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### NOVEL SELF-NANOEMULSIFYING DRUG DELIVERY SYSTEMS (SNEDDS) FOR ORAL DELIVERY OF LIPOPHILIC DRUGS

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#### ABSTRACT

The self-nanoemulsifying drug delivery system (SNEDDS), is a promising Drug Delivery System which is well known for its prospective to improve the aqueous solubility and oral absorption of poorly water soluble drugs (Pouton, 2000). SNEDDS is an isotropic mixture comprising oil, surfactant, co-surfactant and drug that form oil in water emulsion in aqueous environment under placid agitation. It can readily disperse in the aqueous environment of the gastrointestinal tract to form a fine oil-in-water emulsion with a droplet size not exceeding 100 nm under mild agitation for improving the oral bioavailability of poorly water-soluble drugs (Shah et al., 1994; Constantinides, 1995). Compared to conventional metastable emulsions, SNEDDS is a thermodynamically stable formulation with high solubilization capacity for lipophilic drugs, and also can be filled directly into soft or hard gelatin capsules for convenient oral administration. The Self nano-emulsifying Drug Delivery System (SNEDDS) is applicable on BCS Class II and Class IV Drugs for improving water Solubility of poorly water soluble drugs. It is important to prevent the interfacial tension and improving the dissolution as well as absorption rate of drug molecule. It is the novel drug delivery system which is applicable for parenteral, ophthalmic, intranasal and cosmetic delivery of drugs. The review presents an overview of design of formulation, preparation of components, mechanism of self nano emulsification, biopharmaceutical aspects, characterization methods and applications of self nano-emulsifying drug delivery system (SNEDDS) for enhancement of oral bioavailability of poorly water soluble drugs.

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## INTRODUCTION

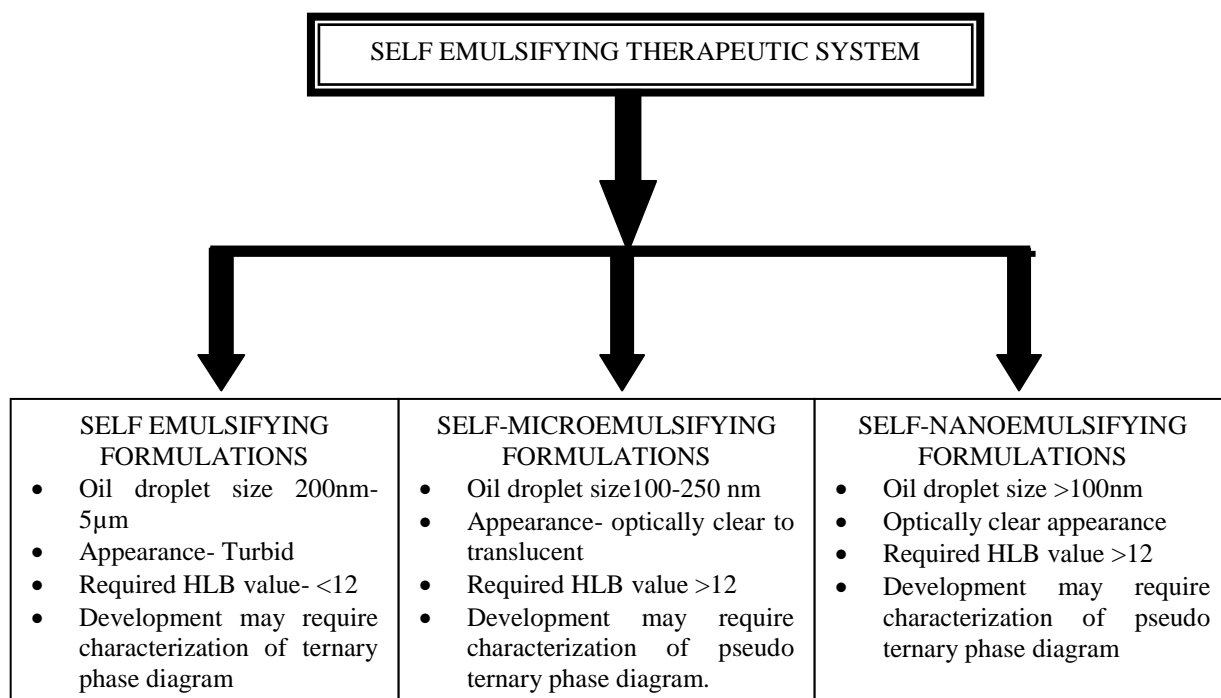
As Oral route is the most preferred route for administration of drugs, but majority of drugs are frequently administered through oral route because of first pass metabolism. But about 40% of new drug candidates have poor aqueous solubility and the oral delivery of such drugs is complicated because of the reason that of their low bioavailability, high inter/intra-subject variability, and no dose linearity.<sup>(1,2)</sup>

To overcome all these problems, different strategies have been developed including the use of lipids, permeation enhancers, surfactants, micronization, salting in/out, cyclo-dextrins, nanonisation and solid dispersions etc. There has been evolving attention in the use of lipid excipients in self-emulsifying lipid formulations (SELFs) because of their competency to solubilize poorly water-soluble lipophilic drugs and to prevail over the problem of poor drug absorption and bioavailability.<sup>(3,4)</sup>

Novel approaches include microemulsions, nanoemulsions, self-emulsifying formulations, self-microemulsifying formulations, and self-nanoemulsifying formulations. Most of them advantageously increase surface area of the drugs to improve solubility behavior, as well as permeation characteristics.<sup>(5,6)</sup>

Self-nanoemulsifying drug delivery systems (SNEDDS) are nanoemulsion pre-concentrates or anhydrous forms of nanoemulsion. These systems are lipid isotropic mixtures of drug, oil and surfactant(s) when introduced into aqueous phase under the aid of gentle agitation, spontaneously form O/W nanoemulsions (usually with globule size > 200 nm). In human body, the agitation required for formation of nanoemulsions is provided by digestive motility of the GI tract. SNEDDS may also contain co-emulsifier or co-surfactant and/or solubilizer in order to facilitate nanoemulsification or improve the drug incorporation in SNEDDS.<sup>(7)</sup>

Nanoemulsions are heterogeneous dispersions of two liquids (oil-in-water or water-in-oil) regardless of method of preparation; they have mean droplet size in the nano scale (20–200 nm). These heterogeneous dispersions were initially known as submicron emulsions; miniemulsions, ultrafine and microemulsions, and regrettably these systems are confused with micro emulsions, which are thermodynamically stable.<sup>(8,9)</sup>



Self-emulsifying drug delivery systems (SEDDS) are isotropic mixtures of oil, surfactant, surfactant and co-surfactant that form fine oil-in-water or water-in-oil emulsion when introduced into aqueous medium under gentle. The design of effective formulation for drugs has long been a major challenge, because drug efficacy can be severely limited by instability or poor solubility in the vehicle.

Due to higher solubilization capacity of nanoemulsion/ microemulsion, they have more thermodynamic stability and offers advantages over unstable dispersions, such as emulsions and suspensions, because they can be manufactured with little energy input (heat or mixing) and has a long shelf life. In case of nanoemulsion, due to the nanosized droplets, there is enormous interfacial area which influences the transport properties of the drug, an important factor influencing the sustained and targeted drug delivery. Also the oily formulations such as microemulsions lead to lymphatic drug absorption and thus by-passes the liver, which is the major site of drug metabolism. The desirability of o/w nanoemulsion system lays in their ability to incorporate hydrophobic drugs into the oil phase thereby enhancing their solubility. Nanoemulsions have been reported to make the plasma concentration profiles and bioavailability of drugs more reproducible.

Although nanoemulsions are one of the best choice for hydrophobic drug delivery system, but being a liquid dosage form it would not be as popular as the solid dosage form. So to cope-off these challenges many attempts have been taken to convert liquid self-emulsifying system to the solid self-emulsifying drug delivery system.

SNEDDS are defined as isotropic mixtures of natural or synthetic oils containing solid or liquid surfactants and one or more hydrophilic solvents. They form fine oil in water (o/w) emulsions on contact with GI fluids. Usually the drug in SNEDDS remains in the solution form throughout its GI transit time whereby they circumvent the dissolution step. It involves digestion of the excipients and formation of different colloidal structures as nanodroplets. The drug gets partitioned into these structures before it is absorbed. The nanodroplets formed are with increased surface area due to decreased interfacial tension and thus they are readily available for absorption of poorly soluble drugs. In addition to increased surface area the common excipients used in the formulation of SNEDDS inhibits P-gp & CYP450 enzymes thereby decreasing intestinal efflux and drug biotransformation respectively. Research also reveals that SNEDDS facilitates the transcellular and paracellular absorption thereby the drug is absorbed through the lymphatics via chylomicron synthesis of the fatty components of the oil phase of the emulsion, thus inhibiting first pass metabolism of drug.

Furthermore, pharmaceutical microemulsions require a high surfactant concentration (about ~20% or more) to enable optimal drug delivery, nanoemulsions can be fabricated with a relatively small concentration of surfactant (3–10%).

SNEDDS contains diverse class of excipients which may affect the performance of a dosage form in various forms. Hence, application of experimental methods like factorial design, Box–Behnken design (BBD), D-optimal design, and mixture design etc for systematic optimization helps in optimizing drug delivery systems to obtain better formulations. Further drug-loaded SMEDDS can be converted into free flowing solid granules (S-SNEDSS) using porous carriers like Aerosil 200, Sylsilia (350, 550, and 750) and Neusilin US2 by adsorption technique.<sup>(10,11)</sup>

### Self Nano emulsifying Drug Delivery Systems for Oral Drug Delivery

The oral route is the most complimented and preferred route of drug delivery. However, more than 50% of drugs delivered via oral route have limited therapeutic efficacy due to poor water solubility.<sup>(12)</sup>

Furthermore, a majority of the new chemical moieties being generated through drug discovery programs also exhibit poor aqueous solubility. The problems associated with such drugs include erratic absorption profile, poor oral bioavailability, high intra/inter-subject variability and lack of dose proportionality.<sup>(13)</sup>

The ability of nano-sized/submicronic emulsions to improve the GI absorption of lipophilic drugs was demonstrated almost three decades ago.<sup>(14)</sup>

### Factors affecting SNEDDS

- Very high dose drugs are not the suitable candidate for SNEDDS, unless they exhibit extremely good solubility in at least one of the components of SNEDDS, preferably lipophilic phase. The drugs exhibit limited solubility in water and lipids are most complicated to deliver by SNEDDS.
- The ability of SNEDDS to maintain the drug in solubilized form is greatly affected by the solubility of the drug in lipid phase. If the surfactant/co-surfactant is contributing to a greater extent for drug solubilization, then there may be a chance of precipitation, as dilution of SNEDDS will cause lowering of solvent capacity of surfactant or co-surfactant.<sup>(15)</sup>

### Suitable drug candidate identification for SEDDS

For lipophilic drug compounds that exhibit dissolution-rate-limited absorption, SEDDS can offer an improvement in rate and extent of absorption, resulting in reproducible blood time profiles. Logically speaking, however, use of SEDDS can be extended to all four categories of biopharmaceutical classification system (BCS) class drugs.<sup>(16)</sup>

### Potential advantages of these systems include

1. Enhanced oral bioavailability enabling reduction in dose such as Ketoprofen<sup>(17)</sup>
2. More consistent temporal profiles of drug absorption e.g. Ontazolast<sup>(18)</sup>
3. Selective targeting of drug(s) toward specific absorption window in GIT<sup>(19)</sup>
4. Protection of drug(s) from the hostile environment in gut e.g. Acetylsalicylic acid<sup>(20)</sup>
5. Control of delivery profiles e.g. Paclitaxel<sup>(21)</sup>
6. Reduced variability including food effects e.g. Cyclosporine<sup>(22)</sup>
7. Protective of sensitive drug substances<sup>(19)</sup>
8. High drug payloads<sup>(19)</sup>
9. Liquid or solid dosage forms e.g. Progesterone<sup>(23)</sup>
10. Emulsion cannot be autoclaved as they have phase inversion temperature, while SMEDDS can be autoclaved<sup>(19)</sup>

### Mechanism of self-emulsification

According to Reiss; self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water<sup>(24)</sup>.

$$\Delta G = \Sigma N \pi r^2 \sigma$$

Where,  $\Delta G$  is the free energy associated with the process,  $N$  is the number of droplets of radius  $r$  and  $\sigma$  represents the interfacial energy.

The two phases of emulsion tend to separate with time to reduce the interfacial area and, subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence<sup>(25, 26)</sup>.

### Composition of SEDDS and SMEDDS

#### Oils:

Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDS owing to their formulation and physiological advantages. Novel semi-synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium-chain triglyceride<sup>(27,28)</sup>. Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation are also valuable in designing of SEDDS.

#### Surfactant:

The choice of surfactants is limited as very few surfactants are orally acceptable. Non-ionic surfactants with high HLB value are used in formulation of SMEDDS including: Ethoxylated polyglycolysed glyceride, Tween 80, LABRFAC CM1O-a mixture of saturated compounds containing 8 carbon polyglycolysed glycosides and other long chain alkyl sulfonate sulfate surfactants, such as sodium dodecyl benzene sulfonate, sodium lauryl sulfate and dialkyl sulfo succinate and quaternary ammonium salts, fatty alcohols such as lauryl, cetyl and stearyl, glyceryl esters, fatty acid esters and polyoxyethylene derivatives are also, employed. Emulsifiers derived from natural sources are expected to be safer than synthetic ones and are recommended for SMEDDS use despite their limited ability to self emulsify. Non-ionic surfactants are known to be less toxic compared to ionic surface-active agents. The high HLB and subsequent hydrophilicity of surfactants is necessary for the immediate formation of o/w droplets and /or rapid spreading of the formulation in the aqueous environment, providing a good dispersing/self-micro emulsifying performance<sup>(29)</sup>.

#### Co-surfactant:

In SMEDDS, generally cosurfactant of HLB value 10-14 is used. Hydrophilic co-surfactants preferably alcohols of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of micro emulsion<sup>(27)</sup>, are used in formulation of SMEDDS.

#### Cosolvents:

Cosolvents may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base which are as follows diethylene glycol, monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, etc<sup>(27)</sup>.

#### Consistency builder:

Materials such as tragacanth, cetyl alcohol, stearic acids and /or beeswax<sup>(30)</sup> are added to alter the consistency of emulsion.

## METHODOLOGIES

### Solubility Studies

The solubility of drug in various oils, surfactants, co-surfactants and Oil; surfactant mixture was measured using shake flask method (8 - 12). An excess amount of Drug was added into each vehicle followed by vortex mixing for 30 sec (Remi mixer, Mumbai). Mixtures were shaken for 48 h at 30°C in a thermostatically controlled shaking water bath, followed by equilibrium for 24 hr. Mixtures were then centrifuged at 3000 rpm for 10 min and the supernatant was filtered through a Millipore membrane filter (0.45µ). Samples were suitably diluted with methanol and drug concentration was obtained via UV validated method.

### Preliminary screening of surfactants

Different surfactants for the oral use were screened for emulsification ability. Briefly, 150 mg of the surfactants were added to 150 mg of the oily phase. The mixtures were gently heated at 50°C for homogenization of the components. Each mixture, 100 mg, was then diluted with distilled water to 100 ml in a stoppered conical flask. Ease of emulsification was judged by the number of flask inversions required to yield homogenous emulsion. Emulsions were allowed to stand for 2 h and their % transmittance was evaluated by UV-Visible spectrophotometer (Shimadzu, Japan) using distilled water as a blank. Emulsions were furthermore observed visually for any turbidity or phase separation.

### Preliminary screening of co-surfactants

The selected oily phase and surfactant were used for further screening of the different co-surfactants for their emulsification ability. Mixtures of 200 mg of co-surfactant, 400 mg cremophor RH40, and 600 mg Sunflower oil were prepared and evaluated in a similar fashion as described in preliminary screening of surfactants.

### Phase diagram Study:

In a pseudo-ternary phase diagram study, systems consisting of oil, surfactant, and as co-surfactant were titrated with water, and self-emulsifying formulations were selected observing regions of infinite dilution.

### Formulation of SNEDDS:

A series of SNEDDS formulations were prepared using Surfactant/ co-surfactant combination and oil. Briefly, accurately weighed drug was placed in a glass vial and oil, surfactant, and co-surfactant were added. Then the components were mixed by gentle stirring on a magnetic stirrer and subjected to vortexing using a cyclomixer (Remi, India) until drug was perfectly dissolved to get a transparent preparation. Then all the mixtures were stored at room temperature for further use.

### EVALUATION OF SNEDDS

#### Self Emulsification and Phase Separation

Various compositions were categorized on speed of emulsification, clarity, and apparent stability of the resultant emulsion<sup>(15, 16)</sup>. Visual assessment was performed by drop wise addition of the concentrate (SNEDDS) into 100, 250 and 1000 mL of distilled water, 0.1N HCl and pH 6.8 phosphate buffer taken in a glass beaker at room temperature, and the contents were gently stirred with glass rod or in a magnetic stirrer at a speed of 100rpm. Immediately they were observed after dilution for assessment for self-nanoemulsification efficiency, appearance (transparency), phase separation, and precipitation of drug. Precipitation was evaluated by visual inspection of the resultant emulsion after 24 hours. The formulations were then categorized as clear (transparent or transparent with bluish tinge), non clear (turbid), stable (no precipitation at the end of 24 hours), or unstable (showing precipitation within 24 hours). The tendency to form an emulsion is assessed as “good” when emulsification occurs rapidly in less than 1 minute with clear (or) transparent appearance. The tendency to form an emulsion is assessed as “bad” when there is less clear emulsion formation. Depending on visual appearance and time taken for self emulsification, formulations are graded as:<sup>(46)</sup>

Grade A: Rapidly forming (within 1min) nano emulsion having a clear (or) bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that formed within 2 minutes.

Grade D: Dull, grayish white emulsion with a slight oily appearance that is slow to emulsify (more than 2 minutes).

Grade E: Formulation Exhibiting either poor or minimal emulsification with large oil lobules present on the surface.

#### Emulsion Droplet Size

The average droplet size is a decisive factor in self-emulsification performance because it will determine the rate and extent of drug release, as well as the stability of the emulsion [80]. Dynamic light scattering (DLS) techniques, photon correlation spectroscopy and microscopic techniques are mainly used for the determination of the emulsion droplet size and Polydispersity index. DLS is ideal for measuring particles or droplets in the diameter of 3 nm to 3 μm. Droplet size distributions can be further verified by cryogenic transmission electron microscopy (cryo-TEM), which offers the possibility to observe the droplet's size and shape. The polydispersity index of SNEDDS reflects the uniformity of particle diameter and can be used to depict the size distribution of nano emulsion droplets.

#### Zeta Potential

Zeta potential is used to identify the charge of the oil droplets of SEDDS. The charge of the oil droplets in conventional SEDDS is negative due to the presence of free fatty acids [96]. For the droplets in SEDDS emulsions, a high zeta potential will confer stability and long shelf life. When the potential is low, attractive forces may exceed this repulsion and the emulsion may break and aggregate. Some investigators consider zeta potential as secondary characterization parameter for SEDDS, because SEDDS are concentrate mixture of drug in oil and surfactant and emulsified in vivo only. The zeta potential of SEDDS emulsion is commonly investigated using Malvern Zeta Sizer and the zeta potential values are calculated using **Smoluchowski equation**.<sup>(47)</sup>

#### Ternary phase diagrams

Ternary or Pseudo ternary phase diagrams are normally constructed with the oil phase, surfactant or mixture of surfactant and co-surfactant, and the aqueous phase, which will reveal the regions of liquid crystal, microemulsion (w/o or o/w) and coarse emulsion<sup>(9)</sup>. Ternary phase diagrams enable comparison of different surfactants and their synergistic effect with co-surfactant. They can also help to determine the optimum concentration ranges of different excipients and to identify the self-emulsification regions. The boundaries of different phase regions can easily be assessed visually.

#### Emulsification time

With the purpose of quantifying the efficiency of emulsification of SEDDS. Pouton<sup>(1)</sup> employed the rotating paddle to promote emulsification in a crude nephelometer. This enabled an estimation of the time taken for emulsification. On completion of emulsification, the SEDDS samples were taken for particle sizing by photon correlation spectroscopy, and further by other characterizations.

#### Turbidity measurement

The turbidity measurements can be carried out to identify the efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time. These measurements are commonly carried out on turbidity meters, and also can be processed in terms of spectroscopic characterization of optical clarity (i.e. absorbance of suitably diluted aqueous dispersion at 400 nm).



### Refractive index and Percentage Transmittance

Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and compared with water (1.333). The percentage transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percentage transmittance > 99 percent, then formulation is of transparent nature.

### Morphology

The morphology of the nanoemulsion droplets can be evaluated by Cryo-Transmission Electron Microscopy (Cryo-TEM), small-angle neutron scattering and 42 small-angle X-ray scattering. Cryo-TEM and small-angle neutron scattering offer the advantage of visualising the particle sizes and shapes. Furthermore, droplets size distributions can be further verified by cryo-TEM. Small-angle X-ray scattering is used to determine the microscale or nanoscale structure of particle systems in terms of such parameters as averaged particle sizes, shapes, distribution and surface-to-volume ratio.

### Viscosity

The rheological properties of the SEDDS formulations are useful to assess their ability to be filled in the soft or hard gelatin capsules. The viscosity of formulations should not be high to create problem in pourability. Conversely, low viscosity may lead to leakage from the capsules.

### Drug Content

SNEDDS containing drug was added in volumetric flask containing methanol. The mixture was stirred vigorously for 2 hr. The sample was analysed for drug concentration after suitable dilution using UV –spectrophotometer.

### In Vitro Dissolution

The in vitro dissolution studies were performed to evaluate the release efficiency of the optimal formulations. Based on the drug content determinations self nanoemulsifying formulations were filled in hard gelatin capsule shells. The dissolution was carried out using dissolution test apparatus USP Type II with a paddle stirrer, maintained at  $37 \pm 5^\circ\text{C}$ , 50 rpm paddle speed. Dissolution was performed in two different mediums viz. 0.1N HCl ( Simulated gastric fluid) and 6.8 pH Phosphate buffer 900 ml. The samples were withdrawn at predetermined time intervals and were analyzed for drug concentration by UV-Visible spectrophotometer after filtration through 0.22  $\mu$  filter.

### CONCLUSION

Self Nanoemulsifying drug delivery system (SNEDDS) is a novel approach for the formulation of poorly water soluble drugs as they have high potential to improve the Bioavailability. Self Nanoemulsifying drug delivery system (SNEDDS) is an isotropic mixture of oils, surfactants, Cosurfactant and co-solvent. When introduced into aqueous phase, it emulsifies spontaneously to produce fine o/w Nanoemulsion under gentle stirring. By the formulation of SNEDDS it exhibits significant improvement of drug solubility, rapid dissolution rate together with the enhanced permeation. The oral delivery of poorly water soluble drugs can be made possible by SNEDDS by improving oral bioavailability. By using this approach it is possible to prolong the release of drug via incorporation of polymer in composition. SNEDDS seems to be appearing as unique and having industrial survivability for future development. and the unique characteristics of this lipid-based dosage form present significant challenges to scientists in many ways like, the safety issues need to be considered, particularly when a new excipient is used in the formulation.

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