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Research Article

DESIGN AND EVALUATION OF CONTROLLED RELEASE MUCOADHESIVE BUCCAL TABLETS OF LISINOPRIL

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ABSTRACT

Lisinopril, a drug widely used in the treatment of hypertension. However, its extensive first pass metabolism results in poor bioavailability. The objective of present research work is to design and evaluate the controlled release of mucoadhesive buccal tablets of Lisinopril with a goal to increase the bioavailability, reduce dosing frequency and improve patient compliance. The tablets were prepared using Carbopol-934, Hydroxy propyl methyl cellulose (HPMC), Hydroxy ethyl cellulose (HEC) as mucoadhesive polymers. Six formulations were developed with varying concentration of polymers. The tablets were evaluated for hardness, weight variation, thickness, percentage of drug content, Surface pH, *in-vitro* studies like swelling, mucoadhesive strength and drug release. Formulation (F4) containing Carbopol-934 and HPMC K4M in the ratio of (2 : 4) showed good mucoadhesive strength (36.8) and maximum drug release of 97.1% in 10 hrs. Swelling increase with increase in concentration of HPMC K4M in tablets. Swelling pH was found to be 6.10. Formulation (F4) follows zero-order drug release. FTIR studied showed no evidence on interaction between drug and polymers. The results indicate that the mucoadhesive buccal tablets of Lisinopril may be good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of Lisinopril through buccal mucosa.

Keywords*:* Lisinopril, Mucoadhesive, Control release, Swelling index, HPMC, Carbopol

INTRODUCTION

Mucoadhesive drug delivery systems are delivery systems, which utilize the property of bioadhesion of certain polymers. Bioadhesion is defined as an ability of a material to adhere a particular region of the body for extended period of time not only for local targeting of drugs but also for better control of systemic delivery. Mucoadhesive buccal drug delivery systems offer many advantages over conventional systems such as ease of administration, rapid termination of therapy and administration to unconscious patients. Drug which are destroyed by the enzymatic/alkaline environment of the intestines are unstable in the acidic environment of the stomach can be administered by this route[1].

From technical point of view, an ideal buccal dosage form must have three properties. It must maintain its position in the mouth for a few hours, release the drug in a controlled fashion and provide the drug release in a unidirectional way towards the mucosa. In regard to the first requirement, strong adhesive contact to the mucosa in established by using mucoadhesive polymers as excipients. If the mucoadhesive excipients are able to control drug release, the second requirement can be fulfilled by preparing a system have uniform adhesiveness and impermeable backing layer. Various mucoadhesive devices such as include tablets, film, patches, discs, strips, ointments and gel have been recently developed[2].

Most of the mucoadhesive materials are either synthetic or natural hydrophilic or water insoluble polymers and are capable of forming numerous hydrogen bonds because of presence of the carboxyl, sulphate or hydroxyl functional groups. Various materials were tested for mucoadhesion. The synthetic materials include Carbopol-934, Hydroxy propyl methyl cellulose (HPMC), Hydroxy ethyl cellulose (HEC), Sodium carboxy methyl cellulose, Polymethyl methacrylates and polycarbophil, while natural polymers include xantium gum, sodium alginate, gelatin, acacia and tragacanth[3]. The bioadhesive polymers can not only cause the adhesion effects but can also control the release rate of drug.

Lisinopril is widely used in the treatment of hypertension which is an ACE inhibitor. It has biological half life (4 to 5 hrs). The objective of present study is to design and evaluate the controlled release of mucoadhesive buccal tablets of Lisinopril with a goal to increase the bioavailability, reduce dosing frequency and improve patient compliance, employing the mucoadhesive polymers like Carbopol-934, Hydroxy propyl methyl cellulose (HPMC), Hydroxy ethyl cellulose (HEC). The buccal tablets were evaluated for hardness, weight variation, thickness, percentage of drug content, surface pH, *in-vitro* studies like swelling, mucoadhesive strength and drug release[4].

MATERIALS AND METHODS

Materials

Lisinopril was received as gift sample from Alembic Ltd., Vadodara , Gujarat. Carbopol-934, Hydroxy Propyl Methyl cellulose (HPMC), Hydroxy ethyl cellulose (HEC) were procured as gift samples from Cipla Ltd., Mumbai, India. All other reagents and chemical used of analytical grade.

Preparation of mucoadhesive buccal tablets[5]

Mucoadhesive buccal tablets, each containing 10 mg Lisinopril were prepared by direct compression method. Composition of various formulations employing Carbopol 934P, HPMC K4M & HEC are shown in Table 1. All the ingredients of tablets were blended in mortar with a pestle for 15 min to obtain uniform mixture. The blended powder was then compressed into 150 mg tablets (at 5-7 kg/cm^2) on a single stoke, 10 station rotary tablet machine (Cadmach Machinery Co. Pvt. Ltd., Ahmedabad, india) with 8mm round shaped flat punch.

Evaluation of tablets

The tablets from different formulation (F1 to F6) were subjected to following tests

Hardness

Tablets were evaluated for their hardness using Monsanto hardness tester.

Weight variation

Ten tablets from each formulation were weighed using an electronic digital balance and the average weight was calculated. The results are shown in Table-2.

Thickness

Tablets were evaluated for their thickness using slide calipers. The results are shown in Table 2.

Content uniformity

Ten tablets from each formulation were taken, crushed and mixed. From the mixture, 10 mg of Lisinopril equivalent of mixture was

extracted thoroughly with 100 ml of methanol. The amount of drug present in extract was determined using UV Spectrometer at 210 nm. The results presented in Table 3.

Surface pH

The surface pH of the buccal tablets was determined in order to investigate the possibility of any *in vivo* side effects. An acidic or alkaline pH may cause irritation to the buccal mucosa. The method developed by Battenberg *et al* was used.

A combined glass electrode was used for this purpose. The tablets were allowed to swell by keeping it in contact with distilled water (pH 6.5 ± 0.05) for 2 hrs at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equiliberate for 1 min. The results are shown in Table 3.

***In vitro* swelling studies[6,7]**

The degree of swelling of bio-adhesive polymers is an important factor affecting adhesive. For conducting the study, a tablet was weighed and placed in a petri-dish containing 5 ml of phosphate buffer at pH 6.8 for 12 hrs, the tablets were taken out from the petri-dish and excess water was removed carefully by using filter paper. The swelling Index was calculated using the following formula and results are summarized in Table 4.

Swelling Index (SI) + (Wt-Wo)/Wo X 100

Where SI= Swelling index.

Wt = Weight of tablets after time at 't'.

Wo = Weight of tablet before placing in the beaker.

***In vitro* mucoadhesive Study[8]**

Mucoadhesive strength of the tablets was measured on a modified two-arm physical balance as described by Quadnich *et al*. The rabbit buccal mucosa was used as biological membrane for the studies. The rabbit mucosa was obtained from the local slaughter house and stored in krebs buffer at 4°C from the time of collection and used within 3 hrs of procurement. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 at 37°C.

The rabbit buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8 at 37° C ± 0.5°C), so that it just touches the mucosal surface. The buccal tablets were suck to lower side of a rubber stopper. The two side of the balance were made equal before the study, by keeping a 5 gms, was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in the position for 1 min contact time. Mucoadhesive strength was assessed in terms of weight (gms) required to detach the tablet from the membrane. Mucoadhesive strength which was measured as force of adhesion in Newton's by using following formula was used (Table 3),

Force of adhesion (N) = Mucoadhesive strength / 100 X 9.81

***In vitro* drug release profile[9,10]**

The United States of Pharmacopoeia (USP) XXIV rotating paddle method was used to study the drug release from the buccal tablets. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8). The release was performed at 37°C ± 0.5°C, with rotation speed of 50 rpm. Samples (5ml) were withdrawn at predetermined time intervals (1, 2, and 3…10 hrs) and volume was replaced with the fresh medium. The samples were filtered through Whatman filter paper and analyzed after appropriate dilution by UV spectrophotometry at 210 nm. The experiments for different formulations (F1 to F6) were conducted in triplicate and average values were recorded and found the release kinetics such as zero order, first order, Higuche and Hixconcrowell were determined & the data are shown in Table 5.

RESULTS AND DISCUSSION

Before designing various formulations, the drug polymer-excipient compatibility studies were conducted by FTIR spectroscopy and the results are presented in Fig. 1& Fig. 2. The results indicate that they were no chemical incompatibility between drug-polymer, polymer-polymer and polymer-excipients.

Total six different formulations (F1 to F6) of Lisinopril buccal tablets were prepared by direct compression techniques using various proportions of polymers and excipients. In order to select the best formulations, various evaluation parameters were checked and subjected to *in-vitro* dissolution studies and their release profiles.

Hardness

The hardness of tablets of different formulation (F1 to F6) was determined as per standard procedure. The average hardness of tablets was found to be 5 to 7 kg/cm. None of the formulations showed deviation for any of the tablets tested

Thickness of tablets

The average thickness of tablets (F1 to F6) determined and results are presented in Table 2. The maximum and minimum average thickness of tablet was found to 3 mm and 2.5 mm respectively. None of the formulation (F1 to F6) deviated from the standards.

Table 1: Composition of mucodhesive buccal tablets

Ingredients	Formulations					
	F1	F2	F3	F4	F5	F6
Lisinopril	10	10	10	10	10	10
Carbopol 934p	25	42.5	60	25	42.5	60
HEC	60	42.5	60	-	-	-
HPMC K4M	-	-	-	60	42.5	25
Sprayed dried lactose	35	35	35	35	35	35
Mannitol	17	17	17	17	17	17
Magnesium stearate	5	5	5	5	5	5

Table 2: Weight variation and thickness of Lisinopril buccal tablets

Formulation code	Average weight of tablet (mg)	Thickness in mm
F1	152.4	2.7
F2	152.1	2.5
F3	153.3	3
F4	1515	2.5
F5	15.4	2.7
F6	150.5	2.5

Content uniformity

The content uniformity of the entire tablet (F1 to F6) was evaluated and the results are presented in Table 3. The maximum percentage of drug content from the different formulations was found to be 100.12 and minimum percentage of drug content was found to be 98.6%. Hence it is concluded that all the formulations are falling within the pharmacopoeial limits.

Surface pH

The surface pH of tablets of each formulation (F1 to F6) was tested and the results are provided in table-3. The maximum and minimum pH values of the formulations were found to be 6.10 and 5.59 respectively. The acceptable pH of saliva is in the range of 5-7 and the surface pH of all tablets is within limits. Hence, the formulations may not produce any irritation to the buccal mucosa.

***In vitro* drug release profile**

The drug release pattern was studied for all formulations (F1 to F6) for 10 hrs following standard procedure and the results are provided in Fig. 5. The drug release pattern of buccal mucoadhesive tablets varied according to their type and ratio of polymers. The most important factor affecting the rate of release from buccal tablet is the drug and polymer ratio. The formulation F1, F2, F3 contained the drug, Carbopol 934p and HEC polymers in the ratio of 1 : 2 : 4, 1 : 3.4 : 3.4 and 1 : 4 : 2 respectively. The in vitro cumulative drug release profile of formulations F1, F2, F3 at 10 hrs showed 86.54%, 85.48% and 84.1% drug release respectively.

Similarly the formulations F4, F5, and F6 contained drug Carbopol 934p and HPMC K4M polymers in the ratio of 1 : 2 : 4, 1 : 3.4 : 4.3 and 1 : 4 : 2 respectively. The *in vitro* cumulative drug release profile of formulations F4, F5 and F6 at 10 hrs showed 97.1%, 95.41% and 93.17 drug release respectively. It was concluded that by increasing the concentration of carbopol 934p in the formulations (F1 to F6), the drug release rate from the tablet was found to be decreased, but when the concentration of secondary polymers HEC and HPMC K4M is increase, the drug release rate was found to be increased. This may be attributed to increased hydration followed by increased swelling of polymers with increase in concentration.

The overall data on the *in vitro* dissolution studies closely indicated that among the six formulations, the formulation F4 was found to be the best with high percentage of drug release (97.1). The cumulative drug release of formulations containing carbopol 934p with secondary polymers was found to be in order of F4>F5>F6>F1>F2>F3.

Table 3: Content uniformity, surface pH, mucoadhesive strength, mucoadhesive force of Lisinopril buccal tablets

Formulation	Percentage hydration				
	1h	2h	4h	8h	12h
F1	48.5	58.8	17.0	88.10	90.1
F2	47.1	57.7	70.3	86.9	89.5
F3	48.5	56.6	69.1	86.5	93.5
F4	50.2	61.7	73.6	90	93.5
F5	48.6	47.2	88.6	89.7	89.7
F6	47.5	57.7	71.2	86.9	89.2

Table 4: *In-vitro* swelling study of Lisinopril buccal tablets

Formulation code	% Drug content	Surface pH	Mucoadhesive strength (g)	Mucoadhesive force (N)
F1	99.2	5.9	28.8	2.79
F2	98.6	5.8	29.2	2.86
F3	99.13	6.0	32.4	3.17
F4	100.12	6.10	36.5	3.58
F5	99.2	5.59	34.5	3.38
F6	98.8	5.9	30.5	2.99

Table 5: Drug release kinetics studies of Lisinopril buccal tablets

Formulation	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Hixon-Crowell (R^2)
F1	0.9911	0.9091	0.8171	0.9249
F2	0.9860	0.8950	0.7940	0.9090
F3	0.9920	0.8990	0.8310	0.9450
F4	0.9940	0.7840	0.9260	0.9030
F5	0.9831	0.8184	0.8490	0.8810
F6	0.9870	0.8150	0.8980	0.9010

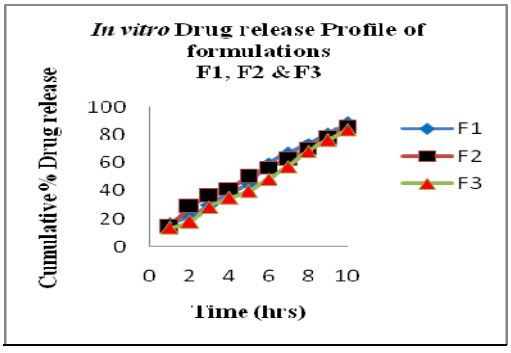

Fig. 1

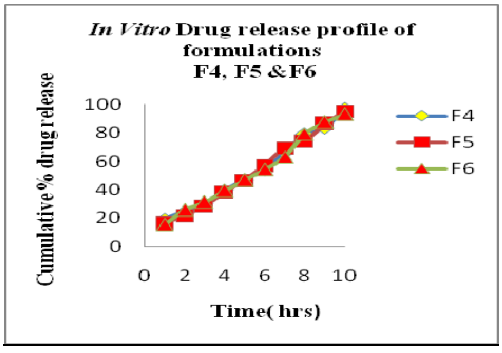

Fig. 2

Kinetic treatment to dissolution data

Kinetic studies i.e. zero-order, first order and Higuchi and Hixcon-Crowell were conducted for all formulations and the data is shown in Table 6.The value of regression correlation co-efficient (R^2) was evaluated for all the formulations which value was close to 0.99. Hence it is conducted that all the formulations are following the zero-order drug release.

CONCLUSION

The overall studies indicated that the polymers Carbopol 934p and HPMC K4M in the ratio of 2 : 4 showed satisfactory mucoadhesive properties. Among the 6 formulations, the formulation F4 using these polymers in the above ratio with drug exhibited significant swelling properties with optimum release profile. Hence it can be concluded that the formulation F4 will be useful for buccal administration for the treatment of anti-hypertensive. So, the mucoadhesive buccal tablets ot Lisinopril may be a good choice to bypass the extensive hepatic first pass metabolism with an improvement in the bioavailability of Lisinopril through Buccal mucosa.

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