MULTIPLE EMULSIONS A COMPREHENSIVE REVIEW

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ABSTRACT

Multiple emulsions are also known as emulsions of emulsions, liquid membrane system or double emulsion. These have been proposed to have numerous uses including their use for enhancement of bioavailability or as a prolonged drug delivery system. Multiple emulsions are often stabilized using a combination of hydrophilic and hydrophobic surfactants. The ratio of these surfactants is important in achieving stable multiple emulsions. The two major types of multiple emulsions are the w/o/w and o/w/o emulsions. The most common multiple emulsions are of W/O/W type which is widely used for pharmaceutical purposes.[2, 3]

KEYWORDS: Multiple emulsions, prolonged drug delivery system.

INTRODUCTION

Multiple emulsions are defined as emulsions in which both types of emulsions, i.e. water-in oil (w/o) and oil-in-water (o/w) exist simultaneously. They combine the properties of both w/o and o/w emulsions. These have been described as heterogeneous systems of one immiscible liquid dispersed in another in the form of droplets, which usually have diameters greater than 1 μm. These two liquids forming a system are characterized by their low thermodynamic stability. Multiple emulsions are very complex systems as the drops of dispersed phase themselves contain even smaller droplets, which normally consist of a liquid miscible and in most cases identical with the continuous phase. Both hydrophilic and lipophilic emulsifiers are used for the formation of multiple emulsions.

Multiple emulsions are promising in many fields, particularly in pharmaceutics and in separation science. Their potential biopharmaceutical applications include their use as adjuvant vaccines, as prolonged drug delivery systems, as sorbent reservoirs in drug overdose treatments and in mobilization of enzymes. Multiple emulsions were also investigated for cosmetics for their polymeric microspheres, and as microcapsules for the protection and reduced deterioration science.

Multiple emulsion system solute has to transverse from inner miscible phase to outer miscible phase through the middle immiscible organic phase, so it is also called as liquid membrane system. The two major types of multiple emulsions are the water-oil-water (w/o/w) and oil-water-oil (o/w/o) double emulsions. The most common multiple emulsions are of W/O/W type, although some specific applications O/W/O emulsions can also be prepared.[14, 2, 5]

Multiple emulsions may find many potential applications in various fields such as chemistry, pharmaceutics, cosmetics, and food. These emulsions have been investigated as controlled-release drug delivery systems (DDS) as ‘emulsion liquid membranes’ for simultaneous liquid extraction and stripping of metals, organic acids and antibiotics, as microcapsules for the protection and controlled release of functional food ingredients, for the formulation of reduced-calorie food emulsion etc. Other applications include the use of multiple emulsions as intermediate products to the preparation of inorganic particles, lipid nanoparticles, polymeric microspheres, biodegradable microspheres, gel micro beads, and vesicles such as polymersomes.

For medical applications, a water-soluble therapeutic component can be solubilised within the inner W1 phase of the emulsion globule, which showed prolonged release properties and lessen toxic effects. The stability and release properties of double emulsion can be improved by varying the type and concentrations of surfactants. Combining targeted delivery with prolonged release would present a tremendous benefit in cancer therapy. The use of double emulsions to accomplish this
combined capability merits consideration. Multiple emulsion system possesses adequate biocompatibility, complete biodegradability and versatility in terms of different oils and emulsifiers being used. Both hydrophilic and hydrophobic drugs can be entrapped and protected, drug targeting especially to reticulo endothelial system (RES), taste masking and for slow or controlled delivery of drugs. Beside these advantages with multiple emulsions, there are certain associated disadvantages like being difficult to formulate, bulky and susceptible to various routes of physical and chemical degradation.\[2\]

Multiple emulsions have not been commercially exploited because of their inherent thermodynamic instability. A number of attempts have been made in last two decades for improving stability by several investigators. These attempts are; polymerization gelling, additives in different phases, surfactant concentration modulation, interfacial complexation, pro-multiple emulsion approach and steric stabilization.

**Method of Preparation of Multiple Emulsions**

Multiple emulsions are usually formed by a two step emulsification process using conventional rotor-stator or high pressure valve homogenizers. The primary w/o or o/w emulsion is prepared under high-shear conditions to obtain small inner droplets, while the secondary emulsification step is carried out with less shear to avoid rupture of the liquid membrane between the innermost and outermost phase. However, the second step often results in highly polydisperse outer drops (if homogenizing conditions are too mild) or in a small encapsulation efficiency (if homogenization is too intensive). Multiple emulsions can alternatively be produced by forcing a primary emulsion through a micro porous membrane or micro fabricated channel arrays into a continuous phase liquid. This results in much less shear than in conventional emulsification processes so that the droplets are intact and both high entrapment efficiency and mono dispersity can be achieved.\[6, 2\]

**Two Step Emulsification Method**

![Figure 1. Formulation Steps of water: oil: water (w/o/w) multiple emulsion](image)

**Stabilization of multiple emulsions**

Stability is the major problem of the multiple emulsions. Four possible mechanisms lead to the instability of W/O/W emulsions are 1) Coalescence of the internal aqueous droplets; 2) Coalescence of the oil droplets; 3) Rupture of the oil film resulting in the loss of the internal aqueous droplets and 4) Passage of the water and water-soluble substances through the oil layer between both water phases. This can occur in two various ways: via reverse micellar transport created by the lipophilic emulsifier and by simple diffusion across the oil phase connected with osmotic differences between both water phases.

The major problem as regards stability is the presence of two thermodynamically unstable interfaces. Two different emulsifiers are necessary for their stabilization: one with a low HLB for the W/O interface and a second one with a high HLB for the O/W interface. There are several approaches to overcome instability and release-problems in double emulsions. Some of those ideas can be summarized as follows.

**The inner phase**

(i) Stabilizing the inner w/o emulsion by mechanically, or in the presence of better emulsifiers, reducing its droplet size
(ii) Forming L2-microemulsions
(iii) Preparing microspheres
(iv) Increasing the viscosity of the inner water.

**The oil phase**

(i) Modifying the nature of the oil phase by increasing its viscosity or by adding carriers
(ii) Adding complexing agents to the oil.
The interfaces
(i) Stabilizing the inner and/or the outer emulsion by using polymeric emulsifiers, macromolecular amphiphiles (proteins, polysaccharides) or colloidal solid particles to form strong and more rigid film at the interface.

Formulation of Multiple Emulsions
There are three different types of multiple emulsions, which they termed A, B, and C. Type A multiple emulsions were those in which only one large internal drop was contained in the secondary emulsion droplet. In type B emulsions, there were several small internal droplets contained in the secondary emulsion droplet, and type C emulsions were those with a large number of internal droplets present. Only the type C systems have applications in drug delivery and drug targeting. The objectives will be to produce a multiple emulsion system that has a high yield of multiple droplets containing the drug entrapped in the innermost phase, and for such a system to have good stability in vitro and the desired release characteristics in vivo. The following factors are identified as being of importance and will be discussed in turn with reference to the w/o/w system: (1) emulsification equipment; (2) nature of the oil phase; (3) volumes of the two dispersed phases; (4) nature and quantity of the emulsifying agents; (5) nature of entrapped materials, including the drug substance; and (6) added stabilizing components (gelling agents etc).[2]

Emulsifying equipment
The primary emulsion can be prepared using a laboratory mixer or homogenizer to provide a good dispersion of droplets within the appropriate continuous phase. The secondary emulsification stage must disperse the primary emulsion into droplets of suitable size for use in delivery vehicles. Excessive mixing, especially at high shear, can cause the primary emulsion droplets to rupture. Low-speed, low-shear mixers should be used, or the system can be shaken by hand. Ultrasonic homogenizers must be used with care for the secondary emulsification step.

Nature of the oil phase
The oil phase to be employed in a pharmaceutical emulsion must be nontoxic. The various oils of vegetable origin (soybean, sesame, peanut, safflower, etc.) are acceptable if purified correctly. Refined hydrocarbons such as light liquid paraffin, squalane, as well as esters of fatty acids (ethyl oleate and isopropyl myristate) have also been used in double emulsions. Oils derived from vegetable sources 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 emulsions (w/o/w) than those produced from vegetable oil. The order of decreasing stability and percentage entrapment has been found to be light liquid paraffin > squalane > sesame oil > maize or peanut oil.

Volumes of the dispersed phases
The quantity of water dispersed in the initial w/o emulsion [expressed as a phase volume ratio, (w/o/w)] can have an influence on both the yield and stability of the final emulsion system.

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 2-7 for the primary surfactant and in the range 6-16 for the secondary surfactant. The concentration of the emulsifiers can also be varied. Too little emulsifier may result in unstable systems, whereas too much emulsifier may lead to toxic effects and can even cause destabilization.

Influence of hydrophilic surfactants on the properties of multiple w/o/w emulsions
It is well known that an emulsifier with an optimum HLB value and with chemical properties compatible with emulsion ingredients is necessary to obtain a stable emulsion.

Tween 80 is very often used in combination with Span 80 in multiple w/o/w emulsions because of its similar chemical structure to Span 80. It has been found in the majority of cases that the most stable emulsions, in particular, are formed when both emulsifying agents are of the same hydrocarbon chain length.

The superior stability of emulsion containing Tween80 can be linked to two factors.
(a) The chemical compatibility of Tween 80 and Span 80 and
(b) The better HLB value.

HLB values of hydrophilic emulsifiers used for multiple W/O/W emulsion.

<table>
<thead>
<tr>
<th>S. N.</th>
<th>Chemical structure</th>
<th>HLB value</th>
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<tbody>
<tr>
<td>1.</td>
<td>Ester</td>
<td></td>
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<tr>
<td></td>
<td>Polyoxethlylated</td>
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<tr>
<td></td>
<td>sorbitanmonooleate</td>
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<tr>
<td></td>
<td>fatty acid esters</td>
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<tr>
<td></td>
<td>Tween 80</td>
<td>15</td>
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<tr>
<td></td>
<td>Tween 20</td>
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<tr>
<td></td>
<td>Polyethoxylated</td>
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<td></td>
<td>derivatives of</td>
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<tr>
<td></td>
<td>stearic acid</td>
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<td></td>
<td>PEG-20 stearate</td>
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<tr>
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<td>PEG-40 stearate</td>
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<tr>
<td></td>
<td>PEG-40/50 stearate</td>
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<td></td>
<td>PEG-100 stearate</td>
<td>18.8</td>
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<tr>
<td>2.</td>
<td>Ether</td>
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<tr>
<td></td>
<td>Polyethoxylated</td>
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<td>Oleth-20</td>
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<tr>
<td>3</td>
<td>Polymer</td>
<td>22</td>
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<tr>
<td></td>
<td>Poloxamer 407</td>
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Comparison of all hydrophilic emulsifier.[2,26]
It was not possible to obtain stable multiple W/O/W emulsions using sucrose esters. Homogeneous emulsions with small oil droplets could be obtained using Tween emulsifiers and Poloxamer. However, the emulsions were very unstable and phase separation occurred after several days. Multiple emulsions containing polyethoxylated stearate were much more stable, but multiple oil droplets are very large compared with other emulsifiers. Multiple emulsions with optimum properties and long-term stability were able to be obtained using polyethoxylated fatty alcohols. The decisive factor is in this case is the hydrophobic chain length. A chain consisting of 16–18 carbon atoms is the ideal chain length. Although the viscosity and droplet size for all emulsifiers vary greatly, NaCl encapsulation immediately after preparation was very high in all cases.

**Effect of Lipophilic Emulsifier**

As the concentration of lipophilic surfactant is increases, the swelling capacity of oil globule is increases, and the more the release is delayed. The influence of the lipophilic surfactant concentration on the swelling of the oil globule can be explained by two different mechanisms. The first one consists in an increase of the rigidity of the second interface by the progressive migration of the lipophilic surfactant. During the second step of multiple emulsion preparation, lipophilic surfactant molecules can diffuse from the first to the second interface, were they produce a synergistic effect resulting in membrane strengthening. The second one involves a delay in the in the aqueous droplet coalescence. In course of swelling of the oil globule, the lipophilic surfactant molecules, which are in excess in oily phase, can diffuse to the first interface to fill up free spaces caused by swelling, when required.

**Nature of entrapped materials**

When formulating a w/o/w system the presence of the drug and other components (especially electrolytes) needs to be considered. The nature of drug (hydrophilic or hydrophobic) also be considered.

**Added stabilizing components**

The stabilizers are added for improve the stability of multiple emulsions. These include gelling or viscosity-increasing agents added to internal and/or external aqueous phases (e.g., 20% gelatin, methylcellulose, and similar thickening agents, as well as complexing agents that will lead to liquid crystalline phases at the o/w interface (e.g., 1-3% cetyl alcohol) and gelling agents for the oil phase (e.g., 1-5% aluminium monostearate)

**Possible mechanism of drug release from multiple emulsions**

In multiple emulsions, the drug is released from internal to external phase through the oily layer by different mechanism. The release rates are affected by the various factors such as droplet size, pH, phase volume and viscosity etc.

- **Diffusion mechanism**
  This is most common transport mechanism where unionized hydrophobic drug diffuses through the oil layer in the stable multiple emulsions. Drug transport has been found to follow first order kinetics and obeyed Fick’s law of diffusion.

- **Micellar transport**
  Inverse micelles consisting of nonpolar part of surfactant lying outside and polar part inside encapsulate hydrophilic drug in core and permeate through the oil membrane because of the outer lipophilic nature. Inverse micelle can encapsulate both ionized and unionized drugs. Recently, the release of tetradecane from a tetradecane/water/hexadecane multiple emulsions was investigated using the differential scanning calorimetry technique. Micellar diffusion rather than molecular diffusion was considered to be the preponderant mechanism for mass transfer.

- **Thinning of the oil membrane**
  Due to osmotic pressure difference, the oil membrane became thin, so the water and drug easily diffused. This pressure difference also provides force for the transverse of molecule.

- **Rupture of oil phase**
  According to this mechanism rupturing of oil membrane can unite both aqueous phases and thus drug could be released easily.

- **Facilitated diffusion (Carrier-mediated transport)**
  This mechanism involves a special molecule (carrier) which combines with the drug and makes it compatible to permeate through the oil membrane. These carriers can be incorporated in internal aqueous phase or oil membrane.

- **Photo-osmotic transport**
  The mechanism of this transport process is not very clear. Transport of the drug through the oil membrane takes place with the help of the light.

- **Solubilisation of internal phase in the oil membrane**
  It is a conspicuous transport mechanism. In this solubilisation of minute amounts of the internal phase in the membrane phase results in the transport of very small quantities of materials.

**APPLICATION OF MULTIPLE EMULSIONS**

**Multiple emulsions in cancer therapy**

Most anticancer drugs are used as emulsions because they are water-soluble. In the form of an emulsion it is possible to control release rates of medicine and suppress strong side effects of the drug. A single emulsion cannot be used since W/O emulsions generally have such a high viscosity that infusion of emulsions to arteries/capillaries via catheters is difficult. Also O/W emulsions are not an option because they do not encapsulate the drug. But W/O/W emulsion systems are suitable drug carriers because of the encapsulation of the drug in the internal water phase and the low viscosity due to the external water phase.
Multiple emulsions in herbal drugs
Apart from its targeted sustained release, producing the herbal drug into emulsion will also strengthen the stability of the hydrolyzed materials, improve the penetrability of drugs to the skin and mucous, and reduce the drugs' stimulus to tissues. So far, some kinds of herbal drugs, such as camptothecin, Bruceajavanica oil, coixenolide oil and zedoary oil have been made into emulsion.

Vaccine/vaccine adjuvant
The use of w/o/w multiple emulsion as a new form of adjuvant for antigen was first reported by Herbert. These emulsions elicited better immune response than antigen alone. Rishendra and Jaiswal developed a multiple emulsion vaccine against Pasteurella multocida infection in cattle. This vaccine contributed both humoral as well as cell-mediated immune responses in protection against the infection.

Oxygen substitute
A multiple emulsion of aqueous oxygen carrying material in oil in outer aqueous phase is suitable for provision of oxygen for oxygen transfer processes. Haemoglobin multiple emulsions in physiologically compatible oil in an outer aqueous saline solution is provided in sufficiently small droplet size to provide oxygen flow through blood vessels to desired body tissues or organs thereby providing a blood substitute.

Inverse targeting
Regarding this approach Talegaonkar and Vyas were prepared poloxamer 403 containing sphere in- oil-in-water (s/o/w) multiple emulsion of Diclofenac sodium by gelatinization of inner aqueous phase and they examined the effect of poloxamer 403 on surface modification for inverse targeting to reticuloendothelial system-rich organs. The results concluded that this multiple emulsion system containing poloxamer has capability to retards the RES uptake of drugs mainly to liver, brain and targeting to non-RES tissues such as lungs, inflammatory tissue.

Multiple emulsions in diabetes
Toorisaka et al. Developed a S/O/W emulsion for oral administration of insulin. Surfactant-coated insulin was dispersed in the oil by ultrasonication, this dispersion was mixed with the outer water phase with a homogenizer and finally, the S/O/W emulsion thus obtained was adjusted to a constant particle size by passage through SPG membrane. The S/O/W emulsion showed hypoglycemic activity for a long period after oral administration to rats.

Multiple emulsions in food
Another possible application of double emulsions is in the food industry. Preliminary studies have been performed in the field of entrapment of a flavour component in a release system. Sensitive food materials and flavours can be encapsulated in W/O/W emulsions. Sensory tests have indicated that there is a significant taste difference between W/O/W emulsions and O/W emulsions containing the same ingredients, and that there is a delayed release of flavour in double emulsions.

Drug over dosage treatment
This system could be utilized for the over dosage treatment by utilizing the difference in the pH. For example:--barbiturates. In these emulsions, the inner aqueous phase of emulsion has the basic buffer and when emulsion is taken orally, acidic pH of the stomach acts as an external aqueous phase. In the acidic phase barbiturate remains mainly in unionized form which transfers through oil membrane into inner aqueous phase and gets ionized. Ionized drug has less affinity to cross the oil membrane thereby getting entrapped. Thus, entrapping excess drug in multiple emulsions cures over dosage.

Taste masking
Multiple emulsions of chloroquine, an antimalarial agent has been successfully prepared and had been found to mask the bitter taste efficiently. Taste masking of chlorpromazine, an antipsychotic drug has also been reported by multiple emulsions.

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