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# Multiple emulsions and its stabilization: A 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. Multiple emulsions are multifarious polydispersed systems where both oil in water and water in oil emulsion exists all together which are stabilized by lipophillic and hydrophilic surfactants respectively. The ratio of these surfactants is important in achieving stable multiple emulsions. Among water-in-oil-in-water (w/o/w) and oil-in-water-in-oil (o/w/o) type multiple emulsions; the former has wider areas of application. Formulation, preparation techniques and in vitro characterization methods for multiple emulsions are reviewed. It finds wide range of applications in controlled or sustained drug delivery, targeted delivery, taste masking, bioavailability enhancement, enzyme immobilization, etc. Multiple emulsions have also been employed as intermediate step in the microencapsulation process and are the systems of increasing interest for the oral delivery of hydrophilic drugs, which are unstable in gastrointestinal tract like proteins and peptides.

**Keywords:** multiple emulsions, surfactant, stability of emulsions

## 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 [1]. 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 μm1. These two liquids forming a system are characterized by their low thermodynamic stability [2]. 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 [3]. Both hydrophilic and lipophilic emulsifiers are used for the formation of multiple emulsions. Multiple emulsions were determined to be promising in many fields, particularly in pharmaceutics and in separation science. Their potential biopharmaceutical applications3 include their use as adjuvant vaccines [4], as prolonged drug delivery systems [5-8], as sorbent reservoirs in drug overdose treatments [9] and in mobilization of enzymes [10-11]. Multiple emulsions were also investigated for cosmetics for their potential advantages of prolonged release of active agent, incorporation of incompatible materials and protection of active ingredients by dispersion in internal phase [12-14]. Also water-in-oil-in-water (W/O/W) multiple emulsions are emulsion systems where small water droplets are en-trapped within larger oil droplets that in turn are dispersed in a continuous water phase. Because of the presence of a reservoir phase inside droplets of another phase that can be used to prolong release of active ingredients [15]. Multiple W/O/W emulsions contain both W/O and O/W simple emulsions and require at least 2 emulsifiers to be present in the system when prepared using the 2-step method, one that has a low Hydrophile-Lipophile Balance (HLB) value to stabilize the primary W/O emulsion and one that has a high HLB value to stabilize the secondary O/W emulsion. The low-HLB surfactant is dominantly hydrophobic and is added to the oil phase. The high HLB surfactant is dominantly hydrophilic and is added to the outer continuous aqueous phase. The concentration ratio of these two surfactants is important to obtain stable and high yields of W/O/W emulsions [16]. A unique property of W/O/W multiple emulsions com-pared to simple W/O emulsions is the diffusion of water through the oil phase because of unbalanced osmotic pressures between the internal and external aqueous phases. The oil layer acts as a membrane separating these two aqueous phases. Polar molecules dissolved in either the internal aqueous phase or the external continuous aqueous phase can pass through the oil layer by diffusion because of the concentration gradient. In the case of water this is driven by osmotic pres-sure. Molecules are often transported via micelles of hydrophobic surfactant present in the oil phase. Water diffusion causes swelling, bursting, or shrinkage of the internal aqueous droplets, affecting the stability of the multiple droplets as well as the release profiles of the active ingredients loaded in the inner dispersed aqueous phase [17]. Most cardiovascular events are attributed to high blood pressure. High blood pressure is quantitatively the largest single risk factor for premature death and disability due to its extremely high prevalence in industrialized countries. Hence, antihypertensive therapy considerably reduces the risk of developing cardiovascular complications that cause a high mortality rate in patients with hypertension [18-19]. Valsartan is a new potent, highly selective and orally active antihypertensive drug belonging to the family of angiotensin II type 1 receptor antagonists. Valsartan inhibits angiotensin II receptors, thereby relaxing blood vessels and causing them to widen, which lowers blood pressure and improves blood flow [20-21]. Valsartan is

well tolerated after single and multiple dosing following single oral doses up to 400 mg and after multiple dosing [22-24] with 200 mg per day. The development of multiple emulsion dosage formulation of certain active ingredients is challenging. When formulating multiple emulsions dosage formulations, the objective is to provide an increased release of valsartan and increased oral bioavailability of valsartan in patient as compared to known solid oral dosage forms of valsartan. Development of multiple emulsions dosage formulation that have improved bioavailability to the known oral dosage forms of valsartan is challenging due to the multiplicity of challenges arising from pharmacokinetic aspects of oral drug delivery. Valsartan has an oral bioavailability of only about 25% with a wide range of 25-40% in humans with large inter- and intra-subject variabilities. Valsartan also has pH dependent solubility whereby it ranges from very slightly soluble in an acidic environment to soluble in a neutral environment of gastrointestinal tract. The permeability of valsartan is low and also pH dependent where it decreases as environmental pH increases from acidic to neutral pH values in the gastro intestinal tract. As a result of these complex biopharmaceutical properties, development of a more releasable and bioavailable dosage form of valsartan with less inter and intrasubject variability is challenging. Accordingly multiple emulsions dosage formulation of valsartan which has enhanced release and bioavailability properties with less inter and intrasubject variability would be desirable. Thus the aim of the present study is to "formulate and evaluate the multiple emulsion of valsartan" [25].

**Method of Preparation**

Multiple emulsions were prepared by two step emulsification process:

**a) Preparation of primary emulsification**

Primary emulsification: 10 ml of distilled water containing 25 mg of drug was gradually added to 14 ml of oil phase containing primary emulsifier (Span40, Span60, and Span 80) and 25mg of drug with continuous stirring at 5000 rpm for 5 minutes. It gives the primary emulsion.

**b) Secondary emulsification [26-28]**

Secondary emulsification: 20 ml of viscous primary emulsion was emulsified further with an external aqueous phase containing secondary emulsifier (Tween80) and 50 mg drug with continuous stirring at 1000 rpm for 10 min. All the formulations were prepared by following the same procedure. Effect of primary emulsifier was observed by evaluating several formulations.

**Types of multiple emulsions**

a) Oil in water in oil (o/w/o) emulsion-In O/W/O systems, an aqueous phase separates internal and external oil phases. In other words, O/W/O is a system in which water droplets may be surrounded in an oil phase, which in turn encloses one or more oil droplets3.
b) Water in oil in water (w/o/w) emulsion-In W/O/W systems, an organic phase separates internal and external aqueous phases. In other words, W/O/W is a system in which an oil droplet may be surrounded by an aqueous phase, which in turn is encloses one or more water droplets. These systems are the most studied among the multiple emulsions

**Advantages of Multiple Emulsions**

a) They can mask the bitter taste and odour of drugs, thereby making them more palatable. E.g. Castor oil, Cod-liver oil, Chloroquine Phosphate etc.
b) They can be used to prolong the release of the drug thereby providing sustained release action.
c) Essential nutrients like carbohydrates, fats and vitamins can all be emulsified and can be administered to bedridden patients as sterile intravenous emulsions
d) Emulsions provide protection to drugs which are susceptible to oxidation.

**Limitations of multiple emulsions**

The main problem associated with multiple emulsions is their thermodynamic instability and their complex structure, which has severely limited their usefulness in the many applications of multiple emulsions [29].

**Stabilization**

It is a phenomenon which depends upon equilibrium between three phases; water, oil and surfactant. Nevertheless, multiple emulsions are thermodynamically unstable. A little emulsifier may result in unstable systems, whereas too much emulsifier may lead to toxic effects and can cause destabilization. Some mechanisms have been identified which leads to instability of multiple emulsions:

1. Coalescence of multiple emulsion droplets or internal droplets.
2. Rupture of oil layer on surface of internal drops.
3. Shrinkage and swelling of internal droplets due to osmotic gradient across the oil membrane.
4. Flocculation of internal aqueous phase and multiple emulsion droplets and Phase separation.

The main problem in regards to stability is the presence of two interfaces which are thermodynamically unstable. So, Two different emulsifiers are necessary for their stabilization; one with a low HLB (Hydrophile-Lipophile Balance) value for W/O interface and the another one with a high HLB value for O/W interface. We can stabilize the emulsions by using electrolytes, by forming polymeric film,by interfacial complexation between non-ionic surfactant and macro molecules. Following approaches we can use to overcome instability in multiple emulsions:

**1.1 The inner phase**

We can stabilize the inner W/O emulsion mechanically, or in presence of better emulsifiers, reducing its droplet size. Also we can achieve our aim by Preparing microspheres and Increasing the viscosity of inner water [30].

**1.2 The oil phase**

By modifying nature of oil phase by increasing its viscosity or by adding carriers or by adding complexing agents to the oil.

**1.3 The interfaces**

This can be done by stabilizing inner and/or outer emulsion by using polymeric emulsifiers, macro molecular amphiphiles or colloidal solid particles to form strong as well as more rigid film at the interface; also by in-situ polymerization at the interface. Hence, stability of multiple

emulsions can be improved by forming a polymeric film or macro molecular complex across the oil/water interfaces

**2. Drug Release Mechanisms**

Drug release in multiple emulsions from internal to external phase occurs via the middle layer. The release rates are affected by various factors such as droplet size, pH, phase volume ratios, viscosity, nature of entrapped material etc.Some of the mechanisms of drug release are as follows:

**2.1 Diffusion mechanism**

Most common transport mechanism where unionized drug (hydrophobic moieties) diffuses via oil layer (semipermeable liquid membrane), especially in stable multiple emulsions. Drug transport has been found to follow first order kinetics and obeyed Fick's law of diffusion [31].

**2.2 Carrier mediated transport**

It involves a special molecule (carrier) which combines with drug and makes it compatible to permeate via the oil membrane. This involves either incorporation of some material into internal aqueous phase of membrane phase, which reacts with permeating compound to render it liposoluble. Carrier compounds effectively pump the permeating compound across membrane; e.g., stearic acid facilitated diffusion of Cu2+ ions. This mechanism is especially effective for transport of highly hydrophilic compounds.

**2.3 Micelle transport**

Since outer lipophilic nature, in this mechanism inverse micelles consisting of non-polar part of surfactant lying outside and polar part lying inside encapsulate hydrophilic drug in core and permeate via the oil membrane.. Inverse micelle can epitomize both ionized and Non ionized drugs. The presence of both lipophilic and hydrophilic surfactants in the oil phase helps in the formation of water swollen inverse micelles, which may act as a mobile carrier for both ionized and unionized drug.

**2.4 Thinning of oil membrane**

Due to osmotic pressure difference oil membrane become thin, so water and drug easily diffuses. This mechanism comes into existence when there is an osmotic pressure difference between two aqueous phases, which also provides force for transverse of molecule. Rupturing of oil membrane can unite both aqueous phases and thus drug could be released easily. Solubilization of minute amounts of internal phase in membrane phase results in transport of very small quantities of materials.

**3. Formulation Technique**

Emulsions are thermodynamically unstable and thus we add emulsifier like surfactant, co polymer to maintain its stability. So two surfactants of opposite nature are added to the system. One stabilizes the w/o ( lipophilic) emulsion while the other stabilizes the o/w ( hydrophilic) emulsion. When emulsion formation takes place, these emulsifiers are adsorbed on the surface of the droplets which prevents them from aggregating.

**3.1 Double emulsification technique**

The first step is formation of a simple w/o or o/w emulsion. In presence of an emulsifier, this is again re- emulsified with excess of water or oil phase to get a multiple emulsion of o/w/o or w/o/w type [32]. Second step is very crucial because fracturing of the internal globules forming simple emulsion of o/w or w/o type may take place depending on various factors. It has a advantage that this technique is easier and gives a high yield.

**3.2 Phase inversion technique**

It is a one-step mechanism. In this, the continuous phase become the dispersed phase and vice-versa, could be considered a good path to produce emulsion which are made up of very small droplets. Phase inversion could be accompanied by altering the temperature and volume fractions of the system and phases respectively and by adding salts or by imposing the flow rates. It has been founded that, if we raise the temperature, nonionic surfactants become more hydrophilic. As a result of this, they change their chemical configuration and phase inversion is done.

**3.3 Membrane emulsification technique**

In this technique the emulsifier used is a glass membrane. The principle which is used is dispersing one phase which is not miscible (dispersing phase) into continuous phase by applying pressure. The particle size of the w/o/w emulsion can be restrained by selecting perfect porous glass membrane.

**4. Methods to stabilize Multiple Emulsions**

**4.1 Stabilization in presence of electrolyte**

Addition of electrolyte resulted in improvement of emulsion stability with respect to coalescence. So, when electrolytes are added in inner layer or outer aqueous layer multiple emulsions migrate across the oils layer and thus migrate to some other aqueous layer. This migration induces changes in osmotic pressure with time and thus alters the stability of multiple emulsions.

**4.2 Stabilization by forming polymeric gels**

In order to improve stability of multiple emulsion, either internal phase (aqueous) or secondary aqueous phase needs to be gelled. Production of gels in aqueous phase leads to system which has greater stability. If the internal aqueous phase is gelled, it will prevent coalescence. And when the outer continues phase is gelled, an opaque emulsion is produced in which the dispersed droplets are held in a network of polymer from where the droplets are released on contact with water.

**4.3 Steric Stabilization**

Emulsion can be stabilized by increasing the repulsion between the dispersed phases that is by increasing the electrostatic or steric repulsion. This can be done by adding an emulsifier. emulsifier are amphiphiles which reduce the interfacial tension between the two phases and contribute to stabilization of dispersed droplet. Both electrostatic and steric forces can prevent aggregation or coalescence and thus stabilize emulsions.

**4.4 Liquid crystal stabilized multiple emulsions**

Liquid crystal at the periphery of multiple emulsion droplets prevents the diffusion of water between inner and outer aqueous system. Liquid structure has a mesomorphic structure between solid and liquid. When a liquid crystal is

present at interface, it acts as emulsion stabilizer as it provides rigidity and less composition fluctuation at interphase.

**5. Micro channel Emulsification**

For the production of monodisperse emulsions, straight through microchannel (MC) emulsification is a new technique. It uses a silicon array of micro machined through-holes, known as a straight-through micro-channel [33]. The oblong straight through MC have channel lengths of 48.7 and 9.6 μm. In contradiction, the systems containing cationic surfactants resulted in the manufacturing of polydispersed O/W emulsions and complete wetting of the dispersed phase on the surface of plate. This showed that a repulsive surfactant–plate surface interaction and a high contact angle value have to be there to achieve a successful straight-through microchannel emulsification. It also showed that it is necessary to keep the negatively charged plate surface hydrophilic when the emulsification process is occurring. Because of the the dispersed-phase flux the straight-through MC emulsification behavior gets affected. [34]. The effect of different concentrations of Sodium Caseinate (0.5, 1, 1.5 gr) in the external aqueous, different portions of primary emulsion (25%, 40%, 50%) and type of hydrophilic emulsifiers in the making and stability of W/O/W emulsions prepared. Sodium caseinate which is a milk protein is a stabilizer at oilwater interfaces is well documented. NaCN is amphiphilic proteins having a strong tendency to adsorb at oil-water interfaces during emulsification thereby reducing interfacial tension.

**Conclusion**

The Multiple Emulsion is one of the advanced drug delivery systems for the improvement of the various characteristics of the drugs like bioavailability, taste, release rate etc. The advances include various novel formulations for the betterment of the drug administration & improvement in the palatability of the drug by incorporating them into the various formulations. The Multiple Emulsion is the complex polydispersed system containing an emulsion incorporated in another emulsion, which can be used in many applications like taste masking, sustained release, delivering the unstable drug & prevention of the drug from the environment etc.

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