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Mini Review

in vitro availability of hydrochlorothiazide from a novel buccoadhesive delivery system formulated with interpolymer complex

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The buccoadhesive and *in vitro* release properties of patches formulated with ethylcellulose (EC) and hydroxypropyl methylcellulose (HPMC) interpolymer complexes of different ratios were studied. The patches containing hydrochlorothiazide (HCTZ) were prepared by casting and thereafter, evaluated using the following parameters: diameter, thickness, swelling behaviour, buccoadhesive strength, drug content analysis and *in vitro* release studies. An adapted Lecomte Du Nouy tensiometer was used to assess the buccoadhesion of the patches on freshly excised buccal mucosa of a pig. The release of HCTZ from the patches was studied in phosphate buffer (pH 7.5). The result of the study indicated that 1:2 ratio of EC and HPMC gave the highest buccoadhesive strength. All the patches had uniform diameters but varied thicknesses with their areas ranging from 2.06 to 2.16 cm^2. The area swelling ratio (ASR) indicated that the patches did not swell up to two times their initial areas, with the batch containing 3:2 ratio of EC and HPMC possessing the highest ASR. Higuchi's analysis of the release mechanism indicated that the release of HCTZ from the patches formulated with 1:1 and 2:1 ratios of EC and HPMC predominantly occurred by a diffusional process. This method could be used as an effective alternative delivery system for HCTZ compared with conventional tablet formulations.

Key words: Hydrochlorothiazide, ethylcellulose, hydroxypropyl methylcellulose, interpolymer complex, area swelling ratio, buccoadhesive delivery.

INTRODUCTION

Bioadhesive delivery systems have received consider-able attention as absorption promoters due to their ability to adhere to the mucin/epithelial cell surface and thereby anchor a dosage form at the site for optimum drug absorption and lead to an overall increase in bioavailability (Hui and Robinson, 1985; Longer et al., 1985; Mortazavi and Smart, 1994; Magi et al., 1994; Caramela et al., 1994). Mucoadhesion utilizes the property of bioadhesion of certain water soluble or swellable polymers which be-come adhesive on hydration and hence can be used for targeting a drug to particular regions of the body where mucus or receptive epithelial cells are present e.g. nasal, buccal, GIT, cervical and vaginal. The formulation can remain attached for extended period of time and this may reduce toxic side effects and increase the therapeutic efficacy of the incorporated drug (Kamath and Park, 1994; Attama et al., 2003). There are several types of controlled- release bioadhesive dosage forms in use, some of which include oral, buccal and nasal bioadhesive controlled- release devices (Ishida et al., 1983). Buccal delivery is the administration of drug via the membranes of the buccal cavity to the systemic circulation in a way to enhance absorption and overall bioavailability (Kamath and Park, 1994; Guptar et al., 1992; Desai and Pramod-Kumar, 2004). This delivery system has been an area of increased interest by drug delivery pharmaceutical scientists (Martin et al., 2003; Salamat-Miller et al., 2005; Cafaggi et al., 2005; Perioli et al., 2004).

Ethylcellulose (EC) is one of the most widely used water -insoluble polymers in pharmaceutical film coating due

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Table 1. Quantities of the polymers and the HCTZ used for the formulation of the patches.

Batch	Polymer composition (g)		HCTZ (g)
	EC	HPMC	
1	1.0	1.0	0.25
2	0.7	1.4	0.25
3	1.4	0.7	0.25
4	0.8	1.2	0.25
5	1.2	0.8	0.25

due to its convenient film formability, good physicochemical property and minimal toxicity (Porter, 1984). Hydroxypropyl methylcellullose (HPMC) swells in water and produces a clear to opalescent viscous colloidal dispersion. It is used as a dispersing and thickening agent (Hjärtstam et al., 1990). Buccoadhesive delivery systems make use of polymers that are highly bioadhesive and do not dissolve before releasing the incorporated drug, rather drug leaches out of the physiologically inert matrix on absorption of minimum amount of aqueous fluid. Hydrochlorothiazide (HCTZ) is a thiazide diuretic (water pill). It decreases the amount of fluid in the body by increasing the amount of salt and water lost in urine and is used to lower blood pressure and to decrease edema (swelling). HCTZ is not metabolized but is eliminated rapidly by the kidney. It is indicated in the management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension (Hardman et al., 2001). Orthostatic hypotension may occur as a side effect of HCTZ therapy and this may be aggravated by alcohol or antihypertensive drugs. It is also easy to become dangerously dehydrated while taking HCTZ in hot weather. Formulating HCTZ as a buccal patch may help the patient terminate the therapy when serious side effects are noticed especially in ambulatory patients in the tropics where hot weather is common and patient monitoring is low. Mixture of these two polymers may help control the release of HCTZ from the formulation and possibly prevent dehydration and orthostatic hypo-tension that may occur with burst release characteristic of immediate release dosage forms during thiazide therapy. In this study, the hydrophilicty of HPMC was modified with hydrophobic EC to reduce the area swelling ratio of the formulated buccal patches when administered in the buccal cavity. The hydrophobic nature of the EC is also expected to moderate the imbibition of aqueous fluid in the buccal cavity as excessive uptake of fluid will lead to loss of bioadhesive strength of the patches and surge in release of HCTZ. This work is aimed at assessing the *in vitro* availability of hydrochlorothiazide from a novel buccoadhesive delivery system formulated with interpolymer complex of HPMC and EC.

EXPERIMENTAL METHODS

Materials

The following materials were sourced locally and used without further purification: hydrocholorothiazide (MSD, U.S.A), ethyl cellulose (Dow-Chemical Co. USA), hydroxypropyl methylcellulose (Shin ETSU, Japan) and dichloromethane (Carlo-Erba, Italy). All other reagents and solvents were of analytical grade and were used as such. Distilled water was obtained from a glass still.

Preparation of HCTZ buccoadhesive patches

The patches were prepared using the quantities of the components as stated in Table 1. Appropriate quantity of HCTZ was weighed and dispersed in a dispersion of the polymers in dichloromethane. The dispersion was poured into circular metal wells (moulds) of uniform diameter and thickness. This was left for 24 h at 28^{o}C for the organic solvent to completely evaporate. The patches formed from inter -complexation of the two polymers during solvent drying and were thereafter manually removed and stored in a desiccator until used.

Evaluation of HCTZ patches

Five patches from each batch were randomly selected and the diameters and thickness were measured with a vernier calliper and micrometer screw gauge respectively. The averages and standard deviations were calculated.

Porosity

Five patches were selected at random from each batch and observed with a microscope for homogeneity, brittle fracture and presence or absence of pores.

Swelling studies

The swelling studies were carried out on the five batches of the patches using phosphate buffer (pH 7.5) as the swelling fluid. Each of the patches was placed in a Petri dish and a 100 ml quantity of phosphate buffer (pH 7.5) was poured into it. The diameter of the patch was measured at 5 min intervals for 60 min. The respective area swelling ratios (ASR) were calculated from the average of three measurements using equation 1 (Attama and Adikwu, 1999).

$$ASR = \frac{A_t}{A_o} \quad \ldots \quad \ldots \quad \ldots \quad (1)$$

Where A_t is area of the patch at t, and A_o is area of the patch at time zero.

Ex vivo buccoadhesive test

The Lecomte Du Nouy tensiometer (model Nr. 3124, A. Kruss Hamburg, Germany) was used for the study. A freshly excised pig buccal mucosa was rinsed with chilled normal saline and used within 2 h post mortem. The mucus surface (3 x 3 cm) cut off from buccal mucosa was each time used for the test. The tissue was pinned on a polythene support of the instrument placed on a metal

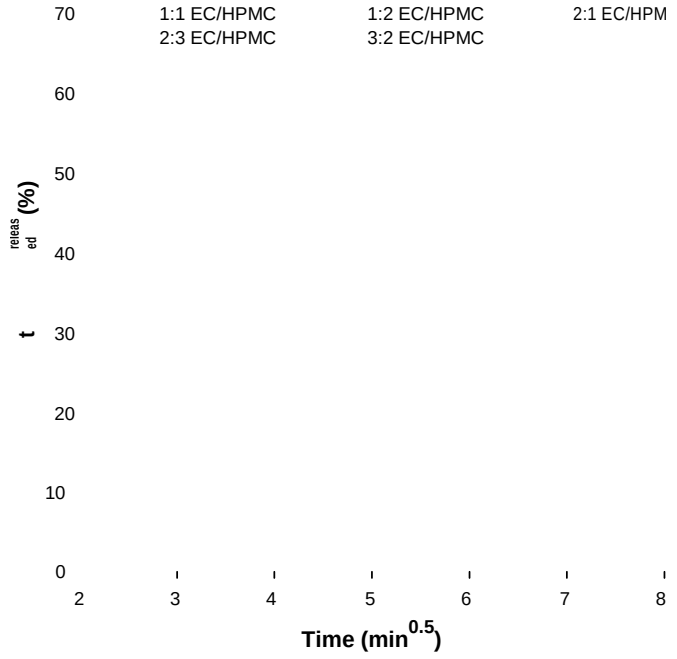

Figure 3. Square root plots of amount of HCTZ released from the patches.

its large amount and penetration of aqueous fluid may be very slow. This delay suggests that delivery of HCTZ as a sustained release formulation may be possible with patches formulated with interpolymer complexes of EC and HPMC. One major advantage of buccal delivery systems is that it is possible to interrupt the medication by removal when the patient wants to eat food or other things and reattaching it in the buccal cavity thereafter. Drug release from buccoadhesive patches of HCTZ may offer advantages over conventional tablet formulations. HCTZ is rapidly eliminated and constant blood level is required for maintenance of blood pressure within tolerable limit. Administration of such formulation may result in controlled and prolonged release of HCTZ without initial burst that may cause orthostatic hypotension especially in ambulatory patients. The release result was further analyzed using Higuchi's diffusion model (Higuchi, 1963). A plot of the amount of drug released against the square root of time when linear, indicates that diffusion is the predominant process of release (Higuchi, 1963). The film batches containing 1:1 and 2:1 ratios of EC and HPMC showed linear plots indicated by their high correlation coefficient (r^2 = *0.9777* and *0.9849* respectively) (Figure 3). This indicated that diffusion was the predominant mechanism of HCTZ release from these patches. Other patches showed non-diffusional release mechanisms as their plots were non- linear.

The findings in these studies give a clue that it may be possible to formulate buccoadhesive delivery systems of hydrochlorothiazide with interpolymer complex derived from ethylcellulose and hydroxypropyl methylcellulose.

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