

EFFECTS OF MUCOADHESIVE POLYMERS COMBINATION ON THE PROPERTIES OF LISINPRIL BUCCAL TABLETS PREPARED BY WET GRANULATION METHOD

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ABSTRACT

Objective: The objective of this study was to prepare and characterize buccoadhesive tablets of Lisinopril using different Mucoadhesive polymers such as HPMC K100M, CMC, Chitosan, and combination.

Methods: Six tablet formulations were prepared by wet granulation method with varying concentrations of polymers using combination of two polymers in each formulation. The prepared tablets were evaluated for physicochemical parameters such as hardness, thickness, content uniformity, weight variation, surface pH, and swelling studies. The prepared tablets were also evaluated for bioadhesive strength and in vitro drug release.

Results: In vitro bioadhesive strength and in vitro release studies showed that formulation (F6) containing HPMC K100M and CMC in the ratio of (4:1) showed good mucoadhesive strength and maximum drug release in 6 hrs. The in vitro release kinetics studies reveal that all formulations fit well with zero order kinetics followed by Korsmeyer-Peppas.

Conclusion: From the results it can be concluded that the formula (F6) will be promising drug delivery in buccal cavity for the treatment of anti hypertension with high possibility of increase in bioavailability due to avoidance of first pass effect .

Keywords: Lisinopril, Buccoadhesive tablets, Wet granulation, Combined polymers.

INTRODUCTION

Mucoadhesive drug delivery system has a high potential of being useful means of delivering drugs to the body throughout targeting the stratified squamous epithelium which is supported by a connective tissue lamina propria in buccal mucosal membrane [1]. Drug penetrating into the membrane passes through net of capillaries & arteries in lamina propria and reaches the systemic circulation through internal jugular vein [2].

This drug delivery system utilizes property of bioadhesion of certain water soluble polymers which become adhesive on hydration and hence can be used for targeting buccal mucosa (lining of the cheek) to the systemic circulation [3].

The mucoadhesive drug delivery system appears to offer a number of advantages, like enhancing drug bioavailability due to avoidance of first-pass metabolism , ease of therapy termination in case of toxicity by removing the dosage form from the buccal cavity, less frequency of administration and therefore better patient compliance , significant cost reduction may be achieved and dose-related local or systemic side effects may be reduced due to targeting of disease sites or tissues and reduction in fluctuation in steady-state levels[4,5]. Hence, adhesive mucosal dosage forms were prepared for oral delivery, in the form of adhesive tablets, adhesive gels, and adhesive patches [6].

From technical point of view, an ideal buccal dosage form must have the following three properties (a) a bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa (b) a vehicle the release the drug at an appropriate rate under the conditions prevailing in the mouth and (c) strategies for overcoming the low permeability of the oral mucosa [7].

The strong adhesive contact to the mucosa is established by using mucoadhesive polymers as excipients. In formulation of buccal mucoadhesive drug delivery system, various polymer structural and functional groupings can have an effect on degree of polymer/mucus interaction and control the release rate of drug [8].

Lisinopril, is a synthetic peptide derivative, is an oral long acting angiotensin converting enzyme inhibitor (ACE) [9]. It is widely used in treatment of hypertension; it has the biological half-life of 12.6 hrs. Its bioavailability is 25% and it is mainly excreted in urine [10].

The aim of the present study was to develop a bioadhesive sustained-release tablets for buccal drug delivery of lisinopril using different polymers (carboxy methyl cellulose, chitosan and hydroxypropylmethylcellulose) in order to increase bioavailability, reduce dosing frequency and improve patient compliance.

MATERIALS AND METHODS

Materials

Lisinopril, Hydroxypropyl methylcellulose (HPMC K100M), Carboxy methylcellulose (CMC) and Chitosan were purchased from Sigma Chemical Co., USA. All other chemicals and reagents used were of analytical reagent grade.

Methods

Preparation of Mucoadhesive Buccal Tablets

Mucoadhesive buccal tablets of Lisinopril were prepared by wet granulation method using different polymers as shown in Table (1). All the ingredients were screened through sieve no. 60 and then blended (except magnesium stearate) for 15 min. A blend of all ingredients was granulated with 95% alcohol. The wet masses were passed through sieve no. 12 and the resulting granules were dried at 40°C. Finally magnesium stearate was added and mixed for 5min. The blend was compressed into 130 mg tablets using a single flat punch (KORSCH Erweka, Frankfurt Germany).

Evaluation of flowability of prepared granules

Fifty gm of the prepared granules will poured through glass funnel which had a distance of 10 cm from the flat surface. The height of the heap (h) formed as well as the radius of the heap (r) was measured. The value of angle of repose was calculated by using the formula: $\tan \theta = h / r$ [11].

Evaluation of Prepared Mucoadhesive Tablets

Thickness, Weight variation test, Hardness

The thickness, weight variation, hardness of buccal tablets was determined using digital micrometer, electronic balance and Monsanto hardness tester respectively. Twenty individual tablets from each batch were used and the average results were calculated according to USP Specification [12, 13].

Table 1: Composition of Lisinopril Buccal Tablets prepared by wet granulation

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Lisinopril	10	10	10	10	10	10
HPMC	32.5	39	52	32.5	39	52
Chitosan	32.5	26	13			
CMC				32.5	26	13
Mannitol	13	13	13	13	13	13
Lactose	26	26	26	26	26	26
P.V.P	13	13	13	13	13	13
Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	130	130	130	130	130	130

Friability

The friability of 10 tablets will determine using Roche friabilator (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets will place in the friabilator and will subject to 100 revolutions. Tablets will dedust using a soft muslin cloth and reweigh [14].

Drug content uniformity

Ten tablets from each formulation were taken, crushed and mixed. From the mixture, 10 mg of Lisinopril equivalent was extracted thoroughly with 100 ml of methanol. The amount of drug present in extract was determined using Shimadzu UV spectrophotometer at 246 nm.

In vitro swelling studies

Buccal tablets were weighed individually (designated as W_0) and in agar gel plates 2% in a petri dish incubated at $37 \pm 1^\circ\text{C}$ for up to 5 hr. At regular intervals of time, the swollen tablets are removed from petri dish, the excess water is removed with the help of filter paper and weighed again (W_t). The swelling index (SI) can be calculated using the following formula [15].

$$SI = [(W_t - W_0) / W_0]$$

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 [16]. A combined glass electrode was used for this purpose. The tablets were allowed to swell by keeping it in contact with distilled water (5ml) (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 equilibrate for 1 min.

In vitro Mucoadhesive Study

Mucoadhesive strength of the tablets was measured on a modified two arm physical balance. Sheep buccal mucosa was used as biological membrane for the studies. The mucosa was obtained from the local slaughter house and stored in 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 . Force needed to detach tablet from mucus membrane is called the mucoadhesive force and is represented in Newton [17].

$$\text{Force of adhesion (N)} = \text{Mucoadhesive strength (g)} / 100 \times 9.81$$

In vitro drug release study

The tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. *In vitro* drug release studies were carried out in 900 ml of phosphate buffer solution pH 6.6 for 6 h using a USP dissolution paddle apparatus (II)

(Copley scientific, UK.) at 50rpm and $37 \pm 0.5^\circ\text{C}$. At predetermined time intervals samples were withdrawn and replaced with fresh medium. The samples were filtered, diluted suitably and then analyzed spectrophotometrically at 246nm. All dissolution studies were performed in triplicate. The mechanism of drug release from the buccal tablets was determined by finding the best fit of the release data to Zero order, First order, Higuchi and Korsmeyer-Peppas plots [18].

RESULTS AND DISCUSSION

The main objective of this study was to develop buccoadhesive tablets to release the drug at mucosal site for extended period of time using two buccoadhesive polymers each time. HPMC K100M, Chitosan and CMC were selected as buccoadhesive polymers for retaining the drug for extended period. All the formulations passes test for Angle of repose, weight variation, content uniformity and show acceptable results with respect to drug content (97 to 99) and friability (0.12 to 0.58%) as shown in Table (2). The high hardness value of range (12.5-14) indicates that the method of preparation of tablets has the main effect on mechanical strength of prepared tablets. The surface pH values of 5 to 6 indicate no risk of mucosal damage or irritation.

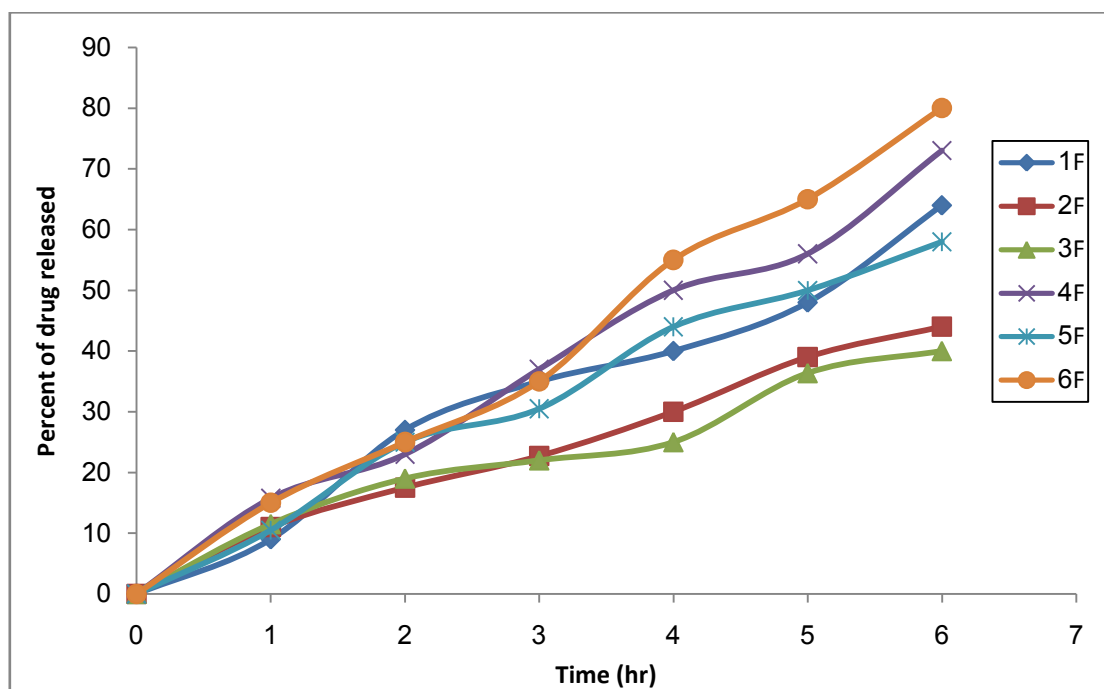
On the modified physical balance and measure the force (N) required detaching the tablet. The bioadhesive property of the prepared tablets of the formulations (F1, F2, and F3) with combined polymers, HPMC K100M and Chitosan showed the bioadhesive strengths of 2.64, 3.12, and 3.43 N respectively. The formulations (F4, F5, and F6) with HPMC K100M and CMC showed the bioadhesive strengths of 3.62, 3.77, and 4.16 N, respectively. The bioadhesion characteristics were affected by the concentration of the bioadhesive polymers. In general, the increase in concentration of polymer increases bioadhesive strength of formulation and specifically as the concentration of HPMC K100M increased, the increases in bioadhesive strength of formulation was higher than other polymers.

Swelling index increased as the weight gain by the tablets increased proportionally with the rate of hydration as shown in Table 2. Swelling index increased with increasing amounts of HPMC K100M whereas chitosan and CMC decreases. The highest hydration (swelling) and consequently the swelling rate of tablets were observed with the formulation F6. This may be due to quick hydration of polymers (HPMC K100M and CMC in ratio of 4:1).

The release profile of drug from all prepared buccal tablets was presented in figure (1). It was concluded that by increasing the concentration of HPMC K100M in the formulation containing secondary polymer (chitosan), the drug release rate from the tablets was found to be decreased and this may be due to ability of HPMC to form complex matrix network which leads to delay in release of drug from the device. But when the secondary polymer was CMC, the retardation of release due to HPMC is to certain point after which the release of drug was found to be increased. This may be due to increased hydration (or) swelling characteristics of polymers with increased concentrations. From the overall data it was found that the formulation F6 showed the maximum percentage of drug release i.e. 80% at the end of 6 h.

Table 2: Physicochemical parameters of Lisinopril buccal tablets

Formula No.	Hardness (Kg/cm ²)	Thickness (mm)	Weight average (mg)	Assay (%)	Surface pH	Mucoadhesive force (N)	Swelling index at 5hr
F1	14.0±0.23	3.20±0.05	132.5±1.4	98±1.9	5.0±0.02	2.64±0.01	1.81±0.007
F2	13.5±0.51	3.15±0.03	133.0±2.7	97±1.2	5.0±0.01	3.12±0.02	2.42±0.012
F3	13.5±0.48	3.21±0.02	131.0±1.9	98±1.7	5.2±0.03	3.43±0.04	2.68±0.037
F4	14.0±0.22	3.16±0.03	131.0±2.2	99±1.4	5.5±0.05	3.62±0.01	1.80±0.021
F5	14.0±0.39	3.15±0.04	130.5±2.6	98±1.3	5.9±0.06	3.77±0.03	2.55±0.062
F6	12.5±0.34	3.21±0.06	130.5±1.4	98±1.8	6.0±0.04	4.16±0.01	3.32±0.033

Fig. 1: *In vitro* Lisinopril release profiles from buccal tablets (F1-F6)

In-vitro drug release data of F1 to F6 were fitted to zero order, first order, Higuchi and Korsmeyer-Peppas equations to ascertain the pattern of drug release (Table 3). The R² values

were found to be higher in zero-order followed by Korsmeyer-Peppas which indicates all the formulations followed zero-order release pattern.

Table 3: Release kinetics of different formulations of Lisinopril buccal tablets

Formula No.	Zero Order (R ²)	First Order (R ²)	Higuchi (R ²)	Korsmeyer-Peppas (R ²)
F1	0.946	0.833	0.873	0.941
F2	0.991	0.971	0.940	0.988
F3	0.965	0.950	0.945	0.962
F4	0.985	0.970	0.895	0.974
F5	0.987	0.881	0.939	0.982
F6	0.987	0.963	0.894	0.982

CONCLUSION

It can be concluded that formulation F6 using combination of two mucoadhesive polymers in ratio of 4:1 (HPMC K100M: CMC) could be used to release the Lisinopril in buccal cavity for extended period of time without the risk of mucosal irritation and as promising alternative routes of administration to avoid first pass effect.

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