International Journal of Pharmaceutics, 6 (1980) 29–42

IN VITRO RELEASE STUDIES ON DRUGS SUSPENDED IN NON-POLAR MEDIA II. THE RELEASE OF PARACETAMOL AND CHLORAMPHENICOL FROM SUSPENSIONS IN LIQUID PARAFFIN

D.J.A. CROMMELIN and C.J. DE BLAEY

Dept. of Pharmaceutics, Pharmaceutical Laboratory, Catherijnesingel 60, 3511 GH Utrecht (The Netherlands)

(Received April 28th, 1980)
(Accepted May 6th, 1980)

SUMMARY

The release of paracetamol and chloramphenicol (water solubility 13 and 3.6 mg · g^{-1}, respectively), suspended in liquid paraffin, to an underlying aqueous layer was investigated as a function of particle size (10–60 μm), concentration (0.5–6% m/m) and the presence of additives (DOSS-Na: di-(2-ethylhexyl) sodium sulphosuccinate and/or water) in the liquid paraffin. A hypothesis was formulated predicting the release to be independent of particle size, concentration and degree of coverage of the interface by particles, if the mass flow of the interface would exceed the dissolution rate of the particles at the interface. This limiting rate would approximate the intrinsic dissolution rate. The experimental results showed that for low concentrations the release was determined by the settling mass flow. With more concentrated suspensions the release was dissolution controlled and in general a good agreement with the proposed hypothesis was found.

Addition of water (0.01 or 0.05% m/m) to the suspensions increased the degree of agglomeration and reduced the degree of interfacial coverage, but did not change the release rate. The presence of 0.2% m/m DOSS-Na in the paracetamol suspensions did not influence the rate either, but in combination with water (0.01 or 0.05% m/m) an increase was observed; the particles did not stay at the interface during dissolution, but they fell through it as such. With chloramphenicol this happened already in the presence of 0.2% m/m DOSS-Na. Water addition enhanced this effect dramatically.

INTRODUCTION

The underlying mechanisms which are involved in the release of drugs suspended in non-polar liquid media are poorly known to date. In a previous paper (Crommelin and de Blaey, submitted) the release characteristics of a readily water-soluble substance (sodium chloride) from liquid paraffin were discussed. Three steps could be discerned in the

release process in the experimental model: (a) transport of the solid to the paraffin–water interface; (b) passage through that interface; and (c) dissolution in the aqueous layer. Transport to the interface was essentially governed by sedimentation. This step (a) was rate-limiting in the case of sodium chloride. Depending, for example, upon the water solubility and surface properties of the compound passage through the interface, dissolution may become rate limiting processes.

In the present paper, the behaviour of less water-soluble substances under circumstances comparable with those occurring with the sodium chloride suspensions will be discussed. The effect of particle size, concentration of solid and the addition of di-(2-ethylhexyl) sodium sulphosuccinate (DOSS-Na) or water to the liquid paraffin phase on the release was studied. Paracetamol (water solubility 13 $mg \cdot g^{-1}$) and chloramphenicol (water solubility 3.6 $mg \cdot g^{-1}$) were chosen as model substances. Their solubility in liquid paraffin is negligible.

METHODS AND MATERIALS

Particle size fractions

Particle size fractions with narrow size distributions were obtained with a centrifugal classifier. Microscopically the mean particle size was assessed according to the projected area method. Paracetamol fractions with arithmetic mean diameters of 9 μm and 16 μm were used. A third fraction containing large particles (mean volume diameter: 60 μm) was contaminated with small particles which stuck to the large ones persistently. The two particle size fractions of chloramphenicol had arithmetic mean diameters of 5 and 27 μm, respectively.

Preparation of the suspensions

To investigate the particle size and concentration influence on the release of paracetamol, the preparation scheme as described previously (Crommelin and de Blaey, submitted) to establish the effect of the same variables on the release of sodium chloride was followed with minor changes, Paracetamol was dried for at least 5 days prior to use in a desiccator containing silica gel under lowered pressure (less that 2 kPa). It appeared that, contrary to the sodium chloride suspensions, in some cases the release profiles of samples taken from the suspensions changed with time during the first 2 h of (end-over-end) rotation of the bottle. The release did not change further when longer rotation times were employed (up to 48 h). For chloramphenicol the same procedure was used except that these suspensions were prepared in a dry box with a relative humidity lower than 5% and that the ultrasonic treatment was dropped. The release profile did not change after 0, 2, 4 and 6 h of rotation at 45 rpm. After 24 h, however, the release sometimes was reduced. To attain a maximum reproducibility both paracetamol and chloramphenicol suspensions were rotated for 2 h after finishing the procedure of preparation unless otherwise stated.

For the study of the influence of DOSS-Na and water on both compounds, the scheme as shown in Fig. 1 for paracetamol was followed. Impurities absorbing on paracetamol or chloramphenicol, which might interfere with DOSS-Na adsorption were removed from the liquid paraffin by adding the ground and dried solid treated prior to use. After shaking and settling, the clear supernatant liquid paraffin, was used for further studies. To

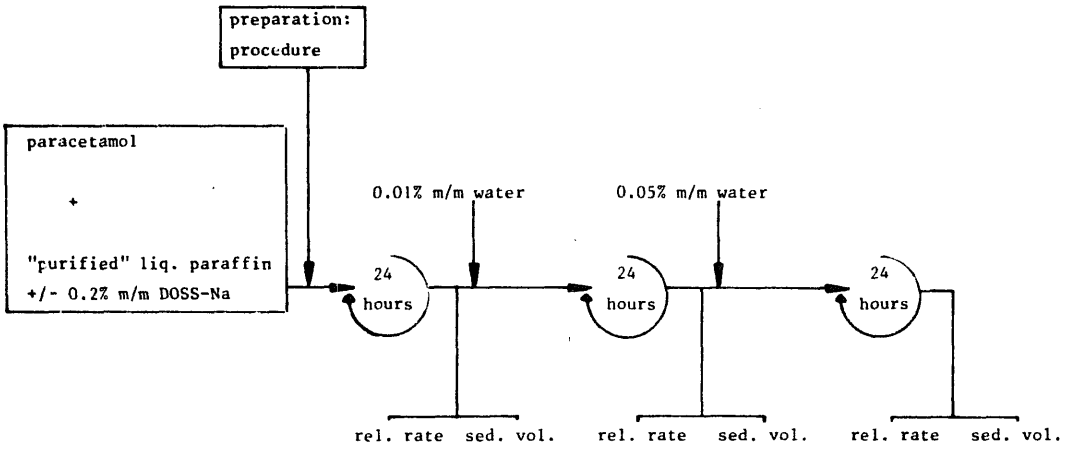

Fig. 1. Experimental scheme (shown for paracetamol) to investigate the influence of the addition of DOSS-Na, water or both on paracetamol and chloramphenicol suspensions. 24 hours = 45 r.p.m. end-over-end suspension bottle rotation for 24 h.

prevent water attraction the suspensions were prepared in a dry box with a relative humidity lower than 5%.

Apparatus for the release measurements

The apparatus described previously (Crommelin and de Blaey, submitted) was used with some minor adjustments: (1) the liquid paraffin–water interface was now situated at the level of the lowest point of the glass tube, creating a more homogeneous flow of the water phase along the interface; (2) a stirring rate of 35 rpm instead of 80 rpm was chosen in order to guarantee an interface as quiescent as possible without introducing noticeable errors due to inhomogeneity of the water phase. The concentration of paracetamol and chloramphenicol in the aqueous layer was determined spectrophotometrically at 242 nm and 278 nm, respectively. All experiments were carried out at 21.0 ± 0.3°C.

Composition of the sediment

The sedimentation volume of the suspensions was determined by placing a 1 cm thick layer into a flat-bottomed glass tube with a similar diameter as used in the release apparatus (3.8 cm). The sedimentation volume is defined as: (height of the final sediment)/(height of the suspensions at t = 0) and the mean fraction of the solid in the sediment is then given by: (fraction of solid (v/v) in the suspension)/(sedimentation volume).

The composition of the sediment as a function of height was assessed by solidifying a settled suspension by immersion into liquid nitrogen. The solidified mass was cut into slices, which were extracted with water and assayed.

Preparation of spheres for contact angle measurements

The solid was heated in liquid paraffin to a few degrees above its melting point, stirred with a magnetic stirrer and poured into a vessel, which was cooled by liquid nitrogen and contained partly solidified petroleum ether. After liquefaction of the petroleum ether the

spheres were collected on a filter, washed with petroleum ether and dried in the open air. Decomposition was reduced as much as possible by keeping the substances only for 30 sec at the elevated temperature and by working in a nitrogen atmosphere.

Position of spheres at the interface

The position of spheres of paracetamol or chloramphenicol at the interface was recorded photographically using a horizontally placed microscope. When non-siliconized cuvettes were used the interface was visible as a sharp boundary, the liquid paraffin layer being dark. Contact angles and dimensions of the sphere during its stay at the interface were determined from pictures viewing the aqueous phase.

Intrinsic dissolution rate

The intrinsic dissolution rate at the interface was determined by positioning discs (diameter 1.65 cm) of the compressed material (force 5×10^4 N) at the interface in contact with the aqueous layer, simulating the situation met during the release experiments with suspensions.

RESULTS AND DISCUSSION

Only when information is available about the behaviour of the solid particles at different stages of the release process in the system under investigation, can an insight be gained into the mechanisms involved. In particular, knowledge of the time needed for a particle, lying on the interface, to contact the aqueous phase, its position in the interface and the intrinsic dissolution rate under the experimental conditions is essential. Then predictions can be made about the influence of particle size and concentration on the release. The required information was collected in introductory experiments, which are discussed first.

Behaviour of a particle at the interface

Sedimentation will be the rate-determining step when interfacial passage and dissolution are relatively fast processes as with sodium chloride. However, for less water-soluble compounds both passage and dissolution may take more time and become rate-limiting. When a particle has reached the liquid paraffin–water interface it can either take an equilibrium position at the interface or pass through it. The extent to which a particle immerses into the water layer strongly depends upon its surface characteristics, mass and shape. Compounds with hydrophilic surfaces tend to immerse deeply, whereas strongly lipophilic substances appear to make no visible contact at all.

The position of single spheres of paracetamol of around 600 μm was observed at the liquid paraffin–water interface. A contact angle (θ) measured through the water phase, of around 90° was found. With this value we calculated, using the techniques described by Princen (1969) and Huh and Scriven (1969), that the maximum upward force on a spherical paracetamol particle with a diameter of 10 μm at the interface surpasses its weight 1.4×10^5 times. By microscopical observation it could further be established that the time required to contact the aqueous layer after reaching the interface depended upon particle size. Single particles of around 5 μm stayed up to 70 sec on the interface

before contacting the aqueous layer. This time decreased sharply for larger particles. With agglomerates consisting of small particles, the time needed by at least one particle in the agglomerate to contact the aqueous layer was greatly shortened. This implies that in the release experiments paracetamol is expected to contact rapidly the aqueous phase, leaving sedimentation and dissolution as the possible release rate-limiting steps. A paracetamol particle will dissolve at the interface and during dissolution it will be able to carry large amounts of other particles, which stay in the paraffin layer above the interface.

Observation of chloramphenicol particles at the interface revealed a similar behaviour. Here also a contact angle of around 90° was found.

Degree of coverage of the liquid–liquid interface

When dissolution is the rate-limiting step, the release rate depends upon the number of particles dissolving at the interface in the aqueous layer. Fig. 2a shows a solitary cubical particle ($0° < \theta < 90°$) at the interface. When the mass flow to the interface exceeds the dissolving mass flow and the interfacial passage is relatively fast, the surplus has to stay on the interface and after some time a sediment will be built up consisting of particles waiting for interfacial passage and dissolution. The degree of agglomeration is an important factor in determining the structure of the sediment on the interface. Non-agglomerated suspensions build up a very tight non-porous sediment on the interface with many points of contact with the water layer. In such a tight packing (Fig. 2b) particle size and concen-

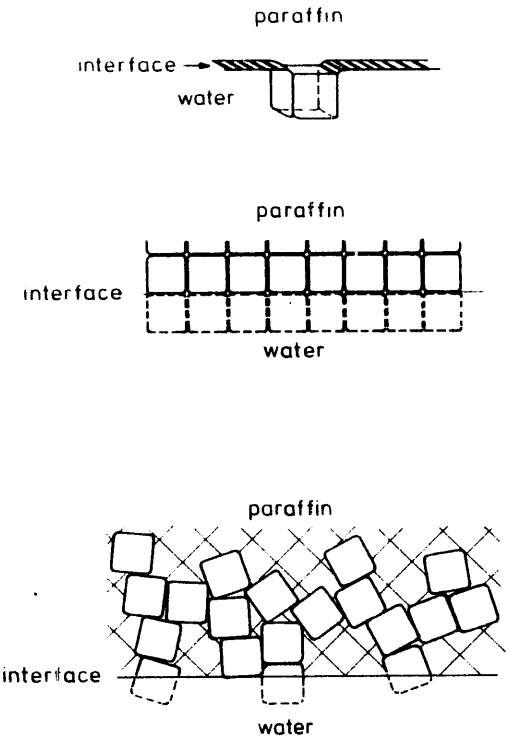

Fig. 2. The position of solid particles at an interface between two liquid phases. Contact angle: $0° < \vartheta < 90°$.

tration will no longer influence the release rate, since independently of particle size the effective surface of particles available to dissolution is equal to the interfacial area. However, agglomerated suspensions have more porous, fluffy sediments, which reduce the number of points of contact with the aqueous layer and thus the area available for dissolution (Fig. 2c).

By three different methods information was collected on the degree of coverage of the interface in the systems under investigation: (a) by determining the mean solid fraction in the sediment; (b) by measuring the distribution of the solid throughout the sediments; and (c) by microscopic observation of the interface. From sedimentation volume measurements the mean solid fractions in the sediment were calculated for the suspensions used in the release study (Table 1).

Thus the mean solid fraction depended upon particle size and concentration. On the whole low values were found. The mean solid fraction in the sediment only equals the degree of coverage of the interface if the solid is equally distributed throughout the sediment. In the literature results have been published of studies dealing with the composition of sediments (Michaels and Bolger, 1962; Blake and Colombera, 1977). Their studies pointed out that the concentration throughout the sediment was not completely constant, but increased towards the bottom. We have analyzed the sediments of two suspensions of paracetamol (3.8% m/m, 16 μm). The concentration appeared to be not fully constant throughout the sediment, but it tended to increase somewhat from the top to the bottom. However, in the slice at the bottom (thickness 0.5 mm) a solid concentration of around 10% v/v was found, which is reasonably close to the value calculated from the sedimentation volume measurements. A drawback of both techniques used above is that

TABLE 1

THE MEAN SOLID FRACTION IN THE SEDIMENT AS A FUNCTION OF PARTICLE SIZE AND CONCENTRATION. DUPLICATE DETERMINATIONS

Compound	Particle size (μm)	Conc. of suspension (% m/m)	Mean solid fraction in sediment (% v/v)
paracetamol	9	5.9	5.9
		3.8	5.0
		2.1	8.3
	16	6.4	9.1
		3.8	12
		2.1	25–30
	large *	9.1	30
chloramphenicol	5	4.4	7.6
		2.3	9.6
		1.0	12 **
	27	4.6	20

* See Methods and Materials.

** Rough estimate because of low sediment height.

the degree of coverage of the interface between the liquid paraffin and the aqueous layer is not necessarily fully comparable with the concentration at the bottom of a suspension after settling. As a direct method to elucidate the situation at the interface, the interface between the suspensions in liquid paraffin and water was observed microscopically during the release. In this way, however, only qualitative information on the degree of coverage can be obtained. It appeared that the interface was by no means fully occupied when suspensions with 9 μm, 16 μm (paracetamol) or 5 μm (chloramphenicol) were viewed. With the larger particle size fractions the degree of coverage was much higher.

Effect of degree of coverage on the release rate

If the particle size is small relative to the effective diffusion layer, the maximum release rate per unit interfacial area (100% coverage of the interface) will be the intrinsic dissolution rate under the chosen conditions. For a disc of paracetamol or chloramphenicol, placed in the central position of the tube of the release apparatus the intrinsic dissolution rate was 0.24 or 0.046 mg cm^{-2} min^{-1}, respectively. We calculated the effective diffusion layer assuming the diffusion layer model to be valid. As the diffusion coefficient of paracetamol was not known the value of a substance with comparable molecular weight and structure (*p*-aminobenzoic acid) was chosen: 0.84×10^{-5} cm^2 s^{-1} (Handbook of Chem. and Phys., 1975/76). For paracetamol the effective diffusion layer thickness was 250 μm. Adjusting the diffusion coefficient used above for the larger molecular weight of chloramphenicol we found a value of 175 μm for this compound. Even at low degrees of coverage of the interface the distance between the particles can be small relative to the effective diffusion layer. Considering spherical paracetamol particles with diameters of 10 μm in a cubical arrangement at the interface ($\theta = 90°$), the distance between the surfaces of neighbouring particles is 17 μm for a 10% degree of coverage. This is small compared with the effective diffusion layer thickness (around 200 μm), implying that the concentration of paracetamol in the void spaces between the particles will be nearly as high as with a fully covered interface. Therefore, it is hypothesized that if the mass flow to the interface exceeds the dissolution rate no influence of particle size, concentration and degree of coverage will occur and that the release rate will approximate the intrinsic dissolution rate. To reach an initial release rate independent of particle size and concentration a number of conditions have to be met: (a) the surface characteristics of the particles allow them to contact the aqueous phase rapidly after reaching the interface and to stay there during dissolution; and (b) the degree of coverage exceeds a minimum level dependent upon the regularity of distribution of the particles over the interface and the diffusion layer thickness. This hypothesis was tested in the following sections.

Particle size and concentration effect

The release curves for the 9-μm paracetamol suspensions up to 6% m/m are shown in Fig. 3. The curves are the mean of two determinations which usually differed only slightly from each other. As long as the mass flow to the interface was smaller than the dissolution rate, sedimentation was rate-limiting (0.41 and 0.77% m/m). Then not only the primary particle size, but also the degree of agglomeration which depended on both concentration and particle size played an important role in determining the sedimentation rate. As discussed in our previous paper agglomeration was likely to occur during settling in the sys-

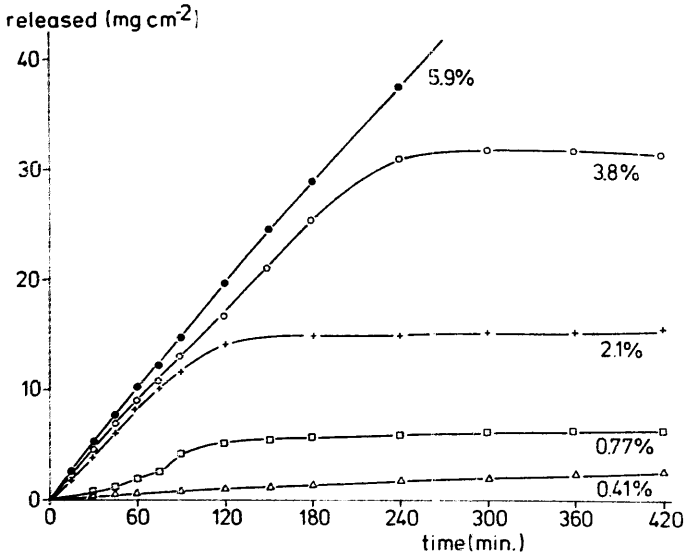

Fig. 3. Influence of concentration of paracetamol on the release (% = % m/m). Particle size fraction: 9 μm, duplicate determinations.

tems under investigation, which explains the sigmoid-shape of the curve of the 0.77% m/m suspension. In particular suspensions with small particles are sensitive to this effect. With the other particle size fractions comparable results were obtained.

In Fig. 4 the maximum release rates occurring during the release process of paracetamol are plotted as a function of the concentration. This maximum rate did not differ from the initial release rate with exception of the 0.8% m/m suspensions with the 16-μm and in particular the 9-μm fraction. In these cases the initial (low) rate is markedly with i, the maximum rate with m. The spreading in particle size for the 9-μm fraction was larger than for the 16-μm fraction, which favoured a fast building up of agglomerate during set-

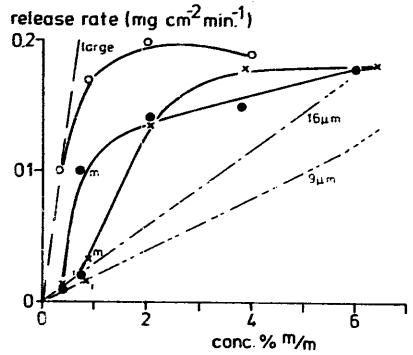

Fig. 4. Maximum release rate (mg · cm^{-2} min^{-1}) vs the concentration of paracetamol. The initial release rate coincided with the maximum release rate, with the exception of the lower concentrations of the 16-μm and 9-μm fractions; then: i = initial, m = maximum; o = large particles; X = 16 μm; • = 9 μm fraction.

tling in the former case. This may explain why with 0.8% m/m suspensions the rate of the 9-μm suspension exceeded the 16-μm one. For the case in which no agglomeration would occur and dissolution would not be the rate-limiting step, the initial release rate for the 0.4% m/m suspensions can be extrapolated to higher concentrations as shown by the broken lines in Fig. 4. For the suspensions with the 9-μm and 16-μm fractions the release rate surpassed this line, which indicated that formation of agglomerates indeed occurred. The degree of coverage of the interface (reflected in the mean solid fraction of the sediment) varied between 5 and 30% (Table 1); however, as was predicted the maximum release rate hardly depended upon this parameter. The intrinsic dissolution rate for a fully covered interface measured with a disc is 0.24 mg cm^{-2} min^{-1}. Relative to this the maximum release rates for the suspensions lay around 80%; thus the intrinsic dissolution rate was approached even at very low degrees of interfacial coverage. The difference between the values of the disc and the suspensions may be attributed to a site-dependent flow of the aqueous phase along the interface. Another possible explanation is provided by the convective diffusion model (Nelson and Shah, 1975). According to this model the dissolved mass rate of a circular area (radius a) does not increase proportional to a^2 but to $a^{5/3}$. Taking this relationship into account, the disc value adjusted to the interfacial area covered by the suspension became 0.18 mg cm^{-2} min^{-1}, which is very close to the experimentally observed rates for the suspensions.

A typical example of the release profiles as a function of the concentration obtained with chloramphenicol is shown in Fig. 5. From these curves and those of the 5-μm fraction the initial (maximum) release rates of chloramphenicol were calculated (Fig. 6). The initial release rates of equally concentrated suspensions were lower for the small particles than for the large ones with the exception of the 5% m/m suspensions where they were equal. The suspensions with two different particle size fractions attained the same maximum release rate in spite of a large difference in degree of coverage of the interface (Table 1).

The intrinsic dissolution rate of a disc of chloramphenicol at the interface was 0.046 mg cm^{-2} min^{-1}. Thus, with suspensions even with low degrees of coverage of the inter-

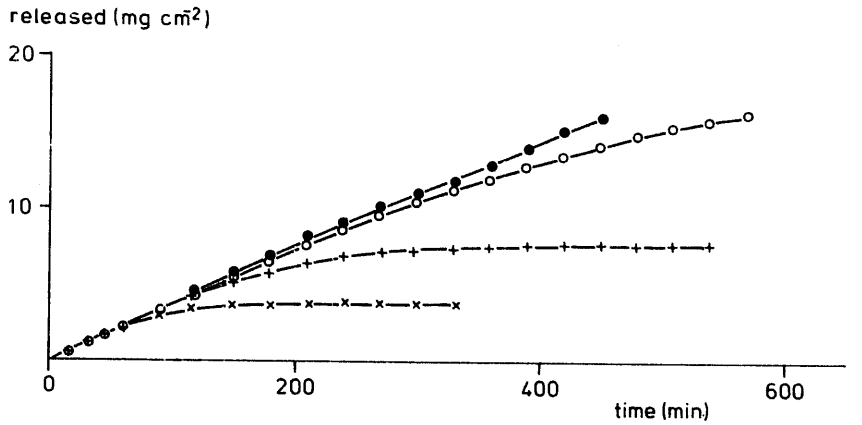

Fig. 5. Influence of concentration on the release of chloramphenicol. Particle size fraction: 27 μm, duplicate determinations. •, 4.6% m/m; +: 0.95% m/m; o, 2.2% m/m; x: 0.46% m/m.

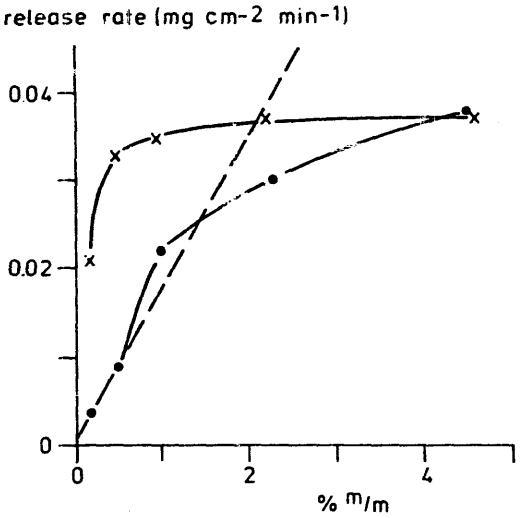

Fig. 6. The release rate as a function of the concentration (% m/m) of chloramphenicol. •: 5 μm fraction; x: 27 μm fraction.

face (around 8%) a rate of 83% of the intrinsic dissolution rate was reached. The difference between the maximum dissolution rate of the suspension and the disc may be explained as was done before for paracetamol. Increasing the stirring rate resulted in an increase of the release rate, which gave additional support to the proposition of a limitation of the release by diffusion-limited dissolution. A peculiarity with the chloramphenicol suspensions was that after a period with a constant release rate, this rate slowed down. Constant levels in the aqueous phase were reached with a permanent sediment on the interface. This effect was much more pronounced with the suspensions containing the small particles. Wetting of the particles did not occur anymore at this stage of the release process. A definite explanation for this phenomenon cannot be offered yet.

Effect of water

With sodium chloride suspensions a large influence of the addition of water on the release rate was observed, due to the formation of stable agglomerates in the suspension. This was ascribed to the formation of liquid bridges between the particles. We investigated to what extent this phenomenon would also occur with paracetamol (5% m/m, 16 μm) and chloramphenicol (5% m/m, 5 μm) suspensions. The experimental scheme is shown in Fig. 1.

From the results (Figs. 7 and 8) it is clear that the initial release rate was not affected by addition of water. Macroscopical and microscopical observation of the suspensions revealed an increased degree of agglomeration after the addition of water; this was confirmed by a lower mean fraction of solid found in the sediment (see Table 2). As was observed with suspensions without water and in agreement with the proposed hypothesis, large changes of the degree of coverage of the interface did not influence the release rate.

Effect of DOSS-Na with or without water

With sodium chloride suspensions DOSS-Na decreased the tendency to agglomerate by

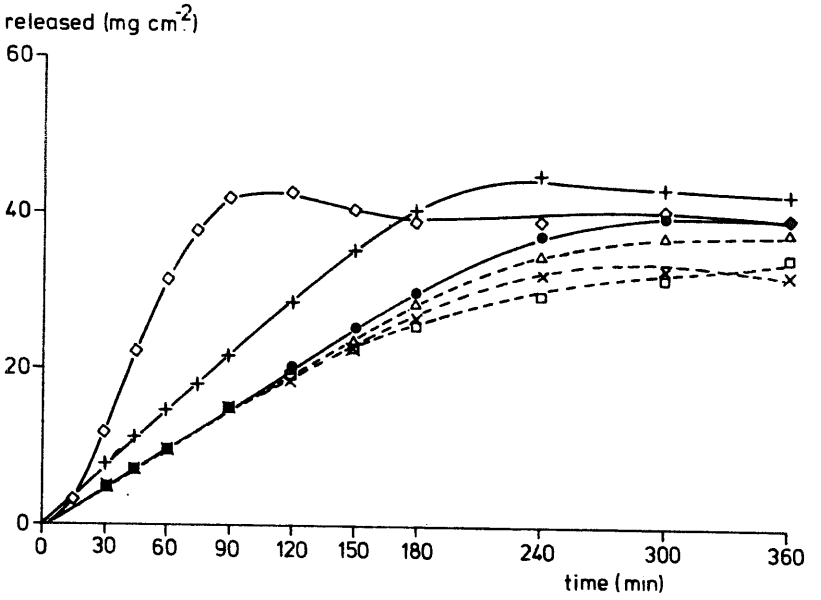

Fig. 7. Release of paracetamol from suspensions containing DOSS-Na, or water or both. Particle size fraction: 16 μm, duplicate determinations.

	DOSS-Na (% m/m)	water (% m/m)
□	0	0
△	0	0.01
×	0	0.05
●	0.2	0
+	0.2	0.01
◇	0.2	0.05

increasing the repulsive forces. The effect of the presence of water was reduced by solubilization. The experimental scheme to investigate the effect of DOSS-Na addition on the release of paracetamol or chloramphenicol from liquid paraffin with or without water is shown in Fig. 1. For paracetamol suspensions with DOSS-Na the mean solid fraction in the sediment decreased compared to the situation without DOSS-Na (Table 2), but the initial release rate did not change. However, with 0.01% and 0.05% m/m water present, this rate increased strongly (Fig. 7). Then the agglomerates of paracetamol no longer stayed at the liquid paraffin interface, but fell through it into the aqueous layer and dissolved rapidly, because of the increase in exposed surface area.

Chloramphenicol suspensions showed a different behaviour. In the presence of 0.2% m/m DOSS-Na alone the release rate was already increased (Fig. 8). This effect was strongly enhanced when water was added (Fig. 9). Here also the fall of agglomerates through the interface into the water layer could be observed. This detachment was investigated in more detail. In the presence of 0.2% m/m DOSS-Na the interfacial tension (du Nouy ring method) between water and liquid paraffin was hardly reduced, while the contact angles for solitary spheres of paracetamol and chloramphenicol only decreased from around 90° to around 70°. Addition of water (0.05% m/m) reduced the interfacial tension and the contact angles slightly further, but still the forces counteracting gravity

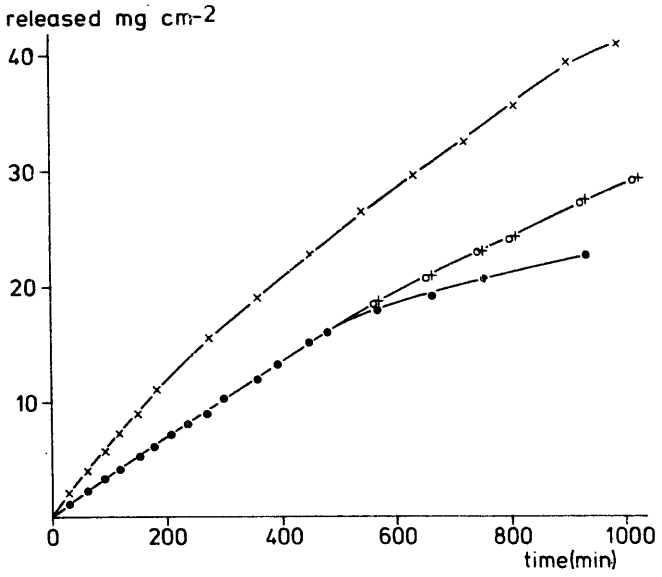

Fig. 8. The influence of addition of water or DOSS-Na to chloramphenicol suspensions on the release; duplicate determinations. Particle size fraction: 5 μm.

	conc. % m/m	DOSS-Na % m/m	water % m/m
•	5.2	0	0
o	5.1	0	0.01
+	5.4	0	0.05
x	5.1	0.2	0

for a single particle in the interface predominated greatly. Only at much higher concentrations of DOSS-Na did the supporting forces fail to keep the spheres at the interface. In suspensions the situation is different. DOSS-Na showed a large affinity for paracetamol

TABLE 2

THE MEAN SOLID FRACTION IN THE SEDIMENT AS A FUNCTION OF THE CONCENTRATION OF WATER AND/OR DOSS-Na PRESENT IN LIQUID PARAFFIN. DUPLICATE DETERMINATIONS. –: NOT AVAILABLE. PARACETAMOL 16 μm, CHLORAMPHENICOL 5 μm.

Concentration DOSS-Na (% m/m)	Concentration water (% m/m)	Mean solid fraction in sediment (% v/v)	
		Paracetamol	Chloramphenicol
0	0	13	12
0	0.01	5.3	4.5
0	0.05	–	5.0
0.2	0	8.9	12
0.2	0.01	4.9	9.5
0.2	0.05	4.3	7.5

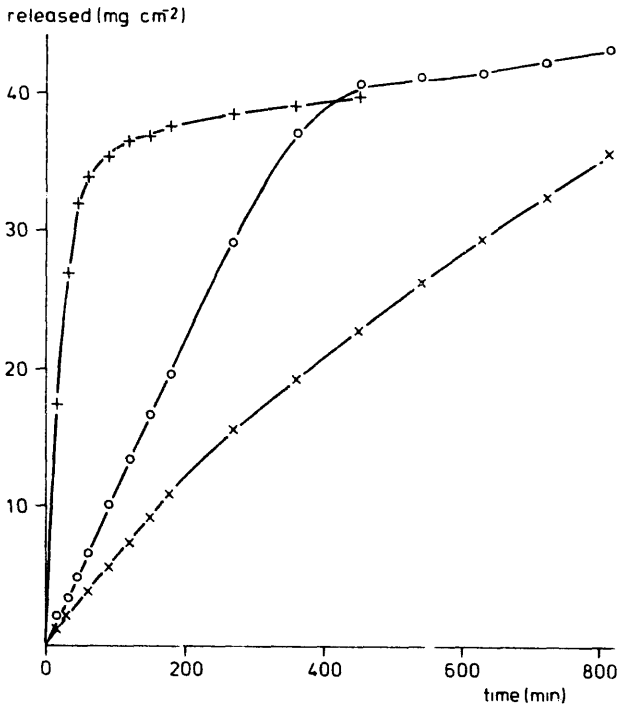

Fig. 9. The influence of addition of DOSS-Na and water to chloramphenicol suspensions on the release. Conc. DOSS-Na: 0.2% m/m duplicate determinations. Particle size fraction: 5 μm.

	conc. % m/m	water % m/m
×	5.1	0
○	5.2	0.01
+	4.9	0.05

and chloramphenicol surfaces and to water droplets present in the paraffin. Due to the rapid segregation process during the release experiments (settling of particles bound together by liquid bridges) DOSS-Na accumulated at the interface. Therefore the concentrations of the surfactant at the interface were much higher with suspensions than in the case of a single sphere. This indicates that one has to be very careful in extrapolating results obtained in single particle experiments to multiparticle systems.

CONCLUSIONS

In a previous article (Crommelin and de Blaey, submitted) we reported that the release process with sodium chloride essentially was governed by sedimentation. In the present paper it was shown that for less water-soluble compounds the release process could be governed either by sedimentation or by dissolution, depending on the relative magnitude of the sedimentation rate and the maximum dissolution rate. Interfacial passage was not a rate-determining factor in the initial stage of the release process. The experimental data were in good agreement with the hypothesis, that in case of dissolution control, the release rate becomes independent of particle size, concentration and of the degree of

coverage of the interface, even down to a very low level of coverage. Due to its lower water-solubility the maximum release rate of chloramphenicol was smaller than that of paracetamol. If the transport rate was less than the maximum dissolution rate, sedimentation limited the release. Then, as in the release process of sodium chloride not only the primary particle size, but also the dimensions of agglomerates which were formed during settling were important. In particular the small particle size fraction of paracetamol was sensitive to agglomeration. The concentration of conversion from a sedimentation- to a dissolution-controlled release depended on all factors that influence these two processes. For example, large particles with a high density, agglomeration, a low water solubility and a thick effective diffusion layer will favour dissolution control at low concentrations. When 0.01% or 0.05% m/m water was added to suspensions of paracetamol or chloramphenicol with dissolution-controlled release, the degree of coverage changed, but the release did not. The latter finding is in agreement with the proposed hypothesis. Suspensions of paracetamol in solutions of 0.2% m/m DOSS-Na in liquid paraffin gave similar results, but when also 0.01% or 0.05% m/m water was added, the particles did not stay at the interface, but fell intact throught it, increasing the release rate strongly. To a certain extent this already happened with chloramphenicol suspensions containing DOSS-Na alone, but the tendency to detach, strongly increased with water present in the paraffin. This detachment was attributed to accumulation of DOSS-Na at the interface after settling, as this surfactant was strongly adsorbed to the solid particles and also accumulated in the water bridges holding the agglomerates together.

ACKNOWLEDGEMENTS

Abstracted from a dissertation submitted by D.J.A. Crommelin to the State University of Leiden. Copies of the thesis are available on request with the first author.

Prof. J. Polderman, University of Leiden, is gratefully acknowledged for his guidance and advice, as are Miss J.R.M. Olierook, T. Schalekamp and N. Veldkamp for their assistance.

REFERENCES

Blake, J.R. and Colombera, P.M., Sedimentation: a comparison between theory and experiment. Chem. Engng. Sci., 32 (1977) 221–228.

Crommelin, D.J.A. and de Blaey, C.J., In vitro release studies on drugs suspended in non-polar media. I. Release of sodium chloride from suspensions in liquid paraffin. Int. J. Pharm., submitted.

Handbook of Chemistry and Physics, 56th edn., C.R.C. Press, Cleveland, Ohio, 1975/76.

Huh, C. and Scriven, L.E., Shapes of axisymmetric fluid interfaces of unbounded extent. J. Colloid Interface Sci., 30 (1969) 323–337.

Michaels, A.S. and Bolger, J.C., Settling rates and sediment volumes of flocculated kaolin suspensions. Ind. Engng. Chem. Fundam., 1 (1962) 24–33.

Nelson, K.G. and Shah, A.C., Convective diffusion model for a transport-controlled dissolution rate process. J. Pharm. Sci., 64 (1975) 610–614.

Princen, H.M., The equilibrium shape of interfaces, drops and bubbles. Rigid and deformable particles at interfaces. In Matyevic, E. (Ed.), Surface and Colloid Sci., Vol. 2, Wiley-Interscience, N.Y., 1969.