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In vivo evaluation of hydrophilic and hydrophobic mucoadhesive semi-solid formulations containing sucralfate and lidocaine for intraoral use

Y. Jacques[a,e,*], T. Nguyen-Xuan[b], E. Ionescu[c], G.P. Ravelli[c], P. Buri[a], P. Baehni[d], R. Gurny[a]

[a]*School of Pharmacy, Department of Pharmaceutical Technology, University of Geneva, 1211 Geneva 4, Switzerland*
[b]*Pharmaceutical Development, Zyma SA, 1260 Nyon, Switzerland*
[c]*Central Clinical Development, Zyma SA, 1260 Nyon, Switzerland*
[d]*School of Dental Medicine, Department of Preventive Dentisty, University of Geneva, 1211 Geneva 4, Switzerland*
[e]*Pharmapeptides, University Campus, International Business Park, 74166 Archamps, France*[1]

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Abstract

Two types of mucoadhesive semi-solid formulations (hydrophilic and hydrophobic) for the treatment of mucositises, stomatitises and aphtae were investigated in healthy human volunteers using a gamma scintigraphic technique. The investigations showed that the clearance of hydrophobic formulations follows zero order kinetics whereas the hydrophilic formulation follows a biphasic elimination pattern. All formulations showed an acceptable tolerance but the subjects' preference went clearly to the hydrophobic formulations. Hydrophobic formulations maintained their adhesive and cohesive properties throughout the test period, loosing less than 10% activity within the first hour, whereas about 50% of the mucoadhesive hydrophilic preparation was eliminated within the same time period.

Keywords: Aphtae; Bioadhesion; Buccal mucosa; Gamma scintigraphy; In vivo evaluation; Lidocaine; Semi-solid formulations; Sucralfate

1. Introduction

Treatments of chronic inflammatory lesions of the oral mucosa such as aphtous stomatitis have often been hampered by the difficulty in maintaining contact between the treatment composition and the mucosa for a prolonged period. Traditional drug delivery systems such as mouthwashes, ointments, gels and buccal tablets remained widely used, but these dosage forms give high initial concentration of active ingredient only for a short period of time because they are rapidly washed away owing to the flow of saliva and/or the mechanical stress generated by the continuous movements encountered in the buccal cavity [1].

The application of a topical dosage form with adhesive properties can enhance the retention time of the formulation at the site of application leading to both an improved therapeutic efficacy and a shortened treatment period. Up to now, various bioadhesive dosage forms such as tablets [2,3], ointments [4–6] and patches [7–10] have been proposed for the treatment of aphtous stomatitis, mainly with corticosteroids drugs. Semi-solid mucoadhesive dosage forms seem especially suitable for the treatment of mouth ulcers because they can be spread as a thin pellicle over a large portion of mucosa. Moreover, as a result of their soft structure, such dosage forms are able to undergo the stretching and contraction strains of the underlying mucosa and, thus, their bioadhesive joint is less prone to premature rupture than the one of tablets and patches. If mucoad-

* Corresponding author. [1] Present address.

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hesive excipients are known to be mainly hydrophilic [11], it appears necessary to evaluate the influence, in a wet environment, of the hydrophilic or hydrophobic nature of the semi-solid bases incorporating these excipients on both adhesive and cohesive properties of the final formulations.

The objective of this study was to evaluate in human volunteers the oral bioadhesiveness of two highly viscous gels of sucralfate and lidocaine previously formulated [12]. Active ingredients have been thus incorporated simultaneously in a hydrophilic and a hydrophobic adhesive base which were both tested in vivo versus two commercially available products using a γ-scintigraphic technique.

2. Materials and methods

2.1. Formulations

The bioadhesive semi-solid formulations tested in this study all contain 9% (w/w) sucralfate powder and 0.2% (w/w) lidocaine hydrochloride. In hydrophobic formulation, drugs were incorporated in a mixture of Plastibase® (66%) and NaCMC 7H3SXF (24.6%). On the other hand, the hydrophilic base consisted of a mixture of chitosan chloride (6%), polycarbophil (2%), sorbitol solution 70% (15%), glycerol (50%), propyleneglycol (5%) and water (12.55%).

Two commercially available mucosa-adhesive formulations were tested as references: (i) a hydrophilic formulation, Pansoral® (Laboratoires INAVA, F-Boulogne), which contains choline salicylate and cetalkonium chloride in a mixture of hydroxyethylcellulose and glycerol; and (ii) a hydrophobic formulation, Solcoseryl® (Solco SA, CH-Basel) containing deproteinized calf blood in a mixture of gelatin, pectin and carboxymethylcellulose in liquid paraffin.

2.2. In vivo testing in healthy volunteers

2.2.1. Trial population and design

The trial group consisted of eight healthy male volunteers. They presented natural dentition with at least 24 teeth, no acute oral problems, no on-going active dental, periodontal or orthodontic treatment, no symptoms of advanced dental or periodontal diseases and no extensive restorative or prosthetic work. Intake of systemic medication was forbidden and the subjects had to stop all oral medication (e.g. fluoride rinsing) one day before the trial. An important exclusion criterion was the participation in another trial using radioisotopes within the 12 months preceding the trial.

The trial was carried out in one centre, with an open, non-randomized design and consisted of four treatment periods of 90 min each (30 min preparation and 60 min testing) separated by three wash-out periods of one week each. The total individual trial duration per subject was 1 month. The test took place in the morning only.

2.2.2. Radiolabelling of the gels and their application

Approximately 2 g of each formulation to be tested was radiolabelled by the addition of 3–4 drops (20 MBq) of technetium-99m DTPA (diethylenetriaminepentaacetic acid). The gel to be tested was then carefully and thoroughly mixed with the technetium. The average final activity per dose and per subject, at the time of administrations ranged from 0.92 to 1.14 MBq.

After the subject had been asked to swallow his saliva, an amount of approximately 100 mg accurately weighted of the formulation was applied topically with a syringe on the right lower premolar region and spread with a small teflon spatula on an area of approximately 1 cm^2 of the oral mucosa. Each test formulation was applied only once throughout the trial.

2.2.3. Gamma scintigraphy

After the sample application, the subjects were seated in front of the γ-camera (Toshiba GCA 602A, Japan) which was connected to a control monitor and an image monitor. The subject's head was supported by an ophthalmic table to position the head 5 cm from the camera. The clearance of the substance was then monitored for 60 min, using dynamic imaging. Images were recorded at the following rate: every 30 sec for the first 11 min, every 60 s for the next 30 min and every 2 min for the last 20 min. The volunteers were asked to stand stock-still during the 60 min of testing. However, if the subject moved, a readjustment was made to avoid artefacts.

At the end of the testing period, the sample residues were manually removed and the volunteers thoroughly rinsed their mouth with water until complete elimination of the residual radioactive tracer. They also commented on any particular sensation or medical problems noticed during the testing period.

2.2.4. Efficacy parameters

Clearance rate was measured every 30 s for 11 min, every 60 s for 30 min and every 2 min for the last 20 min by using dynamic imaging. The percentage of the applied radioactivity remaining on the mucosa after 60 min was calculated by dividing the count rate of the region of interest (ROI) obtained at any time by the total count rate measured immediately after the application. The ROI included the mucosa area of approximately 1 cm^2. Each count rate was corrected for background counts and radioactivity decay.

Table 1
Remaining activity 61.5 min after application

Formulation	Remaining activity (%)	S.D. (%)	n
Formula 1	96.4	5.7	6
Solcoseryl®	92.1	20.3	6
Formula 2	42.5	27.7	7
Pansoral®	58.6	30.6	7

3. Results

Using the described in vivo test, the doses remaining at 61.5 min after application are presented in Table 1. The gels remained in larger amounts more and longer in the case of hydrophobic formulations (formula # 1 and Solcoseryl®) than in the case of the hydrophilic ones (Pansoral® and formula # 2).

The clearance curves (percentage of the residual activity in the mucosal ROI) for the in vivo bioadhesion tests are shown in Figs. 1 and 2.

There was a striking difference in the clearance rate between the hydrophobic and the hydrophilic formulations: the clearance rate of the hydrophilic formulations (Formula 2 or Pansoral®) from the oral mucosa is a biphasic phenomenon (Table 2) with an initial marked drop (approximately up to 5 min) followed by a much slower decrease (Fig. 3). Kinetic analysis of the clearance by non linear least squares gives for the two clearance rates 3.85 and 0.56%/min, respectively. Formula 2 showed a greater initial clearance rate, the second one being similar for the two formulations.

The clearance rate of the hydrophobic formulations follows zero order kinetics and is approximately the same for Solcoseryl® and Formula 1. As to the hydrophobic and hydrophilic formulations, Formula 1 and Formula 2 have a smaller standard deviation than the references.

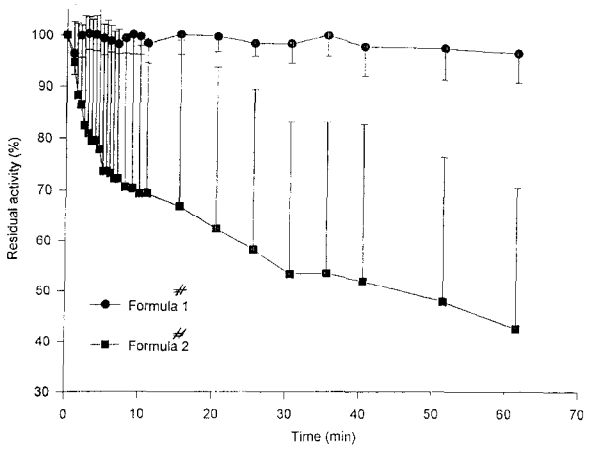

Fig. 1. Clearance rate of Formula 1 and Formula 2.

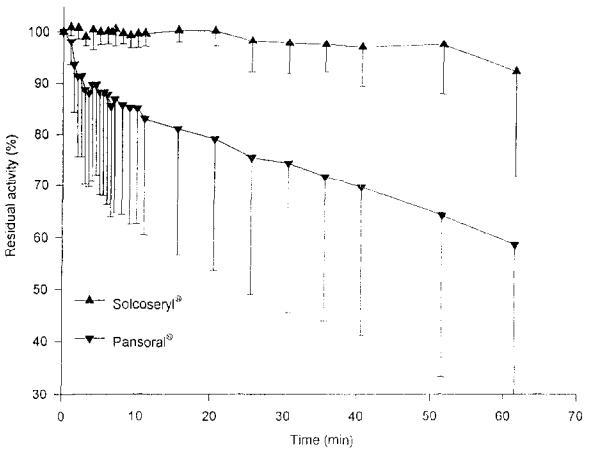

Fig. 2. Clearance rate of Solcoseryl and Pansoral.

Formula 1 and Formula 2 were as well tolerated as the reference samples and even better if one compares with Pansoral® which often produced irritation on application. The safety profile could be also judged from the subjects preferences which went openly to the hydrophobic preparations, namely Formula 1 and Solcoseryl®. Formula 2, besides flowing, produced salivation and irritation of the throat. Again, Formula 1 appeared to be better tolerated than Formula 2.

4. Discussion

As has been previously observed during in vitro evaluation of the same dosage forms [12], hydrophilic formulations exhibited lower mucoadhesive properties towards wet mucosa than hydrophobic ones. Such a phenomenon has been reported by Ishida et al. [5] who observed that the adhesive performances of Carbopol®934 in a hydrophilic base in vitro dramatically dropped in the presence of water while those of the same polymer in a hydrophobic base increased with subsequent hydration.

The significant amount of hydrocolloid together with the use of a lipophilic base in both hydrophobic formulations enhanced mucosal retention. The high content of hydrocolloid gave to the corresponding ointments the ability to displace significant amount of water from the mucosa as illustrated by the in vitro water absorp-

Table 2
Mucosal clearance parameters (mean ± S.E.)

Formulation	k_1 (%/min)	k_2 (%/min)
Formula 1 (hydrophobic)	0.03 ± 0.07	—
Solcoseryl®	0.09 ± 0.25	—
Formula 2 (hydrophilic)	7.21 ± 7.28	0.57 ± 0.23
Pansoral®	3.85 ± 6.68	0.56 ± 0.41

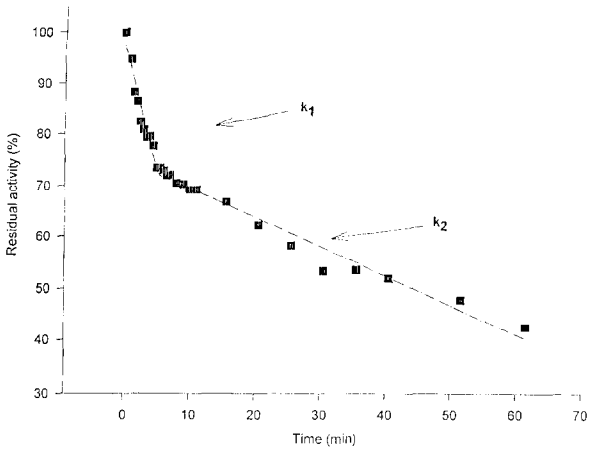

Fig. 3. Elimination kinetics for Formula 2.

tion test described earlier [12]. Water movement, which has been recently considered as a significant factor in mucoadhesion [13], proceeds until the interfacial level of hydration reached an optimum value for maximum mucoadhesion to occur between the functionnal groups of the hydrocolloids and the superficial layers of the buccal epithelium. On the other hand, the hydrophobic bases (polyethylene gel or paraffin oil) avoided overhydration of the dosage forms by the salivary flow and thus maintained the cohesion of the ointment and prevented it from being washed away. The concept of bioadhesive semi-solid formulation based on the dispersion of dry hydrocolloids in a hydrophobic base has been already experienced with Orabase® [14] which is a mixture of pectin, gelatin and NaCMC in a polyethylene gel base, with NaCMC in a polyethylene gel base [15] and with acrylic polymers (Carbopol®934) in oil [16] or in white petrolatum [5]. Polymethylmethacrylate gel (Eudispert®), which fulfilled also this concept, as it is a polymer with both lipophilic methyl groups and hydrophilic carboxyl and esters groups, has been used for the buccal administration of tretinoine [1] and triamcinolone acetonide [4].

A significant amount of the hydrophilic formulation was rapidly washed away from the site of application within the first 5 min, and the overall adhesive performances of this gel contrast markedly with those exhibited by the hydrophobic ointment. Bioadhesive performances of the hydrophilic sucralfate formulation were strongly dependent upon the hydration level of both the mucosa and the dosage form and upon the concentration of mucoadhesive polymer.

The level of hydration at the 'mucosa-mucoadhesive' interface has been known for a long time to be of uppermost importance in the development of adhesive bonds between contacting surfaces [17]. The only hydration degree of the buccal mucosa has been reported to hinder the stickiness of a dry mixture of hydrophilic polymers (hydroxypropylcellulose and Carbopol®934) without preliminary dehydration of the site of application [18] and the detachment force of Carbopol®934 gels from gastric mucus gels was seen to increase when their water content decreased [13]. The in vitro work of adhesion of a bioadhesive tablet containing a mixture of Carbopol®934 and hydroxypropylmethylcellulose decreased not less than in a ten fold manner after prehydration of the tablet [19] and dry dosage forms of hyaluronic acid were more adhesive towards mucin coated surfaces than aqueous gels of the same component [20]. It appears therefore that the presence of additionnal water in a mucoadhesive dosage form enhances the risk of local overhydration impeding the establishment of bioadhesive bonds.

Despite the well known mucoadhesive properties of polycarbophil [21–23] and chitosan [24,25], their concentration in the hydrophilic formulation seemed to be too low to ensure both initial and sustained adhesion to the oral mucosa. According to Peppas et al. [26], at extremely low concentrations of mucoadhesive polymer, although interpenetration of mucus and polymer chains is favoured, the number of polymer chains per unit area is too small to create a stable bond. Mortazavi et al. [13] have shown that Carbopol®934 aqueous gels are able to absorb water from mucus gels when the concentration of the polymer exceeded 12% (w/w) but desorption of water was observed below this concentration. Thus, in the present in vivo experiments, the threshold value of mucoadhesive polymer concentration necessary for water displacement from the mucosa may have been reached with the sucralfate hydrophobic formulation (25%) but not with the hydrophilic one (8%). The water content and the low concentration of bioadhesive polymer of the hydrophilic sucralfate formulation impaired both adhesive and cohesive properties of this preparation.

5. Conclusion

A good correlation was observed between previous in vitro and present in vivo kinetics of elimination of both formulations. Moreover, considering the role of water movement in the mucoadhesion process, in vitro water uptake kinetics appears as a reliable test for the preliminary screening of potential mucoadhesives as the more the rate and extent of water uptake, the more adhesive in vivo the formulations were.

Owing to its ability to extract water from a naturally hydrated mucosa without loosing its cohesive properties, hydrophobic ointment clearly appeared as a better bioadhesive candidate for intraoral administration of sucralfate than hydrophilic gel. The poor bioadhesive performances of the latter, despite the incorporation of well known mucoadhesive polymers, can be attributed to the low concentration of the said polymers and to

the water content of the formulation, both parameters which hampered the first step of the mucoadhesion process i.e. the movement of biological fluid from the buccal mucosa towards the bioadhesive device.

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