

Multiple Emulsions: A Sophisticated Drug Delivery System

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Abstract

Multiple emulsions, also known as "emulsions of emulsions," are complex systems where both w/o and o/w emulsions coexist. They offer advantages like sustained release, taste masking, and improved bioavailability. This review covers preparation methods (two-step emulsification, phase inversion, and membrane emulsification), stability factors, and evaluation techniques. Multiple emulsions show promise in pharmaceutical, food, and cosmetic industries, with applications in cancer therapy, vaccine delivery, and more. Recent advancements are overcoming traditional instability issues, making them viable commercial systems.

KeyWords: Multiple Emulsion, Bioavailability Enhancement; Taste Masking; Pharmaceutical Applications.

1. Introduction

Multiple emulsion is a complicated system known as "emulsions of emulsions" since the dispersed phase's droplets. In a double emulsion, each distributed globule creates a vesicular structure with one or more aqueous compartments separated from the aqueous phase by an oil phase compartment layer. Multiple emulsion is also known as emulsion of emulsion liquid membrane systems, or double emulsion.¹

Multiple emulsion is a novel carrier system which is complex and poly-dispersed in nature where both w/o and o/w emulsion exist simultaneously in a single system. Lipophilic and hydrophilic surfactants are used for stabilizing these two emulsions respectively.

Multiple emulsion systems are an advanced dispersion system representing recent breakthroughs in emulsion technology. In this emulsion system, the dispersed phase contains smaller droplets of the same composition as the external phase, termed multiple emulsions. The process of double emulsification creates such systems; hence they are also called "double emulsions." Like simple emulsions, multiple emulsions are classified into two categories.

- **O/W/O Multiple Emulsion**
- **W/O/W Multiple Emulsion**

Oil/ Water/ Oil (O/W/O):

It contains an inner oil a phase, a water and outer oil phase. the inner oil phase is first dispersed in water to form an oil-in- water emulsion. Then the o/w emulsion is further dispersed in the outer oil phase to form the o/w/o type multiple emulsion.

Water / Oil/Water (W/O/W):

It consists of dispersed oil globules containing smaller aqueous droplets. Each inner aqueous droplets, each inner aqueous droplets, each inner aqueous droplets are separated from the outer aqueous phase by an oil phase layer. The presence of at least two surfactants is required.



Fig. 1: Multiple Emulsion.

Advantages of multiple emulsion:

- They can mask the bitter taste and odor of drugs there by making them more palatable e.g. castor oil, cod liver oil.
- They can be used to prolong the release of the drug there by providing sustained release action.
- To aid diagnosis, intravenous emulsion containing control media leave be produced.
- Emulsion protects drugs that are prone to oxidation and hydrolysis.
- Improved gastrointestinal or dermal absorption.
- Emulsion are commonly utilized in the formulation of externally applied products such as lotions, creams, and salves.
- They can be employed to extend the drugs release, resulting in a longer-lasting effect.

limitations of multiple emulsions:

Multiple emulsions can be prepared by the re-emulsification of primary emulsion or they can be produced when an emulsion inverts from one type to another. For e.g. w/o to o/w emulsions have small size of internal dispersed phase therefore; its not used in therapeutics.

2. Method of Preparation:

The various methods of preparation of multiple emulsions are as follows:

2.1 Two-Step Emulsification

It is the most common method because it's very easy and gives high yield with reproducibility.

This method involves re-emulsification of primary w/o or o/w emulsion using a suitable emulsifying agents, the first o/w or o/w type which is then re-emulsified with an excess of aqueous phase or oil phase in the presence of second emulsifier. This step is carried out in high shear device to produce a very fine droplet. The second emulsification step is carried out in a low shear device to avoid rupturing the multiple droplets.

2.2 Modified Two-Step Emulsification.

This method is different from conventional two-step technique in two points sonication and stirring are used to obtain fine, homogenous and stable o/w emulsion. Continuous phase is poured into a dispersed phase for preparing w/o/w emulsion

2.3 Phase Inversion Method

This method typically involves the addition of an aqueous phase contains the hydrophilic emulsifier to an oil phase consist of liquid paraffin and containing lipophilic emulsifier. An aqueous solution of emulsifier is then introduced successively to the oil phase in the vessel at rate 5 ml/min. while the pin mixer rotates steadily at 88rpm at room temperature. When volume fraction of the aqueous solution of hydrophilic emulsifier exceeds 0.7. the continuous oil phase is substituted by the aqueous phase containing a number of vesicular globules among the simple oil droplets leading to phase inversion formation of w/o/w multiple emulsion.

2.4 Membrane Emulsification Technique

In this o/w/o emulsion is extracted into an external aqueous phase with a constant pressure through a porous glass membrane, which should have controlled and homogenous pores.

The particle size of the resulting emulsion can be controlled with proper selection of porous glass membrane.

The relation between membrane pore size and particle size of w/o/w emulsion exhibits good correlation as described by the following equation:

$$Y = 5.03x + 0.19$$

Where,

X – is the pore size and Y - is the particle size of the multiple emulsions.

Stability of emulsion-

The possible indications of instability include

- Leakage of the contents from the inner aqueous phase.
- Expulsion of internal droplets in external phase.
- Constriction or distension of the internal droplets due to osmotic gradient across the oil membrane.
- Flocculation of internal aqueous phase and multiple emulsion droplets.
- Disruption of oil layer on the surface of internal droplets.
- Phase separation

Breakdown Pathways:

Some of the breakdown pathways that may be involved in w/o/w emulsion destabilization are:

- Coalescence of multiple oil drops, single or multiple.
- Expulsion of single internal droplets.
- Expulsion of more than one internal droplet.
- Coalescence of internal droplets before being expelled.
- Shrinkage of internal droplets due to diffusion.

Methods to Stabilize Multiple Emulsions:

The followings are some of the attempts or studies made to restore or strengthen the stability of multiple emulsions:

- Liquid crystal stabilized multiple emulsions.
- Stabilization in presence of electrolytes.
- Stabilization by forming polymeric film.
- Stabilization by interfacial complexation between non-ionic surfactant and macromolecules.
- Steric stabilization.
- Phase inversion stabilization of w/o/w emulsion.

Formation of Multiple Emulsion:

Florence and Whitehil described three different types of multiple emulsion, which they termed A, B and C. Type A multiple emulsion were those in which only one large internal drop was contained in the secondary emulsion droplet. In type B emulsion, there were several small internal contained in the secondary emulsion droplets present only the type C systems have application in drug delivery and targeting.

Oil Phase

The oil phase to be employed in a pharmaceutical emulsion must be nontoxic. The various oils of vegetable origin (soyabean, sesame, peanut, sunflower etc.) are acceptable if purified correctly. Refined hydrocarbons such as light liquid paraffin, squalene as well as esters of fatty acids, cetyl oleate and isopropyl myristate have also been used in double emulsions. Oil derived from vegetable source are biodegradable; whereas those based on mineral oils are only removed from the body very slowly.

As a general rule, mineral oils produced more stable multiple emulsion (w/o/w) than those produced from vegetable oils.

The order of decreasing stability and percentage entrapment has been found to be

Light liquid paraffin > Squalane > Sesame oil > Maize or Peanut oil

Nature and Quantity of Emulsifying Agents:

Two different emulsifiers lipophilic and hydrophilic are required to form a stable emulsion. In general, for a w/o/w emulsion the optimal HLB value will be in the range 6-16 for the secondary surfactant. The concentration of the emulsifier can also be varied too little. Emulsifier may result in unstable systems, where as too much emulsifier may lead to toxic effects and can even cause destabilization. And excess of lipophilic surfactant can cause the inversion of w/o/w emulsion to simple o/w emulsion.

Phase Volume:

It is very important to have proper order of phase addition while formulation and dispersed phase. Phase should be added slowly into the continuous phase for the formation of a stable multiple emulsion. Optimal (20-50%) internal phase volume can be utilized for the emulsion formation vary high phase volume ratio (70-90%) had also been reported to produce a stable multiple emulsion.

Factors affecting stability of multiple emulsion:

Nature of Entrapped Material

When formulating w/o/w system the presence of the drug and other components (especially electrolytes) needs to be considered the nature of the drug (hydrophilic or lipophilic). Due to the nature of the multiple emulsion the middle phase acts as membrane and osmotic effects may become important. The entrapped solutions may be absorbed at the inner phase resulting in decreasing stability.

Shear and Agitation

High shear disrupts the large percentage of multiple oil drops and hence results in the instability of system due to tremendous increase in effective surface area. Therefore, with increased homogenization time, the yield of the system falls rapidly. Generally high agitation speed is used for primary and low speed is used for secondary emulsification for the preparation of multiple emulsions.

Temperature

Temperature has been only an indirect an emulsification that is attributable to its effect on viscosity, surfactant adsorption and interfacial tension. Generally, for the primary emulsion formulation temperature is kept at 70°C, whereas for multiple emulsion preparation it is kept at 10°C.

Rheology:

The rheological properties of emulsions are influenced by a number of factors including the nature of the continuous phase, the phase volume ration and to lesser extent by particle size distribution for low internal phase. Thus, o/w/o emulsions are generally thicker than w/o/w emulsions and the consistency of w/o/w system can be increased by the addition of gums, clays.

Effects of lipophilic emulsifier

Lipophilic surfactant molecules can diffuse from the first to second interface, where they produce a synergistic effects resulting in membrane strengthening. The second one involves a delay in the aqueous

droplets coalescence, in course of swelling of the oil globule, the lipophilic diffuse to the first interface to fill up free spaces caused by swelling, when required.

2. EVALUATION OF MULTIPLE EMULSION:

Average globule size and size distribution:

The optical microscopy method using calibrated ocular and stage micrometer can be utilized for globule size determination of both multiple emulsion droplets and droplets of the internal dispersed phase. The interior droplet of numerous emulsions is studied using bright. Field micrographs using differential interference contrast optics.

Various other techniques used to characterize colloidal carrier such as coulter counter. Freeze-fracture electron microscopy and scanning electron microscopy are also used to determine the average globule size and size distribution of multiple emulsion. Recently NMR self-diffusion method are adapted to multiple emulsion characterization.

Area of interface:

The formula below can be used to calculate the total of area the interface using the average globules diameter determine.

$$S=6/D$$

Where,

S= Total Area of Interface (Sq.cm)

D= Diameter of Globules (Cm)

Number of globules:

After appropriate dilution of the numerous emulsion. The number of globules per cubic millimeter can be determined using a hemocytometer cell. It is possible to count the globule in five groups of 16 small squares. (for a total of 80 small squares) and the total number of globules per cubic millimeter is compound using the formula.

$$\text{No of globules/ mm}^3 = \frac{\text{no of globule} \times \text{dilution} \times 4000}{\text{no.of small squares counted}}$$

Rheological evaluation

The rheology of multiple emulsion is an important parameter as it relates to emulsion stability and clinical performance. The viscosity and interfacial elasticity are two major parameters, which relate to product rheology.

The viscosity of the multiple emulsion can be measured by Brookfield rotational 0

Interfacial rheology (i.e., interfacial elasticity at the oil-aqueous interface) can be investigated at the mineral oil/water interface using an oscillatory surface rheometer.

Percentage drug entrapment

Percent entrapment of drug or active moiety in the multiple emulsion is generally determined using dialysis, centrifugation, filtration and conductivity measurements. Recently an internal tracer/ maker was used to evaluate the entrapment of an impermeable marker molecule contained the untrapped maker is calculated and the amount entrapped can be thus calculated by deducting untrapped amount from the initially added amount.

In-vitro drug release

The drug released from the aqueous inner phase of a w/o/w emulsion can be estimated using the conventional dialysis technique. The w/o/w emulsion was placed in the dialysis bag and dialyzed against 200 ml of phosphate saline buffer $p^H 7.4 \pm$ at $37 \pm 1^0 c$ and a sink condition was maintained while sink contents were stirred continuously using a magnetic stirrer. Aliquots were withdrawn at different time interval and estimated using standard procedure and the data were used to calculate cumulative drug release profile.

3. APPLICATION OF MULTIPLE EMULSION

- Controlled and sustained drug delivery
- Enhancing oral bioavailability or oral absorption
- Multiple emulsion in cancer therapy
- Multiple emulsion in herbal drugs
- Vaccine/ vaccine adjuvant
- Oxygen substitute
- Taste masking
- Multiple emulsion in diabetes
- Multiple emulsion in food
- Drug over dosage treatment

4. CONCLUSION

In a review, the conclusion of multiple emulsions highlights their role as sophisticated multicompartamental carriers capable of protecting sensitive molecules while enabling controlled, multi-stage release. While traditionally hindered by instability, recent advancements in stabilization and manufacturing techniques are transitioning these "emulsions of emulsions" into viable commercial systems for pharmaceutical, food, and cosmetic industries.

5. FUTURE PROSPECTS

Multiple emulsions have emerged as advanced multicompartamental delivery systems with significant potential in pharmaceutical, cosmetic, and food industries. Although traditional formulations have been

limited by thermodynamic instability, recent progress in formulation science is opening new research and commercial opportunities.

Future research is expected to focus on the following areas:

1. Advanced Stabilization Techniques

The development of novel surfactants, polymeric stabilizers, and Pickering stabilizers (solid particle–stabilized emulsions) may significantly enhance the long-term stability of multiple emulsions. Interfacial engineering and nanostructured materials are promising approaches to prevent coalescence and leakage.

2. Nanotechnology Integration

The combination of multiple emulsions with nanotechnology (nanoemulsions, nanoparticles, liposomes) could improve drug targeting efficiency, reduce systemic toxicity, and enhance therapeutic outcomes, especially in cancer therapy and gene delivery.

3. Targeted and Stimuli-Responsive Drug Delivery

Future systems may incorporate stimuli-responsive components that release drugs in response to pH, temperature, enzymes, or magnetic fields. This will enable site-specific and controlled drug release for chronic diseases such as cancer, diabetes, and autoimmune disorders.

4. Biodegradable and Biocompatible Materials

Greater emphasis will be placed on natural, biodegradable oils and surfactants to improve safety profiles and reduce environmental impact, particularly for long-term therapeutic and food applications.

5. Scale-Up and Commercial Manufacturing

Advancements in membrane emulsification, microfluidization, and continuous processing technologies may overcome scale-up challenges, making large-scale production more feasible and cost-effective.

6. Vaccine and Biologics Delivery

Multiple emulsions hold strong potential as vaccine adjuvants and carriers for proteins, peptides, and mRNA-based therapeutics, where protection of sensitive biomolecules is essential.

7. Personalized Medicine

With progress in precision medicine, multiple emulsions may be tailored for patient-specific dosing and combination therapy, addressing polypharmacy challenges.

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