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Zero order drug delivery from double-layered porous films: release rate profiles from ethyl cellulose, hydroxypropyl cellulose and polyethylene glycol mixtures

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Laminated double-layered films comprising a drug-containing and drug-free layer were prepared using tripelennamine, barbitone, salicylic acid and caffeine dispersed in hydroxypropylcellulose (HPC) attached to ethyl cellulose (EC) films containing various proportions of polyethylene glycol (PEG) or HPC to enhance permeability. Drug release in vitro followed zero-order kinetics, rate constants being dependent on the thickness of the drug-free membrane, which was rate-controlling. Thickness-corrected zero order constants were independent of drug-loading, which did, however, control the duration of release. Permeability coefficient measurements on the same rate-controlling films used as single barrier membranes enabled the effective drug concentration (C_0) at the interface between the laminated membranes to be estimated; C_0 was independent of drug loading and was of the order expected from the aqueous solubilities of the drugs. Release rates were enhanced by addition of hydrophilic polymer to the rate-controlling membranes, either linearly with fraction of additive for PEG to 0·6 or HPC to 0·4, or logarithmically for HPC from 0·4 to 0·8. Enhancement coefficients, which were different for each system, reflected the different mechanisms of hydrophilic polymer action. PEG was leached out rapidly, pores being formed in the matrix. In contrast, HPC was largely retained, so that the enhancement was less. The logarithmic enhancement stemmed from formation of swollen hydrated channels, which, unlike the low HPC fractions or the PEG systems, allowed entry of buffer ions, so that only in these channel systems were the release rates altered by change of the external pH.

In general, sustained-release products liberate their content of therapeutic agent at a rate which diminishes with time, irrespective of whether they are fabricated as tablets, pellets, films or other dosage forms (Samuelov et al 1979). The decrease in flux stems from progressive fall of concentration gradient across the matrix through which the drug diffuses to the exterior. Release kinetics follows either a square root of time law (Higuchi 1961, 1963), a first order equation (Crank 1956) or a more complex pattern (Baker & Lonsdale 1974), according to the diffusional character of the system.

For many purposes, however, a constant release rate would be advantageous, and certain two-compartment products have been claimed to give such zero-order or linear release, examples including medicated bandages (Zaffaroni 1973), pilocarpine-releasing films and capsules (Long & Folkman 1966; Gould & Shepherd 1972) and hydroxypropyl cellulose matrices (Borodkin & Tucker 1975). Such systems comprise an inner reservoir of dispersed drug, termed here the drug supply layer, and an outer layer which behaves as a rate-controlling membrane.

These double-layered dosage forms give linear release for as long a time as the drug supply layer is able to maintain the concentration gradient across the rate-controlling membrane invariant, the latter being the sole regulator of release rate. If C_0 is the effective drug concentration at the inner (drug supply-layer attached) face of the rate-controlling membrane and the outer face is at zero concentration, i.e. perfect sink and stirring conditions are assumed, then on attainment of a steady state the release rate dQ/dt is given by:

$$\frac{dQ}{dt} = k_0' = \frac{PC_0}{x} \quad .. \quad .. \quad .. \quad .. \quad (1)$$

where Q is the quantity of drug released per unit area of membrane surface in time t, k_0' is the apparent zero-order release rate constant and P is the permeability constant for the drug in the rate-controlling membrane the thickness of which is x. This equation is parallel to that governing the

* Correspondence.

behaviour of a barrier-layer membrane operating under quasi-steady state conditions.

Of particular interest is the variation of release rate constant k_0' for different drugs and polymer mixtures. In the present study, use has been made of rate-controlling films comprising mixtures of the hydrophobic polymer ethyl cellulose (EC) with two different hydrophilic polymers. The first, polyethylene glycol (PEG) 4000, was shown in an earlier work on barrier membranes to increase the permeability of EC films drastically in linear relation to the amount added, an effect caused by the leaching out of the soluble polymer and replacement by solvent (Donbrow & Friedman 1975).

The second was hydroxypropyl cellulose (HPC), which appears to be leached out of single films comprising mixtures of HPC with polyvinyl acetate (PVA), added to reduce the permeability of HPC to drugs incorporated in such mixed films (Borodkin & Tucker 1974). The same polymer mixture was used by these workers as the rate-controlling membrane in laminated films (1975). Release rate constants were related logarithmically to the fraction of HPC, which was apparently not leached out of double films, release being attributed to hydration of this polymer. It was our intention to compare the leachable and non-leachable polymers as permeability-changing additives.

The drug supply layer was composed of the selected drug dispersed in HPC. Salicylic acid, caffeine, tripelennamine and barbitone were used as model acidic, neutral and basic drugs. The use of the two-compartment system to obtain linear release was considered briefly in an introductory report (Donbrow & Samuelov 1976).

MATERIALS AND METHODS

Materials

Ethyl cellulose, N-type, ethoxyl content: 47·5 to 49·0%. Viscosity of 5% w/w solution in toluene–ethanol 80:20 (w/w) was 100 c.p.s. Hydroxypropyl cellulose (Klucel LF), food and pharmaceutical grade, average molecular weight 100 00; viscosity of 5% w/w solution in water was 75–150 c.p.s. Both polymers were supplied by Hercules Inc., Wilmington, Delaware, U.S.A. Polyethylene glycol 4000 was of B.P.C. grade (BDH Ltd., Poole, U.K.). Salicylic acid, caffeine and tripelennamine HCl were of U.S.P. grade and barbitone, N.F. grade.

Preparation of films

The *drug supply layer* films were cast from chloroform solutions containing 10% w/v total solute on Teflon-coated plates using the techniques described previously (Samuelov et al 1979).

Tripelennamine was added as an oily liquid, prepared from an aqueous solution of the salt by addition of 5 M NaOH, extraction with chloroform and evaporation of the solvent. The films were allowed to dry completely for 24 h, removed from the plate and air-dried for at least an additional 24 h. The drug content was calculated from the weight ratio of drug and polymer used. Spectrophotometric determination of the drug content after solution of specimen films in chloroform gave results which accorded with the weight ratios.

The *rate-controlling* membranes were prepared by the same casting technique using chloroform solutions containing 10% w/v total polymer mixture. The ratio of the two polymers present (EC with PEG or HPC) was calculated directly from the weight ratio used.

Films were cut into circular discs. The drug supply films were 36 cm^2 in area and were weighed accurately; the rate-controlling membranes were slightly larger. Film thickness of both layers was measured in ten different places by means of a micrometer (Tesa, Switzerland) and mean values calculated.

Films were joined by wetting the rate-controlling membrane minimally using a chloroform spray and pressing the drug-containing film immediately onto the wet surface of the rate-controlling membrane placed on a glass plate, avoiding entrapment of air. The double-layered film was allowed to air-dry for approximately 24 h and inspected to ensure complete adhesion before use.

Determination of release rate

The double-layered films were attached to glass plates using silicone adhesive (Medical Adhesive B, Dow Corning Corp., Midland, Michigan, U.S.A.), with the rate-controlling membrane exposed. To avoid direct drug release, the edges of the drug layer were covered with a silicone lubricant (Dow Corning). The glass plate-membrane assembly was immersed in 500 ml water preheated to 37 °C and the solution was mixed continuously by means of a polystaltic pump (Watson-Marlow) at a rate of 31 ml min^{-1}. To avoid water evaporation, the vessels were kept covered with aluminium foil.

Aliquot samples were withdrawn at various times and replaced by fresh water. The amount of drug released was determined spectrophotometrically, salicylic acid and caffeine in water at 296 nm and 273 nm, respectively, tripelennamine at 246 nm in

0·1 M HCl and barbitone in ammonia buffer (pH 10) at 240 nm. Experiments were duplicated or triplicated and mean results recorded. Reproducibility was within 5% of the mean.

Determination of hydrophilic polymer release from rate-controlling membranes

Films were cut into strips 36 cm² in area, weighed accurately, and shaken with 100 ml water at 37 °C. The polymer leached out was determined gravimetrically after sampling and evaporation.

RESULTS AND DISCUSSION

In contrast to the release patterns given by similar drug dispersions in single films (Samuelov et al 1979) all the drugs and film compositions studied exhibited zero order release from the double film assemblies on immersion in water.

Some examples are shown in Fig. 1 and it is evident that the EC-PEG rate-controlling films function in the same general way as the HPC-PVA combination.

Linearity was maintained for more than 80 to 90% of the release in the most rapid delivery systems, studied to near exhaustion, after which the rate declined, presumably as a result of the decrease in the concentration gradient in the drug layer below saturation. Slower delivery membranes gave linear release throughout the measurement period (10–12 h).

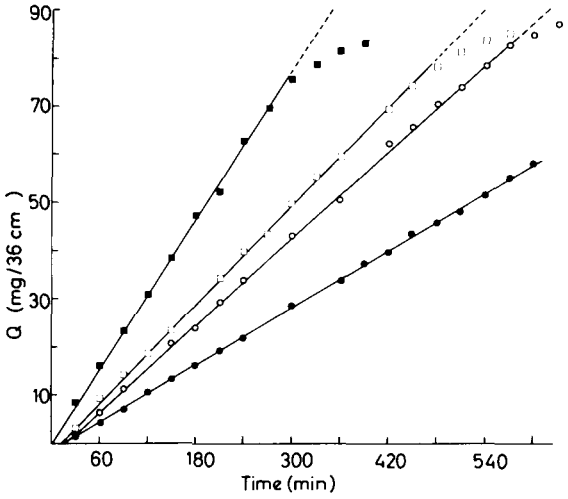

FIG 1. Effect of PEG fraction (f) in rate-controlling membrane on release rate of salicylic acid from drug-supply layer (area 36 cm²; 20% salicylic acid in HPC; Q_0 = 85–100 mg). ●, f 0·1, x = 0·031 mm; ○, f 0·2, x = 0·032 mm; □, f 0·4, x = 0·049 mm; ■, f 0·5, x = 0·042 mm.

Apparent zero order rate constants (k_0' values in eqn (1)) were obtained from the slopes of the Q vs t plots and a typical series is presented in Table 1 for tripelennamine. The rate constants changed systematically with film composition, rising with proportion of hydrophilic polymer in the rate-controlling membrane, as typified by the 20% salicylic films (Fig. 1).

Table 1. Zero-order release rates for tripelennamine from double-layered films. Drug supply layer 20% w/w tripelennamine in hydroxypropyl cellulose.

Rate-controlling membrane			Rate constants	
Hydrophilic polymer fraction	Thickness mm	Drug supply layer Thickness mm	k'_0 mg cm^{-3} min × 10^3	k_0 mg cm^{-1} min × 10^5
PEG				
0·1	0·056	0·102	0·250	0·140
0·2	0·069	0·093	0·521	0·364
0·3	0·068	0·103	0·666	0·453
0·4	0·036	0·100	1·64	0·589
0·5	0·042	0·097	1·97	0·828
0·6	0·049	0·120	1·83	0·898
HPC				
0·1	0·061	0·078	0·127	0·077
0·2	0·064	0·104	0·197	0·126
0·3	0·059	0·088	0·336	0·198
0·4	0·068	0·098	0·427	0·290
0·5	0·053	0·110	0·568	0·460
0·6	0·069	0·123	1·19	0·823
0·7	0·058	0·128	2·25	1·30
0·8	0·063	0·117	3·69	1·96

Correlation coefficient = 0·991 – 0·999.

Lag times (t_{lag}) were measured by backward extrapolation of the linear region to the time axis, enabling use of the integrated form of equation (1):

$$Q = k_0't - k_0't_{lag} \quad .. \quad .. \quad .. \quad .. \quad (2)$$

Although a rank correlation between lag time and membrane thickness was evident in all the drugs excepting caffeine, the expected Barrer (1939) relationship of lag time to membrane thickness squared ($t_{lag} = x^2/6D$, where D is the drug diffusion coefficient in the membrane) did not hold. Lag times were less than 20 min for salicylic acid and barbitone, 20 to 90 min in tripelennamine and zero or negative in caffeine.

Positive lag times appear to be the norm. They could derive from either the build-up of concentration in the rate-controlling membrane from zero initially to the steady-state value, or from the slower rate of diffusional processes before the attainment of equilibration with the solvent. On the other hand, negative lag times, indicative of rapid exit of drug, could arise from the presence of a more concentrated drug layer at the membrane surface, formed during casting, or by partitioning during storage (Baker & Lonsdale 1974).

Increase in thickness of the rate-controlling membrane would also be expected to have a profound effect on its permeability, which is inversely related to the thickness as in simple barrier films. This has been tested on EC-PEG compositions used as single films (Donbrow & Friedman 1975). That the relationship between apparent release rate constant and reciprocal thickness of the external membrane is linear, in accordance with equation (1), is shown in Table 2 for typical laminated film systems.

Table 2. Relationship of drug release rate to reciprocal thickness of the rate controlling membrane.

Rate-controlling membrane Hydrophil. polymer fract.	Thickness mm	Release rate constant (k'_o) mg cm^{-2} min $\times 10^3$	Release rate constant/ reciprocal thickness mg cm^{-1} min $\times 10^5$
Salicylic acid			
0·2 PEG	0·021	6·44	1·35
	0·032	3·97	1·27
	0·053	2·44	1·30
0·4 PEG	0·026	8·92	2·32
	0·049	4·80	2·35
	0·075	3·19	2·40
0·6 HPC	0·042	6·95	2·90
	0·048	6·36	3·02
	0·068	4·63	3·18
Barbitone			
0·2 HPC	0·043	0·080	0·034
	0·068	0·052	0·035
0·4 PEG	0·031	0·316	0·098
	0·053	0·193	0·102
Tripelennamine			
0·6 PEG	0·049	1·83	0·898
	0·032	2·89	0·926
0·5 HPC	0·053	0·568	0·302
	0·068	0·447	0·304
Caffeine			
0·5 PEG	0·036	1·32	0·487
	0·051	0·972	0·496
	0·062	0·798	0·495

Thickness-independent zero order constants, k_o, (equation (3)) eliminate the anomalies evident when comparing the constants for films of progressively changing composition (Table 1):

$$k_o = k_o'x = PC_o \quad \ldots \quad (3)$$

As the rate constant k_o is determined by the operative P and C_o values, experimental k_o values may be utilized for estimation of either C_o or P when one or the other can be measured directly.

In the present case, P values were derived from permeation rate measurements made using the rate-controlling membranes as single barrier films with drug solutions of known concentration (Donbrow & Friedman 1975); HPC-EC films and barbitone permeation were studied by the same method (Samuelov & Donbrow, unpublished data). Consistent permeability character would be expected of a given film composition, whether mounted singly or in laminar combination, provided it was prepared by an identical technique and was unaltered structurally during or after lamination, adequate stirring and zero sink conditions being assumed.

P values for some typical systems are listed in Table 3 together with the k_o values of the corresponding laminated membranes. C_o values thus

Table 3. Calculated drug concentration (C_o) at the internal surface of the rate controlling membrane.

Drug supply layer	Rate-control. membrane. Hydrophil. polymer fraction	Pearmeab. const. (P) cm^2 s^{-1}	Zero order release rate constant k_o mg cm^{-1} min $\times 10^5$	C_o* mg ml^{-1}
Salicylic acid		P $\times 10^8$		
20%	0 (pure EC)	0·27	0·042	2·59
	0·1 PEG	5·10	0·843	2·76
	0·2 PEG	8·89	1·27	2·38
	0·4 PEG	16·50	2·35	2·38
	0·5 PEG	18·60	3·06	2·74
	0·2 HPC	2·97	0·467	2·62
30%	0·2 PEG	8·89	1·20	2·24
	0·4 HPC	5·65	0·955	2·81
40%	0·4 HPC	5·65	0·971	2·86
	0·2 PEG	8·89	1·28	2·40
Caffeine		P $\times 10^{10}$		
20%	0·2 PEG	6·69	0·198	49·41
	0·4 PEG	14·30	0·388	45·32
30%	0·4 PEG	14·30	0·376	43·82
20%	0·2 HPC	7·68	0·210	45·58
	0·5 HPC	14·26	0·354	41·37
Barbitone		P $\times 10^{10}$		
20%	0·2 PEG	4·47	0·047	17·37
	0·5 PEG	13·25	0·114	14·41
40%	0·2 PEG	4·47	0·047	17·56
	0·5 PEG	13·25	0·110	13·81

* C_o values: Salicylic acid; $\bar{x}$ = 2·58; s.d. 0·21; C.V. 8·36.
Caffeine; $\bar{x}$ = 45·10; s.d. 2·93; C.V. 6·50.
Barbitone; x = 15·78; s.d. 1·95; C.V. 12·37.

obtained by use of equation (3) are seen to lie within 8% of the mean in caffeine and salicylic acid and slightly more in barbitone. The effective drug concentration appears to be independent of the actual drug concentration in the supply matrix and also of the composition of the rate-controlling membrane. It is concluded therefore that solution and diffusion of the drug in the supply layer are more rapid than transport through the control film,

so that the rates of the first two processes are not involved in the overall rate constant. Some supporting evidence bearing upon the high dissolution rate of the drug in the supply layer was provided by measurements on single HPC films containing 20% w/w of the drugs, from which release was very rapid, generally less than 1 h for films of similar thickness to those forming the drug supply layer of the laminated products, a result similar to that obtained by Borodkin & Tucker (1974).

For comparison with the calculated C_0 values, saturation solubilities were measured in water at 37 °C. They were of the same order as the C_0 values but the solubility of salicylic acid (3·412 g litre^{-1}) was higher and that of caffeine (36·89 g litre^{-1}) and of barbitone (11·62 g litre^{-1}) lower than the respective C_0 value. These differences are probably due to a combination of salting-out effects and specific drug-HPC interaction effects on solubility in an aqueous HPC medium.

Polymer composition in the rate-controlling films

The addition of suitable hydrophilic substances to hydrophobic polymer films is one of the methods of increasing the permeability (Colletta & Rubin 1964; Fites et al 1970; Shah & Sheth 1972; Borodkin & Tucker 1975, and Donbrow & Friedman 1975).

The film compositions studied were EC containing up to 50 or 60% w/w PEG and up to 80% w/w HPC (Table 1). At higher PEG concentrations the films obtained were defective. HPC was used as the drug supply layer matrix throughout.

Drug delivery rates increased with hydrophilic polymer concentration in both the PEG and HPC systems. In the case of the PEG additive, the k_0 values were linearly related to PEG concentrations for all four drugs (Fig. 2), in accordance with equation (4):

$$k_0 = k_{EC} + E_k f_h \quad .. \quad .. \quad .. \quad .. \quad (4)$$

where k_{EC} is the k_0 value for a 100% EC rate-controlling film, f_h is the fraction of hydrophilic polymer and E_k is the slope, representing the enhancement coefficient of drug delivery. Values of the enhancement coefficients, estimated by the least squares method, are listed in Table 4 and are specific for each drug and polymer mixture.

If both sides of equation (4) are divided by C_0 (see eqn (3)), we obtain:

$$P = P_{EC} + (E_k/C_0)f_h \quad .. \quad .. \quad .. \quad (5)$$

which is one form of an equation obtained by Donbrow & Friedman (1975) for single film

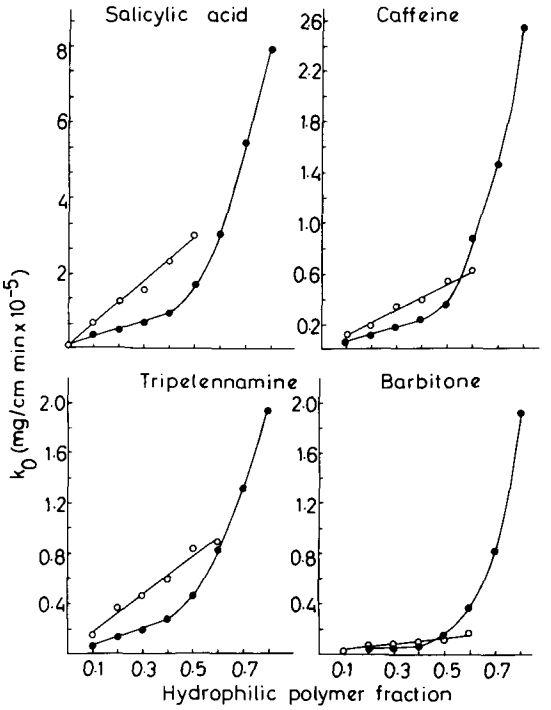

FIG 2. Relationship of k_0 to the fraction of the hydrophilic polymer in the rate-controlling membrane. ○, PEG; ●, HPC.

permeability dependence, where $E_k/C_0 = 100\,E_p$ in that paper. P and E values of membranes used singly or in laminates cannot be compared without independent measurement of C_0 which is difficult in HPC; nor from the calculations presented earlier are aqueous solubilities utilizable. The E_p values for the laminated systems presented in Table 4 are based on mean C_0 values (see footnote to Table 3) and lie within 5% of the single film values for caffeine and salicylic acid, though, for the reasons stated, this is not evidence of identical permeability behaviour. The increased permeability of the single EC-PEG films was considered to be due to leaching out of PEG and formation of water-filled pores, the effect being equivalent to a shortening of diffusional path length through the matrix material related to f_H.

The overall behaviour pattern of EC-HPC films is however quite different from that of EC-PEG films. At low HPC concentrations (up to ca 40% w/w) k_0 was related linearly to the fraction of HPC for all four drugs, except that the rate constants were lower than in the PEG-EC films. The enhance-

Table 4. Linear relationship of k_o to PEG fraction and HPC fraction (0·1–0·4) and log k_o to HPC fraction (0·4–0·8) in the rate controlling membrane.

	PEG in rate-controlling membrane			HPC in rate-controlling membrane		
Drug	Slope $E_k \times 10^{5}$*	$E_p \times 10^{11}$**	$E_p \times 10^{11}$***	Slope $E_k \times 10^{5}$* 0·1–0·4 fractions	Slope E_k'**** 0·4–0·8 fractions	k'_{EC}**** 0·4–0·8 fractions mg cm^{-1} min $\times 10^{7}$
Salicylic acid	5·51	356	370	2·02	2·35	15·3
Caffeine	1·02	3·77	3·6	0·520	2·79	1·61
Barbitone	1·52	3·12		0·192	3·53	0·283
Tripelennamine	0·295			0·711	2·11	4·20

* Equation (4). ** $E_p = E_k/100C_o$. *** Values from Donbrow & Friedman (1975). **** Equation (6).

ment coefficients of equation (4) were also lower using HPC than PEG (Table 4).

However, from 40% w/w HPC content upwards, the rate increased with the fraction of HPC in the film, i.e. there was a positive deviation from linearity (Fig. 2).

The diminished release rates from films having a low HPC content are readily explained by the different solution behaviour of the two hydrophilic polymers: whereas the PEG 4000 was rapidly leached out as in the single films, 90% being recovered from the water in 15 min using 35 μm film containing 30% of the polyglycol, very little HPC was extracted under similar conditions in spite of the water solubility of this polymer. In fact, 30% HPC membranes of 38 μm thickness released only 3·3% of the hydrophilic polymer in 15 and 5·6% in 150 min.

From the films of high HPC content, a much greater fraction of the HPC was released, e.g. from single 60% w/w films of 56 μm thickness. 25·7% of the HPC content was recovered from the water in 30 and 36·5% in 120 min. Nevertheless, the loss of hydrophilic polymer is much less than with PEG and a substantial amount remains in the matrix. Retention of the bulk of this polymer would be expected to yield a less porous matrix than in the PEG type and hence lower k_o values, as found up to $f_H \sim 0{\cdot}5$.

The quasi-exponential elevation of the release rate constant at high HPC content suggests that the membrane undergoes drastic structural modification sufficiently to change the diffusional parameters substantially without affecting the zero order kinetic behaviour. The most probable cause is the greater ability of the HPC to undergo hydration, swelling and change of configuration as it becomes the predominant polymeric component of the membrane; these processes may not occur readily when the matrix consists of 60% or more of the somewhat crystalline polymer EC and the HPC retention is high. This would lead to the formation of more amorphous or gel-like regions with channels of lower density, the amorphous fraction being held to control membrane permeability (Michaels & Bixler 1961). The facility with which HPC absorbs moisture has been demonstrated by a number of workers (Shah & Sheth 1972; Banker et al 1966; Borodkin & Tucker 1974).

In rate-controlling films containing upwards of 40% of HPC, the HPC concentration was related linearly to the logarithm of the zero order rate constant, shown in Fig. 3. The change in membrane behaviour is evident from the deviation from linearity at the low HPC concentrations. Slopes (E_k') of the logarithmic plots corresponding to equation (6) are listed in Table 4 together with k'_{EC} values obtained by extrapolation to $f_{HPC} = 0$. The latter represent hypothetical rate constants from pure EC membranes behaving in accordance with the membranes containing more than 40% HPC.

$$\log k_o = \log k'_{EC} + E_k' f_{HPC} \quad .. \quad .. \quad (6)$$

The same relation holds for HPC - polyvinyl acetate rate-controlling films (Borodkin & Tucker 1975). It is significant that the slopes are not the same as obtained from the non-logarithmic plots at low HPC concentration, and are of the same order for all four drugs.

Drug concentration and release time

Change of drug concentration between 20 and 40% did not influence the release rate nor did change in inner reservoir layer thickness. The data in Table 5 show that similar values of the release rate constant were obtained using similar outer films but different inner layer thicknesses and drug concentrations in the supply layer.

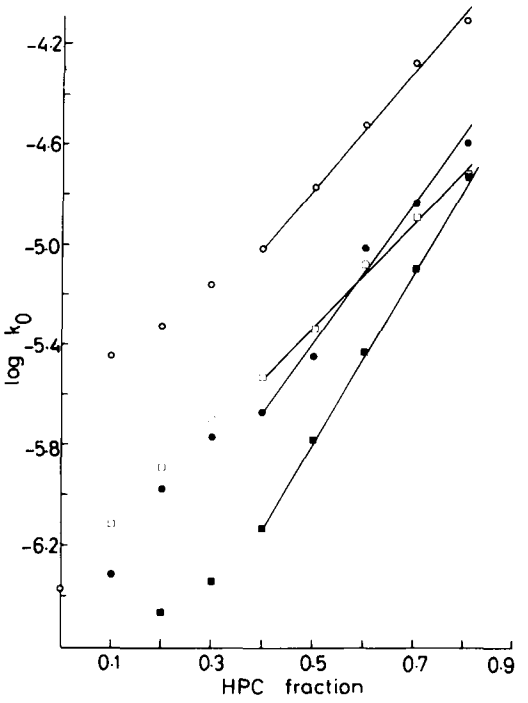

FIG. 3. Relationship of log k_0 to the fraction of hydroxypropyl cellulose in the rate-controlling membrane. ○, salicylic acid; □, tripelennamine; ●, caffeine; ■, barbitone.

It would be anticipated that as the drug concentration falls towards the critical saturation concentration value, the period of linear release with time would diminish and eventually be absent. With 20% or more of drug in the supply layer, linearity was observed for at least 80% of the release, whereas with 10% salicylic acid and a 50% PEG-EC rate-controlling membrane, linear release was not obtained. The drug loading does however control the duration of drug release and, with identical rate-controlling membranes attached, the greater the concentration or thickness of the drug layer (i.e. the greater the initial quantity of drug Q_0) the longer time it will be able to supply drug to maintain a constant concentration gradient across the external membrane. Some $t_{1/2}$ values measured experimentally are included in Table 5, and correspond to the theoretical values predicted using equation (7) derived from equation (2):

$$t_1/_2 = Q_0/2k_0 + t_{lag} \quad .. \quad .. \quad .. \quad (7)$$

Table 5. The effect of drug concentration and film thickness of the drug supply layer on release rate constants and half-life.

Drug supply layer		Rate-control. membrane.			
% w/w Salicylic acid	Thickness mm	Hydrophil. polymer fract.	Thickness (x) mm	Release rate const. (k_0) mg cm^{-1} min $\times 10^6$	Half-life (min)
20	0·105	0·2 PEG	0·032	1·27	317
20	0·143	0·2 PEG	0·030	1·24	431
30	0·110	0·2 PEG	0·035	1·20	497
40	0·099	0·2 PEG	0·033	1·28	590
20	0·108	0·5 HPC	0·045	1·71	215
40	0·111	0·5 HPC	0·048	1·79	453
Tripelennamine					
20	0·097	0·5 PEG	0·042	0·828	512
20	0·128	0·5 PEG	0·045	0·875	680
40	0·100	0·5 PEG	0·044	0·877	980

Nature of the drug

EC films containing PEG 4000 or HPC up to 40% gave identical release rate constants at pH 7 and pH 1 for all four drugs. A similar phenomenon was observed by Donbrow & Friedman (1975) studying the permeability constants of drugs in EC/PEG films.

One may conclude that these films maintain their barrier properties to entry of buffer salt ions and that linear release of the four drugs from such duplex film systems will not be influenced by the pH differences in gastric and intestinal fluids.

On the other hand, different results were obtained using rate-controlling membranes composed of 60% or more of HPC. The zero order release constants (k_0) for salicylic acid in sink solutions adjusted to pH values of 1 and 7 respectively, were: with 60% HPC: 40% EC membranes, $1{\cdot}80 \times 10^{-5}$ and $9{\cdot}66 \times 10^{-5}$ mg cm^{-1} min^{-1}; with 70% HPC: 30% EC membranes, $3{\cdot}46 \times 10^{-5}$ and $15{\cdot}2 \times 10^{-5}$ mg cm^{-1} min^{-1}.

These large differences indicate that the buffers penetrate the hydrated membrane and are able to change the degree of ionization of salicylic acid, increasing the proportion of the free acid at pH 1 and the anion at pH 7 (Samuelov et al 1979); the values of C_0, the concentration gradient, and k_0 are thus raised at the latter pH. The pH effects offer further evidence in support of the proposed swollen channel permeation mechanism operative in the rate-controlling membranes at high HPC concentrations.

The drug release rates were influenced primarily by the drug solubility in each of the layers and the diffusivity through the membrane layer. At low HPC and all PEG concentrations in the rate-controlling membrane, rates decreased in the order:

salicylic acid > tripelennamine > caffeine > barbitone, whereas at high HPC concentration, the order was salicylic acid > caffeine > tripelennamine = barbitone. Although the salicylic acid continues to be released the most rapidly, the rates of the other three drugs approach more closely to each other, that of barbitone in particular increasing greatly. This evidently results from elevated solubility in the hydrated channels.

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