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SPECIALIZED PHARMACEUTICAL EMULSIONS

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SPECIALIZED PHARMACEUTICAL EMULSIONS

DEFINITION

A biphasic system consisting of two immiscible liquids, one of which (the dispersed phase) is finely and uniformly dispersed as globules throughout the second phase (the continuous phase)." Since emulsions are a thermodynamically unstable system, a third agent, the emulsifier is added to stabilize the system.

Emulsifier stabilizes the system by forming a thin film around the globules of dispersed phase

The particle size of the dispersed phase commonly ranges from 0.1 to 100 µm.

Composition

An emulsion usually consists of following three components

1. Aqueous phase
2. Oily phase
3. Emulsifying agent

1. **Aqueous Phase**
   The aqueous phase of an emulsion consists of purified or deionized water which contains water soluble drug, preservatives, flavoring and coloring agents
2. **Oily Phase**
   The oily phase of an emulsion consists of fixed, water or mineral oil which contain oil soluble vitamins and antiseptics. Few example: fixed oils are castor oil, cod liver oil, almond oil, liquid paraffin and volatile oil containing turpentine oil, cinnamon oil etc
3. **Emulsifying Agents**
   It is the component of the emulsion which binds the two immiscible liquids and stabilize the emulsion.

MICRO-EMULSIONS

Definition:

Micro-emulsions are clear, thermodynamically stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a co-surfactant.

Composition of Micro-emulsion

Micro-emulsions is defined as transparent dispersion consisting of,

- Oil
- Surfactant
- Co-surfactant
- Water

Major goals

- The delivery of hydrophilic as well as lipophilic drug as drug carriers because of it's
- Improved drug solublization capacity
- Long shelf life
- Easy of preparation
- Improvement of bioavailability

Advantages

- Increase the rate of absorption
- Increase bio-availability
- Helpful in taste masking
- Eliminates variability in absorption
- Helps in solubilizing lipophilic drugs

Disadvantages

- Use of large concentration of surfactant and co-surfactant necessary for the stabilizing micro droplets.
- Limited solubilizing capacity for high melting substances.
- Micro-emulsion stability is influenced by environmental parameters such as, temperature & pH. These parameters change upon micro-emulsion delivery to the patients.

TYPES OF MICRO-EMULSIONS

Micro-emulsions are of 3 types. They are:

1. O/W Micro-emulsion
2. W/O Micro-emulsion
3. Bi-continuous Micro-emulsion

1. **O/W Micro-emulsion** where in droplets are dispersed in the continuous aqueous phase.
2. **W/O Micro-emulsion** where in water droplets are dispersed in the continuous oil phase.
3. **Bi-continuous micro-emulsion** where in micro domains of oil & water are inter dispersed within the system.

In all the three types of micro-emulsion, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants.

PREPARATION METHODS OF MICRO-EMULSIONS

Following are the different methods used for the preparation of the micro-emulsions:

1. Phase titration method
2. Phase inversion method

1. Phase-titration Method

1. Dilution of an oil-surfactant mixture with water. [W/O]
2. Dilution of a water surfactant mixture with oil. [O/W]
3. Mixing of all components at once, in some systems, the order of ingredients addition may determine whether a micro-emulsion form is not.

2. Phase-inversion Method

1. Temperature range in which an o/w microemulsions inverts to a w/o type.
2. Using non-surfactants: polyoxyethylene are very suspectible to temperature. with increasing the temperature, the polyoxyethylene group becomes

dehydrated, altering critical packing parameter which results in the phase inversion.

3. For ionic surfactants: increasing temperature, increase the electrostatic repulsion between the surfactant head groups thus causing reversal of film curvature. Hence, the effect of temperature is opposite to the effect seen with non-ionic surfactants.

FORMATION OF MICRO-EMULSION

Micro-emulsion is formed when:

- The interfacial tension at the o/w inter phase are brought at very low level.
- The interfacial tension is kept at highly flexible and fluid

Applications

1. Oral delivery system
2. Parenteral delivery system
3. Ophthalmic delivery system
4. Micro-emulsions in detergency
5. Micro-emulsions in cosmetics
6. Micro-emulsions in foods

NANO-EMULSION

Definition

- Nano-emulsions can be defined as oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to 1000 nm.
- NEs are a group of dispersed particles used for pharmaceutical and biomedical aids and vehicles that show great promise for the future of cosmetics, diagnostics, drug therapies, and biotechnologies.
- Due to their small droplet size NEs possess stability against sedimentation or creaming with Ostwald ripening forming the main mechanism of NE breakdown.

- Internal structures depend on relative component amounts, concentrations and other characteristics.
- The relative oil and water domains that form in nano-emulsion systems are usually so small (about 10-20 nm or less in diameter) that they do not scatter light.

Advantages

- NEs have a much higher surface area and free energy than macro emulsions that make them an effective transport system.
- NEs do not show the problems of inherent creaming, flocculation, coalescence, and sedimentation, which are commonly associated with macro-emulsions.
- NEs can be formulated in variety of formulations such as foams, creams, liquids, and sprays
- NEs are non-toxic and non-irritant, hence can be easily applied to skin and mucous membranes.
- Since NEs are formulated with surfactants, which are approved for human consumption (GRAS), they can be taken by enteric route.
- NEs do not damage healthy human and animal cells, hence are suitable for human and veterinary therapeutic purposes.

TECHNIQUES OF PREPARATION

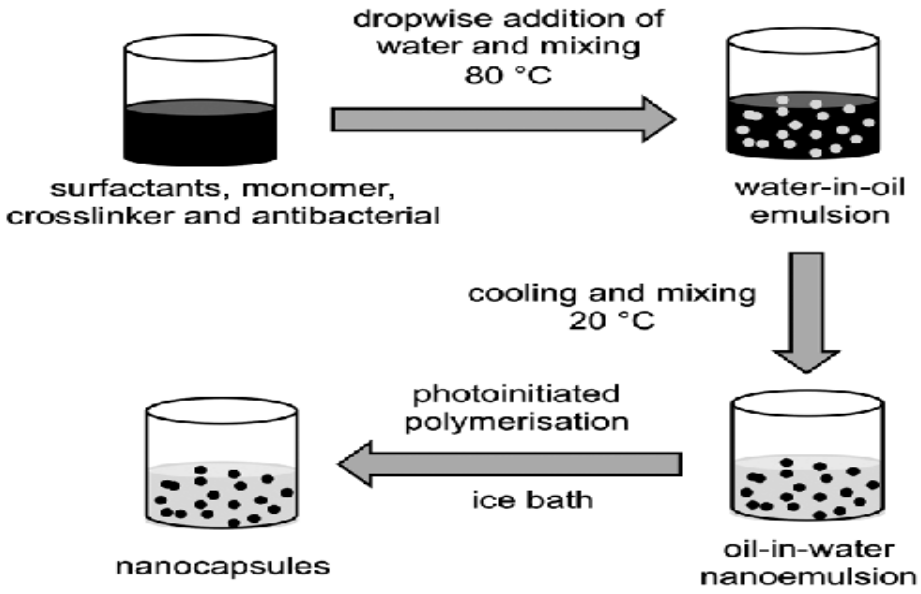
1. High -pressure homogenization
2. Micro fluidization
3. Phase inversion temperature technique.

1. **High -pressure homogenization**
   - This technique makes use of high-pressure homogenizer to produce NEs of extremely low particle size (up to 1nm)
2. **Micro-fluidization**
   - It involves the use of device that is micro fluidizer

- It uses high-pressure positive displacement pump of (500-20000)psi, which forces the product through the interaction chamber, which consists of small channels called “micro channels”.

The product flows through the micro channels on to an impingement area resulting in very fine particles of submicron range. The two solutions (aq. Phase and oily phase) are combined together and processed to obtain a stable nano-emulsion.

Phase Inversion Temperature Technique



APPLICATIONS OF NANO-EMULSIONS

1. Use of nano-emulsions in cosmetics
2. Antimicrobial nano-emulsions
3. Prophylactic in bio-terrorism attack
4. Nano-emulsions as a mucosal vaccines
5. Nano-emulsion as non-toxic disinfectant cleaner
6. Nano-emulsion in the treatment of various other disease conditions
7. Nano-emulsion formulations for improved oral delivery of poorly soluble drugs
8. Nano-emulsions as a vehicle for transdermal delivery
9. Self-nanoemulsifying drug delivery systems
10. Nano-emulsions in cell culture technology

11. Nano-emulsion in cancer therapy and in targeted drug delivery
12. Solid self-nanoemulsifying delivery systems as a platform technology for formulation of poorly soluble drugs
13. Nano-emulsions as a mucosal vaccines
14. Used to deliver either recombinant proteins or inactivated organisms to a mucosal surface to produce an immune response
15. An influenza vaccine and an HIV vaccine, can proceed to clinical trials.
16. This results in a significant systemic and mucosal immune response that involves the production of specific IgG and IgA antibody as well as cellular immunity.

Antimicrobial nano-emulsions

- The NE has a broad-spectrum activity against bacteria (e.g. E. coil, Salmonella, S. aureus), enveloped viruses (e.g. HIV, Herpes simplex), fungi (e.g. Candida, Dermatophytes), and spores (e.g. anthrax).
- The NE particles are thermodynamically driven to fuse with lipid-containing organisms.

Use of nano-emulsions in cosmetics

- NEs support the skin penetration of active ingredients and thus increase their concentration in the skin.
- Another advantage is the small-sized droplet with its high surface area allowing effective transport of the API to the skin.
- Have own bioactive effects. This may reduce the trans-epidermal water loss, indicating that the barrier function of the skin is strengthened.
- NEs are acceptable in cosmetics because there are no inherent creaming, sedimentation, flocculation, or coalescence that are observed with macro-emulsions.

Nano-emulsions as a vehicle for transdermal delivery

- Nano-emulsions as a vehicle for transdermal delivery
- Low systemic absorption
- Site-specificity and increased drug levels at injured tissues
- Reduced toxicity
- Improved pharmacological activity

Parenteral Delivery

- In order to increase the solubility of the drug
- To reduce drug toxicity
- To reduce hypersensitivity
- To reduce pain upon injection
- Formulated as long circulating vehicles
- Control the release rate
- As drug targeting agents
- Alternative formulation to long circulating vesicles

MULTIPLE EMULSION

Definition

Multiple emulsions are vesicular and complex systems. They can be considered as emulsions of emulsions and have shown promise in cosmetic, pharmaceutical and separation sciences.

Pharmaceutical applications of multiple emulsion

- Their potential pharmaceutical applications include uses such as taste masking, adjuvant vaccines, an immobilization of enzymes and sorbent reservoir of overdose treatments, and for enhancement of enteral or dermal absorption.
- Multiple emulsions have been formulated as cosmetics, such as skin moisturizer.
- Prolonged release can also be obtained by means of multiple structures.
- These systems have some advantages, such as the protection of the entrapped substances and the incorporation of several actives in the different compartments.
- Despite their potential usefulness, applications of multiple emulsions have been limited because of thermodynamic instability and their complex structure.

TYPES OF MULTIPLE EMULSION

Multiple emulsions are also considered to be of two types:

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

1. O/W/O systems

An aqueous phase (hydrophilic) separates internal and external oil phases. In other words, O/W/O is a system in which water droplets may be surrounded in an oil phase, which in turn encloses one or more oil droplets. Mixing with an aqueous solution of hydrophilic emulsifier W/O Span 80 W/O/W Tween 80 Mixing with the mixture of oil and hydrophobic emulsifier O/W Tween 80 O/W/O Span 80The simplest multiple emulsions, sometimes called " double emulsions, " are in fact ternary systems, having either a water in oil in water or an oil in water in oil structure, whereby the dispersed droplets contain smaller droplets of a different phase.

2. W/O/W systems

In W/O/W systems an organic phase (hydrophobic) separates internal and external aqueous phases. In other words, W/O/W is a system in which an oil droplet may be surrounded by an aqueous phase, which in turn encloses one or several water droplets. These systems are the most studied among the multiple emulsions. The immiscible oil phase, which separates the 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 the internal aqueous phase.

METHOD OF PREPARATION

1. Two-Step Emulsification (Double Emulsification)
2. Phase Inversion Technique (One step Technique)
3. Membrane Emulsification Technique

1. **Two-Step Emulsification (Double Emulsification)**
   - Two-Step Emulsification (Double Emulsification) emulsification methods involve re-emulsification of primary W/O or O/W emulsion using a suitable emulsifier agent.
   - The first step involves, obtaining an ordinary W/O or O/W primary emulsion wherein an appropriate emulsifier system is utilized.

- In the second step, the freshly prepared W/O or O/W primary emulsion is 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. **Phase Inversion Technique (One step Technique)**
   - An increase in volume concentration of dispersed phase may cause an increase in the phase volume ratio, which subsequently leads to the formation of multiple emulsions.
   - The method typically involves the addition of an aqueous phase containing the hydrophilic emulsifier [Tween 80/sodium dodecyl sulphate (SDS) or Cetyl trimethyl ammonium salt (CTAB)] to an oil phase consisted of liquid paraffin and containing lipophilic emulsifier (Span 80).
   - A well-defined volume of oil phase is placed in a vessel of pin mixer. An aqueous solution of emulsifier is then introduced successively to the oil phase in the vessel at a rate of 5 ml/min, while the pin mixer rotates steadily at 88 rpm at room temperature. When volume fraction of the aqueous solution of hydrophilic emulsifier 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 and formation of W/O/W multiple emulsion

Membrane emulsification procedure

- A membrane emulsification procedure has been developed as a novel emulsification method. In this method, a W/O emulsion (a dispersed phase) is extruded into an external aqueous phase (a continuous phase) with a constant pressure through a Porous Glass Membrane, which should have controlled and homogeneous pores. The particle size of the resulting emulsion can be controlled with proper selection of Porous Glass Membrane as the droplet size depends upon the pore size of the membrane.

Application

- Controlled and sustained drug delivery
- Drug targeting
- Absorption enhancement through GIT
- Vaccine adjuvant
- Immobilization of enzyme

- As a preparative tool for microencapsulation technology
- Food and cosmetics applications
- Miscellaneous
- As sorbent reservoir in drug overdose treatment
- Protection action
- Taste masking action

EMULGELS

Purpose & Objective

- When gel and emulsion are used in combined form the dosage form are referred as emulgel.
- The major objective behind this formulation is delivery of hydrophobic drugs to systemic circulation via skin.

Advantages

- Avoidance of first pass metabolism.
- Avoidance of gastrointestinal incompatibility.
- More selective to a specific site.
- Improve patient compliance.
- Suitability for self medication.
- Providing utilization of drug with short biological half life and narrow therapeutic window.
- Ability to easily terminate medication

Disadvantages

- Skin irritation on contact dermatitis.
- Possibility of allergenic reactions.
- Poor permeability of some drug through skin.
- Drug of large particle size not easy to absorb through the skin.

Method of Preparation

STEP 1: Formulation of Emulsion either O/W or W/O

STEP 2: Formulation of gel base

STEP 3: Incorporation of emulsion into gel base with continuous stirring

Method of Preparation

- The Gel in formulations were prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed and Carbopol 940 in purified water with constant stirring at a moderate speed then the pH are adjusted to 6 to 6.5 using Tri ethanol amine (TEA).
- The oil phase of the emulsion was prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water.
- Methyl and Propyl paraben was dissolved in propylene glycol whereas drug was dissolved in ethanol and both solutions was mixed with the aqueous phase.
- Both the oily and aqueous phases were separately heated to 70° to 0°C; then the oily phase was added to the aqueous phase with continuous stirring until cooled to room temperature.
- And add Glutaraldehyde in during of mixing of gel and emulsion in ratio 1:1 to obtain the emulgel.

CHARACTERIZATION OF EMULGELS

Physical Examination:

- The prepared emulgel formulations are inspected visually for their color, homogeneity, consistency and phase separation.

Rheological Studies*:*

- The viscosity of the different emulgel formulations is determined at 25°C using a cone and plate viscometer with spindle (Brookfield Engineering Laboratories,) and connected to a thermostatically controlled circulating water bath.