

Revolutionizing Emulsions: A Novel Approach to Multiple Emulsions

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ABSTRACT

The development of multiple emulsions is a recent innovation in emulsion technology. Multiple emulsions are complex poly dispersed systems in which both oil in water and water in oil emulsion exist simultaneously and exhibit the properties of both oil in water and water and oil emulsions simultaneously. The dispersed phase of these emulsions contains even smaller droplets that are miscible with the continuous phase. Thus, multiple emulsions may be O/W/O, in which the aqueous phase is between two oil phases, or W/O/W, in which the internal and external aqueous phases are separated by an oil phase. Both hydrophobic and hydrophilic emulsifiers are used in these systems, which affects the yield and stability. It has a number of applications, such as prolonged action, taste masking, more effective dosage forms, improved stability, parenteral preparations, protection against the external environment and enzyme entrapment. These emulsions can also be used to separate two incompatible hydrophilic substances in the inner and outer aqueous phases by separating the middle oil phase. The multiple emulsion system's composition, assessment, and possible uses have been highlighted in this review. The aim of the present study is formulation of multiple emulsions, which contains an additional reservoir that is an extra step for drug partitioning, which effectively retard the release rate of the drug, and the dose decrease frequency.

KEYWORDS: Multiple Emulsions, Preparation Technique, Characterization, Applications.

1. INTRODUCTION

An emulsion is defined as a biphasic liquid dosage form made up of two immiscible liquids, one of which is dispersed as a minute globule into other. The term “dispersed phase” refers to the liquid that is distributed as a minute globules. The liquid in which minute globules are dispersed is known as the “continuous phase”. Premised on their development, emulsions can be categorized into:

a) Simple Emulsion-

Simple Emulsions can also be classified as,

a. Oil-in-water emulsions (O / W) – in which oil will be the disperse phase in a continuous phase of water, as well as,

b. Oil-in-water emulsions (W / O) – in which water will be the disperse phase in a continuous phase of oil.[2]

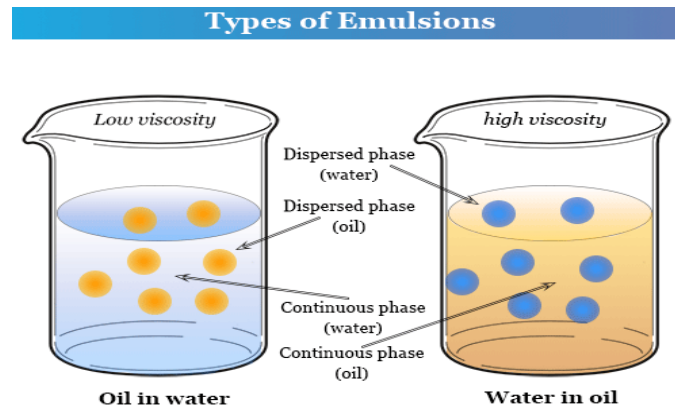


Figure 1. o/w and w/o Emulsion

1.1 MULTIPLE EMULSION :

Multiple emulsion (ME) systems are novel developments in the field of emulsion technology. MEs are complex, poly dispersed systems where both o/w and w/o emulsions exist simultaneously in one system. MEs are also known as emulsion of emulsion in which first primary emulsion is formed which is then dispersed as a minute globule into another known as continuous phase. The dispersed phase of these emulsions contains even smaller droplets that are miscible with the continuous phase. Thus multiple emulsions may be composed of the following two phases. The dispersed phase of these emulsions contains even smaller droplets that are miscible with the continuous phase.[1][3]

Thus, the multiple emulsion may have following two types :

1. **w/o/w** : in w/o/w first w/o emulsion is formed which is then dispersed as a minute globule into water continuous phase. In other words, an organic phase differentiates internal and external aqueous phases.
2. **o/w/o** : in o/w/o first o/w emulsion is formed which is then dispersed as a minute globule into oil continuous phase. In other words, an aqueous phase differentiates internally and externally oil phases.[5][6]

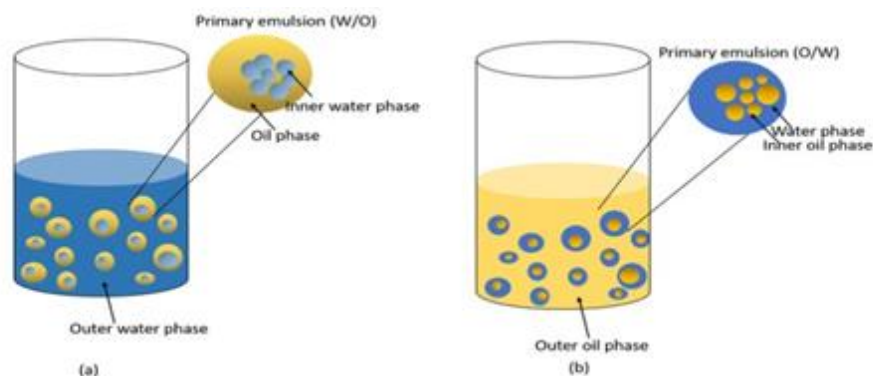


Figure 2. Schema of W/O/W and O/W/O emulsions

The fundamental issue with MEs is inherent instability. The system can be stabilized with a variety of emulsifiers. Low HLB or oil soluble surfactants can stabilize W/O emulsions, while high HLB or water soluble surfactants can stabilize O/W emulsions. Systems with ideal stability can be obtained with

intermediate HLB. These pairs of surfactants can be used to prepare MEs and add a certain amount of stability [1]

Examples of w/o emulsifiers (HLB value : 3 to 6) -

Sr. no.	Name of emulsifier	HLB value
1	Stearic acid	6
2	Mineral oil	4
3	Liquid paraffin	4
4	Beeswax	5
5	Sorbitan monooleate (Span 80)	4.3
6	Sorbitan monostearate (Span 60)	4.7

Examples of o/w emulsifiers (HLB value : 8 to 16) -

Sr .no.	Name of emulsifier	HLB value
1	Cetyl alcohol	15
2	Stearyl alcohol	14
3	Castor oil	14
4	Wool fat	10
5	Polyoxyethylene sorbitan monostearate (tween 60)	14.9
6	Polyoxyethylene sorbitan monooleate (Tween 80)	15.0

2. Formulation

Developing a system with a high yield of multiple droplets containing drugs entrapped in the innermost phase, strong in-vitro stability, and the intended in-vivo release characteristics is the aim of multiple emulsion, formulation.

The following variables are taken into consideration in various emulsion formulations : [7][8]

2.1- Emulsifying instruments: A homogenizer or a laboratory mixer can be used to make primary emulsions that have a satisfactory droplet dispersion within a suitable continuous phase. For usage in delivery vehicles, the primary emulsion needs to be divided into droplets of an appropriate size during the secondary emulsification stage. The primary emulsion droplets may rupture due to excessive mixing, particularly at high shear. Either shake the system manually, or run the mixer at low speed and low shear. Ultrasonic homogenizers should be handled carefully when utilized for preparation of secondary emulsion.

2.2- Nature of oil phase : Toxic oil phases cannot be utilized in numerous emulsions. Vegetable oils like safflower, sesame, peanut, and soybean are suitable as long as they are properly cleaned. Numerous emulsions have also included refined hydrocarbons, like light liquid paraffin and squalene, and fatty acid esters, like oleate and isopropyl myristate. Mineral oils leave the body extremely slowly, but oils from vegetable sources can be biodegraded. Mineral oils tend to yield many emulsions that are more stable than vegetable oils. The following was the sequence of diminishing stability and percentage entrapment: light liquid paraffin > squalene > sesame oil > maize or peanut oil.

2.3-Phase volume ratio : The volume of the dispersed phase in the original W/O or O/W multiple emulsions is known as the phase volume ratio. This could have an impact on the final emulsion system's yield and stability. The dispersed phase must be gradually introduced to the continuous phase in order to create a stable multiple emulsion. When formulating numerous emulsions, an internal phase volume of 22%–50% can be considered ideal. Phase inversion and reduced emulsion stability might result from increasing the volume of dispersed phase.

2.4-Nature and quantity of emulsifiers: Two distinct emulsifiers (lipophilic and hydrophilic), with adjustable concentrations, are needed to generate a stable emulsion. Whereas the other stabilizes the W/O emulsion, the first stabilizes the O/W emulsion. The ideal HLB values for the principal surfactant in the W/O/W emulsion are 2–7 and 6–16. Systems that include too little emulsifier may become unstable, whereas systems that have too much emulsifier may become harmful or potentially destabilize. In order to prepare the primary W/O emulsion, low-HLB surfactant solution in oil was mixed with water. To create several W/O/W emulsions, W/O was then re-emulsified in an aqueous solution containing high-HLB surfactant. The first stage should be done using a high-shear instrument to create very fine droplets. To prevent multiple emulsification rupture, the second emulsification phase should be performed in a low-shear device.

2.5-Nature of the entrapped material: When developing W/O/W, the drug's nature—that is, whether it is hydrophilic or hydrophobic—as well as the presence of additional ingredients, such as proteins, carbohydrates, or electrolytes, should be taken into account. The W/O/W emulsion's oil phase functions as a semi permeable barrier between two aqueous phases when an osmotic gradient is present, allowing water to pass through the oil phase. Internal droplets can expand or contract as a result of this. In contrast to the internal phase, higher osmotic pressure in the external environment causes the oil layer to rupture and the internal aqueous droplets to shrink. Water may go to the internal aqueous phase if the osmotic pressure is higher there. This could cause the internal droplets to enlarge and possibly burst, releasing the contents. If the external aqueous phase's osmotic pressure is larger, internal droplet shrinkage results. In this case, conversely is true. Extreme osmotic pressure differentials across the oil layer allow water to move through so quickly that the oil droplets burst instantly, releasing interior droplets. By making the internal aqueous phase isotonic with the final exterior phase, a tiny amount of sodium chloride can be added to partially remedy this issue.

2.6- Added stabilizing components: In order to increase the stability of multiple emulsions, stabilizers were added. To internal and/or external aqueous phases gelling or viscosity-increasing agents (20% gelatine, methylcellulose, and similar thickening agents), complexing agents (1-3% Cetyl alcohol) were added that result in liquid crystalline phases at the o/w interface and gelling agents (1-4% aluminium monostearate) for the oil phase.

2.7-Shear/ Agitation : The significant increase in effective surface area caused by high shear causes a significant portion of numerous oil drops to be disrupted, which leads to system instability. The system's yield drops quickly as the homogenization time rises. When preparing several emulsions, secondary emulsification is typically carried out at a lower agitation speed than primary emulsification, which typically occurs at a higher speed.

2.8-Temperature: Due to its effects on viscosity, surfactant adsorption, and interfacial tension, temperature only indirectly affects emulsification. The original emulsion formulation is typically kept at 70°C, while the secondary emulsion formulation is retained at 10°C. Dramatic changes in the

composition of emulsions occur when there are significant temperature differences during manufacture, storage, transportation, and use.

2.9-Rheology: A variety of parameters, such as the particle size distribution, phase volume ratio, and continuous phase nature, affect an emulsion's rheological qualities. O/W/O emulsions are often thicker than W/O/W emulsions because, for low internal phase volume emulsions, the emulsion's consistency is comparable to the continuous phase's. The consistency of the W/O/W system can be enhanced by adding gums or clays.

3. Methods of preparations :

3.1- Two-step emulsification : It is also known as double emulsification and it is the most often used technique because it is simple to use and produces a high yield that is repeatable. To prepare w/o/w multiple emulsion, the following steps need to be taken:

a) Preparing the primary emulsion (w/o): Using a magnetic stirrer or homogenizer set at a high speed to create tiny droplets, the aqueous phase is gradually introduced to the oil phase containing lipophilic emulsifier.

b) Preparing double emulsion (w/o/w): Using a magnetic stirrer or homogenizer, the primary emulsion is progressively added to the aqueous phase containing hydrophilic emulsifier at a reasonably slow pace to prevent numerous droplets from rupturing.[2]

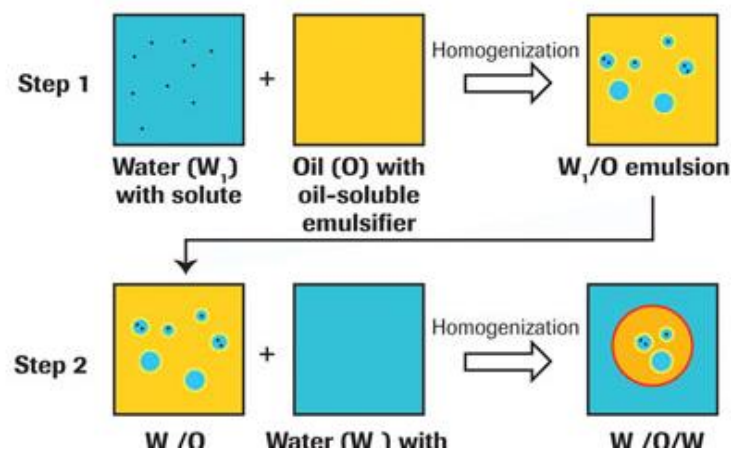


Figure 3. Preparation of w/o/w double emulsion

3.2- Modified two-step emulsification :

This method differs from the conventional two-step technique in the following two points. Sonication and stirring are used to obtain a fine, homogenous, and stable W/O emulsion, and a continuous phase is poured into the dispersed phase to prepare the W/O/W emulsion. Moreover, the composition of the internal aqueous phase–oily phase–external aqueous phase was fixed at 1:4:5, which produced the most stable formulation, as reported for most W/O/W emulsions.[8]

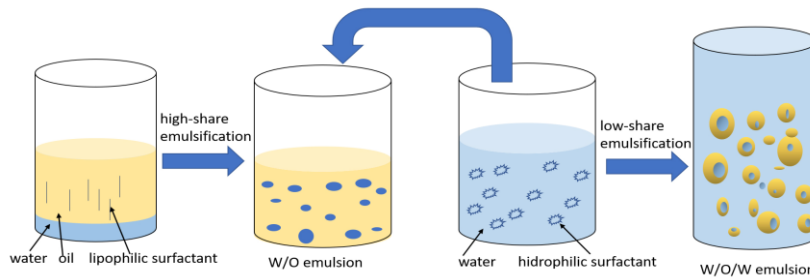


Figure 4. W/O/W double emulsion Modified two-steps Emulsification process

3.3- Phase inversion technique (one step technique) :

This method describes an increase in the volume of dispersed phase which may cause an increase in the phase volume ratio which subsequently leads to the formation of multiple emulsion . It involve the addition of aqueous phase containing the hydrophilic emulsifier to an oil phase containing of liquid paraffin and lipophilic emulsifier.[2]

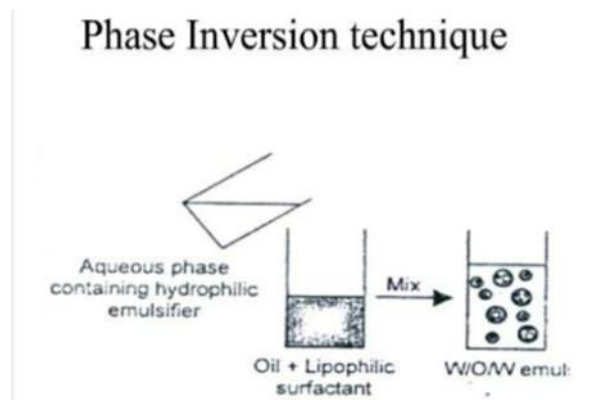


Figure 5. Phase Inversion technique

4. Evaluations of multiple emulsion :

4.1- Globule size: For the newly prepared emulsions and the emulsions stored under varied settings for 28 days, the globule sizes of the prepared multiple emulsions were measured using a light microscope equipped with a digital camera.[10]

4.2- Entrapment efficiency: Percentage Entrapment Efficiency (% EE) was determined by taking freshly prepared W/O/W multiple emulsions and immediately centrifuged at 4000 rpm for 10 min. Then 1ml of the aqueous phase (the lower layer) was precisely withdrawn through 2ml hypodermic syringe and diluted properly with suitable buffer. The solution was filtered with a Millipore filter (0.22 mm in pore size) and drug content was analyzed on UV spectrophotometer. The Encapsulation Efficiency was determined by following equation:[11]

$$\% EE = \frac{[\text{Total drug incorporated} - \text{Free Drug}]}{\text{Total drug}} \times 100$$

4.3- Stability tests: For both primary and multiple emulsions, stability tests were conducted under various storage circumstances. In the stability chamber, samples were maintained at 8 ± 0.1 °C, 25 ± 0.1 °C, 40 ± 0.1 °C, and 75% relative humidity (RH) for the purpose of the testing.

4.4- Organoleptic characteristics: Organoleptic analysis was performed on freshly made primary and multiple emulsions (colour, liquefaction, and phase separation). The colour, liquefaction, and phase separation of primary and multiple emulsions stored under varying storage conditions were observed at different intervals: 0 hours, 1 hour, 1 day, 3 days, 7 days, 14 days, 21 days, and 28 days for a 28-day period.

4.5- Microscopic tests: To verify the several characters, multiple emulsions were examined under a microscope. A glass cover was placed over a drop of many emulsions that had been diluted with water on the glass slide. The cover slide was covered with an immersion oil drop, which was then examined under a microscope [12][13]

4.6- pH determination : A digital pH meter was used to measure the pH levels of the freshly made numerous emulsions that were stored at various temperatures. For the subsequent studies, pH measurements were conducted once more several emulsions following the preparation days 1, 3, 7, 14, 21, and 28.[13]

4.7- In vitro drug release study: The in vitro drug release study was carried out on a simple dissolution cell using a cellophane membrane (thickness: 200 μ m, breaking strength: 2.7 kg/cm²). The cellophane membrane was soaked in distilled water for 6 min prior to release studies. washed frequently four times by changing distilled water, then immersed in 5% v/v glycerol solution for at least 60 min and finally washed with 5 portions of distilled water. 15mL of freshly prepared multiple emulsion was added to a donor chamber made up of a hollow glass tube (2.5 cm in diameter and 10 cm in length), and the membrane was tied to the bottom end of the tube with a nylon string.[11] This tube was dipped into a 250-mL vessel containing 100 mL of PBS (pH 6.8) was stirred at 100 rpm on a magnetic stirrer and maintained at 37 °C. which acted as the receiving chamber. Aliquots (1ML) were collected from the receiving chamber. At predetermined time intervals, and the drug content was determined using UV spectrophotometer at 287.6 nm after suitable dilutions.[14]

4.8- Zeta potential : The design of surface-modified or ligand -anchored multiple emulsions depends critically on zeta potential measurements. With a Zeta-potentiometer and the mobility and electrophoretic velocity of dispersed globules, it can be computed using the Smoluchowski equation as follows:

$$\eta = 4\pi\eta\mu \varepsilon E \times 103$$

In this case, η = Zeta potential (mV).

η = Migration velocity (cm/s) and

μ = Viscosity of the dispersion medium (poise).

4.9- Area of interfaces :

The formula $S = 6/D$ can be used to calculate the total area of interfaces based on the average globule diameter.

where ,S is the interface's total area (square centimetre) .

D = Globule Diameter (cm)

5. Drug release mechanisms :

There are several possible mechanisms by which the active compound may be transferred across the oil layer in a w/o/w system. Some of the mechanisms include :

- a) **Diffusion mechanism:** This is the most common transport mechanism in which unionized hydrophobic drugs diffuse through the oil layer in stable multiple emulsions. Drug transport follows first order kinetics and obeys Fick's law of diffusion.
- b) **Micellar transport:** Recently, the release of tetradecane from tetradecane /water/hexadecane multiple emulsion was investigated using differential scanning calorimetry technique. Micellar diffusion rather than molecular diffusion is considered to be the dominant mechanism for mass transfer.
- c) **Thinning of the oil membrane:** due to the difference in osmotic pressure; thus, the oil membrane became thin and water and drug easily diffused. This pressure difference also provides a force on the transverse part of the molecules.
- d) **Rupture of oil phase:** According to this mechanism rupturing of oil membrane can unite both aqueous phases and thus drug could be released easily.
- e) **Facilitated diffusion (carrier-mediated transport):** This mechanism involves a special molecule (carrier) that combines with the drug and allows it to permeate the oil membrane. These carriers can be incorporated into the internal aqueous phase or the oil membrane.[9][2]

6. APPLICATIONS :

- 1. **Controlled and Sustained Drug Delivery :** Due to the regulated and prolonged release of pharmaceuticals, multiple emulsions have a fundamental promise in clinical treatments. A drug present in the innermost phase in both systems needs to diffuse through many phases and pass interfacial barriers before it can be absorbed, and this diffusion determines the drug's release rate. It has been suggested that liquid membrane systems be used as controlled release drug delivery devices. The in vitro release characteristics of W/O, O/W, and W/O/W emulsions containing the anticancer medication farmorubicin were compared by Hino et al. (2000). After seven hours, the formulation displayed a sustained release pattern similar to the W/O emulsion.[7]
- 2. **Targeted drug delivery system:** Drug targeting minimizes the adverse effects of cytotoxic drugs by specifically concentrating the drug in the desired tissue. However, cytotoxic drugs are highly toxic for non-diseased tissues .Examples of targeted drug delivery system :[2]

Target (tissue / organ)	Drug investigated
Lymphatic system	5-Fluorouracil, Isoniazid
Tumor	Bleomycin
Brain	Rifampicin
Liver	5-Fluorouracil

- 3. **Taste Masking of Drugs:**Multiple emulsions has been employed for taste masking of drugs like chlorpromazine HCl and chloroquine. By dissolving drug in inner aqueous phase of W/O/W emulsion under conditions of good shelf stability, the formulation could be designed to release drug via oil phase in the presence of gastric fluid.[9]
- 4. **Drug Overdose Treatment :**This system could be utilized for overdose treatment by utilizing the difference in pH, e.g., barbiturates. The inner aqueous phase of these emulsions contains basic buffer, and when the emulsion is taken orally, stomach acidic pH acts as an external aqueous phase. In the acidic phase, barbiturate remains mainly in a unionized form, which is transferred via an oil

membrane into the inner aqueous phase and ionized. The ionized drug has less affinity to cross the oil membrane, thus getting entrapped, thereby preventing drug overdose.[9]

5. **Vaccine Adjuvants:** Multiple emulsions improve the immune response to vaccines by stabilizing antigens and encouraging immune cells to absorb antigens, thereby increasing vaccine efficacy.[8]
6. **Topical Formulations:** Multiple emulsions are used in dermatology to provide sustained release of therapeutic agents in creams and ointments for skin conditions like eczema and psoriasis.
7. **Absorption enhancement through gastrointestinal tract:** Enhanced colonic and rectal absorption of insulin reportedly occurs on administration of multiple emulsion containing eicosapentaenoic acid and docosahexaenoic acid.
8. **Bioavailability enhancer :** Multiple emulsions have also been used to improve the bioavailability of lipophilic drugs with high first-pass metabolism. Multiple emulsions increase the bioavailability of drugs either by protecting them in physiological, ionic, or enzymatic environments in the GIT, where they are otherwise degraded, such as protein peptides, or by passing through the hepatic first pass.
9. **Cosmetics :**
 - a) **Skin Care Products:** Multiple emulsions are used in moisturizers, serums, and anti-aging creams to deliver active ingredients such as vitamins and antioxidants deep into the skin. It improves product stability and enhances skin hydration and texture.
 - b) **Sunscreen formulations:** Sunscreen lotions often contain multiple emulsions to ensure uniform coverage and long-term protection against UV radiation. It enhances the dispersion of UV filters and improves skin sensation.
 - c) **Hair Care Products:** Multiple emulsions are used in shampoos, conditioners, and hair treatments for the delivery of conditioning agents and for improving hair manageability and appearance.
 - d) **Makeup Formulations:** Multiple emulsions provide a stable base for foundations, concealers, and tinted moisturizers, ensuring even coverage and long-lasting wear.[7]
10. **Local Immunosuppression :** Delivering immunosuppressive agents locally to the site of target organs is a potential approach to avoid complication of systemic immunosuppression and simultaneously enhance immunosuppressive efficacy. W/O/W multiple emulsion has been developed for the delivery of immunosuppressant. It has been proposed that W/O/W emulsion of tacrolimus possesses pharmacokinetic benefits of local Immunosuppression and has significantly decreased tacrolimus levels in brain and kidney and increased levels in liver and spleen.

7. Conclusion

The multiple emulsion is one of the advanced drug delivery systems for improvement of the characteristics of drugs such as bioavailability, taste, release rate, etc. Advances include the following: various novel formulations for the improvement of drug administration and improved palatability of the drug by incorporating them into the various formulations. The multiple emulsion is the complex poly dispersed system containing an emulsion that is incorporated in another emulsion that can be used in many applications applications, such as taste masking, sustained release, delivery of the unstable drug & prevention of drug exposure from the environment etc.[2]

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