Development of a Method for Study of the Tendency of Drug Products to Adhere to the Esophagus

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Received June 29, 1981, from the *Pharmaceutical Research Laboratories, Orion Pharmaceutical Co., Espoo, Finland*, and the **School of Pharmacy, University of Helsinki, Helsinki, Finland.* Accepted for publication November 9, 1981.

Abstract □ A method to determine the adherence of drugs to the esophagus was developed using isolated swine esophagi. A number of types of tablets and capsules (*e.g.*, of doxycycline) were tested. The results showed that the tendency of products to adhere to the esophagus can be regulated by pharmaceutical properties. It was concluded that the method described is simple, inexpensive, and accurate.

Keyphrases □ Esophagus—study of drug product adherence, doxycycline, swine esophagus □ Adherence—study of drug products in esophagus, doxycycline, swine esophagus

In recent years, many case reports concerning drug-induced esophageal ulceration or stricture in humans have been published. Serious damage has been caused by doxycycline (1–3), emepronium bromide (4–6), potassium chloride (7–9), alprenolol (3), and iron salts (3, 10). The mechanism of injury is not yet well understood, although it is obvious that the lesions were caused by drug substances. The primary reason has apparently been adherence of the drug product to the esophageal wall, allowing high local drug concentrations to be formed. The tendency to adhere is obviously greatest for hard gelatin capsules, but differences between various tablet formulations are also evident. The risk of esophageal lodging can generally be avoided by taking dosage forms with water and, if possible, in an upright position. Despite this, there is a great need for development of new drug products and product coatings with less tendency to adhere to the esophageal mucosa. However, no adequate and simple method for measuring adherence has been available.

The aim of the present investigation was to develop a method for study of the tendency of products to adhere to the esophageal wall, using the isolated swine esophagus. Our results on the effects of various pharmaceutical properties of products on adhesion will be published later.

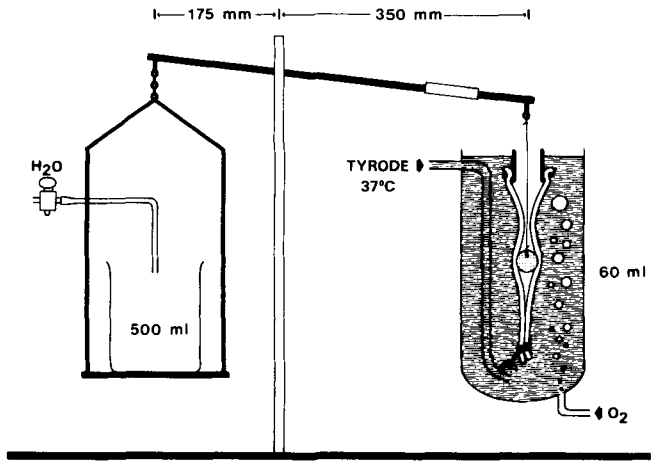

Figure 1—*Measurement system for force needed to detach product from the esophagus and organ bath I.*

EXPERIMENTAL

Isolated Esophagus Preparation—Pigs of both sexes of Landrace and Yorkshire breeds, weighing 90–100 kg were used. Immediately after slaughter, the esophagi were removed and transported to the laboratory in Tyrode solution, kept at ~4°. The composition of the Tyrode solution was (g liter^{-1}): sodium chloride 8.0, potassium chloride 0.2, calcium chloride · $2H_2O$ 0.134, sodium bicarbonate 1.0, sodium dihydrogen phosphate 0.05, and glucose · $1H_2O$ 1.0. During experiments the solution was aerated with pure oxygen and kept at 37°. Segments 6–7 cm long were cut from the esophagus. The segments were mounted in two kinds of organ baths. Organ bath I: The volume of the classic organ bath for isolated preparations was 60 ml (Fig. 1). The lower end of the esophageal segment was tied off and the upper end was attached around a glass tube (diameter 15 mm). The solution in the organ bath was changed at intervals of about 30 min. Organ bath II: The volume of the second organ bath was 2000 ml (Fig. 2). In this preparation, the lower end of the esophageal segment was also attached around a glass tube (diameter 8 mm). There was, therefore, free passage through the preparation, which allowed washing of the mucosa. The Tyrode solution in this organ bath was not changed during the 6-hr experiments.

Recording of Adherence—A hole (diameter of 1 mm) was drilled in the products to be tested. The product was attached to a copper wire (diameter of 0.25 mm) and placed, using a plastic tube as an applicator, in the esophageal preparation for a fixed time. The force needed to detach the product was measured using a modified prescription balance (maximum load 500 g; see Fig. 1). This force was used as a parameter for adherence. The force (F) in newtons was calculated by the equation:

$$F = \frac{0.00981W}{2}$$

where W = amount of water in the beaker in grams. The water flow rate was 280 g min^{-1} (corresponding to 1.37 N min^{-1}).

Characteristics Studied—To discover the usefulness of the preparation the following characteristics were studied: (*a*) the effect of the time for which the product remains in the esophagus upon the force needed to detach it; (*b*) the effect of the surface areas of different products on the force needed for detachment; (*c*) differences between the results obtained using the two different organ baths; (*d*) the effect of washing of the mucosa on adherence; and (*e*) differences in adherence to the esophagus of some commercially available doxycycline preparations.

Drug Products—Hard gelatin capsules[1], sizes 0, 1, 2, 3, 4, and 5, were filled with lactose. Placebo tablets were compressed from a mixture of basic granules (96%), talcum (3%), and magnesium stearate (1%). The

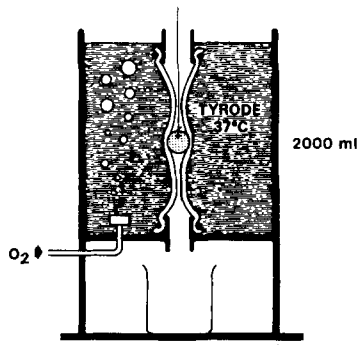

Figure 2—*Organ bath II for isolated esophageal preparations.*

[1] Capsugel AG, Switzerland.

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Table I—Surface Areas of Products Studied

Capsule size	Area, mm^2	Placebo Tablet Diameter, mm	Area, mm^2	Potassium Chloride Tablet Diameter, mm	Area, mm^2
2	349	7	160	7	146
3	286	9	223	9	223
4	244	10	259	10	259
5	196	11	298	11	308
		12	358	12	358

Table II—Mean Force Newtons Per Unit Area (cm^2) Needed to Detach Products from the Isolated Swine Esophagus

Capsule Size	Force, N cm^{-2}	Placebo Tablet Diameter, mm	Force, N cm^{-2}	Potassium Chloride Tablet Diameter, mm	Force, N cm^{-2}
2	0.36	7	0.26	7	0.075
3	0.38	9	0.24	9	0.054
4	0.35	10	0.25	10	0.062
5	0.40	11	0.24	11	0.058
		12	0.24	12	0.056

basic granules contained lactose (78%), corn starch (19%), and gelatin (3%). Potassium chloride tablets were compressed from pure potassium chloride. The diameters of the placebo and potassium chloride tablets were 7, 9, 10, 11, or 12 mm. The shape of all tablets was biconvex. The surface areas of the capsules and tablets were calculated according to geometrical principles and are given in Table I.

As sugar-coated tablets, a commercial product[2] of 11-mm diameter was used. The diameter of the film-coated tablets[3] was also 11 mm. The film-forming material was hydroxypropylmethylcellulose.

In the final part of the present study, six commercially available doxycycline (100–150 mg) products (A–F) and two test formulations (G, H) were studied using the method developed. Products B–E were film-coated tablets. Product F was a capsule formulation (size 3). Products A, G, and H were uncoated tablets.

RESULTS AND DISCUSSION

Initially, the effect of the time interval between administration of the drug and commencement of detachment on the force needed for detachment was studied with four different products. As can be seen from

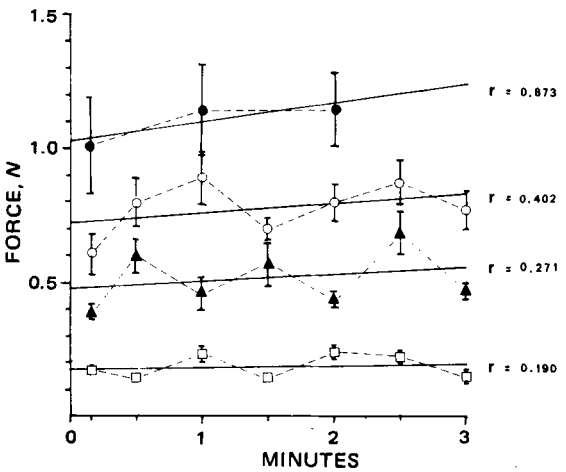

Figure 3—*Effect of the time interval between administration of the drug and commencement of detachment on force needed for detachment of drug. Key: (●) hard gelatin capsule size 2; (○) placebo tablet, diameter 11 mm; (▲) hydroxypropylmethylcellulose film-coated tablet, diameter 11 mm; (□) sugar-coated tablet, diameter 11 mm. Each point represents mean* ±SEM, n = *10.*

[2] Sembrina, Orion Pharmaceutical Co, Finland.
[3] Kaliduron, Orion Pharmaceutical Co, Finland.

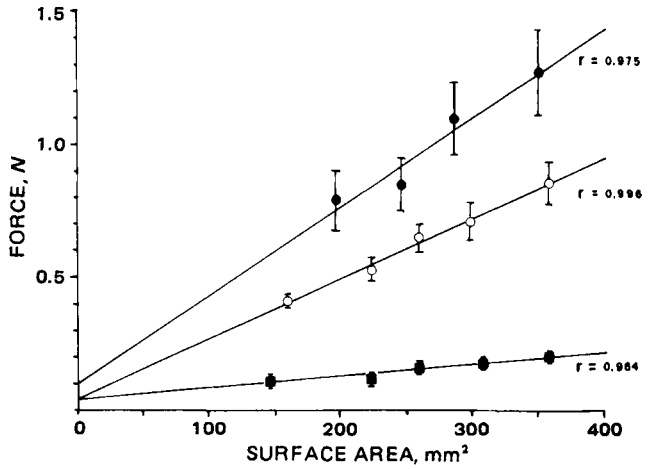

Figure 4—*Effect of surface area of product on the force needed for detachment. Key: (●) hard gelatin capsules, sizes 2, 3, 4, and 5: (○) placebo tablets, diameter 7, 9, 10, 11, and 12 mm; (■) potassium chloride tablets, diameter 7, 9, 10, 11, and 12 mm. Each point represents mean* ±SEM, n = *20.*

Fig. 3, no clear linear or exponential correlation between force and time was noted. In subsequent experiments, an interval of 2 min was usually used. Because of disintegration, hard gelatin capsules could not be left in the esophagus for longer than 2 min. For the same reason, the longest time in experiments using tablets was 3 min.

The results pertaining to the effect of surface area of product on the force exerted for detachment are shown in Fig. 4 and Table II. The forces for gelatin capsules larger than size 2 could not be measured, because the esophageal mucosa became detached from the preparation if forces greater than 1.5 N had to be used. As can be seen from Fig. 4, a significant (p = 0.05–0.001) linear correlation between force and area exists for every product. The force per unit of surface area appears independent of product size (Table II). The intercepts from extrapolation of the lines in Fig. 4 were 0.04–0.1 N. These can be regarded as the magnitudes of force needed to pull the products out of the esophagus, even though they are not adhering.

Three different sizes of placebo tablets (diameters 9, 11, and 12 mm), identical sizes of potassium chloride tablets, two different capsule sizes (2 and 4) and sugar-coated tablets were tested using identical procedures and organ baths I and II (n = 20). No statistically significant differences in results were observed. However, the classic organ bath for isolated preparations (I) was a little easier to handle. This is why most results in the present study were obtained with organ bath I.

Table III—Effect of Washing on Force Needed to Detach the Placebo Tablets from the Isolated Esophagus [a]

Diameter, mm	Force Without Washing, N, mean ± *SD* n = 20	Force after Washing with 5 ml Water, N, mean ± *SD* n = 10
10	0.65 ± 0.23	0.19 ± 0.07
11	0.71 ± 0.30	0.20 ± 0.04
12	0.86 ± 0.34	0.33 ± 0.09

[a] Student's t test; $p < 0.001$.

Table IV—Force Needed to Detach Doxycycline Products from the Isolated Swine Esophagus [a]

Product	Diameter, mm	Force, N, mean ± *SD*	n	t test[b]
Tablet A	9	0.29 ± 0.07	12	
Tablet B	9	0.27 ± 0.05	6	NS
Tablet C	9	0.30 ± 0.08	6	NS
Tablet D	10	0.58 ± 0.15	6	b
Tablet E	10	0.78 ± 0.22	6	b
Capsule F	(size 3)	1.21 ± 0.25	8	b
Tablet G	9	0.17 ± 0.04	8	b
Tablet H	10	0.16 ± 0.05	8	b

[a] Interval between administration and start of detachment was 2 min. [b] Student's t test comparison with Tablet A; $p < 0.001$. NS = not significant.

The effect of washing on adherence was tested using organ bath II. The preparation was washed with 5 ml of water immediately after administration of the drug. The results are shown in Table III. After washing, the force needed for detachment was only about 30% of that without washing.

Doxycycline has caused most of the reported drug-induced injuries to the esophagus (3, 11). The adherence properties of all doxycycline products at present being marketed in Finland were therfore studied. In addition, two experimental formulations of doxycycline were included in the study. As can be seen from Table IV, there were significant differences between the products. Hard gelatin capsules required the most force to dislodge. In addition, the forces for detachment of experimental formulations G and H were significantly lower than those for the best commercially available products.

In the present study about 60 esophageal preparations from 30 different pigs were used, but no marked interindividual variation was observed. The same preparation could be used for 20–30 consecutive measurements without excessive variation in results. If the mucosa was washed, 50–60 measurements with the same preparation were possible. In the experiments, esophagi stored at 4° in Tyrode solution for 24 hr as well as fresh esophagi were used, but no significant differences between the two were noted. The effect of possible spontaneous esophageal contractions on the detaching force was eliminated by using a large number of n-values (usually $n = 20$).

As can be seen from Figs. 3–4 and Table IV there were significant differences in the tendency for adherence, as between pharmaceutical formulations. The adherent tendency of uncoated potassium chloride tablets and sugar-coated tablets was only about 15–20% that of gelatin capsules. Thus, it is reasonable to try to develop drug products with less tendency to adhere. Large sizes should be avoided, especially in the case of drugs that are known to cause esophageal stricture or ulceration.

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ACKNOWLEDGMENTS

Presented in part at 41st International Congress of Pharmaceutical Sciences (FIP), Vienna, September 1981.

Supported by a grant from the National Research Council for Medical Sciences in Finland.

The authors wish to thank the staff of the Helsinki City Abattoir for their assistance.

Erythrocyte Changes in Aqueous Polyethylene Glycol Solutions Containing Sodium Chloride

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Abstract □ The behavior of rabbit erythrocytes in aqueous solutions of polyethylene glycol 300 (I) and polyethylene glycol 400 (II) containing sodium chloride was investigated during 2–120 min incubation at 37°. No hemolysis was found in I (0–10.1%) and II (0–12.9%) solutions in the presence of sodium chloride (0.45–1.35%), but prelytic potassium ion loss and changes in the appearance of the erythrocytes proceeded with the passage of time. The potassium ion loss increased with increasing concentration of polyethylene glycol and/or sodium chloride. The mean cellular volume of erythrocytes decreased temporarily (during the first 2 min) in both I (6.7%) and II (8.6%) solutions containing sodium chloride (0.68–1.35%), and then increased progressively to the same value as that determined by solution of sodium chloride at the same concentration but without polyethylene glycol (~30 and 120 min in I and II solutions, respectively). Both I (10.1%) and II (12.9%) induced a stomatocytic transformation of erythrocytes, but at the higher concentrations (0.9–1.35%) of sodium chloride, II accelerated the progress of spontaneous transformation to echinocytes. The results indicate that these solutions were not isotonic with rabbit erythrocytes.

Keyphrases □ Erythrocytes—changes in aqueous polyethylene glycol solutions, sodium chloride □ Sodium chloride—erythrocyte changes in aqueous polyethylene glycol solutions □ Polyethylene glycol—aqueous solutions containing sodium chloride, erythrocyte changes

The hemolysis of rabbit and human erythrocytes occurs in polyethylene glycol even at iso-osmotic concentrations, while the hemolysis is almost completely inhibited in the presence of a suitable amount of sodium chloride (1, 2). However, little is known about the retention of the normal characteristics of erythrocytes in polyethylene glycol solutions containing sodium chloride.

The experiments described deal with the quantitative variations of hemolysis, potassium ion loss, mean cellular volume, and shape of rabbit erythrocytes produced in aqueous polyethylene glycol 300 (I) and polyethylene glycol 400 (II) solutions with reduced sodium chloride content.

EXPERIMENTAL

Materials—Polyethylene glycol 300[1] and 400[1] in reagent grade were used without further purification. All other reagents and chemicals used were reagent grade or high purity.

Preparation of Solutions—The polyethylene glycol and sodium chloride solutions were weight-in-volume percentage preparations, and were adjusted to pH 7.4 by addition of 3 N HCl. Iso-osmotic concentration of polyethylene glycol was estimated by the freezing point depression data.

Preparation of Erythrocyte Suspension—Fresh rabbit (albino) erythrocytes, using heparin (100 U/ml of blood) as an anticoagulant re-

[1] Wako Pure Chemical Industries, Ltd., Osaka, Japan.

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