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Adherence of various oral dosage forms to the esophagus

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Summary

The potential for various tablets and capsules to adhere to the esophagus or gastrointestinal tract was evaluated in the isolated dog and swine esophagus, using a modification of the procedure of Marvola et al. (1982), in which the swine esophagus was used. The utility of the dog model was demonstrated by showing that comparable adherence values were obtained when the same products were tested in both dog and swine esophagus, and by confirming in the dog model the main findings of Marvola et al. that: (1) force of adherence to the esophagus depends on the type of product, ranking from the greatest to least adherence—hard gelatin capsules, film-coated tablets, uncoated tablets, sugar-coated tablets; (2) for a given product type, adherence increases in proportion to size; and (3) increasing the amount of fluid in the esophagus decreases adherence.

The adherence forces of OROS osmotic systems were the lowest of the film-coated products tested. The adherence force of the OROS system lacking an overcoat of hydroxypropyl methyl cellulose (HPMC) was comparable to the negative control salt tablet, while that of the OROS system containing an HPMC overcoat was slightly higher, but still only about one-quarter of that of the commercial gelatin capsules tested. Additionally, the adherence force of the HPMC-coated OROS system was reduced by increasing fluid in the esophagus, simulating the ingestion of a small

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quantity of water with the system. The HPMC overcoating was removed within 10 min when the system was placed in Ringer's solution at 37°C to simulate the moist conditions in the gastrointestinal (G.I.) tract. Thereafter, adherence of the presoaked systems to the isolated esophageal mucosa was minimal. The results of these studies suggest that OROS osmotic systems such as OSMOSIN have very low adhesiveness relative to many other commercial products.

Introduction

In oral dosage form design, significant effort has been expended over the past several years to achieve prolonged residence time in the upper gastrointestinal (G.I.) tract in the hope of promoting drug absorption. One technique has been based on the development of polymer systems that adhere to the G.I. lining as proposed by Park and Robinson (1982; 1984). Such adherence, however, may cause problems if the drug released is locally irritating to mucosa, as reported for various drugs on esophageal tissue by Carlborg (1980) and recently reviewed by Al-Dujaili et al. (1983). Therefore, in designing and evaluating dosage form performance, assessing whether and/or to what extent the form adheres to esophageal or gastrointestinal mucosa can be of critical importance.

In this report, we present studies in which the isolated esophagus procedure of Marvola et al., with minor modifications, was used to evaluate the adhesiveness of various tablets and capsules, including rate-controlled dosage forms. While the isolated organ does not exactly reproduce the in vivo condition, the literature indicates that use of this model provides a good indication of the relative tendency of various products to adhere to mucosa in vivo.

Materials and Methods

Test products

The drug products tested consisted of 16 capsules and uncoated and coated tablets in a wide range of sizes, described in Table 1.

Isolated esophagus preparation

Dog esophagi were obtained from 10–20 kg animals that had been anesthetized with sodium pentobarbital for an experimental procedure not involving the esophagus. Esophagi from 100 kg swine were obtained from a slaughterhouse. Esophagi were removed and placed in cold Tyrode's solution immediately after death of the animals and were used within 30 h.

The method of Marvola et al. (1982) was used, with a modification that permitted direct recording of the force required to remove the products from the mucosa. As illustrated in Fig. 1, a 6–8 cm section of esophagus was mounted in an organ bath containing oxygenated Tyrode's solution maintained at 37°C by circulation through

TABLE 1

ADHERENCE OF VARIOUS ORAL DOSAGE FORMS IN THE ISOLATED DOG ESOPHAGUS

Type of product	Product name	Manufacturer	Shape	Size	Detachment force (g) [a]	n [b]
Uncoated tablet	Negative control (salt tablet)	ALZA	round	8 mm	10 ± 1	54
	Thermotab	Beecham	round	11 mm	25 ± 5	28
	Yeast	Squibb	round, thick	11 mm	169 ± 25	8
Sugar-coated tablets	Estinyl	Schering	round	8 mm	[c]	
	Cafergot	Sandoz	round	10 mm	5 ± 1	21
Film-coated tablets	OSMOSIN system	Merck Sharp & Dohme	round	8 mm	55 ± 4	52
	OROS push-pull system	ALZA	round	10 mm	9 ± 2	30
	Oyster shell calcium	Rexall	round	11 mm	162 ± 24	20
	Klotrix	Mead Johnson	round	12 mm	96 ± 11	31
	Erythrocin 250 mg	Abbott	round	13 mm	123 ± 14	26
	Myadec	Parke Davis	oval, thick	10 × 19 mm	162 ± 29	8
	SK-Erythromycin 500 mg	Smith Kline & French	oblong, thick	10 × 19 mm	288 ± 50	5
Hard gelatin capsules	Hispril	Smith Kline & French	capsule	no. 3	162 ± 10	56
	Oruvail	May & Baker	capsule	no. 3	213 ± 21	15
	Vibramycin	Pfizer	capsule	no. 2	219 ± 17	35
	Micro-K Extencaps	A.H. Robins	capsule	no. 0	355 ± 36	14

[a] Mean ± S.E.

[b] n = total number of tests. All products except Estinyl, yeast and SK-Erythromycin were tested in at least two dog esophageal preparations.

[c] Determined in swine esophagus only (see Fig. 3).

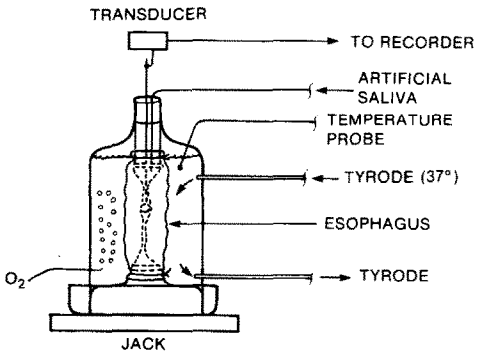

Fig. 1. Apparatus for measuring force of adherence of oral dosage forms in the isolated esophagus.

a water bath. The lumen of the esophagus remained closed except at the points of attachment at each end, and thus did not contact the Tyrode's solution. The organ bath was mounted on a lab jack. A solution [1] based on the composition of dog and human saliva (Dittmer, 1961) was trickled into the esophagus through a small tube at a rate of 1 ml/min, unless otherwise specified. For convenience we refer to this solution as artificial saliva, even though it lacked mucin and certain other known constituents of saliva. The test product was attached to a wire and placed within the section of esophagus. The other end of the wire was mounted above the esophagus on a force-displacement transducer (Model FTO3C, Grass Instruments, Quincy, MA) calibrated with a standard weight and connected to a recorder (Brush 200, Gould, Cleveland, OH). After a specified time, the product was removed from the esophagus by lowering the jack at a constant rate of approximately 1 cm/s, and the detachment force, in grams, was registered on the recorder. The sensitivity of this method was about 5 g, and the practical upper limit about 500 g.

Thirty to 50 tests were run on each esophageal preparation. Each preparation was monitored throughout the testing sequence by observing the adherence of a negative control (uncoated salt tablet, ALZA) and a positive control (no. 3 capsule, Hispril, Smith Kline and French). If the results from these controls did not fall in the usual range, the experiment was terminated.

Experimental design

Esophageal adherence of 15 products comprising primarily commercial tablets and capsules of various sizes was determined in isolated dog esophagus, as shown in Table 1. Each product was placed in the esophagus and allowed to remain in contact with the mucosa for 1 min before the force required to remove it was measured. In addition, to study whether duration of contact with the mucosa influences adherence, HPMC-overcoated OROS systems (OSMOSIN) were allowed to remain in the esophagus for 1, 3 or 5 min before removal. To compare isolated dog esophagus

[1] In mEq/l: NaCl 61, KCl 11, $CaCl_2$ 4, $NaHCO_3$ 45, H_3PO_4 0.2, glucose 1.1, plus 3 g/l bovine serum albumin.

to the swine model, 9 products were tested in esophagi of both animals.

The effect of taking fluid with medication was simulated by increasing the flow of artificial saliva through the isolated dog esophagus, from 1 ml/min to 2, 4 and 8 ml/min (in that order). The esophageal preparation was allowed to equilibrate for 5 min each time the flow rate was increased. Five each of OSMOSIN and Myadec tablets were tested at each flow rate. They were allowed to contact the mucosa for 1 min before removal.

The potential adhesiveness of HPMC-coated tablets after their exposure to a moist environment, like that prevailing in the G.I. tract, was studied by presoaking the OSMOSIN in Ringer's solution—without agitation—at 37°C for periods of 10 min, 1 h, 3 h or 6 h. To test adhesiveness, the presoaked product was placed in the isolated dog esophagus in contact with the mucosa for 1 min before removal.

Results and Discussion

We observed consistent results between esophagi used immediately and those used up to 30 h after removal. Our observations indicate that the artificial saliva trickled into the lumen served to maintain moist conditions while preserving the mucin during several hours of testing. Thus, we feel that this preparation closely resembles conditions in the normal esophagus in vivo.

The detachment forces 1 min after placement in the dog esophagus are shown in Table 1 and Fig. 2 for 15 different products. Because of variability observed between both individual tests and between esophagi, a total of at least 14 tests in at least 2 dog esophageal preparations were conducted for most products. This variability was also described by Marvola et al. (1982).

In general, detachment force was greatest for hard gelatin capsules and intermediate for film-coated products. Within the film-coated group, the OROS push-pull systems exhibited minimal adherence to the esophageal mucosa. These systems had a semipermeable membrane, but not an HPMC color overcoat. Other products showing minimal adherence values were sugar-coated tablets (e.g. Cafergot) and certain uncoated tablets (e.g. salt tablet and Thermotab).

The highest detachment forces were seen with Micro K Extencaps. In some tests a force greater than 500 g—sufficient to suspend the entire preparation from its platform—did not dislodge this product. When this happened, or in tests where the capsule or wire broke, the maximum force recorded was taken as the detachment force. Therefore, the actual adherence force for products in the upper range may be higher than indicated by the mean values in this study.

The results in swine (Fig. 3) were generally comparable to those in the dog. Minor differences in relative adherence values may be attributed to the smaller number of tests done in the swine esophagus.

Our data are in good agreement with the published results of Marvola's group (Marvola, 1982; Marvola et al., 1982, 1983). They found that the relative force of adherence generally ranked hard gelatin capsules > film coated tablets > uncoated tablets > sugar-coated tablets; adherence increased in proportion to product size.

Uncoated salt tablets were used as negative controls in our studies on the basis of their reported low adherence values. Our studies confirmed these results. Many commercial salt tablets and capsules, however—such as the potassium formulations tested in this study and by Marvola et al. (1983)—have a greater tendency to adhere to esophageal mucosa.

The OROS elementary osmotic pump and push-pull osmotic pump are oral dosage forms in which the rate of drug delivery to the G.I. tract is osmotically controlled (Theeuwes, 1981). In each, the tablet-shaped system containing drug and osmotic agent is coated with a semipermeable membrane, and may, as in the case of the OSMOSIN product, have an additional overcoat of HPMC. The HPMC coating becomes tacky when exposed to moisture, but dissolves within a few minutes. In the swine esophagus, Marvola et al. demonstrated moderate adherence of HPMC-coated tablets, compared with other formulations, such as hard gelatin capsules, and adherence increased in proportion to product size (Marvola 1982; Marvola et al.,

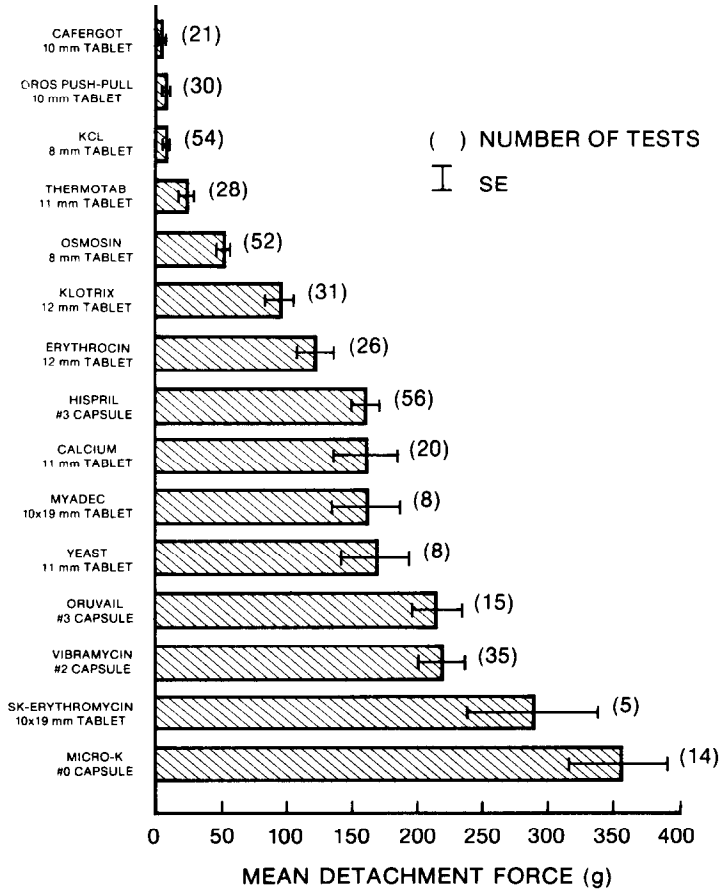

Fig. 2. Adherence of various oral products in the isolated dog esophagus 1 min after placement. All products except yeasts and SK-Erythromycin were tested in at least two preparations.

1983). Adherence force is undoubtedly also proportional to the quantity of water-soluble polymer (HPMC or gelatin) present, since it is the polymer that goes through a tacky phase. The quantity of polymer on HPMC-coated tablets (e.g. OSMOSIN) is approximately 3 mg, while gelatin capsules generally have ten times this quantity of polymer.

The possibility that OSMOSIN may stick in the gastrointestinal tract, exposing a small area of mucosa to high concentrations of drug and salt, has been raised by Beckett and refuted by Davis and his colleagues in a recent series of letters (Beckett, 1983a, b and c; Wilson et al., 1983). Florence et al. (1983) have reported that in their test OSMOSIN had a greater tendency to adhere to swine esophageal mucosa ex vivo than other products tested. However, in their brief report only OSMOSIN is discussed, and the comparative data are not provided.

In our studies, the adherence value for the OSMOSIN product was in the lower 15th percentile of the test range, and was similar to the adherence values for 7- and 9-mm HPMC-coated tablets reported by Marvola's group (Marvola, 1982; Marvola et al., 1982). Adherence of the OSMOSIN product did not change when the mucosal

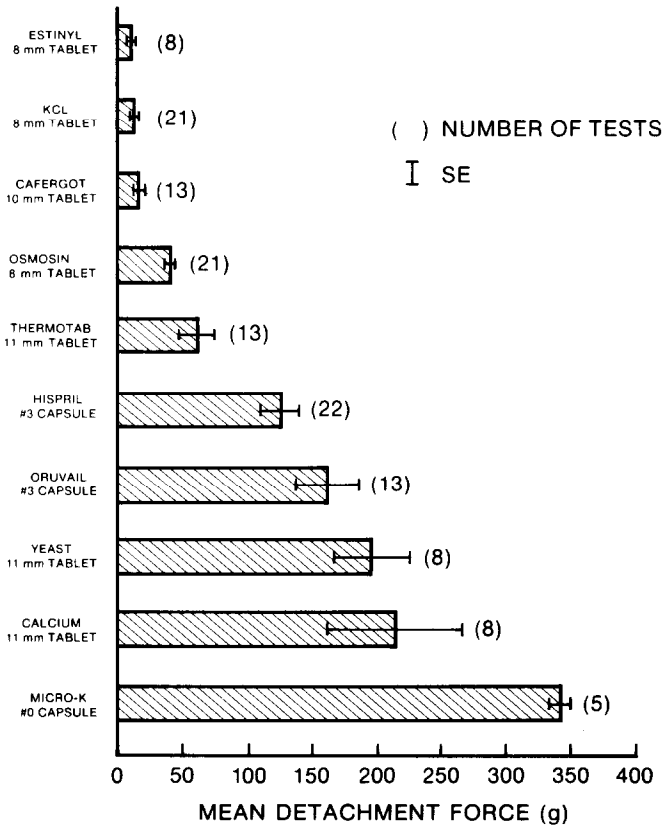

Fig. 3. Adherence of various oral products in the isolated swine esophagus 1 min after placement. Products were tested in 1–3 preparations.

TABLE 2

EFFECT OF MUCOSAL CONTACT TIME ON THE FORCE OF ADHERENCE OF THE OSMOSIN SYSTEM IN THE ISOLATED DOG ESOPHAGUS

Contact time (min)	Detachment force (g)		n
	Mean	S.E.	
1	43	4	22
3	48	4	16
5	53	6	22

contact time was varied between 1 and 5 min (Table 2). Marvola et al. (1982) also reported that detachment force of HPMC-coated tablets, as well as other products, was independent of mucosal contact time.

Fig. 4 shows that increasing the flow rate of artificial saliva in a dog esophagus decreased the 1-min force of adherence of two film-coated products, OSMOSIN and Myadec tablets. Adherence of the OSMOSIN system dropped to near background level at a flow of 8 ml/min (total of 8 ml in the 1-min test, which should be comparable to taking the tablet with 1 or 2 swallows of water). These results confirm those of Marvola, who found that increasing the fluid in the isolated esophagus decreased the adherence of all types of products (Marvola, 1982; Marvola et al., 1982).

Presoaking the OSMOSIN for 10 min with no agitation effectively removed the HPMC color overcoat. These results suggest that in clinical use, the HPMC is likely to be removed within minutes after the product reaches the upper G.I. tract where fluid is plentiful. The adhesiveness of the systems after removal of the overcoat, as estimated in the 1-min esophageal adherence test, dropped to the minimum within 10 min of presoaking and remained at the minimal level throughout the 6-h study period (Table 3).

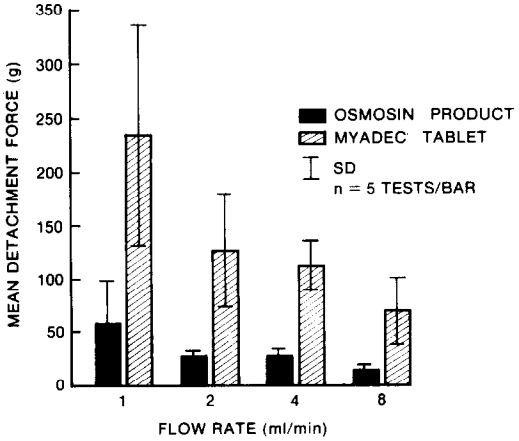

Fig. 4. The effect of increasing the rate of saliva flow in an isolated dog esophagus on the adherence of two film-coated products 1 min after placement.

TABLE 3

ESOPHAGEAL ADHERENCE OF OSMOSIN SYSTEMS[a] PRESOAKED IN RINGER'S SOLUTION TO SIMULATE MOIST CONDITIONS IN THE GASTROINTESTINAL TRACT

Presoak time	Detachment force (g)		n
	Mean	S.E.	
0	43	4	22
10 min	10	1	14
1 h	8	1	14
3 h	5	1	6
6 h	3	1	6

[a] 1-min contact in isolated dog esophagus.

Conclusions

Our results support the following conclusions.

(1) The isolated dog esophagus is comparable to the swine esophagus model of Marvola et al. (Marvola, 1982; Marvola et al., 1982).

(2) Esophageal force of adherence of different types of products varies, depending partly on the amount of water-soluble polymer on the product's surface. In general, the adherence of hard gelatin capsules > film-coated tablets > sugar-coated tablets > uncoated tablets.

(3) Adherence increases with increasing size of tablets and capsules.

(4) The force of adherence of the HPMC-coated OROS osmotic systems, including OSMOSIN, to the esophageal wall is about an order of magnitude lower than that of the commercial gelatin capsules tested and is about the same as commercial film-coated tablets. It decreases further by another order of magnitude after the HPMC color overcoat dissolves. In clinical use, the HPMC color overcoat of the OSMOSIN product is likely to be removed within minutes after the product enters the G.I. tract.

(5) In this ex vivo test, the OROS push-pull system without HPMC overcoat, and the OSMOSIN after dissolution of the overcoat, have minimal adhesive qualities, compared with all other products tested.

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