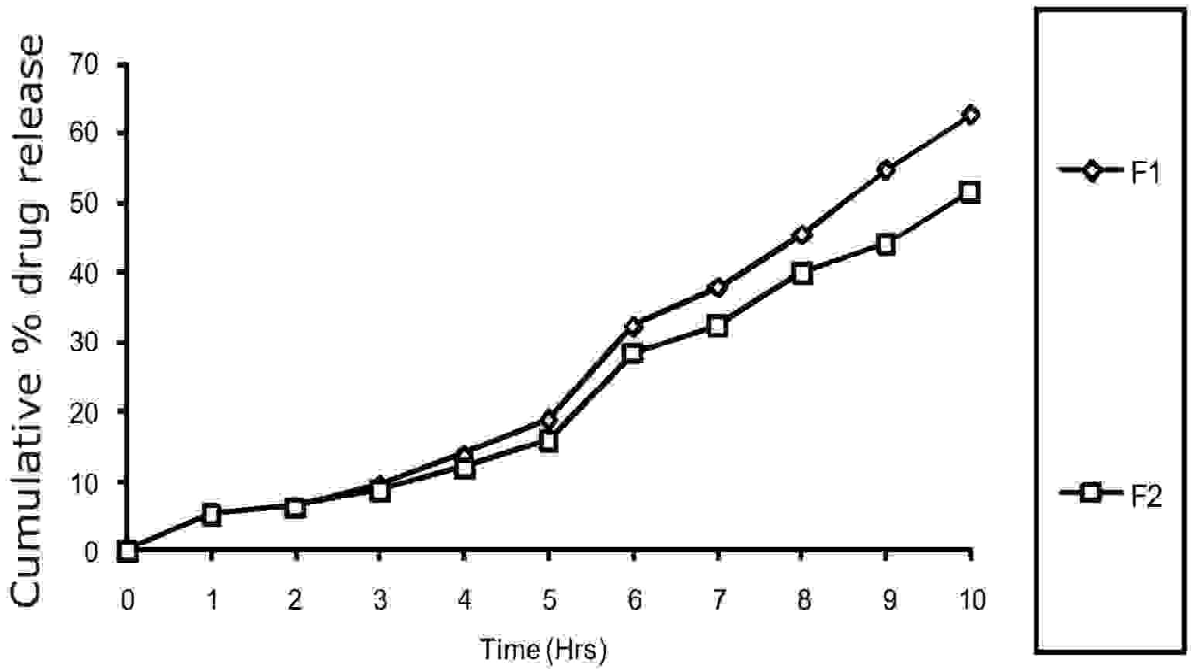

Figure 3: Ex vivo permeation studies of carvedilol

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