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"IN VITRO" STUDIES ON BUCCOADHESIVE TABLET FORMULATIONS OF HYDROCORTISONE HEMISUCCINATE

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ABSTRACT

Different bioadhesive and matrix-forming polymers were evaluated using "in-vitro" tests to identify a potentially convenient "in-vivo" formulation for the sustained delivery of hydrocortisone hemisuccinate to the oral cavity. The selected composition allows an erosion-diffusion mechanism coherent with the low hydrosolubility of the drug and with potential advantages for both the patient and the manufacturer.

INTRODUCTION

The oral cavity possesses one of the most easily accesible organic mucosa, and it is readily available for contact with a wide range of substances such as water, food, and others of clearly heterogeneous origin. For this reason it can be frequently affected by pathologies, detectable in the inside buccal surface, consequent upon aggressions from external factors, or from endogenous phenomena such as hypovitaminosis, etc.

Although the topical delivery of certain drugs to the buccal cavity, such as antifungal agents (1), antibacterial (2), or topical corticosteroids (3) has been previously studied with a view to treating such conditions, the constant salivary drainage and the ease of unintentional swallowing has raised an obvious interest in assuring the local presence of the drug during the time necessary to exert its therapeutic action. Needless to say the object is to retain the pharmaceutical dosage form in the mouth in the most confortable way for the patient, without interfering with normal activities such as speaking, eating, etc.

Apart from some studies using adhesive gels or buccal patches, the highest hopes have been currently focused on the performance of buccoadhesive tablets.

In this context some experiments with cetylpiridinium chloride (4), codeine phosphate (5), and testosterone (6) have been described, and in the topical antiinflammatory field the work of Nagai and Mashida (7), devoted to the delivery of triamcinolone acetonide from a bilayer bioadhesive tablet, is well known.

In the present work the "in-vitro" behaviour of several pharmaceutical compositions of hydrocortisone hemisuccinate, formulated as buccoadhesive matrix tablets have been studied, with the object of evaluating their potential usefulness for the "in-vivo" treatment of aphthous stomatitis and other gingival ulcers.

The technology and compositions of the studied formulations are easily transferable to the industrial level, representing an obvious advantage compared to other more sophisticated approaches with their consequent cumbersome industrial procedures. Furthermore, one of them, containing a particular maize starch instead of the more irritant polyacrilic derivatives, is expected to have optimal gingival tolerance. With this type of formulation a 24-hour "in-vitro" delivery of hydrocortisone hemisuccinate to the bucal cavity is guaranted eventually resulting in the complete erosion of the tablet, thereby obviating the need to remove any undisintegrated residual fragment.

MATERIALS AND METHODS

Materials

The following synthetic polymers were used: Medium viscosity hydroxypropylcellulose (HPC, Nisso HPC-M, Nippon Soda, Japan), hydroxypropylmethylcellulose (HPMC, Methocel E4M Premium, Colorcon, USA), and polycarbophil (PCP, Noveon AA1, Goodrich, USA). A modified roll dried maize starch (RDMS, Cerestar, Italy) was also used, and hydrocortisone hemisuccinate and magnesium stearate (MS) were obtained from Impex Química, and Juliá Parrera respectively, both from Spain.

Salivary fluid was simulated by using a solution of inorganic salts (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4 and 8.0 g NaCl per litre of water) at pH = 6.75, according to Bottenberg et al. (8).

Preparation of Buccoadhesive Tablets

The tablets were prepared by directly mixing the polymers, magnesium stearate and hydrocortisone hemisuccinate (5 mg) in a stainless steel cubic blender (Erweka, Germany) during 10 minutes, and finally tableting the mixture in a single punch eccentric press (EKO Korsch, Germany) at 2 mm thickness. The ratios between the components in each formulation were as shown in Table 1.

TABLE 1.
Buccoadhesive Tablet Dimensions and Compositions (w/w, %)

	A	B	C	D
Hydrocortisone hemisuccinate	12.5	7.1	8.3	8.3
HPC	65.0	40.0	16.7	65.9
PCP	21.2	26.5	25.0	-
HPMC	-	25.7	49.2	-
RDMS	-	-	-	25.0
MS	1.3	0.7	0.8	0.8
Tablet diameter (mm)	5	7	6	6
Total tablet weight (mg)	40	70	60	60

Study of Swelling

Six weighed tablets of each composition were separately placed in a series of preweighed glass tubes closed at the bottom by a stainless steel mesh. Each device was vertically placed in a plastic Petri dish containing 50 ml of simulated salivary fluid. The increasing weight of the set (tablet plus device) was determined after 30 minutes, at one hour intervals during 8 hours, and finally at 24 hours.

Study of "In-Vitro" Adhesion

The "in-vitro" adhesion was measured in terms of the force needed to pull out the flat surface of a tablet from a layer of aqueous gelatine gel (15% w/w) simulating the gingival mucosa.

The tablet was glued by one flat surface to a small platinum lamina with cyanoacrylate adhesive, and was suspended from a balance. The adhesive tablet was lowered to just contact the surface of the gelatine, which was mounted on a platform. Tablet and gelatine layer were then pressed together with a force of

20 grams during 1 minute. After this time the platform was carefully lowered until the tablet clearly pulled free of the gelatin. The maximum wire tension reached to this breaking point was recorded, and represented the strength of the former adhesive bond. Ten replicates were carried out for each formulation and mean values calculated.

"In-Vitro" Release of Hydrocortisone Hemisuccinate

Release studies were carried out using an USP nº III dissolution apparatus (Biodis II, Caleva, UK) set to a rate of 20 up-downward alternative strokes per minute, and fitted with an automatic sampling system linked to an UV-spectrophotometer (Uvikon 940, Kontron, Germany) using a flow-through cell with observations at 247 nm. The set of on-line instruments was monitorized using software precisely developed to manage the complete system from an additional microcomputer. As dissolution fluid a volume (1500 ml) of simulated saliva at 37ºC was used. This volume was distributed in a rack of six glass vessels (250 ml each).

In this experiment the tablet was also glued to a plastic dish placed at the bottom of the reciprocating basket in the dissolution apparatus, thereby allowing the drug dissolution from only one tablet side (flat surface and perimetric edge).

RESULTS AND DISCUSSION

The degree of swelling of bioadhesive polymers is an important issue affecting adhesion (9), and again in this study a relationship was found between the swelling rate, expressed as weight increase, and the "in-vitro" bioadhesion force (Figs. 1 and 2). The adhesion results are strongly dependent on the chemical structure of the polymer used since the surface of the simulated biological membrane and the surface of the adhesive produce an interfacial layer where bonds are formed. The initial dimensions of the adhered surface or the total tablet weight are of less importance.

Thus, in the formulations A to C (with a similar PCP content) the swelling capacity and adhesion force were regulated by the HPMC to HPC ratio. The hydrosolubility of HPMC, despite to its only moderate swelling properties, promote liquid entry and entrappement in the HPC network. High HPC contents without the initiating action of HPMC produce a smaller swelling effect (formula A).

The HPC was introduced in these formulations in order to prevent a significant adhesion loss when increasing amounts of HPMC need to be used to facilitate a more rapid dissolution of hydrocortisone hemisuccinate. In all these cases, however, the very important swelling rate and consequent artificial saliva intake, resulted in an interfacial viscosity which was sufficient to avoid

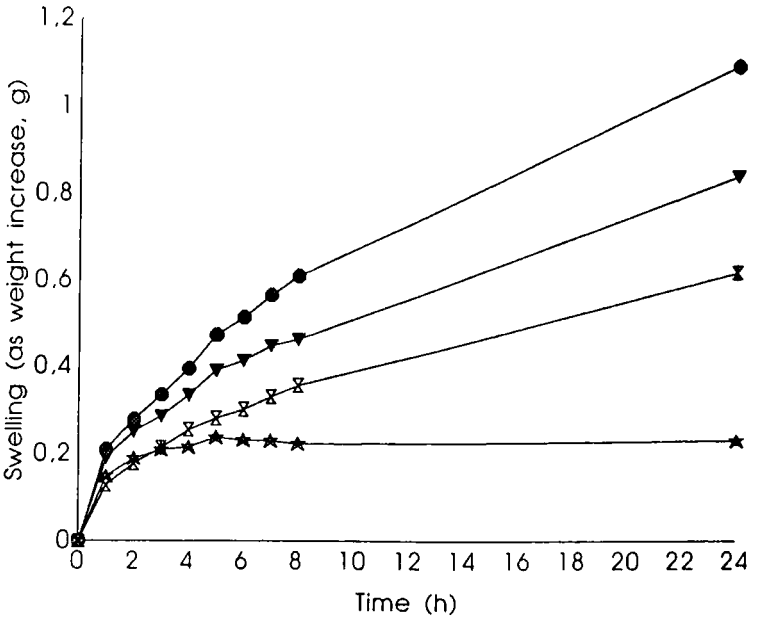

FIGURE 1

Swelling profiles of hydrocortisone hemisuccinate tablets: A (-⧖-), B (-●-), C (-▼-) and D (-★-).

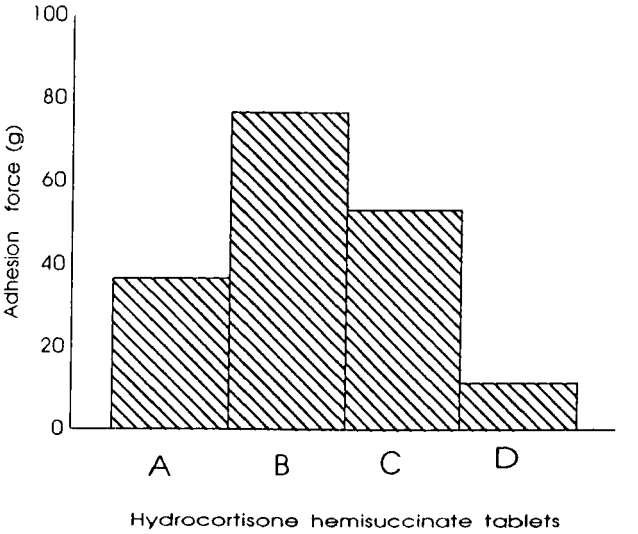

FIGURE 2

Mean adhesion forces for the buccoadhesive tablets.

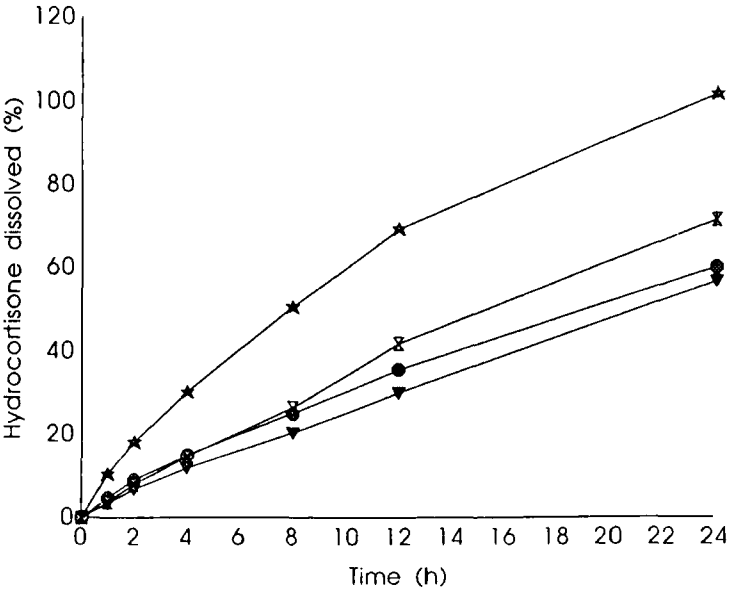

FIGURE 3

Dissolution curves for hydrocortisone hemisuccinate tablets. Same key as Fig.1.

any eventual tablet drop. An analogous and useful behaviour was observed with the formulation D, which obviously differs with respect to the former formulations due to its particular composition containing RDMS. The capacity of salivary liquid intake for the tablets containing this material was practically saturated after the second hour in the swelling test, showing a completely different performance compared with the formulations containing HPC-HPMC. Nevertheless, a mixture with polyacrylic acid has been formerly suggested as the proper way to get a long term adhesion with starch derivatives (8, 10 y 11).

The "in-vitro" dissolution profiles of the tablets considered in this study are shown in Fig.3. Although it has been generally established that a key factor in obtaining a good release is the swelling potential of the bioadhesive formulation (8, 12), it is clear that when scarcely soluble drugs are investigated the use of a combined diffusion-erosion mechanism is necessary, and in this case simple swelling is less advantageous (5). This approach is used with formulation D, yielding the highest "in-vitro" dissolution profile reaching a total dose delivery in 24 hours through a pseudo-first order kinetics ($k=0.0986\ h^{-1}$). In contrast, an evident lack of usefulness can be observed for the formulation B, producing a similar profile of dissolution with respect to formulations A or C despite

important differences in swelling . Of the compositions studied, the formula A shows adhesion force and swelling values closer to formulation D, and even contains very similar amounts of HPC, but the presence of PCP enables the dissolution of hydrocortisone hemisuccinate at a convenient rate due the formation of an insoluble hydrogel within which the drug release strictly follows a diffusion kinetics.

Of the various buccoadhesive formulations containing hydrocortisone hemisuccinate studied, evident advantages could be observed for composition D in terms of complete dose delivery together with an "in-vitro" sustained release covering 24 hours. The low hydrosolubility of the drug necesitates the use of a medium soluble bulk erodible polymer to initiate the swelling-diffusion mechanism. These characteristics were identified in RDMS, which in the proposed combination with HPC (avoiding the use of polyacrylic acid compounds due to their eventual irritant effects on the mucosa (8)) produces a buccoadhesive tablet formulation with correct "in-vitro" adhesion properties and dissolution profile. Furthermore the additional advantage of being totally eroded after 24 hours leaving no exhausted device to be removed supports the potential clinical usefulness of that formulation for the delivery of hydrocortisone hemisuccinate to the environment of discrete buccal lesions.

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