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IN VITRO RELEASE STUDIES ON DRUGS SUSPENDED IN NON-POLAR MEDIA I. RELEASE OF SODIUM CHLORIDE FROM SUSPENSIONS IN LIQUID PARAFFIN

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SUMMARY

The release of a readily water-soluble substance (sodium chloride) from a liquid paraffin phase to an underlying water phase was investigated as a function of particle size (10–50 μm) and concentration (up to 10% m/m). Transport of the suspended particles to the interface by sedimentation was the rate limiting step. The release rate increased with primary particle size and concentration. The small particles showed a more pronounced concentration dependence than the large ones. During settling, agglomerates were formed. But, mild shear rates kept the primary particles in the deglomerated state. Low concentrations of DOSS-Na (di(2-ethylhexyl) sodium sulphosuccinate) up to 0.2% m/m in liquid paraffin reduced the degree of agglomeration, while trace amounts of water (0.01 and 0.05% m/m) showed the opposite effect. The observed phenomena are discussed on basis of the DLVO-theory, supplemented with considerations about forces due to gravity, shear and liquid bridge formation, and the kinetics of agglomeration.

INTRODUCTION

Non-polar media are frequently used as vehicles for the suspension of drugs. The release of drug particles from these media in liquid state in vivo can be the rate-controlling step in the absorption process. This situation can occur, for instance, after administration of fatty suspension suppositories. The mechanisms involved in the release of solids from this type of suspensions are poorly known. Therefore, the purpose of the present study was to gain an insight into these mechanisms. A model system was used in which the experimental conditions were well defined. This system essentially consisted of a liquid paraffin suspension in contact with an aqueous layer (see Fig. 1). Three kinetic steps can be discerned in the release process: transport to the interface by sedimentation, passage through the interface and dissolution in the aqueous layer.

Sodium chloride was chosen as a typical example of a readily water-soluble substance wherein the influence of particle size, concentration and additives was investigated.

METHODS AND MATERIALS

Particle size

Classified fractions of sodium chloride were obtained. The particle size distributions, determined according to the projected diameter method, approximated a normal distribution. The mean particle diameters and standard deviations were: 47 ± 10 μm, 10 ± 2 μm and 8 ± 2 μm.

Preparation of the suspensions used to establish concentration and particle size effects

All materials used in the preparation of the suspensions were dried at 100–110°C and kept in desiccators containing silica gel. However, sodium chloride was heated at 180°C for at least 5 days under pressures below 2 kPa to remove surface impurities (Lad, 1968). After cooling, the sodium chloride was mixed with a small amount of liquid paraffin in a mortar and transferred to a container which was filled with liquid paraffin to obtain the required concentration. Suspensions with particles smaller than 20 μm were treated ultrasonically (50 kHz) for 5.5 min and mixed for 2 min during this treatment with a high speed mixed (20,000 rpm). The suspensions with size fractions larger than 20 μm were only mixed ultrasonically for half a minute, because high speed mixing of these larger particles resulted in the particle to stick persistently to the glass wall.

Procedure to investigate the effect of shear on the state of dispersion

Immediately following the high speed mixing and the ultrasonic treatment, a sample was taken from the suspension to measure the release. The remainder of the suspension was rotated end-over-end at 45 rpm for 270 min. After 30, 60, 90, 180 and 270 min, samples were drawn from the rotating suspension and release experiments were performed.

Special treatment of suspensions (8 μm) used to study the influence of water and DOSS-Na (di(2-ethylhexyl) sodium sulphosuccinate)

To eliminate moisture contamination during the preparation of the suspensions, the preparation was performed in a dry-box (relative humidity <5%). No ultrasonic treatment was applied. To remove impurities in the liquid paraffin, which might interfere with the adsorption of DOSS-Na on sodium chloride, the paraffin was pretreated with anhydrous sodium chloride. After settling of the sodium chloride powder, the supernatant liquid paraffin was subsequently used to prepare the suspensions.

Investigation of the effect of water

In these experiments the effect of addition of small amounts of water (suspension B) and the subsequent pretreatment with anhydrous sodium chloride (suspension C) on this effect was investigated. Three suspensions (A, B and C) containing 5% m/m sodium chloride were prepared as follows: A was the reference suspension, prepared in the usual way. In case B and C, 0.01% (or 0.05%) m/m water was added to the liquid paraffin.

After rotation for 2 h end-over-end at 45 rpm the liquid paraffin was divided into equal parts. One part was used for the preparation of suspensions B (0.01% or 0.05% m/m water); to the other 10% m/m ground and dried sodium chloride was added and after shaking the liquid paraffin was put aside for 24 h to get a clear supernatant, which was used for the preparation of suspension C. After preparation, the suspensions were rotated end-over-end for 2 h at 45 rpm. The water content of the liquid paraffin, determined by the Karl Fischer method was less than 40 mg kg^{-1} water. The solubility of water in liquid paraffin is between 60 and 80 mg kg^{-1}.

Investigation of the effect of DOSS-Na

DOSS-Na was first dissolved in the liquid paraffin in different concentrations up to 0.2% m/m. This was used to prepare suspensions containing 5% or 0.2% m/m sodium chloride. The suspensions were rotated end-over-end at 45 rpm for periods of 0.5, 2, 3 and 4 h. The adsorption isotherm of DOSS-Na on sodium chloride was determined according to the method described by Barr et al. (1948).

Apparatus for release measurements

The apparatus is shown in Fig. 1 and was adapted from the set up developed to investigate the release of drugs from suppositories (Cox and Breimer, 1973; de Blaey and Rutten-Kingma, 1977). Essential in this system is the constant interfacial area during the release process. The eccentrically placed open tube (diameter 3.8 cm) with its bottom 2 cm below the water surface was siliconized providing a flat paraffin–water interface at the tube wall. In all experiments a 1 cm suspension layer was put on top of the aqueous layer. The experiments were performed at 21.0 ± 0.3°C. The dissolution of sodium chloride was followed conductimetrically. In preliminary experiments (Crommelin, 1979) we found that the release rate was independent of the stirrer rate in the range under investigation (60–100 rpm) and of the distance of the stirrer from the bottom (1–2 cm). A stirrer rate of 80 rpm and a distance of the stirrer from the bottom of 1 cm were used in all experiments. Increasing the tube diameter did not influence the release. All experi-

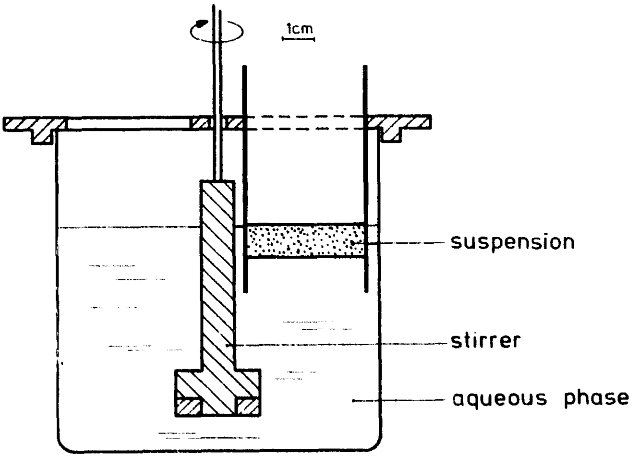

Fig. 1. Scheme for experimental model for the determination of the release rate.

ments were carried out at least in duplicate. The reproducibility of the determinations depended upon the tendency to agglomerate. With strongly agglomerating suspensions the $t_{50\%}$-values (time needed for the release of 50% of the total mass available) had a coefficient of variation of 7%; with negligible agglomeration this was only 2%.

Microscopic observation of the suspensions

A microscope was placed horizontally. Siliconized and non-siliconized cells with pathlengths between 0.2 and 2 cm were used. The settling of particles in the liquid paraffin, their behaviour at the interface and their dissolution could be followed visually and with a time lapse camera. Measures were taken to exclude interference by heat convection.

Sedimentation rate measurements

Sedimentation rates were determined by measuring the weight increase with time of a pan during settling of a suspension. The weight increase of the pan (diameter 5 cm), provided with a rim (height 0.9 cm) to prevent loss of sedimented material, was monitored with an electrobalance. The pan was placed 1 cm below the surface of the suspension.

RESULTS AND DISCUSSION

Particle size and concentration effects

The results obtained with concentrations in a range between 0.1% and 10% m/m are shown in Figs. 2 and 3 for the 10 μm and 47 μm size fractions, respectively. The release rates increased with particle size and concentration. For the 10 μm fraction the $t_{50\%}$-ratio

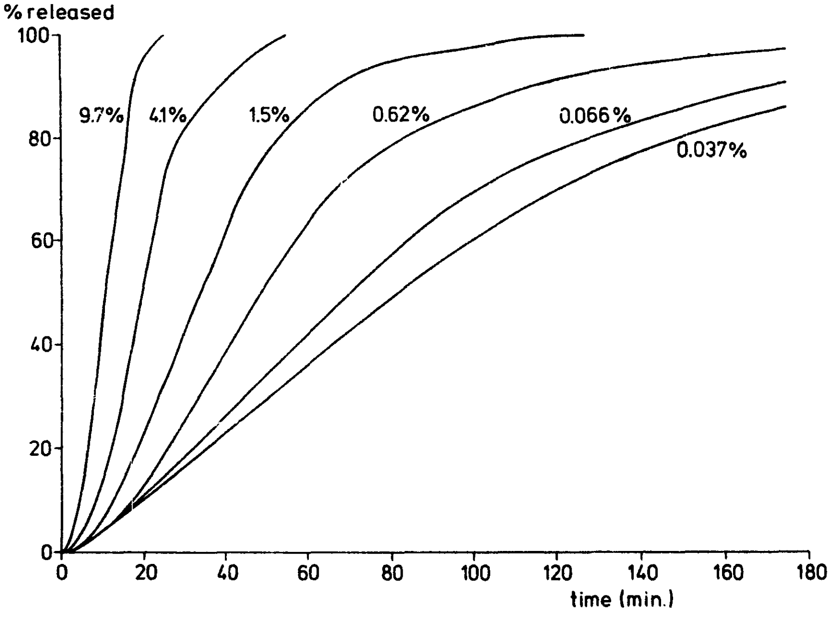

Fig. 2. Release of sodium chloride as a function of concentration. Particle size fraction: 10 μm.

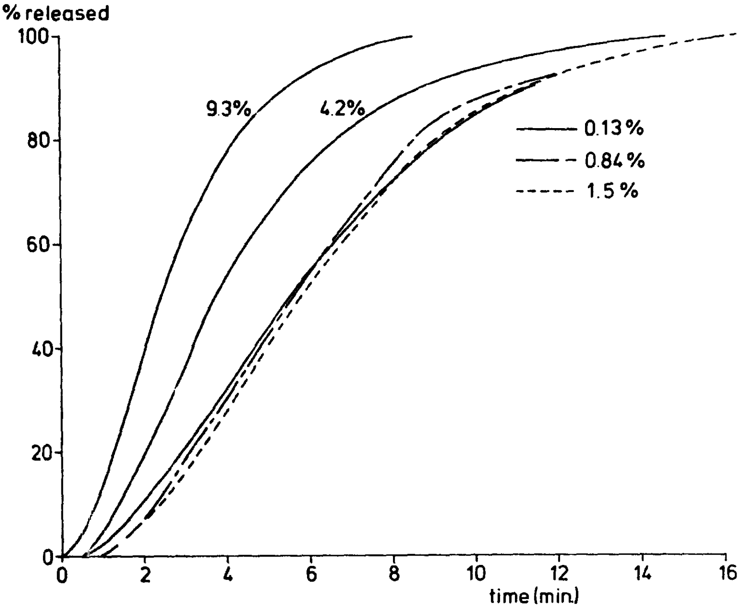

Fig. 3. Release of sodium chloride as a function of concentration. Particle size fraction: 47 μm.

between 0.037% and 9.3% m/m suspensions was about 8, while this ratio was only 2 for the 47 μm fraction.

To explain the observed phenomena required a mechanistic insight into each of the 3 steps depicted in Fig. 1, namely, transport to the interface, passage through the paraffin–water interface and dissolution.

Microscopic observation of the interface showed that both the interfacial passage and the dissolution of sodium chloride took only a very short time relative to the time required for sedimentation under the chosen conditions. Furthermore, the results of the sedimentation rate measurements agreed well with the release profiles. From these findings, we concluded that sedimentation was the rate controlling step in the release kinetics.

This implied that all factors which influence sedimentation like primary particle size, density, viscosity and state of dispersion also influence the release. The increase of the release rate with particle size is easily understood from Stokes' law. Microscopic observation of settling suspensions (10 μm) showed that the degree of agglomeration and therefore the release, increased with the concentration of sodium chloride. Whether particles will collide during settling depends upon the relative magnitude of drag and gravitational forces due to differences in shape and mass and forces due to electrostatic and van der Waals interactions (DLVO-theory). We analyzed the system under investigation with respect to the relative magnitude of these forces (Crommelin, 1979). The purpose of this analysis was to find out to what extent existing theories on agglomeration could predict the observed phenomena.

To obtain estimates of the electrostatic force, values for the required parameters were used as reported in the literature for comparable systems. Calculations showed that electrostatic repulsive forces between two spherical sodium chloride particles (diameters around 10 μm) in a non-polar medium like liquid paraffin are small relative to mechanical forces tending to bring particles together, even under favourable conditions for electrostatic repulsion, and small differences in particle size. Therefore electrostatic repulsion will not prevent particles from collision.

After collision, van der Waals forces tend to keep the particles together, whereas the resultant of drag and gravitational forces working on an agglomerate during settling, usually tends to break it up. As exact data are lacking for the minimum distance between the particles and the effective Hamaker constant for the system under investigation, it was not possible to calculate the exact limiting dimensions of the agglomerates from theory. However, approximate calculations using a low estimate for the effective Hamaker constant (0.04×10^{-20} J) and a high estimate for the interparticle distance (1 nm) predicted that binary agglomerates of spherical particles with diameters around 10 μm will be stable, if only gravity is involved and that formation of much larger agglomerates is likely. The experimental results showed that, indeed, stable agglomerates were formed. For the 9.7% m/m suspension of the 10 μm fraction the effective Stokes' diameter of the agglomerates was 54 μm.

The suspensions with the 10 μm fraction showed a larger influence of the concentration on the degree of agglomeration during settling than those with the 47 μm fraction. This is attributed to differences in the formation rate of agglomerates (Ives, 1978). For suspensions containing fractions with different mean particle size but comparable size distributions and similar concentrations, the mass of agglomerated particles will become larger with decreasing particle size, if sedimentation over a certain distance is studied. If some binary agglomerates have been formed, the rate of agglomeration will increase (Parfitt, 1973).

During settling in undisturbed systems agglomerates were built up. To investigate whether the shear rates generated by gentle rotation were sufficient to prevent agglomeration, suspensions with particles of around 10 μm in concentrations varying between 0.2% and 5% m/m were prepared. The maximum shear rates generated in the flask during rotation were in the order of magnitude of 200 $\sec^{-1}$. The results in Fig. 4 show that only with the 4.8% m/m suspension the $t_{50\%}$-values tended to decrease after 30 min. The release of the other suspensions did not depend on their life-time after reduction of the high shear forces occurring during preparation. This indicated that shear forces in the rotating flask were sufficient to break down agglomerates.

Effect of water

In non-polar media, water adsorbs strongly on polar particles like sodium chloride. With increasing concentrations multilayers will be formed, which can affect the stability of the dispersions by changing the surface potential and the double-layer thickness. Above certain concentrations of water, liquid bridges are formed between the particles. Princen (1968) treated the theoretical problem of quantifying the forces acting on two spheres coupled through a liquid bridge. Essential information on the shape of the bridge can be obtained using the equations derived by Kruyt and van Selms (1943). Calculations showed that the interparticle force due to one liquid bridge between two sodium chloride spheres (solid density, 2140 kg m^{-3}; diameter, 10 μm; interfacial tension, 20×10^{-3} N m^{-1}; contact angle of water on sodium chloride in liquid paraffin: 0°) in a 5% m/m suspension with 0.05% m/m water is 6×10^{-7} N. This force surpassed the separating forces

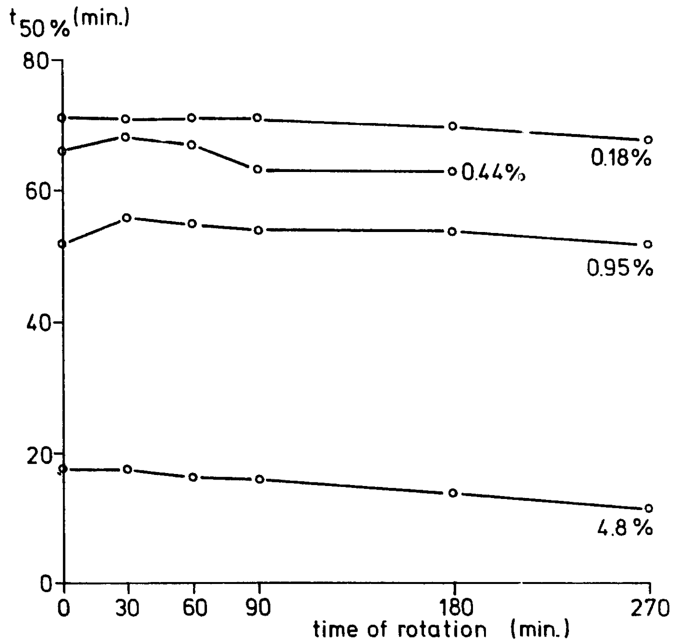

Fig. 4. The $t_{50\%}$ of the release process as a function of time of rotation and concentration. Particle size: around 10 μm.

due to electrostatic repulsion or gravitation and therefore keeps the two spheres together. Applying shear also may induce breakdown of agglomerates. Using the equations derived by Albers and Overbeek (1960) to calculate shear forces in a laminar field of flow, it turned out that binary agglomerates under the conditions mentioned above are stable to shear rates up to about 45×10^3 sec^{-1}. In our experiments the suspensions were rotated for 2 h at 45 rpm after finishing the high speed mixing. As the maximum shear rates in our experiments were estimated to be in the order of magnitude of 200 sec^{-1}, we expected the suspensions with 0.05% m/m water to be strongly agglomerated.

Typical sets of release curves with 0.01% m/m and 0.05% m/m water are shown in Figs. 5 and 6 respectively.

As predicted, addition of water significantly enhanced the release rate. A concentration of 0.05% m/m induced a larger increase than 0.01% m/m; the effect of 0.01% m/m was more variable. Microscopic and macroscopic observation of the B-suspensions revealed that agglomerates were already present during rotation. In particular, the curves with 0.05% water were almost linear, indicating that no additional agglomeration occurred during settling. The C-suspensions, which, after water addition, had been shaken with sodium chloride, did not show the increase of the release rate as observed with the B-suspensions. Thus water appeared to bind strongly on sodium chloride, for the treatment with 10% m/m ground and dried sodium chloride (suspension C) was sufficient to remove the water added and to restore the 'dry' situation (A). The sigmoidal shape of the curves of the A- and C-series is attributed to agglomeration during settling.

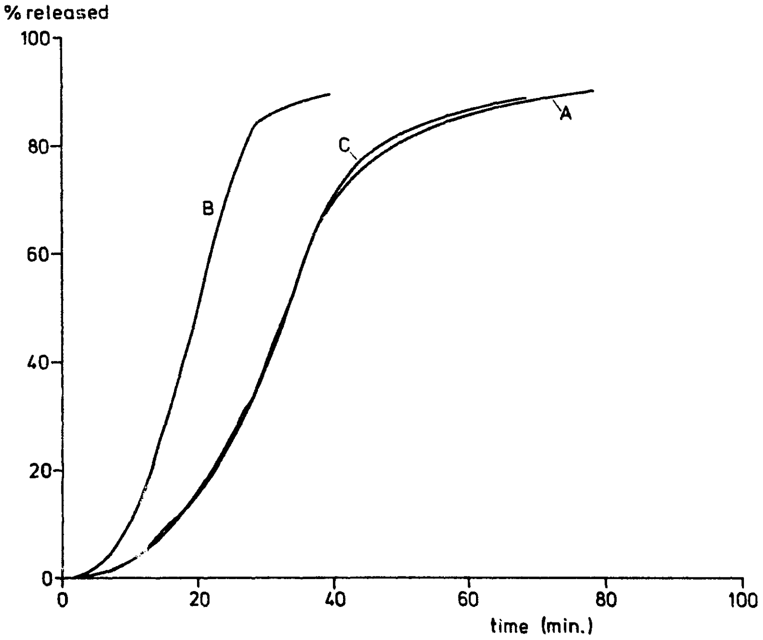

Fig. 5. Influence of addition of water (0.01% m/m) on the release. For experimental procedure (A, B and C): see Materials and Methods. Mean curves of duplicate determinations. Concentration of sodium chloride: about 5% m/m.

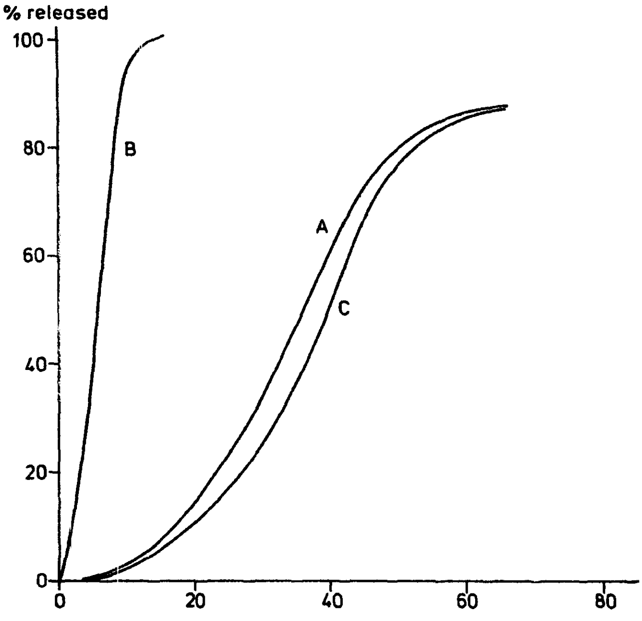

Fig. 6. Influence of addition of water (0.05% m/m) on the release. For experimental procedure (A, B and C): see Materials and Methods. Mean curves of duplicate determinations. Concentration of sodium chloride: about 5% m/m.

Effect of DOSS-Na

For suspensions in the absence of additives we can predict that electrostatic repulsive forces between particles even with large surface potentials would be insufficient to prevent agglomeration due to a large double-layer thickness. It is known (Kitahara, 1967) that DOSS-Na stabilizes colloidal dispersions in non-polar media by electrostatic repulsion. This compound influences the surface potential and strongly reduces the double-layer thickness. Calculations showed that now stabilization might occur in the case of surface potentials of reasonable magnitude (60 mV), if sodium chloride particles with dimensions of around 10 μm approach each other during settling (Crommelin, 1979). The experimental results supported these considerations.

For the 5% m/m sodium chloride suspensions the $t_{50\%}$-values with different DOSS-Na concentrations are found in Fig. 7. Besides, some drawn curves of the release after 4 h of rotation are presented in Fig. 8. Microscopic observation of interfacial transport of sodium chloride revealed that DOSS-Na did not prohibit interfacial passage.

For these suspensions the $t_{50\%}$-values are used for convenience to indicate the trend; however, they have to be interpreted with care because of the sigmoidal shapes of the curves, particularly with DOSS-Na present. Surfactant concentrations as low as 0.002% m/m significantly retarded the release of sodium chloride. Further increases in concentration resulted only in small additional retardation. Adsorption determinations showed that, with the 5% m/m sodium chloride suspensions, 0.0024% m/m DOSS-Na was sufficient for a complete monolayer coverage.

The chance to collide decreases with the concentration of solid. Therefore the effect of DOSS-Na was not so significant, when the release of suspensions containing 0.2% m/m

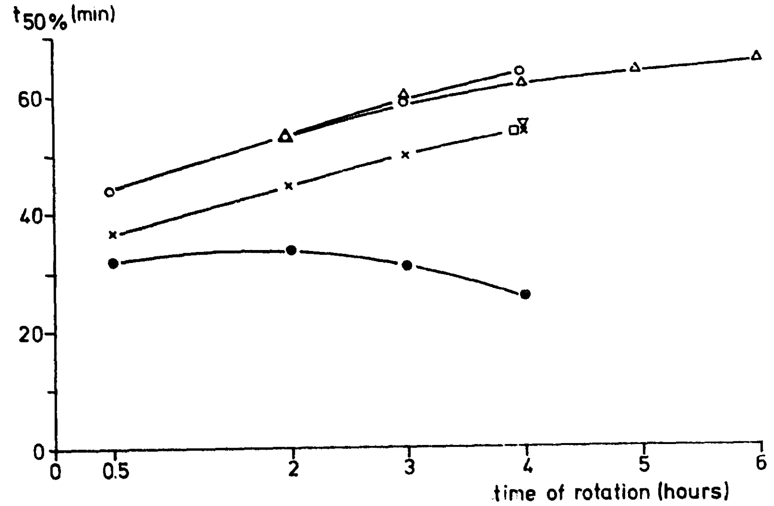

Fig. 7. Influence of concentration of DOSS-Na on the release as a function of the time of rotation. Concentration of sodium chloride: about 5% m/m. n, number of experiments. ●, no DOSS-Na (n = 1); × = 0.002% m/m DOSS-Na (n = 1); □, ▽, 0.02% m/m DOSS-Na (n = 3); △, ○, 0.2% m/m DOSS-Na (n = 1).

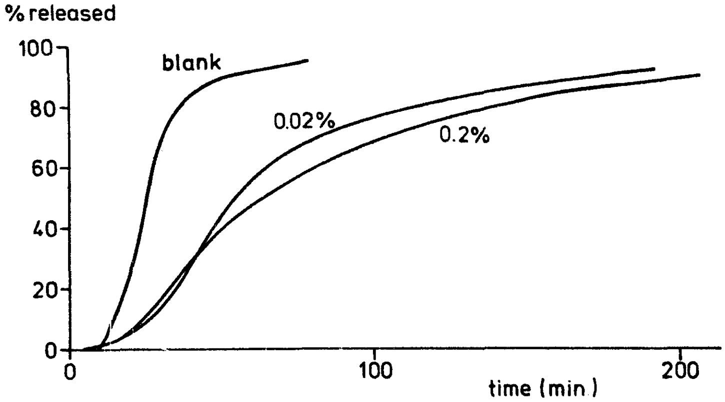

Fig. 8. Influence of concentration of DOSS-Na (% m/m) on the release after 4 h of rotation. Concentration of sodium chloride: about 5% m/m, n = 1, blank = 0% m/m DOSS-Na.

sodium chloride instead of 5% m/m was determined. A typical example of the curves obtained is shown in Fig. 9.

Effect of both DOSS-Na and water

The results of the addition of 0.01% m/m and 0.05% m/m water to 5% m/m sodium chloride containing suspensions after 4 and 5 h of rotation respectively, are shown in Fig. 10. As water was added as a 1% m/m emulsion of water in liquid paraffin (emulsified by ultrasonic treatment) this initially gives more chance for the sodium chloride particles to form liquid bridges than when the sodium chloride was added to a homogeneous dispersion of water in liquid paraffin as occurred with the suspensions shown in Figs. 5 and 6.

A reasonable mechanistic interpretation of these results is that 0.01% m/m water was bound in micelles in suspensions with 0.2% m/m DOSS-Na. A review on the solubilizing

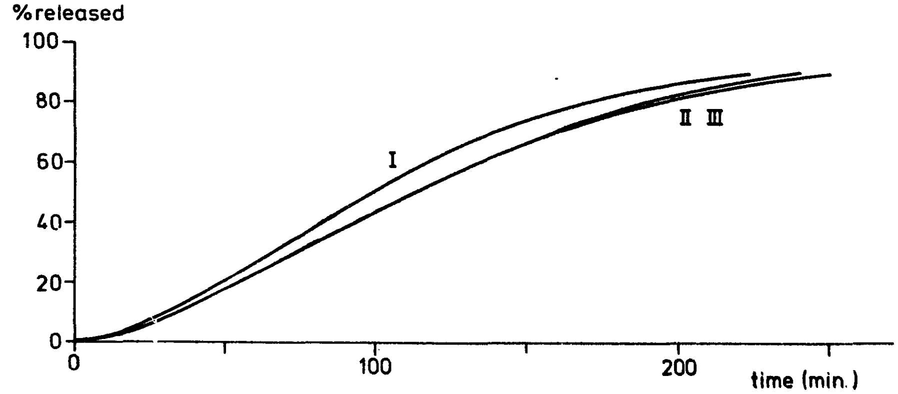

Fig. 9. Influence of concentration of DOSS-Na on the release after 4 h of rotation. Concentration of sodium chloride: about 0.2% m/m. I = 0% m/m DOSS-Na, II = 0.2% m/m DOSS-Na, III = 0.002% m/m DOSS-Na.

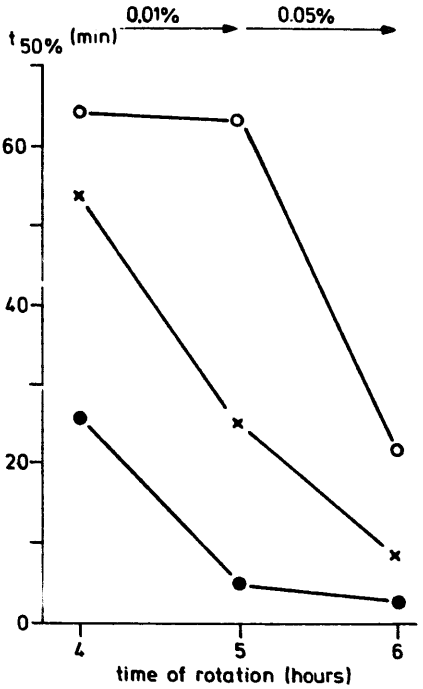

Fig. 10. Influence of addition of water on the release with different concentrations of DOSS-Na. Concentration of sodium chloride: about 5% m/m. ● = 0% m/m DOSS-Na; × = 0.002% m/m DOSS-Na; o = 0.2% m/m DOSS-Na.

capacity of DOSS-Na in non-polar media is given by Rosen (1978). Depending on the system, one molecule of DOSS-Na can solubilize between 3.5 and 10 molecules of water. By turbidity measurements of the liquid paraffin/water system, we assessed that 0.2% m/m DOSS-Na could not fully solubilize 0.05% m/m water (ratio: 6 molecules water to 1 molecule DOSS-Na). When sodium chloride is present in liquid paraffin–water, attraction by the suspended solid will compete with solubilization, which will complicate the situation. As it was found that stable agglomerates were formed with 0.05% m/m, it appeared that there was an excess of insolubilized water that was responsible for agglomeration through liquid bridges strong enough to withstand shear forces in the rotating flask. This also happened when lower concentrations of DOSS-Na were present (0.002% m/m).

CONCLUSIONS

In the model system used the release of sodium chloride, chosen to represent a readily water-soluble drug, suspended in liquid paraffin was controlled by the transport to the interface. Interfacial passage and dissolution was rapid. The degree of agglomeration which strongly depends on primary particle size and concentration, was of utmost importance. In principle the tendency to agglomerate can be predicted from theory, taking electrostatic, van der Waals, drag and gravitational forces between particles into account. However, at present in particular, values for the van der Waals forces are difficult to obtain because of lack of appropriate data for the Hamaker constant and minimum interparticle distance.

A low concentration of DOSS-Na or water changed the state of dispersion dramatically via electrostatic repulsion and liquid bridge formation, respectively. When both compounds were present, the ultimate effect on the state of dispersion and thus the release depended upon their respective concentrations. DOSS-Na has a limited capacity to solubilize water; then the formation of liquid bridges was prevented.

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