International Standard Serial Number: 0976-1403

Deccan J. Pharmaceutics and Cosmetology 1(2): April-June 2010

DECCAN PHARMA JOURNAL SERIES

ARMS Online Publications

www.deccanpharmajournals.com

Formulation And Evaluation Of Unidirectional Buccal Patches Of Diltiazem Hydrochloride

Patel Vishnu M*; Patel Anandkumar K.; Modasiya Moin. K. ; Trivedi Darshan. G.
Department of Pharmaceutics,
APMC College of Pharmaceutical Education and Research, Motipura,
Himatnagar-383001, Gujarat State, INDIA.
E-mail: mmalai2003@yahoo.co.in

Abstract:

Buccal adhesive patches of Diltiazem hydrochloride were prepared using sodium alginate as a bioadhesive polymer and different concentration of PEG-4000 as solubilizer. The patches were prepared by solvent casting method. The patches were evaluated on the basis of their physicochemical characteristics, weight variation, drug content uniformity, folding endurance, ex-vivo mucoadhesive strength, ex-vivo residence time, surface pH, in-vitro drug release, and in-vitro buccal permeation study.

Patches containing <2% PEG-4000 exhibited drug release over a period of 240 minutes without erosion. The mechanism of drug release was found to be by non-Fickian diffusion and followed zero-order kinetics. Addition of PEG-4000 generally enhanced the release rate. The ex-vivo mucoadhesive strength was performed using sheep buccal mucosa on modified physical balance. Optimized patches (F4) showed satisfactory bioadhesive strength 32±2.0 gm, and ex-vivo residence time 272 ± 0.25 minutes. Swelling index of sodium alginate buccal patches was directly proportional to concentration of PEG-4000. The surface pH of all patches was within satisfactory limit (7.0±1.5) and hence patches should not cause irritation in the buccal cavity. Good correlation coefficient was observed between in-vitro drug release and in-vitro drug permeation study with correlation coefficient of 0.9985.

Key words: diltiazem hydrochloride; buccal patches; bioadhesive polymer

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.

In the present study Sodium alginate was used as natural bioadhesive polymer. The effect of solubilizer PEG 4000 on surface pH, swelling study, in-vitro drug release, ex-vivo mucoadhesive strength, ex-vivo residence time, and in-vitro 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 Research Lab), Glycerine, PEG 4000, other chemicals and reagents were of analytical grade.

Formulation of Buccal adhesive patches

Diltiazem hydrochloride Buccal adhesive patches were prepared by solvent casting method[6]**.** Sodium alginate was dispersed in distilled water with constant stirring. Drug and PEG 4000 were added separately in distilled water and mixed with sodium alginate dispersion with constant stirring to get homogenous mass. Glycerine (2.5 ml) was added with constant stirring in each formulation. . Final homogenous mass was degassed and casted in glass petridish and was allowed to dry for overnight at ambient temperature covered with inverted glass funnel for uniform drying and was cut into 16 mm diameter using specially fabricated punch so each patch containing 20 mg of diltiazem hydrochloride. Patches were stored in airtight glass container. Blank patches were also prepared with same methodology. The composition of buccal adhesive patches is shown in Table 1.

Table 1: Composition of different buccal patches of Diltiazem hydrochloride

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem hydrochloride (mg)	640	640	640	640	640	640	640	640	640
Sodium alginate (gm)	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
PEG-4000 (mg)	~	75	100	125	150	175	200	250	500
Glycerol (ml)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Distilled water (ml)	100	100	100	100	100	100	100	100	100

Surface pH

The method adopted by Bottenberg et al, was used to determine surface pH of the patches[7]. A combined glass electrode was used for this purpose. The patches 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 patch and allowing it to equilibrate for 1 minute.

Swelling Study

Buccal patches 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 three hours, the patches were removed from the petridishes and excess surface water was removed carefully using the filter paper. The swollen patches were then again weighed (W2), and swelling index (SI) was calculated using the following formula[9].

SI = (W2 –W1) /W1 x100

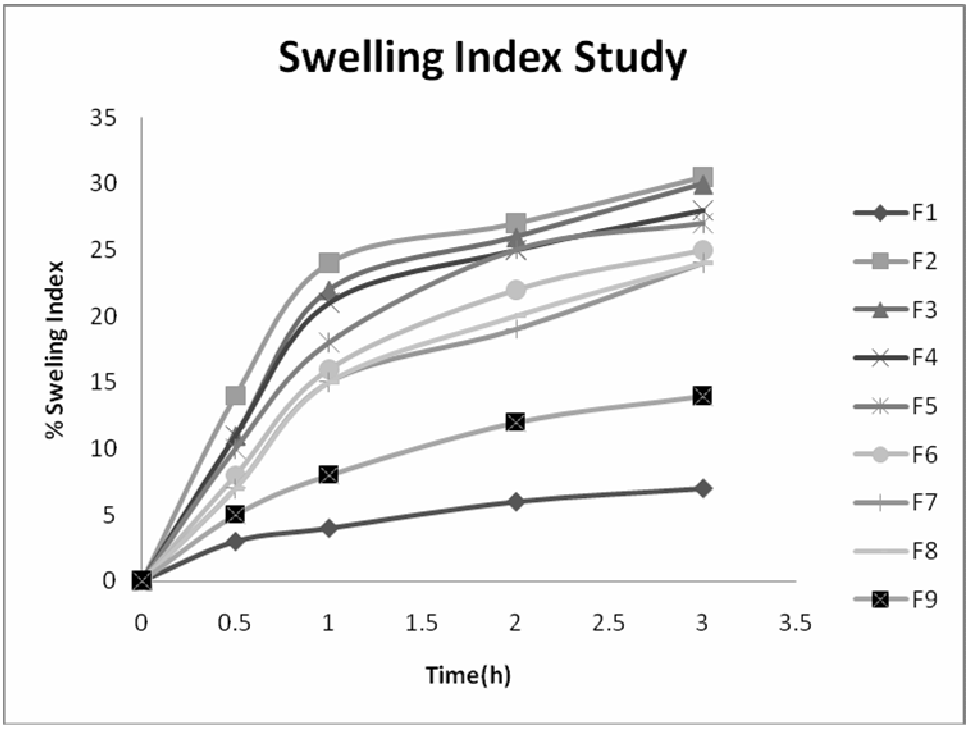

Figure 2: Swelling index study of buccal patches of Diltiazem hydrochloride.

***Ex-Vivo* buccoadhesive Strength**

Bioadhesive strength of the buccal adhesive patch 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^{o}C) just touches the mucosal surface. The patch 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 patch 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 patch detached from the mucosal surface. The weight, in gram, required to detach the patch 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 patches 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 patch 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^{o}C ± 1^{o}C. After 2 minutes, a 150-rpm stirring rate was applied to simulate the buccal cavity environment, and patch adhesion was monitored till detachment of patch. The time for the patch 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 patches. The dissolution medium consisted of 200 ml of isotonic phosphate buffer pH 6.8. The release was performed at 37±0.5^{o}C, with a rotation speed 50 rpm. The one side of buccal patch was attached to the glass patch with instant adhesive (cyanoacrylate adhesive). The patch 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 UV 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^{0}C. Freshly obtained sheep buccal mucosa was mounted between the donor and receptor compartment. The patch was placed on the mucosal surface 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).

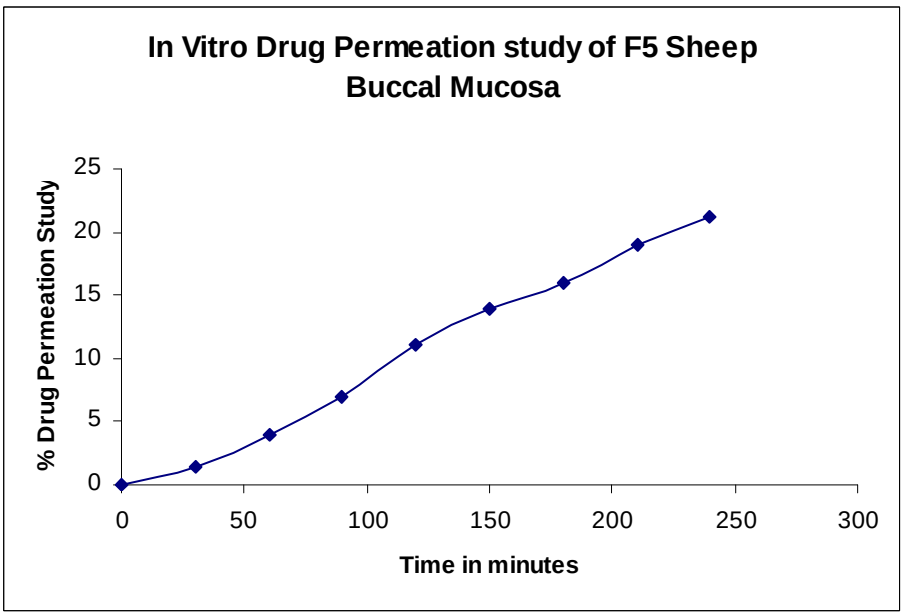

Figure 3: *In Vitro* Drug Permeation Study of optimized batch F5 through Sheep Buccal Mucosa

Results and Discussion

In the present study, buccoadhesive patches of sodium alginate were prepared and optimized on the basis of ex-vivo buccoadhesive strength and in-vitro drug release study. The prepared buccal patches of diltiazem hydrochloride were good in appearance, Patches thickness ranged from 0.51(0.07) to 0.58 (0.04) mm; with a weight range from 72 (±0.81) to 84 (±0.99) mg, and diameter of 16-mm. Content uniformity of the drug was found to be satisfactory in the range of 98.90 (±1.05) % to 100.38 (±0.35) % when performed in phosphate buffer 6.8. The surface pH of the prepared patches was within satisfactory limit (7 ± 1.5 unit), showed these formulations couldn't cause any kind of irritation at site of application.

Swelling was major mechanism of drug release from patches. Swelling index was higher in patches containing higher amount of PEG-4000 (Figure 1).

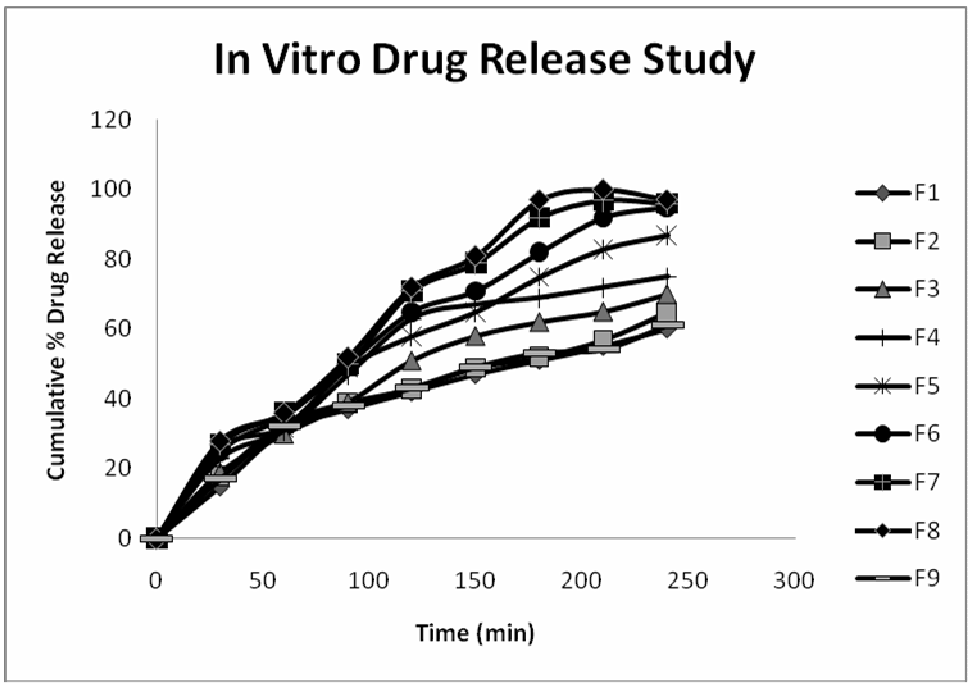

Figure 1: *In vitro* drug release from buccal patches of Diltiazem hydrochloride.

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. It is represented as the weight required for detachment of the patch from the membrane and this gives buccoadhesive strength of patch in gram. Sheep buccal mucosa was used as biological membrane for ex-vivo buccoadheisve study. Plain patches showed higher mucoadhesive strength (21.5±1.8 gm) than medicated patches. The incorporation of PEG-4000, a water-soluble hydrophilic polymer and water-soluble drug has significantly reduced the bioadhesive strength of the buccal patches. Bioadhesive strength of optimized patch (F4) was found to be 12±2.0 gm. This may be due to mannitol's partial confirmation and liner configuration which facilitated interaction between the adhesive sites (- OH groups) and mucosal layer. Patches containing PEG 4000 revealed comparative low buccoadhesion due to PEG's poor bioadhesive property[12]. The plain patches showed higher ex-vivo residence time (490 minutes). The incorporation of PEG-4000 and drug induced significant reduction in ex-vivo residence time. (t-test, $P<0.05$) of the patches. The optimized patches (F4) showed 272± 0.25 minutes ex-vivo residence time on sheep buccal mucosa. The drug released was increased linearly with the increasing concentration of PEG-4000.

The maximum in-vitro release was found 99.84 ±1.25 % over a period of 240 minutes in batch F4, containing 1.8% PEG-4000. Patches containing more than 2% PEG-4000 showed eroded well in dissolution study. These showed that PEG-4000 has also significant effect on release behavior of the drug from sodium alginate based matrix. Patches containing PEG-4000 more than 2% showed zero-order with erosion-diffusion mechanisms while patches containing PEG-4000 less than 2% showed nearer to zero order ($r^2 = 0.8998$) with peppas kinetic exponent.

Optimized patches showed 21.21 % drug permeation through sheep buccal mucosa. Good correlation coefficient was observed between in-vitro drug release and in-vitro drug permeation study with correlation coefficient of 0.9985. The drug stability in buccal patch was confirmed by FT-IR spectroscopy.

Table 2: Characteristics of Buccal patches of Diltiazem hydrochloride.

Batch Code	Folding endurance	Surface pH	% Drug content	Thickness (mm)
F1	>200(0)	7.41(0.12)	99.68(0.15)	1.02(0.02)
F2	>200(0)	7.93(0.02)	97.65(0.21)	1.14(0.04)
F3	>200(0)	7.08(0.14)	100.38(0.35)	1.12(0.09)
F4	>200(0)	6.92(0.05)	97.95(0.26)	1.03(0.01)
F5	>200(0)	7.93(0.03)	98.15(0.45)	0.96(0.05)
F6	>200(0)	7.02(0.08)	99.25(0.25)	1.18(0.02)
F7	>200(0)	7.82(0.10)	100.78(0.13)	1.17(0.04)
F8	>200(0)	6.85(0.16)	98.15(0.43)	1.08(0.03)
F9	>200(0)	7.32(0.17)	97.78(0.56)	0.98(0.08)

Conclusion

The buccoadhesive patches of Diltiazem hydrochloride prepared using natural bioadhesive polymer sodium alginate showed satisfactory buccoadhesion and better drug release profile. PEG-4000 showed good release enhancers. The drug release was found to be satisfactory with diffusion controlled mechanism.

REFERENCES:

1 Kemken J. et al. *J Pharm Pharmacol*. 1991; 43: 679.

2 De Vries M.E. et al. *Crit. Rev. Ther. Drug Carrier Syst.* 1991; 8: 271-303.

3 Chidambaram N. et al. *Drug Dev Ind Pharm*.1995; 21: 1009-1036.

4 Tripathi K.D., Antianginal Drugs in Essentials of medical pharmacology; 4th edition, Published by Jaypee Brothers, India, 1992; 532.

5 Ahuja A. et al. *Indian J. Pharm. Sci*., 1995; 57 (1): 26-30.

6 Sawayanaga Y. et al. *Chem Pharm Bull*. 1982; 30: 3297-3301.

7 Bottenberg P. et al. *J Pharm Pharmacol*. 1991; 43: 457-464.

8 Kemken J. et al. *Math Find Exp Clinical Pharmacol*. 1991; 13: 361-365.

9 Parodi B. et al. *Drug Dev Ind Pharm*. 1996; 22:445-450.

10 Gupta A. et al. *Indian drugs*.1992; 30: 152-155.

11 Han R.Y. et al. *Int J Pharm.* 1999; 177: 201-209.

12 Walle T. et al. *Clin. Pharmacol,Ther*. 1978; 24: 668-677.

13 Lee C.H. et al. *J.Control Release*. 1996. 39:93-103.