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RELEASE OF DRUGS FROM FATTY SUPPOSITORY BASES II. A RATE-LIMITING INTERFACIAL PROCESS

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SUMMARY

In this report the effect of particle size on the release rate of sodium salicylate (a highly water-soluble drug) from fatty suppository bases is studied. In vitro it could be shown by comparing sedimentation measurements and release measurements that a rate-limiting process which is operating on the lipid side of the interface is causing the particle size effect. An equation is proposed describing the release flow as a function of particle size. It is shown that the time needed for the drainage of liquified lipid between a particle and the interface, a process which is essential for the drug to arrive at its dissolution site, is of the same order of magnitude as the time required for a wetted particle of a highly water-soluble drug to dissolve in an aqueous phase. This may imply that, in addition to the dissolution process, the drainage effect under certain conditions could become rate-limiting in the release of drugs from suppositories and thus for rectal absorption rate. Although the drainage time for a single particle layer appeared to be rather independent of particle size, reduction of particle size leads to an increase in the number of layers and consequently to a summation of drainage times for the same weight of drug.

In vivo it is shown that probably an increase in 'concentration viscosity' (increasing the concentration of particles in the base) does not have a negative effect on absorption rate from the rectum, whereas an increase in the 'fluid viscosity', does have a negative effect on absorption rate for suppository bases and liquid-paraffin enemas. Since the drainage time is not influenced by the concentration of particles in the base but only by the viscosity of the lipid phase while the bulk transport of particles through the base is influenced by both effects, it is concluded that in line with in vitro data the drainage time of particles determines the release flow of highly water-soluble drugs also in vivo.

INTRODUCTION

For highly water-soluble drugs such as sodium salicylate, release and absorption from fatty suppositories is determined by the transport of particles through the base (part 1 of

this study). In vitro this transport is accomplished by sedimentation into the direction of the base/water interface. We have previously found a faster release rate by increasing the concentration of drug particles in the base and by increasing the particle size. In vivo studies by Hennig (1959) and Rutten-Kingma (1977) have stressed the importance of the spreading behaviour of fatty suppository bases. We have shown in the first part of the study (Schoonen et al., 1979) that for drugs such as paracetamol or acetylsalicylic acid the absorption profiles can be explained only if it is assumed that the suppository base is spreading under influence of a pressure exerted by the rectum wall on the melting suppository.

It is difficult to understand how in vivo, sedimentation in the thin-layer of a spreading base is operating, although we and others (Stuurman-Bieze et al., 1978; Moolenaar et al., 1979; Rutten-Kingma et al., 1979) did show that highly water-soluble drugs incorporated in suppositories in the form of coarser particles are absorbed more rapidly than in the form of smaller size fractions. Especially the results of some in vitro experiments could not be explained with a sedimentation process as the rate-limiting step. This appeared to be the case for micronized fractions of highly water-soluble drugs such as sodium salicylate and sodium benzoate in comparison with the results of the micronized fractions of their acids (salicylic acid and benzoic acid).

For the acids, a rate-limiting step in the transport of solute away from the interface (part 1 of this study) occurs and therefore the sedimentation flow is faster than the release flow.

As the salts have about the same density as the acids the release flow should be at least as high as the release flow of the acids; that is, if sedimentation is also the rate-limiting step for the salts. However, the flow of the salts is about 6 times slower than expected (Schoonen et al., 1976; Stuurman-Bieze et al., 1978) indicating that some interfacial process could be rate-limiting.

In this study such a rate-limiting process is investigated in vivo and in vitro for highly water-soluble drugs, in order to find an explanation for the release and absorption behaviour of these drugs.

THEORETICAL

In a model system as shown in Fig. 1, drug particles are sedimenting rapidly creating a dense column of particles just above the interface. Then the mass flow per unit interface (Φ_s) away from the lipid/water interface is determined by: (1) the time (t_a) particles need

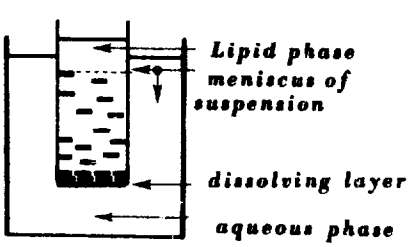

Fig. 1. Model for rapidly sedimenting particles, in which the release rate is determined by the interfacial processes of drainage and dissolution.

to approach and cross the interface; and (2) the time (t_d) particles need to dissolve at the interface. As only one layer of particles is dissolving at the interface at time = t, it can be written as:

$$\Phi_s = \frac{M_1}{S_b(t_a + t_d)} \tag{1}$$

where: M_1 = mass of one layer of particles and S_b = area of interface. To evaluate the influence of particle size on Φ_s, each variable that is dependent on particle size should be expressed in it: for one layer of particles

$$M_1 = N \cdot \rho \cdot \alpha \cdot l_0 \cdot w_0 \cdot h_0 \tag{2}$$

where: N = number of particles in one layer; ρ = density; α = shape factor; and l_0, w_0, h_0 = initial length, width and height of a particle. Approximating the shape of a sodium salicylate crystal to a flat cylinder, then l = w and $\alpha = \pi/4$, which gives:

$$M_1 = N \cdot \rho \cdot \frac{\pi}{4} \cdot w_0^2 \cdot h_0 \tag{3}$$

As crystals of sodium salicylate are dissolving at the interface with the h diameter in vertical position (perpendicular to the interface), the area of interface, S_b, can be expressed as follows:

$$S_b = N \cdot \pi \cdot w_0^2/4\beta \tag{4}$$

where β = the fraction of the interface that is occupied by particles. It was shown earlier (Schoonen et al., 1979) that individual crystals of potassium ferricyanide, dissolving at an interface, have a lifetime that is proportional with their initial width:

$$t_d \propto w_0 \tag{5}$$

Assuming that for sodium salicylate the ratio w_0/h_0 = constant, it may be written:

$$t_d = A \cdot h_0 \tag{6}$$

where A = the reciprocal of a dissolution rate constant. As the relationship between t_a and the particle size is not known under the experimental conditions, it is written as:

$$t_a = B \cdot h_0^n \tag{7}$$

where B is a consant. Substitution of Eqns. 3, 4, 6 and 7 into Eqn. 1, and rearranging gives:

$$\Phi_s = \rho \cdot \beta \frac{1}{A + B \cdot h_0^{n-1}} \tag{8}$$

Evaluation of Eqn. 8

In Fig. 2, plots of the mass flow vs particle size for various values of the exponent n are shown. Curve A results when n = 0, then, according to Eqn. 7, t_a is constant and independent of particle size (h_0). At high values of h the curve approaches a maximum value for the flow (Φ_s^{max}); then the release is determined by the dissolution rate and the influence of t_a is negligible.

Under these circumstances particle size variation has no effect on the mass flow as the

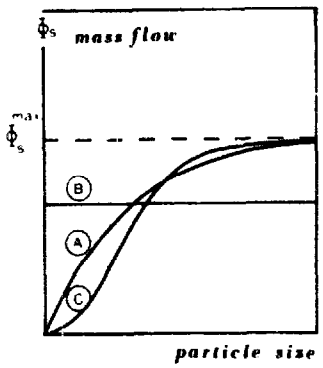

Fig. 2. Plot showing the influence of different values for the exponent n in Eqn. 8. A: n = 0; B: n = 1; C: n = −1.

total wetted area of the particles dissolving in one layer is independent. Since particle reduction to 1/n increases the number of particles to n^3 and in a single layer the number of particles increases to n^2, it follows that the number of layers increases with n. The total t_a for all layers will therefore increase linearly with n, causing the particle size-dependent effect on the release flow. Drugs dissolving rapidly in water are likely candidates to show this effect, since t_d is small and may be in the same order of magnitude as t_a.

The wetting process for these drugs with low contact angles is almost instantaneous and it is assumed therefore that the time-consuming step is not the crossing of the interface itself but the drainage of the viscous liquified lipid between the particle and the interface (t_a = drainage time).

Reynolds (1886) and Hartland (1968) have investigated this drainage time for flat plates and spheres respectively and found for both geometries that the drainage time (t_a) is proportional to particle size. If this linear relationship is also valid for many drug particles approaching the lipid/water interface simultaneously, then n = 1 and according to Eqn. 8, Φ_s is constant and independent of particle size. For any particle size a constant $\Phi_s < \Phi_s^{max}$ will be found. This case is represented by curve B (Fig. 2). Thus if this theory is valid for drug particles, the particle size effects found in vivo cannot be explained by a rate-limiting interfacial process. Finally the drainage time may be inversely related to particle size ($n < 0$). Then the S-shaped curve results that is drawn in Fig. 2 for the case $n = -1$.

EXPERIMENTAL

In vitro determinations

The lipid phases used, particle determinations, sedimentation measurements and release measurements are described in part one of this study. Tablets of sodium salicylate with a diameter of 1.01 cm, were made with a manual press (force: 11.76 kN) without any additives. Viscosity was measured in a Haake, Viscometer R.V. 3. Drainage time of individual crystals was determined by measuring the time between the arrival of a particle at the interface and the wetting of the particle. The wetting of sodium salicylate crystals is

an almost instantaneous process.

The interface was projected on a screen (magnification: ±50X) and the measurement was done visually with the aid of a stopwatch. The non-linear curve fitting was performed with a standard program developed by the Vogelback Computer Center; Northwestern University (Statistical Package for the Social Sciences, version 7.0, June 27, 1977).

Human experiments

Healthy human subjects, ranging from 25 to 37 years of age and in body weight from 64 to 95 kg, participated in the study. No drugs were taken for two weeks prior to and during the study. The volunteers were asked to remain in a sitting position. No discomfort following application of the rectal dosage forms was reported by the volunteers with one exception: some volunteers reported a defaecation reflex after administration of a micro-enema in which 11.6% sodium salicylate was dispersed in liquid-paraffin with a low viscosity (20 mPa · s). The micro-enemas were administered using a plastic disposable syringe to which a plastic application tube was connected. The tube was introduced in the rectal lumen enabling quantitative emptying of the syringe into the rectum.

In the suppository studies blood samples of 8 ml were taken using Venoject tubes (Terumo Corporation) with 5 mg EDTA-sodium granules from the vein in the right arm. In the micro-enema studies in which drug absorption is very rapid, samples were taken with the aid of a butterfly needle permitting frequent sampling. Plasma was obtained by centrifugation of the blood samples.

Salicylate concentration in plasma was measured by reverse-phase high pressure liquid chromatography as described by Moolenaar et al. (1979).

RESULTS AND DISCUSSION

In the model system as described in the theoretical section with liquid paraffin as the lipid phase and sodium salicylate as the solid phase the effect of particle size of the drug on release flow (Φ_s) was investigated. Also the sedimentation measurements were carried out for some size fractions to be able to discriminate between the interfacial processes and sedimentation in the bulk of the lipid phase as the rate-limiting step in the release process (Table 1). Below a certain concentration (the critical concentration) release flow is about equal to the sedimentation flow indicating that here transport through the bulk of the liquid is the rate-determining process. Thus Φ_s is proportional with concentration of particles in the base and the sedimentation rate (part 1 of this study).

For the smaller particles ($\bar{d}_g$ = 25 μm, 35 μm and 88 μm) it appeared that Φ_s is not increasing linearly with concentration but at a faster rate than expected, due to an increase in sedimentation velocity of the particles.

If a surface active agent (span 80) is added to the suspension the sedimentation velocity remains constant as can be seen in Table 2, where the settling time per centimeter column of suspension (t_s) in liquid-paraffin is shown for 2 drugs, sodium salicylate and paracetamol. It was concluded from these results that agglomeration of the particles causes the increase in settling rate for the smaller particle sizes. This phenomenon (also demonstrated for sodium chloride, paracetamol and chloramphenicol by Crommelin, 1979) increases substantially the transport rate of small particles. Above the critical concentra-

TABLE 1

RELEASE FLOW (Φ_s) (mg · cm^{-2} · min^{-1}) AND SEDIMENTATION FLOW (Φ_p) (mg · cm^{-2} · min^{-1}) FOR VARIOUS PARTICLE SIZES AND CONCENTRATIONS OF SODIUM SALICYLATE

$\bar{d}_g$ = 25 μm			$\bar{d}_g$ = 35 μm			$\bar{d}_g$ = 88 μm		$\bar{d}_g$ = 259 μm			$\bar{d}_g$ = 390 μm		$\bar{d}_g$ = 485 μm	
Conc.	Φ_s	Φ_p	Conc.	Φ_s	Φ_p	Conc.	Φ_s	Conc.	Φ_s	Φ_p	Conc.	Φ_s	Conc.	Φ_s
0.17	0.05	0.06	0.1	0.05	0.04	0.1	0.21	0.1	0.5	0.5	0.2	2.7	0.2	9.2
0.34	0.14	0.18	0.2	0.16	0.15	0.2		0.2	1.2	1.2	0.4	5.7	0.5	25
0.7	0.39	0.40	0.4	0.55	0.60	0.3	0.74	0.25	1.5	1.5	0.6	9.2	0.6	30 [a]
1.0	0.67	0.70	0.5	0.71	1.0	0.5	1.24	0.5	2.8	2.8	0.8	12.0	0.8	26
1.4	0.81 [a]	1.25	0.6	0.78		1.0	2.4	1.0	6.6	5.6	1.2	16.5	0.9	29
1.7	0.71	1.30	0.7	0.92		1.25	3.4	1.5	10	7.5	1.4	19.7	1.0	31
2.0	0.75	1.9	0.8	1.1 [a]		1.5	4.0 [a]	2.0	12	11	2.1	23.4	1.5	28
			1.0	1.1	2.4	2.0	4.1	3.0	16 [a]		2.4	25.0 [a]	2	31
			1.5	1.2		4.0	4.2	4.0	17		2.8	25.9	3	32
			2.0	1.2				11.6	18		3.7	25.7	4	31
			3.0	1.3							4.2	25.8		

[a] Critical concentration.

TABLE 2

INFLUENCE OF CONCENTRATION AND ADDITION OF SPAN 80 ON SETTLING TIME PER CENTIMETER COLUMN OF SUSPENSION

Sodium salicylate							Paracetamol						
$\overline{d}_g$ = 259 μm		$\overline{d}_g$ = 35 μm		$\overline{d}_g$ = 25 μm			$\overline{d}_g$ = 69 μm			$\overline{d}_g$ = 35 μm			
Conc. (%)	t_p (min)	Conc. (%)	t_p (min)	Conc. (%)	t_p (min)	t_p^1 (min)	Conc. (%)	t_p (min)	t_p^1 (min)	Conc. (%)	t_p (min)	Conc. (%)	t_p^1 (min)
0.1	1.57	0.1	23	0.17	36	51	0.1	6	7	0.1	19	0.1	40
0.2	1.44	0.2	16	0.34	23	38	0.2	6	7	0.2	19	0.5	30
0.5	1.56	0.4	12	0.69	21	58	0.3	4	–	0.3	18	0.6	31
1.0	1.55	0.5	10	1.03	18	58	0.4	–	9	0.4	13	0.75	30
2.0	1.58	1.0	10	1.38	13	59	0.5	–	8	0.5	10	0.9	35
							1.0	3	8	1.0	4	1.0	36

t_p^1 = with 1% Span 80.

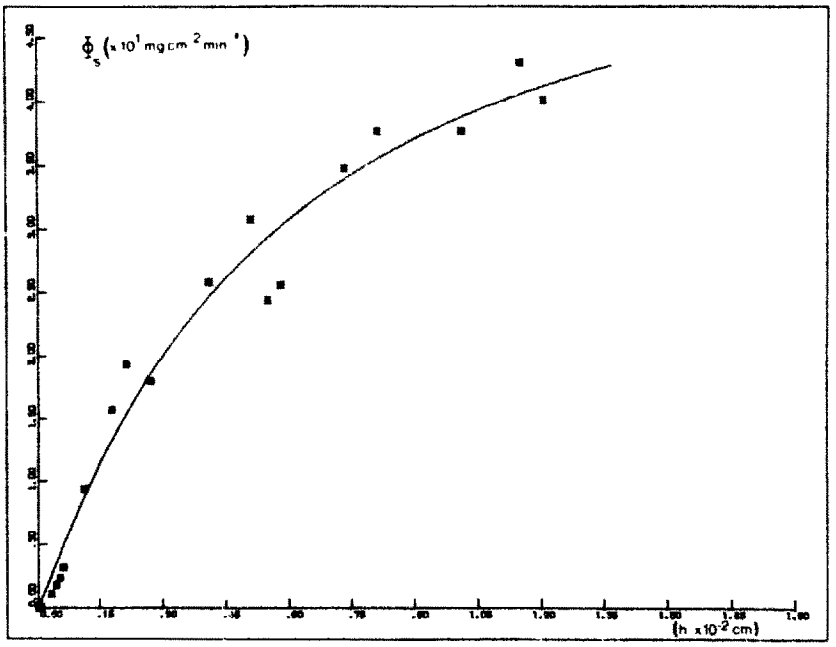

Fig. 3. Plot showing the computer fit of Eqn. 8 on the measured maximum release flow of 20 size fractions of sodium salicylate.

tion all particle sizes show a maximum release flow whereas the sedimentation flow (when it could be measured at these concentrations) is still increasing.

Thus it is not the sedimentation in the liquid-paraffin that is the rate-limiting step at the higher concentrations but some interfacial process. It was shown for paracetamol in part 1 of this study that a maximum release flow was caused by the slow dissolution of the paracetamol crystals at the interface. In the case of sodium salicylate, however, the maximum release flow is dependent on particle size. Moreover the mass flow from a tablet of sodium salicylate is about 50 mg cm^{-2} min^{-1} and therefore only the release of very coarse size fractions may be rate-limited by the dissolution of its particles. Evidently there is an interfacial resistance on the lipid side of the interface for the particles investigated.

Fig. 3 represents a plot of the maximum release flow of 20 size fractions of sodium salicylate vs their particle size. The experimental values were fitted according to Eqn. 8 by a non-linear curve-fitting program to evaluate β, A, B and n. The values for these

TABLE 3

VALUES FOR VARIABLES IN EQN. 8

β	A	B	n	
0.91	19.99	0.070	−0.088	+ first 5 points
1.07	19.99	0.224	+0.074	− first 5 points
1.00	20.00	0.136	−	n set at 0.00

parameters are shown in Table 3. The first 5 experimental points (Fig. 3) all fall below the fitted curve. Because these smaller particle sizes of sodium salicylate show the phenomenon of agglomeration, probably resulting in a negative effect on drainage time, a second run was performed without these 5 points (Table 3). The slightly negative value for n has changed into a slightly positive one, and the experimental points were more randomly distributed around the fitted curve. Thus very probably the weakly sigmoid shape of the curve that is induced by the low particle sizes is caused by the agglomerated state of these particles. Approximating $n = 0$, a third run was performed, including the first 5 points. The final value of β, A and B are also shown in Table 3. For $n = 0$ the drainage time (t_a) is independent of particle size. Substitution of the value for B in Eqn. 7 gives:

$$t_a = 0.136 \text{ min} = 8 \text{ s} \tag{9}$$

Thus the results indicate that an interfacial process is operating in vitro that is independent of particle size as explained in the theoretical section for curve A (Fig. 2). Obviously this result is also conflicting with the theory for single objects approaching an interface in which t_a is linearly related with particle size (Reynolds 1886; Hartland 1968). Crommelin (1979) investigated individual particles of sodium chloride approaching a liquid-paraffin/water interface. He observed that larger particles had shorter drainage times than smaller ones and so it may well be that the theory developed on macroscopic models as spheres and flat plates with smooth surfaces is not valid for small particles with an irregular shape. We have therefore measured the drainage time for individual crystals of sodium salicylate from various size fractions (Table 4).

It appeared that the orientation of the particles is very important. Although all crystals are dissolving at the interface with the h-dimension vertically oriented, most crystals fell edge on through the liquid-paraffin (sodium salicylate crystals are flat platelets: width/height $\simeq 9.5$). If the crystals reached the interface in this orientation all size fractions were wetted within a second; however, if the particles had time to change their orientation close to the interface, drainage times increased substantially. For the coarsest particles ($\bar{d}_g = 1309$ μm) the drainage times went up to 15 s; for the smallest size fractions ($\bar{d}_g = 533$ μm), up to 3 min. The results therefore show a high variation and an increase in $\bar{t}_a$ with particle size (Table 4). Thus the results found for single crystals of sodium salicylate are not in accordance with the theory of Reynolds and Hartland. In a multiparticulate system other factors besides the orientation may further complicate the picture. For instance, the influence of the weight of the particle column on the particles to be wetted

TABLE 4

MEAN DRAINAGE TIME ($\bar{t}_a$) AND VARIATION (v) [a] OF 40 CRYSTALS OF SODIUM SALICYLATE IN EACH SIZE FRACTION

$\bar{d}_g$	1309	1143	960	771	697	552	523
$\bar{t}_a$	3.1	3.8	7.7	9.5	19.7	20	24
v (%)	115	193	171	172	175	128	169

[a] v = standard deviation/$\bar{t}_a$ × 100%.

is not known and also the time it takes for a particle to find a pore in the rapidly dissolving particle layer may add to the interfacial resistance. The use of the term 'drainage time' for multiparticulate systems may therefore be questioned. Since this term conveniently discriminates the transport process at the interface from that in the bulk of the lipid it is used in this study, but certainly the drainage of particles in the system under investigation cannot be readily compared with the drainage of macroscopic models with smooth surfaces, as studied by Reynolds and Hartland.

The curve in Fig. 3 approaches a limiting value for Φ_s, that should be the flow for the dissolution rate-limited case: this flow, Φ_s^{max}, may be calculated from Eqn. 8 by substituting the values for β and A in the equation since $B \cdot h^n = 0$ in this case. The calculated value: $\Phi_s^{max} = 65\ mg \cdot cm^{-2} \cdot min^{-1}$ is about 30% higher than the flow from a tablet surface: $\Phi_s \simeq 50\ mg \cdot cm^{-2} \cdot min^{-1}$. As we also found a higher Φ_s^{max} for very coarse particles of paracetamol as compared with a tablet surface of paracetamol, it is obvious that the mass flow from a tablet can only be a rough indication of the Φ_s^{max} for particles at an interface. That there is a similarity between tablet dissolution and the dissolution rate-limited case of particles at an interface is also indicated by the value found for β (β = 1.00; Table 3), suggesting that the particle system may be viewed as a plate without pores. This phenomenon is being investigated at the moment and the results will be reported at some future date. Summarizing the results for sodium salicylate in the liquid-paraffin/water system it is concluded that an interfacial resistance is present at the interface.

The existence of a maximum release flow for each particle size (Table 1) and the high values for the sedimentation flow as compared with the maximum release flow for a certain particle size is excluding the possibility that the particle size effect on flow rate is caused by differences in transport rate in the bulk of the lipid phase. It was shown for paracetamol and salicylic acid that if dissolution of a multiparticulate system at an interface is the rate-limiting process, it is independent of particle size (Crommelin, 1979; Schoonen et al., 1979). Therefore the particle size effect on flow rate for rapidly dissolving drugs such as sodium salicylate can only be caused by a transport process at the lipid side of the interface. Consequently Eqn. 8 gives the mass flux as a result of the two transport processes at the interface: drainage and dissolution, in which the influence of particle size on drainage time is left open. Fitting the experimental values according to Eqn. 8 reveals an almost constant drainage time (8 s) and it is concluded therefore that the parti-

TABLE 5

RELEASE FLOW (mg/min) FROM SUPPOSITORIES WITH 3 CONCENTRATIONS OF SODIUM SALICYLATE

$\bar{d}_g$ (μm)	30	44	58	107	171	204
5.8%	3	13	16	15	16	14
11.6%	3	15	30	37	31	30
17.4%	3	14	29	54	52	47

Each value is the mean value of two measurements.

cle size effect on flow rate is caused solely by the linear increase in number of particle layers as particle size is reduced. To investigate whether the influence of drainage time on release also occurs in suppositories, we measured the release rate from suppositories in vitro in an apparatus described previously (Schoonen et al., 1976). The release of 3 concentrations (5.8%; 11.6%; 17.4%) was measured for various size fractions of sodium salicylate from Witepsol H 15. Table 5 shows the results. The mass flow given in Table 5 is the maximum flow obtained from the concentration–time curve by measuring angle between the curve and the x-axis.

For the smaller size fractions ($\bar{d}_g = 30$ μm and $\bar{d}_g = 44$ μm) all concentrations gave the same release rate, indicating that here also the viscous drainage of the interface determines the release rate. For the size fractions, $\bar{d}_g = 107$ μm; $\bar{d}_g = 171$ μm; $\bar{d}_g = 204$ μm, each concentration has reached a constant release flow that is proportional to the concentration. Here the melting process is rate-limiting as the total amount of sodium salicylate was released within 10 min. In the apparatus the solid core of the suppository rests on the interface between the already melted mass and the aqueous phase. Therefore all the drug particles within a layer of freshly liquified base are released almost instantaneously if the viscous drainage is fast enough. This is the reason for the proportionality between release flow and concentration for the coarser size fractions.

The viscous drainage as the rate-limiting step for the smaller size fractions explains why a micronized fraction of sodium salicylate is released slower than a micronized fraction of salicylic acid (Schoonen et al., 1976). In both cases sedimentation of the micronized particles in the base is faster than the transport of the drug across the interface, due to agglomeration of the particles. The acid may dissolve in the base just above the interface whereas the particles of sodium salicylate have to cross the interface. The convective diffusional flow of salicylic acid molecules across the interface and in the aqueous phase (phosphate buffer, pH = 7.4) evidently proceeds more rapidly than the viscous drainage of the salt particles. This result was also found for sodium benzoate/benzoic acid (Stuurman-Bieze et al., 1978) and to a lesser extent for sodium phenobarbital/phenobarbital (Schoonen et al., 1976) indicating that a rate-limiting interfacial transport is a general phenomenon in the release of drugs from non-polar media.

Subsequently we attempted to demonstrate that viscous drainage is also a relatively slow and rate-limiting step in the release of highly water-soluble drugs in vivo. The question then arises which criterion can be used to discriminate between the two hypotheses: (1) a rate-limiting transport through the bulk of the base; or (2) viscous drainage at the interface, as both mechanisms are predicting an increase in flow with increasing particle size.

In vitro various concentrations of drug could be used, as sedimentation flow is proportional to concentration and in the case of an interfacial rate-determined process, release flow is independent of concentration. However, these constant values for the release flow in the latter case are measured in a system where the lipid phase is not moving and sedimentation of particles is able to create a dense packing of particles above the interface. In vivo the suppository is spreading upward into the direction of the colon under influence of the abdominal pressure and therefore it is unlikely that in the moving base a packing of equal density is reached in the neighbourhood of the interface. The only variable left to discriminate between the two hypotheses is viscosity, but here also things are complicated

TABLE 6

VISCOCITY MEASUREMENTS [a] FOR THE PREPARATIONS ADMINISTERED RECTALLY

Suppositories	(mPa.s)	Micro-enemas + 10% sodium salicylate	(mPa.s)
10% sodium salicylate	53	Low visc. liq. paraffin	21
20% sodium salicylate	91	Low visc. liq. paraffin + 10% talcum	34
10% sodium salicylate 5% aerosil 972	336	Low visc. liq. paraffin + 20% talcum High visc. liq. paraffin	117 75

[a] The preparations with 5% aerosil 972 and 20% talcum showed a significant non-Newtonian rheological behaviour. These results therefore are a mean value of a 2-point measurement.

since the in vitro experiments indicated that the interface transport as well as sedimentation are affected by viscosity. It is important in this respect to realize that for suspensions the term 'viscosity' may be used for two different phenomena: (1) the viscosity of the fluid phase itself, 'fluid viscosity'; and (2) the viscosity as influenced by the amount of particulate matter in the suspension: 'concentration viscosity'. In vitro the viscous drainage is dependent on the 'fluid viscosity' but not on the 'concentration viscosity', whereas sedimentation is affected by both. Therefore in vivo experiments were carried out in which the 'concentration viscosity' and the 'fluid viscosity' were varied separately.

Moolenaar et al. (1979) had already verified that sodium salicylate showed the particle size effect as expected for highly water-soluble drugs. To avoid differences in absorption rate due to an unequal spreading of the particles within the base, the micronized fraction of sodium salicylate was used in the following experiments. The viscosities of all preparations used are shown in Table 6. The 'fluid viscosity' of a Witepsol H 15 suppository containing 11.6% sodium salicylate was increased by adding 5% of Aerosil 972. The 'concentration viscosity' was changed by adding 23.2% of sodium salicylate instead of 11.6%. Figs. 4 and 5 show the results. An increase in 'fluid viscosity' decreases the absorption rate, whereas an increase in 'concentration viscosity' even results in plasma values that are

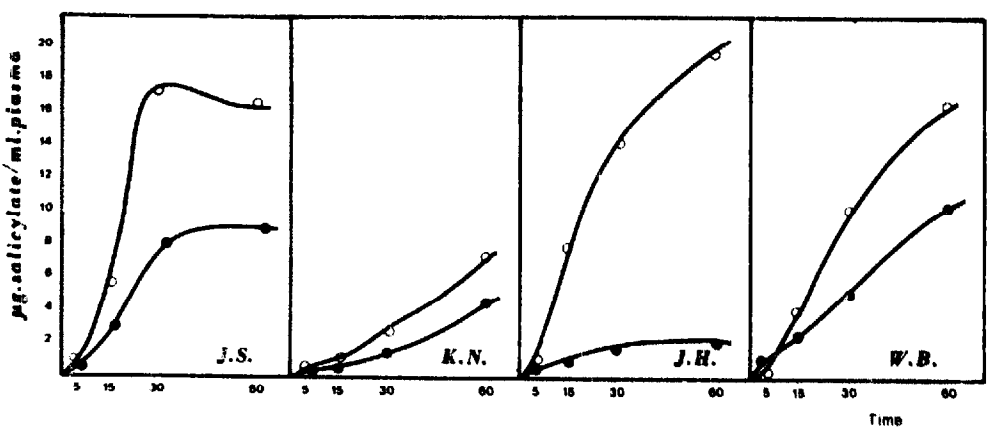

Fig. 4. Absorption of sodium salicylate from Witepsol H 15 suppositories with a different 'fluid' viscosity. o——o, 11.6% Na.sal (micr.); ●——●, 11.6% Na.sal (micr.) +5% Aerosil 972.

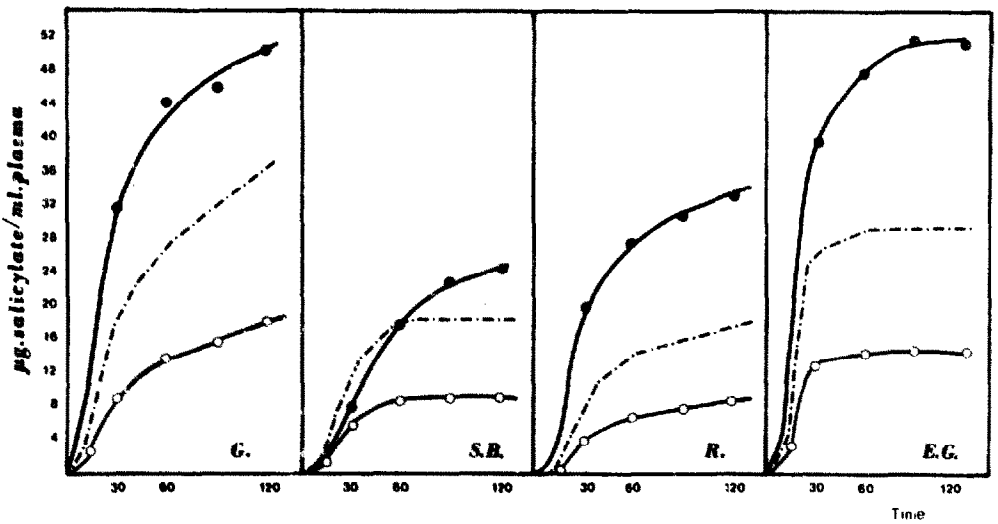

Fig. 5. Absorption of two concentrations of sodium salicylate from Witepsol H 15 suppositories. o——o, 11.6% Na.sal (micr.); •——•, 23.2% Na.sal (micr.); - - - - - - expected absorption of 23.2% Na.sal (twice the plasma values of 11.6% Na.sal).

more than twice as high compared with the controls. If the bulk transport of particles through the base is the rate-limiting step, it was expected that the increase in absorption rate should be less than the increase in concentration because the higher viscosity should have a negative effect on absorption rate. Suspensions of micronized sodium salicylate in

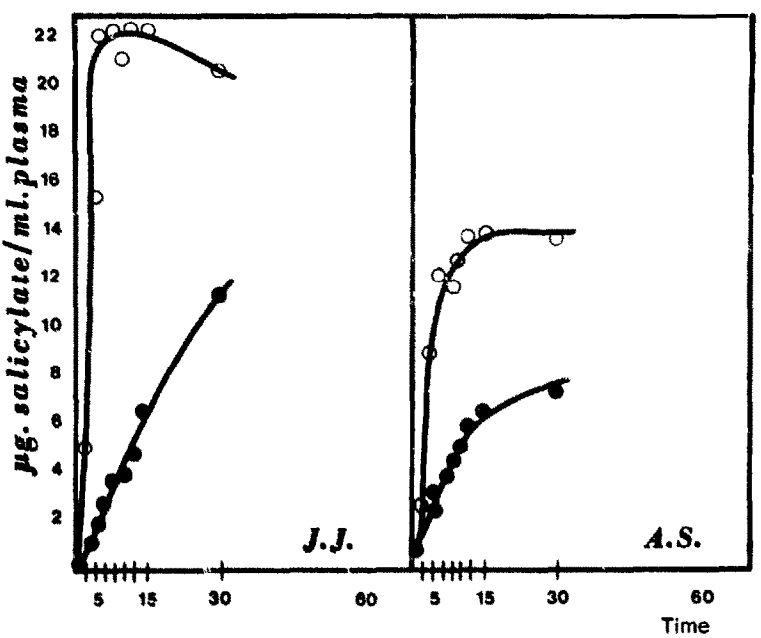

Fig. 6. Absorption of sodium salicylate from liquid-paraffin enemas with different 'fluid' viscosity. o——o, 11.6% Na.sal (micr.), liq. paraffin 21. mPa.s; •——•, 11.6% Na.sal (micr.), liq. paraffin 75 mPa.s.

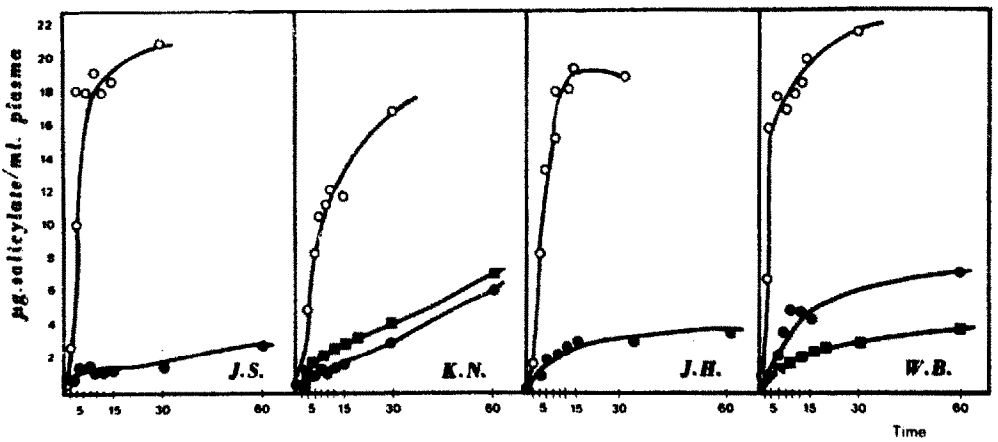

Fig. 7. Effect of talcum addition on absorption of sodium salicylate from liquid-paraffin enemas. ○———○, liq. paraffin (21 mPa.s); ●———●, 20% talc 117 mPa.s); ■———■, +10% talc (34 mPa.s).

these high concentrations did not settle at all in vitro. The suspension is one aggregated mass, that may form a resistance against the deformation that is exerted by the pressure of the rectum wall on the molten suppository. This might explain the almost 3-fold increase in absorption rate as in such a system the particulate matter may be pressed across the interface, resulting in a lower drainage time. It is difficult to explain this in vivo behaviour of the suppositories with a rate-limiting step in the bulk transport of particles in the base, whereas the results are in accordance with the viscous drainage hypothesis.

The 'fluid viscosity' was also varied in micro-enemas consisting of 11.6% sodium salicylate in 4 ml of liquid-paraffin with different viscosities (Table 6). In these systems the melting behaviour of suppositories is avoided and also differences in spreading are less likely. Fig. 6 shows that in this system variation in 'fluid viscosity' gave the same results as for suppositories. To illustrate the importance of particle behaviour at the interface we have finally added talcum to the micro-enemas. Talcum is insoluble in liquid-paraffin and in water and the particles remain at the interface effectively blocking the interfacial passage of the sodium salicylate particles (Fig. 7). To get an impression of the influence of 'concentration viscosity' in this case two volunteers received micro-enemas with 10% and 20% of talcum. The two experiments do not permit definite conclusions but the results indicate that 'concentration viscosity' has no effect on absorption rate, making it probable that talcum expresses its influence on absorption rate by 'poisoning' the lipid/water interface.

Summarizing the in vivo results it is concluded that: (1) the addition of materials that elevate the 'fluid viscosity' lower the absorption rate and that an increase in 'concentration viscosity' even shows the opposite effect; (2) the addition of materials that are insoluble in the lipid and aqueous phase forms an interfacial resistance that severely limits the release process in vivo; and (3) the foregoing conclusions support the viscous drainage hypothesis as the explanation for the particle size effect on release and absorption of highly water-soluble drugs.

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