REVIEW ARTICLE

Technology, Recent Advancement, and Application of Multiple Emulsions: An Overview

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Abstract

Multiple emulsions are complex polydispersed organizations where both oil-in-water and water-in-oil emulsion are present simultaneously, which are stabilized by lipophilic and hydrophilic surfactants, respectively. To achieve stable multiple emulsions, the proportion of these surfactants is critical. Between the two types of multiple emulsions, water-in-oil-in-water (W/O/W) and oil-in-water-in-oil, the former has a wider range of applications and is thus investigated in more depth. Multiple emulsion development, preparation procedures, and *in vitro* evaluation methodologies have all been updated. Numerous elements impacting the stability of multiple emulsions, as well as stabilization strategies, are explored in detail, with a focus on W/O/W type multiple emulsions. Multiple emulsions are a possible carrier because they have desirable drug release mechanisms and rates, as well as a favorable *in vivo* fate. It has a wide range of uses, including regulated, targeted distribution, flavor masking, bioavailability augmentation, enzyme immobilization, and so on. In the microencapsulation process, several emulsions have also been regarded an intermediate phase. They are the systems of increasing interest for the oral delivery of hydrophilic drugs, which are unbalanced in the gastrointestinal tract such as proteins and peptides. It will provide a novel carrier system for the administration of pharmaceuticals, cosmetics, and medicinal agents as procedures for preparation, stabilization, and rheological characterization of multiple emulsions advance. Formulation, stabilization procedures, and prospective uses of various emulsion systems are all considered in this assessment.

Key words: Emulsifying agent, Membrane emulsification, Multiple emulsions

INTRODUCTION

Multiple emulsions are complicated systems known as "emulsions of emulsions", since the dispersed phase's droplets contain even smaller dispersed 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.[1-3] Multiple emulsions are also known as emulsions of emulsions, liquid membrane systems, or double emulsions.

The fundamental reason for adopting water-in-oil-in-water (W/O/W) and oil-in-water-in-oil (O/W/O) type multiple emulsions for delayed drug delivery is that the drug in the innermost phase is compelled to partition itself through several phases before being released at the absorption site. As a result, the drug's partition and diffusion coefficient, as well as the strength of the intermediate membrane phase, a multimolecular layer of oil, water, and emulsifier molecules at both interfaces of multiple emulsion systems, influence drug release.[4]

Multiple emulsion systems are a more complicated sort of dispersion system that is new breakthroughs in emulsion technology. The emulsion system in which the dispersed phase contains smaller droplets with the same composition as the exterior phase is known as multiple emulsions. Double emulsification enables this, which is why the systems are referred to as "double emulsions." Multiple emulsions, like simple emulsions, are divided into two categories:

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- O/W/O emulsion system
- W/O/W emulsion system

An aqueous (hydrophilic) phase separates the internal and external oil phases in O/W/O systems. To put it another way, O/W/O is a system in which water droplets can be engulfed by oil droplets, which, in turn, encloses one or more oil droplets. Internal and external aqueous phases are separated in W/O/W systems by an organic (hydrophobic) phase [Figure 1]. To put it another way, W/O/W is a system in which oil droplets are encircled by an aqueous phase, which then encloses one or more water droplets. Among the several emulsions, these are the ones that have been investigated the most. The liquid membrane is an immiscible oil phase that separates two miscible water phases and operates as a distinct barrier and semi-permeable membrane for the pharmaceuticals or moieties entrapped in the internal aqueous phase.

Emulsions are heterogeneous systems in which a single immiscible liquid is spread as droplets and stabilized by a third component known as an emulsifying agent. These two liquids are also chemically inert, resulting in systems with low thermodynamically stable stability. Emulsions are classified into two types based on how they are made: Simple emulsions and multiple emulsions.

SIMPLE EMULSION

It can be divided according to its continuous phase or dispersed phase as:

Oil-in-water emulsions (O/W)

Where oil is the disperse phase in a continuous phase of water.

Water-in-oil emulsions (W/O)

Where water is the disperse phase in a continuous phase of oil.[5]

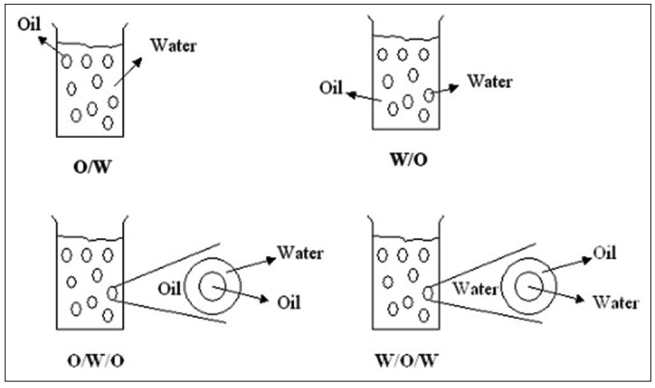

Figure 1: Multiple emulsion

MULTIPLE EMULSION

Multiple emulsions are more complex than their two-phase counterparts from formulation, stability, and drug release. They are a helpful tool in achieving sustained release drug delivery for different routes.[6]

The goal of this research is to create numerous emulsions with an additional reservoir that acts as an extra stage in partitioning the medication, effectively slowing the drug's release rate, and reducing dose frequency. Multiple emulsions are novel carrier systems complex and polydispersed where both W/O and O/W emulsions exist simultaneously in a single system.

These two emulsions are stabilized with lipophilic and hydrophilic surfactants, respectively. The dispersed phase droplets are sometimes known as "emulsions of emulsions" because they contain even smaller dispersed 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. Because the solute must cross from the inner miscible phase to the outer miscible phase through the middle immiscible organic phase in multiple emulsion systems, it is also known as a liquid membrane system.[7]

ADVANTAGES OF MULTIPLE EMULSIONS

- They have the ability to disguise the bitter taste and odor of medications, making them more pleasant
- For example, castor oil, cod liver oil, chloroquine phosphate, etc.
- They can be employed to extend the drug's release, resulting in a longer-lasting effect
- Essential nutrients such as carbohydrates, fats, and vitamins can all be emulsified and administered to bedridden patients as a sterile intravenous emulsion
- Emulsion protects drugs that are prone to oxidation and hydrolysis
- To aid diagnosis, intravenous emulsions containing contrast media have been produced
- Emulsions are commonly utilized in the formulation of externally applied products such as lotions, creams, and salves
- Improved gastrointestinal or dermal absorption.[6]

LIMITATIONS OF MULTIPLE EMULSIONS

The fundamental issue with multiple emulsions is their thermodynamic instability and complicated structure, which significantly limits their utility in a wide range of applications.[8]

TYPES OF MULTIPLE EMULSIONS

There are two major types of multiple emulsions:

W/O/W emulsion system

An organic (hydrophobic) phase separates the internal and external aqueous phases in the W/O/W system. To put it another way, W/O/W is a system in which oil droplets are encircled by an aqueous phase, which then encloses one or more water droplets as show in Figure 2.

O/W/O emulsion system

The internal and external oil phases of O/W/O systems are separated by an aqueous (hydrophilic) phase. In other words, O/W/O is a system in which one or more oil droplets are encircled by water droplets in the oil phase.[9]

The goals will be to develop a multiple emulsion system with a high production of numerous droplets carrying the medication entrapped in the innermost phase, as well as to ensure that the system is stable *in vitro* and has the appropriate release properties *in vivo*.[10]

FORMULATION OF MULTIPLE EMULSIONS

Florence and White Hil described three different types of multiple emulsions: A, B, and C. Only one substantial internal drop was contained in the secondary emulsion droplet in type A multiple emulsions. Several tiny interior droplets were included in the secondary emulsion droplet in type B emulsions, while several internal droplets were present in type C emulsions. Drug delivery and drug targeting are only possible with type C systems as show in Figure 3.[10]

Oil phase

In a pharmaceutical emulsion, the oil phase must be harmless. Vegetable oils (soybean, sesame, peanut, safflower, and so on) are suitable if filtered properly. In double emulsions, refined hydrocarbons such as light liquid paraffin, squalane, and fatty acid esters (ethyl oleate and isopropyl myristate) have been employed.[1] Biodegradable oils are generated from vegetable sources, whereas mineral oils are very slowly eliminated from the body.

Mineral oils created more stable multiple emulsions W/O/W than those made from vegetable oils in general.[2] Light liquid paraffin>squalane>sesame oil>maize or peanut oil are of diminishing stability and percentage entrapment.[11]

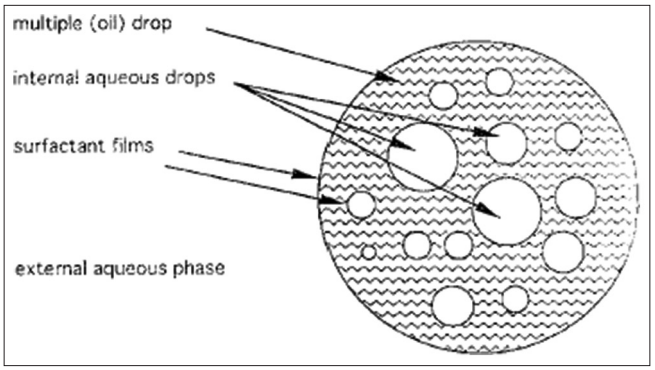

Figure 2: Schematic representation of a water-in-oil-in-water double emulsion droplet

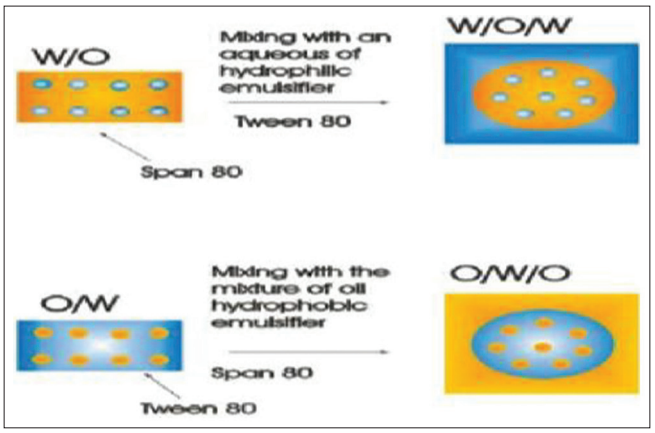

Figure 3: Schematic diagram of water-in-oil-in-water and oil-in-water-in-oil emulsions

Nature and quantity of emulsifying agents

Two different emulsifiers (lipophilic and hydrophilic) are required to form a stable emulsion. In general, the best HLB value for a W/O/W emulsion will be in the range 2–7 for the primary surfactant and 6–16 for the secondary surfactant. The concentration of the emulsifiers can also be varied. Too little emulsifier might create system instability, whereas too much emulsifier can induce harmful effects and even destabilization.[12] The inversion of a W/O/W emulsion to a simple O/W emulsion can be caused by an overabundance of lipophilic surfactant.

Phase volume

When formulating a stable multiple emulsions, the order of phase addition is critical, and the dispersed phase should be added slowly into the continuous phase. For the emulsion formulation, an appropriate internal phase volume (22–50%) can be used. It has also been observed that a high phase-volume ratio (70–90%) can yield a stable multiple emulsions.

PREPARATION METHOD OF MULTIPLE EMULSIONS

Multiple emulsions can be prepared by reemulsifying a main emulsion, or they can be produced when an emulsion inverts from one type to another, such as W/O to O/W. Because the internal dispersed phase of O/W emulsions is tiny, it is not used in medicines.[13]

Phase inversion technique or single-step technique

The creation of multiple emulsions can be caused by a rise in the dispersed phase volume, which causes an increase in the phase-volume ratio. The approach entails mixing an aqueous phase carrying a hydrophilic emulsifier (Tween 80/sodium dodecyl sulfate) with a liquid paraffin oil phase containing a lipophilic emulsifier (Span 80).

In a pin mixer vessel, a well-defined volume of the oil phase is placed. After that, at a rate of 5 ml/min, an aqueous emulsifier solution is added to the oil phase in the container. At the same time, at room temperature, the pin mixer rotates at 88 rpm.

When the aqueous solution's volume fraction approaches 0.7, the continuous oil phase is replaced by an aqueous phase containing a number of vesicular globules among the simple oil droplets, resulting in phase inversion and the creation of a W/O/W multiple emulsion as show in Figure 4.[5]

Two-step emulsification method (double emulsification)

It is the most widely used approach since it is simple and produces a high yield with great reliability. Reemulsification of a primary emulsion produces several emulsions. In this method two stages involved.

> Obtaining an ordinary W/O or O/W primary emulsion wherein an appropriate emulsifier system is utilized.

The freshly prepared W/O or O/W direct emulsion is reemulsified with an excess of the aqueous phase or oil phase. The final prepared emulsion could be W/O/W or O/W/O, respectively as show in Figure 5.[2]

Modified two-step emulsification technique

In two ways, this procedure differs from the traditional two-step method. To create a good, homogeneous, and stable W/O emulsion, sonication and stirring are used. To make a W/O/W emulsion, a continuous phase is poured into a dispersed phase. The ratio of internal aqueous phase to oily phase to exterior phase is set at 1:4:5, resulting in the most stable formulation observed for most W/O/W emulsions as show in Figure 6.[9]

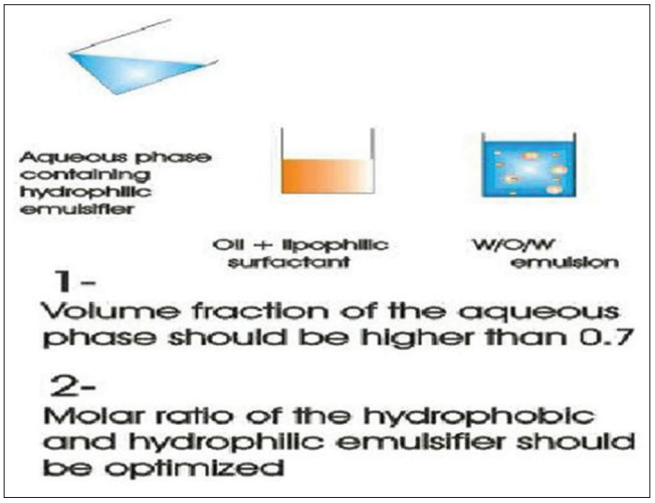

Figure 4: Phase inversion technique (one-step method)

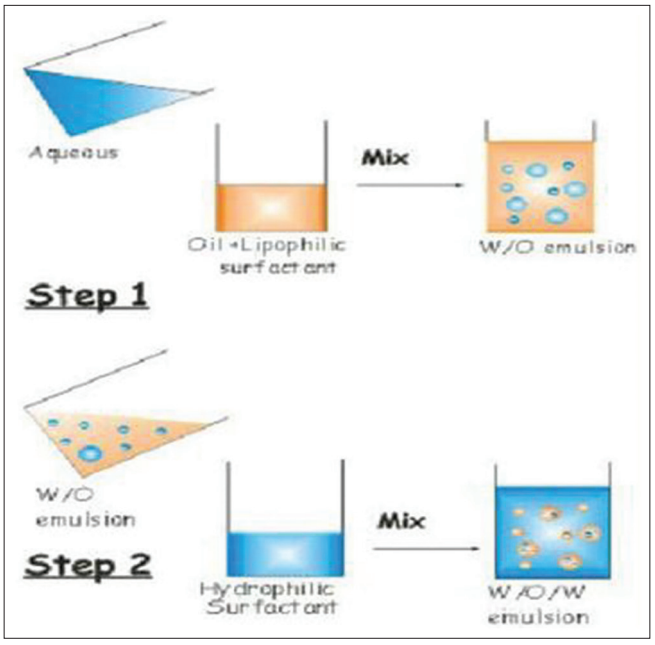

Figure 5: Two-step emulsification method

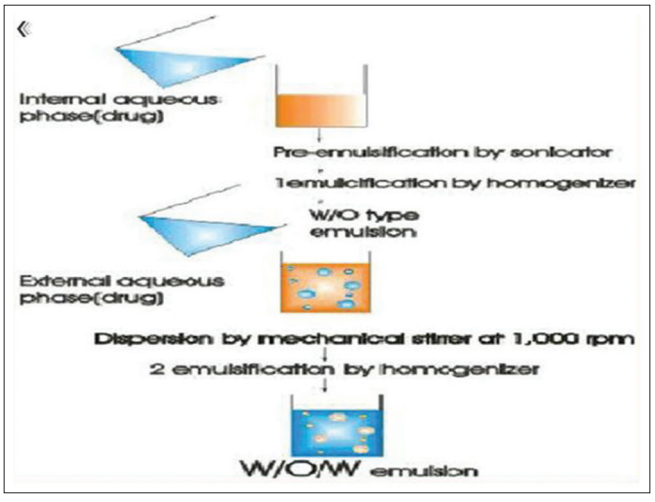

Figure 6: Modified two-step emulsification technique

Membrane emulsification technique

In this process, a W/O emulsion (dispersed phase) is extruded at a consistent pressure into an external aqueous phase (continuous phase) through a porous glass membrane with regulated and homogeneous pores. With the right porous glass membrane, the particle size of the W/O/W emulsion can be regulated. The relationship between membrane pore size and emulsion particle size demonstrates a strong correlation, as shown by the formula:

$$Y= 5.03X + 0.19$$

Where,
X= the pore size
Y= the mean particle size

A microporous glass membrane with narrow pore size range was used successfully for preparing stable simple O/W and W/O/W type emulsions.[14-16]

Microchannel emulsification

Using a standard homogenizer, the emulsion was created by first homogenizing a mixture of water and oil phases. The resultant W/O emulsion was then driven into a second water phase containing a suitable emulsifier for oil phase stabilization through the microchannel device.[14,15]

STABILITY OF MULTIPLE EMULSIONS

Multiple emulsion stability is a phenomenon that occurs when water, oil, and surfactant are in equilibrium. Multiple emulsions, unfortunately, are thermodynamically unstable. Instability can manifest itself in a variety of ways: [5]

- The contents of the inner aqueous phase are leaking out
- Expulsion of internal droplets in the external phase
- Internal droplet constriction or distension caused by an osmotic gradient across the oil membrane
- Flocculation of the inner aqueous phase and multiple emulsion droplets
- Disruption of the oil layer on the surface of internal droplets
- Phase separation.

FACTOR AFFECTING STABILITY OF MULTIPLE EMULSION NATURE OF ENTRAPPED MATERIAL

When formulating a W/O/W system, the drug and other components (especially electrolytes) need to be considered. The nature of the drug (hydrophilic or hydrophobic) also is considered. Due to the nature of the multiple emulsions, the middle phase acts as a membrane, and osmotic effects may become significant. The entrapped solutions may interact with the surfactant, or the surface-active drugs may be adsorbed at the interphase, resulting in decreased stability.[3]

Shear/agitation

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

Temperature

The temperature has only an indirect effect on emulsification attributed to its impact on viscosity, surfactant adsorption, and interfacial tension. In general, the primary emulsion formulation temperature is kept at 70°C, whereas for multiple emulsion preparations, it is held at 10°C. Significant temperature variations during manufacturing, storage, transport, and use lead to drastic modifications within emulsions.

Rheology

The rheological properties of emulsions are influenced by several factors, including the nature of the continuous phase, the phase-volume ratio, and to a lesser extent by particle size distribution. For low internal phase-volume emulsions, the consistency of the emulsion similar to the continuous phase; thus, O/W/O emulsions are generally thicker than W/O/W emulsions, and the addition of gums and clays can increase the thickness of a W/O/W system.

Effect of lipophilic emulsifier

As the concentration of lipophilic surfactant increases, the swelling capacity of the oil globule is increased, 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 of an increase of the rigidity of the second interface by the progressive migration of the lipophilic surfactant. During the second step of multiple emulsion preparations, lipophilic surfactant molecules can diffuse from the first to the second interface, producing a synergistic effect resulting in membrane strengthening. The second one involves a delay in the aqueous droplet coalescence. In the course of swelling of the oil globule, the lipophilic surfactant molecules, which are in excess in the oily phase, can diffuse to the first interface to fill up free spaces caused by swelling when required.[17]

Added stabilizing components

The stabilizers are added to improve the stability of multiple emulsions. These include gelling or viscosity increasing agents added to internal and 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% aluminum monostearate).[2]

METHODS TO STABILIZE MULTIPLE EMULSIONS

Some of the attempts or studies to repair or strengthen the stability of numerous emulsions are listed below: [7]

- Multiple emulsions were stabilized using liquid crystals
- Stabilization when electrolytes are present
- Formation of a polymeric coating for stabilization
- Interfacial complexation of non-ionic surfactant and macromolecules for stabilization
- Steric stabilization
- W/O/W emulsion phase inversion stabilization.

By lowering internal aqueous droplet coalescence, interfacial complexation increases the stability of W/O/W emulsions. Physical interaction between a non-ionic lipophilic surfactant (present in the oil phase) and a macromolecule (e.g. bovine serum albumin and gelatin) present in the internal aqueous phase of the W/O/W emulsion[17-20] is referred to as interfacial complexation. This complex interfacial forms at the primary W/O contact and takes the shape of a tough membrane that grows overtime.[18,20] Solutes are released slowly from such a mechanism.

The formation of a polymeric gel in the internal or external aqueous phase of W/O/W emulsions gives these systems good stability.[21-23] The gel can be generated by *in situ* polymerization or by adding a gelling agent to the two aqueous phases.[22,23] Using gamma radiation may effect crosslinking between gelling agent molecules in either the aqueous or solid phases. Gelling provides stability by preventing the coalescence of numerous droplets (by gelling the external aqueous phase) and preventing the coalescence of internal aqueous droplets (by gelling the inner aqueous phase) (by gelling the internal aqueous phase). To minimize creaming and coalescence of numerous droplets in a W/O/W system, a viscosity enhancer (such as hydroxypropylmethylcellulose, polyvinyl pyrrolidone, acacia, and gelatin) can be added to the two aqueous phases.[2,24,25]

Several research has suggested using hypertonic inner aqueous phase to reduce (or delay) aqueous phase separation from W/O/W emulsions.[26-29] The proportion of solute entrapment in the internal aqueous phase of W/O/W emulsions rose as the concentration of solute (glucose or sodium chloride) in the inner aqueous phase increased. The aqueous phase separation was delayed in these emulsions, and the proportion entrapped decreased less with time. The thickening of the oil membrane acts as a stabilizing mechanism. Because of the high viscosity of these emulsions, flocculation and phase separation are delayed. To combat osmotic instability, judicious use of osmotic additives in the internal or external aqueous phase, as required by the system, can be done.[30] The addition of osmotic agents to the external aqueous phase to correct osmotic imbalance also results in drug release from W/O/W emulsions.[31,32] Creaming can be reduced by adjusting the density difference between the oil and aqueous phases. They mixed lipiodol ultrafluid with isopropyl myristate to create a combination with the same density as water.

BEHAVIOUR OF MULTIPLE EMULSIONS IN BIOLOGICAL SYSTEM

Multiple emulsions have been administered by oral, parenteral (i.v., i.m., and s.c.), and topical routes (nasal, ocular, and transdermal) routes. After oral administration, ME is almost absorbed entirely from the lymphatic pathway associated with intestinal lipoproteins, namely, chylomicrons, produced by enterocytes. They may directly be absorbed through the intestinal macrophage system and Peyer's patches to gain access into mesenteric lymph from where they are drained into circulation through the thoracic lymph duct. Thus, they can carry bioactives within them, avoiding degradation in the intestine and the liver. After parenteral (iv. or im) administration, the emulsions are readily taken up by the circulatory macrophage system to lymphatics and liver into the fat metabolism pathway. Other parenteral routes allow emulsion droplets to reach neighboring lymphatic nodes through the interstitial spaces of lymphatic arteries, which are more porous than blood capillaries with strong intracellular connections.[5]

POSSIBLE MECHANISM OF DRUG RELEASE FROM MULTIPLE EMULSIONS

A separate method is used in multiple emulsions to release the medicine from the internal to the exterior phase through the oily layer. Droplet size, pH, phase volume, and viscosity, among other things, have an impact on release rates. The different mechanisms are:

Diffusion mechanism

When a unionized hydrophobic medication diffuses through the oil layer in a stable multiple emulsions, this is the most typical transport method. It was discovered that drug transport followed first-order kinetics and obeyed Fick's law of diffusion.

Micellar transport

Because of the exterior lipophilic character, inverse micelles with a non-polar surfactant component on the outside and a polar component on the interior encapsulate the hydrophilic medication in the core and pass through the oil membrane. Both ionized and unionized medicines can be encapsulated in inverse micelles.

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

Thinning of the oil membrane

Due to the osmotic pressure difference, the oil membrane became thin, so the water and drug quickly diffused. This pressure differential also acts as a force on the molecule's transverse motion.

Rupture of oil phase

According to this mechanism rupturing of oil, the membrane can unite both aqueous phases, and thus, drug could be released quickly.

Facilitated diffusion (carrier-mediated transport)

This process entails the use of a specific molecule (carrier) that binds to the medicine and allows it to pass across the oil membrane. The internal aqueous phase or oil membrane can be used to carry these carriers.

Photo-osmotic transport

This transport process mechanism is not entirely clear. The medicine is transported across the oil membrane with the help of light.

Solubilization of internal phase in the oil membrane

It is a conspicuous transport mechanism. This solubilization of minute amounts of the internal phase in the membrane phase results in the transport of minimal quantities of materials.[7]

EVALUATION OF MULTIPLE EMULSIONS

Average globule size and size distribution

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

Various other techniques used to characterize colloidal carriers 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 emulsions. Recently, NMR self-diffusion methods are adapted to multiple emulsion characterization.

Area of interfaces

The formula below can be used to calculate the total area of the interface using the average globule diameter determined:

$$S = 6/D$$

Where,
S = Total area of interface (sq.cm)
D = Diameter of globules (cm)

Number of globules

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

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

Rheological evaluation

When it comes to emulsion stability and clinical performance, the rheology of multiple emulsions is a crucial characteristic to consider. Two important metrics that describe product rheology are viscosity and interfacial elasticity.

The viscosity of the multiple emulsions

Brookfield rotational viscometer can be used to measure it. Using an appropriate spindle, samples are sheared for 1 min at 100 rpm.

Interfacial rheology

An oscillatory surface rheometer can be used to explore interfacial rheology (i.e. interfacial elasticity at the oil aqueous contact) at the mineral oil/water interface.

Zeta potential

The zeta potential measurements are pivotal in the designing of surface modified or ligand anchored multiple emulsion systems. The zeta potential and surface charge can be calculated using Smoluchowski equation from the mobility and electrophoretic velocity of dispersed globules using the zeta potentiometer. Zeta potential was calculated using the following formula:

$$\zeta = 4\pi\eta\mu \times 103$$

εE

Where,

ζ = Zeta potential (mV)

η = Viscosity of the dispersion medium (poise)

μ = Migration velocity (cm/s)

ε= Di electric constant of the dispersion medium

E = Potential gradient (voltage applied/distance b/w electrodes)

Percentage drug entrapment

Dialysis, centrifugation, filtration, and conductivity assays are commonly used to quantify the percentage of drug or active moiety entrapment in various emulsions. An internal tracer/marker was recently used to assess the trapping of an impermeable marker molecule in the W/O/W emulsion's inner aqueous phase. The unentrapped marker is determined, and the quantity trapped is determined by subtracting the unentrapped amount from the initially added amount.

In vitro drug release

Using the traditional dialysis procedure, the medication released from the aqueous inner phase of a W/O/W emulsion can be measured. The W/O/W emulsion was dialyzed against 200 ml of phosphate saline buffer pH 7.4 at 371°C with a sink condition maintained. The contents of the sink, on the other hand, were continuously swirled using a magnetic stirrer. The data were utilized to compute cumulative drug release profiles after aliquots were withdrawn at varied time intervals and approximated using normal technique.

APPLICATIONS OF MULTIPLE EMULSIONS

Because the oil layer between the two aqueous phases can act as a membrane controlling solute release, the most potential use of multiple emulsions is in the area of sustained release medication formulation. To separate hydrocarbons, liquid membrane emulsions of the O/W/O type have been utilized, with the aqueous phase acting as the membrane and a solvent acting as the exterior phase. In contrast, the W/O/W system may extract pollutants from wastewater, which serves as the exterior phase.[7]

Controlled and sustained drug delivery

In clinical treatments, the primary promise of multiple emulsions (both W/O/W and O/W/O) is the extended and controlled release of medicines. The drug in the innermost phase of both systems must pass through multiple steps before it can be absorbed by the system. Because of their decreased viscosity, W/O/W emulsions for parenteral distribution are easier to handle, utilize, and inject.

Enhancing oral bioavailability or oral absorption

To improve oral bioavailability from the stomach, several medications have been included in multiple emulsions. Heparin, insulin, griseofulvin, and other similar drugs are examples. The oral absorption of griseofulvin was enhanced by generating a W/O/W emulsion, which could improve the drug's therapeutic impact.[5]

Multiple emulsions in cancer therapy

Because most anticancer medicines are water soluble, they are employed as emulsions. It is feasible to manage the rate of drug release and decrease the drug's severe adverse effects using an emulsion. However, because W/O emulsions have such a high viscosity, infusion of emulsions into arteries and capillaries through catheters is difficult. Furthermore, because O/W emulsions do not encapsulate the drug, they are not an alternative. W/O/W emulsion systems, on the other hand, are good drug carriers because the drug is encapsulated in the internal water phase and the external water phase has a low viscosity. It is necessary to construct a very stable W/O/W emulsion in which countless submicron water droplets are trapped before using W/O/W emulsions as drug delivery systems. Higashi *et al*. used W/O/W emulsions made with iodinated poppy seed oil and water-soluble epirubicin to develop a novel drug delivery strategy for treating hepatocellular carcinoma. When injected into the liver through the hepatic artery, the emulsion collects in the tumor's tiny arteries.[7]

Multiple emulsions in herbal drugs

Producing the herbal medication as an emulsion will increase the stability of the hydrolyzed components, improve drug penetrability through the skin and mucous, and lessen the drug's stimulus to tissues, in addition to providing targeted, prolonged release. Some herbal medications have been made into emulsions so far, including camptothecin, *Brucea javanica* oil, coixenolide oil, and zedoary oil.[7]

Inverse targeting

Talegaonkar and Vyas used this method to create a poloxamer 403 containing sphere in an O/W (S/O/W) multiple emulsion

of diclofenac sodium by gelatinization of the inner aqueous phase, and they investigated the effect of poloxamer 403 on surface modification for inverse targeting to organs with a reticuloendothelial system (RES). According to the findings, this multiple emulsion system including poloxamer has the ability to reduce medication RES uptake primarily in the liver and brain while also targeting non-RES tissues such as the lungs and inflammatory tissue.[33]

Vaccine adjuvant

Herbert was the first to report the use of W/O/W multiple emulsion as a new type of antigen adjuvant.[34] The immunological response induced by these emulsions was superior to that elicited by antigen alone.[35] *Pasteurella multocida* infection in cattle was treated with a multiple emulsion vaccination. To protect against the disease, this vaccination elicited both humoral and cell-mediated immune responses. These multiple emulsion-based vaccines might be successfully used in the effective management of hemorrhagic septicemia, according to the findings. Multiple W/O/W emulsion formulations containing influenza virus surface antigen hemagglutinin have recently been developed and described in Wistar albino rats *in vitro* and *in vivo*. For assessing hemagglutinin and *in vitro* antigen release, the SDS-PAGE technique was used. Results suggested that multiple emulsion formulations carrying influenza antigen have an advantage over conventional preparation and can be effectively used as one of the vaccine delivery systems with adjuvant properties. The same researchers determined in another study that several emulsion and nanoparticle formulations carrying influenza virus surface antigen hemagglutinin were more effective than the traditional vaccine in generating an immunological response in rats.[36-40]

Oxygen substitute

The provision of oxygen for oxygen transfer operations can be accomplished with a multiple emulsion of aqueous oxygen-carrying substance in oil in the outer aqueous phase. Insufficiently small droplet size hemoglobin numerous emulsions in physiologically suitable oil in an external aqueous saline solution are provided to facilitate oxygen passage through blood vessels to desired bodily tissues or organs, hence producing a blood replacement. A method for converting hemoglobin, a fragile substance, into high hemoglobin content W/O/W multiple emulsions with high yields and high oxygen exchange activity is described.[7]

Multiple emulsion for local immunosuppression

A potential approach to avoid the complication of systemic immunosuppression and simultaneously enhance immunosuppressive agents locally to the site of the target organs. W/O/W multiple emulsion has been developed for the delivery of immunosuppressants.

Bioavailability enhancer

Multiple emulsions have also been used to improve the bioavailability of lipophilic drugs, which have high first-pass metabolism. Multiple emulsions boost drug bioavailability by protecting pharmaceuticals in the GITs physiological, ionic/enzymatic milieu, where they would otherwise be destroyed, such as proteins and peptides, or by bypassing hepatic first-pass metabolism.

Enzyme immobilization

Multiple emulsions can be used to carry out enzyme conversion of water insoluble, highly lipophilic substrates like steroids. The enzyme is contained in a microdroplet "water pool," while the substrate solution is contained in the organic phase. Urease has been immobilized using hydrocarbon-based liquid surfactant membranes, for example.

Multiple emulsion in diabetes

Mullaicharam *et al*. created the S/O/W emulsion for insulin administration by mouth. Ultrasonication was used to distribute surfactant-coated insulin in the oil. With the help of a homogenizer, this dispersion was combined with the outer water phase, and the resulting S/O/W emulsion was tested for hypoglycemic characteristics.[7]

Multiple emulsion in food

In the food sector, multiple emulsions can be utilized. W/O/W emulsions can encapsulate sensitive food ingredients and tastes. Sensory experiments have revealed that taste release in double emulsions is delayed.[7]

Drug over dosage treatment

This technique could be used to treat overdosage with the use of a pH differential, such as barbiturates. The principal buffer in these emulsions is the inner aqueous phase of the emulsion. When the emulsion is swallowed, the stomach's acidic pH functions as an exterior aqueous phase. Barbiturate is mostly unionized in the acidic phase, where it passes through the oil barrier into the inner aqueous phase and is ionized. Ionized drugs have a lower propensity for crossing the oil barrier, resulting in entrapment. Overdosage is thus cured by encapsulating the extra medicine in numerous emulsions.[41-42]

Taste masking

Multiple chloroquine emulsions, an antimalarial drug, have been successfully made and proven to effectively disguise the bitter taste.[43-46] Taste masking of chlorpromazine, an antipsychotic drug, has also been reported by multiple emulsions.

CONCLUSIONS

The multiple emulsions are one of the advanced drug delivery systems for improving the various characteristics of the drugs such as bioavailability, taste, and release rate. The advances include different novel formulations for the betterment of the drug administration and 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 such as taste masking, sustained release, delivering the dangerous drug, and prevention of the drug from the environment.

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REFERENCES

1. Davis SS, Hadgraft J, Palin KJ. In: Becher P, editor. Encyclopedia of Emulsion Technology. Vol. 2. New York: Marcel Dekker; 2005. p. 159.
2. Florence AT, Whitehill D. Stabilization of water/oil/water multiple emulsions by polymerization of the aqueous phases. J Pharm Pharmacol 1982;34:687-91.
3. Florence AT, Whitehill D. Some features of breakdown in water-in-oil-in-water multiple emulsions. J Colloid Interface Sci 1981;79:243-56.
4. Sinha VR, Kumar A. Multiple emulsions an overview of formulation, characterization, stability and applications. Indian J. Pharm Sci 2002;64:191-9.
5. Vyas SP, Khar RK. Targeted and Controlled Drug Delivery Novel Carrier Systems. 1st ed. New Delhi: CBS Publishers and Distributors; 2002. p. 303-30.
6. Khokra SL, Parashar B, Dhamija HK, Kumar K, Arora S. Formulation and evaluation of novel sustained release multiple emulsion containing chemotherapeutic agents. Int J PharmTech Res 2012;4:866-72.
7. Lachman L, Lieberman HA. The Theory and Practice of Industrial Pharmacy. New Delhi: CBS Publishers and Distributors; 2009. p. 502-32.
8. Mullaicharam AR, Qasmi MA. Preparation and evaluation of prolonged emulsions. Int J Inst Pharm Life Sci 2012;2:22-9.
9. Vyas SP, Khar RK. Targeted and Controlled Drug Delivery Novel Carrier Systems. 1st ed. New Delhi: CBS Publishers; 2004.
10. Rajesh K, Murugesan K, Nanjaian M. Multiple emulsion: A review. Int J Recent Adv Pharm Res 2012;2:9-19.
11. Prajapati SB, Bhatt H, Koli A, Dharamsi A, Shah SA. An overview of preparation, evaluation and applications of multiple emulsions. Int J Pharm Res Schl 2013;2:142-50.
12. Davis SS, Walker I. Measurement of the yield of multiple emulsion droplets by a fluorescent tracer technique. Int J Pharm 1983;17:203-13.
13. Nimberkar TP, Wanjari BE, Sanghi DK, Gaikwad NJ. Formulation and evaluation of sustained release multiple emulsion of hydroxprogesterone. Int J Pharm Pharm Sci 2012;4:76-80.
14. Vasiljevic D, Parojcic J, Primorac M, Vuleta G. An investigation into the characteristics and drug release properties of multiple W/O/W emulsion systems containing low concentration of lipophilic polymeric emulsifier. Int J Pharm 2006;309:171-7.
15. Garti N. Double emulsions scope, limitation and new achievements. Colloids Surf A Physicochem Eng Aspects 1997;123-124:233-46.
16. Lin TH, Lin SY. Encapsulation and prolonged release behaviour of w/o/w type multiple emulsions. J Chin Chem Soc 1988;35:463-70.
17. Khan AY. Potentials of Liquid Membrane System: An Overview. Vol. 5. Pharmainfo; 2007.
18. Omotosho JA, Law TK, Whateley TL, Florence AT. Colloid. Surfaces 1986;20:133.
19. Law TK, Florence AT, Whateley TL. Release from multiple W/O/W emulsions stabilized by interfacial complexation. J Pharm Pharmacol 1984;36:2-10.
20. Gaiti N, Aserin A, Cohen Y. Mechanistic considerations on the release of electrolytes from multiple emulsions stabilized by BSA and nonionic surfactants. J Controll Release 1994;29:41-51.
21. Nakhare S, Vyas SP. Preparation and characterization of multiple emulsion based systems for controlled diclofenac sodium release. J Microencapsul 1996;13:281-92.
22. Nakhare S, Vyas SP. Prolonged release of rifampicin from internal phase of multiple w/o/w emulsion systems. Indian J Pharm Sci 1995;57:71.
23. Florence AT, Whitehill D. Multiple w/o/w emulsions stabilised with poloxamer and acrylamide gels. J Pharm Pharmacol 1980;32 Suppl):64.
24. Roy S, Gupta BK. *In vitro-in vivo* correlation of indomethacin release from prolonged release w/o/w multiple emulsion system. Drug Dev Ind Pharm 1993;19:1965-80.
25. Omotosho JA. The effect of acacia, gelatin and polyvinylpyrrolidone on chloroquine transport from multiple w/o/w emulsions. Int J Pharm 1990;62:81-4.
26. Vaziri A, Warburton B. Improved stability of w/o/w multiple emulsions by addition of hydrophilic colloid components in the aqueous phases. J Microencapsul 1995;12:1-5.
27. Matsumoto S. Methods for preparing liquid/liquid type multiple-phase dispersions. J Soc Cosmet Chem Jpn 1978:31:12(1):5-12.
28. Adeyeye CM, Price JC. Effect of dextrose in the internal aqueous phase on formation and stabiblity of W/O/W multiple emulsions. Drug Dev Ind Pharm 1990;16:1053-71.

29. Matsumoto S, Inoue T, Kohda M, Ikura K. Water permeability of oil layers in W/O/W emulsions under osmotic pressure gradients. J Colloid Interface Sci 1980;77:555-63.
30. Kawashima Y, Hino T, Takeuchi H, Niwa T. Stabilization of water/oil/water multiple emulsion with hypertonic inner aqueous phase. Chem Pharm Bull 1992;40:1240.
31. Collings AJ. British Patent No. 1235667; 1971.
32. Mishra B, Pandit JK. Multiple water-oil-water emulsions as prolonged release formulations of pentazocine. J Controll Release 1990;14:53-60.
33. Rajesh K, Murugesan K, Nanjaian M. Multiple emulsions: A review. Int J Recent Adv Pharm Res 2012;2:9-19.
34. Vladisavljevic GT, Williams RA. Recent developments in manufacturing emulsions and particulate products using membranes. Adv Colloid Interf Sci 2005;113:1-20.
35. Talegaonkar S, Vyas SP. Inverse targeting of diclofenac sodium to reticuloendothelial system rich organs by sphere-in-oil-in-water (s/o/w) multiple emulsions containing poloxamer 40. J Drug Target 2005;13:173-8.
36. Herbert WJ. Multiple emulsions. A new form of mineral-oil antigen adjuvant. Lancet 1965;11:771.
37. Verma R, Jaiswal TN. Protection, humoral and cell mediated immune responses in calves immunized with multiple emulsion haemorragic septicaemia vaccine. Vaccine 1997;15:1254-60.
38. Omotosho JA, Whateley. TL, Florence AT. vgb Methotrexate transport from internal phase of multiple w/o/w emulsion. J Microencap 1989;6:183.
39. Kita Y, Matsumoto S, Konezawa D. An attempt at measuring the stability of w/o/w type multiple phase emulsions by analysing the concentrationof ions. Nippon Yaguku Kaishi 1978;11:14.
40. Okochi H, Nakano M. Preparation and evaluation of W/O/W type emulsions containingvancomycin. Adv Drug Del Rev 2000;45:5.
41. Bozkir A, Hayta G. Aration and evaluation of multiple emulsions water-in-oil-in-water (w/o/w) as delivery system for influenza virus antigens. J Drug Target 2004;12:157-64.
42. Ma GH, Sone H, Omi S. Preparation of uniformsized polystyrene polyacrylamide composite microspheres from a W/O/W emulsion by membrane emulsification technique and subsequent suspension polymerization. Macromolecules 2004;37:2954.
43. Akram W, Joshi R, Garud N. Inulin: A promising carrier for controlled and targeted drug delivery system. J Drug Deliv Ther 2019;9:437-41.
44. Bozkir A, Hayta G, Saka OM. Comparison of biodegradable nanoparticle and multiple emulsion containing influenza virus antigen on the *in vivo* immune response in rats. Pharmazie 2004;59:723-5.
45. Chiang CW, Fuller GC, Frankenfeld JW, Rhodes CT. Potential use of liquid membranes for drug overdose treatment: *In vitro* studies. J Pharm Sci 1978;67:63-6.
46. Florence AT, Omotosho JA, Whateley TL. In: Morton R, editor. In Controlled Release of Drugs: Polymers and Aggregated Systems. New Jersey, USA: VCH Publishers; 1989. p. 163-83.

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