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Effect of Solubilizers and cross- linking agent on Buccoadhesive dosage form of Diltiazem hydrochloride

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ABSTRACT

Buccoadhesive disk of diltiazem hydrochloride were prepare by solvent casting method. Sodium alginate was used as bioadhesive polymer. Polyethylene glycol 4000 and mannitol were used as solubilizers. One of each formulation was cross-linked with calcium chloride (0.1 % w/v). The disks were evaluated for surface pH, swelling index, surface diameter study, in-vitro drug release, ex-vivo buccoadhesion and ex-vivo residence time on sheep buccal mucosa. Studies were carried out to evaluate the effect of cross-linking agent on the swelling and buccoadhesive characteristics of sodium alginate buccal disks. Addition of solubilizers in less concentration (0.5%) improved the drug release without erosion of the disks (batch F2 and F4). Buccal disks containing PEG – 4000 had less buccoadhesion than disks containing mannitol. PEG-4000 containing disks showed higher in-vitro drug release rate than mannitol containing disks. It was found that crosslinked disks (batch F1 and F3) of sodium alginate controlled the swelling profile; eroded well during release study without affecting the buccoadhesion of the disks. Cross-linked disks showed more than 80 % drug release within 3 hours by erosion-diffusion mechanism followed by first order release kinetic. Good in-vitro drug release and in-vitro buccal permeation was observed in selected buccal patch.

Introduction

Development of novel drug delivery systems has been one of the major thrust areas of pharmaceutical research these days. Buccal cavity has wide variety of functions and it acts as an excellent site for the absorption of drugs.[1] A buccal route offers many advantages over conventional routes of delivery with an improved bioavailability due to the avoidance of degradation in the gastrointestinal tract and hepatic first-pass metabolism.[2,3]

Diltiazem hydrochloride is a benzathiazepine calcium channel blocker with peripheral and coronary vasodilatory properties [4]. It is widely used in the treatment of various cardiovascular disorders particularly in the treatment of angina pectoris and systemic hypertension. Although it is well absorbed from the gastrointestinal tract, its bioavailability is very low (40 %) due to extensive first pass metabolism [5]. Also diltiazem hydrochloride with half-life of 4.5 hours, low molecular weight (450.48), optimum oil/buffer partition coefficient (octanol/water partition coefficient is 158 at pH 7.4) [5] makes it a suitable candidate for administration by buccal route. Since buccal route bypass first pass metabolism, the dose of diltiazem hydrochloride could be reduced.

Sodium alginate was used as natural bioadhesive polymer. The effect of solubilizers (Mannitol and PEG 4000) and cross-linking agent (calcium chloride) on surface pH, swelling, invitro drug release, exvivo buccoadhesion, exvivo residence time, and invitro buccal permeability were evaluated.

Material and Methods

Diltiazem hydrochloride was gifted from Torrent Pharma (Ahmedabad, Gujarat, India). Carbopol – 940 (Goodrich Chem Co.Ohio, USA), Sodium alginate (Bombay ResearchGlycerine, PEG 4000, and Mannitol (Nice Chemical Pvt. Ltd). Other chemicals and reagents were of analytical grade.

Formulation of Buccoadhesive Disks

Diltiazem hydrochloride buccoadhesive disks were prepare by solvent casting method [6]. Sodium alginate was dispersed in distilled water with constant stirring. Drug, mannitol and PEG 4000 were added separately in distilled water and mixed with constant stirring to get homogenous mass. Batch of F_1 and F_3 were crosslinked by dropwise addition of calcium chloride solution (0.1%w/v) to above homogenous mass. Glycerine (2.5 % w/w) was added with constant stirring in each formulation. Final homogenous mass was degassed and casted in glass petridish lubricated with glycerine.

Prepared film was allowed to dry for overnight at ambient temperature covered with inverted glass funnel for uniform drying.

Film was cut into 16 mm diameter using specially fabricated punch so each disk containing 20 mg of drug. Disks were stored in airtight glass container. Black disks were also prepared with same methodology. The composition of buccoadhesive disks is shown in Table 1.

Surface pH

The method adopted by Bottenberg et al, was used to determine surface pH of the disks[7]. A combined glass electrode was used for this purpose.

The disks were allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature, and pH was noted by bringing electrode in contact with the surface of the disk and allowing it to equilibrate for 1 minute.

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Swelling Study

Buccal disks were weighed individually (W1) and placed separately in 2% agar gel plates[8] and incubated at 37 ±1°C. At regular one-hour time interval until 3 hours, the disks were removed from the petridishes and excess surface water was removed carefully using the filter paper. The swollen disks were then again weighed (W2), and swelling index (SI) was calculated using the following formula.[9]

SI = (W2 –W1) /W1 x100

Surface Diameter

The initial diameter of disk (D_0) was noted (16.0±0.1 mm) and place in 9 cm diameter petridish. 75 ml distilled water was then added and disk diameter (D_1) was measured at 20, 40, 60, 90,120 and 180 minutes. The increasing surface diameter was measured by D_1-D_0.

Ex-Vivo buccoadhesive Strength

Bioadhesive strength of the buccal adhesive disk was measured on a modified physical balance using the method described by Gupta et al .[10] The fresh sheep buccal mucosa was cut into pieces and washed with isotonic phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with isotonic phosphate buffer pH 6.8. Glass vial was placed and tightly fitted in glass beaker filled with isotonic phosphate buffer (pH 6.8, 37±1°C) just touches the mucosal surface. The disk was stuck to the lower side of rubber stopper with cynoacrylate adhesive. Two side of the balance was balanced with five gm weight on the right hand side pan. A weight of five gm was removed from the right hand side pan, which lowered the pan along with the disk over the mucosa. The balance was kept in this position for five minutes contact time. The water (equivalent to weight) was added slowly with infusion set (100 drops /min) to the right-hand side pan until the disk detached from the mucosal surface. The weight, in gram, required to detach the disk from the mucosal surface gave the measure of buccoadhesive strength.

Ex-Vivo Residence Time

The ex-vivo residence time was performed (n=3) after application of the buccal disks on freshly cut sheep buccal mucosa.[11] The fresh sheep buccal mucosa was fixed on the internal side of a beaker with cynoacrylate glue. A side of each disk was wetted with one drop of isotonic phosphate buffer pH 6.8 and was pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The beaker was filled with 200 ml of isotonic phosphate buffer pH 6.8 and was kept at 37°C ± 1°C. After 2 minutes, a 150-rpm stirring rate was applied to simulate the buccal cavity environment, and disk adhesion was monitored till detachment of disk. The time for the disk to detach from the sheep buccal mucosa was recorded as residence time.

In-Vitro Drug Release

The USP XXIII rotating paddle method was used to study the drug release from buccal disks. The dissolution medium consisted of 200 ml of isotonic phosphate buffer pH 6.8. The release was performed at 37±0.5°C, with a rotation speed 50 rpm. The one side of buccal disk was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was allocated in the bottom of the dissolution vessel. Samples (5ml) were withdrawn at pre-determined time intervals and replaced with fresh medium .The samples were filtered through 0.45 µm whatman filter paper, and assayed spectrophotometrically at 236 nm (Shimadzu, SPD-10 A VP, Japan)

In-Vitro buccal permeation

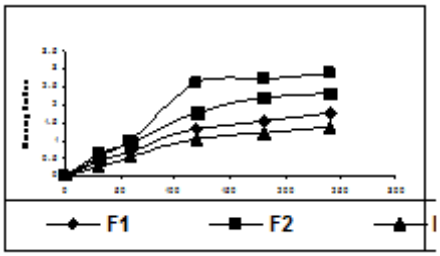
The in-vitro buccal permeation study through the sheep buccal mucosa was performed using Keshary-Chien type glass diffusion cell at 37±0.2°C. Freshly obtained sheep buccal mucosa was mounted between the donor and receptor compartment. The disk was placed with the core facing the mucosa and the compartments clamped together. The donor compartment was filled with 1 ml of isotonic phosphate buffer pH 6.8. The receptor compartment (15 ml capacity) was filled with isotonic phosphate buffer pH 7.4 and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm. 1 ml sample was withdrawn at pre-determined time intervals and analyzed for drug content at 236 nm using a UV-spectrophotometer (Shimadzu, SPD-10 A VP, Japan).

Results and Discussion

Buccoadhesive formulations containing sodium alginate as a natural bioadhesive polymer. 0.5 % concentration was optimized for mannitol and PEG-4000 and 0.1% concentration of calcium chloride as crosslinking agent was optimized on the basis of invitro drug release, mucoadhesion and swelling studies. The prepared buccal disks of diltiazem hydrochloride were good in appearance, with an average thickness of 0.75 mm, with weight of 90 mg, and diameter of 16-mm. Content uniformity of the drug was found to be satisfactory when performed in phosphate buffer 6.8.

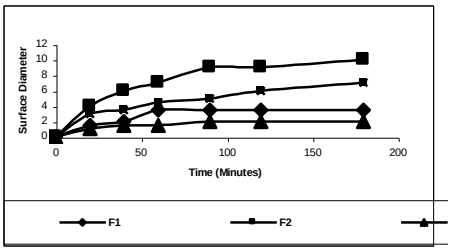
From data of fig 1, patches containing mannitol had lesser swelling compared to PEG-4000 containing disk, indicated that mannitol had negative effect in response to swelling.

Figure 1: Swelling index of buccoadhesive disks of diltiazem hydrochloride



Crosslinked disks (F_1 and F_3) were found with less water uptake capacity when compared to uncrosslinked disks (F_2 and F_4). Addition of crosslinking agent may increase the crosslinking density and reduced the interlink length, so chain extensibility may be lowered.

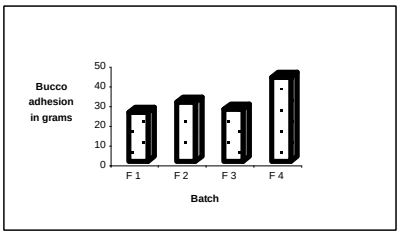
Figure 2: Surface diameter of buccoadhesive disks of diltiazem hydrochloride



Disks containing mannitol (batch F_3 and F_4) showed less surface diameter of swelling disks than disks containing PEG-4000 (batch F1 and F2). Swelling index and surface diameter studies showed that addition of 0.1 % calcium chloride as crosslinking agent could control the swelling of the buccal disks. An effective buccal mucosal delivery device must maintain contact with mucous membrane overlying the epithelial tissue. The parameter is very critical for successful utilization of buccal

dosage forms. Figure 3 shows that mannitol containing disks (F_3 and F_4) exhibited higher buccoadhesion than disks containing PEG 4000 (F_1 and F_2), may be due to mannitol's partial confirmation and liner configuration which facilitated interaction between the adhesive sites (- OH groups) and mucosal layer. Disks containing PEG 4000 revealed comparative low buccoadhesion than mannitol containing disks due to PEG's poor bioadhesive property[12]. Ex-vivo mucoadhesive strength showed that buccoadhesive strength was not much affected by crosslinking agent, which was used in 0.1% concentration.

Figure 3: Buccoadhesion of buccoadhesive disks of diltiazem hydrochloride

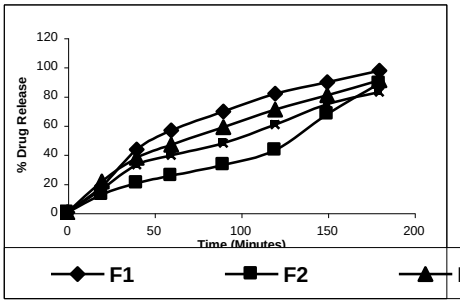


All buccal disks showed satisfactory residence time on sheep buccal mucosa. Uncrosslinked disks (F_2 and F_4) showed higher exvivo residence time (disks F2= 221 min, F4= 236 min.) than cross-linked disks (F1 and F3) (disks F1=211 min., F3=222 min.). Good correlation was observed between ex vivo buccoadhesive strength and ex vivo residence time with correlation coefficient of 0.9998; these results showed that Buccoadhesive strength was not affected by addition of crosslinking agent in low concentration (0.1%).

In Vitro Drug Release

Figure 4 shows that initially, drug release was found to be higher in mannitol containing disks (F_3 and F_4), but overall drug release was found to be higher in PEG 4000 (F_1 and F_2) disks. Addition of cross linking agent in low concentration (0.1%) had not much significant effect on drug release, though higher release of crosslinked disks may be due to dual mechanism of drug release both by erosion and swelling diffusion of the crosslinked disks. It was observed that crosslinked disks eroded well during dissolution studies. The release data showed that for uncrosslinked disks the release mechanism was swallowed type and for crosslinked disk the drug release followed diffusion-erosion mechanism.

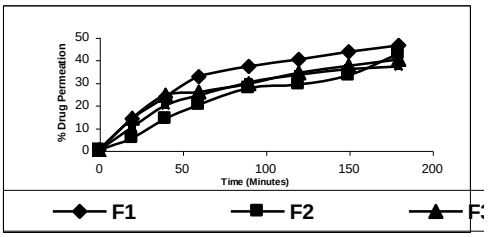
Figure 4: Invitro drug release of buccoadhesive disks of diltiazem hydrochloride



In-Vitro buccal permeation

All the buccal disks showed satisfactory invitro drug permeation through sheep buccal mucosa. The maximum invitro drug permeation was observed in buccal disk F1, which showed also higher invitro drug release. Good correlation was observed between invitro drug release and invitro buccal permeation with correlation coefficient of 0.9681.

Figure 5: Invitro buccal permeation of buccoadhesive disks of diltiazem hydrochloride



Conclusion

The buccoadhesive disks of Diltiazem hydrochloride prepared using natural bioadhesive polymer sodium alginate showed satisfactory buccoadhesion and better drug release profile. Addition of crosslinking agent i.e. calcium chloride in low concentration (0.1 % w/w) could control swelling without affecting drug release profile but decreased the buccoadhesion and residence time slightly. PEG-4000 and mannitol showed good release enhancers. The drug release was found to be higher with erosion diffusion mechanism from the cross-linked disks as compared to uncross linked disks which showed drug release with diffusion controlled mechanism.

Figure 6: Correlation between in-vitro drug release and in-vitro buccal permeation of buccoadhesive disks of diltiazem hydrochloride

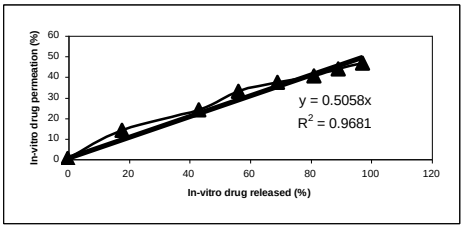


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Table I: Composition of different batches of buccoadhesive disks of diltiazem hydrochloride

Batch Code	F1	F2	F3	F4
Sodium alginate (%)	4	4	4	4
PEG-4000 (%)	0.5	0.5	-	-
Mannitol	-	-	0.5	0.5
Calcium chloride (0.1% w/v)	0.1	-	0.1	-
Glycerine (%w/w)	2.5	2.5	2.5	2.5