International Journal of Pharmaceutics, 4 (1979) 141–152

RELEASE OF DRUGS FROM FATTY SUPPOSITORY BASES I. THE RELEASE MECHANISM

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(Received May 30th, 1979)
(Revised version received September 25th, 1979)
(Accepted September 27th, 1979)

SUMMARY

A model for drug release from fatty suppository bases is presented that explains in vitro measurements on drugs with various physicochemical characteristics, such as paracetamol (slowly dissolving in water) sodium salicylate (rapidly dissolving in water) and salicylic acid (soluble in lipid).

The in vitro results are compared with in vivo experiments on rectal absorption in man. Results indicated that for suspensions of all the drugs investigated, dissolution takes place at the interface between the suppository base and the surrounding fluid. The release process therefore includes a flow of particles in the suppository base into the direction of the interface and a flow of solute away from the interface. Either of these flows may be rate limiting dependent on the water solubility of the drug, and may determine the effect of concentration and particle size on release rate.

INTRODUCTION

Suppositories composed of a fatty base and a drug dissolved or suspended in that base are quite different from other dosage forms which are used for oral and rectal medication. This kind of suppository is characterized by the existence of an interface between molten base and water layer present along the epithelium membrane. To explain transport of drug from this delivery system a fourth compartment, representing the suppository base, should be added to the three that are commonly used to describe the absorption process (see Fig. 1).

The amount of drug absorbed per unit time (mass flow) depends on two factors:

(1) *The total area of interface in contact with the rectum wall.* After melting of the suppository base, this area is determined by the volume of the rectum and the volume of the suppository. The rectum volume is influenced by the abdominal pressure on the

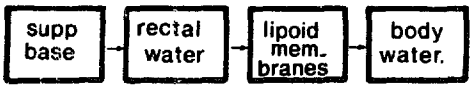

Fig. 1. Four compartments to describe release and absorption from fatty suppositories.

rectum wall. This pressure may create a force on the melting suppository to spread along the rectum wall resulting in an enlarged interface. Also, a more voluminous suppository will give rise to a larger interface. It seems irrelevant therefore to investigate the spreading of the suppository base in vitro, but it will be demonstrated that in vitro measurements may predict under which conditions the effect of area will be observed in vivo.

(2) *The rate of flow per unit interface.* Since variables that have an influence on flow rate of drug are different for the various compartments, it is of importance to know if there is a rate limiting step that determines the overall rate. For instance, a change in viscosity of the base will have no effect on release if dissolution of the drug in water is the rate-limiting step.

An interface with a well-defined, constant, area can be prepared in vitro by placing a tube containing the lipid phase vertically in a water vessel. In this way transport of drug can be studied within the lipid phase, and also across the lipid/water interface itself.

Although a simple quantitative relationship between the in vitro release of drugs from fatty suppositories and in vivo absorption should not be expected, it is possible now to describe qualitatively the effects of various parameters such as water solubility, lipid solubility, concentration in the base and particle size on the release from fatty suppository bases.

In the present study a release model is proposed that explains the influence of these parameters. The model is evaluated by a combined in vitro and in vivo investigation.

THE RELEASE MODEL

In a model system consisting of two fluid phases with a constant interfacial area in which the drug is released from the lipid phase into the water phase, two cases can be identified (Fig. 2):

(I) where the drug is insoluble in the lipid phase and

(II) where the drug is soluble in the lipid phase.

(I) Drug insoluble in lipid

In this case mass transport consists of three consecutive steps: (1) sedimentation of drug particles in the suppository base, to the lipid/water interface; (2) wetting of the particles by the water phase and (3) dissolution of the drug in the aqueous phase. Since the particles of the drug investigated did not fall through the water phase after wetting and remained attached to the lipid phase it is clear that dissolution takes place in a narrow region at the interface.

Assuming at time $t = 0$ a homogeneous suspension of particles with a uniform size, the

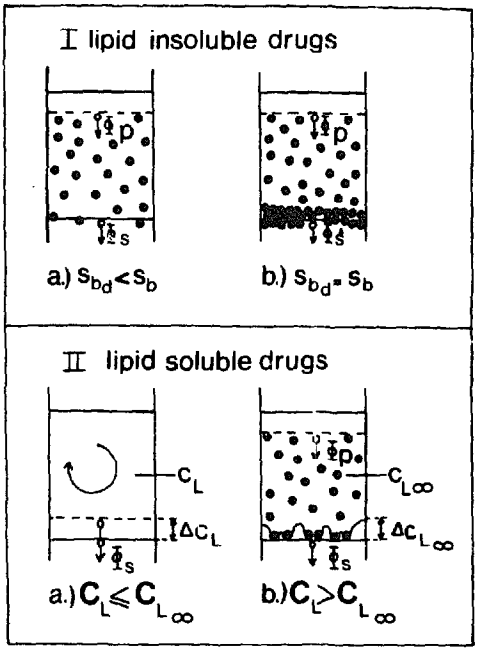

Fig. 2. The release model (symbols: see text): Ia, for drugs dissolving rapidly in water; Ib, for drugs dissolving slowly in water; IIa, for drugs dissolved completely in the base; IIb, for drugs dissolved partially in the base.

mass flow of particles (ϕ_p) through a horizontal plane in the lipid phase will be:

$$\phi_p = C \cdot V_t/t \tag{1}$$

in which: C = concentration of particles in the suspension; t = time; V_t = volume of drug suspension transported through the plane in time t. As V_t equals the area of the plane (S_b) times the distance across which the particles are sedimenting in time t, it may be written:

$$V_t = S_b \cdot v_s \cdot t \tag{2}$$

where v_s = sedimentation rate. Substitution of Eqn. 2 into Eqn. 1 gives:

$$\phi_p = C \cdot S_b \cdot v_s \tag{3}$$

Thus for a constant area of interface the mass flow in the lipid phase is proportional to concentration of drug and sedimentation rate.

Dissolution of a solid is described by the equation of Noyes–Whitney:

$$\phi_s = K_w \cdot S\,(C_{W\infty} - C_{w_t}) \tag{4}$$

where ϕ_s = mass flow of solute; K_w = dissolution rate constant; S = area of solid in con-

tact with solvent; C_{w_∞} = saturation concentration in solvent; C_{w_t} = concentration in the bulk of liquid at time = t.

If the total area of particles at the interface in contact with the water phase is S_d, and dissolution takes place under sink conditions (concentration in bulk of surrounding fluid is about zero), it may be written:

$$\phi_s = K_w \cdot S_d \cdot C_{w_\infty} \tag{5}$$

As the mass flow for a certain area of interface is constant in time, there is also a constant relationship (α) between S_d and the part of the interface that is occupied with particles S_{b_d}.

$$S_d = \alpha \cdot S_{b_d} \tag{6}$$

Theoretically S_d is independent of particle size, if porosity at the interface does not change and the shape of the different sized particles is the same. This can be envisioned as follows: suppose a certain area of interface is occupied with n particles of size d and surface βd^2, (β = shape factor), then the total surface available at the interface is: $S_d = n\beta d^2$. Now, if these particles are milled to a size, $\frac{1}{a} \cdot d$, then the amount of particles increases until $a^3 n$, but as there is only one layer of particles at the interface, the amount of particles at the interface is $a^2 n$.

The surface of one particle now is $\beta(\frac{1}{a} \cdot d)^2$, therefore the total available surface at the interface is: $a^2 n \cdot \beta(\frac{1}{a} \cdot d)^2 = n\beta d^2 = S_d$.

If there is no resistance at the interface two cases can be identified: (a) until $S_{b_d} = S_b$ the interface is not fully occupied by particles and there is no accumulation of particles at the interface (Fig. 2). Therefore $\phi_s = \phi_p$ and the release of drug is determined by the mass flow through the lipid phase. As sedimentation rate is proportional with the square of particle size and is inversely related with viscosity of the base these parameters, especially particle size, and also concentration (Eqn. 3) will have an effect on release rate; (b) if the mass flow through the lipid phase is increased for a given system by increasing concentration and/or particle size, S_{b_d} will approach S_b. When $S_{b_d} = S_b$, dissolution flow is maximal (Eqns. 5 and 6) and a further increase will give rise to accumulation of material above the interface (Fig. 2, Ib). Thus release is dissolution rate-limited and independent of the concentration in the base, particle size and viscosity. The mass flow in this case should be about the same as the mass flow from a dissolving tablet surface of the same material.

If there is an interfacial resistance present, accumulation of drug particles at the interface will be measured by a lower value for the maximum mass flow.

(II) Drug soluble in lipid

In the scheme as shown in Fig. 2, IIa, it is assumed that no concentration gradient develops in the bulk of the lipid phase due to convection (concentration S_1 in lipid is less or equals saturation concentration C_{l_∞}). If there is no accumulation of solute at the inter-

face, mass flow is equal in both phases and the resistance to flow in the lipid phase may be added to the resistance in the water phase.

For dissolution of a solid in water a rate constant K_w (Eqn. 4) was defined. If it is assumed that transport of solute away from the solid/water interface is rate-limiting, then $1/K_w$ is also the resistance for transport of solute away from the lipid/water interface when the hydrodynamic conditions are the same. Therefore, flow per unit interface of a saturated solution of solute from the lipid phase will always be lower than the flow from a solid surface of the same material (a tablet for instance) if the resistance in lipid is not negligible.

When drug is present in a concentration that is higher than its saturation concentration in lipid, particles are sedimenting into the hydrodynamical boundary layer of the lipid, effectively lowering the resistance (Fig. 2, IIb). It will be demonstrated that flow is increasing linearly with the area of interface that is occupied by particles (S_{b_d}).

As the value for S_{b_d} is influenced by ϕ_p and ϕ_s in exactly the same way as is described for solids that are not dissolving in lipid, and dissolution in the lipid phase also takes place at the interface, the same model can be used as for lipid insoluble drugs.

Now, the effect of particle size on mass flow will be measured only between the flow at saturation concentration C_{l_∞} and the maximum flow, which is again determined by C_{w_∞} and K_w. Usually lipid-soluble drugs dissolve slowly in water, therefore the release of these drugs may be interpreted as a special case of Ib (Fig. 2).

EXPERIMENTAL

Materials; particle size determinations

All drugs and lipid phases (Witepsol H15, liquid paraffin 0.075 Pa.s., liquid paraffin 0.03 Pa.s., petroleum-ether, olive oil) are commercially available and meet the requirements of the Dutch Pharmacopoeia, Ed. VII. Sieving was accomplished with the aid of a Fritsch model analysette 3 and an Alpine model A 200LS for size fractions >100 μm.

For the smaller size fractions a centrifugal classifier (Alpine) was used. Micronized fractions were prepared with a jet mill, Gem. T model 1047. Particle sizes were determined microscopically. According to the procedure described by Hatch and Choate (1929), a mean geometrical diameter ($\bar{d}_g$) and standard deviation (σ_g) were obtained.

Tablets of sodium salicylate (sieve fractions 10–20 μm and 125–250 μm), paracetamol (acetaminophen) (sieve fractions 500–600 μm and <20 μm) and salicylic acid (micronized fraction) were made with a manual press (force: 11.76 kN), without any additives.

Sedimentation measurements

A Cahn RG-HV electrobalance was used in determining the settling rate of the powders at various concentrations in liquid paraffin (20°C) and Witepsol H15 (37°C).

The height of the sedimentation cylinder (glass) was 17 cm and the diameter 5.3 cm. The pan had a diameter of 3 cm and was placed 9 or 15 cm beneath the meniscus of the suspension.

Release rate measurements

The release rate apparatus for suppositories as shown in Fig. 3 was described earlier (Schoonen et al., 1976).

Suppositories are allowed to melt against a glass plate that is fixed in a vessel containing 900 ml of water. In the molten suppository particles are sedimenting to the interface and release is measured under conditions of natural convection. Above the plate the solution is stirred and from here samples are taken.

Release rate across a constant interface was measured cumulatively from methacrylate polymer [1] tubes about 15 cm long, with an internal diameter of 1 cm in a water vessel of the same material (1.5 liters). A stirring rate was chosen that did not influence the dissolution rate of the slowly dissolving drugs; transport of solute away from the interface was accomplished by natural convection. Concentration was measured spectrophotometrically (Beckmann, model 25).

Also release rate was measured in a slightly modified continuous-flow recording system (Fig. 4) as described earlier (Schoonen et al., 1979). In this system it was also possible to measure the part of the interface that was occupied by a single layer of salicylic acid crystals by photographing the interface from above through the lipid phase. At the same time the flow from these crystals could be measured spectrophotometrically (Beckmann, model DB-GT).

RESULTS AND DISCUSSION

In previous studies (Schoonen et al., 1976; Moolenaar, 1979; Stuurman-Bieze et al., 1979) it was shown that in vitro and in vivo release was affected by particle size variation. For certain drugs coarser particle size fractions absorbed more rapidly than smaller size fractions (sodium benzoate; sodium salicylate; sodium phenobarbital) for other drugs the smaller size fractions absorbed more rapidly (paracetamol; acetylsalicylic acid) whereas for some drugs particle size variation had no effect at all (benzoic acid).

Clearly the influence of particle size on the release from fatty suppository bases is different for the various drugs used. To investigate if the theoretical release model could explain these differences, the release from a constant interface between liquid paraffin or olive oil and water was studied for three drugs: paracetamol (acetaminophen) (insoluble in lipid and slowly dissolving in water), sodium salicylate (insoluble in lipid and rapidly dissolving in water), and salicylic acid (lipid-soluble and slowly dissolving in water). By using liquid paraffin (olive oil in the case of salicylic acid) the influence of melting time is avoided as well as the effect of surface active agents that may be present in suppository bases.

If, for a certain concentration and particle size the mass flow of drug is equal for sedimentation and release measurements, then it may be concluded that dissolution of particles at the interface is relatively fast and that a resistance in particle transfer across the interface is negligible (case Ia of the release model).

[1] Perspex

Paracetamol

Results of the measurements for paracetamol are shown in Fig. 3. Included is the mass flow per unit area of dissolving tablets of paracetamol under the same hydrodynamical conditions.

For a suspension of this drug there is a critical point at a certain concentration for each particle size above which the mass flow is constant and is about the same as the flow from a dissolving tablet surface. Evidently the mass flow is dissolution rate-limited above the critical point (case Ib of the release model). As can be seen, the influence of particle size is negligible and release is independent of concentration.

The question now arises whether this situation will be present in vivo. Usually a higher dose is recommended when a higher blood level of drug is required in a single dose situation in order to obtain a rapid therapeutic effect. However, in the case of a dissolution rate-limited release, the mass flow per unit interface is constant and independent of concentration of the drug in the suppository. As a consequence a higher dose primarily

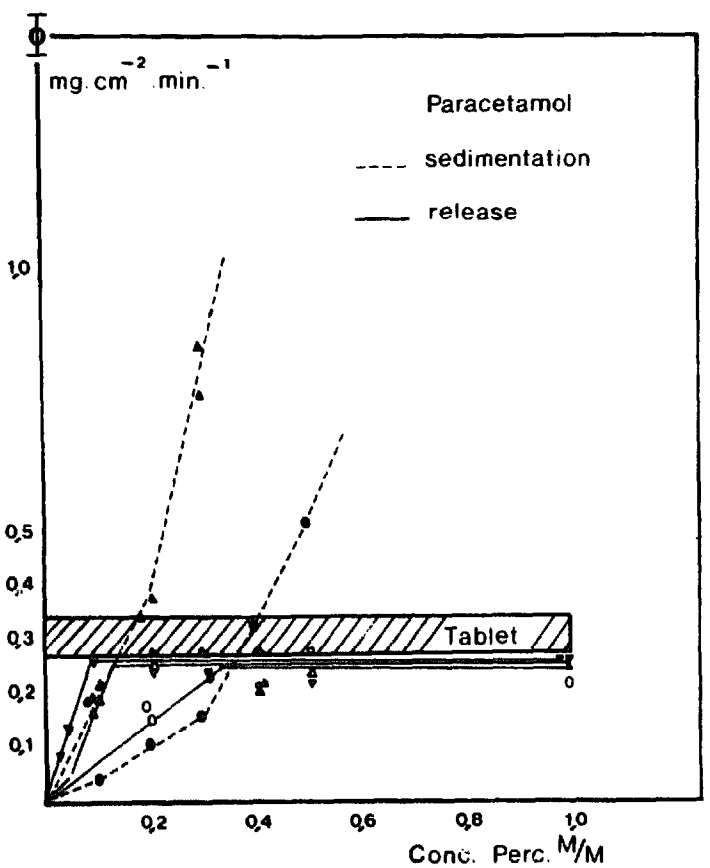

Fig. 3. Release flow (———) and sedimentation flow (- - - - - -) of paracetamol compared with the dissolution rate limited flow as measured from tablets. (lipid phase: liquid paraffin, 0.075 Pa · s). (▼———▼: $\bar{d}_g$ = 157 μm · σ_g = 1.45); (▲———▲: $\bar{d}_g$ = 69 μm · σ_g = 1.30); (●———●: $\bar{d}_g$ = 35 μm · σ_g = 1.33).

will give rise to a prolonged absorption process. In order to obtain higher plasma concentrations, it will be more rational in that case to enlarge the interface by increasing the volume of the suppository.

The spreadability of the base in the rectum, however, may interfere with this scheme. The area of interface in situ is not known and it may well be that the interface is only partially occupied by drug particles. Then a higher concentration will have the same effect as an enlarged interface. It is generally assumed that smaller particles are spreading more easily with the base than a course fraction. Fig. 3 shows that release of paracetamol is dissolution rate-limited already at a concentration of 0.5% even for very small size fractions. Therefore, it can be safely stated that this will also be the case in vivo, where the usual concentrations in the suppository are 12.5–25% (500–1000 mg in a suppository of 3 ml). As the release per unit interface is constant and is the same for each particle size, it was expected that if smaller particles will occupy a greater part of the available interface due to more complete spreading with the base, they should give a higher absorption rate.

Indeed a substantially lower absorption rate was found for paracetamol if a size fraction 125–250 μm was used in the suppository, compared with smaller particles (20–35 μm of micronized fraction) (Table 1: values from Moolenaar, 1979).

As it was expected that a micronized fraction would spread completely with the base occupying all the available interface, it was investigated with this fraction whether concentration and volume changes would show the predicted behaviour for the dissolution rate-limited case.

The results (Moolenaar, 1979) confirm the proposed release model, since the higher

TABLE 1

RESULTS FROM IN VIVO MEASUREMENTS: C_{max} AND t_{max} AS A MEASURE FOR ABSORPTION RATE OF DRUGS IN PLASMA AND URINE

Dose	% dissolved in base	Fraction	C_{max} ± S.D.	t_{max} ± S.D.	N [a]	Plasma/ urine
Paracetamol	0	<20	5.8 ± 0.7 (μg/ml)	150 ± 25	6	plasma
1000 mg		125–250 μm	2.6 ± 0.3 (μg/ml)	180 ± 30	6	plasma
Sodium benzoate	0	<20 μm	40.0 ± 10.4 (mg)	105	10	urine
472 mg		125–250 μm	48.3 ± 14.8 (mg)	60	10	urine
Sodium salicylate	0	<20 μm	13.0 ± 4.5 (μg/ml)	120 ± 40	6	plasma
431 mg		125–250 μm	25.8 ± 5.2 (μg/ml)	45 ± 15	6	plasma
Salicylic acid	4	<20 μm	20.0 ± 4.2 (μg/ml)	110 ± 30	6	plasma
400 mg		125–250 μm	19.7 ± 3.9 (μg/ml)	130 ± 30	6	plasma
Benzoic acid [b]	6	<20 μm	90 (mg)	30 – 60	8	urine
400 mg		125–250 μm	90 (mg)	30 – 60	8	urine
Acetylsalicylic	1.5	<20 μm	4.1 ± 0.4 (μg/ml)	35 ± 15	8	plasma
acid 500 mg		125–250 μm	2.2 ± 0.3 (μg/ml)	45 ± 15	8	plasma

[a] Number of volunteers.
[b] Preliminary investigation.

concentration results in a prolonged drug absorption whereas the initial absorption rate, as judged by the initial plasma concentrations, is equal for a 500 and a 1000 mg dose. Also a decrease in volume lowers the absorption rate considerably.

Sodium salicylate

Sodium salicylate shows a completely different behaviour. It can be seen from Fig. 4 that release flow and sedimentation flow are almost identical for a particle size fraction of $\bar{d}_g = 259$ μm. This is the maximum particle size that can be used in preparing suppositories in order to ensure "content uniformity". The sedimentation flow typically determines the overall release flow.

Although the ϕ_s^{max} from a tablet surface shows some variability, the values are much higher than in the case for the flux across a lipid/water interface of the size fraction of $\bar{d}_g = 259$ μm (Fig. 4).

Evidently the measured maximum release flow is limited by the rate of transport in the base rather than by the dissolution process at the interface. As the viscosity of a suppository base (Witepsol H15) at 37°C (62 m Pa · s) is not very different from the viscosity of liquid paraffin at 20°C (75 m Pa · s) the release of sodium salicylate from Witepsol H15 will also not be dissolution rate-limited in vitro as well as in vivo.

The results found in our laboratory confirm the model for the highly water soluble drugs: sodium salicylate, sodium phenobarbital and sodium benzoate, that a coarse size fraction is released faster than a small size fraction.

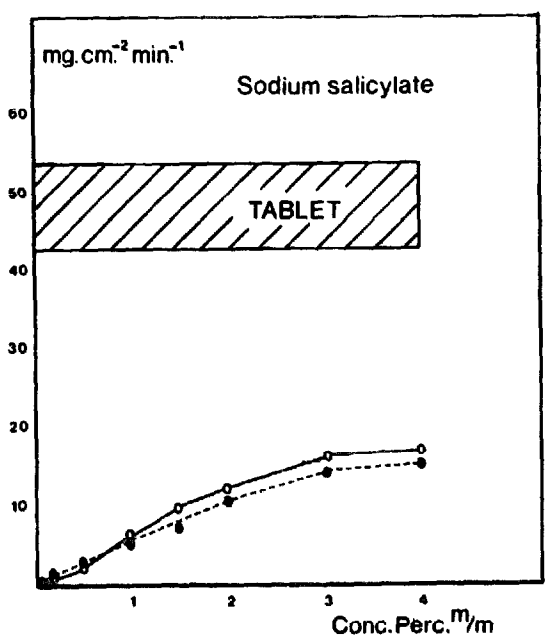

Fig. 4. Release flow (———) and sedimentation flow (- - - - -) of sodium salicylate compared with the dissolution rate limited flow as measured from tablets (●———●: $\bar{d}_g = 259$ μm · $\sigma_g = 1.53$).

These experiments show that transport through the base is rate-limiting, which explains the effect of particle size on the release of these drugs (Moolenaar, 1979; Stuurman-Bieze et al., 1978).

Salicylic acid

For the lipid-soluble drug salicylic acid, it was first investigated to what extent particles at the interface lower the resistance to flow in the lipid phase. Therefore one layer of dissolving crystals at the interface of a saturated solution of salicylic acid in olive oil was photographed and the release measured spectrophotometrically.

Fig. 5 shows the correlation between the measured area of particles occupying the interface and the mass flow.

From Table 2 it can be seen that regardless of particle size, release from olive oil is increased at least 6 times when the interface is fully occupied by particles and is equal to the mass flow of a dissolving tablet surface. This result shows that the resistance to flow for dissolved salicylic acid in olive oil is negligible as sufficient particles are present at the interface.

Thus the diffusional–convective flow of solute away from the interface is rate-limiting, as was the case for paracetamol, and it is concluded therefore that this class of drugs may be considered as a special case of drugs dissolving slowly in water.

A micronized fraction of salicylic acid in a concentration of 2.3% (1% particles) already reached the ϕ_s^{max} (Table 2). This explains why particle size has little or no influence on the in vitro release rate of lipid-soluble drugs from suppositories of salicylic acid, phenobarbital and benzoic acid (Schoonen et al., 1976).

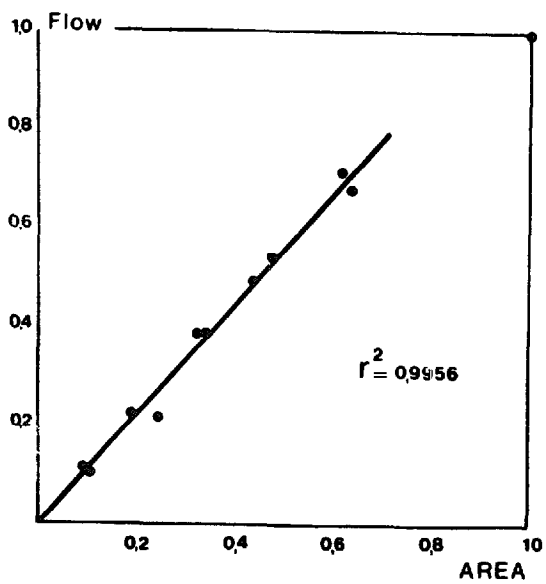

Fig. 5. Correlation between the fraction of interfacial area, occupied by one layer of salicylic acid crystals and the fraction of release flow from these crystals (release flow = measured mass flow – flow of saturated solution).

TABLE 2

RELEASE FLOW OF SALICYCLIC ACID FROM OLIVE OIL (20°C).

Conc. of particles, percent m/m	0	0.125	0.25	0.5	0.75	1	2.5	5	Φ_s^{max}
Φ_s in mg · cm^{-2} · min^{-1} micronized	0.023 [a]	–	0.04	0.10	0.10	0.15	0.15	0.14	0.15 [b]
Φ_s in mg · cm^{-2} · min^{-1} $\bar{d}_g$ = 147 μm, σ_g = 1.41		0.09	0.11	0.16	–	0.16	–	–	

[a] Flow of saturated solution (±1.3%).
[b] Flow measured from tablet surface.

In vivo these results were confirmed in our laboratory for salicylic acid and benzoic acid by Moolenaar (1979) and Stuurman-Bieze et al. (1978), respectively (Table 1).

Small size fractions of paracetamol exhibited a faster release than a coarse fraction due to the larger part of the interface that is occupied by the smaller particles. As paracetamol is insoluble in the suppository base, release can only take place from wetted particles, whereas the acids, which dissolve in Witepsol H15 to the extent of about 4–6%, can also be transported by diffusion to the aqueous phase from the part of the interface that is devoid of particles.

This may be the reason for the fact that these acids have the same release and absorption rate for a coarse size fraction and a micronized powder. We (Moolenaar, 1979) have also investigated acetylsalicylic acid that dissolves in Witepsol H15 to only 1.5%. The release from the part of the interface where no particles are present will be lower for this acid than for salicylic acid and benzoic acid. It was found that a micronized fraction of acetylsalicylic acid is absorbed from the rectum considerably faster than a coarse fraction and this acid therefore shows the same behaviour as paracetamol (Table 1).

CONCLUSIONS

(1) *Water solubility* has a profound effect on release and absorption rates of drugs from fatty suppository bases. It is the driving force in the transport away from the interphase, both in the case that the drug dissolves in water directly or diffuses across the interface (lipid-soluble drugs). It is this factor that determines whether release is rate-limited in the first or second compartment (Fig. 1), and this is important even for the direction in which release flow is affected by concentration and particle size variation. Dissolution for all drugs takes place at the lipid/water interface. The maximum release flow is reached when transport of solute in the second compartment is rate limiting.

(2) *Concentration* of drug in the suppository has no effect on release *per unit* interface, when the release is rate-limited in the second compartment. This is the case for drugs slowly dissolving in water, e.g. paracetamol (insoluble in lipid), and the lipid-soluble

drugs (e.g. salicylic acid, benzoic acid, phenobarbital): for the part of the interface that is occupied with particles. It is shown for paracetamol that the *volume* of the suppository has an effect on absorption rate for drugs slowly dissolving in water. Therefore it is more rational in these cases to change the volume of the dosage form rather than to change the dose if it is desired to influence the initial blood levels. Increasing the dose in suppositories of equal volume for these drugs predominantly influences the time during which absorption takes place, and this may be looked upon as a simple method to induce a prolonged release.

(3) *Particle size* effects on release *per unit* interface are measured for drugs that are insoluble in lipid and dissolve rapidly in water, such as sodium salicylate, sodium benzoate and sodium phenobarbital: coarse size fractions release more rapidly than micronized fractions. If release rate is limited in the second compartment, dissolution rate *per unit* interface is independent of particle size. In this case the effect of particle size is determined by the area of interface that is occupied by the particles of drugs which are not (or slightly) soluble in lipid (paracetamol, acetylsalicylic acid). Micronized fractions release more rapidly than coarse size fractions.

(4) *Lipid solubility* is the driving force for dissolution, diffusional and convective transport of solute in the first compartment. If doses are used higher than the saturation concentration in the suppository, the particles present may easily increase the release rate by moving into the hydrodynamical boundary layer of the lipid phase. The release from the part of the interface occupied with particles is then rate-limited in the second compartment by the low water solubility of these drugs. Particle size effects are negligible for these drugs, as lipid solubility reaches values of 4% or more (salicylic acid, benzoic acid, *not* acetylsalicylic acid).

ACKNOWLEDGEMENTS

The authors are indebted to K. Reuvers, J. Dijkstra and G.W. de Vries-Nijboer who did most of the experiments, and to D.K. F. Meijer for critically reading the manuscript.

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