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Review Article.....!!!

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MULTIPLE EMULSIONS: A REVIEW ARTICLE

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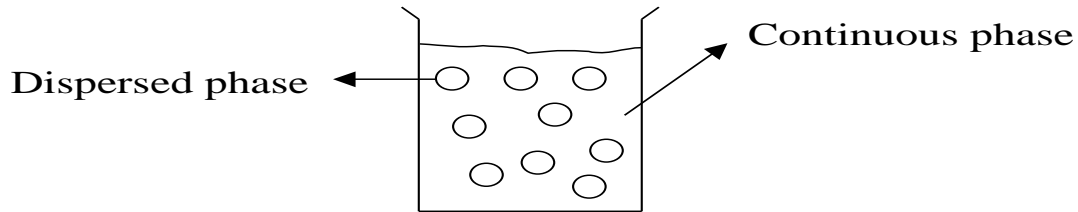
ABSTRACT

Multiple emulsions have been proposed to have numerous uses including their use for enhancement of bioavailability or as a prolonged drug delivery system. But the inherent instability of this system needs to be overcome before they find potential application in pharmaceuticals. Multiple emulsions are often stabilized using a combination of hydrophilic and hydrophobic surfactants. The ratio of these surfactants is important in achieving stable multiple emulsions. This review gives overview of potential of multiple emulsions to improve bioavailability with the hypothesis that improvement of drug release profile.

INTRODUCTION

Emulsion:

“They are thermodynamically unstable system consisting of at least two immiscible liquid phase, one of which is dispersed as a globules in the other liquid phase which is continuous phase.”



Classification of emulsion:

It is based upon the nature of Dispersion Phase

1. Oil-in-water (o/w) (globule size is 0.1-100 μm)
2. Water-in-oil (w/o) (globule size is 0.1-100 μm)
3. Micro Emulsion (globule size is 0.01 μm)
4. Fine Emulsion (globule size is 0.25-25 μm)

Multiple emulsions:

Multiple emulsions are the emulsion systems in which the dispersed phase contains smaller droplets that have the same composition as the external phase.

Synonyms: Double Emulsion and Liquid Membrane Systems

Types of Multiple emulsions

- Oil-in-water-in-oil (O/W/O) emulsion system
- Water-in-oil-in-water (W/O/W) emulsion system

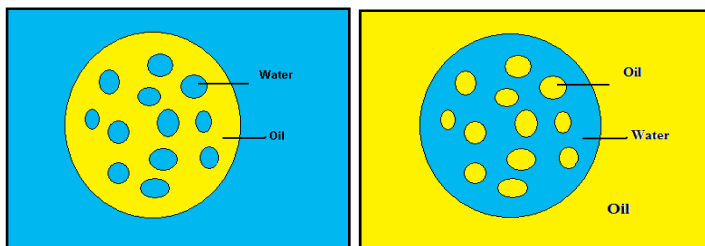
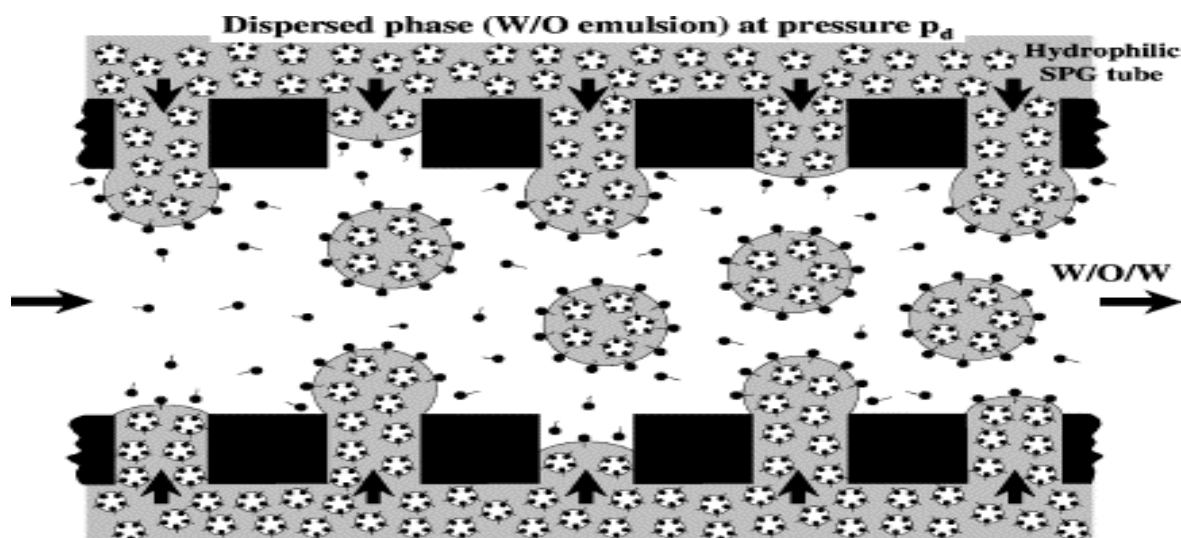


Diagram of W/O/W Emulsion



Emulsifying Agents

Agents which stabilize emulsions by Preventing / reducing the coalescence of dispersed globules. They act as bridge between the polar & non-polar phase & thus reduce the Interfacial tension.

Bancroft's Rule

1. It describes the relationship between Nature of Emulsifying Agent & Types of Emulsion Formed.
2. The solubility of agent is expressed by HLB Scale, i.e., Hydrophilic Lipophilic Balance which is proposed by Griffin.
3. Higher the HLB value of an agent, the more the Hydrophilicity.
4. HLB value 1 oil soluble agent.
5. HLB value 20 water soluble agent.
6. Combinations of emulsifying agent impart better stability than single agent.

Classification of Emulsifying Agents

A. Natural: 1. Plant – Acacia, Guar gum, Pectin

2. Animal: Gelatin, Wool fat, Egg-yolk

3. Mineral: Bentonite, Veegum

B. Synthetic: Carbopol, Silicone dioxide

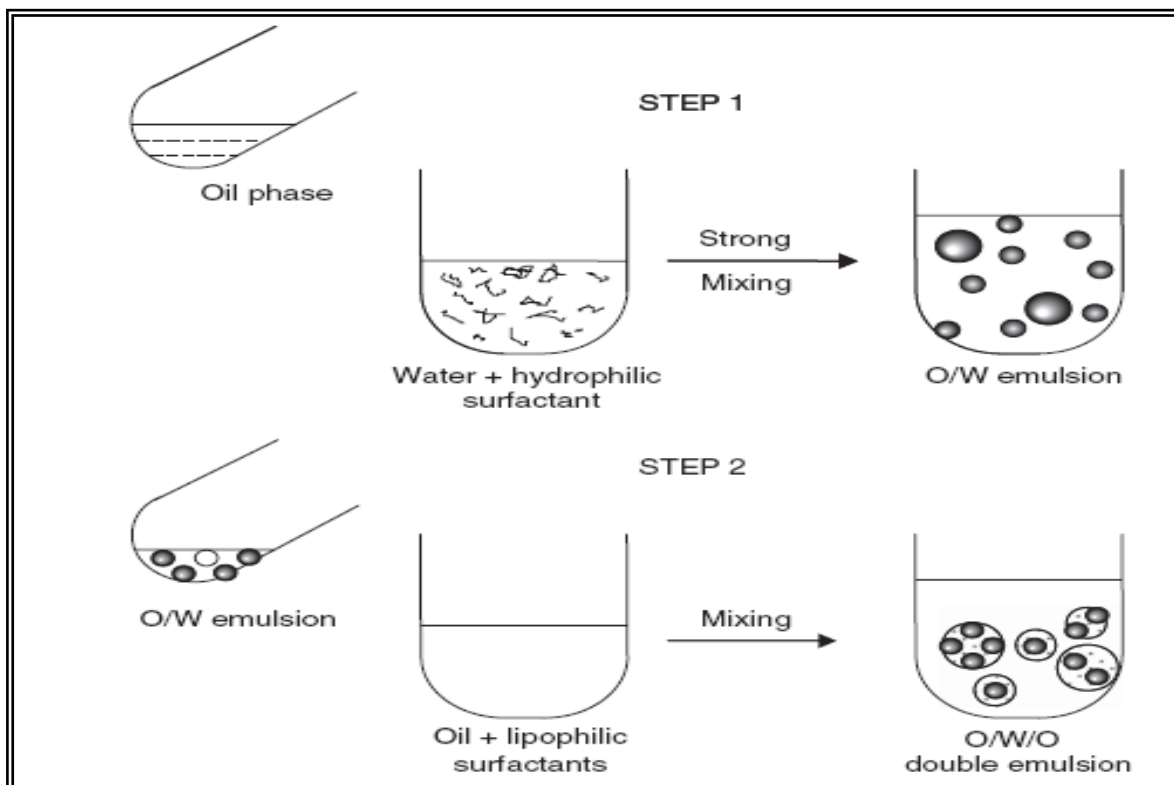
C. Semi synthetic: Methyl cellulose, CMC, HMC

Methods of Preparations Multiple emulsions

1. Conventional Method
2. Modified Two Steps Emulsification Method
3. Phase Inversion Technique
4. Membrane Emulsification

1. Conventional Method

❖ A) O/W and O/W/O Emulsion.

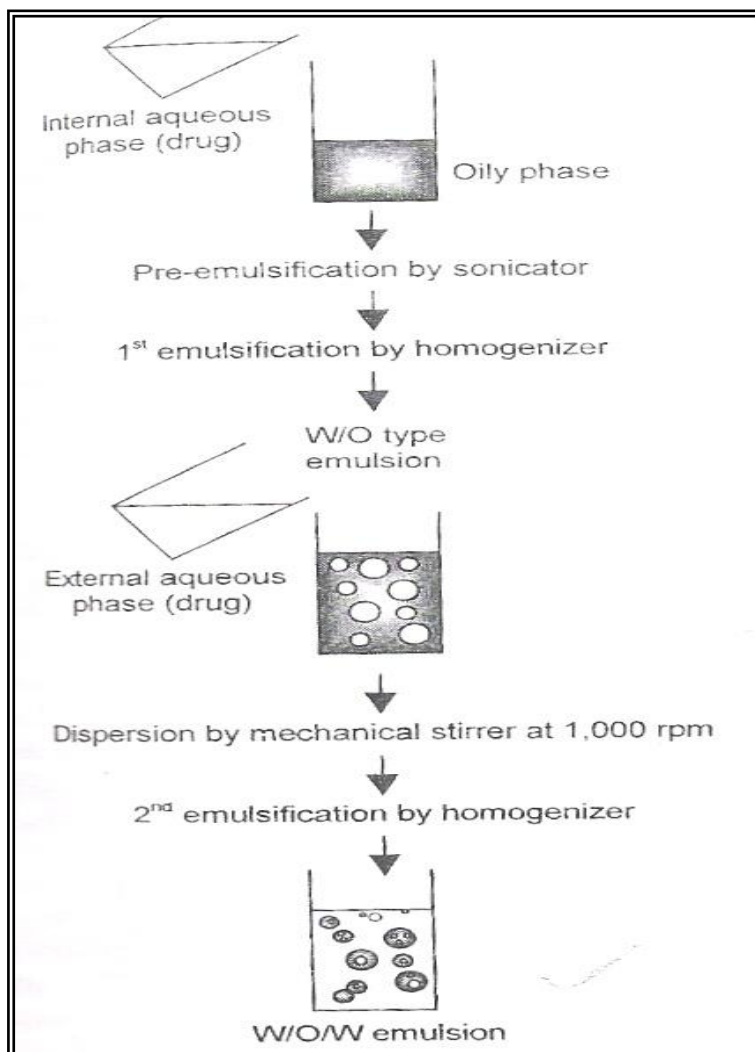


2. Modified Two Steps Emulsification Method

A) O/W and O/W/O Emulsion.

- Step:-1
 - In Formulation of O/W Emulsion,
Oil is mix with hydrophilic surfactant by strong mixing to form **oil in water** emulsion. (O/W)
- Step:-2
 - In Formulation of O/W/O Emulsion,
Above O/W Formulation mix with oil phase to form **oil in water in oil** double emulsion. (O/W/O)

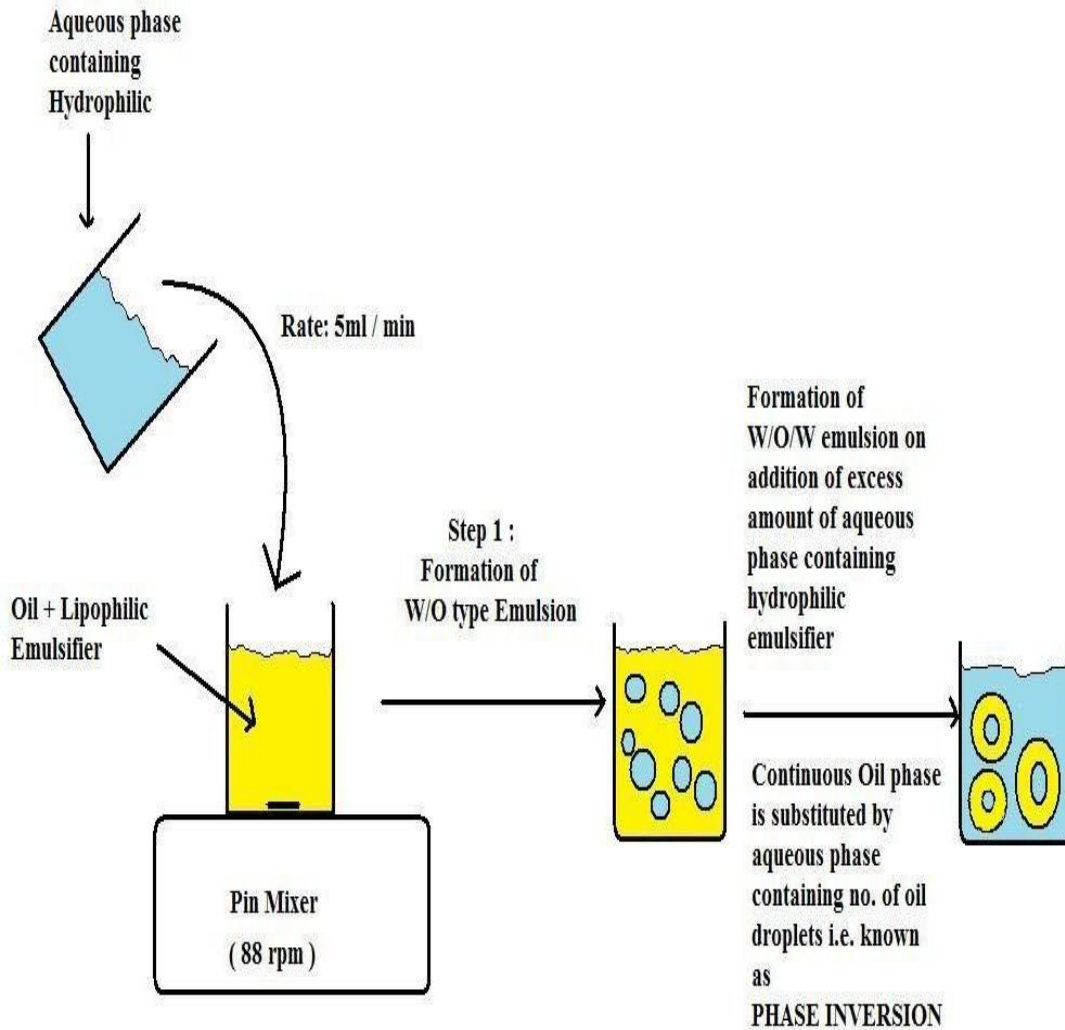
B) O/W/O Emulsion.



B) O/W/O Emulsion

- In Second Type of multiple emulsion (B), Internal aqueous phase as drug mix with oil phase by using sonicator this Method known as pre-emulsification, then homogenizer is use for mixing to form W/O type of emulsion, External aqueous Phase (Drug) is mix with above W/O by mechanical stirrer at 1.000 rpm, then second emulsification done by homogenizer to form **W/O/W** Emulsion.

3. Phase Inversion Technique



- **In Phase inversion technique.**

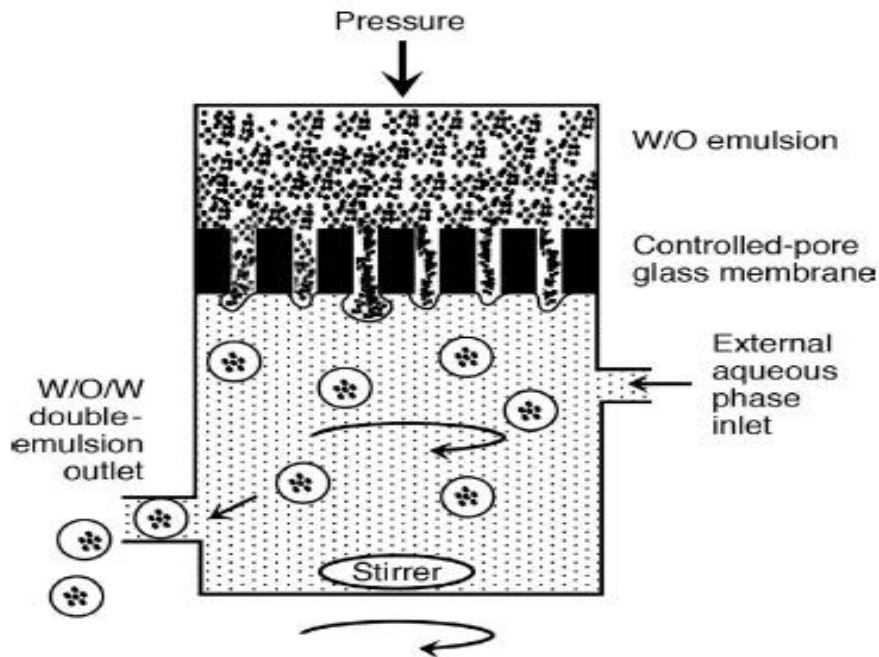
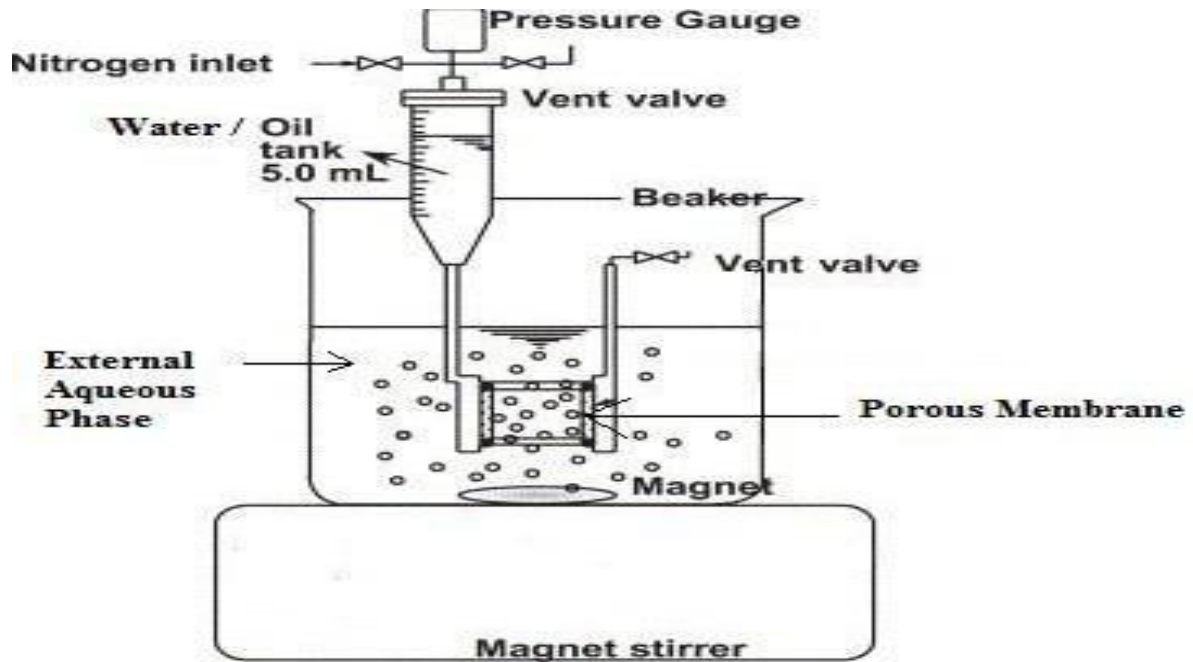
- Step:-1

Aqueous phase mix with oil and lipophilic emulsifier at rate 5 ml/min by using pin mixer, at 88 rpm to form **O/W** emulsion.

- Step:-2

Aqueous emulsion O/W emulsion mix with aqueous phase containing hydrophilic emulsifier, this is a continuous oil phase substituted by aqueous phase containing number of oil droplets known as Phase Inversion.

4. Membrane Emulsification



- In Membrane Emulsification,

Nitrogen as inert gas use to create interfacial tension by applying pressure to O/W emulsion for the purpose of stabilization. The O/W emulsion Tank having 5ml volume, as the vent of tank opens the emulsion mix with water phase which stabilizes interfacial film, after passing this interfacial film through the porous membrane aqueous layer bind with above stabilize emulsion to form **W/O/W** type of multi emulsion.

Evolution of Multiple Emulsions

1. Average Globule Size And Size Distribution:

Methods used are:

- Optical Microscopy,
- Light Scattering,
- Bright field Microscope,
- Coulter-Counter Tech.,
- Scanning Electron Microscope.

2. Area of Interfaces: It can be determined by following formula.

$$S = 6/d$$

where, S = Total area of Interface(sq.cm)

d = Diameter of Globules (cm)

3. No. of Globules: It can be measured using the Haemocytometer cell.

For this Emulsion is properly diluted.

And the globules in five groups of 16 small squares (total 80 small squares) are counted & the total no. of globules per cubic mm are calculated using the Formula :

$$\text{No of globules} \times \text{Dilution} \times 4000$$

$$\text{No of globules/mm}^3 = \text{No of small squares counted}$$

4. Rheological Evaluation: It is important parameter as it relates to Emulsion stability & clinical performance. major parameters : -Viscosity and Interfacial Elasticity

Viscosity can be measured by Brookfield Rotational Viscometer.

Interfacial Elasticity can be investigated at the mineral oil/water interface using an Oscillatory Surface Rheometer.

5. **Zeta Potential:** It is used to determine surface charge by the help of mobility & electrophoretic velocity of dispersed globules Hence it is used to predict Particle-Particle Interaction.

6. **% Drug Entrapment :** It can be determined by using :

Dialysis,

Centrifugation

Internal Tracer / Marker was used to evaluate the entrapment of drug molecule.

7. *In-Vitro* Drug Release

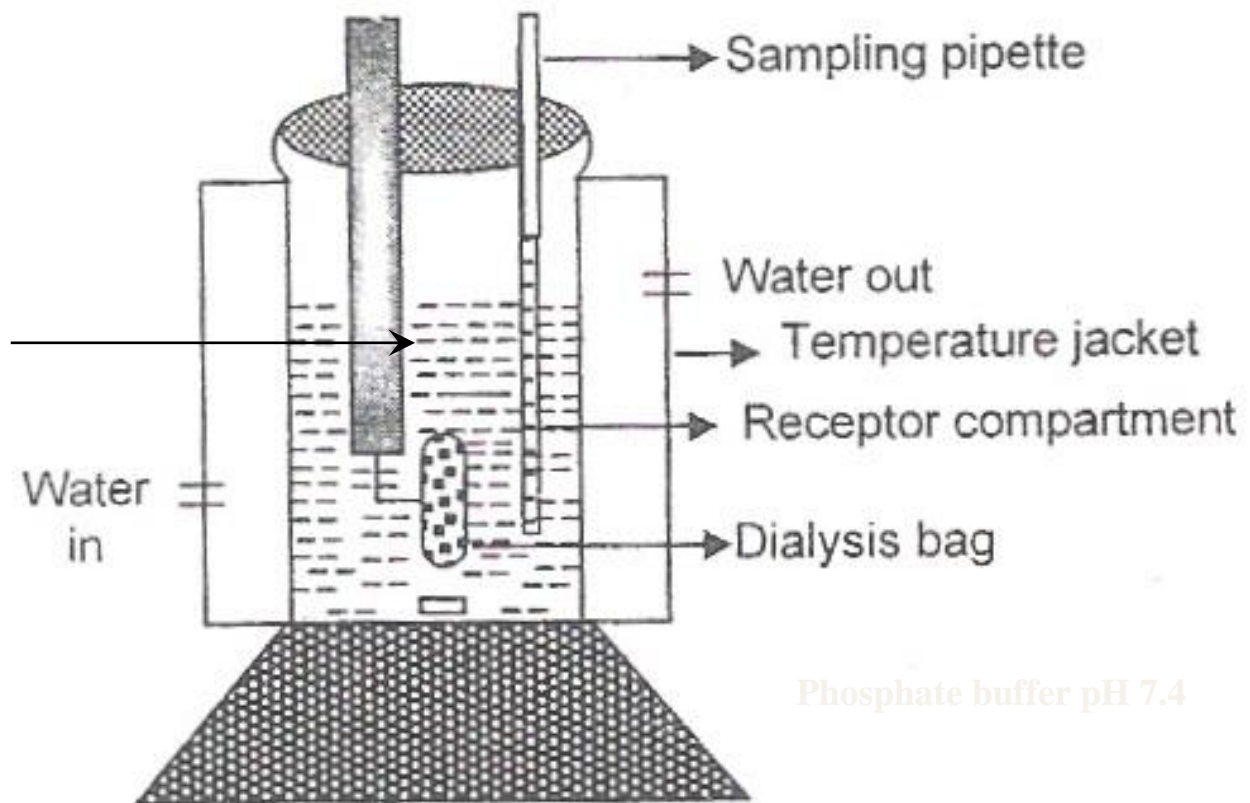
It was investigated by Nakhare & Vyas in 1995.

It is estimated by using Conventional Dialysis Technique.

Emulsion is placed in Dialysis Bag, and dialyzed against Phosphate buffer at 37°C.

Sink condition was maintained and it was stirred by using magnetic stirrer.

And Cumulative drug release was calculated



8. *In-vitro* Stability Study

1. Phase Separation - It is determined by keeping it at room temperature.
2. Photomicrography - It is the analysis of mean droplet diameter as a function of time.
3. Possible Indication of Instability of M.E.

+Leakage of contents from the Inner Phase.

Distension of internal droplets due to Osmotic Gradient

9. **Breakdown Pathway:**

In case of W/O/W emulsion,

It involves rupture of the oil layer, leads to loss of internal aqueous drops, Due to the Depletion of the Concentration of Primary Emulsifier.

Factors Affecting Stability of Multiple Emulsions

- 1) Method of preparation.
- 2) Phase volume.
- 3) Concentration, Nature and Ratio of emulsifier.
- 4) Rheological properties.

Drug Release Mechanisms and Models

(1) Diffusion mechanism: This is most obvious transport mechanism where unionized hydrophobic drug diffuses through the oil layer (Semi permeable liquid membrane) in the stable multiple emulsions.

(2) Micellar transport: Inverse micelles play key role in this transport mechanism. Inverse micelles consisting of non-polar part of surfactant lying outside 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 drug.

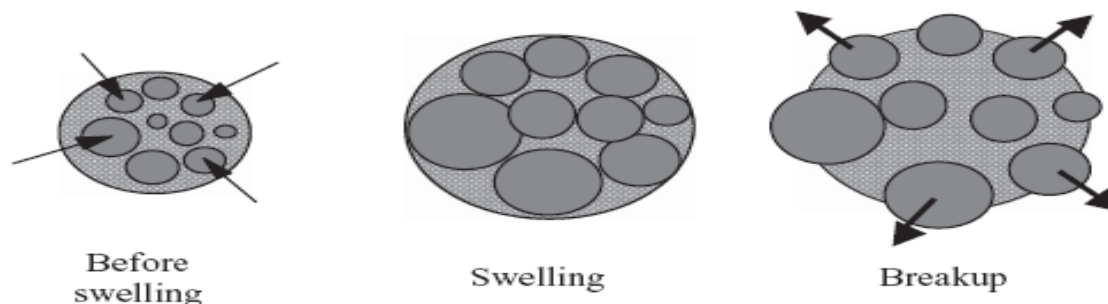
(3) Thinning of the oil membrane: Transport of water through thin oil membrane region. In this area, it is easier for the water or drug to permeate because of small oily region. Thinning of the oil membrane takes place primarily due to osmotic pressure difference between two aqueous phases.

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

(5) Facilitated diffusion (Carrier-mediated transport): This mechanism involves a special molecule (carrier) for the transfer of hydrophilic, ionic molecule from internal to external aqueous phase. This carrier molecule combines with the drug and makes it compatible to permeate through the oil membrane (Lipophilic, nonionic).

This type of mechanism behaves like ‘pumping system’ where the carrier molecule act as pump and transfer drugs from internal to external aqueous phase.

(6) Release by Breakup after Swelling: The swelling/breakdown process occurs only if there is a concentration gradient between the internal and the external aqueous phases.



Application of Multiple emulsions

- Multiple emulsions in controlled release drug delivery.
Curcumin extract nano encapsulated in chitosan and cross linked with tripolyphosphate via multiple emulsions shows 96.28% encapsulation efficacy with controlled release.
- Multiple emulsion in protein delivery
Insulin delivery – EPA, DHA, INSULIN multiple emulsion result shows DHA facilitate intestinal insulin absorption without inducing serious damage.
- Drug Targeting (e.g. Cancer targeting.)
- Vaccine Adjuvant because, w/o type of emulsion has high consistency & hence it is difficult to inject. So, it is Re-emulsified (W/O/W) which is easily administered and give better action. Immobilization of Enzyme.
- As a preparative tool for Microencapsulation Technology.
- In Food & Cosmetic preparation.
- Absorption enhancement through GIT. (e.g. W/O/W emulsion of Griseofulvin)
- Vitamin supplement.
- Hemoglobin M.E. as an oxygen delivery system.
- Miscellaneous

Extraction or Separation:

W/O/W type can extract heavy metals & contaminants from waste water.

O/W/O type can separate Hydrocarbons.

Treatment of Drug Overdose:

Removal of Acidic drugs like Barbiturates and Salicylates from GIT by use of W/O/W system.

Taste Masking of drugs:

Chlorpromazine HCL and Chloroquine

Conclusion:

Multiple emulsion have been propose to have numerous is uses including their use for enhancement of bioavailability or as a prolong drug delivery system but the inherent stability of this system need to be overcome before they find potential application in pharmaceuticals. Multiple emulsions are often stabilizing using a combination of hydrophilic and hydrophobic surfactants.

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