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Release of salicylic acid from aqueous triglyceride vehicles containing surfactants *

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Summary

Release of salicylic acid from triglyceride vehicle containing 10% m/m polyoxyethylene stearates and different amounts of water was studied using an in vitro dialysis method.

Inclusion of water in the vehicle increases the amount of salicylic acid released as well as increasing the release rate, when the amount of water exceeds 5% m/m. Except for the most hydrophobic polyoxyethylene stearate studied, polyoxyethylene stearates retarded the release of salicylic acid. This release decreased as the number of oxyethylene units in surfactant molecule increased and as the solubilizing capacity of polyoxyethylene stearates for salicylic acid decreased.

Although release of salicylic acid increases with increasing amounts of water in the vehicle, the influence of the water content on surfactant effects is rather slight.

Introduction

Surfactants used in ointment or suppository bases may produce structural changes in the skin barrier or mucous membrane as well as interacting with the drug used and thus changing its release properties. In the interaction the chemical structure of the surfactant and the composition of the vehicle probably play an important role.

Most commercial ointment bases contain water. The molecular and micellar behaviour of surfactants and also the interaction between drug and surfactant in the

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vehicle containing water are probably different, as was found in anhydrous vehicles (Turakka et al., 1983).

The objectives of this study were to investigate how polyoxyethylene stearate surfactants affect release of salicylic acid from a triglyceride vehicle containing different amounts of water. Special attention was paid to the structure of the hydrophilic part of the surfactant, e.g. the length of the polyoxyethylene chain. We also studied the solubilization of salicylic acid in water solution and the relationship between release characteristics and solubilization.

Materials

The *salicylic acid* used was of analytical grade (purissimum, Fluka AG), its initial concentration in the vehicle was 5% m/m.

Four polyoxyethylene stearates [1] (Atlas Chemicals, Wilmington, DE, U.S.A.), differing only in the length of the hydrophilic polyoxyethylene chain, were chosen as *surfactants* (Table 1). Surfactants are referred to by their trade names. The commercial products were used without further purification. To avoid differences among batches, however, the same batches were used throughout the study.

The *vehicle* was of a mixture of homogeneous triglycerides tricaprin (techn.), trilaurin (purum) and trimyristin (purum) (Fluka AG) in the proportions 2 : 1 : 1, as used previously (Turakka et al., 1983). Water was included in the vehicle in amounts of 5, 15 or 30% m/m for studying the effect of water content.

To avoid the effect of surfactant concentration, which usually affects the drug release (Turakka, 1978; Turakka et al., 1983), the amount of surfactant in the vehicle was kept constant (10% m/m). The total amount of base (triglycerides, surfactant, water and drug) was always 2 g. The vehicles were prepared immediately before the release experiments.

Anhydrous and aqueous triglyceride vehicles without surfactants were used as reference vehicles.

TABLE 1

THE SURFACTANTS STUDIED AND THEIR PROPERTIES

Chemical name	Trade name	HLB	Mol. wt.	Pour point (°C)
Polyoxyethylene-20 *-stearate	Myrj 49	15.0	1149	34–39
Polyoxyethylene-30-stearate	Myrj 51	16.0	1590	36–40
Polyoxyethylene-50-stearate	Myrj 53	17.9	2471	45–49
Polyoxyethylene-100-stearate	Myrj 59	18.8	4673	ca. 44

* Nominal number of oxyethylene units per molecule

[1] Kindly supplied by Flinkenberg, Helsinki, Finland.

Methods

The amount of salicylic acid released was followed by a simplified *continuous-flow dialysis method*, described in detail previously (Turakka, 1978; Turakka et al., 1983).

The vehicle was separated from the aqueous sink using a membrane of cellulose ester type (Dialyzer tubing No. 3787-D42, Arthur H. Thomas, Philadelphia, U.S.A.).

For *solubility determinations* an excess (1.5 g) of salicylic acid was added to 30 ml volumes of water or surfactant solutions contained in 100 ml conical flasks. The flasks were shaken for about 48 h in a shaking apparatus (Bühler SM) at 25°C. After equilibration, the samples were filtered through 0.45 μm Gelman filters and diluted to the appropriate concentration. The diluted samples were assayed for salicylic acid using a UV-spectrophotometer (Pye Unicam SP 1750 A) at 296 nm.

Solubilizing capacities based on weight (mg drug/g surfactant) and on molarity (mol drug/mol surfactant) were calculated according to the method of least-squares by plotting the quantities of salicylic acid brought into solution by surfactants ($S-S_0$, see Fig. 6) versus the concentration of the surfactant, as described previously (Turakka, 1980).

Results and Discussion

Release from vehicles without surfactants

After an initial lag phase, the amount of salicylic acid released from anhydrous and aqueous triglyceride vehicles is a linear function of the square-root of time (Fig. 1), as one would expect for systems where a suspended drug is in equilibrium with a dissolved drug and the total drug concentration is maintained at a value much greater than its solubility in the vehicle (Higuchi, 1961; Roseman et al., 1976).

When water (> 5% m/m) is included in the vehicle, both the amount of salicylic acid released and the release rate increase. The amount of drug released also increases with increasing amounts of water (Fig. 1 and Fig. 5). When the amount of water is increased from 15 to 30% m/m, however, the extent of the increase in drug release is diminished. A small amount of water (i.e. 5% m/m) slightly decreases the release of salicylic acid (Figs. 1 and 5).

Effect of surfactants

Polyoxyethylene stearate surfactants do not change the release profile of salicylic acid; they merely enhance or retard the release (Figs. 2 and 3), depending on the length of the oxyethylene chain in their molecules (Fig. 4). Compared to release from respective reference vehicles (with the same amount of water), it was found that a surfactant with a short polyoxyethylene chain (e.g. Myrj 49) enhances the release of salicylic acid; and with increasing numbers of the oxyethylene units in the surfactant molecule (e.g. Myrj 51, 53 and 59), the release is retarded (Fig. 4). Apparently, however, there is a limiting number of oxyethylene units; and above this limiting number the extent of the decrease in salicylic acid release is diminished. On the other

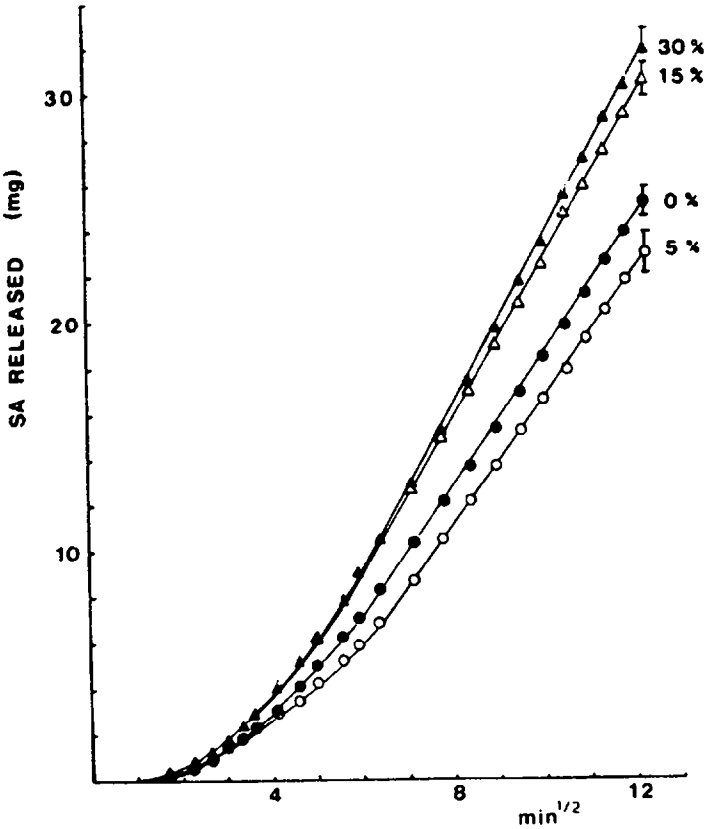

Fig. 1. Release of salicylic acid from triglyceride vehicles containing 0, 5, 15 or 30% m/m water. Mean values of 6–17 experiments and S.E.M.s are seen.

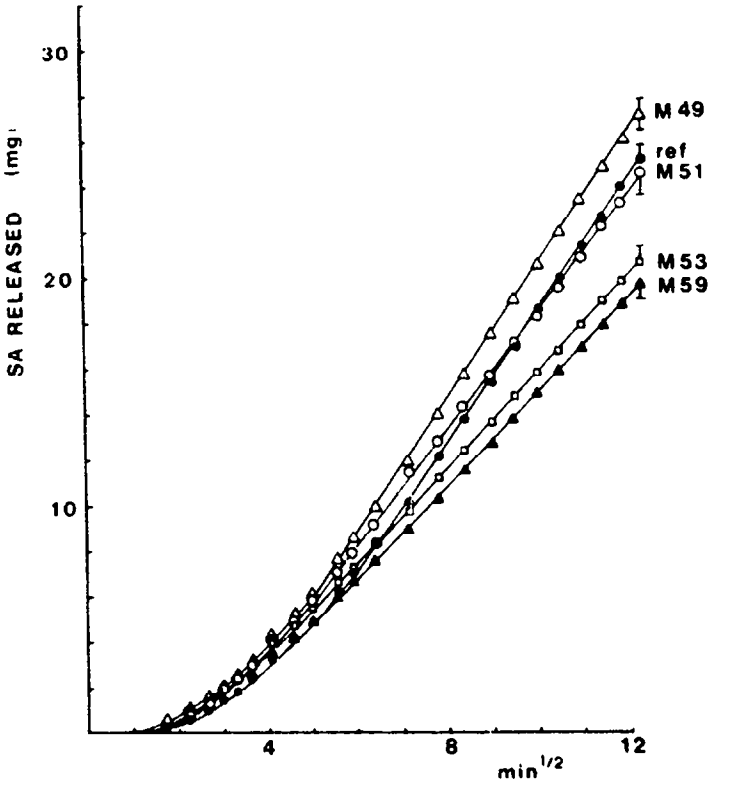

Fig. 2. Effect of polyoxyethylene stearates on the release of salicylic acid from anhydrous triglyceride vehicle: ref = triglyceride vehicle without surfactants; M 49, 51, 53 and 59 are Myrj 49, 51, 53 and 59, respectively. Mean values of 6–17 experiments and S.E.M.s are seen.

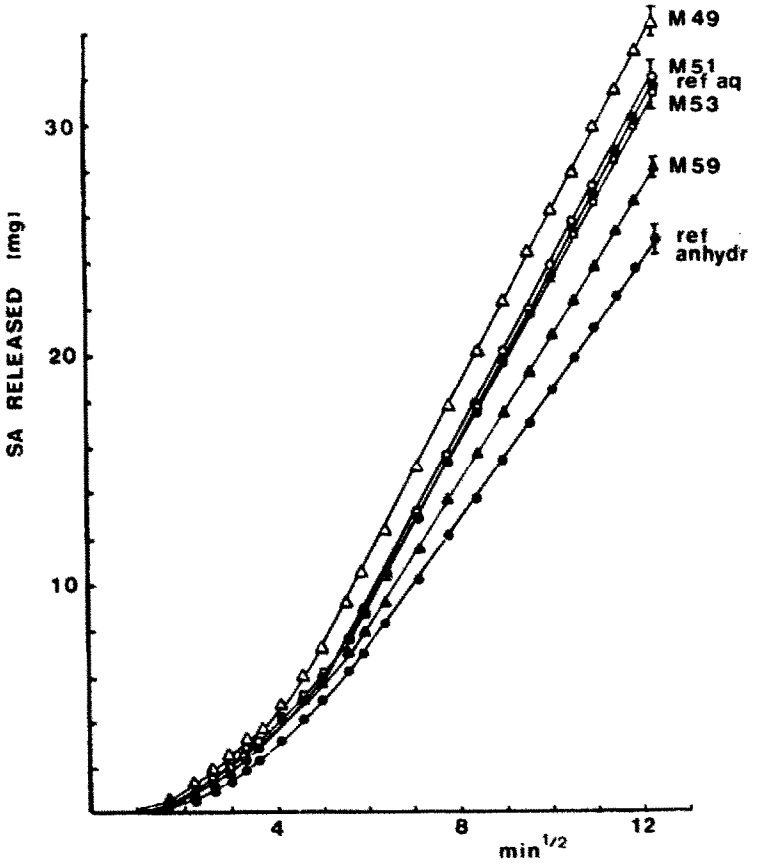

Fig. 3. Effect of polyoxyethylene stearates on the release of salicylic acid from triglyceride vehicle containing 30% m/m water: ref aq = triglyceride vehicle with 30% m/m water; ref anhydr = anhydrous triglyceride vehicle; M 49, 51, 53 and 59 as in Fig. 2. Mean values of 6–8 experiments and S.E.M.s are seen.

hand, the limiting number decreases with increasing amount of water in the vehicle (Fig. 4).

Although release of salicylic acid increases with increasing amount of water in the vehicle, in practice the differences in surfactant effects are rather slight compared to release from the reference vehicle containing the same amount of water (Figs. 4 and 5).

Solubilization of salicylic acid

An increase in the length of the polyoxyethylene chain reduces the solubilizing capacity of the polyoxyethylene stearates for salicylic acid calculated on the basis of weight (Table 2); i.e. an increase in the hydrophilicity of the surfactant decreases the ability of the surfactant to solubilize salicylic acid in water solution (Fig. 6) when the same weights of surfactants are used. A similar relation between solubilizing capacity and surfactant structure was found in the studies of Collett et al. (1972). When solubilizing capacities are calculated on a molar basis (mol salicylic acid/mol surfactant), solubilization increases as the chain length is increased (Table 2); and, in

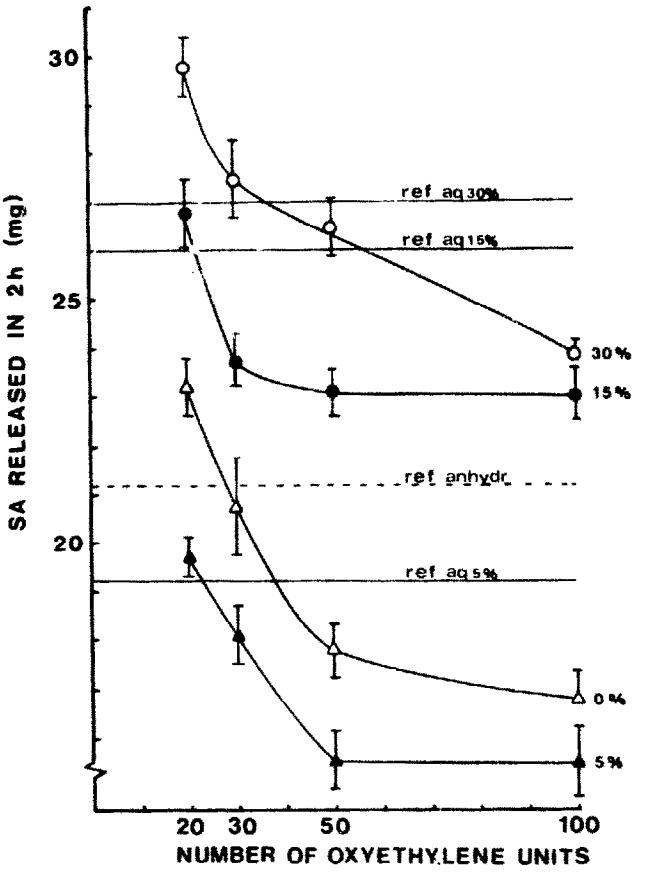

Fig. 4. Amount of salicylic acid released in 2 h from vehicles containing 0, 5, 15 or 30% m/m water and 10% m/m polyoxyethylene stearates versus the nominal number of oxyethylene units in surfactant molecule. Mean values of 6–9 experiments and S.E.M.s are seen.

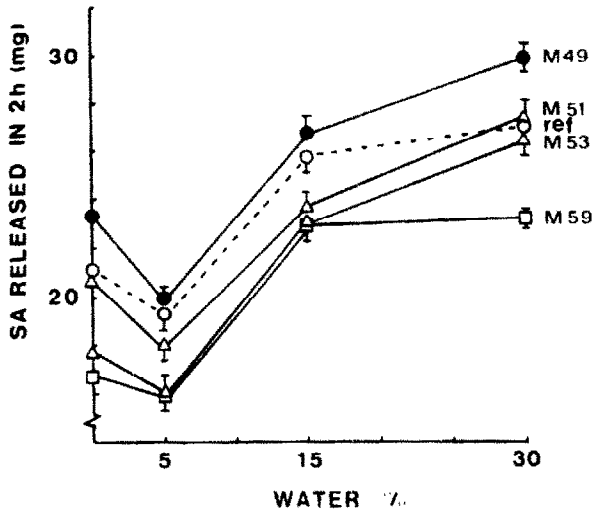

Fig. 5. Amount of salicylic acid released in 2 h versus the water content in the vehicle. M 49, 51, 53 and 59 as in Fig. 2.

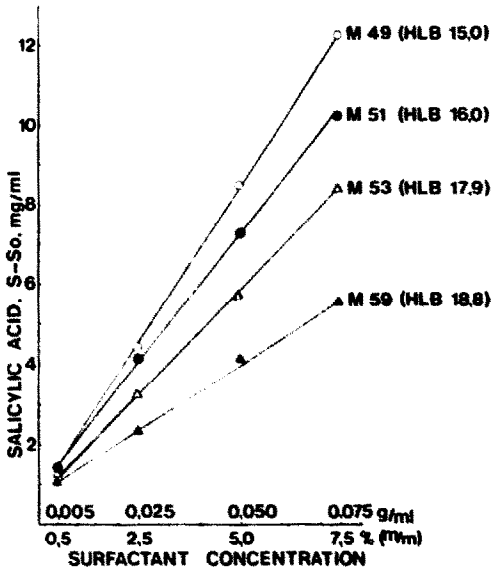

Fig. 6. Solubilization of salicylic acid by polyoxyethylene stearates at 25°C. S = total solubility in surfactant solution; S_0 = solubility in water; M 49, 51, 53 and 59 as in Fig. 2.

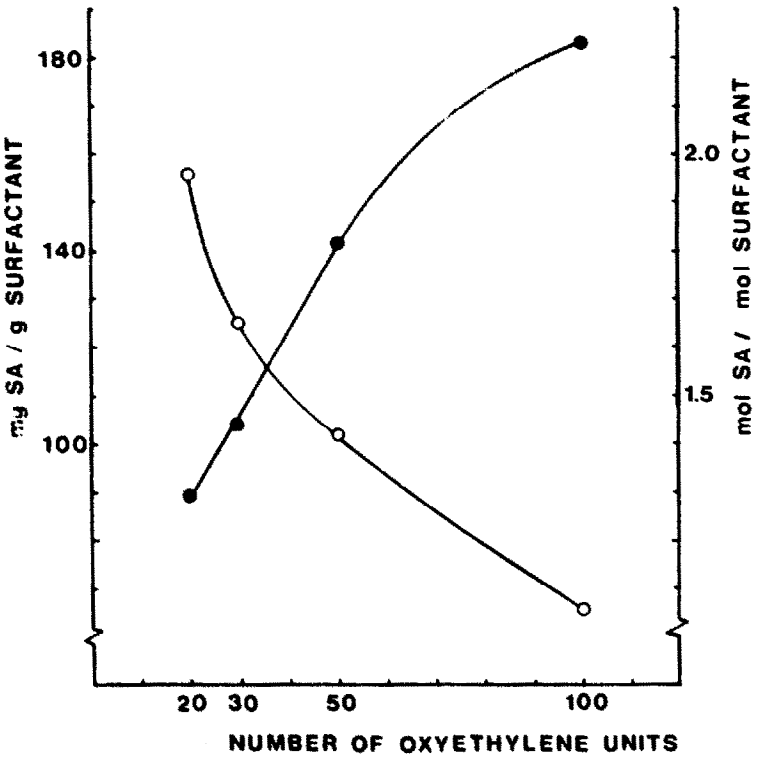

Fig. 7. Solubilizing capacity of polyoxyethylene stearates for salicylic acid in water solution versus the nominal number of oxyethylene units in surfactant molecule. Solubilizing capacity calculated on the basis of weight (○) and on the molarity (●).

TABLE 2

SOLUBILIZING CAPACITIES OF SURFACTANTS

Surfactant	Solubilizing capacity	
	mg drug/g surfactant	mol drug/mol surfactant
Myrj 49	155.9	1.30
Myrj 51	125.1	1.44
Myrj 53	101.7	1.82
Myrj 59	65.9	2.23

agreement with the findings of Collett et al. (1975), with a longer oxyethylene chain the extent of this increase diminishes (Fig. 7).

Increasing the number of oxyethylene units in the surfactant molecule usually means decreasing the number of surfactant molecules per micelle (Mulley, 1964; El-Sabbagh et al., 1978), and in the case of polyoxyethylene stearates, smaller hydrophobic cores. Micelles having smaller cores can thus accommodate less salicylic acid, which are located predominantly in the hydrophobic core of the micelles (Collett et al., 1975; Turakka, 1980).

In considering the relation between solubilization and release of salicylic acid in this study, it is more relevant to consider solubilization capacities on the basis of weight, because the weight of the surfactant was kept constant in the release studies. Accordingly, the surfactant that solubilizes the most salicylic acid (e.g. Myrj 49) also enhances its release. As the solubilizing capacity of the surfactant decreases, the release of salicylic acid is retarded (Myrj 51, 53 and 59) compared to its release from

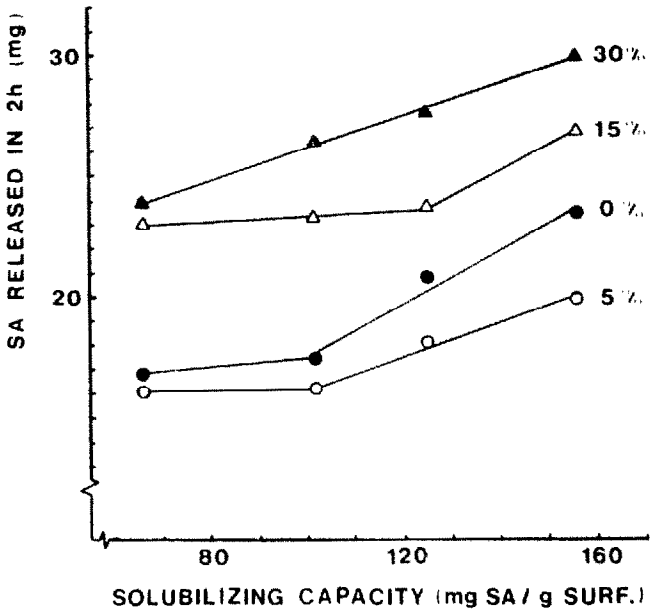

Fig. 8. Relationship between the amount of salicylic acid released in 2 h from vehicles containing different amounts of water and solubilizing capacity of the surfactants in water solution.

the reference vehicle containing the same amount of water (Figs. 2–5, Table 2).

When the amount of water in the vehicle exceeds 30% m/m, the amount of salicylic acid released is directly proportional to the solubilizing capacity of the surfactant (Fig. 8).

Salicylic acid does not behave in the same way, however, in the presence of the polyoxyethylene ethers studied previously (Turakka et al., 1983). In that case the release of salicylic acid increased as the length of the hydrophobic part of the polyoxyethylene ethers decreased (Turakka et al., 1983) and as solubilizing capacity decreased (Turakka, 1980). Therefore, the chemical structure of the surfactant is of special importance.

Differences in the effects of polyoxyethylene-ethers and -esters may be explained in terms of different partitioning of these surfactant molecules between the triglycerides and the water phase, as was also expected for the different effects of polyoxyethylene ethers having different hydrophobic parts (Turakka et al., 1983).

Owing to water molecules diffused through the membrane, there is an aqueous medium between vehicle and membrane. In aqueous media the surfactant molecules form micelles. With increasing hydrophilicity of the surfactants, i.e. with increasing length of the oxyethylene chain, the surfactants have more affinity for the water phase. Accordingly, Myrj 49, which solubilizes salicylic acid the most, probably has the least affinity for water and stays mainly in the triglyceride vehicle. The more hydrophilic polyoxyethylene stearates (Myrj 51, 53 and 59) transfer to water in the order of their hydrophilicity. In the water phase they form micelles. The more surfactant molecules there are in the water, the more micelles there are and the more the release of salicylic acid is retarded, because the micellar drug does not participate in the process of transfer through the membrane (Withington et al., 1973). Thus release of salicylic acid is determined by the interaction of surfactant and vehicle. The partitioning of surfactant molecules between the triglyceride vehicle and the water phase is especially important.

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