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The behaviour of a fast-dissolving dosage form (Expidet) followed by γ-scintigraphy

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Summary

The residence time in the mouth and the distribution of a fast-dissolving dosage form have been followed by γ-scintigraphy in a group of healthy young adults. This was facilitated by incorporation of micronised radiolabelled ion exchange resin (10 mg) into the formulation. Reduction of the amount of resin to 2.5 mg decreased the rate of clearance due to trapping in the macrostructure (papillae) of the tongue. Incorporation of salivary stimulants into the formulation did not alter the rate of dissolution of the dosage form. Measurements of the release rate of oxazepam or lorazepam from the formulation whilst it was in the buccal cavity indicates that little drug absorption occurs from the superior surface of the tongue over short time periods.

Introduction

Buccal dosage systems offer advantages in the delivery of cardiovascular drugs such as glyceryl trinitrate where the avoidance of first pass effect and rapid absorption is an accepted clinical advantage in the relief of anginal pain. Recently a new type of dosage form based on a freeze-dried mixture of drug and fast-dissolving excipients has been introduced to deliver sedative drugs such as benzodiazepines. The Expidet formulation disintegrates rapidly in the mouth enabling rapid delivery of drug to the absorption site. A major advantage of this preparation is that it can be taken without water.

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The technique of gamma scintigraphy has been applied previously to follow the in vivo behaviour and dissolution of conventional buccal dosage forms when placed in various sites in the mouth (Davis et al. 1982; Hardy et al. 1982). In the present study, the deposition and clearance of a fast-dissolving formulation for benzodiazepine delivery has been followed by incorporation of technetium-99m-labelled micronised 'Amberlite' CG400 resin during manufacture. This marker was chosen since both drugs under investigation are relatively insoluble in the buccal cavity. The solubilities of lorazepam and oxazepam are approximately 6.8 mg/100 ml and 2.4 mg/100 ml at pH 6 and 8, respectively. The effect of modifications to the formulation by incorporation of the salivary stimulants citric acid and talin/saccharin on the rate of dissolution of the dose form was also investigated.

In addition, the buccal absorption of lorazepam and oxazepam incorporated into Expidet formulations has been followed over short time periods to establish whether significant absorption of the benzodiazepines occurs during the dissolution phase immediately after ingestion.

Materials and Methods

Materials

Preparation of dosage form for imaging study

Amberlite CG400 (Cl) was micronised using a 5-cm airjet mill and the milled resin suspended in water in a 2-litre measuring cylinder and allowed to sediment for 30 min. The liquid above the sediment bed was decanted and centrifuged at a relative centrifugal force (RCF) of 50 *g* (500 rpm) for 10 min. The liquid was again decanted and centrifuged at an RCF of 200 *g* (1000 rpm) for 60 min and the resulting sediment dried at 105° C. The resin thus prepared had a mean particle size (volume percentage) by Coulter Counter of 17.75 microns (S.D. 4.73 microns).

600 mg of resin were labelled by suspending the resin in ^{99m}Tc sodium pertechnetate (~ 2000 MBq) in 5 ml saline. The mixture was left for 5 min then oven-dried at 105° C for 60 min. The dose forms were then made up by substituting the resin on a weight-for-weight basis into standard Expidet formulations for the 2.5-mg lorazepam or the 10-mg oxazepam products. Two further formulations were prepared by inclusion of 1 mg citric acid (Formulation 3) or saccharin sodium/talin, 0.1 mg and 0.02 mg respectively (Formulation 4), into each unit with 10 mg ^{99m}Tc-labelled Amberlite resin. At the time of administration the units contained 2–4 MBq of activity.

Preparation of dosage form for buccal absorption study

The Expidet formulations were made up using the standard formula and procedure but incorporated an additional 100 mg of labelled marker (^{99m}Tc-labelled diethylenetriaminepentaacetic acid, ^{99m}Tc-DTPA). On the morning of the trial each Expidet formulation contained approximately 0.25 MBq (^{99m}Tc-DTPA) and either 2.5 mg lorazepam (Formulation 5) or 10 mg oxazepam (Formulation 6).

Methods

Subjects

A total of 23 healthy male subjects participated in the studies. All subjects entering the trial were non-smokers, within 10% of the mean group weight and were not taking any medication. Written informed consent was obtained from each volunteer and the protocol was approved by the local Ethical Committee. One week prior to the study, the subjects had a medical examination and were entered into the trial if fit. The subjects were instructed to refrain from alcohol for 24 h prior to the study and to come to the study after fasting overnight.

Imaging study

The subjects sat in front of the γ-camera to allow lateral images of the buccal cavity and upper oesophagus to be taken. The images were taken with a high-resolution parallel-hole collimator. A single Expidet formulation was placed on the tongue without water and the subject was instructed to swallow normally. Acquisition of data over a period of 9 min was started as soon as the subject placed the Expidet formulation on his tongue. After the end of the image the subject was requested not to move and his head was outlined with a cobalt-57 pen. The subject then stood and a 60-s image of the stomach and lower oesophagus was taken.

Buccal absorption study

A separate series of experiments using 15 of the subjects was carried out to determine the extent of buccal absorption of each of the two benzodiazepines administered as Formulations 5 and 6. Each subject placed one Expidet formulation on his tongue and held it there without swallowing for a specified time of either 30, 60, 90 or 120 s, the periods being randomised throughout the trial. At the end of the set time period the mouth contents were washed out with 200 ml of water and the contents spat into a beaker. These were collected into plastic or glass containers, a further

10 ml being used to rinse the beaker. 2×1 ml aliquots of the total volume (210 ml) were taken for γ-counting and the remaining washings (208 ml) retained for analysis. Analysis was performed by HPLC using the method of Patwardhan et al. (1980), as modified by Scott et al. (1983) and the extent of drug absorption was then calculated with reference to the recovery of the radioactive marker. The set time periods were separated by a minimum interval of 2 h.

Data analysis

Imaging study

Data recorded during the experiments were processed to calculate the distribution vs time profile in 3 regions of interest created on the γ-camera. The 3 regions clearly discriminated in the lateral images were the buccal cavity, the glottis and the upper oesophagus. After correction for decay and background contribution, graphs were constructed of activity against time for each of the subjects. The group mean and S.D. at each time point were then calculated for each preparation.

Results

Imaging studies

Two images from the study are shown in Fig. 1. The formulation dissolved rapidly and swallowed activity could be seen in the oesophagus by 30 s. Within 15 s the Expidet formulation had completely dissolved. On completion of the experiment about 8% of the resin incorporated into the formulation remained in the glottal area; that from the oesophagus had completely cleared (Fig. 2).

Fig. 3 shows the buccal clearance of the formulations containing 2.5 mg or 10 mg of resin for a group of 6 subjects. From the individual data, the mean times ± S.E.M. for 50% clearance were 190 ± 70 s and 50 ± 20 s for the formulations containing 2.5 and 10 mg of resin, respectively.

The effect of incorporation of citric acid or

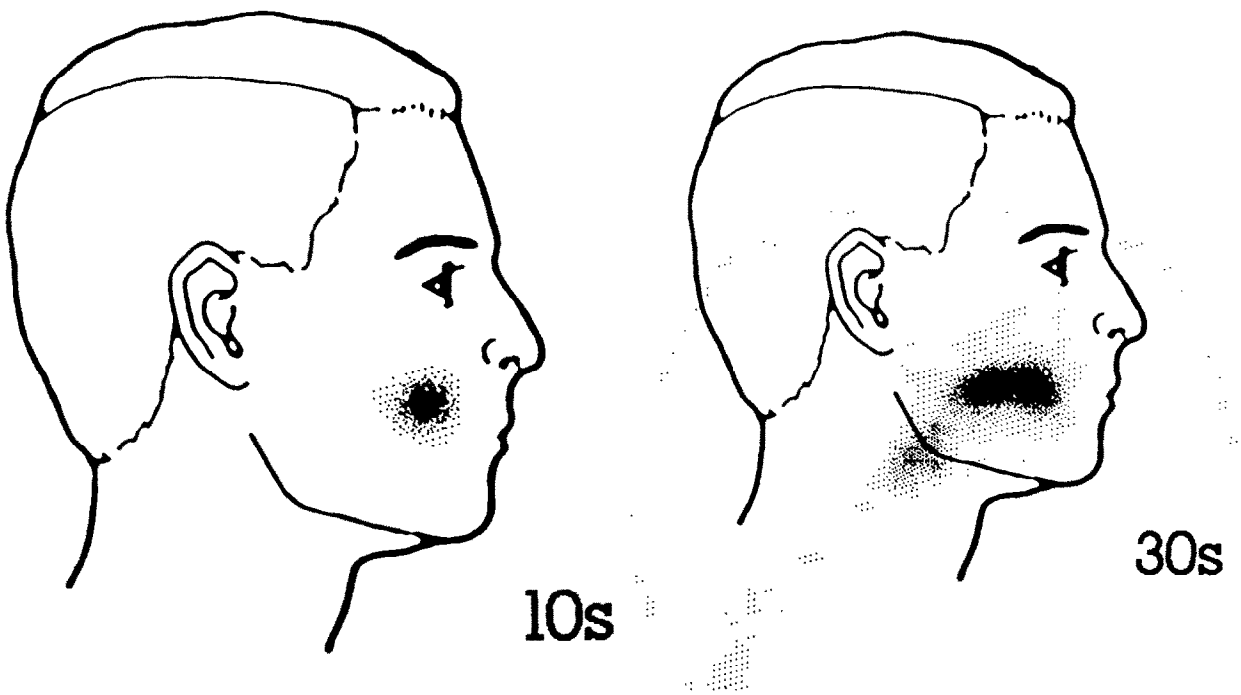

Fig. 1. Scintigraphic images of the dissolution of Expidet formulations containing 10 mg micronised ion exchange resin labelled with technetium-99m.

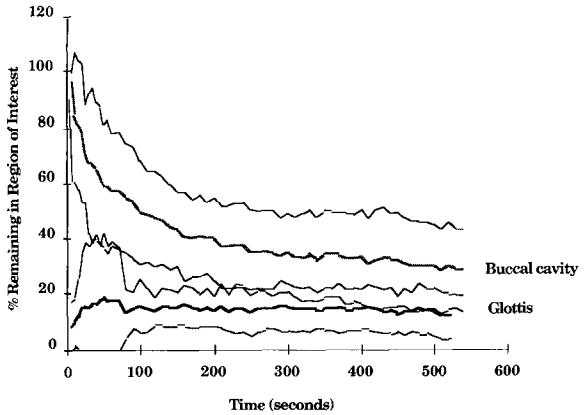

Fig. 2. Distribution and clearance of the labelled Expidet from the glottis and buccal cavity. Mean ± S.D. shown, 8 subjects per group.

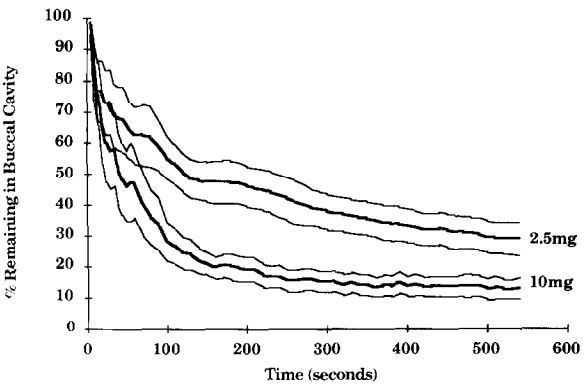

Fig. 3. Buccal clearance of the formulations containing 2.5 mg or 10 mg of resin for a group of 6 subjects (mean ± S.D.).

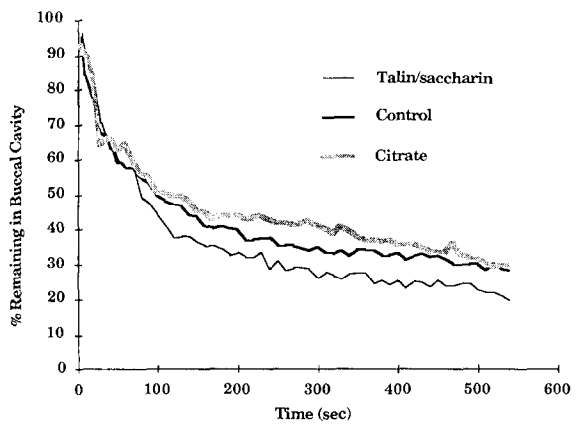

Fig. 4. The effect of incorporation of citric acid or talin/saccharin into the Expidet formulation. Mean traces from 6 subjects per group.

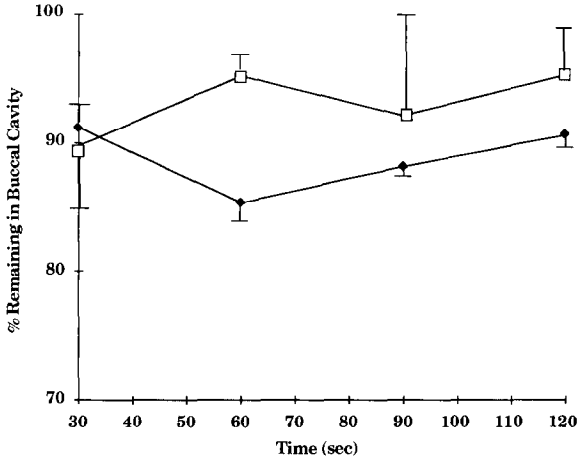

Fig. 5. Buccal absorption of oxazepam (□) and lorazepam (◆) in a group of 8 subjects (mean ± S.D.).

talin/saccharin into the formulation was studied in a separate group of 6 subjects (Fig. 4). As may be seen, no effect of salivary stimulants on the rate of dissolution was apparent with a mean 50% clearance for each formulation between 80 and 100 s.

Buccal absorption of oxazepam or lorazepam over the study period in 8 subjects is shown–Fig. 5. Between 85 and 95% of the drug was recovered in the buccal washings, and plots of the percentage activity remaining vs time for each subject had slopes of zero suggesting that negligible absorption of the drug took place during the time that the formulation was in contact with the tongue.

Discussion

Scintigraphic images taken of the spread of the formulation from frontal and lateral planes showed that, although dispersion of the formulation was rapid, the material did not spread laterally across the floor of the buccal cavity. This observation is important since it may account for some of the results obtained in the present study. As was noted in Fig. 4, clearance of Formulation 1 containing 10 mg resin was significantly faster than that of Formulation 2 containing 2.5 mg resin.

However, calculation of the total activity remaining on the tongue in each case shows the absolute amount of resin to be similar after about 50 s. Thus the differences represent the "capacity factor" of the papillary surface of the tongue since the amount retained in each case is about 1 mg resin.

Incorporation of the salivary stimulants made little difference to the rate of dissolution of the formulation. This is probably due to the lack of sensitivity of the middle of the tongue to stimulation by acidic materials. It is well established that a few drops of a 1% aqueous citric acid placed onto the tip of the tongue elicits a strong salivary response. However, the same dose placed on the back of the tongue is less effective. The submandibular and sublingual salivary ducts discharge saliva onto the floor of the mouth, wetting the sides of the tongue and cheek surfaces. During the act of swallowing the tongue curls back against the hard palate and saliva moves along the floor of the mouth to enter the glottal area at the base of the tongue. Although the posterior third of the tongue contains mucus glands the quantity of secretion is small relative to that produced by the submandibular and sublingual glands. Thus increased saliva flow may not result in more aqueous phase available for dissolution of a dosage form on the tongue surface.

Previous studies have reported that the absorption of lorazepam when administered sublingually is essentially complete within 15 min (Greenblatt et al., 1982). However, this group did not distinguish between the swallowed fraction of the dose and that absorbed buccally. The present study indicates that little of either drug is absorbed in the buccal cavity for the time that a fast-dissolving formulation is in the mouth.

Finally, there has been much concern that patients may swallow tablets or capsules with little or no water whilst lying down in bed. Both tablets and capsules have been shown to have delayed transit under these conditions (Channer and Virjee, 1982; Hey et al., 1982). This may cause the unit to become lodged in the oesophagus with the risk of oesophageal ulceration, particularly in patients in whom oesophageal transit is abnormal. Fast-dissolving medications may offer a method of overcoming this problem, when the patient is bed-ridden and easy access to fluid is not convenient.

'Expidet' is a trade mark of American Home Products Corp.

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