International Journal of Pharmaceutics, 66 (1990) 169-174
Elsevier

IJP 02263

Deposition of a model substance, ^{99m}Tc E-HIDA, in the oral cavity after administration of lozenges, chewing gum and sublingual tablets

L.L. Christrup[1], S.S. Davis[2], M. Frier[3], C.D. Melia[2], S.N. Rasmussen[4], N. Washington[5], I.R. Wilding[2] and C. Andersen[6]

[1]Department of Pharmaceutics, Royal Danish School of Pharmacy, Copenhagen (Denmark), [2]Department of Pharmaceutical Science, University of Nottingham, Nottingham (U.K.), [3]Department of Medical Physics, Queen's Medical Centre, Nottingham, (U.K.), [4]Department of Biological Science, Royal Danish School of Pharmacy, Copenhagen (Denmark), [5]Department of Physiology and Pharmacology, Medical School, Queen's Medical Centre, Nottingham, (U.K.) and [6]Fertin Laboratories A/S, Vejle (Denmark)

(Received 10 July 1990)
(Accepted 7 August 1990)

Key words: Dosage form; Oral cavity; Gamma-scintigraphy

Summary

The deposition and clearance of a model substance, ^{99m}Tc E-HIDA, in the oral cavity/upper oesophagus and in the stomach after administration of lozenges, chewing gum and sublingual tablets has been followed by gamma scintigraphy in a group of healthy male volunteers. Following administration of sublingual tablets, the residence time of the model substance in the oral cavity was significantly longer than following administration of chewing gum. The residence time following administration of lozenges was found to be the shortest.

Introduction

Chewing gum has previously been described as a drug delivery system for high clearance drugs such as salicylamide (Christrup et al., 1988), verapamil (Christrup et al., 1990) and nicotine (Russel et al., 1980; Jarvis et al. 1982; Benowitz et al., 1987) and for drugs intended to act locally in the mouth such as nystatin (Andersen et al., 1990), miconazole (Pedersen and Rassing, 1990), sodium fluoride (Bruun and Givskov, 1978), neomycin-gramicidin (Wertalik and Bonorden, 1968), metronidazole and penicillin (Emslie, 1967) and sulfathiazole (Harrison and Ress, 1945)

Chewing gum may be a suitable system for delivery of drugs to the oral cavity or the throat, since it may release the drug slowly and thereby provide a longer period of drug contact with the mucosa than, for example lozenges, which are often erroneously chewed and swallowed.

As a vehicle for high-clearance drugs intended to be absorbed through the oral mucosa, chewing gum might be considered an alternative to buccal and sublingual tablets. It would be expected that the drug would be more effectively distributed in the oral cavity following administration by chew-

Correspondence: L.L. Christrup, Department of Pharmaceutics, Royal Danish School of Pharmacy, 2 Universitetsparken, Copenhagen, DK-2100, Denmark.

ing gum than if delivered by sublingual or buccal tablets. Thus the drug might be absorbed more effectively since the area available for absorption would be larger. However, since the process of mastication promotes salivation, there may be a greater proportion of swallowed drug following administration of chewing gum when compared to sublingual or buccal tablets. Therefore the possible improvement gained by efficient distribution of the drug might be lost by the reduction in drug available for absorption through the oral mucosa.

Benowitz et al. (1987) have suggested a mathematical model to estimate buccal vs. gastrointestinal absorption following administration of nicotine chewing gum. This model is based upon pharmacokinetic data on nicotine and its major metabolite cotinine.

The technique of gamma scintigraphy has been used previously to evaluate the in vivo behaviour of buccal dosage forms, including aspects of dissolution and the buccal absorption of drugs (Davis et al., 1982, 1983; Hardy et al., 1982; Wilson et al., 1987).

In the present study the deposition of a model substance ^{99m}Tc E-HIDA (*N*-(*N'*-(2,6-dimethylphenyl))carbamoylmethyl iminoacetic acid) in the oral cavity, the oesophagus and in the stomach after administration in lozenges, chewing gum and sublingual tablets has been compared, in order to obtain information on how effectively a drug is spread in the oral cavity and how quickly it is swallowed. E-HIDA was chosen as the model substance because it was released from chewing gum with the same rate and to the same extent as verapamil, which, as described by Christrup et al. (1990), is a potential drug to administer in chewing gum.

Materials and Methods

Materials

Radiolabeling of the E-HIDA

^{99m}Tc pertechnetate in 1 ml saline was obtained by elution from a generator (Elumatic III, CIS (U.K.) Ltd, High Wycombe, U.K.) and was used to prepare ^{99m}Tc E-HIDA. Preparation was done by reconstituting a kit of E-HIDA (product code N103, Amersham International) with ^{99m}Tc pertechnetate eluted from the generator and diluting to a final volume of 1.0 ml with 0.9% sodium chloride injection.

Preparation of the dosage forms

(i) Lozenges containing 625 mg lactose, 1875 mg sorbitol and ^{99m}Tc E-HIDA (total activity 3 MBq) were compressed using 15 mm biconcave punches.

(ii) Sublingual tablets containing 20 mg lactose, 80 mg sorbitol and ^{99m}Tc E-HIDA (total activity 3 MBq) were compressed using 6 mm biconcave punches.

(iii) Chewing gum containing 700 mg gum base, 1050 mg sorbitol, 200 mg hydrogenated glucose syrup, 20 mg solid paraffin, 30 mg flavour and ^{99m}Tc E-HIDA (total activity 3 MBq) was prepared using a conventional technique (Cherukuri et al., 1982).

Methods

Subjects

Six healthy male subjects participated in the study. All subjects who entered the trial were non-smokers, did not wear dentures and were not taking any medication. Written informed consent was obtained from each volunteer and the protocol was approved by the Nottingham University Ethical Committee. The subjects were instructed to abstain from alcohol for 24 h prior to the study and were fasted overnight.

Treatment

The three dosage forms were given to each subject using a cross-over design with 24 h between each administration. Since no carry-over effect was expected randomisation was not believed necessary, consequently all subjects received the dosage form in the following order: chewing gum, lozenges and sublingual tablets.

Chewing gum. Each subject chewed a piece of gum for 10 min and was instructed to chew at a rate of approx. 1 chew/s and to swallow normally.

Lozenges. Each subject placed one lozenge in the mouth and was carefully instructed to suck and not to chew the dosage form and to swallow normally.

Sublingual tablets. Each subject placed one tablet under the tongue and the subject was instructed to swallow normally.

Following administration of the dosage form, the subjects were placed in front of a gamma-camera to allow lateral 60-s images of the buccal cavity and the upper oesophagus to be acquired. The subjects then stood and a 60-s image of the stomach was taken. Images were taken at 1, 2, 5, 10, 15, 20, 30, 45, 60 and 80 min or until all the ^{99m}Tc E-HIDA had disappeared from the oral cavity.

During imaging the dosage forms were removed from the oral cavity and the amount of ^{99m}Tc E-HIDA remaining in the dosage form was determined by placing the dosage form on the measuring surface of the gamma camera.

The gamma camera system was a Maxicamera II with a 40 cm field of view (General Electric Medical Systems, London, U.K.), fitted with a low energy collimator and linked to an NMS 80 computer (Nodecrest Corp., West Byfleet, U.K.).

Data analysis

Data recorded during the study were processed to calculate the activity time profiles in the following two regions: the buccal cavity/glottis/upper oesophagus and the stomach. After correction for decay, background contribution and differences in total activity between doses, a graph of activity against time was constructed for each administration.

The area under the activity-time curves (AUC) obtained from the oral cavity were calculated by the trapezoidal rule with addition of the residual area, calculated as the last measured activity divided by the elimination constant calculated from the terminal log-linear phase.

A paired one-tailed *t*-test was used to compare the mean AUC and $t_{1/2}$ values obtained after administration of lozenges, chewing gum and sublingual tablets. $P<0.05$ was considered significant.

Results

The dissolution time of the lozenges was 5–8 min and for disintegration of the sublingual tablets 5–9 min. The mean in vivo release profiles of ^{99m}Tc E-HIDA from the dosage forms are shown in Fig. 1.

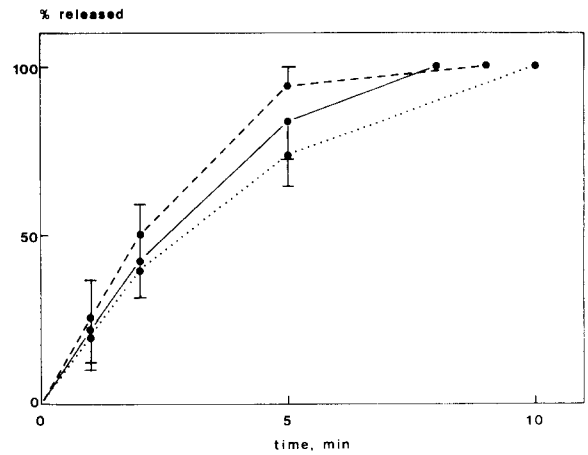

Fig. 1. Release profiles of ^{99m}Tc E-HIDA from chewing gum (···), lozenges (—) and sublingual tablets (---). Each point and vertical bar show mean±S.D., $n=6$.

Figs 2a, 2b, 3a, 3b, 4a and 4b show the activity-time profiles for the oral cavity and for the stomach after administration of lozenges, chewing gum and sublingual tablets, respectively.

The stomach data was obtained from anterior images alone to give an indication of clearance. Gastric residence of the radiolabel was not calculated since this would have required both anterior and posterior views to have been taken and the geometric mean obtained.

Table 1 shows the dissolution times for the lozenges and sublingual tablets, the disappearance half-lives, $t_{1/2}$ and the AUC values obtained from the activity-time curves in the oral cavity/upper oesophagus obtained from each individual.

The disappearance half-life was significantly greater ($p=0.002$) following administration of sublingual tablets than following administration of chewing gum. Following administration of chewing gum the half-life was significantly greater ($p=0.014$) than following administration of lozenges.

The area under the activity-time curves was significantly greater ($p=0.021$) following administration of sublingual tablets than following administration of chewing gum. Following administration of chewing gum the area was significantly

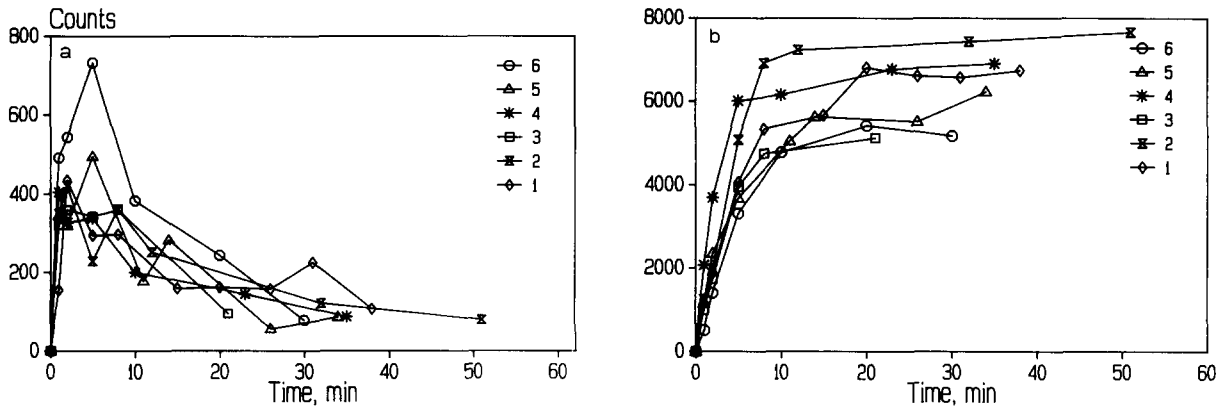

Fig. 2. (a) Activity time profile from the oral cavity/upper oesophagus after administration of lozenges. (b) Activity time profile from the stomach after administration of lozenges.

greater (p=0.007) than following administration of lozenges.

From the images taken during the study it was not possible to distinguish any difference in the spread of ^{99m}Tc E-HIDA in the oral cavity, glottis and upper oesophagus following administration of lozenges, chewing gum and sublingual tablets.

Discussion

From Fig. 1 it appears that there is little difference in the release rate of ^{99m}Tc E-HIDA from the three different dosage forms, perhaps as a consequence of the volunteers being carefully instructed not to chew the lozenge. Wilson and Washington (1989) have compared the in vivo release rate of ^{99m}Tc-DTPA from a chewable capsule formulation after sucking and chewing and as expected found that release proceeded more rapidly when chewing than when sucking the system.

The inter-subject variation following sublingual application in this study is relatively small compared to that reported previously by Davis et al. (1983). The sublingual tablets used in that study, however, contained ^{99m}Tc-DTPA, which is more water soluble than ^{99m}Tc E-HIDA. In addition the tablet released the model substance over a longer

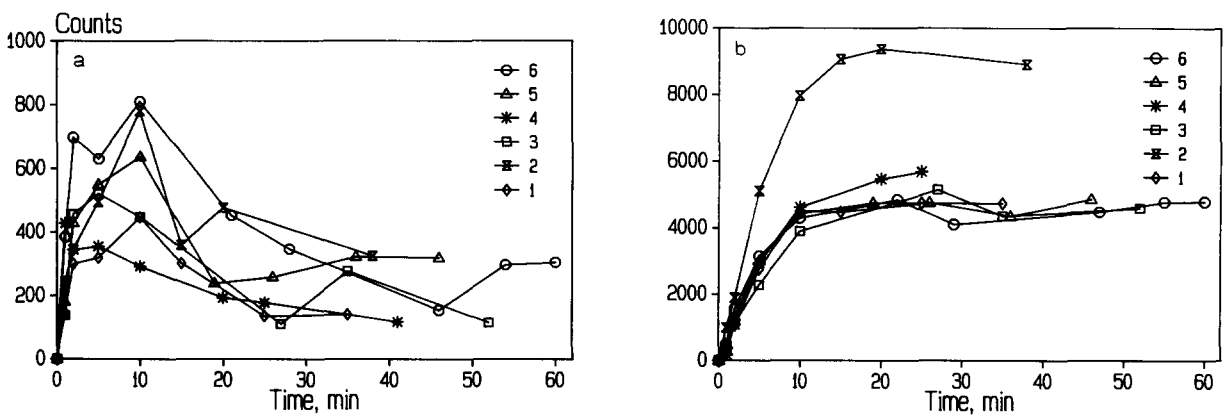

Fig. 3. (a) Activity time profile from the oral cavity/upper oesophagus after administration of chewing gum. (b) Activity time profile from the stomach after administration of chewing gum.

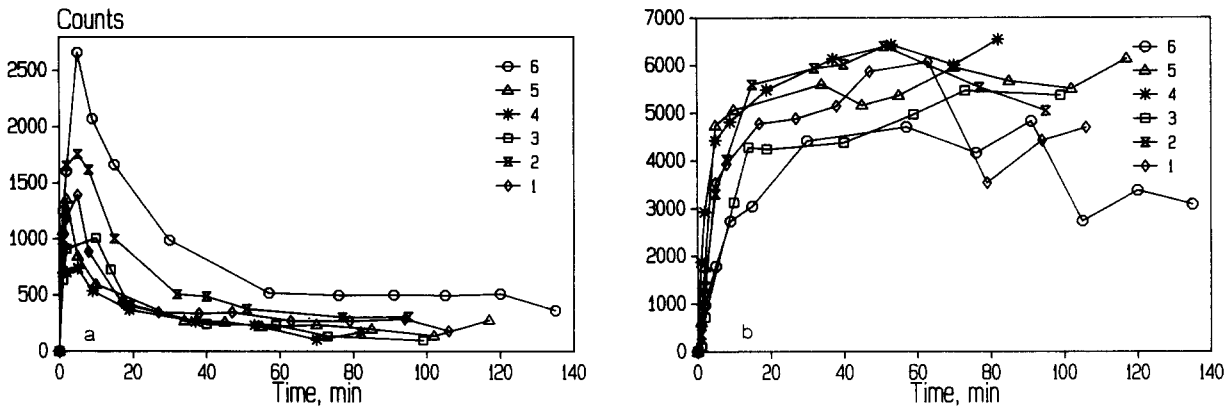

Fig. 4. (a) Activity time profile from the oral cavity/upper oesophagus after administration of sublingual tablets. (b) Activity time profile from the stomach after administration of sublingual tablets.

period of time (approx. 20–50 min, $n=3$). Davis et al. (1983) also showed that the release of ^{99m}Tc-DTPA from a sustained release tablet proceeded more rapidly when the tablet was placed behind the lower front incisors than when it was placed in the buccal cavity. Jenkins and Krebsbach (1985) have compared the spread of charcoal particles placed at various locations in the oral cavity. When the particles were placed under the tongue, the whole mouth became covered within 1–3 min, whereas administration to the lower right and left buccal vestibule covered that side of the tongue only. Hence, saliva flow may be responsible for the difference in release rates observed by Davis et al. (1983).

Wilson et al. (1987) found that incorporation of salivary stimulants made little difference to the rate of dissolution of a formulation placed on tongue the surface.

Although we found little difference in the release rate of ^{99m}Tc E-HIDA there was a significant difference in the disappearance half-lives ($t_{1/2}$) and the area under the activity-time curves (AUC) for the three delivery systems. This may be due to divert effect of the dosage forms upon the salivary flow, which leads to an alteration in the clearance kinetics.

From the results in Table 1, and Figs 2a, 3a and 4a it can be seen that there is a great individual difference in AUC values obtained from the activity time profiles from the oral cavity, probably due to individual differences in salivary secretion rates.

TABLE 1

AUC and $t_{1/2}$ for the activity in the oral cavity/upper oesophagus and dissolution times for the lozenges and sublingual tablets

Subject no.	Lozenge			Chewing gum		Sublingual tablet		
	AUC (counts h)	$t_{1/2}$ (min)	Diss. time (min)	AUC (counts h)	$t_{1/2}$ (min)	AUC (counts h)	$t_{1/2}$ (min)	Diss. time (min)
1	11172	21.7	6	12288	18.2	60916	46.6	7
2	11931	23.3	8	32202	32.2	80935	54.0	8
3	6491	6.8	8	20222	21.4	37213	38.2	7
4	8604	16.5	5	13440	26.4	41374	64.3	5
5	8148	9.0	9	28853	26.5	47525	57.3	5
6	11178	8.7	8	31278	15.4	167958	75.4	9
Mean	9580	14.3	7.3	23047	23.3	72634	56.0	6.8
S.D.	2158	7.2	1.5	8959	6.2	49306	13.1	1.6

Subjects who obtained long dissolution times for the lozenge and the sublingual tablets achieved the highest activity in the oral cavity.

From the individual activity versus time profiles it appears as expected that subjects having relative high activity in the mouth have a relatively low activity in the stomach, probably due to differences in salivary secretion rates. It also appears that at the end of the application period the highest activity in the stomach is obtained after administration of lozenges followed by chewing gum and then sublingual tablets.

Conclusion

The results from the present study indicate that sublingual tablets are superior to chewing gum as a delivery system for drugs intended to be absorbed through the oral mucosa, while chewing gum is superior to lozenges as delivery system for drugs intended to act locally in the mouth or throat.

Acknowledgements

The funding supplied by The Danish Medical Research Council and Fertin Laboratories A/S, Vejle, Denmark is gratefully acknowledged.

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