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Review Article

Recent advancements and applications of multiple emulsions

Anisha Agrawal*, Sunisha Kulkarni, Shyam Bihari Sharma

School of Studies in Pharmaceutical Sciences, Jiwaji University, Gwalior, Madhya Pradesh, India

***Correspondence Info:**
Anisha Agrawal,
School of Studies in Pharmaceutical Sciences, Jiwaji University, Gwalior, Madhya Pradesh, India
Email: anisha.agrawal374@gmail.com

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Abstract

Multiple emulsions are complex polydispersed systems where both oil-in-water and water-in-oil emulsions exists simultaneously, stabilized by lipophilic and hydrophilic surfactants respectively. These emulsions are also known as emulsions of emulsions, liquid membrane system or double emulsions. Multiple emulsions can be classified into two types, namely water-in-oil-in-water (W/O/W) and oil-in-water-in-oil (O/W/O) emulsions. These emulsions find wide range of applications in controlled and sustained drug delivery, targeting of bioactives, vaccine adjuvants, delivery of proteins and peptides, enzyme immobilization, taste masking and treatment of drug overdose. The aim of this article was to provide a detailed review of types, preparation methods, formulation approaches, evaluation parameters, release mechanisms and applications of multiple emulsions.

1. Introduction

Multiple emulsions are novel carrier systems which are complex, polydispersed, multiphase systems consisting of at least two immiscible liquids i.e., both w/o and o/w emulsions exists simultaneously in a single system. Lipophilic and hydrophilic surfactants are used for stabilizing these two emulsions respectively. The droplets of dispersed phase contain even smaller dispersed droplets themselves, thus also called as **"emulsions of emulsions"**. The inner dispersed droplets in multiple emulsions are separated from outer liquid phase by a layer of another phase [1].

The solute has to transverse from inner miscible phase to outer miscible phase via middle immiscible organic phase, prior to release at absorption site, thus also known as **liquid membrane system**. Partition and diffusion coefficient of drug and strength of middle membrane phase, which is a multimolecular layer of oil, water and emulsifier at both the interfaces of multiple emulsion, controls the drug release from these systems. This extends the classical definition to include **"liquid droplets and/or liquid crystals dispersed in liquid"** [2]. These are heterogeneous preparation composed of two immiscible liquids, i.e. oil and water, one of which is dispersed as fine droplets uniformly throughout the other. The phase presented as small droplets are called **dispersed, discontinuous** or **internal phase** and the supporting liquid is known as **continuous** or **external phase**. Droplet diameter in multiple emulsions may range from 0.1 to 100 µm. It consists of large and poly dispersed droplets that are thermodynamically unstable with a strong tendency for coalescence, flocculation and creaming. This may lead emulsions to reverse back to separate oil and water phase by fusion or coalescence of droplets, thus it is required to add third component which kinetically stabilizes multiple emulsions, known as **emulsifying agent**/**emulsifier**.

Multiple emulsions are prepared from oil and water by emulsification of an existing emulsion so as to provide two dispersed phases. These emulsions have promising applications in various fields such as chemistry, pharmaceutics, cosmetics etc., and have also been investigated as controlled-release drug delivery systems (DDS), as **'emulsion liquid membranes'** for various applications [3]. These may be used as intermediate products in preparation of inorganic particles, lipid nanoparticles, polymeric microspheres, biodegradable microspheres, gel microbeads and vesicles such as polymerosomes. Many potential pharmaceutical applications for multiple emulsions are aimed for slow and sustained release of active matter from an internal reservoir into continuous phase. They can also serve as an internal reservoir to entrap matter from outer diluted continuous phase into inner confined space. The active matter will dissolve in part in inner phase, in part at the internal and occasionally at external interface. Protection of sensitive and active molecules from oxidation in external phase can also be observed [1].

1. Types

Based on nature of dispersed medium multiple emulsions are of two types, oil-in-water-in-oil (O/W/O) and water-in-oil-in-water (W/O/W). The most common multiple emulsions are W/O/W type; however for some specific applications O/W/O emulsions can also be used [4].

1.1 W/O/W emulsion system:

In W/O/W system, an organic phase (hydrophobic) separates internal and external aqueous phases. In other words, W/O/W is a system in which oil droplets may be surrounded by an aqueous phase, which in turn encloses one or more water droplets. The immiscible oil phase, which separates two miscible aqueous phases is known as "liquid membrane" and acts as a diffusion barrier and semipermeable membrane for the drugs or moieties entrapped in internal aqueous phase.

1.2 O/W/O emulsion system:

In O/W/O system, an aqueous phase (hydrophilic) separates internal and external oil phase. In other words, O/W/O is a system in which water droplets may be surrounded in oil phase, which in turn encloses one or more oil droplets.

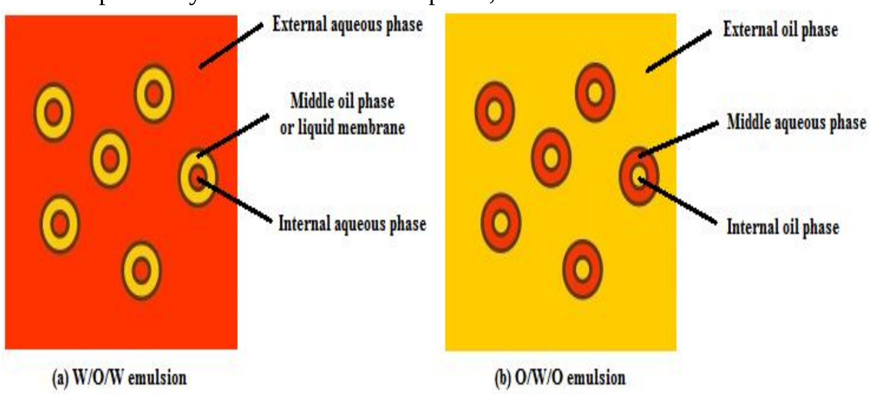

Figure 1: Types of Multiple Emulsions [5]

Advantages [4]**:-**

1. Masks bitter taste and odor of drugs, thereby making them more palatable.
2. Prolongs release of drug, thereby providing sustained release action.
3. Essential nutrients like carbohydrates, fats and vitamins can all be emulsified.
4. Can be administered to bed ridden patients as sterile intravenous emulsions.
5. Provides protection to drugs which are susceptible to oxidation or hydrolysis.
6. Enhancement of enteric or dermal absorption.
7. Hydrophilic as well as hydrophobic drugs can be entrapped.
8. Enhances bioavailability and thus increase in drug dosing intervals.

Disadvantages:-

1. Thermodynamically unstable, have complex structure, which leads to short shelf life of product.
2. These are packaged in a plastic/glass container, so care should be taken in handling and storage.

2. Methods of Preparation

Multiple emulsions can be formed by re-emulsification of a primary emulsion or they can be produced when an emulsion inverts from one type to another, for e.g.: W/O to O/W. The various methods of preparation of multiple emulsions are as follows –

2.1 Two-step emulsification

Multiple emulsions may be prepared by re-emulsification of primary emulsion using a suitable emulsifier agent. The first step involves preparation of primary emulsion W/O or O/W where an appropriate emulsifier system is utilized.

Then, the freshly prepared W/O or O/W primary emulsion is further re-emulsified with an excess of aqueous phase or oil phase. The finally prepared emulsion could be W/O/W or O/W/O respectively [2].

In this case, lipophilic surfactant is used to promote formation of W/O emulsion. This emulsion is then poured into solution or dispersion of secondary surfactant in water. Secondary surfactant in this case, is hydrophilic to promote O/W emulsification in which oil phase is the W/O emulsion. The second emulsification step is crucial as it can lead to fracture of internal globules forming simple emulsion of either W/O or O/W type depending on number of factors, such as nature and quantity of emulsifying agent. These have been previously used to enhance stability of ascorbic acid and vitamin A [7].

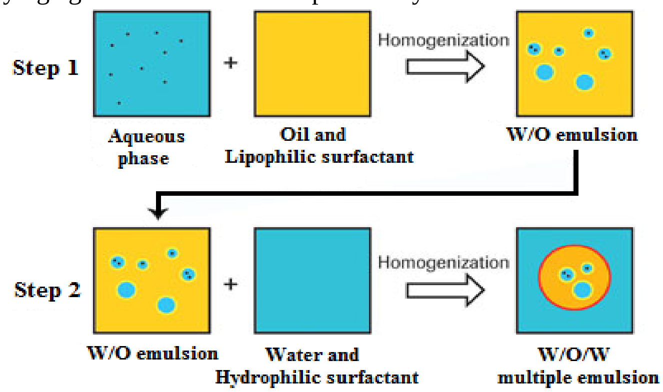

Figure 2: Two-step emulsification method [6]

2.2 Modified two-step emulsification

This method is different from conventional two-step technique in following two points: Sonication and stirring are used to obtain fine, homogenous and stable W/O emulsion; a continuous phase is poured into dispersed phase for preparing W/O/W emulsion. Moreover, the composition of internal aqueous phase-oily phase-external aqueous phase is fixed at 1:4:5, which produce most stable formulation as reported for most W/O/W emulsion [2].

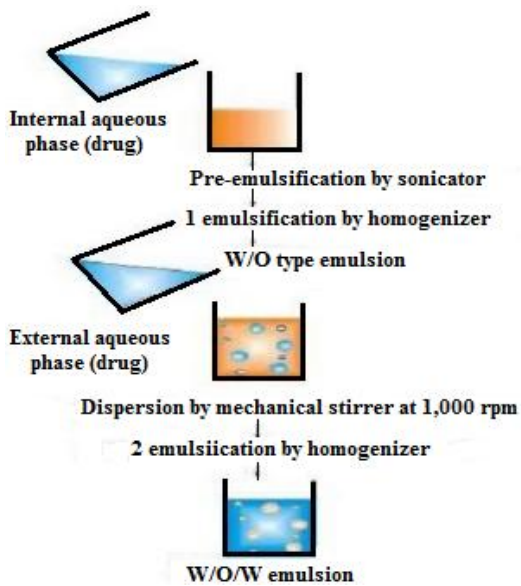

Figure 3: Modified two-step emulsification method [5]

2.3 Phase inversion method

Phase inversion of emulsion occurs when concentration of dispersed globules in dispersion medium is quite high i.e. the globules are packed very closely in suspending fluid. The method involves addition of an aqueous phase containing hydrophilic emulsifier, such as Tween 80 to an oil phase consisting of liquid paraffin and lipophilic emulsifier, such as Span 80. A well-defined volume of oil phase is placed in vessel of pin mixer. An aqueous solution of emulsifier is then introduced successively to oil phase in vessel at a rate of 5 ml/min, while pin mixer rotates steadily at 80 rpm at room temperature. When volume fraction of aqueous solution of hydrophilic emulsifier exceeds 0.7, the continuous oil phase is substituted by aqueous phase containing a number of vesicular globules among simple oil droplets, leading to phase inversion and formation of W/O/W multiple emulsion [7].

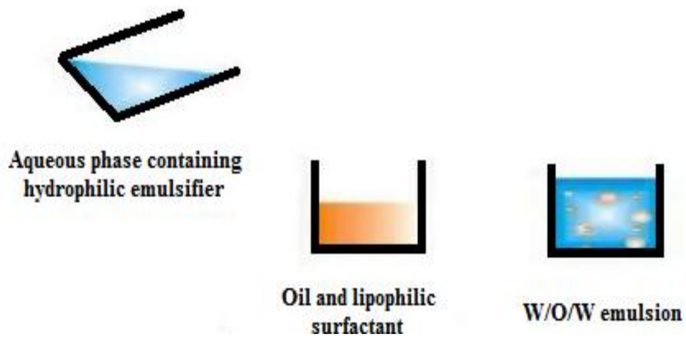

Figure 4: Phase inversion method [5]

2.4 Membrane emulsification method

This procedure has been developed as novel emulsification method. Here, a W/O emulsion (dispersed phase) is extruded into an external aqueous phase (continuous phase) with a constant pressure via a porous glass membrane, which should have homogeneous pores. The particle size of resulting emulsion can be controlled with proper selection of porous glass membrane as droplet size depends upon the pore size of membrane. The relation between membrane pore size and particle size of W/O/W emulsion exhibits correlation as described by the equation:

$$Y = 5.03\,X + 0.19$$

Where, X = pore size,

Y = mean particle size of multiple emulsion

3. Stabilization

Stability is the major problem of multiple emulsions. It is a phenomenon which depends upon equilibrium between water, oil and surfactant. However, multiple emulsions are thermodynamically unstable. Five mechanisms have been identified which leads to instability of multiple emulsions:

1) Coalescence of multiple emulsion droplets/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;
5) Phase separation.

The major problem in regards to stability is the presence of two thermodynamically unstable interfaces. Two different emulsifiers are necessary for their stabilization: one with a low HLB value for W/O interface and a second one with a high HLB value for O/W interface. There are several approaches to overcome instability in multiple emulsions which are as follows [1]:

The inner phase:

i. Stabilizing inner W/O emulsion mechanically, or in presence of better emulsifiers, reducing its droplet size;
ii. Preparing microspheres;
iii. Increasing viscosity of inner water.

The oil phase:

i. Modifying nature of oil phase by increasing its viscosity or by adding carriers;
ii. Adding complexing agents to the oil.

The interfaces:

i. Stabilizing inner and/or outer emulsion by using polymeric emulsifiers, macromolecular amphiphiles or colloidal solid particles to form strong and more rigid film at the interface;
ii. By in-situ polymerization at the interface.

Therefore, stability of multiple emulsions can be improved by forming a polymeric film or macromolecular complex across the oil/water interfaces. Omotosho et al., 1986 have suggested using macromolecules and nonionic surfactants to form such stabilizing complexes. The film is formed through interfacial interaction between macromolecules such as albumin and nonionic surfactants.

4. Formulation

The objective of multiple emulsion formulation is to produce a system that has high yield of multiple droplets containing 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 considered important in multiple emulsion formulation [1] [2]:

4.1 Emulsifying equipment

Primary emulsions can be prepared using laboratory mixer or homogenizer in order to provide a good dispersion of droplets within 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.

4.2 Nature of oil phase

Oil phase to be employed in multiple emulsions must be nontoxic. The various oils of vegetable origin such as soybean, sesame, peanut, safflower etc. are acceptable if purified correctly. Refined hydrocarbons such as light liquid paraffin, squalene as well as esters of fatty acids such as ethyl oleate and isopropyl myristate have also been used in multiple emulsions. Oils derived from vegetable sources are biodegradable, whereas those based on mineral oils are removed from body very slowly. Generally, mineral oils produces more stable multiple emulsions than those produced from vegetable oils. The order of decreasing stability and percentage entrapment has been found to be as: light liquid paraffin > squalene > sesame oil > maize or peanut oil.

4.3 Phase volume ratio

Phase volume ratio is volume of dispersed phase in the initial W/O or O/W multiple emulsions. This may have an influence on the both the yield and stability of final emulsion system. It is essential that dispersed phase should be added slowly into continuous phase for formulation of a stable multiple emulsion. An optimal 22-50% internal phase volume can be utilized for the formulation of multiple emulsions. Increasing the volume of dispersed phase may lead to decreased stability of emulsions and phase inversion may also occur.

4.4 Nature and quantity of emulsifiers

Two different emulsifiers i.e. hydrophilic and lipophilic are required to form a stable emulsion, their concentration may be varied. One stabilizes O/W emulsion while the other stabilizes W/O emulsion respectively. In W/O/W emulsion, optimal HLB value would be in range of 2-7 for primary surfactant and 6-16 for secondary surfactant. Too little emulsifier may result in unstable systems, whereas too much emulsifier may lead to toxic effects and even cause destabilization. In these emulsion, primary emulsion W/O is first prepared using water and low-HLB surfactant solution in oil. Then, W/O is re-emulsified in an aqueous solution of high-HLB surfactant to produce W/O/W multiple emulsion. The first step should be carried out in a high-shear device to produce very fine droplets. The second emulsification step should be carried out in a low-shear device to avoid rupturing the multiple droplets.

4.5 Nature of entrapped material

While formulating W/O/W, presence of drug and other components, such as electrolytes, proteins, or sugars needs to be considered, along with the nature of drug, i.e. hydrophilic or hydrophobic. Under influence of osmotic gradient, oil phase of W/O/W emulsion acts as semipermeable membrane between two aqueous phases, resulting in passage of water across oil phase. This may either lead to swelling or shrinking of internal droplets. Higher osmotic pressure in external environment, compared to that in internal phase, leads to shrinkage of internal aqueous droplets, and rupture of oil layer. If osmotic pressure is higher in internal aqueous phase, water may pass to this phase resulting in swelling of internal droplets, which may burst to release contents. The reverse is true if osmotic pressure is higher in external aqueous phase causing shrinkage of internal droplets. If osmotic pressure difference across oil layer is extreme, then passage of water is so rapid that immediate rupture of oil drops occurs with expulsion of internal droplets. This can be partially solved by addition of small amounts of sodium chloride to internal aqueous phase so that this phase is isotonic with final external phase.

4.6 Added stabilizing components

Stabilizers are added to 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 O/W interface (e.g., 1-3% cetyl alcohol) and gelling agents for oil phase (e.g., 1-5% aluminium monostearate).

4.7 Shear/Agitation

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

4.8 Temperature

Temperature has only an indirect effect on emulsification that is attributed to its effect on viscosity, surfactant adsorption and interfacial tension. Generally, for primary emulsion formulation temperature is kept at 70˚C, whereas for secondary emulsion it is kept at 10˚C. Large temperature variations during manufacturing, storage, transport and use leads to drastic modifications within emulsions.

4.9 Rheology

Rheological properties of emulsions are influenced by number of factors, including nature of continuous phase, phase volume ratio, and to lesser extent by particle size distribution. For low internal phase volume emulsions, consistency of emulsion similar to continuous phase; thus, O/W/O emulsions are generally thicker than W/O/W emulsions, and consistency of W/O/W system can be increased by addition of gums, clays.

5. Evaluation

5.1 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 as well as droplets of internal dispersed phase. Based on this technique, multiple emulsions can be classified as coarse (>3 µm diameter), fine (1-3 µm diameter) and micro-multiple emulsion (<1 µm diameter). Bright field micrographs equipped with differential interference contrast optics have been used to characterize internal droplet of multiple emulsions. Various other techniques used to characterize colloidal carriers like Coulter counter, freeze fracture electron microscopy and SEM is used to determine average globule size and size distribution of multiple emulsions [7].

5.2 Area of interfaces

Average globule diameter can be used in calculation of total area of interface using the formula:

$$S = 6/D$$

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

D = Diameter of globules (cm)

5.3 Number of globules

Number of globules/cubic mm can be measured by haemocytometer cell after appropriate dilution of multiple emulsions. The globules in five groups of 16 small squares (total 80 small squares) can be counted and total number of globules/cubic mm is calculated using the formula:

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

5.4 Rheological evaluation

Rheology, i.e. viscosity and interfacial elasticity of multiple emulsions are an important parameter as it relates to emulsion stability and clinical performance. Viscosity of multiple emulsions can be measured by Brookfield rotational Viscometer. Samples are sheared for one min at 100 rpm, using an appropriate spindle and readings are taken after equilibrium of indicator dial. Interfacial film strength can be evaluated by interfacial rheology measurements, i.e. elasticity of W/O and O/W components of W/O/W multiple emulsions and these data may relate to emulsion stability.

5.5 Zeta potential

Zeta potential measurements are pivotal in designing of surface modified or ligand anchored multiple emulsions. It can be calculated by using Smoluchowski equation from mobility and electrophoretic velocity of dispersed globules using Zeta-potentiometer, calculated by the formula:

$$\zeta = \frac{4\pi\eta\mu}{\varepsilon E} \times 10^3$$

Where, ζ = Zeta potential (mV)

η = Viscosity of the dispersion medium (poise)

µ = Migration velocity (cm/s)

ε = Dielectric constant of the dispersion medium

E = Potential gradient (Voltage applied)

5.6 Percentage drug entrapment

Percentage drug entrapment or active moiety in multiple emulsions is generally determined using dialysis, centrifugation, filtration and conductivity measurements. Recently an internal tracer/marker was used to evaluate entrapment of impermeable marker molecule contained in inner aqueous phase of W/O/W emulsion. The unentrapped marker is calculated and the amount entrapped can be calculated by deducting unentrapped amount from the initially added amount.

5.7 *In-vitro* drug release

Drug released from aqueous inner phase of W/O/W emulsion can be estimated using the conventional dialysis technique. W/O/W emulsion can be placed in dialysis bag and dialyzed against 200 ml of phosphate saline buffer (PBS, pH 7.4) at 37±1˚C and sink condition should be maintained while the contents stirred continuously by magnetic stirrer. Aliquots can be withdrawn at different time intervals estimated using standard procedure and data can be used to calculate cumulative drug release profile.

5.8 *In-vitro* stability studies

Emulsion stability can be determined by phase separation on storage of W/O/W emulsions. Freshly prepared multiple emulsions allowed standing for one week at room temperature and volume of aqueous phase separated is measured at suitable time intervals.

6. Drug Release Mechanisms

Drug release in multiple emulsions from internal to external phase occurs via the middle layer by different mechanisms. 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 [7]: –

6.1 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.

6.2 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 Cu^{2+} ions. This mechanism is especially effective for transport of highly hydrophilic compounds.

6.3 Micelle transport – Inverse micelles consisting of nonpolar part of surfactant lying outside and polar part inside encapsulate hydrophilic drug in core and permeate via the oil membrane because of outer lipophilic nature. Inverse micelle can encapsulate both ionized and unionized drugs. The presence of both lipophilic and hydrophilic surfactants in the oil phase facilitates the formation of water swollen inverse micelles, which may act as a mobile carrier for both ionized and unionized drug.

6.4 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.

6.5 Rupture of oil phase – Rupturing of oil membrane can unite both aqueous phases and thus drug could be released easily.

6.6 Solubilisation of internal phase in oil membrane – In this mechanism, solubilisation of minute amounts of internal phase in membrane phase results in transport of very small quantities of materials.

7. Applications

Multiple emulsions are finding immense use because of their vesicular structure with innermost phase closely similar to that of liposomal vesicles and selective permeability characteristic of liquid membranes. An O/W/O multiple emulsions may appear to be more advantageous since the extra partitioning step with drug initially in the internal oil phase is anticipated to be the rate-limiting factor that may define the drug release characteristics. Various prominent applications of multiple emulsions are due to the fact that biological fluids are miscible with water and W/O/W multiple emulsions is anticipated to perform essentially as a simple W/O emulsion shortly after parenteral administration [7]. Also, external aqueous phase makes administration much easier than W/O emulsions (oil is an external phase), which are highly viscous and difficult to inject. Some important applications of multiple emulsions are as follows –

7.1 Controlled and Sustained Drug Delivery – The basic potential of multiple emulsions in clinical therapeutics is in the prolonged and controlled release of drugs. In both systems drug present in innermost phase has to cross several phases before it is available for absorption and release rate is governed by its ability to diffuse via various phases and cross interfacial barriers. Various researchers have worked on liquid membrane system and recommended their use as controlled release drug delivery system [1]. Hino et al., 2000 compared *in-vitro* release profile of W/O, O/W and W/O/W emulsion loaded with anticancer drug Famorubicin. The formulation showed sustained release pattern which was comparable to that from W/O emulsion within 7 hours.

7.2 Targeting of Bioactives – An important prerequisite for success in application of pharmacologically active agents is site specificity. This is especially applicable to cancer chemotherapy in which supply of cytotoxic drugs into non-diseased tissues led to serious side effects. Multiple emulsions can be used as lymphotropic carriers for targeting of bioactives. The administration of lipid vehicle (O/W, W/O or W/O/W) systems intramuscularly or intraperitoneally results in emulsion droplets reaching lymphatic system and regional lymph nodes. Thus targeting can be achieved at various levels using multiple emulsions loaded with appropriate bioactive agents. Takahashi et al., 1973 studied delivery of labelled 5-flurouracil to regional lymph nodes following intratesticular administration. The formulation showed that emulsion droplets reached regional lymph nodes within 15 min and remained there for more than 7 days. W/O/W system also gave highest levels within the regional lymph nodes, than other systems such as aqueous solution, W/O and O/W emulsions [7].

7.3 Vaccine Adjuvant – Use of multiple emulsions as a new form of vaccine adjuvant was first described by **Herbert** in 1967. Standard W/O emulsion as vaccine adjuvant possess high consistency and hence difficult to inject. The re-emulsification of W/O emulsion to W/O/W, render them consistent enough for administration and antibody responsive than W/O system. These vaccines contribute to both humoral as well as cell-mediated immune responses in protection against the infection. It was concluded that multiple emulsion-based vaccine could be successfully used in effective control of haemorrhagic septicaemia. Recently, W/O/W emulsion formulations, containing influenza virus, surface antigen hemagglutinin was prepared and was characterized *in-vitro* and *in-vivo* in wistar albino rats. Results suggested that multiple emulsion formulations carrying influenza antigen have advantage over conventional preparation and can be effectively used as one of the vaccine delivery system [2].

7.4 Delivery of Proteins and Peptides – Multiple emulsions are unique in that a true liquid phase is maintained separate from an external aqueous phase. This may be especially important for bioactive molecules that cannot be appropriately stabilized in solid state. The separation of aqueous phases enables highly specialized environments, conducive to protein activity. The physical instability of conventional systems remains a major factor limiting their wider application. Attempts to improve physical stability of aqueous dispersions via interfacial complexation and use of microemulsions could improve short-term stability. Toorisaka et al., 2003 developed S/O/W emulsion for oral administration of insulin. Surfactant-coated insulin was dispersed in oil by ultrasonication, which was mixed with outer water phase with a homogenizer and finally, the S/O/W emulsion thus obtained was adjusted to a constant particle size by passage via SPG membrane. S/O/W emulsion showed hypoglycaemic activity for a long period after oral administration to rats [7].

7.5 Local Immunosuppression – A potential approach to avoid complication of systemic immunosuppression and simultaneously enhance immunosuppressive efficacy is to deliver immunosuppressive agents locally to the site of target organs. W/O/W multiple emulsion has been developed for the delivery of immunosuppressant. It has been proposed that W/O/W emulsion of tacrolimus possess pharmacokinetic benefits of local immunosuppression, and has significantly decreased tacrolimus levels in brain and kidney, and increased levels in liver and spleen.

7.6 Absorption Enhancement via GIT – Omotosho, 1990 found increased oral absorption of griseofulvin from W/O/W emulsion in comparison to O/W emulsion and tablet dosage forms. Administration of griseofulvin in W/O/W emulsion may lead to enhancement of therapeutic efficacy of drug. Kajita, 2000 evaluated vancomycin hydrochloride loaded multiple emulsions incorporated with unsaturated fatty acids to improve the mucosal absorption of poorly absorbed drugs from rat intestinal loops *in-situ*. The emulsion incorporating C18 unsaturated fatty acids or docosahexaenoic acid markedly enhanced drug absorption after colonic and rectal dosing and were proved useful carriers for improving absorption of poorly absorbable drugs via the intestinal tract. A similar system was investigated for increase in rectal bioavailability for insulin.

7.7 Oxygen delivery system – Multiple emulsions has also been extended as stable oxygen carrying system. A concentrated solution of haemoglobin (Hb) was encapsulated in the form of Hb-in-oil-in-water (Hb/O/W). Studies using mineral oil reported that Hb multiple emulsions have several important characteristics that are compatible and in accordance with blood composition that makes it a suitable blood substitute. These include satisfactory rheological properties and good hydrodynamic stability compared to whole blood, high encapsulation efficiency with little methaemoglobin generation, and satisfactory oxygen affinity and co-operative efficiency as compared to whole blood [4].

7.8 Enzyme Immobilization – Enzymatic conversion of water insoluble, highly lipophilic substrates, such as steroids, can be carried out in multiple emulsions. The enzyme is contained in a microdroplet 'water pool', whereas organic phase contains substrate solution. Hydrocarbon based liquid surfactant membranes have been used to immobilize Urease. Immobilized enzyme retains catalytic activity and recovered by simple mechanical destruction of liquid membrane. It is used mainly in kidney diseases.

7.9 Cosmetics and Health Care – The basis of most cosmetics and toiletries is an emulsion of either type O/W or W/O. These are also used for moisturizing, nutritive and protective action, when applied in forms of sunscreens, hand creams, makeup cleansers, shaving creams, antiperspirants etc. Use of stable multiple emulsion of $O_1/W/O_2$ has been reported as sun protection or makeup formulation. Laugel et al., 2000 reported incorporation of silicones within O/W/O multiple emulsions loaded with dimethicones, as an efficient means of modulating penetration and distribution of drugs in the skin. Use of silicones within O/W/O multiple emulsions has two principal advantages: (1) silicones with lowest molecular weight decreases oily touch; (2) due to large range of viscosity, silicones influences skin distribution of actives after topical application [7].

7.10 Drug Overdose Treatment – This system could be utilized for overdose treatment by utilizing the difference in pH, e.g.:- barbiturates. The inner aqueous phase of these emulsions has basic buffer and when emulsion is taken orally, acidic pH of stomach acts as an external aqueous phase. In acidic phase barbiturate remains mainly in unionized form which transfers via oil membrane into inner aqueous phase and gets ionized. Ionized drug has less affinity to cross oil membrane thus getting entrapped and drug overdose can be prevented [3].

7.11 Taste Masking of Drugs – Multiple emulsions has been employed for taste masking of drugs like chlorpromazine HCl and chloroquine. By dissolving drug in inner aqueous phase of W/O/W emulsion under conditions of good shelf stability, the formulation could be designed to release drug via oil phase in the presence of gastric fluid [2].

8. Future Perspectives

Multiple emulsions have shown promising and potential applications in pharmaceutical research and development over the last two decades. Their major applications in the field include sustained and controlled drug delivery. Their potential use in imaging and diagnosis has also generated some interest in the recent past. One of the unique advantages of multiple emulsions is facile and inexpensive method of preparation. The challenge facing pharmaceutical scientists today is the long-term instability of multiple emulsions. Use of amphiphilic macromolecules instead of low molecular weight surfactants has shown some improvement in their stability. Currently, the ideal multiple emulsions are likely to be prepared by membrane separation technique using polymeric amphiphilies as emulsifiers with viscosity enhancing agents and electrolytes to control the osmotic pressure. This area of stabilization is still in an initial stage and needs more extensive work for drug delivery applications. The future trend in multiple emulsion formulations may see a replacement of interior emulsion with thermodynamically stable nanostructures or microemulsions. It is expected that in future this technique will be used more frequently for the delivery and targeting of many drugs [8].

9. Conclusion

Multiple Emulsions is one of the advanced drug delivery systems for improvement of various characteristics of drugs like bioavailability, taste, release rate etc. The advances include various novel formulations for betterment of the drug administration and improvement in the palatability of drug by incorporating them into various formulations. These are used in various pharmaceutical applications as it has a remarkable degree of biocompatibility, completely biodegradable, hydrophilic and hydrophobic drugs can be entrapped, protection from inactivation by the endogenous factors etc. These can be used in many applications like taste masking, sustained release, delivering the unstable drug etc. [7].

References

[1] Kumar R., Kumar M.S. and Mahadevan N. Multiple emulsions: A review. *International Journal of Recent Advances in Pharmaceutical Research*. 2012; 2(1): 9-19.

[2] Prajapati S.B., Bhatt H., Koli A., Dharamsi A. and Shah S.A. An overview of preparation, evaluation and applications of multiple emulsions. *International Journal for Pharmaceutical Research Scholars*. 2013; 2(1): 142-150.

[3] Deshmukh R.L. Multiple emulsion: Strategic and technology. *Asian Journal of Pharmaceutical Education and Technology*, 2014; 2(2): 1-19.

[4] Bhatia N., Pandit S., Agrawal S. and Gupta D. A review on multiple emulsions. *International Journal of Pharmaceutical Erudition*. 2013; 3(2): 22-30.

[5] www.slideshare.net

[6] www.prepardfoods.com

[7] Vyas S.P. and Khar R.K. Multiple emulsions: Novel carrier systems. CBS Publishers and Distributors. First Edition, 2004; 303-328.

[8] Madaan V., Chanana A., Kataria M.K. and Bilandi A. Emulsion technology and recent trends in emulsion applications. *International Research Journal of Pharmacy*. 2014; 5(7): 533-542.

[9] Ghosh S. Formulation and Characterization of multiple emulsions with various additives. *International Journal of Research in Pharmaceutical and Biomedical Sciences.* 2011; 2(2): 751-759.

[10] Nimbekar T.P., Wanjari B.E., Sanghi D.K. and Gaikwad N.J. 2012. Formulation and evaluation of sustained release multiple emulsion of hydroxyprogestrone. *International Journal of Pharmacy and Pharmaceutical Sciences*. 4(1): 76-80.