A REVIEW ON NANOEMULSIONS EXPLAINED: TECHNIQUES, BENEFITS, AND APPLICATIONS

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Abstract:

Nanoemulsions are tiny mixtures of two liquids that normally don't mix, like oil and water. They can either have water droplets in oil (W/O) or oil droplets in water (O/W), and they're stabilized by special substances called surfactants that help keep them from separating. These ultrafine dispersions have unique properties that make them useful for various applications, especially in drug delivery.

Despite their potential, there's still limited knowledge about how to develop, manufacture, and manipulate nanoemulsions. This is partly because traditional methods of making and stabilizing emulsions don't fully apply to nanoemulsions. This gap in understanding is what this review aims to address.

We will dive into the details of different components used in nanoemulsions, the techniques for making them, the conditions needed for production, and how they behave structurally. We'll also discuss how they can break down (destabilization mechanisms) and their applications in delivering drugs. Our goal is to spark interest among those looking to explore this exciting area of research.

Keywordes: *Emulsion, Micro emulsion, Nano emulsion, Surface tension, Zeta potential.*

Introduction:

Emulsions are mixtures of two liquids that don't naturally blend, like oil and water. To create these mixtures, we use mechanical force and surfactants—special molecules that help reduce the surface tension between the two liquids.

1. Surfactants: These are amphiphilic molecules, meaning they have both hydrophilic (water-attracting) and hydrophobic (water-repelling) parts. They help keep the emulsion stable by reducing the attractive forces that cause the liquids to separate.
2. Hydrophilic-Lipophilic Balance (HLB): This is a measure that helps us choose the right surfactant for our emulsion.

- Surfactants with low HLB values (3-8) are good for creating water-in-oil (W/O) emulsions.

- Those with high HLB values (8-18) work well for oil-in-water (O/W) emulsions.

3. Critical Packing Parameter (CPP): This parameter describes the shape and size of the surfactant molecules and gives insight into how they will behave in the emulsion.

a) Micro-emulsions:

- These are clear, stable mixtures that look uniform.

- They are made using oil, water, surfactants, and sometimes co-surfactants, and typically contain very small particles ranging from 1 to 100 nanometers, usually around 10 to 50 nanometers.

- Micro-emulsions are thermodynamically stable, meaning they won't separate over time.

b) Nano-emulsions:

- Similar to micro-emulsions, nano-emulsions also consist of tiny particles but are created through mechanical means rather than spontaneously forming.

- They have a droplet size on the nanoscale and offer different properties compared to traditional emulsions.

Macroemulsions are mixtures of at least two liquids that don't blend well, like oil and water. These emulsions are not naturally stable; instead, they rely on kinetic factors to stay mixed.

- Thermodynamic Instability: Macroemulsions are considered thermodynamically unstable, meaning they can separate over time. Their stability relies on the size of the droplets and the composition of the emulsion.

1. Droplet Size: The droplets in macroemulsions are usually larger than 1 micrometer. Because of this larger size, they can be affected by gravity, leading to settling or separation.
2. Preparation Methods: Different methods for making emulsions can result in varying droplet sizes, which can significantly impact stability. This means that how you mix the liquids matters a lot.
3. Mini-emulsions and Ultrafine Emulsions: Emulsions with droplet sizes between conventional emulsions and microemulsions (specifically, sizes ranging from 20 to 500 nanometers) are referred to as mini-emulsions or ultrafine emulsions. These smaller droplets can help improve stability and other properties.

- Macroemulsions are larger, less stable mixtures that can benefit from careful preparation techniques to enhance their stability and performance. Smaller emulsions, like mini-emulsions, offer more stability due to their reduced droplet sizes.
- Submicron emulsions, including translucent emulsions and nano-emulsions, have very small droplet sizes. Because of their tiny droplets, nano-emulsions can look clear or transparent. They are also more stable due to a phenomenon called Brownian motion, which keeps the droplets suspended and prevents them from settling or separating.

1. Metastability: Unlike microemulsions, which are stable, nano-emulsions are considered metastable. This means they can stay mixed for a while but aren't permanently stable. You can dilute them with water without affecting the size of the droplets.

2. Preparation Methods: To create these tiny droplets, you usually need to use high-energy mechanical methods. This can include:
   - High-shear stirring: Mixing at high speeds to break up droplets.
   - High-pressure homogenization: Forcing the mixture through a narrow space to create pressure that breaks up the droplets.
   - Ultrasound: Using sound waves to create high-energy conditions that break the droplets apart.
3. Energy and Surfactant Needs: These methods require a lot of energy to overcome something called Laplace pressure, which resists the breaking of larger droplets. You also need to use more surfactant at the surface to help reduce this pressure.
4. Industrial Challenges: The need for high energy and surfactant makes these processes less practical for large-scale industrial applications, as they can be costly and complicated.

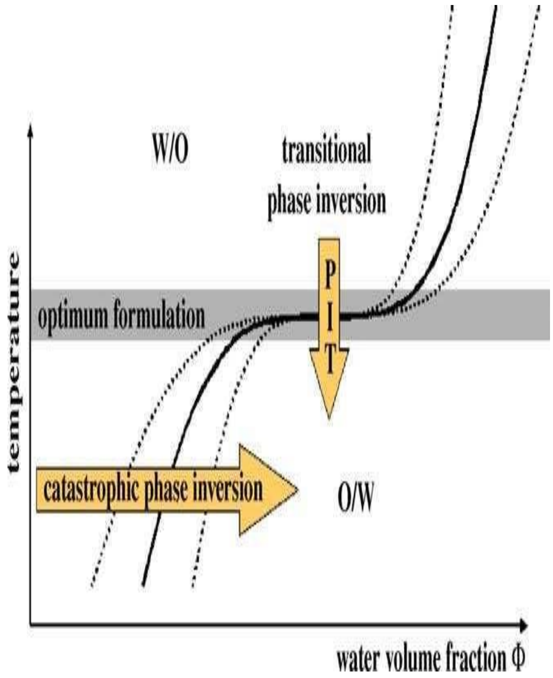


Fig.Schematic illustration of both catastrophic and transitional phase inversion for the preparation of finely dispersed O/W emulsions. The solid black line marks the inversion locus, the dotted lines the hysteresis zone. Within the optimum formulation zone and at the inversion locus, the interfacial tension is minimal. During low-energy emulsification, this ultralow interfacial tension is employed for the formation of finely dispersed droplets, while the final emulsion should be far away from these regions to enhance emulsion stability.

When creating very small droplets in emulsions, there are low-energy methods that rely on the natural properties of the materials involved.

1) Low-Energy Emulsification: This approach changes the surfactant's curvature, which helps in forming smaller droplets. For non-ionic surfactants, you can achieve this by adjusting the temperature:

- Phase Inversion Temperature (PIT) Method: At lower temperatures, you get an oil-in-water (O/W) emulsion. As you increase the temperature, it can shift to a water-in-oil (W/O) emulsion. Cooling the system can lead to a point where the curvature is zero and the surface tension is minimal, allowing for the creation of tiny oil droplets.

2) Other Parameters: Besides temperature, factors like salt concentration and pH can also affect the emulsion. This is based on the concept of surfactant affinity difference (SAD), which helps understand how surfactants behave under different conditions.

3) Emulsion Inversion Point (EIP) Method: By gradually adding water to oil, you can transition the system from forming W/O emulsions to O/W emulsions. This is particularly effective with short-chain surfactants that create flexible layers at the oil-water boundary. At the inversion point, minimal surface tension occurs, promoting the formation of fine droplets.

4) Droplet Size Factors: The study investigated how to prepare O/W emulsions using a mixture of two non-ionic surfactants commonly found in creams and lotions. They found that you need a specific amount of surfactant to create submicrometer-sized droplets.

5) Mapping Phase Behavior: By testing different surfactant-to-oil ratios and adding water gradually, they mapped parts of the phase diagram. They discovered that the final droplet size depended more on the ratio of surfactant to oil rather than the amount of water added. This indicates that the droplet size is influenced by the structure formed during the phase inversion.

Emulsion:

Emulsions are dispersions made up of two immiscible liquid phases which are mixed using mechanical shear and surfactant. Particle size of this conventional emulsion grows continuously with time and hence finally separation occurs at gravitational force thus these emulsions are thermodynamically unstable.

Here's a simplified overview of the main theories explaining how emulsifiers work to stabilize emulsions:

1. Surface Tension Theory

This theory suggests that emulsifiers reduce the surface tension between two immiscible liquids (like oil and water). By lowering this tension, emulsifiers help the liquids mix better and decrease the repelling forces between them, making it easier for droplets to stay dispersed.

2. Oriented-Wedge Theory

According to this theory, emulsifiers form a monolayer around the droplets of the internal phase (like oil droplets in water). These emulsifiers position themselves based on how well they dissolve in each liquid. Their curved shape around the droplets helps keep the droplets separate and stable.

3. Plastic or Interfacial Film Theory

This theory describes how emulsifiers create a thin film at the boundary between the two liquids. By adsorbing onto the surface of the droplets, the emulsifiers form a protective layer that prevents the droplets from coming into contact and merging (coalescing). A stronger, more flexible film provides better physical stability to the emulsion.

4. Repulsion Theory

This theory explains that emulsifiers create a film around the droplets that allows them to repel each other. This repulsion keeps the droplets suspended in the surrounding liquid, preventing them from clumping together.

5. Viscosity Modification

According to this theory, emulsifiers increase the viscosity of the continuous phase (the liquid in which the droplets are dispersed). This thicker liquid helps keep the droplets suspended, creating a stable mixture.

Types:

Following are different types of emulsions:

1. Water-in-oil (w/o)
2. Oil-in-water (o/w)
3. Water-in-oil-in-water (w/o/w)
4. Oil-in-water-in-oil (o/w/o)

Metod Of Preparation:

1. Dry Gum Method:

The Dry Gum Method is a classic technique used to prepare emulsions, particularly oil-in-water (O/W) emulsions. This method is often employed in pharmaceutical and cosmetic formulations. Here's a breakdown of the process and key points:

1. Ingredients:

- Oil Phase: Typically a fixed oil.
- Water Phase: Usually purified water.
- Emulsifying Agent: A gum, such as acacia gum or tragacanth, is commonly used.

2. Procedure:

- Initial Mixing: The emulsifying agent (gum) is first mixed with the oil phase in a dry form. This creates a thick paste.
- Incorporating Water: Gradually, a small volume of water is added to the mixture while continuously stirring. The water is incorporated slowly to ensure a stable emulsion is formed.
- Emulsification: Once the emulsion starts to form, more water can be added gradually until the desired volume is achieved.
- Stirring: The mixture is stirred continuously to ensure uniform dispersion of droplets.

3. Characteristics:

- The Dry Gum Method typically results in a stable emulsion due to the formation of a protective film around the dispersed droplets.
- This method is particularly effective for emulsifying agents that can absorb and retain water.

Advantages:

- Simplicity: The technique is straightforward and does not require specialized equipment.
- Stability: Emulsions prepared by this method tend to have good stability due to the gum's ability to create a thickened interface.
- Versatility: It can be adapted for various formulations, including creams and lotions.

Applications:

- Pharmaceuticals: Used to create ointments and creams that require stable emulsions.

- Cosmetics: Commonly used in lotions and creams to ensure even distribution of oils in water-based formulations.
- Food Products: Sometimes employed in the production of food emulsions like salad dressings and sauces.

2. Wet Gum Method:

The Wet Gum Method is another traditional technique for preparing emulsions, particularly oil-in-water (O/W) emulsions. It is commonly used in the pharmaceutical, cosmetic, and food industries. Here's an overview of the method.

1. Ingredients:
   - Oil Phase: A fixed oil is typically used.
   - Water Phase: Purified water.
   - Emulsifying Agent: A gum, such as acacia gum or tragacanth, which acts as the emulsifier.
2. Procedure:
   - Hydration of Gum: The emulsifying agent (gum) is first mixed with a small amount of water to form a thick paste. This allows the gum to hydrate fully.
   - Incorporating Oil: Once the gum is hydrated, the oil phase is gradually added to the mixture while continuously stirring. This helps create a stable emulsion.
   - Emulsification: The mixture is stirred until the oil is uniformly dispersed in the water phase. Additional water can be added as needed to achieve the desired consistency.
   - Final Mixing: The emulsion is mixed thoroughly to ensure a smooth and stable product.
3. Characteristics:
   - The Wet Gum Method typically results in a stable emulsion due to the hydrophilic properties of the gum, which helps stabilize the oil droplets in water.
   - The method is particularly effective for emulsifying agents that require hydration for optimal performance.

Advantages:

- Stability: Emulsions prepared using the Wet Gum Method are often stable due to the formation of a thick layer of gum around the oil droplets.
- Ease of Use: The method is relatively straightforward and does not require complex equipment.
- Versatility: Suitable for a wide range of applications in pharmaceuticals, cosmetics, and food products.

Applications:

- Pharmaceuticals: Used for making creams, ointments, and emulsions that require a stable mixture of oil and water.
- Cosmetics: Commonly found in lotions and creams, ensuring an even distribution of ingredients.
- Food Industry: Can be used to prepare emulsions like sauces, dressings, and creams.

3. In Situ Soap method:

The in situ soap method is a technique used to prepare emulsions, particularly in the context of creating oil-in-water (O/W) emulsions. This method involves the formation of soap (or emulsifying agents) during the emulsion preparation process, rather than using pre-made emulsifiers.

1. Concept:

   - The in situ soap method relies on the reaction of fatty acids (usually from oils or fats) with a strong base (such as sodium hydroxide or potassium hydroxide) to produce soap. This soap acts as the emulsifying agent that stabilizes the emulsion.

2. Ingredients:
- Oil Phase: Typically consists of a fixed oil or fat that contains fatty acids.
- Base: A strong alkaline substance, commonly sodium hydroxide or potassium hydroxide.
- Water Phase: Purified water is used to create the emulsion.

3. Procedure:
- Preparation of Soap: The base is added to water to create an alkaline solution. This is then mixed with the oil phase. The alkaline solution reacts with the fatty acids in the oil, resulting in the formation of soap.
- Emulsification: As the soap is formed, it helps to stabilize the oil droplets in the water phase. Continuous mixing is essential to ensure a uniform dispersion of oil droplets.
- Adjusting pH: The pH of the emulsion may be adjusted after emulsification to optimize stability and performance.

4. Characteristics:
- The in situ soap method produces emulsions that have good stability due to the presence of soap, which reduces the interfacial tension between oil and water.
- The soap molecules form a protective layer around the oil droplets, preventing coalescence.

Advantages:
- Cost-Effectiveness: Using in situ generated soap can be more economical than using commercial emulsifiers.
- Versatility: This method can be adapted to different types of oils and fats, making it suitable for various applications.
- Simplicity: The process is straightforward and can be carried out with relatively simple equipment.

Applications:
- Pharmaceuticals: Used for preparing creams, ointments, and emulsions where stability is crucial.
- Cosmetics: Common in lotions and creams, providing effective emulsification and stabilization.
- Food Industry: Utilized in certain food products to create stable emulsions like sauces and dressing.

4. Mechnical Method:

Emulsions are mixtures of two immiscible liquids, typically oil and water, that require an emulsifying agent to stabilize them. The mechanical method of creating emulsions involves physical processes to disperse one liquid into the other. Here are some key points about the mechanical method of emulsion preparation:

1. Basic Principles:

- Dispersing Phase: One liquid (usually oil) is dispersed into the other (usually water).

- Emulsifying Agents: Stabilizers like surfactants (e.g., lecithin, mono- and diglycerides) are often used to prevent the coalescence of dispersed droplets.

2. Mechanical Techniques:

- Homogenization: This process uses high pressure to force the mixture through a narrow gap, breaking the droplets into smaller sizes. It's commonly used in food processing and pharmaceuticals.

- Stirring: Simple mechanical stirring can create emulsions, especially with emulsifying agents, but may not produce a stable emulsion.

- Ultrasonication: High-frequency sound waves create cavitation bubbles that collapse, generating shear forces that help to disperse the liquid phases.

- High-Shear Mixing: Specialized equipment (like high-shear mixers) provides intense mechanical shear, efficiently breaking down droplets into finer sizes.

3. Factors Influencing Emulsion Stability:
- Droplet Size: Smaller droplets tend to be more stable due to increased surface area.
- Viscosity: Higher viscosity can help stabilize emulsions by slowing the movement of droplets.
- Temperature: Temperature affects viscosity and solubility of emulsifying agents, influencing stability.
- pH and Ionic Strength: These can affect the charge and interactions of emulsifying agents.

4. Applications:

- Food Industry: Mayonnaise, salad dressings, and sauces.
- Cosmetics: Creams and lotions.
- Pharmaceuticals: Drug delivery systems.
- Paints and Coatings: To improve texture and application.

5. Advantages and Disadvantages:
- Advantages: Allows for the creation of stable emulsions without the need for chemical emulsifiers, scalable for industrial applications.
- Disadvantages: Can require significant energy input, and some mechanical methods may lead to heat generation, potentially affecting sensitive components.

Conclusion:

Mechanical methods of emulsion preparation are essential in various industries, offering a range of techniques that can be tailored to specific applications. Understanding the principles and factors involved can help optimize the stability and quality of emulsions.

Advantages Of Emulsion:

• To solubilise hydrophobic or oil soluble drugs

• To enhance drug absorption through

• To enhance topical absorption of drugs

• To mask the disagree able taste and odour of drugs

• To enhance palatability of nutrient oils

Disadvantages Of Emulsion:

• Less stable as compared to other dosage forms

• Possesses short shelf-life

• Creaming, cracking (breaking), flocculation and phase inversion are common problems observed during storage of emulsion

Nanoemulsion:

- **Definition and Characteristics:**

  Nanoemulsions are fine dispersions of two immiscible liquids (typically oil-in-water (O/W) or water-in-oil (W/O)) that are stabilized by surfactants.

  The mean droplet size is generally less than 500 nm, which gives them a distinct appearance that ranges from clear to hazy, contrasting with the milky white appearance of coarse emulsions due to larger droplet sizes.

- **Comparison with Microemulsions:**

Though nanoemulsions and microemulsions may share similar droplet sizes, they differ significantly in structure and stability.

Microemulsions are thermodynamically stable systems, while nanoemulsions are kinetically stable and may separate over time.

- **Applications and Dosage Forms:**

Nanoemulsions can be formulated into various dosage forms, including:

i. Liquids
ii. Creams
iii. Sprays
iv. Gels
v. Aerosols
vi. Foams

Routes of Administration: They can be administered via multiple routes, such as:

i. Topical
ii. Oral
iii. Intravenous
iv. Intranasal
v. Pulmonary
vi. Ocular

- **Advantages of Nanoemulsions:**

1. Higher Solubilization Capacity: They can solubilize hydrophobic drugs more effectively than simple micellar dispersions.

2. Enhanced Kinetic Stability: The small droplet size helps prevent common destabilization processes like creaming and coalescence.

3. Improved Drug Delivery:

- Parenteral Applications: They can protect drugs from harsh conditions and target specific organs using the enhanced permeability and retention effect.

- Oral Applications: Their small droplet size increases the rate of drug dissolution and bioavailability, especially for poorly soluble drugs.

4. Reduced First-Pass Metabolism: Some nanoemulsions can facilitate direct lymphatic absorption, enhancing bioavailability and allowing for lower dosages.

5. Masking Taste: They can effectively mask bitter tastes, improving patient compliance.

- **Mechanism of Drug Release:**

- Drug release from nanoemulsions involves the partitioning of the drug from the oil phase into the surfactant layer, followed by diffusion into the aqueous phase.

- As the drug diffuses, it undergoes nanoprecipitation, significantly increasing its surface area and accelerating dissolution in accordance with the Noyes-Whitney equation.

- **Factors Influencing Bioavailability:**

- Transport Mechanisms: Nanoemulsions can facilitate both paracellular and transcellular transport across biological membranes.

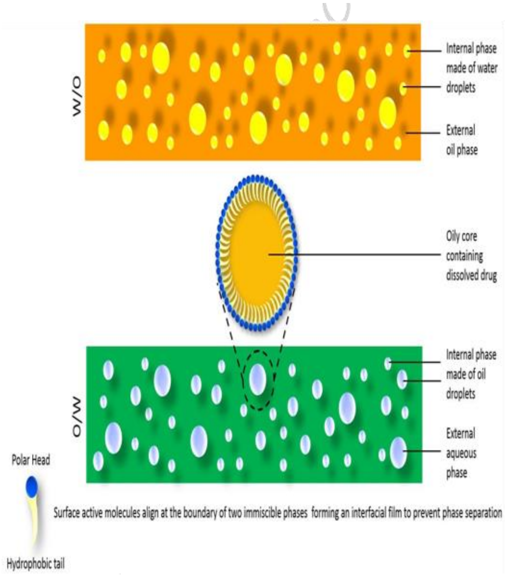
- Gastric Retention: Prolonged retention in the stomach due to mucosal entanglement can further enhance bioavailability.

- **Challenges and Considerations:**

Despite their numerous advantages, the development and manufacturing processes of nanoemulsions remain complex and less understood. The need for optimizing composition to achieve desired release profiles while maintaining stability is crucial for effective drug delivery systems.

In conclusion, nanoemulsions hold great promise in various fields, particularly in pharmaceuticals and cosmetics, by leveraging their unique properties for enhanced drug solubility, stability, and bioavailability. Continued research into their formulation and application will be essential for fully realizing their potential.

Nanoemulsions offer unique advantages in drug delivery, but they also have limitations that need careful consideration. They can be challenging to stabilize, especially for substances with high melting points, which cannot be easily solubilized. It's crucial to use non-toxic ingredients—ideally those classified as Generally Recognized As Safe (GRAS)—when developing nanoemulsions for human use.



One major drawback of using low-energy methods to create nanoemulsions is the need for a large amount of surfactants. Excessive surfactant can disrupt cell membranes, making internal use problematic. Additionally, the cost of manufacturing nanoemulsions can be high, as it often requires expensive equipment.

Types Of Nanoemulsion:

Nanoemulsions are tiny mixtures of liquids, and they can be classified into different types based on how the liquids are organized:

1. Biphasic Nanoemulsions: These have two main phases:

- O/W (Oil in Water): Oil droplets are dispersed in water.

- W/O (Water in Oil): Water droplets are dispersed in oil.

2. Multiple Nanoemulsions: These are more complex, like a layer of oil containing tiny water droplets, which is then mixed into a larger amount of water (W/O/W).

- Phase Volume Ratio: This measures the relative volumes of the internal phase (the droplets) and the continuous phase (the surrounding liquid). It helps determine how many droplets there are and how stable the mixture will be.

- Surfactants: These are substances that help stabilize the emulsions. If the main surfactant is water-soluble, it will favor the O/W type. If it's oil-soluble, it will favor the W/O type.

- Stability and Inversion: The polar part of a surfactant is better at preventing the droplets from merging together (coalescing). For O/W emulsions, you can have a lot of oil without losing stability, but W/O emulsions can easily flip to O/W if you add more water.

- Phase Inversion: If you increase the internal phase (Φ) of a W/O emulsion beyond 40%, it can change into an O/W emulsion.

Detection Methods:

- Fluorescence: Some oils will glow under UV light. In an O/W nanoemulsion, you'll see dots of fluorescence, while in a W/O nanoemulsion, the entire area will light up.

- Conductivity Tests: These can also help identify if the nanoemulsion is O/W or W/O.

Components Of Nanoemulsion:

1. Oil/Lipid Concentration: In oil-in-water (O/W) nanoemulsions, the amount of oil or lipids usually ranges from 5% to 20%. However, it can sometimes go up to 70% depending on the formulation.

2. Choosing Oils: The type of oil or lipid used is often based on how well it can dissolve the drug intended for delivery. Common oils used include:

- Soybean oil
- Sesame oil
- Cottonseed oil
- Safflower oil
- Coconut oil
- Rice bran oil

These oils are classified by their fatty acid chain lengths into:

- Long-chain triglycerides (LCT)
- Medium-chain triglycerides (MCT)
- Short-chain triglycerides (SCT)

3. Common Carriers: Vitamin E (D-α-Tocopherol) is frequently used as a carrier in nanoemulsions. Other substances like oleic acid and ethyl oleate are also used for various applications, including oral, topical, and injectable nanoemulsions.

4. Marine Oils: There's ongoing research into using marine oils, like salmon oil, for emulsification. These oils are rich in polyunsaturated fats (having multiple double bonds) and may offer health benefits, especially for patients with heart issues who might not tolerate regular oils.

5. Impact on Bioavailability: The type of oil used can affect how well the active ingredients in the nanoemulsion are absorbed by the body. For example, research has shown that curcumin nanoemulsions made with LCT and MCT are absorbed better than those made with SCT, as they are digested less.

Surfactants are special molecules that help stabilize nanoemulsions by lowering the tension at the oil-water interface, preventing tiny droplets from clumping together. They have both hydrophilic (water-loving) and hydrophobic (water-repelling) parts, which makes them effective at adsorbing to the interface quickly. This adsorption provides stability through either steric (physical space) or electrostatic (charge) means, or a combination of both.

One well-known surfactant used in nanoemulsions is lecithin, which comes from egg yolks or soybeans. Other surfactants used in commercial injectable products include sodium deoxycholate (a bile salt) and cremophor EL (a castor oil derivative). Various types of Tween and Span surfactants are also popular, as well as Solutol HS-15, poloxamers, sodium dodecyl sulfate, and amphiphilic proteins like casein and β-lactoglobulin. Polysaccharides such as gums and starch derivatives, along with PEG-based block copolymers, are also common.

Choosing the right surfactant or a blend is crucial because it affects not only the size and stability of the nanoemulsion but also its safety, how it behaves in the body, and how effectively it works. For instance, while poloxamer 188 is useful, using it in concentrations above 0.5% can be harmful to the kidneys.

Surfactants can also serve as tools for targeting cancer treatments by attaching specific ligands for better targeting. Sometimes, co-surfactants are added to strengthen the structure of the interfacial film. Common co-surfactants include substances like propylene glycol, polyethylene glycol, ethanol, glycerine, and others. These help improve the overall performance and stability of the nanoemulsion.

Conclusion:

The present results demonstrate the importance of the way of emulsification on the droplet size distribution. When emulsifying via emulsion phase inversion, finely dispersed oil droplets can be achieved, much smaller than by mechanical emulsification solely. We demonstrate that a critical surfactant concentration is necessary for emulsification via the EIP method. While low interfacial tension might facilitate the droplet formation, the resulting droplet size distribution mainly depends on the surfactant-to-oil ratio, suggesting that the size of the droplets is governed by the lamellar or bicontinuous structure formed at the inversion point.

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