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Research Article

Development and Evaluation of Mucoadhesive Chlorhexidine Tablet Formulations

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Abstract

Purpose: *To formulate mucoadhesive chlorhexidine tablets and evaluate their drug release characteristics and mechanism.*

Methods: *Chlorhexidine buccal adhesive tablets were prepared by direct compression using a blend of hydroxypropyl methylcellulose (HPMC) and chitosan as the bioadhesive polymers. Their dissolution properties were assessed according to USP 24 (paddle method). In order to determine the mode of drug release from the tablets, the release data were subjected to various release kinetic models. The bioadhesive strength of the tablets was also evaluated.*

Results: *The results showed that as the proportion of HPMC in the blend increased, drug release rate decreased, with the lowest release rate observed when HPMC alone was used as the bioadhesive polymer ($p < 0.001$). Both the type and ratio of the polymers used influenced release kinetics. Also, bioadhesion force increased with increasing proportion of HPMC in the tablets, with the highest adhesion force shown when HPMC was the only polymer used, and lowest when chitosan was used alone ($p < 0.01$).*

Conclusion: *The chlorhexidine formulations developed showed promise as a bioadhesive delivery system for the drug.*

Keywords: *Mucoadhesive tablets; Chlorhexidine; HPMC; Chitosan; Release properties; Bioadhesive strength.*

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INTRODUCTION

A major difficulty in the effort to eradicate infections of the oral cavity is the dilution and rapid elimination of topically applied drugs due to the flushing action of saliva. The delivery system in which the drug is incorporated is, therefore, an important consideration and such a system should be formulated to prolong drug retention in the oral cavity. Efficient local delivery of actives such as dental bleaches and antimicrobials to the oral cavity is compromised by a number of factors that dramatically reduce residence time, most notably the shear forces associated with speaking, swallowing and mastication, as well as dilution and washout caused by continuous saliva production [1].

Typical polymers that have been used as mucoadhesive drug carriers are poly (acrylic acid), poly(methacrylate acid), cellulose derivatives, poly(ethylene oxide), lectin and chitosan [2]. Many attempts have been undertaken to improve the mucoadhesive properties of polymers by preparing copolymers, polymer conjugates or interpolymer complexes.

Buccal patches are generally based on bioadhesive polymers which, once hydrated, adhere to the buccal mucosa and withstand salivation, tongue movements and swallowing for a significant period of time. Successful buccal delivery requires at least three of the following: (a) a bioadhesive to retain the drug in the oral cavity and maximize the intimacy of contact with the mucosa; (b) a vehicle that releases the drugs at an appropriate rate under the conditions prevailing in the mouth; and (c) strategies for overcoming the low permeability of the oral mucosa. The three steps of formation of bioadhesive bonds are: (a) wetting and swelling of polymer; (b) entanglement of polymer and mucin chains and (c) formation of week chemical bonds between entangled chains [3].

Chlorhexidine is a bis-bis-guanide widely used to treat skin and mucosa infections efficiently against a wide range of microbial species. Senel *et al* designed a formulation containing chitosan for local delivery of chlorhexidine to the oral cavity. Release of chlorhexidine from the gels was maintained for 3 h [4]. Hita-Iglesias *et al* studied the effectiveness of chlorhexidine gel versus chlorhexidine rinse in reducing alveolar osteitis in mandibular third molar surgery. They showed that the topical application of bioadhesive chlorhexidine gel to the surgical wound during the postoperative week may decrease the incidence of alveolar osteitis after extraction of the mandibular third molar [5].

In this study, tablets containing chlorhexidine were formulated and evaluated for their release characteristics and bioadhesive strength.

EXPERIMENTAL

Materials

Chlorhexidine was purchased from Shaher Daru, Tehran, Iran, while polycarbophil and Carbopol 914P were obtained from BF.Goodrich (USA). Hydroxypropyl methylcellulose (HPMC K15M) from Colorcon (UK) and chitosan (Fluka, Switzerland) were also used.

Preparation of bioadhesive tablets

Flat-faced 9 mm chlorhexidine buccal adhesive tablets were prepared by direct compression in a hydraulic press (Spectalab, India) at a constant compression pressure from mixtures of the ingredients. The composition of the tablet formulations is given in Table 1.

Table 1: Composition of 55.5 mg chlorhexidine mucoadhesive tablet formulations

Formulation code	HPMC (mg)	Chitosan (mg)
F1	55.50	---
F2	---	55.50
F3	37.00	18.50
F4	18.50	37.00
F5	27.25	27.25

In vitro dissolution

The dissolution tests were performed using the paddle method of USP 24. with the aid of a dissolution apparatus (Erweka, DT 800 Germany) rotating at 100 rpm [6]. The dissolution medium was 900 ml phosphate buffer (pH 6.8) and the temperature was set at 37 ^{0}C. Samples of the solution were withdrawn at definite time intervals. The dissolution media was then replaced by fresh dissolution fluid to maintain a constant volume. The solution was passed through a filter and then the concentration of chlorhexidine in solution was measured with an ultraviolet spectrophotometer (Spectonic Genesys 2, USA) at a wavelength of 257 nm. The test was carried out in triplicate and the results expressed as mean ± standard deviaition (SD).

Analysis of drug release kinetics

In order to investigate the mode of drug release from the tablets, the release data were subjected to the following release models: zero order, first order, square root of time and Korsemeyer-Peppas, as shown in Eqs 1 – 4, respectively.

$$Q = k_o t \quad \text{..... (1)}$$
$$\ln (100 - Q) = \ln Q_0 - k_1 t \quad \text{..... (2)}$$
$$Q = k_H t^{1/2} \quad \text{..... (3)}$$
$$Q = k_p t^n \quad \text{..... (4)}$$

where Q is drug released at time, t, while k_0, k_1 and k_H are coefficients of the respective equations; k_p is a constant incorporating structure and geometric characteristics of the release device; and n is the release exponent indicative of the mechanism of release. When n approximates to 0.5, a Fickian/diffusion-controlled release is implied; $0.5 < n < 1.0$ indicates non-Fickian transport; and $n = 1$ is zero order (case II transport). When the value of n approaches 1.0, it can be said that release approximates zero order [7].

Determination of bioadhesive strength

To evaluate bioadhesive strength, a tensile tester apparatus, similar to an Instron model 4301 tensile tester, was fabricated. The male albino rat (200 - 250 g) was killed under ether anaesthesia and the hairless skin was isolated from the dorsal section of the abdomen. The skin (mucosa side) was fixed across the opening (area: 2 cm^2) of a diffusion cell filled with phosphate buffer (pH 6.8). The test was carried out in triplicate as previously described [7] and the results expressed as mean ± standard deviation (SD). The animal studies were approved by the Research Ethics Committee of the Council of Mazandaran University of Medical Sciences (ref no. 87-3).

Statistical analysis

A one-way ANOVA with Tukey's post hoc test was used to analyze the dissolution and bioadhesion data, with the aid of SPSS software, version 10. Confidence limit was set at 95 %.

RESULTS

Fig 1 shows the effect of HPMC/chitosan ratio on the release rate of chlorhexidine. The results show that as the concentration of HPMC increased, the release rate decreased. The lowest release rate was observed with formulation F1 containing containing HPMC but no chitosan while formulation F2 which contained only chitosan exhibited the highest release rate.

Table 2: The kinetic release parameters for chlorhexidine mucoadhesive tablets formulations

Batch	Zero order		First order		Higuchi's		Korsmeyer-Peppas		
	k_0 ($\%h^{-1}$)	R^2	k_1 (h^{-1})	R^2	k_H ($\%h^{-1/2}$)	R^2	K_p ($\%h^{-n}$)	n	R^2
F1	0.0012	0.9863	-0.0024	0.9416	0.0332	0.9265	0.0425	0.54	0.8679
F2	0.0028	0.9890	-0.0227	0.8686	0.0454	0.9595	0.0540	0.57	0.9245
F3	0.0019	0.9991	-0.0066	0.8511	0.0501	0.9689	0.0406	0.59	0.9456
F4	0.0021	0.9906	-0.0141	0.8222	0.4470	0.9443	0.3169	0.55	0.9684
F5	0.0020	0.9957	-0.0073	0.9040	0.0448	0.9564	0.1977	0.59	0.9639

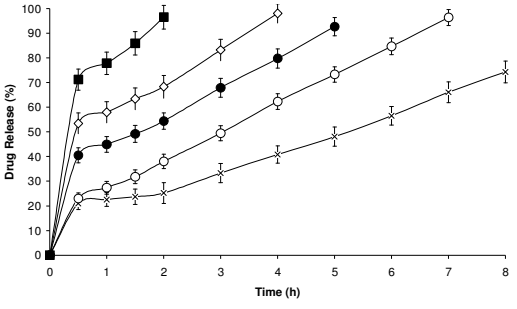

Figure 1: *In vitro* release of chlorhexidine from formulations F1 (▲, HPMC alone); F2 (■, chitosan alone) , F3 (○, HPMC:chitosan, 0.75:0.25); F4 (□, HPMC:chitosan, 0.25:0.75); and F5 (●, HPMC:chitosan, 0.5:0.5. Note: Error bars denote standard deviation.

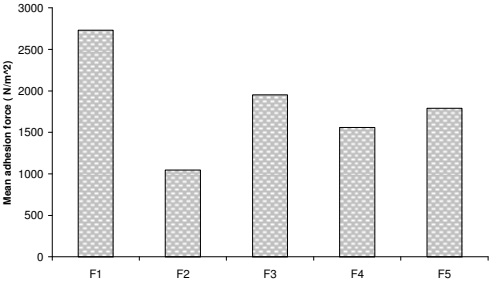

Figure 2: Bioadhesive strength of chlorhexidine formulations. ***Note:*** F1 = HPMC alone; F2 chitosan alone; F3 = HPMC: chitosan, 0.75:0.25; F4 = HPMC: chitosan, 0.25:0.75; F5 = HPMC: chitosan, 0.5:0.5.

The results of the kinetic analysis of the data are shown in Table 2. Altering the type of polymer and polymer ratio influenced the release kinetics of chlorhexidine from the buccoadhesive tablets. Kinetic analysis of the release data showed that polymer ratio influenced drug release kinetics. Furthermore, high correlation coefficients were achieved with the various release models.

The bioadhesive strengths of the mucoadhesive tablets are shown in Fig 2. The results show that bioadhesive strength increased with increase in the concentration of HPMC with the highest value exhibited by formulation F1 which contains only HPMC. On the other hand, the lowest adhesive strength was manifested by formulation F5 which contained only chitosan.

DISCUSSION

Due to its bioadhesive property, mucoadhesive tablets are expected to remain in the oral cavity and release its drug content for a long period of time, thus providing sustained therapeutic effect.

HPMC is a semi-synthetic ether derivative of cellulose. It has been a dominant hydrophilic vehicle used in controlled release dosage forms because of its non-toxic nature, ease of compression, and capacity to accommodate high levels of drug loading [8]. One of its most important characteristics is high swellability which exerts a significant influence on the release kinetics of a incorporated drug in it. Upon contact with water or biological fluid, the fluid diffuses into the device, resulting in polymer chain relaxation leading to volume expansion. The

incorporated drug then diffuses out of the system [9]. Chitosan, a cationic natural biopolymer produced from deacetylation of chitin, has been widely used for drug carrying devices in controlled drug delivery systems [10]. The incorporation of a drug into chitosan matrix to form a monolithic device can expand the use of this biopolymer. Depending on the amount of chitosan, film thickness, and dissolution medium, the liberation of drug from the chitosan films varies from fast to slow release [11].

Drug release

Incorporation of HPMC decreased the release rate of drug because the polymer absorbs water and forms a gelatinous barrier layer at the surface of the tablet matrix, unlike chitosan which does not form a gel layer. Thus, increasing the level of HPMC in the tablet produced a stronger gel layer around the matrix resulting in decreased penetration of the solvent molecules in to the matrix and outward diffusion of drug molecules into the dissolution medium. Usually, water diffusivity depends on the total concentration of viscosity-inducing agents in a systems and this governs diffusion of water into matrix systems. Furthermore, erosion can play a role in drug release. Resistance of the gel layer to erosion is usually controlled by the viscosity grade of the HPMC used. Water soluble drugs are released primarily by diffusion of dissolved drug molecules across the gel layer whilst poorly water soluble drugs are released predominately by erosion mechanisms [12].

Kinetic analysis of the release data showed that varying HPMC/chitosan ratio affected the release kinetics of chlorhexidine from the buccoadhesive tablets and the high correlation coefficients were achieved with the various models. The release exponent, n, of the Korsemeyer-Peppas model, which was > 0.5 but less than 1, indicates a coupling of diffusion and erosion mechanisms, i.e., the so-called anomalous diffusion. The Korsemeyer-Peppas model is a generalization of the observation that superimposes two apparently independent mechanisms of drug transport, namely, Fickian diffusion and a case-II transport which describes drug release from a swollen polymer. When n takes the value 0.5 it indicates diffusion-controlled drug release while the value 1.0 indicates swelling-controlled drug release. Values of n between 0.5 and 1.0 can be regarded as an indicator for both phenomena, i.e., anomalous transport, as stated above [7].

Drug release from swollen polymer matrix matrices is based on glassy-rubbery transition of the polymer which occurs as a result of water penetration into the matrix. Although interactions between water, polymer and drug are the primary factors in release control, several formulation variables also influence drug release rate to a greater or lesser degree. Thus, drug loading, drug polymer ratio, drug particle size, HPMC viscosity could also have modifiers chlorhexidine release [13].

Bioadhesive strength

In the buccal region, a tablet may be adhered either to the buccal tissue (cheek) or the gingival. For local drug delivery, the highly keratinized epidermis of the gingival will present a barrier to systemic absorption. Examples of oral cavity diseases for which buccal dosage forms have been designed include aphthous stomatitis, oral candidiasis, and periodontal disease [14].

Various classes of polymers have been investigated for their mucoadhesive properties, such as hydrogen-bonding functional groups, suitable wetting properties, swelling/water load properties, and sufficient flexibility for entanglement with tissue mucus network. The mucosal surface are covered with a mucus layer, in which mucins are the major component [15]. Mucins are highly glucosylated glycoproteins with a large peptide backbone and oligosaccharides as side chains. As a result, mucins are

negatively charged at physiological pH. Mechanisms of polymer attachment to mucosal surfaces are not yet fully understood. However, certain theories of bioadhesion have suggested that it might occur via physical entanglement (diffusion theory) and/or chemical interactions, such as electrostatic, hydrophobic, hydrogenbonding, and Van der waals interactions [16].

In general, mucoadhesion is considered to occur in three stages, namely, wetting, penetration and mechanical interlocking between polymer and mucus membrane [15]. It is understood that mucoadhesive polymers could interact with mucous glycoprotein by forming physical and chemical entanglements, followed by hydrogen bonds with sugar residues on oligosaccharide chains that result in the formation of a strengthened mucous gel network that allows the formulations to remain adhesive for an extended period of time [17].

As stated earlier, increase in the concentration of HPMC resulted in increased mucoadhesive strength. This is in agreement with the findings of Ikinci et al who also observed that bioadhesion force increased with increasing HPMC concentration in tablets [18]. HPMC is a long chained, nonionic polymer and so its mucoadhesion is attributable to the formation of physical (including hydrogen) bonds with the mucus components. It possesses a large number of hydroxyl groups that are responsible for adhesion. Formation of hydrogen bonds between the hydrophilic functional groups of mucoadhesive polymers and the mucus layer or the mucosal surface is a prerequisite for extensive and longer mucoadhesion [17]. The increased sites for bond formation may explain the increase in bioadhesion with increase in its concentration.

Unlike most known bioadhesive polymers, chitosan is positively-charged through its free amino groups in the deacetylated glucosamine residues. Its polycationic nature is unusual among biopolymers in general. It has been shown to interact with mucin and liposomes coated with it have also been shown *in vivo* to have prolonged residence time in the gastrointestinal (GI) tract of rats relative to uncoated liposomes [19]. It is capable of developing additional molecular attractive forces by electrostatic interactions with negatively charged mucosal surfaces or negatively-charged sialic acid groups of the mucus network [17].

The higher mucoadhesive potential observed with formulations containing only HPMC is probably due to the controlled rate of hydration of HPMC as a non-ionic polymer. This might have prevented the tablet from quick over-hydration and formation of slippery and weak mucilage that are easily removable from the mucosal surface. On the other hand, chitosan might have formed weaker, more easily fractured gels due to its comparatively low molecular weight in addition to very low rate of swelling, resulting in low mucoadhesive strength [17].

CONCLUSION

The results obtained demonstrate that chlorhexidine tablets for mucoadhesive delivery are feasible. Optimum drug release and bioadhesive properties can be achieved when HPMC only was used as the mucoadhesive polymer matrix.

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