

Impact of Solvent Relaxation NMR on The Stability of Creams

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Abstract- *Stability is one of the primary issues with forming an emulsion. An emulsion's stability is influenced by the density of the oily and aqueous phases, the dispersed phase's integrity, and the size and distribution of the particles in the internal phase. [1] Several procedures, including phase inversion, flocculation, coalescence, creaming, Ostwald ripening, and cracking, can cause emulsions to lose their stability and there is a necessity to develop non-invasive techniques to probe opaque systems. [2] This project was conceived to assess whether solvent relaxation Nuclear Magnetic Resonance (NMR) is a feasible technique with which to evaluate the stability of an emulsion using three different types of Tween non-ionic surfactant as the emulsifier (Tween 20 also called Polysorbate 20, Tween 60 also called Polysorbate 60 & Tween 80 also called Polysorbate 80), two different types of fatty alcohol (Cetyl alcohol and Stearyl alcohol) together with Rutile Titanium dioxide. The goal was to understand the impact of the Rutile TiO_2 on any physical changes. The Carr-Purcell-Meiboom-Gill pulse sequence was used to quantify T_2 relaxation time by measuring the R_2 and R_{2SP} of the samples. In all cases a rapid interchange water molecule was observed which is demonstrated by the linearity on a semi log plot of water-based system. A number of distinct observations were evident. For all concentrations between fatty alcohols the water R_{2sp} and R_2 remains constant regardless of the kind of Tween used, showing that the inclusion of Tween doesn't impact the relaxation solvent systems. By contrast, aqueous systems with rutile show a marked difference as the intensity of waxes decreases faster than water. This work has shown that solvent relaxation can provide molecular level information on the structure of creams.*

Indexed Terms- *Stability, emulsions, NMR, non-ionic surfactant, fatty alcohols*

I. INTRODUCTION

It is often said that the art and science of formulation go hand in hand. A formulator skilled in the development of an emulsion system must address numerous challenges when creating any product that delivers an active ingredient [3]

The efficacy of the active ingredient is significantly influenced by its formulation, wherein various factors such as the type of active(s), the make-up of the emulsion's oil phase, the composition of the emulsion's water phase, the emulsification procedure, and possibly additional features such as temperature, pH, ionic strength, mixing speed, mixing time and the system's rheological properties all have an impact on how the active ingredient is delivered. As the emulsifier performance is dependent on the active ingredients of the emulsion, the main task of a formulator is to produce a formulation with the greatest possible delivery of these active ingredients, while minimizing production costs, and boosts the quality of cosmetic products. [3]

The use of creams or oil in water (o/w) emulsions is the usual method for administering drugs topically. In their most basic form, emulsions consist of an aqueous phase, a hydrophobic phase, and an emulsifying agent. The stability of the product is determined by the colloidal structures that are created by these constituent parts, which also determine its viscoelastic properties. [3] Creams are naturally unstable, and over time, the interior part will usually consolidate, even though the free energy is reduced by the surface-active ingredient. The level of agitation between the two phases determines the surface area of any given internal phase volume, which has a big impact on the system's overall stability. [4,5]

Ternary systems (which is a three-component system) having surfactants and fatty alcohols in surplus of water are frequently used in pharmaceutical and cosmetics (such as skin and hair care products) applications to topically and transdermally transferring the active substance to the skin [6]. The physicochemical characteristics, rheology, and multiphase structure of these systems have recently received significant attention within the research community [7-10]. In general, the continuous phases of the equivalent semisolid o/w emulsions can be represented by these systems as models.

A common cream consists of an oil and water mixture. Since oil does not easily dissolve or disperse in water, an emulsifier—a dispersing agent—is added to the mixture to facilitate this process. Thus, an emulsion that has a water phase and an oil phase is a cream.

The variations in the consistency of topical hydrophilic creams are linked to the use of different batches of excipients used to make the creams, this is because creams are not 100% stable and therefore change with time. It is the work of the formulator to extend the time, it does imply that excipient batch variation may alter creams' bioavailability as well as their shelf life. [11] The surface area and stability which translate to the shelf life of the cream are connected via the interfacial energy, so if the energy reduces, the surface area increases, and the stability of the cream improves.[11] Creams offer several advantages in pharmaceutical and dermatological applications. They allow the incorporation of both aqueous and oleaginous components, enabling the release of numerous integrated medications, and their rheological characteristics can be controlled. [12] Numerous researchers have investigated the effects of creams on drug release and absorption, particularly when they are utilized as carriers in topical dermatological applications [13].

II. WHAT IS AN EMULSION?

An emulsion is a distribution of one or more non-miscible liquid phases in the form of small droplets within another liquid phase. [14]



Figure 1: Oil and Water emulsion [14]

The additional phase often transforms into the internal phase which is the dispersed phase. According to Bancroft's rule, the phase where an emulsifier is more soluble is the continuous phase. Usually, the phase with the highest volume transforms into the exterior phase. The phase that the stirrer is placed in inevitably transforms into the exterior phase which is the dispersed medium. [14]

The stability of an emulsion can be defined as its ability to maintain their properties. The type and composition of the oil, the ratio of surfactants to oil, the ionic strength, pH, the concentration of emulsifier, oxidation, and the processing conditions all affect how stable an emulsion is. The mechanism that leads to instability of an emulsion includes flocculation, coalescence, phase inversion and gravitational separation (creaming/sedimentation). [15]

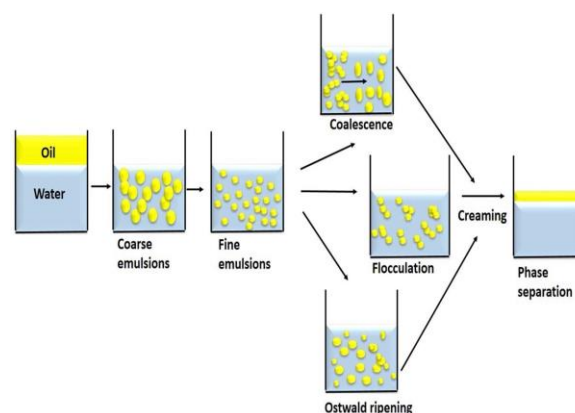


Figure 2: Schematic illustration of instability mechanisms in an emulsion system [15]

III. EMULSIFIERS

In general, a range of surface active as other excipient are used to stabilise emulsion. These are typically called emulsifiers. The development, stability, and effectiveness of oil-in-water emulsions can frequently be enhanced by combinations of two or more different emulsifiers.

The kind of emulsifier used influences the ability of the final product to stabilise emulsions as well as its functional qualities and ease of emulsion formation. Therefore, when manufacturing emulsion-based goods, choosing an appropriate emulsifier is one of the most crucial choices. [16] Amphiphilic molecules are molecules that self-assemble in aqueous solution to form unique structures including micelles, vesicles, and tubules, such as, phospholipids, proteins, polysaccharides, and other surface-active polymers, are frequently used as emulsifiers because they have both groups that are hydrophilic and hydrophobic on the same molecule. [17-19]

IV. MATERIALS AND METHODS

A key aspect of this project is to evaluate whether solvent relaxation is an appropriate tool to characterize dispersion of particles such as Titanium (IV) oxide in a media with surfactants and fatty alcohol. This chapter will focus on the materials and the methods used together with the surfactants and fatty alcohol involved.

MATERIALS

Tween 20, 60 & 80, Stearyl alcohol, Cetyl alcohol and Titanium (IV) oxide rutile have all been used for this experiment without any form of chemical modification.

Chemical	CAS number	Supplier	Aspect	Chemical formula
Tween 20	9005-64-5	Sigma Aldrich	Clear yellow viscous liquid	C ₅₈ H ₁₁₄ O ₂₆
Tween 60	9005-67-8	Sigma Aldrich	Dark yellow viscous liquid	C ₆₄ H ₁₂₆ O ₂₆
Tween 80	9005-65-8	Sigma Aldrich	Amber liquid	C ₆₄ H ₁₂₄ O ₂₆
Titanium (IV) oxide rutile	1317-80-2	Thermo Scientific	White to off-white powder	TiO ₂
Cetyl alcohol	36653-82-4	TCI	White waxy solid	C ₁₆ H ₃₄ O
alcohol (1-octadecanol)	112-92-5	TCI	White granule	C ₁₈ H ₃₈ O

Table 1: List of chemicals used in the experiment.

METHOD

A benchtop XIGO Nanotools Acorn Area spectrometer with a resonance frequency of 13 MHz has been utilized for the NMR measurements to evaluate the spin-spin relaxation time (T₂) of the solvent. This non-intrusive and non-destructive device uses nuclear magnetic resonance (NMR) to determine the surface area of nanoparticles dispersed in a liquid. The NMR makes use of the CPMG pulse sequence. It is attached to a chiller, which maintains the equipment at a constant 25 ± 0.5 °C. For each measurement, 500 µL of the sample was placed into the 5 mm NMR tube. The signal was averaged across three scans, and a magnetization decay curve, M_{xy}(t) versus time (t), was gathered.

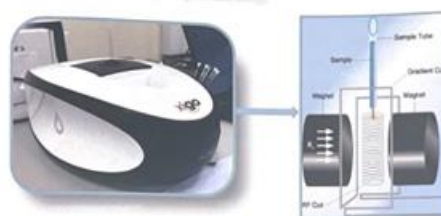


Figure 3: The bench top Xigo Nanotools Acorn Area is a simple low field NMR spectrometer resonance frequency of 13 MHz using a CPMG pulse sequence that measures the spin spin relaxation time (T) in few minutes. The figure in the right-hand side shows the internal components of the instrument. [20]

Tween 20, 60 & 80 surfactants together with Stearyl alcohol & Cetyl alcohol and Rutile Titanium oxide were tested. Sample preparation processes are summarized below:

Stock solution of Tween was prepared at the concentration of 10%w/v. The weighted amount of Tween was introduced into a vial, followed by the addition of water. This solution was used as a solvent for all the experiments.

Stock solution of Rutile Titanium oxide was prepared at the concentration of 10%w/v. The weighted amount of Rutile Titanium oxide was introduced into a vial, followed by the addition of water. This solution was used as a solvent for all the experiments. In fact, using a larger concentration of liquid waxes rather than tablets waxes was simpler. For all the

studies, Stearyl and Cetyl alcohol was added directly as a powder because the tablet waxes were also added as a powder in the sample using a mortar.

A serial dilution was prepared by varying the concentration of Rutile TiO₂ between 0.1% - 5% w/v while keeping the Tween and the fatty alcohol constant 5% w/v.

Another serial dilution was made where Rutile TiO₂ was kept constant at 0.9% w/v and varying the concentration of the Tween and the fatty alcohol between 1-5% w/v.

All samples were heated to 70°C which is the melting point of the wax.

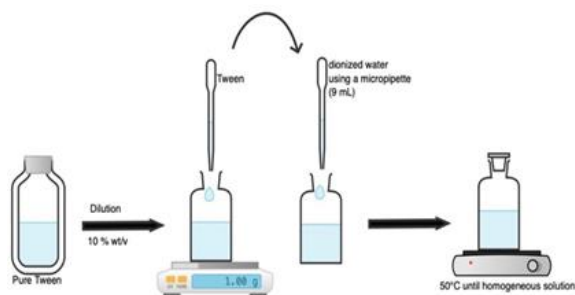


Figure 4: The process of making the stock solution of Tween and Rutile Titanium (IV) Oxide

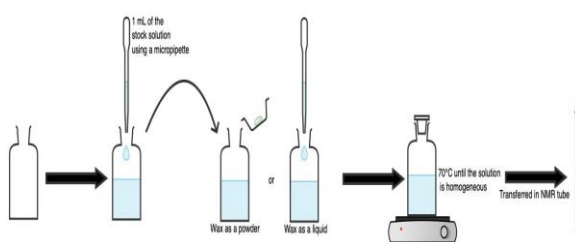


Figure 5: The process of making the samples.

V. RESULTS AND DISCUSSION

Studies on different Tweens have been done in water-based systems to look at the potential effects of different Tween compounds on solvent relaxation. In all cases a rapid interchange water molecule was observed which is demonstrated by the linearity on a semi log plot.

For all concentrations between the different alcohols used and water R_{2sp} and R_2 remains constant

regardless of the kind of Tween used, showing that the inclusion of Tween doesn't impact the relaxation solvent systems.

Depending on the composition of the samples, phase separation is invariably observed, and at quite different rates. This is challenging from an experimental point of view as reproducibility of the data will be less likely than desired. That said, there are few techniques that can access information on the stability of these systems, and hence one reason for exploring the use of the solvent relaxation NMR.

For these systems, a rapid interchange of water molecules was observed.^[21] As may be seen the data are exactly the same, decays are very similar hence, we can conclude that the presence of the interface does not significantly perturb the dynamics of the water i.e. for any concentration ranging from 0.1 to 5% Tween, R_2 and R_{2SP} stay consistent regardless of the kind of Tween used, the inclusion of Tween will not impact solvent relaxation in systems containing waxes. By contrast, aqueous systems with rutile show a marked difference as the intensity of waxes decrease faster than water.

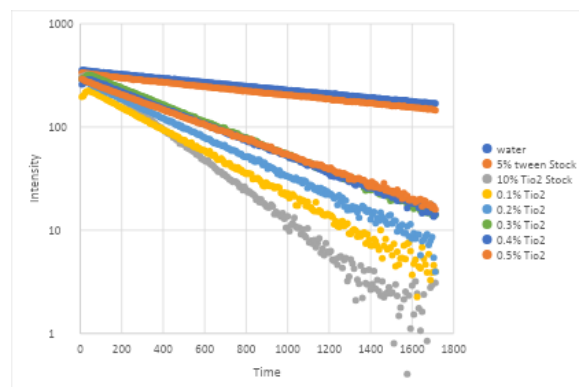


Figure 6: Typical raw data of intensity against time for a series of sample studied within this work.

Therefore, we'll focus on the impact of the rutile titanium on the dispersion of the waxes' effect on solvent relaxation.

Practically, the study focused on the investigation of different Tween compounds (Tween 20, 60 & 80) in an emulsion system with the introduction of different concentration of Rutile Titanium (IV) oxide, and fatty alcohol (Stearyl and Cetyl alcohol). The key

aspect being explored was the interplay between the length of the alkyl chain of the wax in different alkyl length polysorbates.

A matrix of experiment was constructed in which the concentration of Tween 20, 60 & 80 and Stearyl alcohol was varied in turn, whilst holding the concentration of Rutile Titanium dioxide at fixed values. Stearyl alcohol also known as 1-octadecanol, is a white waxy substance with a C18 length alkyl chain together with Rutile Titanium (IV) oxide an off-white powdery substance. Consider the experiment where rutile was held at 0.9%w/v and Tween 20, 60 & 80 at 1-5% w/v and Stearyl alcohol at 1-5% w/v see figure 22 and 23. The R_2 and R_{2SP} have been plotted against Stearyl alcohol concentration.

No matter the nature of Tween, R_2 and R_{2SP} have a linear correlation with $C_{18}OH$ concentration. Also, we have the same impact of the hydrophobic tail length on R_2 and R_{2SP} .

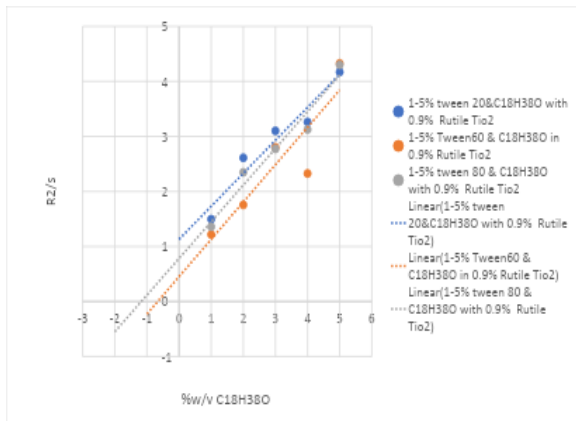


Figure 7: 1-5% Tween 20, 60,80 & $C_{18}H_{38}O$ with 0.9% TiO_2

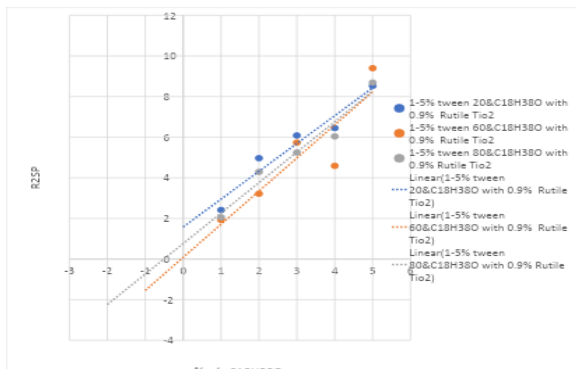


Figure 8: 1-5% Tween 20, 60,80 & $C_{18}H_{38}O$ with 0.9% TiO_2

Broadly speaking, there is a linear increase in R_2 and R_{2SP} with wax concentration. Within these three data sets, there is no significant dependence on Tween headgroup size.

Also, we have the same impact of the hydrophobic tail length on R_2 and R_{2SP} . Collectively, these various observations suggest that the solvent is able to “see” the rutile, but little impact is provided by the surfactant or wax headgroup regions, although these do facilitate the exposure of the rutile surface.

Interestingly, at higher rutile concentrations, the effect is constant i.e., it reaches a plateau value above 1wt%, though it is evident that the Tween headgroup again has no impact.

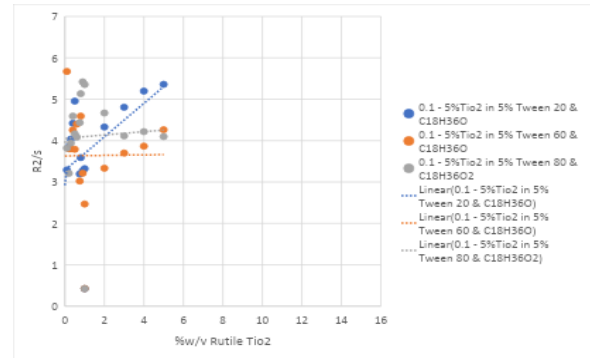


Figure 9: 0.1-5% Rutile TiO_2 in 5% T20,60,80& $C_{18}H_{38}O$

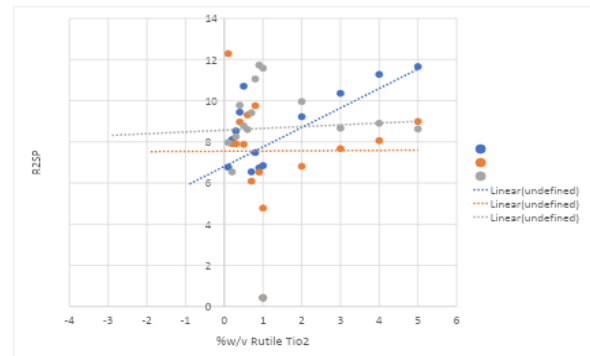


Figure 10: 0.1-5% Rutile TiO_2 in 5% T20,60,80& $C_{18}H_{38}O$

Cetyl Alcohol is also known as Hexadecanol is a white flaky powder with a C_{16} length alkyl chain

together with Rutile Titanium (IV) oxide an off-white powdery substance. Intensity against time have been plotted and we can see fast exchange in the system, R_2 and R_{2SP} have been plotted against Cetyl alcohol concentration.

In each Tween, we consequently observe the similar behaviour in R_2 and R_{2SP} there is a linear increase in R_2 and R_{2SP} with wax concentration in figure 11 and 12.

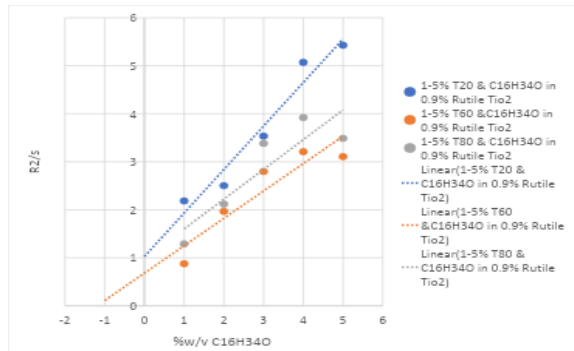


Figure 11: 5% Tween 20, 60,80 & C₁₆H₃₄O with 0.9% TiO₂

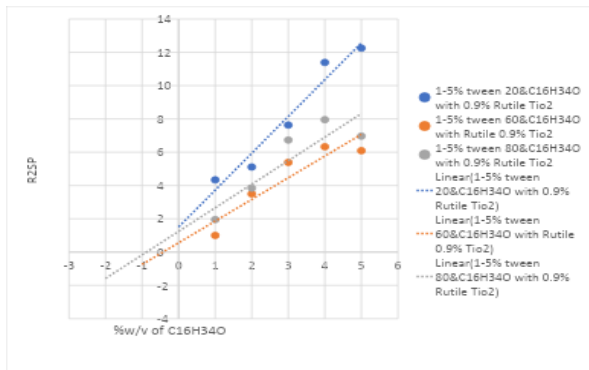


Figure 12: 5% Tween 20, 60,80 & C₁₆H₃₄O with 0.9% TiO₂

Cetyl alcohol has little effect on solvent relaxation. Moreover, we can deduce that R_2 and R_{2SP} are higher than the longer hydrophobic tail of polysorbate. In fact, the lengths of polysorbate 20, 60 and 80 are, C₁₆, and C₁₈, respectively with a double bond.

However, samples with Cetyl alcohol formed a fast-separating unstable emulsion as compared to samples with Stearyl alcohol.

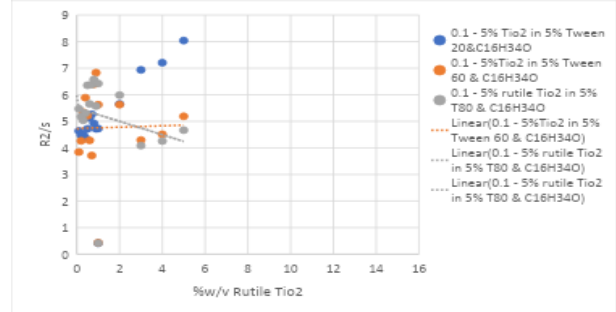


Figure 13: 0.1-5% Rutile TiO₂ in 5% T20,60,80&C₁₆H₃₄O

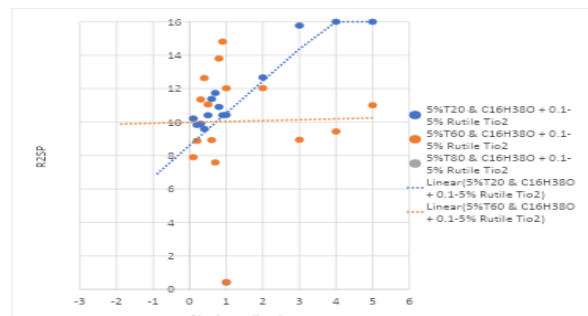


Figure 14: 0.1-5% Rutile TiO₂ in 5% T20,60,80&C₁₆H₃₄O

CONCLUSION AND FURTHER WORK

The purpose of this research was to investigate the possibilities of solvent relaxation NMR by first looking at the emulsion stability of creams. The cream in question was made up of water, fatty alcohols, different polysorbates together with Rutile Titanium dioxide. Experiments showed that solvent relaxation was unaffected by the various polysorbates.

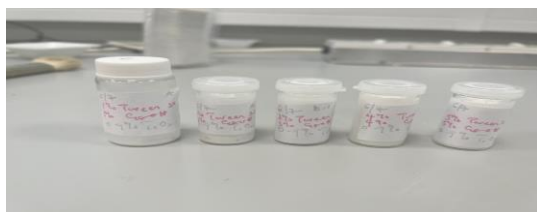
Prior to now research has been done by a fellow team member to investigate the impact of water, fatty alcohols and different polysorbates.

A proportionate association between R_2 and R_{2SP} and the sample's visual aspect was then found utilizing Cetyl alcohol with the Rutile Titanium dioxide. Similarly, using Stearyl alcohol and Rutile Titanium dioxide, a proportionate relationship between R_2 and R_{2SP} , the hydrophobic tail of polysorbate, was found. The main hypothesis has been shown that solvent relaxation can be used to study the stability of emulsion creams.

To complete the research in this report, one variable that seen significant in this work is the effect of temperature and how it affects the reproducibility of the results. it would be interesting to explore the effect of temperature variation on the system. Also try to understand the impact of homogenization of the cream on the R_2 and R_{2SP} relaxation., other composition of the oily phase in the emulsion could be changed (using Dodecanol $C_{12}OH$ for example or different ratios of waxes).

APPENDIX

Pictures of some sample preparation used for the project work.



1-5% Tween 20 with $C_{18}OH$ and 0.9% TiO_2



1-5% Tween 60 with $C_{18}OH$ and 0.9% TiO_2

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