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Review Article

A Review On Multiple Emulsions

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Multiple emulsions are complex polydispersed systems where both oil in water and water in oil emulsion exists simultaneously 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. With the advancement in techniques for preparation, stabilization and rheological characterization of multiple emulsions, it will be able to provide a novel carrier system for drugs, cosmetics and pharmaceutical agents.

Keywords: Multiple Emulsions, Fate of ME's, Stability of Emulsions.

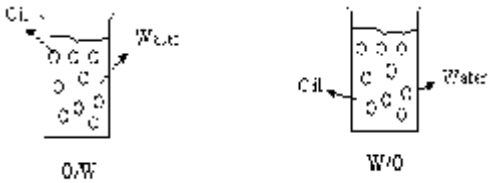
INTRODUCTION:

Emulsions may be described as heterogeneous systems, where one immiscible liquid is dispersed in the form of droplets and stabilized by a third component called emulsifying agent. These two liquids are also chemically non-reactive and form the systems that are characterized by a low thermodynamically stability. Based on their formation, emulsions can be divided into:

- Simple Emulsion and
- Multiple Emulsions.

Simple Emulsions can be divided according to their continuous phase or dispersed phase as

- Oil-in-water emulsions (O/W) - where oil is the disperse phase in a continuous phase of water, and
- Water-in-oil emulsions (W/O) - where water is the disperse phase in a continuous phase of oil [4].



Multiple Emulsions:

Multiple emulsions are more complex than their two-phase counterparts from the standpoint of formulation, stability, and

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drug release. They are useful tool in achieving sustained release drug delivery for different routes [2].

The present study aims towards formulation of multiple emulsions, which contain an additional reservoir that is an extra step for partitioning of the drug, which can effectively retard the release rate of the drug and decrease the dose frequency.

Multiple emulsions are novel carrier system which are complex and poly dispersed in nature where both w/o and o/w emulsion exists simultaneously in a single system. Lipophilic and hydrophilic surfactants are used for stabilizing these two emulsions respectively. The droplets of the dispersed phase contain even smaller dispersed droplets themselves, therefore also called as "emulsions of emulsions". Each dispersed globule in the double emulsion forms a vesicular structure with single or multiple aqueous compartments separated from the aqueous phase by a layer of oil phase compartments. In multiple emulsion system solute has to transverse from inner miscible phase to outer miscible phase through the middle immiscible organic phase, so it also called as liquid membrane system [6].

1.1 **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 droplets [3].

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 [3].

1.2 **Advantages of Multiple Emulsions:**

a. They can mask the bitter taste and odor 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 bed ridden patients as sterile intravenous emulsions

d. Emulsions provide protection to drugs which are susceptible to oxidation or

hydrolysis.

e. Intravenous emulsions of contrast media have been developed to assist in diagnosis.

f. Emulsions are used widely to formulate externally used products like lotions, creams, liniments,

g. Enhancement of enteric or dermal absorption [5].

1.3 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 [5].

1.4 Preparation of Multiple Emulsion

Multiple emulsions can be prepared by the re-emulsification of a primary emulsion or they can be produced when an emulsion inverts from one type to another, for example W/O to O/W. The O/W emulsions have small size of internal dispersed phase therefore; it is not used in therapeutics [3].

a) Phase Inversion Technique or Single Step Technique

The increase in volume of dispersed phase may cause an increase in the phase volume ratio, which subsequently leads to the formation of multiple emulsions. The method involves the addition of an aqueous phase containing the hydrophilic emulsifier (Tween 80/Sodium Docedyl Sulphate) to an oil phase consisted of liquid paraffin and containing liophillic emulsifier (Span 80).

A well defined volume of oil phase is placed in a vessel of pin mixer. An aqueous solution of emulsifier is then introduced successively to the oil phase in the vessel at a rate of 5 ml/min, while the pin mixer rotates steadily at 88 rpm at room temperature.

When volume fraction of the aqueous solution exceeds 0.7, the continuous oil phase is substituted by the aqueous phase containing a number of the vesicular globules among the simple oil droplets, leading to phase inversion and formation of W/O/W multiple emulsion [4].

b) Two-Step Emulsification

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 small encapsulation efficiency (if homogenization is too intensive) [4].

c) Membrane Emulsification Technique

- In this, a W/O emulsion is extruded 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:

$Y = 5.03 X + 0.19$

Where, X is the pore size, Y is particle size of the multiple emulsions [3].

3. Stability of Multiple Emulsions

Multiple Emulsion stability is a phenomenon, which depends upon the equilibrium between water, oil and surfactant. Unfortunately multiple emulsions are thermodynamically unstable. 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 [4].

4. Breakdown Pathways:

Some of the breakdown pathways that may be involved in W/O/W emulsion destabilization are:

i. Coalescence of multiple oil drops, single or multiple.
ii. Expulsion of Single Internal Droplets.
iii. Expulsion of More than one Internal Droplet.
iv. Coalescence of Internal Droplets before being expelled.
v. Shrinkage of Internal Droplets due to diffusion.

5. Methods to Stabilize Multiple Emulsions:

The followings are some of the attempt 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 [6].

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6. Behaviour of Multiple Emulsions in Biological System:

ME's have been administered by oral, parentral (i.v., i.m., s.c.) and topical routes (nasal, ocular, transdermal) routes. After oral administration ME is almost absorbed entirely from lymphatic pathway in association with intestinal lipoproteins namely chylomicrons, produced by enterocytes. They may directly be absorbed through intestinal macrophage system & Payers Patches to gain access into mesenteric lymph from where they are drained into circulation through thoracic lymph duct. Thus, they are able to carry bioactives within them avoiding degradation in intestine as well as liver. After parenteral (i.v. or i.m.) administration the emulsions are readily taken up by circulatory macrophage system to lymphatics as well as liver into fat metabolism pathway. Through other parenteral routes, the emulsion droplets gain access to nearby lymphatic node through interstitial spaces of lymphatic vessels which are relatively porous as compared to blood capillaries which have tight intracellular junctions [4].

7. 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.The various Mechanisms are:

a) 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.

b) 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 lipophillic nature. Inverse micelle can encapsulate both ionized and unionized drugs.

Recently, the release of tetradecane from a tetradecane/water/hexadecane multiple emulsion was investigated using the differential scanning calorimetry technique. Micellar diffusion rather than molecular diffusion was considered to be the preponderant mechanism for mass transfer.

c) 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.

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) 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.

f) 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.

g) Solubilization of internal phase in the oil membrane

It is a conspicuous transport mechanism. In this solubilization of minute amounts of the internal phase in the membrane phase results in the transport of very small quantities of materials [6].

8. Applications of Multiple Emulsions:

The most promising use of multiple emulsions is in the area of sustained release, drug formulation since the oil layer between the two aqueous phases can behave like a membrane controlling solute release. Liquid membrane emulsions of the o/w/o type have been used to separate hydrocarbons where the aqueous phase serves as the membrane and a solvent as the external phase. The system w/o/w on the other hand can extract contaminants from waste water, which acts as the external phase [7].

a) Controlled & Sustained Drug Delivery

The basic potential of ME's in clinical therapeutics is in the prolonged and controlled release of drugs. In both systems drug contained in innermost phase partitions through several phases prior to release at the site of absorption and the rate of release is governed by its ability to diffuse through various phases and cross interfacial barriers [4].

b) Enhancing Oral Bioavailability or Oral Absorption

The various drugs have been incorporated in Multiple Emulsions for the enhancement of the increase of Oral bioavailability from the stomach. For eg: Heparin, Insulin, Griseofulvin etc. The Griseofulvin's oral absorption was increased by forming W/O/W emulsion & which may lead to the enhancement of therapeutic effect of the drug [4].

c) 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. However, 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. For the application of W/O/W emulsions as drug delivery systems it is important to prepare a very stable W/O/W emulsion in which countless submicron water droplets are encapsulated. Higashi and coworkers prepared such a new drug delivery system for treating hepatocellular carcinoma (HCC) using W/O/W emulsions prepared with iodinated poppy-seed oil (IPSO) and water soluble epirubicin. The emulsion accumulates in the small vessels in the tumor when injected to the liver via the hepatic artery [6].

d) 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 [6].

e) 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. It was concluded that this multiple emulsion based vaccine can be successfully used in the effective control of haemorrhagic septicaemia [6].

f) 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. Hemoglobin multiple emulsion 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. A process is provided wherein hemoglobin, a fragile material, is formulated into high hemoglobin content water-in-oil-in-water multiple emulsions while maintaining high yields and high oxygen exchange activity [6].

g) 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 [6].

h) Multiple Emulsion in Diabetes

The S/O/W emulsion for oral administration of insulin has been developed by Toorisaka et al. 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 studied for their hypoglycemic properties [6].

i) Multiple Emulsion in Food

The ME's can also be used in Food industry. Sensitive food materials and flavors can be encapsulated in W/O/W emulsions. Sensory tests have indicated that there is a delayed release of flavor in double emulsions [6].

j) Drug over dosage treatment

ME's can be utilized for the over-dosage treatment by utilizing the difference in 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 [6].

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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