Membrane-Coated Tablets: A System for the Controlled Release of Drugs

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Abstract □ Membrane-coated tablets were developed to provide a dosage form which exhibits zero-order kinetics. The delivery system consisted of a soluble tablet core surrounded by a porous membrane which controls the diffusion rate. In the system studied, the diffusion rate of potassium chloride was found to be more constant than with other controlled-release products and independent of pH changes within the physiological range. The release profile of a drug can be varied by changing the composition of the membrane. Substantial amounts of the active substance can be loaded into membrane-coated tablets. The membrane protects the gastric mucosa from direct contact with the undissolved active substance. This delivery system has a potential for use with all water-soluble agents where a controlled release is desirable.

Keyphrases □ Controlled release of drugs—membrane-coated tablets, zero-order delivery, potassium chloride, potential use for all water-soluble drugs □ Delivery systems—membrane-coated tablets, controlled release, potassium chloride

The concept of the slow release of drugs has attracted much interest, and numerous delivery systems are commercially available. The purpose of these preparations is to release the drug continuously during its passage through the GI tract, thereby giving a constant plasma concentration over a long period of time and possibly reducing side effects. Slow-release delivery would be suitable for drugs with a rapid clearance from plasma or drugs that cause adverse effects locally or systemically. An ideal slow-release preparation depends only on the dissolution rate of the active substance. Factors such as mechanical influence, enzymes, viscosity, surface tension, pH, and salt concentration should not affect the release of the active substance. However, the absorption phase must be completed within 8–10 hr for most drugs to achieve good biological availability (1). Drug dissolution from tablets prepared by a technique called membrane coating, using potassium chloride as a model drug, is described.

Uncoated and enteric-coated potassium chloride tablets cause side effects in the GI tract with a high degree of frequency (2). The only difference between the standard tablets and the enteric-coated ones has been the localization of the ulceration in the gut. Several cases of duodenal ulceration resulting in stenosis of the intestine have been caused by enteric-coated potassium chloride tablets (3, 4).

If potassium chloride is delivered at a constant rate for a longer period of time while in the GI tract, the side effects can be minimized. Newer controlled-release potassium chloride tablets have a slow dissolution rate, which gives

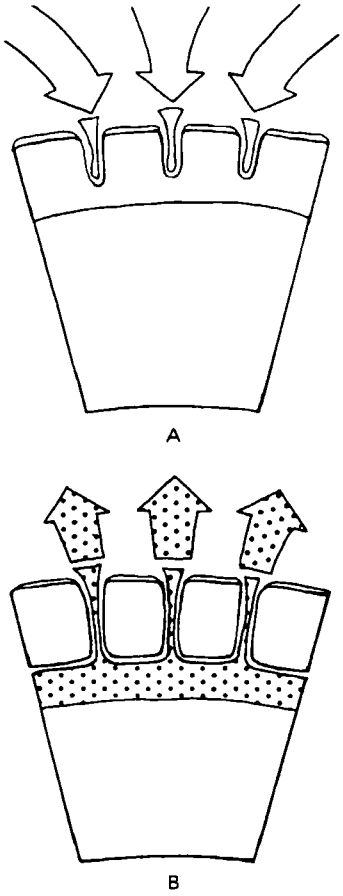

Figure 1—*Segment of membrane-coated tablet (A) liquid penetrating into the membrane, dissolving the sucrose particles and (B) drug solution diffusing through the membrane.*

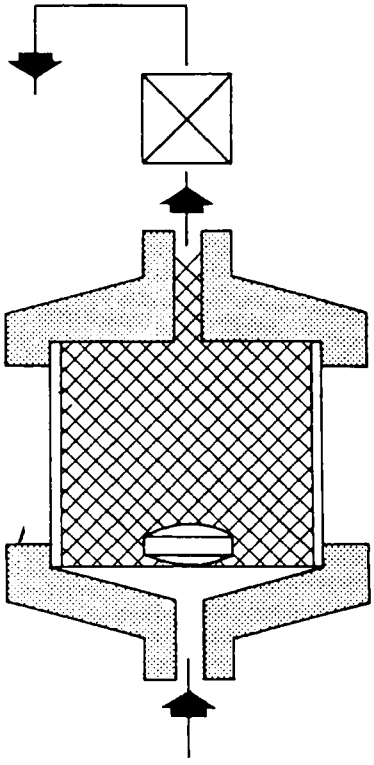

Figure 2—*Sketch of the flow-through cell.*

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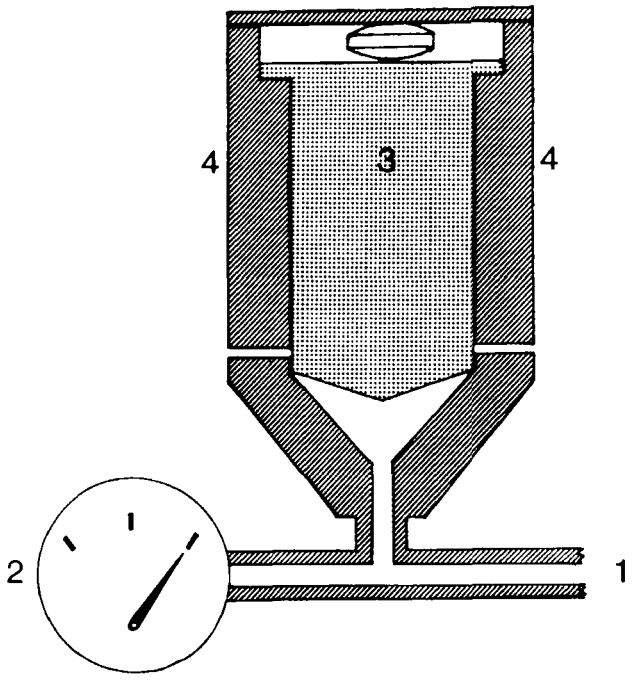


Figure 3—*Sketch of the equipment for testing mechanical resistance of coating shells. Key: (1) air inlet; (2) manometer; (3) plunger; (4) cylinder.*

a considerably lower concentration of the drug in the GI tract and, consequently, a lower frequency of adverse reactions (5, 6). The principle of delivering drugs by solution diffusion through a rate-controlling microporous membrane has been shown earlier to be dependable (7). This report describes a practical way to utilize this technique.

Membrane coating involves coating a tablet with a porous, water-permeable membrane, which is insoluble in the GI tract. The gastric juices penetrate the tablet through the pores and dissolve the drug (Fig. 1).

The following quality controls must be met when choosing a water-insoluble polymer. It must have low toxicity and be unaffected by the GI fluids and by the motility of the intestinal system. It should have good solubility in a nontoxic solvent, appropriate for tablet coating, and give films of good mechanical stability. After testing several different polymers (cellulose derivatives, nylon, and various acrylic polymers) we decided to investigate a polyvinyl chloride plastic. This polymer combines the favorable properties of good mechanical resistance and satisfactory adhesion to the potassium chloride surface of the tablet core.

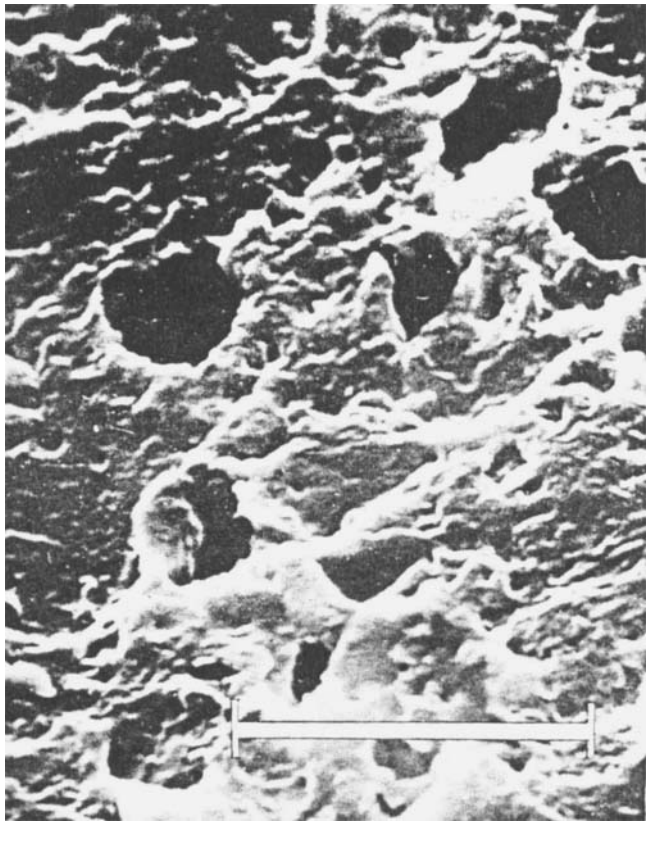
EXPERIMENTAL

Preparation of Tablet Core—Potassium chloride was granulated with a 50% solution of polyvinyl pyrrolidone in ethanol–acetone (1:1). A 32-g volume of the solution was mixed with 1000 g of KCl. The wet granulation was screened through a 0.5–0.7-mm aperture and dried in a forced-air oven at 40° for 2 hr. Circular, biconvex tablets with a 12-mm diameter were compressed to a hardness of 8 kp[1]. The disintegration time in water at 37° was 8 min[2]. The tablet weight was 1016 mg, of which 1000 mg was potassium chloride.

Preparation of Membrane-Coated Tablets—The polymeric film coatings were applied to the tablets in batch sizes of 5000 in a conven-

[1] Tablet hardness tester, Schleuniger & Co., Zürich, Switzerland.
[2] Measured by equipment from Manesty Machines Ltd., Liverpool, England.

A



B

Figure 4—*Scanning electron microphotographs of the membrane coat of potassium chloride tablets: (A) membrane with suspended sucrose crystals and (B) the membrane after dissolution of the crystals. The bar indicates 10 μm.*

Table I—Reproducibility of the Membrane-Coating Process [a]

Batch	Potassium Chloride Released During 1st hr, %	Time for 90% release of Potassium Chloride, hr
A	16.9	5.9 ± 0.6 0.4
B	15.9	5.8 ± 0.8 0.6
C	16.7	5.8 ± 0.6 0.5
D	17.0	6.1 ± 0.8 0.5

[a] Six tablets were analyzed out of each of the four batches, using the rotating-basket method. The values for 90% release also show the two most extreme values obtained in the analysis.

tional 50-cm diameter coating pan without baffles. Coating consisted of 13% w/v polymer[3] in acetone. Because of their high viscosity, it was not possible to use more concentrated solutions. Different amounts of micronized sucrose (particle size <10 μm) was suspended in the polymer solutions. Coating was achieved by spraying the various suspensions on the moving bed of tablets with an airless sprayer[4], using a 0.1-mm nozzle. Spray rate was 30 ml/min. Coating was continued until the weight of the coat on each tablet was 50 mg.

Drug Diffusion Studies—Potassium chloride diffusion from tablets was followed by using the modified beaker method (8, 9), the ascending-column method (10, 11), and the rotating-basket method (USP/NF). Diffusion studies according to the beaker method were performed using 1000 ml of dissolution medium at 37° and a paddle stirrer rotating at 60 rpm. Studies with the rotating-basket method were carried out in a 1000-ml cylindrical vessel at 37° with the tablet held in a 40-mesh stainless steel basket. Rotating speed was 100 rpm. The ascending-column method utilized a flow-through cell 25-mm high with a 14-mm diameter. The tablet was placed on a net at the bottom of the cell (Fig. 2). Fresh dissolution medium (37°) was pumped through the cell at a rate of 40 ml/min, and the concentration of potassium chloride was measured at the outlet every 3rd min. Results obtained by the three methods for determining drug diffusion from membrane-coated tablets showed excellent agreement.

Deionized water was used as the dissolution medium, except in the pH influence studies. In these experiments, artificial gastric juice without pepsin was used according to USP XIII, pH 1.2. Artificial intestinal juice was prepared according to USP XIII, without pancreatin, and potassium

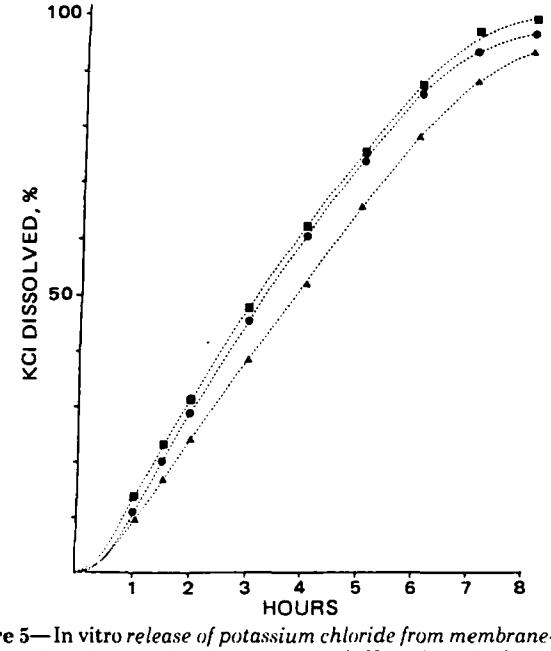


Figure 5—In vitro *release of potassium chloride from membrane-coated tablets using the rotating-basket method. Key: deionized water (●), artificial gastric juice (▲), and artificial intestinal juice (■).*

[3] High purity polyvinyl chloride, Chemoswed Co., Malmö, Sweden.
[4] Nordson Corp., Amherst, Ohio.

Table II—Influence by Membrane Coating Composition on the Release of Potassium Chloride (Rotating-Basket, 37°)

Batch	1	2	3	4
Ratio soluble–insoluble components (w/w)	1.81	2.12	2.57	2.82
Time for 50% dissolution (min)	121	88	64	48

dihydrogen phosphate substituted with sodium dihydrogen phosphate, pH 7.5. Potassium chloride concentrations were determined by conductometry in most experiments. In the pH influence studies, however, atomic absorption spectrometry was used for potassium. Slow-release potassium chloride preparations[5] used in the comparison studies were purchased commercially.

Measurement of Membrane Strength—The mechanical resistance of the membrane coat was measured on empty coating shells after the complete release of potassium chloride. Empty coating shells were obtained by placing membrane-coated potassium chloride tablets in a large volume of distilled water for 24 hr. When the drug was diffused from the tablets and the solid core was replaced with liquid the shells floated and became layered beneath the liquid surface. The visible appearance of the tablets did not change. A tool was developed for checking the mechanical resistance of the membrane-coated shell (Fig. 3). The empty coating shell was compressed in a cylinder by a piston which was regulated by compressed air. The resistance of the coating shell against the movement of the piston was registered by a manometer. Compressed air (8 kg/cm^2) reached the throttle valve and penetrated the cylinder. The piston moved upward and pressed the coating shell against the lid of the cylinder. When the coating shell was compressed or burst, the channels were free and the air escaped. This procedure was recorded by a manometer which showed the pressure of the air in kp/cm^2 at the moment the coating shell burst. The maximal air pressure at the compression represents a measure of the mechanical resistance of the membrane.

RESULTS AND DISCUSSION

Characteristics of the Membrane Coating—The coating consists of a water-insoluble polymer and a dispersed water-soluble pore-creating substance. When a membrane-coated tablet is swallowed, the gastric juice dissolves the pore forming substance (Fig. 1). The structure of the membrane can be seen in Fig. 4, as observed by scanning electron microscopy before and after removal of the water-soluble material.

The amount of residual monomer (vinyl chloride) was determined by GC. The accuracy of the method is ~1 ppm, and our results show that the content of monomer is <1 ppm. The pore-forming substance consists of micronized sucrose, which proved to be ideally suited with regard to toxicity and solubility.

Drug Diffusion Studies—The diffusion of dissolved substances from the tablet through the pores can be calculated by using Fick's first law of diffusion.

$$q = D\,(C_s - C_u)\,\frac{A}{h} \qquad \text{(Eq. 1)}$$

where q is the rate of diffusion, D the diffusion constant, A the surface area, and h the thickness of the diffusion layer.

As long as the membrane coating contains a saturated solution together with solid drug substance the concentration inside the coating shell, C_s, is much higher than the concentration outside the coating shell, C_u. For potassium chloride C_s is ~25%, while C_u in our *in vitro* studies has reached maximally 0.1%. Thus, the diffusion has taken place during sink conditions (which means C_u is negligible compared with C_s) and Eq. 1 is reduced to:

$$q = D\,\frac{C_s}{h}\,A \qquad \text{(Eq. 2)}$$

This implies that the diffusion should proceed at a constant rate (zero-order reaction). At the point where no solid substance is left within the membrane coating, the rate of diffusion declines with decreasing concentration (first-order reaction).

The release pattern of active substance from a membrane-coated tablet is shown in Fig. 5. When the release of potassium chloride begins, the sucrose particles in the membrane are dissolved. The rate increases sharply to a maximum in a few minutes.

Theoretically, 70–80% of the potassium chloride should be released

[5] Kalium-Duretter, 0.75 g, Hässle Sweden (formulation A); Slow-K, 0.6 g, Ciba (formulation B).

Table III—Diffusion of Potassium Chloride During 6 hr from Three Different Formulation Principles

Hours	Percent Released from Tablets[a]		
	Membrane-Coated Tablets	Formulation A	Formulation B
1st	16.7	39.6	32.4
2nd	19.8	17.2	25.5
3rd	17.4	11.3	16.0
4th	15.6	8.7	11.2
5th	13.7	6.7	7.8
6th	10.7	4.9	5.3
Total	93.9	88.4	98.2

[a] The figures given are mean values of six single tablet analyses. Released potassium chloride is expressed as percentage of the total content of the different products. The amounts of potassium chloride were: membrane-coated tablets, 1 g; formulation A, 0.75 g; and formulation B, 0.6 g.

at a constant rate. In practical situations, however, the rate decreases slowly and linearly until ~80% of the content is released. At this point there is no solid potassium chloride left in the shell and the rate accordingly decreases rapidly.

The effect of the dissolution medium pH on the potassium chloride diffusion was studied. Figure 5 shows the release pattern in deionized water, artificial intestinal juice (pH 7.5), and artificial gastric juice (pH 1.2). The three media, which represent the physiological pH range, did not influence the diffusion significantly. As can be seen from Fig. 5, the amount of potassium chloride dissolved in 6 hr varies between 80 and 90%.

The reproducibility of the coating process is high. Table I shows release characteristics of four consecutive batches of membrane-coated potassium chloride tablets. The ratio of soluble components to insoluble polymer in the coating material influences the release rate. The importance of this ratio is evident from the data in Table II. A high ratio of soluble/insoluble components gives a high-porosity coating. This ratio is used to produce tablets with a desired release pattern.

Studies on the Membrane Strength—The main factor influencing shell hardness was found to be the thickness of the membrane. Minor changes from the composition of the membrane given in the *Experimental* section do not significantly alter the mechanical strength of the membrane. The compression resistance of membrane-coated tablets measured according to the method described in the *Experimental* section is ~7 kp. To investigate if this is sufficient for the *in vivo* conditions, a study was performed on the empty shells after passage through the GI tract. One membrane-coated tablet/day was given to ten volunteers during 2 days. The stools were collected and the empty shells were examined for ruptures. No ruptures of the membrane were found. (Tablets of different membrane-coat thickness were prepared for this study and checked for membrane strength, which ranged between 5.2 and 7.2 kp.) This proves that the mechanical stability is sufficient to withstand passage through the human GI tract.

Comparison with Other Controlled-Release Principles Used for Potassium Chloride—The membrane-coated potassium chloride tablet was compared with two commercially available slow-release formulations of potassium chloride. These formulations utilize the so-called embedment principle, which means that potassium chloride is embedded in a carrier substance that either forms an insoluble matrix (formulation A) from which the potassium chloride diffuses (12), or a wax matrix (formulation B) which releases the potassium chloride by a combination of diffusion and erosion. Determinations of potassium chloride have been performed according to the method described in the *Experimental* section (rotating basket, 37°).

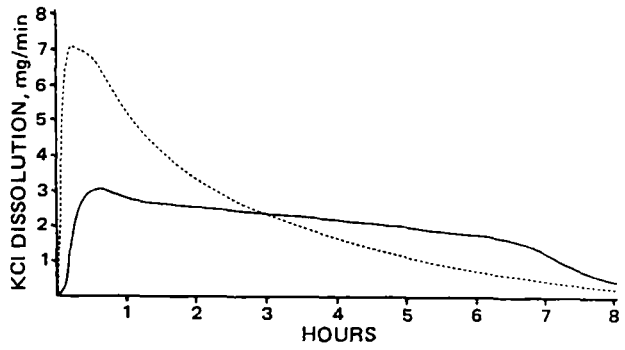


Figure 6—In vitro *release rate of potassium chloride from membrane-coated tablets [1 g (—)] and formulation B [0.6 g (- - - -)]. Data for formulation B have been recalculated in relation to 1 g of KCl.*

As can be seen from Table III, the two commercially available preparations initially released large amounts of active substances. The rate of release then gradually decreased. Membrane-coated tablets, however, gave a slower and more uniform release during the 6-hr period. Figure 6 shows a comparison between membrane-coated tablets and formulation B. An ideal formulation would show a constant diffusion rate, thereby releasing constant amounts of active substance each hour until no more substance remained in the tablet. In the study the membrane-coated tablets have a release pattern that is closer to the ideal situation.

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