INTRODUCTION
Emulsions may be described as heterogeneous systems, where one immiscible liquid is dispersed in another in the form of droplets and stabilized by a third component called emulsifying agent. The emulsions can be divided into -
1. Oil in water (O/W) emulsions.
2. Water in oil (W/O) emulsions.

- O/W emulsion system involve dispersion of oil droplets (dispersed phase) in aqueous (continuous) phase. This emulsion is generally formed if the aqueous phase constitutes more than 45% of the total weight and a hydrophilic emulsifier is used. The globule size is 0.25 to 10 microns.
- W/O emulsions involve dispersion of droplets of aqueous phase (dispersed phase) in oil (continuous) phase. This emulsion is generally formed if the oily phase constitutes more than 45% of the total weight and a lipophilic emulsifier is used. These are used for cosmetics. They are employed for treatment of dry skin and emollient applications.\(^1\)

1. Multiple Emulsions
Multiple emulsions are more complex than their two-phase counterparts from the standpoint of formulation, stability, and drug release. They are useful tool in achieving sustained release drug delivery for different routes.\(^2\)

The present study aims towards formulation of multiple emulsions, which contain an additional reservoir that is an extra step for partitioning of the drug, which can effectively retard the release rate of the drug and decrease the dose frequency. Multiple emulsions are novel carrier system which are complex and poly dispersed in nature where both w/o and o/w emulsion exists simultaneously in a single system. Lipophilic and hydrophilic surfactants are used for stabilizing these two emulsions respectively. The droplets of the dispersed phase contain even smaller dispersed droplets themselves, therefore also called as "emulsions of emulsions". In multiple emulsion system solute has to transverse from inner miscible phase to outer miscible phase through the middle immiscible organic phase, so it also called as liquid membrane system.\(^3\)

1.1 Types of multiple emulsions
1) Water/oil/water (w/o/w)
It consists of dispersed oil globules containing smaller aqueous droplets: each inner aqueous droplets is separated from the outer aqueous phase by an oil phase layer. The presence of at least two surfactant is required.\(^3\)

2) Oil/water/oil (o/w/o)
It contain an inner oil phase, a water phase and outer oil phase. The inner oil phase is first dispersed in water to form on oil-in –water emulsion. Then the o/w emulsion is further dispersed in the outer oil phases to form the o/w/o type multiple emulsion.\(^3\)
Figure 1: Multiple emulsion a) w/o/w double emulsion b) o/w/o double emulsion.

1.2 Advantages of Multiple Emulsions
a. They can mask the bitter taste and odor of drugs, thereby making them more palatable. E.g. Castor oil, Cod-liver oil, Chloroquine Phosphate etc.

b. They can be used to prolong the release of the drug thereby providing sustained release action.

c. Essential nutrients like carbohydrates, fats and vitamins can all be emulsified and can be administered to bed ridden patients as sterile intravenous emulsions

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

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

f. Emulsions are used widely to formulate externally used products like lotions, creams, liniments.[5]

1.3 Methods of preparation
1) Two step emulsification (double emulsification)
   It is the most common method because it is very easy and gives high yield with reproducibility. This method involves re-emulsification of primary w/o or o/w emulsion using a suitable emulsifying agents. The first step involves the preparation of primary emulsions either o/w or w/o type which is then re-emulsified with an excess of aqueous phase or oil phase in the presence of second emulsifier. This step is carried out in high shear device to produce a very fine droplets. The second emulsification step is carried out in a low shear device to avoid rupturing the multiple droplets.[1]

2) Modified two steps emulsification
   This method is different from conventional two step technique in two points sonication and stirring are used to obtain fine, homogenous and stable o/w emulsion. Continuous phase is poured a dispersed phase for preparing w/o/w emulsions.[1]

3) Phase inversion technique (one step technique)
   The method typically involves the addition of an aqueous phase contains the hydrophilic emulsifier to an oil phase consists of liquid paraffin and containing lipophilic emulsifier. An aqueous solution of emulsifier is then introduced successively to the oil phase in the vessel at rate of 5ml/min while the pin mixer rotates steadily at 88 rpm at room temperature. When volume fraction of the
aqueous solution of hydrophilic emulsifiers exceeds 0.7 the continuous oil phase is substituted by the aqueous phase containing a number of the vesicular globules among the simple oil droplets leading to phase inversion formation of w/o/w multiple emulsion.\(^1\)

![Phase Inversion technique](image)

**Figure 4: Diagram of phase inversion technique.**

4) Membrane emulsification technique
This method uses low shear forces to produce emulsions. Particle size of the emulsion can be controlled with the proper selection of the porous glass membrane. The relation between membrane pore size and particle size of w/o/w emulsion exhibits good correlation as described by the following equation.

\[
y = 5.03 \times x + 0.19
\]

Where x is the pore size and y is the mean particle size of the multiple prepared using membrane emulsifier technique.\(^1\)

1.4 Stability of emulsions
The possible indications of instability includes:
- Leakage of the contents from the inner aqueous phase.
- Expulsion of internal droplets in external phase.
- Constriction or distension of the internal droplets due to osmotic gradient across the oil membrane.
- Flocculation of internal aqueous phase and multiple emulsion droplets.
- Disruption of oil layer on the surface of internal droplets.
- Phase separation.\(^1\)

**Drug release mechanisms**
There are several possible mechanisms by which the active compound may be transferred across the oil layer in a w/o/w system. Some of the mechanisms include:

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

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

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

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

e) **Facilitated diffusion (Carrier mediated transport)**
This mechanism involves a special molecule (carrier) which combines with the drug and makes it compatible to permeate through the oil membrane. These carriers can be incorporated in internal aqueous phase or oil membrane.\(^3\)

4) **Applications of multiple emulsions**
On the basis of these facts multiple emulsions system have been studied widely according to the practical utility. Some of the important applications are described in the table no. 1.\(^6\)
Table no 1: Biomedical and pharmaceutical applications of multiple emulsions

<table>
<thead>
<tr>
<th>Applications</th>
<th>Drug entrapped</th>
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<tbody>
<tr>
<td>Enhanced oral bioavailability</td>
<td>Heparin, Insulin</td>
</tr>
<tr>
<td>Masking action</td>
<td>Chlorpromazine, Choloroquin</td>
</tr>
<tr>
<td>Enzyme immobilization</td>
<td>Urease, Lipase, Amylase</td>
</tr>
<tr>
<td>Drug over dosage treatment</td>
<td>Salicylates, Barbiturates</td>
</tr>
<tr>
<td>Vaccine adjuvants</td>
<td>Influenza virus, Tetanus</td>
</tr>
<tr>
<td>Prolonged action</td>
<td>Pilocarpine, Hemoglobin</td>
</tr>
<tr>
<td>In cancer therapy</td>
<td>Bleomycin, Cyst amine</td>
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</table>

a) Controlled and sustained drug delivery
The in vivo release of water soluble drugs from a stabilized w/o/w emulsion was studied in rats. The cefadroxil and cephradine concentration in rat plasma following intravenous administration of their w/o/w emulsion were considerably prolonged as compare to their respective aqueous solution. Antipyrine attain rapid systemic concentration following administration as w/o/w emulsion.[1]

b) Vaccine adjuvant
Multiple emulsions have been investigated as vaccine adjuvants. The result indicate the peptide vaccination using a formulation based on high molecular weight non-ionic block co-polymer in a simple water – in oil or a multiple emulsion can induce virus specific cell responses and confer enough protection to prevent the establishment of a persistent infection.[1]

c) Multiple emulsions for local immunosuppression
It has been proposed that a w/o/w emulsion would possess the pharmacokinetic benefits of local immunosuppression and evaluated the hypothesis in a rat model. There were no significant difference between the parameters of w/o/w emulsion and based on whole blood data. These data suggest that the w/o/w emulsion applicable as intra-venous drug carrier for local immune suppression.[1]

d) Absorption enhancement through gastrointestinal tract
Enhanced colonic and rectal absorption of insulin reportedly occurs on administration of multiple emulsion containing eicosapentaenoic acid and docosahexaenoic acid.[7]

e) Delivery of proteins and peptides
Multiple emulsion are unique in that liquid phase is maintained separate from an external aqueous phase. This may be especially important for bio-active molecules that cannot be appropriately stables in the solid state. In addition the separation of aqueous phase enables highly specialized environments conducive to protein activity. The physically in stability of system renin a major factor limiting their wider application.[1]

f) Haemoglobin multiple emulsion as an oxygen delivery system
Multiple emulsion technology has been extended as a stable oxygen carrier system. A concentrated solution of hemoglobin was encapsulated in the form of Hb - in –oil –in- water multiple emulsion. This include satisfactory rheological properties and good stability compare to whole blood, high encapsulation of concentration of the Hb and high encapsulation efficacy with little met hemoglobin generation and satisfactory oxygen affinity and co-operative efficiency to whole blood.[3]

g) Enzyme immobilization
The enzyme is contained in a micro droplet water pool whereas the organic phase contains the substrate solution. Immobilization enzyme retained catalytic activity band recovered by simple mechanical destruction of the liquid membrane. This technique is used in kidney diseases. Reduction and separation of nitrates and nitrites by both liquid membrane encapsulated enzyme as well as whole cell has been reported.

h) Bioavailability enhancer
Multiple emulsions has also been used to improve bioavailability of lipophilic drugs which have high first pass metabolism. Multiple emulsion increase bioavailability of drugs either by protecting drugs in physiological, ionic or enzymatic environment in the GIT where otherwise these gets degraded like protein peptides or by passing the hepatic first pass metabolism.[1]

i) Targeted drug delivery system
Drug targeting minimize the adverse effect of drugs by specifically concentrated in drug is desired tissue several micro particular interest for the cytotoxic drugs because of high toxicity for non-diseased tissues.

Table no 2: Examples of the targeted drug delivery system.

<table>
<thead>
<tr>
<th>Target(Tissue/ Organ)</th>
<th>Drug investigated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphatic system</td>
<td>5-Fluorouracil, isoniazid</td>
</tr>
<tr>
<td>Tumor</td>
<td>Bleomycin</td>
</tr>
<tr>
<td>Brain</td>
<td>Rifampicin</td>
</tr>
<tr>
<td>Liver</td>
<td>5-fluorouracil</td>
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j) Treatment of drug overdose
Multiple emulsion of w/o/w types are used for the treatment of drug overdosing. A w/o/w emulsion system was designed to remove acidic drugs like barbiturates and salicylates from the gastro intestinal tract by entrapping unionized drug permeating through the oil...
membrane into inner basic phase where it is converted to an oil insoluble anion.

**k) Cosmetic and health care**

Multiple emulsions are used for moisturizing nutritive and protective action. However more complex multiple emulsion systems are also used for moisturizing, nutritive and protective action, when applied in the form of sunscreens, hand creams, makeup cleansers, shaving creams and perfume preparations.[1]

**Future perspectives**

Multiple emulsions have been exploited in various applications like pharmaceutics, cosmetic food and separation technique. There potential pharmaceutical application include use for red blood cell, treatment of drug overdosing, taste masking, immobilization of enzymes, enhancement of gastro intestinal absorption, and as carrier for sustained release drug delivery. In addition to this application w/o/w emulsion have been used as intermediates for the preparation of microsphere.

With the evolution of various newer techniques preparation, stabilization and rheological characterization of these specialized emulsion systems they can serve as potential carriers for drugs, cosmetics and pharmaceutical agents.[1]

**CONCLUSION**

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

**REFERENCES**