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Effect of Dosage Form and Formulation Factors on the Adherence of Drugs to the Esophagus

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Abstract □ In recent years, many case reports concerning esophageal injuries caused by drugs have been published. The primary cause has apparently been the adherence of the drug product to the esophagus. In the present study, the adherent tendency of a number of types of tablets and capsules were tested *in vitro* using a recently developed isolated porcine esophagus preparation. The results showed that the tendency of products to adhere to the esophageal mucosa can be modified to a great extent by shape and formulation. Products with low adherence can be obtained by film coating with aqueous dispersions or by sugarcoating. In contrast, gelatin capsules and some cellulose films appear to have a high tendency to adhere to the esophagus.

Keyphrases □ Tablet coatings—effect on adherence, isolated porcine esophagus, potassium chloride □ Potassium chloride—adherence to isolated porcine esophagus, effect of tablet shape, formulation, and coatings □ Drug formulations—effect of additives and coatings on adherence, isolated porcine esophagus

In recent years, many reports concerning esophageal injuries caused by drugs (*e.g.*, doxycycline, emepronium bromide, and potassium chloride) have been published (1–9). The primary cause has apparently been adherence of the drug product to the esophageal mucosa. The tendency to adhere has obviously been greatest for hard gelatin capsules, but differences between various tablet formulations have also been evident. In a previous paper, a study of the tendency of drug products to adhere to the esophageal wall, using the isolated porcine esophagus, was published (10). In the present investigation the effect of the pharmaceutical characteristics of dosage forms on the adherence was studied.

EXPERIMENTAL

Isolated Esophagus Preparation—The isolated porcine esophagus preparation and its usefulness has been described previously (10). Pigs of both sexes were of the Landrace or Yorkshire breeds, weighing 90–100 kg. Immediately after slaughter, the esophagi were removed and transported to the laboratory in Tyrode's solution. Segments (6–7 cm long) were cut from the esophagus and mounted in a classic organ bath for isolated preparations.

Recording of Adherence—A hole was drilled in the products to be tested. The product was attached to a copper wire and placed in the esophageal preparation for 2.0 min (gelatin capsules, 1.0 min). The force needed to detach the product was then measured using a modified prescription balance (10); the force used was taken as a measure of adherence.

Drug Products—Hard gelatin capsules[1] sizes 1, 2, 3, 4, and 5 were filled with lactose. Oval soft gelatin capsules[2] (length 12 or 15 mm) were left empty. The round soft gelatin capsule formulation studied was a commercially available product[3] (diameter 7 mm). The uncoated placebo tablets were compressed from a mixture of basic granules (96%), talc (3%), and magnesium stearate (1%). The basic granules contained 78% lactose, 19% cornstarch, and 3% gelatin. Potassium chloride tablets were compressed from pure potassium chloride. To obtain products with low adherent properties metal tablets were compressed from an alloy of bismuth, lead, tin, and cadmium (5:3:1:1). The shapes, diameters, and areas of all formulations are given in Tables I–III.

The sugar-coated tablets were all commercially available products[3]. The coating suspension used contained 47 g of sucrose, 4 g of polyethylene glycol 6000, 8 g of calcium sulfate, 2 g of titanium dioxide, 30 g of purified water, and 3 g of other ingredients. The dusting powder contained calcium sulfate and talc (1:1). The coating suspension and powder were used in an approximate ratio of 9:5.

To investigate the effect of film coatings on the adherence of drugs to the esophagus, biconvex tablets were coated with different film coatings. The compositions of the hydroxypropyl methyl cellulose-containing solutions (I–V) are given in Table I. The other coating solutions were as follows: VI, 10.0 g of cellulose acetate phthalate, 0.5 g of castor oil, and 89.5 g of acetone; VII, 14.0 g of polyethylene glycol 6000, 6.0 g of cellulose acetate phthalate, 1.0 g of stearic acid, 0.3 g of castor oil, 0.3 g of sorbitan

[1] Capsugel AG, Switzerland and Eli Lilly and Co.
[2] R. P. Scherer Ltd, England.
[3] Orion Pharmaceutical Co, Finland.

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Table I—Compositions of Coating Solutions I–V

Ingredient	Amount in the Coating Solution, g I	II	III	IV	V
Hydroxypropyl methyl cellulose	7	5	6	6	7
Titanium dioxide	—	3	—	—	7
Talc	—	1	—	—	—
Sucrose	—	—	8	—	—
Lactose	—	—	—	8	—
Ethyl cellulose pseudolatex[a]	—	—	—	—	22
Triacetin	—	—	—	—	1
Purified water	—	—	66	66	63
Ethyl alcohol	68	71	20	20	—
Methylene chloride	25	20	—	—	—

[a] Aquacoat ECD-30; FMC Corp.

Table II—Effect of Tablet Shape on the Force Needed to Detach the Product from the Isolated Esophagus

Formulation	Force per Unit Area[a], $mN \cdot mm^{-2}$ Biconvex Tablets	Flat Tablets[b]	Capsule-Shaped Tablets[b]
Uncoated placebo	2.40 ± 0.72	2.92 ± 0.88*	1.77 ± 0.53**
Potassium chloride	0.56 ± 0.11	0.64 ± 0.13*	0.41 ± 0.09***
Metal	0.56 ± 0.08	0.66 ± 0.10***	0.44 ± 0.09***

[a] Means ± *SD*; $n = 20$. [b] Student's t test, compared with the corresponding value of the biconvex tablets: (*) $p < 0.05$, (**) $p < 0.01$, (***) $p < 0.001$.

Table III—Effect of Tablet Coatings on the Force Needed to Detach the Tablets from the Isolated Esophagus

Tablet Coating	Diameter, mm	Area, mm^2	Detaching Force[a], N	Force per Unit Area, $mN \cdot mm^{-2}$
Uncoated	7	160	0.41 ± 0.08	2.56
	9	223	0.53 ± 0.08	2.38
	10	259	0.65 ± 0.22	2.51
	11	299	0.71 ± 0.21	2.37
	12	358	0.86 ± 0.26	2.40
Sugarcoated	6	101	0.08 ± 0.02	0.65
	8	190	0.13 ± 0.03	0.68
	10	277	0.16 ± 0.02	0.58
Film coating I	9	226	0.55 ± 0.18	2.43
	11	350	0.64 ± 0.27	1.83
Film coating II	9	316	0.79 ± 0.20	2.50
	11	350	0.93 ± 0.20	2.66
Film coating III	7	127	0.20 ± 0.04	1.57
	9	240	0.33 ± 0.10	1.38
	11	336	0.47 ± 0.13	1.40
Film coating IV	7	127	0.38 ± 0.14	2.99
	9	209	0.55 ± 0.20	2.63
	11	316	0.78 ± 0.32	2.47
Film coating V	11	298	0.31 ± 0.08	1.04
Film coating VI	11	329	0.39 ± 0.15	1.19
Film coating VII	11	299	0.91 ± 0.24	3.04
Film coating VIII	12	379	0.31 ± 0.08	0.82
Film coating IX	10	259	0.18 ± 0.09	0.69
Film coating X	9	214	0.24 ± 0.05	1.12

[a] Mean ± *SD*; $n = 20$.

monooleate, 12.0 g of ethyl alcohol, and 64.0 g of acetone; VIII, 4.2 g of shellac, 1.4 g of polyethylene glycol 6000, 12.6 g of titanium dioxide, 4.2 g of talc, 1.4 g of povidone, 1.4 g of sorbitan monooleate, 4.2 g of iron oxide, and 40.6 g of isopropyl alcohol; and IX, 16.7 g of methacrylate copolymer[4], 8.0 g of talc, 3.5 g of titanium dioxide, 1.5 g of iron oxide, 0.5 g of hydroxypropyl methyl cellulose, and 68.3 g of purified water. In addition, a placebo product coated with a copolymer of vinyl acetate and crotonic acid[5] (X) was investigated. The product was supplied by the manufacturer.

In the final part of the present study, 10 commercially available potassium chloride products were studied. The coatings of these products are described on the basis of information given by the manufacturers or their Finnish agents.

[4] Eudragit E 30 D; Röhm Pharma, West Germany.
[5] BASF CE 5142; BASF, West Germany.

Table IV—Effect of Material, Size, and Shape of Gelatin Capsules on the Force Needed to Detach the Products from the Isolated Esophagus

Formulation	Area, mm^2	Detaching Force[a], N	Force per Unit Area, $mN \cdot mm^{-2}$
Hard gelatin capsule			
No. 2	330	1.30 ± 0.31	3.94
No. 3	283	1.10 ± 0.28	3.89
No. 4	220	0.85 ± 0.18	3.86
No. 5	160	0.64 ± 0.20	3.88
Oval soft gelatin capsule			
Length 15 mm	350	0.88 ± 0.27	2.51
Length 12 mm	268	0.80 ± 0.25	2.99
Round soft gelatin capsule (7 mm)	154	0.39 ± 0.14	2.53

[a] Mean ± *SD*; $n = 15$.

RESULTS AND DISCUSSION

The effect of shape on the force needed to detach the products from the isolated porcine esophagus is shown in Table II. Detachment force was greatest for flat tablets and lowest for capsule-shaped tablets. Capsule-shaped tablets may therefore be preferable for drugs known to cause esophageal ulceration.

The adherence of biconvex tablets of different surface areas and coatings is shown in Table III; the same data for various gelatin capsules are shown in Table IV. There were no significant differences in adherence to the esophagus between the hard gelatin capsules made by the two different manufacturers.

As the results show, the tendency to adhere was greatest for hard gelatin capsules. Calculated per unit area, it was six times as high as that for sugarcoated tablets, which had the lowest tendency to adhere. The force needed to detach the soft gelatin capsules was significantly lower than that for the hard gelatin capsules. However, soft gelatin capsules seemed to stick to the esophagus to the same degree as the most adherent tablet formulations in this study.

If the specific adherence of the film coatings is examined, it can be seen that the very common coating material hydroxypropyl methyl cellulose (I) belongs to the middle group of all formulations studied. The tendency of the hydroxypropyl methyl cellulose film to adhere could be adjusted by the use of additives. If sucrose (III) was added, the adherent tendency decreased significantly. The mixture of hydroxypropyl methyl cellulose and ethyl cellulose pseudolatex (V) led to a still lower adherence. In contrast, the addition of lactose (IV) or titanium dioxide and talc (II) increased the tendency to stick.

The common enteric coating cellulose acetate phthalate film (VI) had a fairly low adherent tendency, as did the coatings of shellac (VIII), methacrylate copolymer (IX), and the copolymer of vinyl acetate and crotonic acid (X). When polyethylene glycol 6000 (VII) was used as the main film-forming material, the adherence was, in contrast, considerable.

The results relating to the uncoated placebo tablets should not be interpreted as indicating that the adherent tendency of uncoated tablets is always high. The conclusion relates to the present situation in which tablets were compressed from granules containing lactose and cornstarch. Previous results have shown, however, that uncoated tablets containing other ingredients can have a very low tendency to adhere to the isolated esophagus (10).

The forces needed to detach the commercially available potassium chloride products from the esophagus are shown in Table V. Adherence of the worst formulation was ~3.2 times as great as that of the best formulation. The forces per unit area in Table V are in good agreement with the results in Table III. Sugarcoated tablets had a low adherent tendency, and the specific adherence of the hydroxypropyl methyl cellulose films were 2.1–2.4 $mN \cdot mm^{-2}$ as compared with 1.8–2.4 $mN \cdot mm^{-2}$ in Table III. It is noteworthy that the adherence of hydroxypropyl methyl cellulose decreased as a consequence of adding silicic acid. Ethyl cellulose seemed to have fairly substantial adherent properties.

Although gelatin capsules appeared to have the greatest tendency to adhere to the isolated porcine esophagus, the present results show that many tablet formulations could have a similar tendency to adhere. However, by selecting a proper coating material this tendency can be diminished. The classic sugarcoating seems to be a good choice in this respect. The addition of sucrose to film coatings also reduces adherence. Film coating with aqueous dispersions (IX and V) also results in products

Table V—Force Needed to Detach the Commercially Available Potassium Chloride Formulations from the Isolated Porcine Esophagus

Drug Product	Amount of Potassium Chloride, g	Coating Material	Detaching Force[a], N	Mean Force per Unit Area, $mN \cdot mm^{-2}$
A	1.0	Polyvinyl chloride; sucrose crystals	0.38 ± 0.03	0.9
B	0.6	Sugarcoating	0.39 ± 0.01	0.9
C	1.0	Hydroxypropyl methyl cellulose; silicic acid	0.54 ± 0.04	1.1
D	0.5	Hydroxypropyl methyl cellulose	0.78 ± 0.06	2.4
E	0.75	Hydroxypropyl cellulose	0.93 ± 0.09	2.6
F	0.75	Hydroxypropyl methyl cellulose	0.94 ± 0.12	2.2
G	1.0	Hydroxypropyl methyl cellulose	0.98 ± 0.13	2.1
H	0.75	Special wax; talc	1.00 ± 0.11	2.8
I	1.0	Special wax; talc	1.10 ± 0.13	2.4
J	0.75	Ethyl cellulose	1.20 ± 0.10	2.2

[a] Mean ± *SD*; $n = 18$.

with low adherence. In contrast, sparingly water-soluble ingredients (talc, titanium dioxide, and ethyl cellulose) and, in addition, lactose, mostly increase adherence.

On the basis of this research it seems possible to develop pharmaceutical products having a very low tendency to adhere to the esophageal mucosa. It seems desirable to develop such products in the case of drugs known to cause esophageal strictures or ulcerations, in particular.

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High-Performance Liquid Chromatographic Analysis of Iodochlorohydroxyquin and Hydrocortisone in Ointments and Creams

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Abstract □ A simple isocratic, high-performance liquid chromatographic (HPLC) assay procedure was developed for the simultaneous determination of iodochlorhydroxyquin and hydrocortisone in ointments and creams using phenyl salicylate as an internal standard. Ointment samples were extracted by direct dissolution in ether. Homogeneous suspensions of the creams were prepared in the mobile phase. The samples were spiked by the addition of standard iodochlorhydroxyquin, standard hydrocortisone, and the internal standard and subsequently extracted with the mobile phase. HPLC was performed using a reverse-phase microparticulate C-18 column, a precolumn, and a UV detector set at 256 nm. A mobile phase containing methanol and 0.05 *M* phosphoric acid (70:30) was employed at a flow rate of 1 ml/min. The percent iodochlorhydroxyquin and hydrocortisone found to be present in eight commercial products is reported.

Keyphrases □ Iodochlorhydroxyquin—simultaneous determination with hydrocortisone, ointment and cream, high-performance liquid chromatography □ Hydrocortisone—simultaneous determination with iodochlorhydroxyquin, ointment and cream, high-performance liquid chromatography □ High-performance liquid chromatography—simultaneous determination of iodochlorhydroxyquin and hydrocortisone, ointment and cream

Iodochlorhydroxyquin (I) is used alone or in combination with hydrocortisone (II) as an antimycotic, antibacterial, and anti-inflammatory agent in topical preparations. Because of its toxicity, several analytical procedures have been developed for the determination of I in biological fluids (1–7). The present pharmacopeial assay method for I in creams or ointments (8, 9) is time consuming, requires heating during the extraction procedures (which can lead to decomposition of I), and involves the use of an IR spectrophotometric assay procedure. Other IR spectrophotometeric procedures specific for I in pharmaceutical products have also been described (10, 11). However, these methods are cumbersome, require a large sample, and involve the use of carbon disulfide in the assay procedure. The pharmacopeial methods for assaying II in creams and ointments (12) depend on the oxidation of the α-ketol side chain by either triphenyltetrazolin chloride or blue tetrazolin. Base concentration, water, air, solvent, and light are known to interfere with color formation in the tetrazolin reaction (13). Excipients that interfere with color formation include sorbitan monooleate, lanolin, and stearic acid (14).

This work describes a high-performance liquid chro-

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