

“An Update Review on Recent Advancements in Multiple Emulsion”

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Abstract:-Emulsions are scatter systems of two immiscible or inadequately miscible liquid phases. Emulsion can be classified as simple oil-in-water (O/W) or water-in-oil (W/O) emulsions and multiple water-in oil-in-water (W/O/W) or oil-in-water-in-oil (O/W/O) emulsions. W/O/W emulsions had been used as drug delivery system (DDS).Preparation of mono dispersed multiple emulsion is important in DDS to improve their stability and to make possible control of their properties. This review described five methods to prepare multiple emulsions viz. two-step emulsification method, modified two-step emulsification method, phase inversion method & membrane emulsification. With the progression in techniques for preparation, stabilization and rheological characterization of multiple emulsions, it will be able to provide a new carrier system for drugs, cosmetics and pharmaceutical agents.

Keywords: Multiple Emulsions, o/w/o & w/o/w, Emulsifying agent, Stability of Emulsions

I. INTRODUCTION

Emulsions may be described as heterogeneous systems, where one immiscible liquid is dispersed in the form of droplets and stabilized by a third constituent called emulsifying agent. These two liquids are also chemically nonreactive and form the systems that are characterized by a low thermodynamically stability.

Based on their formation, emulsions can be divided into:

1. Simple Emulsion and
2. Multiple Emulsions.

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

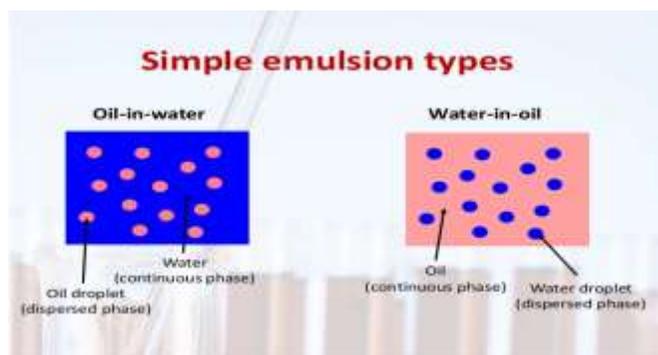


Figure 1 simple emulsion

a. Oil-in-water emulsions (O/W) – where oil is the disperse phase in a continuous phase of water, and *b. Water-in-oil emulsions (W/O)* – where water is the disperse phase in a continuous phase of oil ¹

Multiple Emulsions:-

Multiple emulsions are multifaceted systems, termed "emulsions of emulsions", i.e. the droplets of the dispersed phase contain even smaller dispersed droplets themselves. 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.^{1,2,3} Multiple emulsions are also known as emulsions of emulsions, liquid membrane system or double emulsion.

The basic rationale for the use of W/O/W & O/W/O type multiple emulsions as a means of extended delivery of drugs is that the drug Multiple emulsions are multifaceted systems, termed "emulsions of emulsions", i.e. the droplets of the dispersed phase contain even smaller dispersed droplets themselves. 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.^{2,3,4}

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Types of Multiple Emulsions

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 ⁶.

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 semi

permeable membrane for the drugs or moieties entrapped in internal aqueous phase.

2. *O/W/O emulsion system*: In O/W/O system, an aqueous phase (hydrophilic) separates internal and external oil phase.

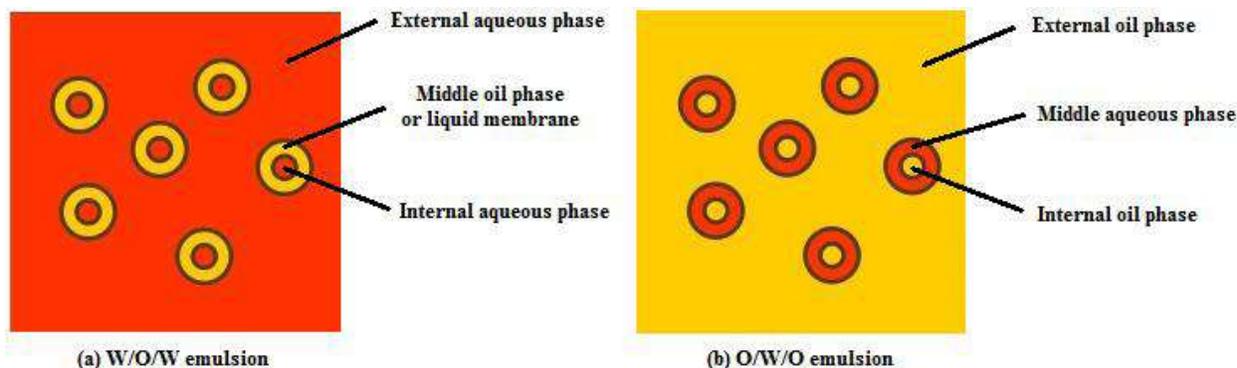


Figure 2: Types of Multiple Emulsions ⁷

Advantages ⁶ :-

1. Masks bitter taste and odor of drugs, thereby making them more edible.
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 vulnerable 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 unbalanced, 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.

Formulation of Multiple Emulsions

Florence and Whitehil ¹⁴ described three different types of multiple emulsions, which they termed A, B, and C. Type A multiple emulsions were those in which only one large internal drop was contained in the secondary emulsion droplet. In type B emulsions, there were several small internal droplets contained in the secondary emulsion droplet, and type C emulsions were those with a large number of internal droplets present. Only the type C systems have applications in drug delivery and drug targeting. ¹⁵

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.

Oil Phase

The oil phase to be employed in a pharmaceutical emulsion must be nontoxic. The various oils of vegetable origin (soybean, sesame, peanut, safflower, etc.) are acceptable if purified properly. Refined hydrocarbons such as light liquid paraffin, squalane, as well as esters of fatty acids (ethyl oleate and isopropyl myristate) have also been used in double emulsions ¹² Oils derived from vegetable sources are biodegradable, whereas those based on mineral oils are only removed from the body very slowly. As a general rule, mineral oils produced more stable multiple emulsions (w/o/w) than those produced from vegetable oils ¹³ The order of decreasing stability and percentage entrapment has been found to be light liquid paraffin > squalane > sesame oil > maize or peanut oil. ¹⁶

Nature and Quantity of Emulsifying Agents

Two different emulsifiers (lipophilic and hydrophilic) are required to form a stable emulsion. In general, for a w/o/w emulsion the optimal HLB value will be in the range 2-7 for the primary surfactant and in the range 6-16 for the secondary surfactant. The concentration of the emulsifiers can also be varied. Too little emulsifier may result in unstable systems, whereas too much emulsifier may lead to toxic effects and can even cause destabilization. ¹⁷ An excess of lipophilic surfactant can cause the inversion of w/o/w emulsion to simple o/w emulsion.

Phase Volume

It is very important to have proper order of phase addition while formulation and dispersed phase should be added slowly into the continuous phase for the formulation of a stable multiple emulsion. An optimal (22-50%) internal phase volume can be utilized for the emulsion formulation. Very

high phase volume ratio (70-90%) had also been reported to produce a stable multiple emulsion.

Factor Affecting Stability of Multiple Emulsion

Nature of Entrapped Material

When formulating a w/o/w system the presence of the drug and other components (especially electrolytes) needs to be considered. The nature of drug (hydrophilic or hydrophobic) also is considered.¹⁵ Due to the nature of the multiple emulsions, the middle phase acts as a membrane, and osmotic effects may become important. The entrapped solutions may interact with the surfactant or the surface active drugs may be adsorbed at the inter phase, resulting in decreased stability.¹⁴

Shear/Agitation

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

Temperature

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

Rheology

The rheological properties of emulsions are influenced by a number of factors, including the nature of the continuous

phase, the phase volume ratio, and to 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 consistency of a w/o/w system can be increased by the addition of gums, clays.

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 –

Two-step emulsification

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

Then, the recently 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.⁸ 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.⁹

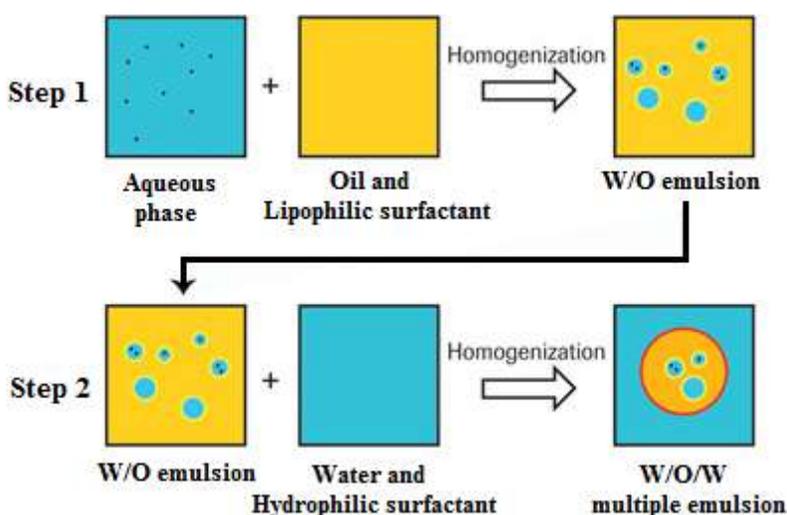


Figure 3: Two-step emulsification method¹⁰

Modified two-step emulsification

This method is unusual 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 emulsion⁸

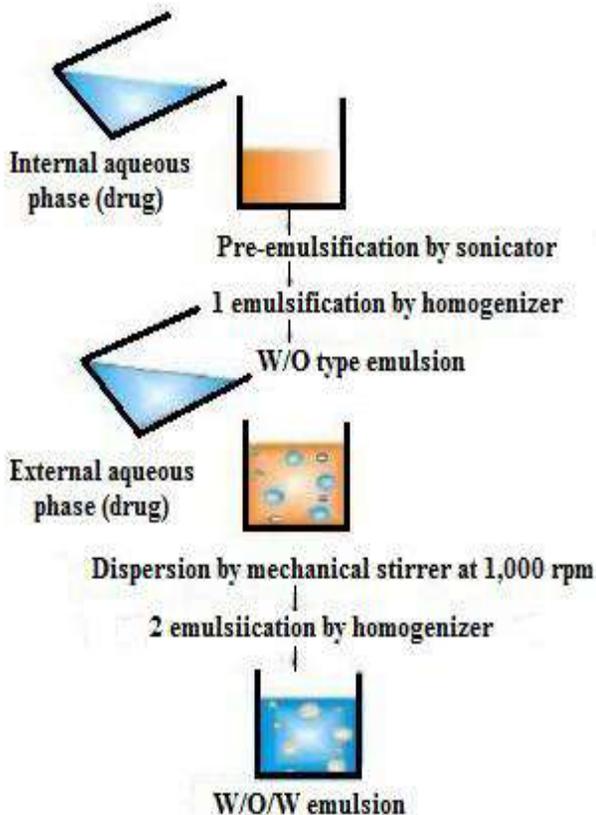


Figure 4: Modified two-step emulsification method⁷

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 emulsion⁹.

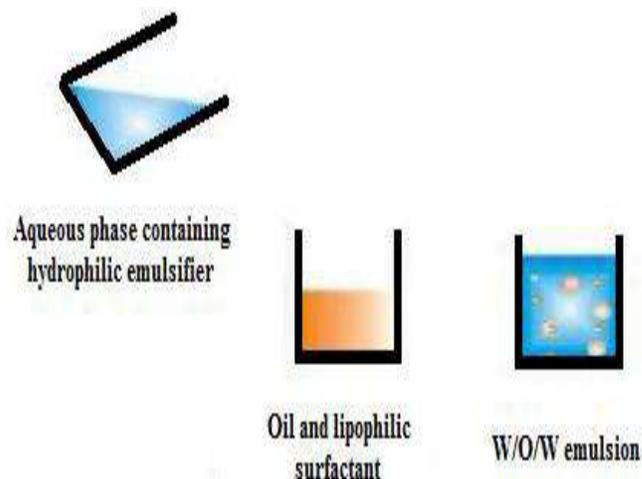


Figure 5: Phase inversion method⁷

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

Stabilization of multiple emulsions

Stability is the major problem of the multiple emulsions. Four possible mechanisms lead to the instability of W/O/W emulsions are

- 1) Coalescence of the internal aqueous droplets;
- 2) Coalescence of the oil droplets;
- 3) Rupture of the oil film resulting in the loss of the internal aqueous droplets and
- 4) Passage of the water and water soluble substances through the oil layer between both water phases. This can occur in two various ways: via reverse micellar transport created by the lipophilic emulsifier and by simple diffusion transversely the oil phase connected with osmotic differences between both water phases. The major problem as regards stability is the presence of two thermodynamically unstable interfaces.

Two different emulsifiers are necessary for their stabilization: one with a low HLB for the W/O interface and a second one with a high HLB for the O/W interface.

There are several approaches to overcome instability and release problems in double emulsions. Some of those ideas can be summarized as follows.

The inner phase

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

The oil phase

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

The interfaces

- (i) Stabilizing the inner and/or the outer emulsion by using polymeric emulsifiers, macromolecular amphiphiles (proteins, polysaccharides) or colloidal solid particles to form strong and more rigid film at the interface.¹¹

Possible mechanism of drug release from multiple emulsions

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

- *Diffusion mechanism*

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

- *Micellar transport*

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

- *Thinning of the oil membrane*

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

- *Rupture of oil phase*

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

- *Facilitated diffusion (Carrier-mediated transport)*

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

- *Photo-osmotic transport*

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

- *Solubilisation of internal phase in the oil membrane*

It is a conspicuous transport mechanism. In this solubilisation of minute amounts of the internal phase in the membrane phase results in the transport of very small quantities of materials.^{18,19}

Evaluation of Emulsion:-^{20,21}

Evaluation of an emulsion can be determined by various methods. Some methods was given below.

1. Dilution test
2. Dye test
3. Conductivity test
4. Macroscopic examination
5. Globule size analysis
6. Accelerated stability testing

Applications of Multiple Emulsions

Controlled and Sustained Drug Delivery

The basic potential of multiple emulsions (both w/o/w and o/w/o) 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 for the system. W/O/W emulsions for parenteral delivery are more convenient to handle, use, and inject due to lower viscosity of these systems.

Inverse Targeting

Regarding this approach Talegaonkar and Vyas were prepared poloxamer 403 containing sphere in oil-in-water (s/o/w) multiple emulsion of diclofenac sodium by gelatinization of inner aqueous phase and they examined the effect of poloxamer 403 on surface modification for inverse targeting to reticuloendothelial system rich organs. The results accomplished that this multiple emulsion system containing poloxamer has capability to retards the RES uptake of drugs mainly to liver, brain and targeting to non-RES tissues such as lungs, inflammatory tissue.²²

Vaccine Adjuvant

The use of w/o/w multiple emulsion as a new form of adjuvant for antigen was first reported by Herbert²³. These emulsions elicited better immune response than antigen alone. Rishendra and Jaiswal²⁴ 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 could be successfully used in the effective control of hemorrhagic septicemia. Recently, multiple water-in-oil-in-water (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. SDS-PAGE technique was used for evaluating hema gglutinin and in vitro release of antigen respectively. Results suggested that multiple emulsion formulations transport influenza antigen have advantage over conventional preparation and can be efficiently used as one of the vaccine delivery system with adjuvant properties. In another report by the same researchers they accomplished that multiple emulsion and nanoparticle formulations containing influenza virus surface antigen Hemagglutinin were more efficient in eliciting an immune response in rats than the conventional vaccine.^{25,26,27,28}

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. A hemoglobin multiple emulsion in physiologically compatible oil in an external 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 where in hemoglobin, a fragile material, is formulated into high hemoglobin content water-in-oil-inwater multiple emulsions while maintaining high yields and high oxygen exchange activity.

Multiple Emulsion for Local Immunosuppression

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

Bioavailability Enhancer

Multiple emulsions have also been used to improve bioavailability of lipophilic drugs, which have high first pass metabolism. Multiple emulsion increases bioavailability of drugs either by protecting drugs in physiological, ionic/enzymatic environment in the GIT where otherwise these gets degraded like proteins, peptides or by passing the hepatic first pass metabolism.

Enzyme Immobilization

Enzymatic conversion of water insoluble, highly lipophilic substrates, such as steroids, can be carried out in a multiple emulsion. The enzyme is contained in a microdroplet 'water pool', whereas the organic phase contains the substrate solution. For example hydrocarbon based liquid surfactant membranes have been used to immobilize Urease.

Drug over Dosage Treatment

This system could be utilized for the over dosage treatment by utilizing the difference in the pH. For example:-barbiturates. In these emulsions, the inner aqueous phase of emulsion has the basic buffer and when emulsion is taken orally, acidic pH of the stomach acts as an external aqueous phase. In the acidic phase barbiturate remains mainly in unionized form, which transfers through oil membrane into inner aqueous, phase and gets ionized. Ionized drug has less affinity to cross the oil membrane thereby getting entrapped. Thus, entrapping excess drug in multiple emulsions cures over dosage.^{29,30,31}

Taste Masking

Multiple emulsions of chloroquine, an antimalarial agent has been successfully prepared and had been found to mask the bitter taste efficiently^{32, 33, 34}. Taste masking of chlorpromazine, an antipsychotic drug has also been reported by multiple emulsions.

II. CONCLUSION

The Multiple Emulsion is one of the superior drug delivery systems for the enhancement of the various characteristics of the drugs like bioavailability, taste, release rate etc. The advances comprise various new formulations for the betterment of the drug administration & improvement in the palatability of the drug by incorporating them into the various formulations. 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.

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