
Development and Evaluation of Muco-adhesive Buccal Tablets of Lignocaine Hydrochloride.

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Lignocaine hydrochloride was formulated as a buccal tablet to provide prolonged relief from pain associated with tooth extraction. The tablet was prepared using suitable mucoadhesive polymers. Optimized tablets contained lignocaine hydrochloride 15 mg, Carbopol-934P 15.2 mg, sodium carboxy methyl cellulose 60.8 mg, mannitol 4 mg, Polyvinyl pyrrolidone-K30 5 mg, magnesium stearate 2 mg, saccharin sodium 0.2 mg and mint flavor (dried) 0.1 mg. Dissolution studies showed 86.66% release of drug in 360 min. Bio-adhesive strength was found to be 31.96 g. Adhesion time was greater than 6 h. Surface pH was found to be 7.02. The formulation was also subjected to *in vitro* permeation studies, *in situ* release studies, *in vitro* swelling studies and *in vivo* evaluation in healthy volunteers. The optimized tablets were also subjected to other quality control tests. Stability studies showed that the formulation was stable for more than two years.

Extensive efforts have recently been focussed on targeting a drug or drug delivery system in a particular region of the body for extended period of time, not only for local targeting of drugs but also for the better control of systemic drug delivery¹. The concept of mucoadhesives was introduced in the early 1980s². Mucoadhesive buccal drug delivery systems offer many advantages such as ease of administration, rapid termination of therapy and administration to unconscious patients. Drugs which are destroyed by the enzymatic/alkaline environment of the intestines or are unstable in the acidic environment of the stomach can be administered by this route. It permits localization of the drug to the oral cavity for a prolonged period of time and significant reduction in the dose can be achieved, thereby reducing dose related side effects³⁻⁶.

Local delivery to the oral mucosa has a number of applications as treatment of toothache, treatment of periodontal infections, bacterial and fungal infections, treatment of pathos and dental stomatitis⁷⁻⁹. Pain is defined as a localized sensation or discomfort, distress or agony resulting from

the stimulation of the specialized nerve endings¹⁰. Agents used for treatment of pain include analgesics, antidepressants and local anesthetics. The disadvantages with these agents include their side effects like short duration of action and painful injection. Lignocaine hydrochloride can be used topically as a gel, but it has a very short retention time and the drug leaches into the oral cavity. A mucosal dosage form of lignocaine hydrochloride was prepared by Ishida *et al.*⁹ using hydroxy propyl cellulose and carbopol for the treatment of toothache. Recently, lignocaine patch 5% (Lidoderm, Endo Pharmaceuticals) has been approved by US FDA for the treatment of postherpetic neuralgia¹¹. The present work is aimed at preparing a formulation of lignocaine hydrochloride as a buccal tablet, which would provide sustained effect in relief of pain associated with tooth extraction. To achieve the goal of providing the prolonged effect, buccal tablets were prepared using various muco-adhesive polymers¹², which would sustain the effect of the drug for a period of 6 h.

MATERIALS AND METHODS

Lignocaine hydrochloride was obtained as a gift sample from Astra-IDL Ltd. Bangalore. Carbopol 934P, sodium CMC

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DVP, Mannitol, PVP-K30, HPC-M, HPMC-K4M, sodium alginate, guar gum, mint flavour, saccharin sodium were obtained from Ranbaxy Research Laboratories, Gurgaon, New Delhi. All other reagents and chemicals used were of analytical grade.

Preparation of mucoadhesive tablets:

The tablets were prepared using various mucoadhesive polymers. Polymer interference study was carried out to eliminate the possibility of polymers interfering with the analysis of the drug. 0.05% w/v solutions of the polymers were prepared and analyzed colorimetrically at 625 nm¹³. The tablets were prepared using various polymer combinations (CP 934P:HPMC-K4 M; CP 934P:Guar gum; CP 934P:sodium CMC (DVP); CP 934P:sodium alginate; CP 934P:HPC-M; CP 934P:PVP K-30) in varying ratios, i.e., 1:2, 1:4, 2:3 and 3:2. The ingredients were mixed by trituration in a glass pestle and mortar. The mixture was then compressed using a 13 mm diameter die on a hydraulic press at a pressure of 5 tons for 5 s. Each tablet weighed approximately 100 mg with a thickness of 0.7-0.8 mm and a diameter of 13 mm. Among different combinations carbopol 934P and sodium CMC DVP mixed in a ratio of 1:4 gave the maximum percentage of drug release *in vitro*. To this formulation varying concentrations of mannitol, PVP K-30, magnesium stearate was added to get the optimized formulation. The composition is given in Table 1.

In vitro test studies:

The dissolution test apparatus (USP II) consisted of a 250 ml glass beaker. This was kept in a jacketed vessel of

TABLE 1: FORMULA FOR OPTIMIZED FORMULATION OF LIGNOCAINE HYDROCHLORIDE.

INGREDIENTS	WEIGHT (mg)
Lignocaine hydrochloride	15.0
CP-934P	15.2
SCMC (DVP)	60.8
Mannitol	4.0
PVP-K30	5.0
Magnesium stearate	2.0
Saccharin sodium	0.2
Mint flavour (dried)	0.1

Optimized formula of lignocaine hydrochloride obtained after adding different polymers in varying ratios.

water maintained at 37±1° Buccal tablet was stuck on to the Teflon block in the depression provided (so as to allow one sided release from the tablet). The Teflon block was lowered into the glass cylinder containing 100 ml of isotonic phosphate buffer pH 6.6. This vessel was maintained at 50 rpm under stirring conditions by means of a paddle fabricated for the purpose in a dissolution apparatus. At various time intervals samples of dissolution media were withdrawn and replaced immediately with an equal amount of fresh fluid. The samples were analyzed colorimetrically (Spectronic 21 Bausch and Lomb) at 625 nm against a prepared blank¹³. A graph was plotted between the cumulative percent drug released in the fluid versus time and is shown in fig. 1.

Measurement of bioadhesive strength and surface pH:

An apparatus designed earlier in our laboratory was used for the determination of bio-adhesive strength. Bio-adhesive strength of the tablet was measured on a modified physical balance using the method described by Gupta *et al.*¹⁴ using bovine cheek pouch as a model membrane. The method used to determine surface pH of the formulation was similar to that used by Bottenberg *et al.*¹⁵ A combined glass electrode was used for the purpose. The tablets were allowed to swell by keeping them in contact with 1 ml of distilled water (pH 6.6±0.05) for 2 h and pH was noted by bringing the electrode in contact with the surface of the formulations and allowing it to equilibrate for 1 min.

In situ release studies:

For carrying out *in situ* release studies and determination of duration of bioadhesion/erosion, a flow through ap-

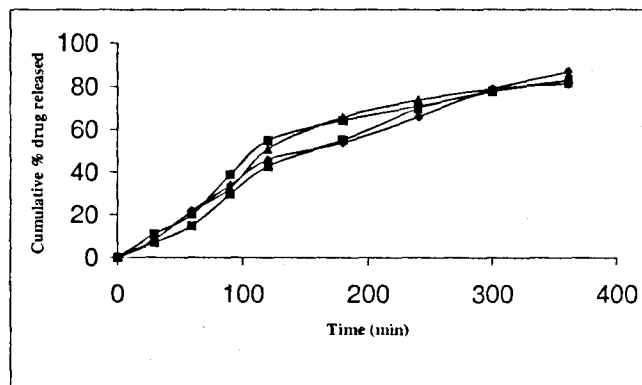


Fig.1: Plot of cumulative percent drug released *in vitro* vs. time of the optimized tablet formulation

In vitro release profile of four formulations (No. 1 -■-, No. 2 -●-, No. 3 -▲-, no. 4 -◆-) of lignocaine hydrochloride in isotonic phosphate buffer pH 6.6. (N=3).

paratus was designed based on the modification of a flow device cell¹⁶. The flow through cell was made of glass and had a length of 10.5 cm and a diameter of 2.1 cm. It was closed at one end and open at the other. A small inlet tube of 0.5 cm diameter was attached to one end of the cell. In the center of the lower base there was a cavity of 1.6 cm length and 1.5 cm depth for placement of the bovine mucous membrane. Bio-adhesive formulation was placed on top of the mucous membrane. Drug release occurred from only one side of the tablet (flat and perimetric edges). Isotonic phosphate buffer pH 6.6 (simulating the salivary pH) was pumped at a flow rate of 0.65 ml/min using flow regulators. This corresponded to the mean resting salivary flow rate. Sample (5 ml) was removed at different time intervals from the reservoir till the tablet eroded completely or dislodged whichever was earlier. The cumulative percent drug released was determined by measuring the absorbance colorimetrically at 625 nm.

***In vitro* buccal permeation studies:**

These studies were carried out using modified version of a Franz diffusion cell. It consisted of upper cylindrical chamber open from above and containing the bovine buccal mucosa at its base. Lower chamber was in the form of a closed cylinder containing the sampling port and had a teflon coated magnetic needle at the base. The junction between the two chambers was designed in such a manner that the skin did not shift from its place. The mucosal membrane was separated and then placed between the two chambers. The two chambers were tied with the help of springs so that the buccal membrane did not move from its place. The upper chamber was filled with 10 ml of isotonic phosphate buffer pH 6.6 and the lower chamber with 10 ml of Isotonic phosphate buffer pH 7.4. The tablet was stuck on to the buccal membrane. The membrane was stabilized in order to remove the soluble components till the absorbance of solution of lower chamber came to zero. Sample (5 ml) was withdrawn from the lower chamber at different time intervals, filtered and then analyzed. The whole assembly was maintained in a memmert type hot air oven at $37 \pm 10^\circ$.

***In vitro* swelling studies:**

The degree of swelling of bio-adhesive polymer is an important factor affecting adhesion. For conducting the study ten weighed tablets were separately placed in a series of preweighed glass tubes closed at the bottom by stainless steel mesh of size 120. Each tube was vertically placed in a beaker containing 50 ml of simulated salivary fluid (Isotonic phosphate buffer pH 6.6) such that the tablet remained in

contact with it. Sampling was conducted in random order at different time intervals. The tablets were weighed, (wet weight) dried at 40° for 24 h and again reweighed (dry weight). The percent wet weight recovered was calculated by using the following formula¹⁷; % Wet weight recovered = $(\text{Wet weight} - \text{Dry weight}) / \text{Dry weight} \times 100$.

***In vivo* evaluation of muco-adhesive tablet:**

In vivo evaluation was done to determine the time of complete erosion/adhesion of the selected formulation and compared the same with *in vitro* erosion time. Side effects produced by the formulation were also tested to investigate the acceptability of different polymers for use in muco-adhesive formulations. The study was conducted on six healthy human volunteers (age 21-28). Informed consent was obtained from the volunteers before the study. Food was prohibited from before until the end of the study. The volunteers were given muco-adhesive tablets, along with written instruction sheets. They were instructed to press the tablets against the cheek pouch for about 30 s They were asked to record the time of tablet insertion and nature of the tablet after adhesion (erosion or dislodgement of tablets). The volunteers were asked to complete a questionnaire after trial for scoring irritation, discomfort if any, taste, dry mouth, salivation and heaviness at the place of attachment produced by the formulations. The optimized tablet was evaluated for salivary concentrations. Samples of saliva (2 ml) were taken prior to the application of the formulation and at 30, 60, 90, 120, 180, 240, 300 and 360 min after the application of the tablets. The samples were suitably diluted and concentration of lignocaine hydrochloride in the saliva was determined. The maximal salivary concentration (C_{\max}) and time to reach maximum concentration (T_{\max}) were determined from the concentration time curve. The area under the curve (AUC 0-6 h) was also calculated.

Stability studies on muco-adhesive tablets:

Stability studies were performed according to WHO guidelines¹⁸. Stability of the formulation under accelerated storage conditions of temperature and humidity was studied. Effect on surface pH, release profile, hardness, content uniformity and friability was also tested.

RESULTS

Evaluation of muco-adhesive tablets:

In vitro release curve from the optimized tablet is shown in fig.1. Out of all the formulations developed the optimized formulation exhibited the maximum drug release *in vitro*, i.e., 86.66%. (N=3; SD= ± 1.36 .) The bioadhesive strength of the

optimized formulation was found to be 31.96 g and the results are shown in fig. 2. The Surface pH of the optimized tablet was found to be 7.025 which is very close to the neutral pH indicating that it will not cause any irritation in the oral cavity. The results are shown in fig 1. The optimized formulation released only 4.13% drug across the bovine cheek pouch membrane in 6 h concluding that the drug is not going into the systemic circulation and has a local effect. The tablets did not show any appreciable change in their shape and form during 6 h of swelling studies. *In situ* release studies revealed that the drug concentration remained well above the minimum effective concentration (4-10 mg/ml) in saliva for a period of 6 h¹⁹. This formulation exhibited C_{max} of 8.5 mg/ml, T_{max} of 150 min and AUC (0-6 h) of 1857 $\mu\text{g}\cdot\text{min}/\text{ml}$.

In vivo evaluation of muco-adhesive tablets:

Muco-adhesive tablets did not cause any irritation or hindrance to the volunteers and their taste was acceptable. Severe side effects like taste alteration, dry mouth, or excessive salivation were not observed with the tablets. In healthy volunteers, the concentration of drug was well above its MEC (4-10 mg/ml) in saliva for a period of 6 h. The C_{max} , T_{max} , and AUC were found to be 9.4 mg/ml, 150 min and 2178 mg.min/ml respectively. A lot of interindividual variation was observed for the time of erosion and drug release as shown in fig 2. This can be attributed to the variation in the physiology of the individuals, their salivary flow rate and the movement pattern of the tongue. *In vivo* release curve is shown in fig 2. A correlation co-efficient of 0.7100 was obtained between the mean drug concentration attained *in vitro* and *in vivo*. Using 't' test it was found that it was statistically significant at 5% confidence level.

Stability studies on muco-adhesive tablets:

Stability studies at 40° and 75% RH for 3 mo indicated that the decrease in drug content was less than 1.88%. There

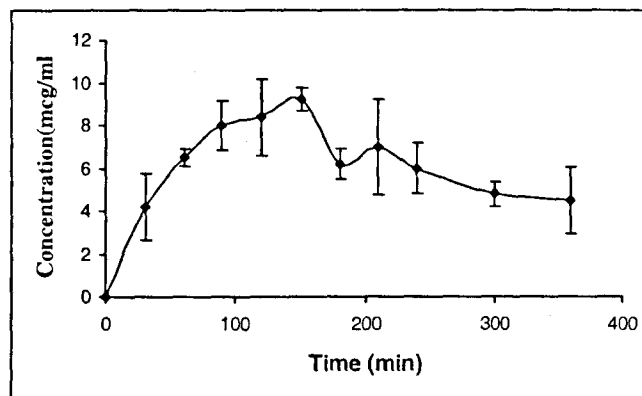


Fig. 2: *In vivo* release curve of optimized muco-adhesive tablet.

In vivo release profile of lignocaine hydrochloride in isotonic phosphate buffer pH 6.6 for a period of 6 h. (N=6).

was negligible effect on the surface pH, hardness, friability, content uniformity after the studies. The degradation rate constant was found to be $2.3 \times 10^{-64}/\text{d}$. Since the value is very small it can be concluded that very less degradation occurred in case of tablets. A shelf life of 24 mo was proposed for the formulation.

DISCUSSION

The present study was aimed to develop a new muco-adhesive system for the delivery of lignocaine hydrochloride. An attempt was made to formulate lignocaine hydrochloride tablets using new polymers, which have not been tried earlier for this drug. A new dosage form was developed using various mucoadhesive polymers in varying ratios. Carbopol 934-P and sodium CMC (DVP) in a ratio of 1:4 exhibited the maximum drug release *in vitro* i.e. 86.66% as compared to other polymers. The release of active medicament was above MEC for a period of about 6 h. This is because carbopol has excellent gelling properties and helps

TABLE 2: IMPORTANT PARAMETERS OF OPTIMIZED MUCO-ADHESIVE TABLETS IN HUMAN VOLUNTEERS.

PARAMETERS	VOLUNTEER NO.						MEAN, n=6, (\pm S.D.)
	I	II	III	IV	V	VI	
Adhesion time (min)	360	350	330	345	340	345	345(10.0)
C_{max} ($\mu\text{g}/\text{ml}$)	9.2	8.5	9.5	10.5	9.6	7.9	9.2(1.02)
T_{max} (min)	120	150	180	150	120	180	150(26.8)
AUC (0-6h.) $\mu\text{g}\cdot\text{min}\cdot\text{ml}^{-1}$	2030	2145	2075	2205	2195	2424	2178(138.7)
T > MEC (min)	360	360	360	360	360	360	360

Salivary concentrations of lignocaine hydrochloride in six healthy volunteers.

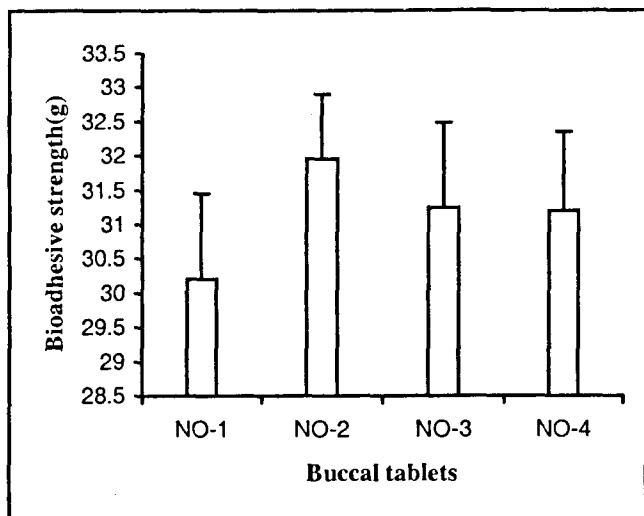


Fig. 3: Bioadhesive strength of four formulations of lignocaine hydrochloride.

Bioadhesive strength of buccal tablets containing carbopol 934P and sodium CMC (DVP) (N=3).

in sustaining the effect. Sodium CMC also has binding and gelling properties. Hence the combination of carbopol and sodium CMC (DVP) helped to sustain the concentration above MEC for about 6 h. Surface pH was close to the neutral pH (7.025) indicating that the formulation would not be irritant to the mucosa. Moreover it would also remain at the site of action for a prolonged period of time since it has a bioadhesive strength of 31.96 g. Further more hardness of 5.41 kg/cm² and friability of 5.5% supports the strength of the tablet. The *in vivo* evaluation studies revealed that the concentration was well above its minimum effective concentration (4-10 mg/ml) for a period of 6 h. The C_{max} , T_{max} and AUC (0-6 h) were found to be 9.4 µg/ml, 150 min, 2178 µg.min/ml respectively indicating that the effect is expected to last for 6 h thus saving the patient from pain and discomfort resulting from tooth extraction procedures. Because of lack of irritation and acceptable taste it may be concluded that the mucoadhesive dosage form developed in the laboratory can act as an alternative formulation for lignocaine hydrochloride and can be used for patients to provide local anaesthetic effect especially in children, who are scared of taking injections.

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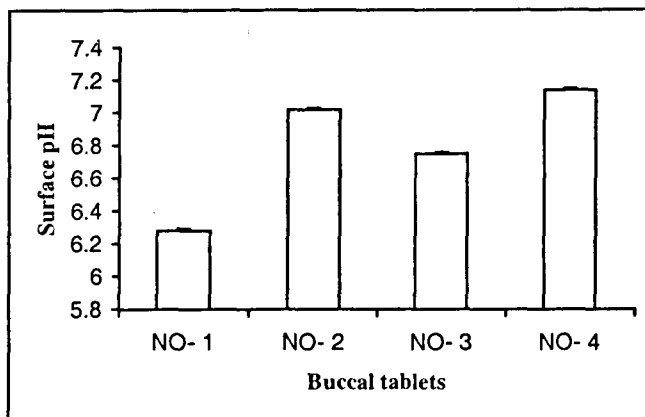


Fig. 4: Surface pH of four formulations of lignocaine hydrochloride.

Surface pH of buccal tablets containing carbopol 934P and sodium CMC (DVP) (N=3).

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