Design and Evaluation of Diltiazem Hydrochloride Buccal Patches

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Diltiazem hydrochloride buccal patches were prepared using different polymers in various proportions and combinations. The *in vitro* drug release from the formulations was studied using commercial semi-permeable membrane. The physico-chemical parameters of the formulations were evaluated. The zero order release formulation F2 (drug reservoir with 3% HPMC and 3% EC as rate controlling membrane) was subjected to graphical treatments according to Higuchi equation and Peppa's equation which confirmed that the release mechanism is by diffusion. Formulation F2 was also subjected to *in situ* diffusion studies using a fresh goat cheek pouch membrane, which has shown good correlation with *in vitro* release. The expected release for an extended period of 12 h was observed in formulation F2.

Extensive efforts have been focussed on targeting drugs to a particular region of the body for an extended period of time. Drug delivery via the buccal mucosa offers such a novel route of drug administration. Diltiazem hydrochloride, a drug used in the treatment of angina pectoris has recently become very popular for the treatment of old age hypertension[1,2]. The drug is well absorbed from the gastrointestinal tract, but its bioavailability is low due to extensive first pass metabolism[3]. Since buccal route bypasses first pass effect, the dose of diltiazem hydrochloride could be reduced by 80%. The physico-chemical properties of diltiazem, its suitable half-life (4.5 h), optimum oil/water partition coefficient (octanol/buffer partition coefficient is 158) and low molecular weight (450.98) make it suitable candidate for administration by the buccal route[4]. The aim of this study was to prepare and evaluate buccal patches of diltiazem hydrochloride in order to overcome bioavailability problems, to reduce dose-dependent side effect and frequency of administration.

Diltiazem hydrochloride (DTZ) was a generous gift by Kopran Limited, Mumbai. The polymers used were hydroxy propyl methyl cellulose (15 cps), ethyl cellulose (20 cps), polyvinyl pyrrolidone, polyvinyl alcohol which were procured from S.D. Fine Chem., Boisar, Gujarat and eudragit RL-100 from Rohm Pharma GmbH, Weiterstat, Germany.

Buccal patch containing drug reservoir was prepared by solvent casting technique[5]. Small patches of 1 cm^2 in area containing 30 mg of DTZ were punched out from the films using a specially fabricated mould (Table 1). A rate controlling membrane was casted on a glass plate using the polymer ethyl cellulose (3%) by incorporating dibutyl phthalate (30% w/w) of polymer) as plasticizer. A membrane of 1.44 cm^2 in area was cut and both sides of the drug reservoir were sealed using this membrane to control the release.

In vitro release studies were carried out by tying Sigma dialysis membrane to one end of the open cylinder which acted as donor compartment. A buccal patch containing 30 mg of DTZ was placed inside the compartment. Samples of 1 ml were withdrawn at periodic intervals from the receptor compartment containing 25 ml of phosphate buffer (pH 6.6) and the drug content was analyzed colorimetrically at 495 nm[6]. *In vitro* drug release data was graphically treated in order to determine the order of drug release from the matrix. The formulation F2 (drug reservoir with 3% HPMC and 3% EC as rate controlling membrane) has shown the regression value of 0.9721 for the zero order plot and the total amount of drug released at the end of 12 h was 88.2% (Table-1)

*For Correspondence

TABLE 1 : EFFECT OF POLYMER ON DRUG RELEASE AND BIOADHESIVE STRENGTH

	Formulation Code									
Composition	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
HPMC(%)	4	3	-	-	-	-	-	-	-	-
PVP(%)	-	-	0.5	0.5	-	-	-	-	-	-
PVA(%)	-	-	-	-	0.5	0.5	-	-	-	-
EC(%)	-	-	2	2.5	2	2.5	-	-	-	-
Eudragit RL 100(%)	-	-	-	-	-	-	3	4	-	-
HPC(%)	-	-	-	-	-	-	-	-	3	4
Plasticizer (% w/w of polymer)										
Glycerol	30	30	-	-	-	-	-	-	30	30
Castor oil	-	-	30	30	30	30	30	30	-	-
Cumulative % drug release* (at the end of 12th hour)	77.20	88.20	74.90	61.20	72.00	60.60	77.10	65.50	80.00	78.90
Bioadhesive strength* (g)	5.10	4.80	2.40	2.10	2.20	2.10	2.73	3.30	4.90	5.40

F1 to F10 represent various formulations prepared using Hydroxy Propyl Methyl Cellulose (HPMC), Poly Vinyl Pyrrolidone (PVP) Poly Vinyl Alcohol (PVA), Ethyl Cellulose (EC) and/or Hydroxy Propyl Cellulose (HPC)
*denotes that the values are average of three determinations

TABLE 2 : REGRESSION VALUES OF HIGUCHI PLOT AND SLOPE VALUES OF PEPPAS PLOT

Formulation Code	Regression values of Higuchi Plot	Slope values of Peppa's Plot
F1	0.9700	0.6079
F2	0.9876	0.4816
F3	0.9773	0.6483
F4	0.9775	0.5528
F5	0.9969	0.6330
F6	0.9801	0.4629
F7	0.9829	0.6190
F8	0.9909	0.6833
F9	0.9943	0.7090
F10	0.9959	0.7664

F1 to F10 represent various formulations prepared

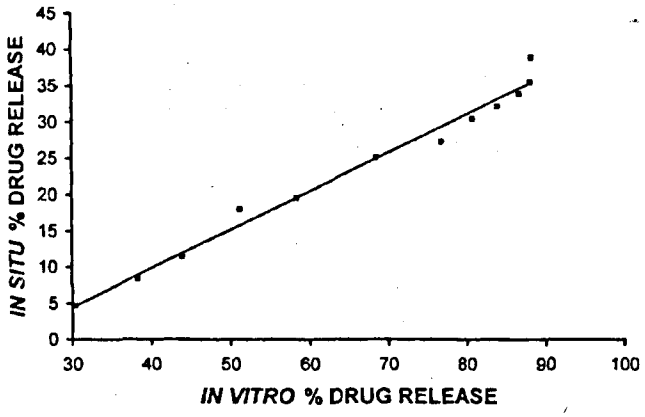

Fig. 1: *In vitro-in situ* correlation plot

***In vitro-in situ* correlation of the release of DTZ from F2 formulation containing a drug reservoir with 3% HPMC and 3% EC as rate controlling membrane. The correlation coefficient value was found to be 0.9916**

which is the highest value among all the formulations. Regarding the bioadhesive strength[7] measured on a modified physical balance, the formulation F2 has shown considerably good value when compared with other formulations. Hence formulation F2 was selected for further studies.

The *in vitro* release data were subjected to Higuchi's and Peppa's plots to determine the mechanism of release and swellability of polymer matrix. The correlation value of Higuchi's plot of the formulation F2 was 0.9876 (Table-2) which indicates that the drug release from the matrix is by diffusion. The slope value of Peppa's plot was 0.4816 (Table 2) which confirms that the drug release is mediated solely by diffusion mechanism.

The prepared formulations were evaluated for moisture absorbtion[8], moisture loss[8], thickness, weight variation and drug content. The intactness of the formulation F2 (drug reservoir with 3% HPMC and 3% EC as rate controlling membrane) showing zero order and maximum release was confirmed by IR studies on Perkin-Elmer (577) Grating Infrared spectrophotometer using KBr disc method.

Stability studies on the best formulation F2 revealed no significant changes at 4° and 45°. However, changes occurred at 60°, which could be attributed to a loss of moisture from the formulation. When formulation F2 (drug reservoir with 3% HPMC and 3% EC as rate controlling membrane) was subjected to *in situ* diffusion studies, a drug permeation of 38.8% was observed in 12 h across freshly obtained goat cheek pouch membrane. *In vitro-in situ* correlation was carried out to find the therapeutic efficacy of the formulation F2. The correlation coefficient was found to be 0.9916, which confirms the correctness of *in vitro* release method followed (Fig. 1).

In conclusion, these results indicate that formulation F2 (drug reservoir with 3% HPMC and 3% EC as rate controlling membrane) of DTZ has achieved the objectives of prolong release, decreased frequency of administration and thus improved patient compliance.

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