RESEARCH PAPER

Received 5 May 1994
Indian J.Pharm.Sci. 1995,57(1), pp. 26-30

Development of Buccal Tablets of Diltiazem Hydrochloride

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In an attempt to develop mucoadhesive buccal drug delivery system, multilayered tablets of diltiazem hydrochloride were prepared which gave an *in-vitro* drug release of 86%. *In-situ* testing was done using bovine cheek pouch membrane in a Franz diffusion cell.

DILTIAZEM (DTZ) is a calcium channel blocker which is widely employed in the treatment of various cardiovascular disorders. Although it is very well absorbed from the gastrointestinal tract, its bioavailability is low due to extensive first pass metabolism (1). Since buccal route bypasses first pass effect, the dose of DTZ could be reduced by 80%. The aim of this study was to prepare and evaluate buccal tablets of DTZ. HCl using bioadhesive polymers in order to overcome bioavailability problems and to reduce dose dependent side effects.

The physico-chemical properties of this drug, its suitable half life (4.5 hrs), optimum oil/water partition coefficient (octanol/buffer partition coefficient is 158 at pH 7.4) (2), low molecular weight (450.98) makes it a suitable candidate for administration by the buccal route.

EXPERIMENTAL

DTZ. HCl was obtained from M/S Pharmax Corporation, Delhi and the polymers were obtained from M/s Ranbaxy Laboratories, Delhi. Isotonic phosphate buffer was prepared according to USP (3).

Preparation of buccal tablets

DTZ. HCl and polymers were passed through sieve 200 and mixed by trituration using a glass mortar and pestle. These were compressed into 13 mm diameter, 1 mm thickness and 150 mg average weight tablets, on an infra-red hydraulic press (Riken-Power, Japan) using a compression force of 200 Kg/cm^2 and a compression time of 10 seconds.

For multi-layered tablets, the ingredients (50 mg) of the core were compressed at 50 kg/cm^2 for 5 seconds using a 8 mm die punch set in a manner similar to that described above. The core was then removed and placed in the centre of a 13 mm die and the ingredients (150 mg) of cap layer poured over it and recompressed at 50 kg/cm^2 for 5 seconds. The upper punch was removed and the mixed ingredients (100 mg) of the backing layer were then added over the cap. It was then subjected to a compression force of 150 kg/cm^2 for 20 seconds.

Measurement of bioadhesive strength

Bioadhesive strength of prepared DTZ buccal tablets was measured on a modified physical balance using the method described by Gupta et al (4).

Dissolution studies

Dissolution rate of the drug from buccal tablets was studied using a modified USP dissolution rate test apparatus. The modification consisted of an internal compartment made up of a 150-ml glass beaker (i.d. 40 mm) into which was placed a teflon cylinder (40 mm diameter, 20 mm height) having a

cavity (13 mm diameter, 4 mm depth) on one side. The tablet was inserted into the cavity of teflon cylinder so that the core faced the dissolution medium (100-ml isotonic phosphate buffer, pH 6.6 at 37° C). A stirrer was lowered so that it remained at least 1 cm above the tablet surface and stirring was done at 50 r.p.m. Samples (3 ml) were withdrawn and replaced by fresh dissolution medium and absorbance read at 237 nm. Preliminary studies indicated that the polymers used in the study did not interfere with the estimation of the drug at this wave length.

Water absorption study

This was done on 1% agar gel plates (5). The tablets were placed with the core facing the gel surface and incubated for 4 hrs. at 37°C. The tablets were weighed before and after standing on the agar plate and examined for any physical change.

In-situ Diffusion studies

In-situ studies of the diffusion of DTZ from buccal tablets was carried out using the Franz diffusion cell. Fresh bovine cheek pouch membrane was attached to the top of lower compartment. The buccal tablet with core facing the membrane was covered with a glass cap from three sides. The donor compartment was filled with isotonic phosphate buffer pH 6.6, whereas the receptor compartment had a buffer of pH 7.4 and a magnetic needle. The assembly was maintained at 37°C and stirred magnetically. Samples were withdrawn at various time intervals during a 4 hr. period.

RESULTS AND DISCUSSION

The polymers for the development of DTZ buccal tablets were selected on the basis of bioadhesive property, non-toxicity, non- irritancy, stability and compatibility with the drug. Carbopol 934 was combined with either hydroxypropyl cellulose (HPC-L), hydroxypropylmethyl cellulose K4M (HPMC K4M) or polyvinyl pyrrolidone K30 (PVP K30). **Table I** gives the cumulative percentage drug release and the bioadhesive strength of buccal tablets prepared using varying ratios of different polymers. Formulations M3 and P4 were selected for further study as these had good bioadhesive strength and drug release.

Effect of addition of either citric acid or sodium bicarbonate

In order to enhance the release of drug from buccal tablets either citric acid or sodium bicarbonate was added to the formulation M3. Sodium bicarbonate caused a decrease in drug release as DTZ. HCl may have converted to free base with resultant decreased solubility. Also diltiazem is known to decompose in alkaline pH (6). However, the addition of 6% w/w citric acid led to a significant increase in drug release (to 63%).

Effect of addition of polyethylene glycol 4000

PEG 4000 is sometimes used to increase the solubility or release of drug. Addition of 12% PEG 4000 to formulation P4 containing 6% citric acid enhanced the initial release i.e. in the first 30 minutes from 20% to 50% even though cumulative percent release after 6 hrs. was not significantly effected and remained at 65%. Further increase in PEG 4000 concentration led to excessively sticky tablets which would not come out of the die.

Development of optimized formulation

Based on the above studies a multilayered optimized formulation was developed. **Table II** gives its composition. The core consisted of the drug, citric acid, PEG 4000 and a freeze dried polymer matrix of carbopol and PVP (1:4). The freeze drying of the polymers is considered to enhance the release of the drug from the matrix (7,8). The cap layer surrounded the core from three sides so that the release of the drug will be limited from the side adhering to buccal mucosa. It will also aid in bioadhesive of the tablet

Table-I: The Effect of Polymer Ratio on the Bioadhesive Strength and Drug Release

Composition	Formula Code											
	H_1	H_2	H_3	H_4	M_1	M_2	M_3	M_4	P_1	P_2	P_3	P_4
DTZ.HCl	20	20	20	20	20	20	20	20	20	20	20	20
Carbopol 934	40	26.7	53.3	32	40	26.7	20	32	40	32	48	16
HPC-L	40	53.3	26.7	48	—	—	—	—	—	—	—	—
HPMC-K4M	—	—	—	—	40	53.3	60	48	—	—	—	—
PVP-K 30	—	—	—	—	—	—	—	—	40	48	32	64
Polymer ratio	1:1	1:2	2:1	2:3	1:1	1:2	1:3	2:3	1:1	2:3	3:2	1:4
Cumulative % Drug release* (at 4 hrs)	9	14	11	13	11	13	17	13	8	15	10	27
Bioadhesive strength (g)*	11	5	6	6	13	15	8	19	7	16	17	24

*Average of three determinations

Table-II: Composition of Optimized Formulation

Composition	Core	%W/W Cap	Back
DTZ.HCl	60	—	—
Citric acid	6	—	—
PEG 4000	12	—	—
Talc	4	—	—
Freeze dried mix of Carbopol-PVP 1:4	18	—	—
Carbopol-934	—	40	12.5
PVP-K30	—	60	37.5
Magnesium stearate	—	—	45.0
Tartrazine	—	—	0.04
Lemon Oil	—	—	0.002
Saccharin Sodium	—	—	5

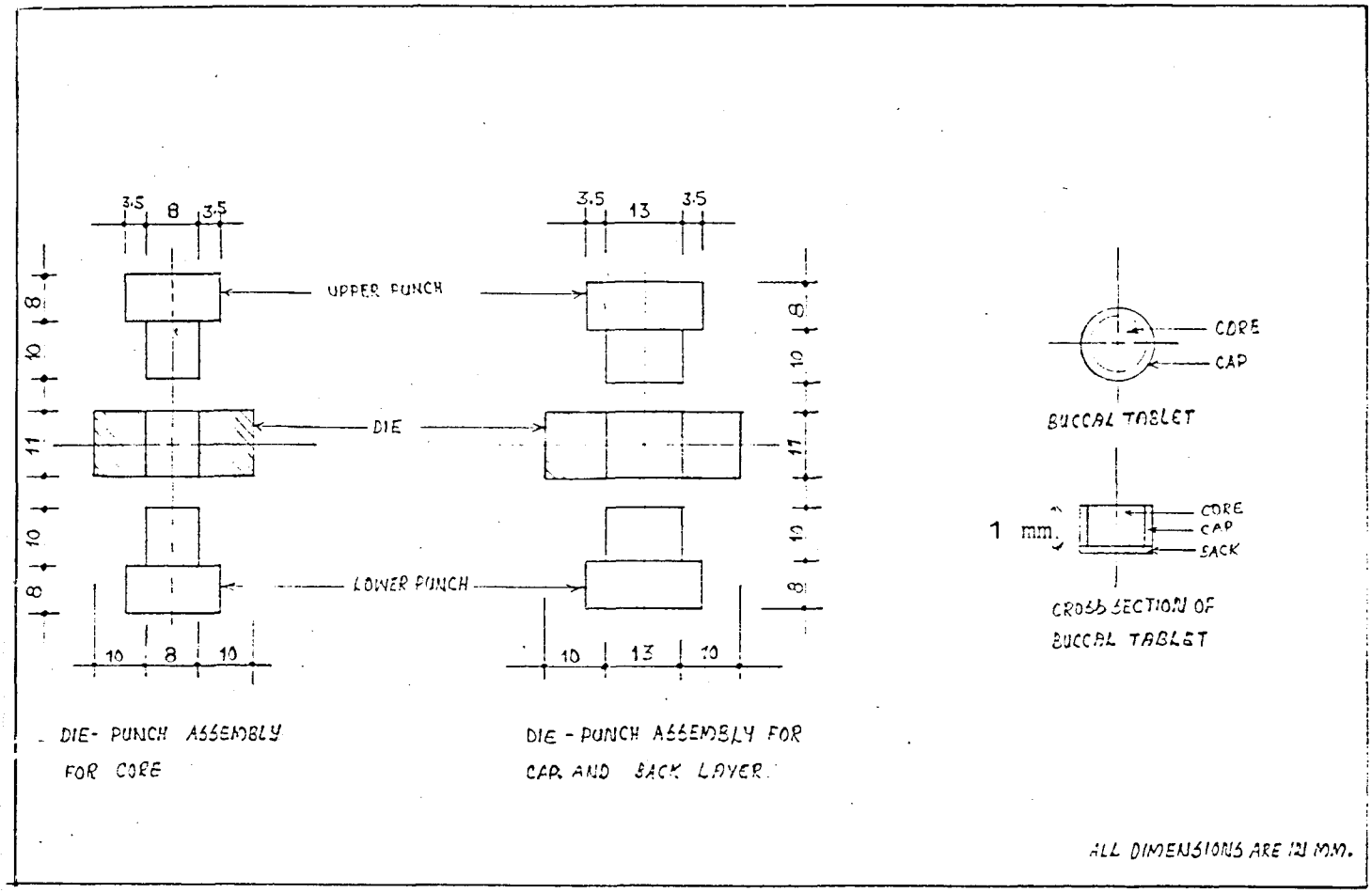

Fig. 1 Die-punch assemblies and schematic illustration of buccal tablet.

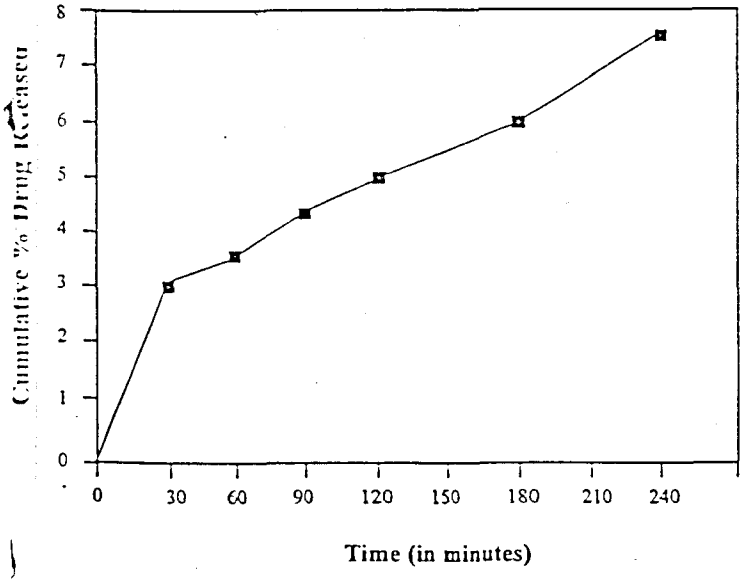

fig.3 In-situ dissolution study of DTZ buccal tablet

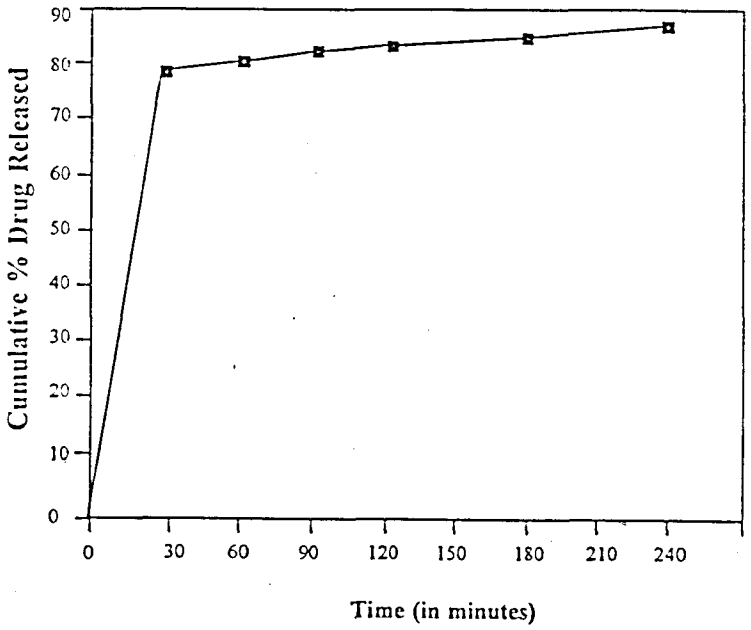

fig. 2 In-vitro dissolution study of DTZ buccal tablet

backing layer contained flavour and a sweetener. **Fig. 1** gives the dimensions of punch and die and also the physical structure and dimensions of buccal tablets.

The tablets were found to be satisfactory when evaluated for weight variation, friability and drug content uniformity. The results of the water absorption study indicated that the tablets did not show any appreciable change in their shape and form during the 4 hours they were kept on agar plate. Swelling of the surface in contact with 1% agar gel was noted and the optimized tablet had a 42.6% gain in weight due to absorbed water after 4 hrs.

The formulation had a bioadhesive strength of 15.2 g and an **in-vitro** release of 86% DTZ was obtained from dissolution study at the end of 4 hrs. (**Fig.2**). When the formulation was subjected to **in-situ** diffusion studies using Franz-diffusion cell a drug release of 7.3% was obtained (**Fig.3**). The **in-vitro** drug release correlated well with the **in-situ** release with a correlation coefficient of 0.74. The drug release followed a first order pattern as a plot of log of % drug remaining *Versus* time was linear ($k = 0.0222\ min^{-1}$ **in-vitro** and $5.4 \times 10^{-3}\ min^{-1}$ **in-situ**).

ACKNOWLEDGEMENT

The authors are grateful to Janab Hakeem Abdul Hameed, Chancellor, Jamia Hamdard for providing facilities.

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