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Report

Capsules with Prolonged Action. III. Release of Active Ingredients from Cast Films[1-3]

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In the preceding paper we described a gelation process and the development of sustained-release soft gelatin capsules containing codeine or theophylline. Applying this process to indomethacin and nifedipine as active ingredients led to insufficient release rates of the products. To investigate this phenomenon two simple membrane models were used, i.e., a cast drug-free membrane composed of different ratios of polyethylene glycol 400 in a matrix of 5% ethylcellulose, 10% sesame oil, and 57 to 69% citric acid triethyl ester and a cast drug-containing membrane with the same excipients. Codeine and indomethacin were able to penetrate drug-free membranes. The amount of drug diffused through the membrane correlates with the solubility data. Theophylline, which is insoluble in the matrix system, does not penetrate through a drug-free matrix. Nifedipine is enriched within the matrix because of its high partition coefficient into the matrix material, and therefore, little release is observed. From a drug-containing matrix, theophylline and nifedipine were released according to Higuchi's equation [*J. Pharm. Sci.* 52:1145–1149 (1963)], although the absolute amount of nifedipine released is limited because of its high solubility in the membrane material. For codeine and indomethacin there was no linear relationship between the amount of drug released and the square root of time. These results agree with the findings for capsules obtained from the gelation process.

KEY WORDS: soft gelatin capsules; sustained release; gel formation; ethylcellulose; polyethylene glycol; citric acid triethyl ester; diffusion model.

INTRODUCTION

The preceding paper (1) described the development of a sustained-release soft gelatin capsule based on a gelation process. The release of codeine and theophylline was studied with the USP paddle method. The results gave no information on the mechanism of drug release. When using indomethacin and nifedipine as drugs, it was found that the delivery of both substances was very poor. In order to find the reasons for this phenomenon, two simple membrane models were investigated. The first model consisted of a drug-free membrane that separates a saturated drug solution from a large acceptor compartment. The diffusion coefficients of the drug molecules in the membrane were measured to understand the differences in drug release with the capsule formulations. The physical parameters such as diffusion area and the volumes of donator and acceptor compartments were kept constant to guarantee comparable results. Similar previous experiments (2–5) revealed that a zero-order drug delivery can be obtained if the drug concentration is constant and perfect sink conditions are offered by the acceptor compartment.

The second membrane model uses drug-containing membranes to simulate the drug release from capsule fillings under defined conditions. It was expected that the liberation of the drug follows Eq. (1).

$$Q = [D\,t(2A - C_s)C_s]^{1/2} \quad (1)$$

in which Q is the amount of drug released at time t from a unit area, D is the diffusion constant, A is the amount of drug, and C_s is the solubility of the drug in the dissolution fluid (6). However, the equation is valid only if the membrane structure undergoes no significant alteration during the experiment (6). As known from the capsule formulations, a large amount of the membrane components will be leached out. How this would influence the release kinetics is described here.

MATERIALS AND METHODS

Materials

Ethylcellulose (Ethocel premium grade) with an ethoxyl content of 48.5 to 49.5% was used; the viscosity of a 5% (w/w) solution in toluene–ethanol (80:20, w/w) was 20 cps (Dow Chemical). Sesame oil and polyethylene glycol (PEG) 400 were pharmaceutical grade (Mainland, Hoechst AG, both D-Frankfurt). Citric acid triethyl ester (Citroflex-2),

[1] Part I, *Pharm. Ztg.* (in press); Part II, preceding article in this issue.

[2] Dedicated to Prof. Dr. Elsa Ullmann on the occasion of her 75th birthday.

[3] Part of the thesis of B. Stockebrand, Marburg, 1985.

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99.9%, was obtained from Pfizer-Corp. (D-Wiesbaden). All chemicals for manufacturing artificial gastric and intestinal juice were reagent grade (E. Merck AG, D-Darmstadt). Codeine and theophylline were Ph.Eur. grade (Boehringer Ingelheim, D-Ingelheim). Indomethacin and nifedipine were from R. P.Scherer (D-Eberbach). Filtration of samples was carried out with filtration set GWSP 02500, 0.22 μm (Millipore, D-Eschborn), and 5-ml plastic syringes (B. Braun, D-Melsungen).

Preparation of Membranes

Membranes without drugs were cast (500 mg) on a glass plate previously moistened with a drop of 1,2-propylene glycol. The temperature of the mixture was 50°C. After cooling to room temperature the glass plates were carefully dipped into a petri dish filled with 50 ml of distilled water. While the glass plate sank down, the membrane floated on the water surface and was left there for 3 hr. The hardened membrane was cut into round disks with a diameter of 22 mm.

Determination of Film Thickness

Each round membrane disk was cut into two equal parts and the thickness was measured under a microscope at five points. The mean value was taken as the film thickness.

Permeation and Dissolution Studies

The membranes without drugs were fixed at one end of a 20-ml open glass tube. The plastic cap in which a hole of 22-mm diameter (Fig. 1) had previously been punched held the membrane. The glass tube was filled with 10 ml of a suspension of the drug containing twice the amount necessary for a saturated solution. The same fluid was filled into both the glass tube and the dissolution vessel (Fig. 2). The drug-containing membranes were prepared in the same way and placed on the surface of 1000 ml water using the paddle apparatus. They were fixed by mounting a microscope slide close to the water surface. During the first 2 hrs, 5-ml samples were withdrawn at 15-min intervals, assayed spectrophotometrically, and put back into the vessel. After 2 hr the samples were taken hourly and handled in the same way.

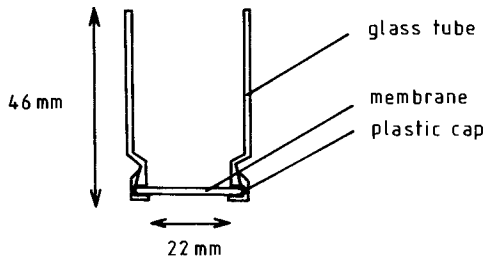

Fig. 1. Glass tube fitted with the membrane for permeation studies. The tube was filled with 10 ml of a saturated drug solution and mounted in the dissolution fluid so that the surface of the drug solution and the dissolution fluid were at the same level.

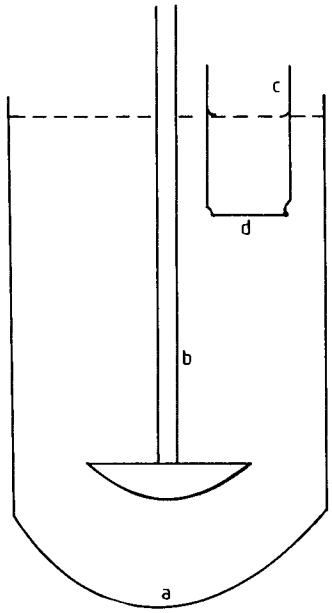

Fig. 2. Glass tube mounted in the paddle vessel. The surfaces of the saturated drug solution and dissolution fluid were adjusted to the same level in order to avoid any pressure on the membrane. (a) Paddle vessel; (b) stirrer; (c) glass tube; (d) membrane.

Analytical Equipment

The dissolution apparatus used was a USP paddle with 1000 ml fluid; the speed of the stirrer was 50 rpm; the temperature was 37 ± 0.5°C. A PMQ II photometer was used, with 2-cm cuvettes (Zeiss D-Oberkochen). The wavelength was 285, 271, 318, and 238 nm for codeine, theophylline, indomethacin, and nifedipine, respectively. All experiments with nifedipine were carried out under protection from light.

Determination of the Partition Coefficient Between Membrane and Dissolution Fluid

The membrane was shaken for 24 hr in a half-saturated solution. The amount of drug in solution was essayed spectrophotometrically. The partition coefficient was calculated by Eq. (2):

$$V_k = \frac{M_L \cdot m_M}{m_L \cdot M_M} \qquad (2)$$

where M_L is the amount of dissolution fluid (g), m_L is the amount of drug in the dissolution fluid (mg), M_M is the weight of the membrane (g), and m_M is the amount of drug in the membrane (mg).

Determination of the Absorption of the Drugs by Ethylcellulose

Codeine, 30 mg, theophylline, 300 mg, indomethacin, 50 mg, and nifedipine, 10 mg, were dissolved in 1000 ml of the dissolution fluid chosen for the drugs. One hundred milligrams of ethylcellulose (fraction of 0.2 to 0.5 mm) was added

Table I. The Composition and Thickness of Membranes Used for Permeation Studies

	Membrane no.			
	28/5	25/5	20/5	16/5
Ethylcellulose (%)	5	5	5	5
PEG 400 (%)	28	24	20	16
Sesame oil (%)	10	10	10	10
Citroflex-2 (%)	57	61	65	69
Thickness (μm)	187.6	308.6	380.0	430.9
sdv of thickness (%)	6.27	9.47	6.79	13.65
Area of exposure (mm^2)	380	380	380	380

and the mixtures were stirred overnight in the vessel of a paddle apparatus, while the temperature was maintained at 37°C. After filtration of a sample the amount of drug in solution was essayed.

RESULTS

Diffusion Through Drug Free-Membranes

Membranes with four different amounts of polyethylene glycol 400 were studied (Table I). The amounts of ethylcellulose and sesame oil were kept constant, while citric acid triethyl ester (Citroflex-2) was used to fill up to a constant weight of 135 ± 5 mg for each membrane after leaching out the polyethylene glycol. Because of the various amounts of polyethylene glycol 400, the thickness of the finished membranes ranged from 187.6 to 430.9 μm. The area of diffusion was exactly 380 mm^2. The compositions and properties of the membranes are summarized in Table I.

The glass tubes fitted with the membranes were filled with 10 ml of the drug suspension and dipped into the acceptor fluid. They were fixed as shown in Fig. 2.

The fastest diffusion was observed for codeine. The membrane 28/5 (Table II) yields 14.15 $mg \cdot hr^{-1}$ diffused codeine, while for the same membrane a diffusion of 1.69 $mg \cdot hr^{-1}$ indomethacin was measured. For theophylline and nifedipine, no diffusion was registered. Because of the pH-dependent solubility of indomethacin, the experiment was also carried out with a buffer of pH 6.0 (USP XXI), where the diffusion was sevenfold slower than at pH 7.5.

The results of diffusion measurements are shown in Fig. 3. After 15 min the diffusion rate was constant, and straight lines were obtained for all membranes tested with codeine and indomethacin. The diffusion rate was directly proportional to the polyethylene glycol content of the membranes. Indomethacin at pH 6.0 shows a very slow diffusion. For this reason only the results for a membrane containing a high amount of polyethylene glycol are shown. Theophylline does not penetrate the membranes tested. Nifedipine was absorbed by the membranes, resulting in a yellowish color, and almost no diffussion was observed.

The diffusion coefficients for codeine and indomethacin (Table II) were calculated from Eq. (3):

$$D = \frac{dm}{F \cdot V_k \cdot C_s} \cdot \frac{dm}{dt} \tag{3}$$

where dm/dt is the amount of drug diffused per area ($mg \cdot hr^{-1}$), d is the thickness (mm), F is the area of the membrane (mm^2), V_k is the partition coefficient, and C_s is the solubility of the drug in the acceptor fluid ($mg \cdot ml^{-1}$). With $0.242 \cdot 10^{-2}$ mm^2 hr^{-1} the diffusion coefficient for codeine exceeds that of indomethacin with $0.102 \cdot 10^{-2}$ mm^2 hr^{-1} (mean values). In the experiments in which indomethacin was used in pH 6.0 buffer, a diffusion coefficient of $0.98 \cdot 10^{-2}$ mm^2 hr^{-1} was obtained. The diffusion results are summarized in Table II.

Diffusion from Drug-Containing Membranes

For codeine the membranes had the same composition as shown in Table I. Thirty milligrams of the drug, particle size 20 to 40 μm, was suspended in 270 mg of the membrane material, to give a total weight of 300 mg. For the other drugs, the amount of ethylcellulose was decreased in order to obtain greater release rates. The amount of polyethylene

Table II. Results of Permeation Studies for Codeine and Indomethacin Through Ethylcellulose Membranes

Drug	Membrane no.	v^a ($mg\ hr^{-1}$)	v^a ($mmol\ hr^{-1}$)	S^b ($mg\ ml^{-1}$)	$V_k{}^c$	D^d ($10^{-2}\ mm^2\ hr^{-1}$)
Codeine	28/5	14.15	4.726	9.8	2.88	0.248
	24/5	8.70	2.906			0.251
	20/5	6.90	2.305			0.246
	16/5	5.50	1.838			0.222
						$\bar{X} = 0.242$
Indomethacin (pH 7.5)	28/5	1.69	0.473	4.8	2.37	0.093
	24/5	1.44	0.403			0.103
	20/5	1.22	0.342			0.108
	16/5	1.04	0.290			0.103
						$\bar{X} = 0.102$
Indomethacin (pH 6.0)	28/5	0.24	0.066	0.51	2.37	0.098

[a] v is the diffused amount of drug per unit area of exposure (380 mm^2).
[b] S is the solubility of the drug in the dissolution medium.
[c] V_k is the partition coefficient membrane/dissolution medium.
[d] D is the diffusion constant of the drug molecule in the membrane.

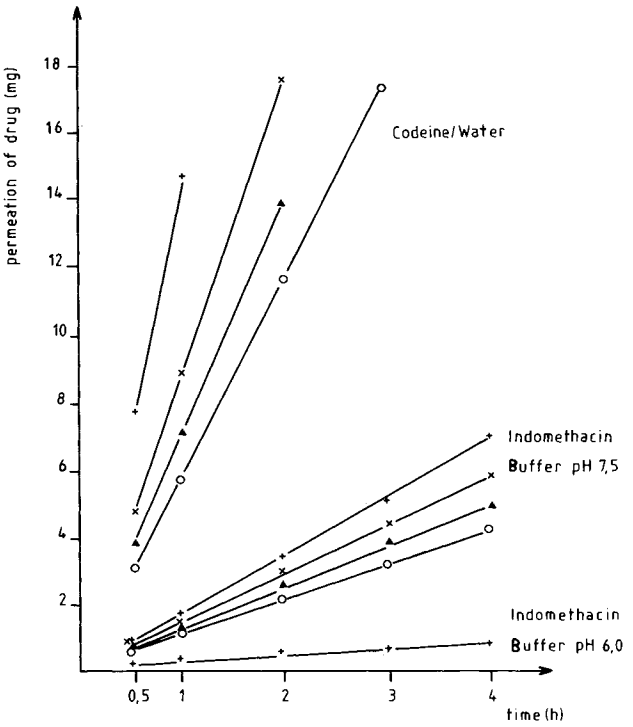

Fig. 3. Permeation of codeine and indomethacin through membranes consisting of ethylcellulose, polyethylene glycol 400, sesame oil, and citric acid triethyl ester according to Table I. (○——○) Membrane 16/5; (▲——▲) membrane 20/5; (×——×) membrane 24/5; (+——+) membrane 28/5. USP paddle method, 1000 ml dissolution fluid; speed of the stirrer, 50 rpm; temperature, 37°C.

glycol 400 ranged from 20 to 35% for the same reason (Table III).

Indomethacin and nifedipine were dissolved in the membrane material. The membranes contained 75 mg indomethacin or 20 mg nifedipine, and the total weight was again 300 mg. The theophylline membranes contained 300 mg of the suspended drug (particle size fraction, 40 to 80 μm), and the whole membrane had a mass of 550 mg. The membrane diameter was 22 mm^2 and the area was 380 mm^2 for all membranes studied.

The swimming membrane disk gave the following drug release rates. Codeine (Fig. 4) was released quickly, and the kinetics were comparable to those of the soft gelatin capsules (1). However, drug release was not exactly linear with the square root of time. The thickness of the disks decreased from 2.4 mm at the beginning of the experiment to 1.2 mm after 6 hr.

The release pattern of theophylline is the same as a matrix-type one. In all cases straight lines were obtained if the amount of drug dissolved is plotted against the square root of time (Fig. 5). The membranes were leached out completely, and a three-dimensional network consisting of ethylcellulose and sesame oil remained. A complete disintegration of the network was observed with the membrane 35/2 after 4 hr, and the drug was completely dissolved.

The release of indomethacin (Fig. 6) is slow compared with the release rate of codeine, although the formulations contain less ethylcellulose and more polyethylene glycol 400. The membranes containing 35% polyethylene glycol in the matrix reveal a relatively fast release. All release profiles become flat after the second hour, indicating that only indomethacin near the surface will be leached out.

The thickness of the membranes decreases from 2.5 to 1.8 mm, so that one can conclude that only a small quantity of the membrane material is leached out.

Figure 7 shows the release of nifedipine from the membranes listed in Table III. As expected, the delivery was poor. After 6 hr, 36% were released from formulation 35/2. The delivery is linear with the square root of time, and the thickness of the membranes decreased from 2.4 to 2.0 mm after 6 hr.

DISCUSSION

Codeine, indomethacin, and, with limitations, nifedipine were able to penetrate a drug-free membrane composed of ethylcellulose, sesame oil, citric acid triethyl ester, and polyethylene glycol. The penetration depends on the type of drug used and on the content of polyethylene glycol, which is quickly leached out by the dissolution medium.

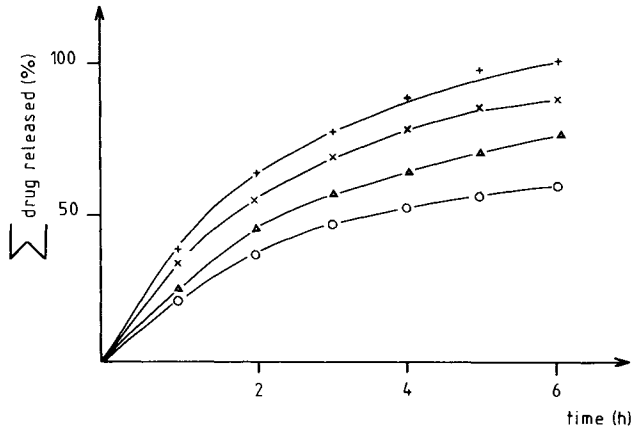

Fig. 4. The release of codeine from drug-containing membranes. (○——○) Membrane 20/2; (▲——▲) membrane 24/2; (×——×) membrane 28/2; (+——+) membrane 35/2 (as shown in Table II).

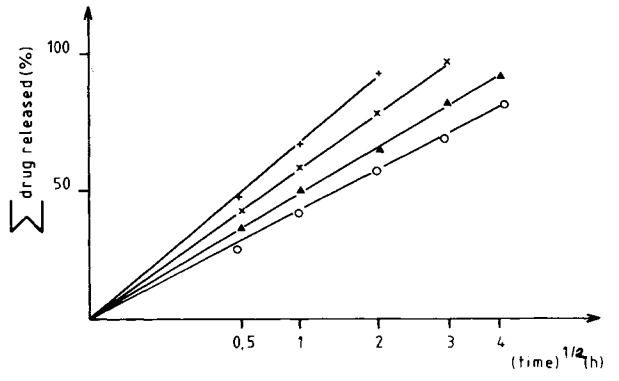

Fig. 5. The release of theophylline from drug-containing membranes. (○——○) Membrane 20/2; (▲——▲) membrane 24/2; (×——×) membrane 28/2; (+——+) membrane 35/2 (as shown in Table II). Paddle method with 1000 ml distilled water and 50 rpm.

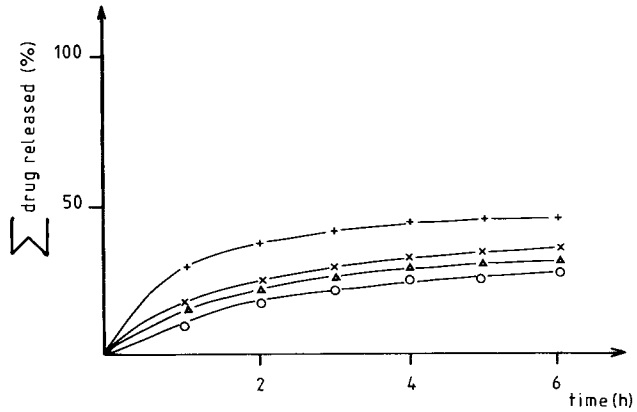

Fig. 6. Release of indomethacin from drug-containing membranes. (○——○) Membrane 20/2; (▲——▲) membrane 24/2; (×——×) membrane 28/2; (+——+) membrane 35/2 (as shown in Table II). Paddle method with 1000 ml artificial intestinal juice (without pancreatin), pH 7.5, and 50 rpm. The curve with the highest amount of PEG 400 shows the highest delivery of the drug.

Theophylline which is insoluble in the matrix material does not penetrate. The rate of diffusion is influenced by

- the solubility of the drug in the matrix material,
- the solubility of the drug in the acceptor phase, and
- the partition coefficient of the drug between the membrane material and the acceptor phase.

The diffusion of the four drugs codeine, indomethacin, theophylline, and nifedipine can be correlated with the above parameters. Codeine and indomethacin reveal nearly the same partition coefficient of 2.88 and 2.37, respectively. The faster release of codeine is due to its relatively high diffusion constant of $0.242 \cdot 10^{-2}$ mm^2 hr^{-1} compared with that of indomethacin, $0.102 \cdot 10^{-2}$ mm^2 hr^{-1} (Table II). The diffusion of indomethacin correlates furthermore with the solubility of the drug at different pH values (see indomethacine pH 7.5 and pH 6.0). Theophylline, which is insoluble in the matrix material, consequently does not penetrate the membranes. In contrast, nifedipine is highly soluble in the matrix material, showing a partition coefficient of 611. Because of this

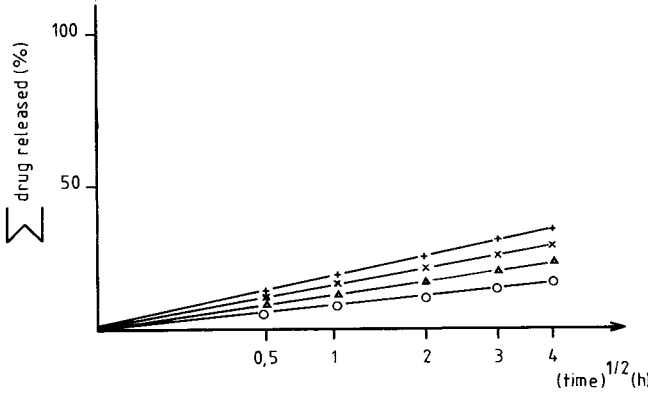

Fig. 7. Release of nifedipine from drug-containing membranes. (○——○) Membrane 20/2; (▲——▲) membrane 24/2; (×——×) membrane 28/2; (+——+) membrane 35/2 (as shown in Table II). Paddle method with 1000 ml artificial gastric juice, pH 1.2 (without pepsin), and 50 rpm.

Table III. Composition of Membranes Containing Theophylline, Indomethacin, or Nifedipine[a]

	Percentage			
	35/2	28/2	24/2	20/2
Ethylcellulose	2	2	2	2
PEG 400	35	28	24	20
Sesame oil	10	10	10	10
Citroflex-2	53	60	64	68

[a] The membranes containing indomethacin and nifedipine had a total weight of 300 mg and contained 75 and 20 mg of the drug, respectively.

value and its poor solubility in the acceptor phase, nifedipine will be enriched in the membrane, which is visible by the resulting yellowish color. Different amounts of polyethylene glycol lead to membranes of various thicknesses. The permeability is therefore directly dependent on the membrane's thickness. Whether high amounts of polyethylene glycol, which is leached out rapidly, leave an ethyl cellulose system behind that is unproportionally permeable can not be decided from the presented results.

The drug-containing membranes reveal a clear dependency between the amount of polyethylene glycol and the release rate. Similar relations are reported in the literature for several other drugs (3,4). The leaching out of the polyethylene glycol and a fraction of the citric acid triethyl ester (Citroflex-2) decreases the thickness of the membrane. Drugs that are relatively well soluble in the matrix such as indomethacin and nifedipine (15 and 22%, respectively) tend to leach out slowly. Especially nifedipine forms a lipohilic compartment which retains most of the drug and the Citroflex-2. In general, release rates from drug-containing membranes are low for indomethacin and nifedipine. Theophylline is liberated in a way which makes the formulation of a sustained-release product possible. The mechanism of drug release for nifedipine and theophylline follows Higuchi's equation (6). However, codeine and indomethacin do not follow this law. This different behavior could be explained by the dissolution of codeine in the matrix material, while indomethacin is not able to pass the membrane in the same way as shown in Fig. 3.

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