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Influence of surfactants on drug release from hydroxypropylmethylcellulose matrices

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Summary

The ability of ionic surfactants to retard the release of drugs from hydroxypropylmethylcellulose (HPMC) matrices has been characterised. The concentration of the surfactant within the matrix is an important parameter affecting release. However, the hydrocarbon chain length of the surfactant does not appear to be a major factor influencing the liberation rate of the drug. It has been found that the surfactant is only effective when both it and the drug are ionised and when they have opposite charges. Conductimetric techniques have been used to show that chlorpheniramine can form poorly water soluble complexes with sodium alkylsulphates. It is postulated that such complexes would form in situ within the HPMC matrix and that drug release from these systems would rely principally upon erosion of the HPMC matrix.

Introduction

The use of hydroxypropylmethylcellulose (HPMC) in the preparation of controlled release dosage forms has been well documented (Christensen and Dale, 1962; Lapidus and Lordi, 1966, 1968; Daly et al., 1984; Ford et al., 1985a and b). On exposure of such matrices to aqueous fluids the HPMC polymer hydrates and forms a gel layer at the tablet periphery. Drug is liberated by a combination of diffusion through and attrition of this gel layer (Huber et al., 1966). The principal advantage of an HPMC matrix formulation is that drug release rates are generally independent of processing variables such as compaction pressure, drug particle size and the incorporation of a lubricant (Ford et al., 1985a).

Daly et al. (1984) observed that the anionic surfactant sodium dodecylsulphate (SDDS) could retard the release of a cationic drug (chlorpheniramine maleate) from HPMC matrices. This effect was attributed to the binding of the surfactant to the polymer, thereby causing an increase in gel viscosity. SDDS has been shown to have such an effect upon a number of polymers including polyvinylpyrrolidone (Saito, 1960), polyethyleneoxide (Szmereková et al., 1984), polyvinylacetate (Saito, 1967) and cationic cellulose ethers (Leung et al., 1985). However, SDDS has also been shown to interact with drug compounds, examples include interactions with phenothiazines (Tomlinson et al., 1979), azo dyes (Abe et al., 1984) and

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quinine (Suzuki et al., 1972). SDDS can also interfere with the penetration rate of water into HPMC powders (Rassing and Davis, 1986).

Gaylord and Schor (1985) have patented a cellulose-based controlled release system which utilises an anionic surfactant (dioctyl sodium sulphosuccinate) to retard the release of ascorbic acid. The surfactant, however, decreased the amount of drug released only during the first hour.

The objectives of the present study were to characterise further the effect of surfactants on drug release from HPMC matrices, to ascertain which surfactant properties are most important in regulating release and finally to determine the principal mechanism by which the surface-active agents act.

Materials and Methods

Materials

Methocel K100M, K4M and K100 (Colorcon Ltd., Orpington, U.K.) were the HPMC grades employed. The Methocel K range has a 22% methoxyl and an 8% hydroxypropyl content. Grades 100M, 4M and 100 indicate that 2% aqueous solutions of these polymers have viscosities (at 20 °C) of approximately 100,000, 4000 and 100 centipoise, respectively (Dow technical Literature on "methocel"). The test drugs were chlorpheniramine maleate BP (Pharmax Ltd., Bexley, U.K.) and sodium salicylate BP (Thornton and Ross Ltd., Huddersfield, U.K.). Lactose (Whey Products, Crewe, U.K.) was employed as a diluent.

The alkylsulphates sodium *n*-octylsulphate (SOS), *n*-hexadecylsulphate (SHDS) and *n*-octadecylsulphate (SODS) (Lancaster Synthesis, Morecambe, U.K.) were all specially purified materials. Sodium *n*-tetradecylsulphate (STDS) and *n*-decylsulphate (SDS) (Eastman Kodak Co., New York, U.S.A.) were 99% pure. Sodium dodecylsulphate (SDDS) (BDH Chemicals, Poole, U.K.) was a specially pure grade. The alkylcarboxylates sodium laurate and stearate (BDH Chemicals Poole, U.K.) were both purified grades; the sodium salts of caprylic acid and palmitic acid (Sigma Chemicals Co., St. Louis, U.S.A.) were 99% pure. One cationic surfactant, cetylpyridinium bromide (Sigma Chemicals Co., St. Louis, U.S.A.) was tested.

Matrix preparation

Each powder was sieved and the 125–180-μm size fraction was used. Matrices were prepared to the following general formula:

HPMC	70% w/w
drug	15% w/w
surfactant	X% w/w
lactose	$15 - X$% w/w

where X had a value of 0, 2, 5, 10 or 15. The ingredients were mixed and the blend was directly compressed, using 5-mm-diameter flat-faced punches, on a Manesty F3 single-punch tableting machine. The upper punch compaction pressure used was 170 N mm^{-2} ($\pm$20 N mm^{-2}). Each matrix weighed 50 mg ($\pm$3 mg).

Dissolution studies

The release of drug from the matrices was monitored using a method based upon the USP (1980) paddle apparatus. 900 ml of dissolution medium was introduced into each of 5 one-litre glass vessels. The temperature of the medium was maintained at 37 °C ($\pm$1 °C) and the paddle speed was set to 100 revolutions/min. Dissolution was continuously recorded using a spectrophotometer (Kontron, model Uvikon 810) connected to a microcomputer (Commodore model 8032). The dissolution fluid was either 0.1 N hydrochloric acid or phosphate buffer (pH 7.0) to represent simulated gastric and intestinal conditions, respectively.

Conductimetric titrations

In order to study the interaction of chlorpheniramine with anionic surfactants, automatic conductimetric titrations were carried out based upon the method described by Mukhayer et al. (1975). The apparatus consisted of a conductivity bridge connected to a dip-type conductivity cell

contained in a thermostated beaker, the contents of which were maintained at 37 °C. The titration mixture was agitated using a magnetic stirrer and the measured conductivity was recorded in the form of a continuous trace on a chart recorder. A motorised syringe delivered the titrant at a controlled rate.

Triple-distilled water was used to prepare all solutions. For each titration 75 ml of a chlorpheniramine solution was pipetted into the jacketed beaker and allowed to equilibrate to 37 °C. The glass syringe was carefully filled with a standard solution of surfactant and mounted on the synchronised motor apparatus. The surfactant was added slowly and continuously to the chlorpheniramine solution and the change in conductance was noted directly on the chart recorder. The titration end-point was marked by a sudden change in the rate of conductance rise. A clouding of the beaker contents is usually observed at this point due to the separation of a complex. The solubility product of the complex, K_{sp}, can be calculated using Eqn. 1:

$$K_{sp} = [\text{Drug}] \times [\text{Surfactant}] \quad (1)$$

where [Drug] is the concentration of the chlorpheniramine and [Surfactant] is the surfactant concentration at the end-point. A number of titrations were performed varying the concentration of chlorpheniramine added to the jacketed beaker.

Results and Discussion

Surfactant concentration

The release of chlorpheniramine maleate from Methocel K100M matrices was retarded by the anionic surfactant SDDS (Fig. 1). The rate of drug release was reduced as more surfactant was added to the formulation. In each case the percentage of drug liberated was linearly related to the square root of time. These findings agree with the results obtained by Daly et al. (1984) who observed a similar effect with matrices prepared from Synchron (a modified form of HPMC).

A plot of the release rate constant, k (obtained by calculating the gradient of the percentage released vs root time curve) against the weight percentage of the surfactant in the matrix, shows that the release rate changes linearly with the amount of surfactant present (Fig. 2). The slope of this curve (-0.33 min$^{-1/2}$) provides a value which characterises the effect of SDDS on chlorpheniramine release from Methocel K100M matrices in pH 7 buffer.

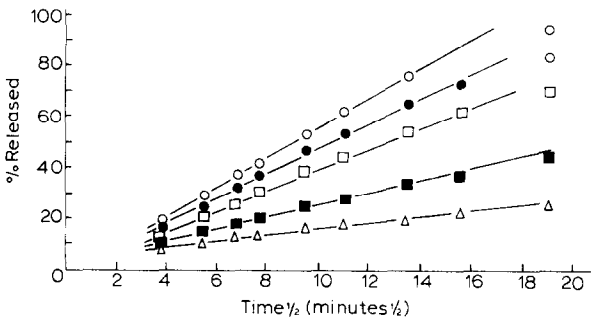

Fig. 1. Effect of SDDS concentration on chlorpheniramine release from K100M matrices (pH 7). (○), 0% w/w; (●), 2% w/w; (□), 5% w/w; (■), 10% w/w; (△), 15% w/w.

Chain length

The characterisation described above was repeated for matrices containing other sodium *n*-alkylsulphate homologues. The slopes of the k vs

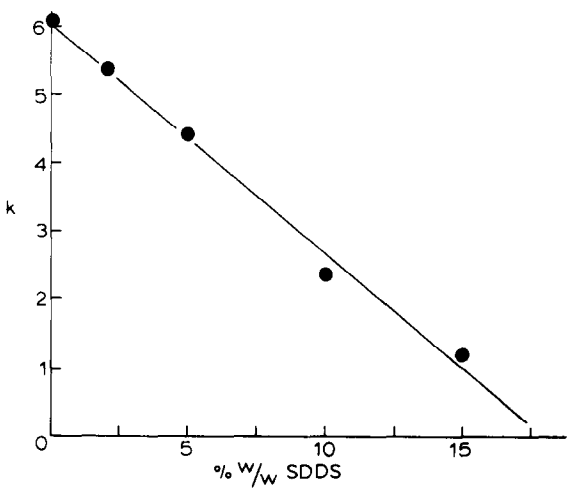

Fig. 2. Plot of k vs % w/w SDDS for chlorpheniramine release from K100M matrices (pH 7). Slope = -0.330 min$^{-1/2}$; intercept = 6.01 min$^{-1/2}$; correlation coefficient = 0.995.

percentage surfactant curves were calculated and are quoted in Table 1. At first sight it appears that the shorter-chain homologues are more efficient at retarding release. This observation is contrary to that expected since long-chain surfactants should give rise to stronger interactions (hydrophobic effect) and provide a greater barrier to drug diffusion. However, on a constant-weight basis a short-chain surfactant will contain more molecules than the same weight of a higher homologue. Therefore, it is more appropriate to plot k against a parameter related to the number of surfactant molecules present in the formula. One such parameter, M_s, can be defined by Eqn. 2.

$$M_s = \frac{1000 \times \%\text{w/w surfactant}}{\text{mol. w. of surfactant}} \quad (2)$$

A plot of k against M_s for the sodium alkylsulphates (Fig. 3) produced one straight line implying that the ability of the alkylsulphates to inhibit chlorpheniramine release is independent of surfactant hydrocarbon chain length. The slope of this particular curve (-0.097 $\text{min}^{-1/2}$) characterise the ability of the sodium *n*-alkylsulphates to retard the release of chlorpheniramine maleate from Methocel K100M matrices.

It was interesting to note that the retarding ability of the surfactant appeared to be saturable. This was particularly noticeable when the relatively short-chain surfactant sodium octylsulphate was incorporated into the matrices. One possible explanation for this effect is that all the available binding sites for the surfactant have been taken and any excess surfactant will become redundant.

TABLE 1

Linear regression analysis for k versus % w/w alkylsulphate plots (pH 7)

Surfactant	Slope ($\text{min}^{-1/2}$)	Intercept ($\text{min}^{-1/2}$)	Correlation coefficient
SOS	−0.287	5.88	0.981
SDS	−0.326	5.64	0.965
SDDS	−0.330	6.01	0.995
SHDS	−0.275	5.80	0.983
SODS	−0.260	6.04	0.989

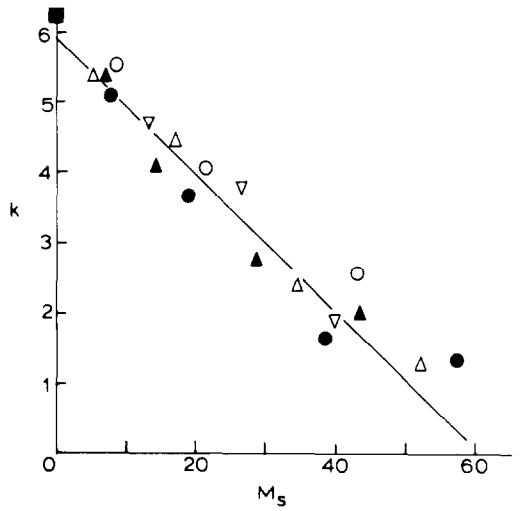

Fig. 3. Plot of k vs M_s for sodium alkylsulphate effect on chlorpheniramine release from K100M matrices (pH 7). (○), SOS; (●), SDS; (△), SDDS; (▲), SHDS; (▽), SODS. Slope = -0.097 $\text{min}^{-1/2}$; intercept = 5.93 $\text{min}^{-1/2}$; correlation coefficient = 0.979.

Headgroup

In order to assess the importance of the surfactant headgroup, matrices were prepared containing sodium carboxylates. These surfactants have a COONa headgroup instead of the OSO_3Na group present in the alkylsulphate molecule. The results were comparable to those obtained with matrices containing alkylsulphates. Sodium carboxylates retarded chlorpheniramine release from K100M matrices (in pH 7 buffer), the effect being greater as more surfactant was added. The shorter-chain homologues were again found to be more effective on a weight basis, but not when the data had been corrected for the number of surfactant molecules in the formula. The slope of the k vs M_s plot (-0.066 $\text{min}^{-1/2}$) characterises the ability of carboxylates to retard chlorpheniramine release. Since this slope is less than that obtained with the alkylsulphates it is apparent that the sulphate headgroup is more effective. This difference between the two series of surfactants may be due to an ionisation effect. A saturated solution of chlorpheniramine maleate was found to have a pH value of between 4 and 5. Such a solution would suppress the ionisation of sodium carboxylates

(salts of relatively weak acids with pK_a values greater than 5). The ionisation of alkylsulphates would not be significantly affected since they are only incompatible with acids below pH 2.5 ("Martindale", 1982). It appears, therefore, that surfactant ionisation is an important factor controlling drug liberation from these matrices.

Acidity

All the analyses described previously were repeated using 0.1 N hydrochloric acid as the dissolution medium instead of pH 7 buffer. The k vs M_s plots (Fig. 4) indicate that only the alkylsulphates could retard chlorpheniramine release in acidic media, but the effect was less dramatic than that observed in pH 7 buffer. As before, these results can be explained by comparing the ionic states of the surfactants at low pH. In acids the carboxylates will revert to their unionised, acidic forms, and will be unable to bind ionically either to the chlorpheniramine cation or to the polymer; they will then behave as inert diluents. The alkylsulphates are salts of stronger acids and are only incompatible with solutions of a pH less than about 2.5. Even though the dissolution fluid had a pH of approximately 1, the microenvironment within the matrix is likely to have been buffered to some extent such that sufficient alkylsulphate molecules remained ionised and were capable of interacting ionically either with the drug or the polymer.

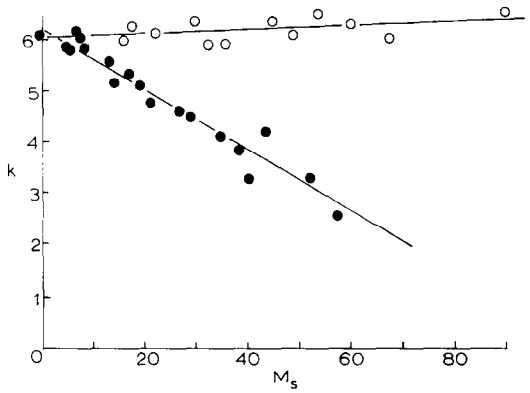

Fig. 4. Plot of k vs M_s for anionic surfactants' effect on chlorpheniramine release from K100M matrices (pH 1). (○), Sodium carboxylates; (●), sodium alkylsulphates. For the alkylsulphates, slope = -0.059 $min^{-1/2}$; intercept = 6.25 $min^{-1/2}$; correlation coefficient = 0.966.

Drug effects

So far the retardation of chlorpheniramine, a cationic drug, by the use of anionic surfactants has been observed; it has been shown that the ionisation of the surfactant is critical. In order to assess the importance of the ionic condition of the drug, matrices containing the anionic drug sodium salicylate were tested. The anionic surfactant SDDS proved ineffective, whereas the cationic surfactant cetylpyridinium bromide was capable of retarding the release of the anion in pH 7 media (Fig. 5). These results together with the data presented for chlorpheniramine and anionic surfactants imply that the surfactants act by interacting ionically with the drug. Hence, only anionic surfactants will retard cationic compounds and vice versa. However, if the retardant is converted to an unionised form (as observed with the sodium carboxylates in low-pH media) then a drug/surfactant ionic interaction is not possible and so release is not impaired. Similarly, if the drug is unionised the surfactant should again be ineffective. This was in fact observed when Methocel K100M matrices containing sodium salicylate and cetylpyridinium bromide were analysed in 0.1 N hydrochloric acid (Fig. 6). The salicylate would have been converted to its poorly soluble acidic form preventing an ionic interaction with the cetylpyridinium ion.

It is interesting to note that the release profiles

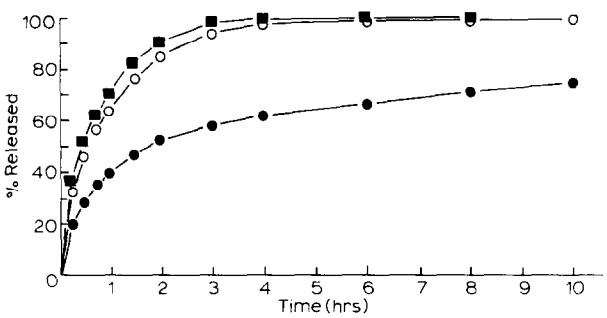

Fig. 5. Effect of ionic surfactants on sodium salicylate release from K100M matrices (pH 7). (○), Lactose control; (●), cetylpyridinium bromide; (■), SDDS.

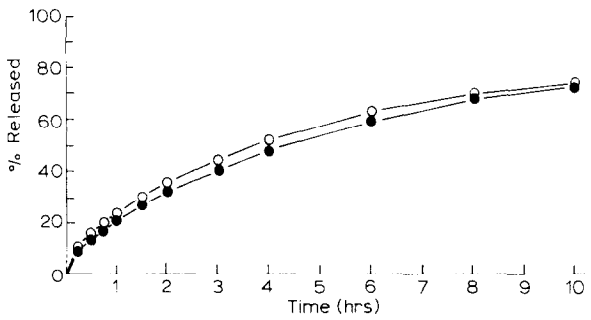

Fig. 6. Effect of cetylpyridinium bromide on sodium salicylate release from K100M matrices (pH 1). (○), Lactose control; (●), cetylpyridinium bromide.

for sodium salicylate from matrices containing cetylpyridinium bromide are very similar in both pH 7 and pH 1 media (Figs. 5 and 6). Therefore, cetylpyridinium bromide has effectively rendered the system pH independent. This could be a very useful property for oral drug delivery systems because they experience media of varying pH within the gastrointestinal tract. However, the problem with using any cationic surfactant is its inherent oral toxicity.

Conductimetric titrations

Conductimetric titrations were performed in an attempt to provide evidence for the theory that retardation of drug release from HPMC matrices was due to a drug/surfactant ionic interaction.

Mukhayer et al. (1975) described a typical conductivity curve for the titration of SDDS against a solution of a phosphonium compound. At low concentrations of added SDDS there is little interaction and a linear relationship exists between conductivity and surfactant concentration. A sudden change in the rate of conductivity increase coincides with the separation of a drug/surfactant complex and the solution going turbid. This was used as the titration end-point. Addition of SDDS to a chlorpheniramine solution produced changes similar to those just described, indicating that the drug and the surfactant interacted to form a poorly water-soluble complex. No such interaction was observed for the titration of SDDS against a solution of sodium salicylate.

Further titrations were carried out varying the initial chlorpheniramine concentration. A plot of log [chlorpheniramine] (CPM) against log [SDDS] (the concentrations of drug and surfactant in the mixture at the titration end-point) produced a straight line with a slope of approximately one (Fig. 7), indicating that a 1 : 1 complex was formed between the drug and the surfactant. This was expected since both compounds provide monovalent ions.

The solubility product, k_{sp}, was calculated using Eqn. 1 and a mean value of 1.83×10^{-7} M^2 was obtained. Such a low value implies that the complex would precipitate readily within the gel layer during the hydration process. Release of drug should then depend upon both the dissolution rate of the precipitate and the erosion rate of the gel layer. The number of chlorpheniramine ions that complex within the HPMC matrix will obviously depend upon the number of surfactant molecules present. The surfactant effect will become constant once all the available chlorpheniramine has been complexed. The addition of more surfactant to the formulation will then be unnecessary because it will not impede drug release further.

SDS and STDS also formed poorly water-solu-

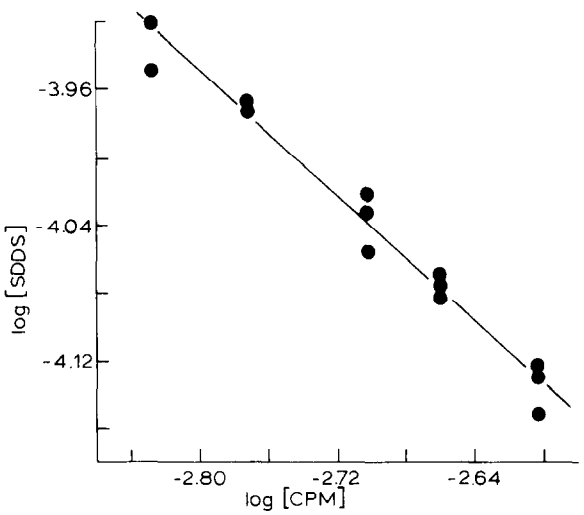

Fig. 7. Plot of log [SDDS] against log [CPM] for complexation. Slope = −0.924; intercept = −6.534; correlation coefficient = 0.987.

ble complexes with chlorpheniramine. The mean solubility products were calculated to be 2.73×10^{-6} M^2 (for the 10 carbon homologue) and 2.85×10^{-9} M^2 (for the 14-carbon homologue), indicating that the longer the surfactant chain length the lower the aqueous solubility of the complex. This is to be expected since longer hydrocarbon moieties have both an increased molecular size and a greater hydrophobicity. The log of the K_{sp} values decreased linearly with increasing chain length. Each additional CH_2 group changed the log k_{sp} value by a factor of 0.64. This is equivalent to changing K_{sp} by a factor of ca. 4. These results are in good agreement with those of Mukhayer et al. (1975) who studied the interaction of alkylsulphates with a phosphonium salt. They found each CH_2 group to alter K_{sp} by a factor of 3.6.

However, in each case K_{sp} is so low that erosion of the HPMC gel layer should become the principal mechanism for liberating drug from such matrices.

Drug/surfactant complex formation thus appears to be the major barrier to drug release from Methocel K100M matrices. The theory proposed by Daly et al (1984) that the surfactant binds to the polymer increasing gel viscosity may be valid for Synchron (a low molecular weight grade of HPMC), but is inappropriate for Methocel K100M since viscosity has only a minimal effect upon release from high-molecular-weight grades of HPMC (Fig. 8) (Ford et al., 1985a and b).

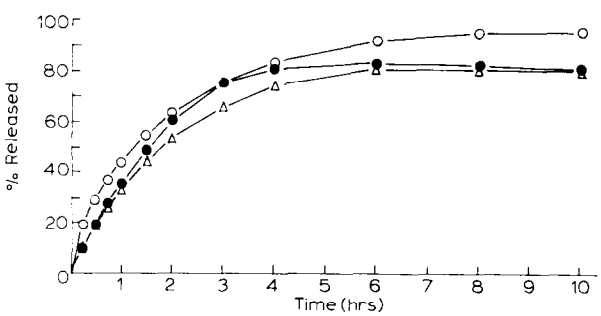

Fig. 8. Effect of HPMC viscosity on chlorpheniramine release (pH 7). (○), K100M; (●), K100; (△), K4M.

Conclusions

The following conclusions can be drawn from the results of this study.

(i) The retarding effect of ionic surfactants on drug release from HPMC matrices is dependent upon the number of surfactant molecules present and relies upon the drug and the surfactant having opposite charges.

(ii) The effect of the surfactant appears to be independent of its hydrocarbon chain length, but is modified by the pH of the environment which may alter the ionisation state of both the drug and the surfactant.

(iii) The principal mechanism by which surfactants retard drug release from HPMC matrices is by a drug/surfactant ionic interaction. The resultant complex has a low aqueous solubility ensuring that the erosion of the HPMC matrix becomes a more important factor in the liberation of the drug.

Acknowledgements

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