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Pickering Emulgel As Novel Topical Drug Delivery System

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ABSTRACT

Topical drug delivery systems have become crucial for treating localized skin conditions, providing targeted action with minimal systemic side effects. Emulgels, combining emulsions and gels, offer a controlled delivery system that accommodates both hydrophilic and hydrophobic drugs. Discovered a century ago, Pickering emulsions have been extensively studied in recent decades. This type of emulsion is uniquely stabilized solely by solid particles positioned at the oil-water interface. By properly selecting and adjusting the types and properties of solid emulsifiers, Pickering emulsions can be utilized in various industries, such as biomedicine, food, fine chemical synthesis, and cosmetics. This review highlights the importance of Pickering emulgels over classical emulsions. In this review, composition, synthesis and characterization parameters of Pickering emulgels are presented. The objective of this article is to provide a broad view of how the PE can serve as a good choice for local drug delivery because of its excellent penetration properties and its future uses.

Keywords: Pickering emulgel, topical drug delivery, pharmaceutical applications

INTRODUCTION:

For the past few decades, the human body has been treated with drugs to cure illnesses through various routes, including parenteral, sublingual, oral, and rectal routes. Topical medication delivery is often employed in cases of localized skin infections, such as fungal infections, or when other drug administration systems prove ineffective. Topical drug delivery is a localized drug delivery system [1]. Topical drug delivery involves applying a formulation containing medication directly to the skin to treat skin conditions. This method involves applying the drug directly to the affected area, ensuring targeted action with minimal systemic side effects. Topical treatments can include creams, ointments, gels, and patches, each designed to deliver active ingredients efficiently to the site of infection or inflammation. This approach is particularly advantageous for skin-related

conditions, providing direct relief and reducing the risk of adverse reactions associated with systemic drug delivery [2][3].

Advantages of topical drug delivery systems are:

- Bypassing first-pass metabolism.
- Minimizing the risks and discomfort associated with intravenous therapy and various absorption issues like pH variations, enzyme presence, and stomach emptying time.
- Offering the convenience of stopping the drug application as needed.
- The ability to easily discontinue the medication when necessary.
- The capability to deliver the drug more selectively to a specific site [1][4][5].

Disadvantages of topical drug delivery:

- Limited ability of certain drugs to penetrate the skin.
- Risk of skin irritation or contact dermatitis.
- Challenges in absorbing drugs with larger particle sizes through the skin.
- Potential for allergic reactions [6].

STRUCTURE AND FUNCTIONING OF SKIN [7][8]

The skin is one of the largest sense organs in the human body that does several essential functions and acts as the first line of defense. It makes up about 10% of the total body mass and has an average area of 1.7 m^2. The skin can absorb topically applied ingredients, making it an increasingly most preferred route for delivering a variety of drug molecules. The skin is made up of three main components: the epidermis, the dermis, and the hypodermis. The epidermis is the outermost layer, the dermis is located beneath it, and the hypodermis, also known as the subcutaneous layer, is a fatty tissue layer that provides insulation and acts as a cushion to protect the body.

1. **Epidermis:** The epidermis, the outermost layer of the skin, is non-vascular and directly exposed to chemicals applied externally. Composed of layers of stratified squamous epithelial cells, it acts as a protective barrier. The epidermis consists of five layers: the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. The outermost layer, the stratum corneum, is the thickest and contains 20 to 30 cells, while the innermost layer is known as the stratum basale.
2. **Dermis:** The primary function of this layer is to support and give nourishment to epidermal cells physically. It consists of two layers: the reticular layer and the papillary layer. Both layers contain elastic fibers, fibrillin, and collagen. This layer also includes hair follicles, blood vessels, and nerve endings, as well as important glands like sweat and sebaceous glands. Also, it contains small blood vessels that provide the epidermis with nutrients, flexibility, and oxygen.

3. **Subcutaneous layer:** It consists of fatty tissues and cells that serve as a protective cushion for the body and provide insulation.

The skin, covering about 20 square feet, is the body's largest organ. It helps regulate body temperature, protects against germs and environmental factors, and allows us to perceive sensations like cold, heat, and touch. The skin is made up of three layers:

- The outermost layer, the epidermis, forms our skin tone and acts as a waterproof barrier.
- The dermis, located beneath the epidermis, contains sweat glands, hair follicles, and tough connective tissue.
- The deeper subcutaneous tissue, or hypodermis, is composed of fat and connective tissue.

Pathways of Penetration into skin:

Topically applied drugs can penetrate the skin through three primary mechanisms:

Intercellular: This involves the movement of drugs through the spaces between epithelial cells.

Intracellular (Transcellular): This refers to the movement of drugs directly through the epithelial cells.

Follicular: In this pathway, the hair follicle acts as a channel for drug absorption.

EMULGEL:

In the mid-1980s, emulsion-gels started gaining prominence as topical semisolid dosage forms in pharmaceuticals. Emulgels are a combination of emulsion and gels, serve as a controlled drug delivery system for topically applied medications [7]. They consist of either water-in-oil or oil-in-water emulsions that are mixed with a gelling agent to create a gel [9][10]. Gels are new dosage forms that are used to deliver active pharmaceutical ingredient (API) to the site of action. Gels have three-dimensional and cross-linked structures to entrap small drug particles in network of colloidal solid particles and exhibit controlled release [11][12]. In comparison to ointments or creams, gels have a higher water content, which enhances drug solubility and facilitates easier drug migration [13][14]. Gels have a significant drawback that they cannot effectively deliver hydrophobic medications. To overcome this limitation, emulgels are developed. Emulgels combine the benefits of gels, allowing even hydrophobic drugs to be effectively entrapped and released at the site of action [11].

Advantages of emulgel: [1][15][16][17]

- **Better for hydrophobic drugs:** Hydrophobic drugs are incorporated into the oil phase using emulgel, and then oily globules are dispersed in the aqueous phase to create an oil-in-water (o/w) emulsion. This emulsion is then blended with the gel base, potentially enhancing the stability and release of the medication.
- **Enhanced stability:** Emulgel formulations offer greater stability compared to other transdermal systems. While creams can undergo phase inversion or exhibit hygroscopic properties similar to powders, leading to instability, and ointments may suffer from rancidity due to their oily base, emulgels do not face these problems.
- **Controlled Release:** Emulgels can extend the effects of drugs with a shorter half-life. They are effective with both hydrophobic medications (o/w emulgel) and hydrophilic medications.
- **Greater Loading Capacity:** Emulgels can hold more drug compared to other advanced methods like niosomes and liposomes. Their extensive network allows for higher loading capacity, whereas niosomes and liposomes, being nanoscale with vesicular properties, may experience leakage and lower trapping efficiency.

Disadvantages of emulgels:[18]

- Some medications have poor skin permeability.
- Bubbles may form during the preparation of emulgel.
- Drugs with large particle sizes are difficult for the skin to absorb.
- Emulgel can cause skin irritation or allergic reactions, known as contact dermatitis.

PICKERING EMULGEL:

Emulsions are thermodynamically unstable systems where a surface-active agent (emulsifying agent) helps disperse droplets of one immiscible liquid into another. Typically, pharmaceuticals in liquid form leads to faster absorption and higher bioavailability, depending on the substance's physicochemical properties. To enhance absorption and therapeutic efficacy, medications with water- or organic-fluid-insoluble active ingredients can be formulated as emulsions or suspensions with well-dispersed liquid droplets [19][20].

Technological innovations have eliminated the need for emulsifying agents. Pickering emulsions, stabilized exclusively by finely divided solid particles such as alginates, present a suitable alternative. They improve formulation quality, provide good viscosity, and ensure long-term stability. Despite the challenge of their thermodynamic instability in pharmaceutical technology, Pickering emulsions are an excellent solution for preparing topical medications and administering drugs to the skin. The main difference between a classical

emulsion and a Pickering emulsion is that classical emulsions use molecular surfactants to stabilize the mixture, whereas Pickering emulsions rely on solid particles at the interface between two liquid phases to act as the stabilizing agent [19][21][22].

In a Pickering emulsion (Pickering, 1907), droplets are stabilized against coalescence solely by the accumulation of solid particles at the interface between two immiscible liquids, typically referred to as the oil and water phases [23]. Benefits of Pickering emulsions include: (i) solid particles enhance emulsion stability by reducing coalescence; (ii) many solid particles can impart useful properties to the prepared materials, such as conductivity, responsiveness, and porosity; (iii) some food-grade solid particles have lower toxicity, making them safer for in vivo use [23][24].

Constituents of Pickering emulgels: [7][25][26][27]

1. **Aqueous Phase:** To prepare the aqueous phase of the emulgel, aqueous ingredients are required. Common agents for this phase include alcohol, distilled water, and regular water.
2. **Oil Phase:** Mineral oils are commonly used in topical emulsions, either alone or in combination with soft or hard paraffin, for their role in delivering drugs and enhancing sensory perception while providing occlusive effects. Castor oil is also utilized in oral treatments, distinct from stable oils like fish liver oil, and it has local laxative properties. Vegetable oils such as Arachis, cottonseed, and maize oils are biodegradable and used as dietary supplements.
3. **Emulsifying agents:** Emulsifiers play a crucial role in controlling the emulsification process and ensuring stability. Despite emulsions being thermodynamically unstable systems, selecting the appropriate emulsifying agent can significantly enhance their stability. Mineral oils such as liquid paraffin, which have HLB (hydrophilic-lipophilic balance) values less than 8, are commonly used in water-in-oil emulsion formulations. In contrast, nonionic surfactants like spans and tweens, with HLB values greater than 8, are preferred for oil-in-water emulsions. They enhance the emulsion's manufacturing process and control its stability throughout its temporary shelf life, which can vary from days to months or even years. Emulsifying agents like polyethylene glycol 40 stearate, polyoxyethylene sorbitan (Span 80), sorbitan mono-oleate, stearate, stearic acid (Tween 80), and others are employed in the preparation of emulsions for commercial products.
4. **Gelling agents:** These gelling agents are designed to provide gel-like behavior and enhance the consistency of dosage forms. Studies have shown an inverse correlation between the concentration of the gelling agent and the release of medication. Compared to Carbopol-based emulgels, those based on HPMC (Hydroxypropyl Methylcellulose) demonstrate better drug release. Various gelling agents such as Carbopol 934, HPMC 2910, and HPMC K4M are commonly employed in these formulations.
5. **Permeation enhancers:** These penetration enhancers work by interfering with various pathways, such as altering the lipid composition of the stratum corneum, interacting with intracellular proteins, or

modifying the absorption of medications into the skin's structures. Examples of such enhancers include oleic acid, clove oil, lecithin, eucalyptus oil, and menthol, each employed in emulgel formulations in varying concentrations.

STEPS FOR SYNTHESIS OF PICKERING EMULGEL

STEP-1 Preparation of o/w or w/o emulsion: The oil phase of the emulsion is formulated by dissolving the hydrophobic emulsifier, such as Span, into an oil vehicle such as liquid paraffin. Simultaneously, hydrophilic emulsifiers like Tween are dissolved in pure water to form the aqueous phase. The drug is dissolved in ethanol, and preservatives such as methyl and propyl parabens are dissolved in humectants like propylene glycol. These solutions are then combined and homogenized using a consistent blending technique. The mixture, comprising the aqueous and oil phases heated to 70°C to 80°C, undergoes continuous blending where the oil phase is gradually incorporated into the aqueous phase. Upon completion, the emulsion is allowed to cool to room temperature, facilitating its formation [28][29].

STEP-2 Preparation of gel(thickening) phase: The polymer is dissolved in purified water using mechanical agitation to form the gel phase. Subsequently, the pH of the solution is adjusted to 6-6.5 using either NaOH or triethanolamine [30].

STEP-3 Formulation of Pickering emulgel: The thickening phase is gradually incorporated into the emulsion in 1:1 ratio to get the emulgel formulation.

CHARACTERIZATION OF PICKERING EMULGEL:

Physical appearance: The synthesized Pickering emulgel was evaluated for its color, odor, homogeneity, phase separation and consistency [31].

pH determination: The pH of the prepared Pickering emulgel was determined by using digital pH meter. pH meter was kept in a beaker containing the emulgel and equilibrated for 1minute and pH was measured for 3 times and average was taken [32].

Zeta potential: The zeta potential of the prepared emulgel was measured using a Malvern DLS, Zetasizer-ZS90, UK zeta potential analyzer. The emulgel was added to the sample cell, which is left to acclimate to room temperature for two minutes before the measurement was taken [33].

Rheological studies: The viscosity of the prepared emulgel was measured using a Brookfield viscometer with spindle 7. The viscometer assembly was connected to a water bath maintained at a constant temperature of 25°C. The emulgel sample was placed in a beaker covered with a thermostatic jacket. The spindle was allowed to freely immerse in the emulgel, and the viscosity reading was recorded [26].

Swelling index: To measure the swelling index of the prepared topical emulgel, one gram of the emulgel was placed on a piece of porous aluminum foil. This foil was then placed in a 50 ml beaker containing 10 ml of 0.1 N NaOH. Samples were removed from the beaker at various time intervals, reweighed, and then allowed to dry in a designated area. The swelling index (SW) is calculated using the formula:

$$SW(\%) = \frac{W_t - W_o}{W_o} \times 100$$

SW% = Percent equilibrium swelling

W_t = weight of emulgel swelled after time t

W_o = initial weight of emulgel at time zero [26][34]

Optical microscopy: The formulated emulgel was viewed under the Lmi microscope at 20x magnification for investigate the nature of emulgel. Emulgel was applied on the glass slide and seen under the light microscope [31].

Spreadability: The spreadability of the gel formulations was tested using two glass slides of standard diameter. The gel to be assessed was applied to one slide, and the other slide is placed on top, creating a sandwich with the gel between the two slides. The slides were pressed together to remove any trapped air. The lower slide was held firmly in place by a clamp, while the upper slide is allowed to move freely due to the force of a weight attached to it. 20g weight was carefully attached to the upper slide. The time it took for the upper slide to completely separate from the lower slide was recorded [35].

Particle size: The size and distribution of globules in emulgel was determined by using a Malvern zeta sizer. 1g sample of the emulgel was dissolved in filtered water and stirred to ensure homogeneous dispersion. The sample was then injected into the zeta sizer's photocell. The device measures the distribution and calculates the average diameter of the globules [36].

Drug content evaluation: To determine the drug content in an emulgel, take one gram of the emulgel and stir it in a suitable solvent until it is fully dissolved. Filter the solution to obtain a clear filtrate. Measure the absorption of this clear solution using a UV spectrophotometer. Prepare a standard plot of the drug using the same solvent. Calculate the concentration and drug content by plotting the absorbance value on the standard plot. The drug content is determined using the formula: **Drug Content = (Dilution Factor × Volume Taken × Concentration) × Conversion Factor.** [37]

Extrudability Test: To perform the extrudability test, a lacquered aluminum collapsible tube containing the emulgel was used. The force in newtons required to extrude a 0.5 cm ribbon of the emulgel within ten seconds was measured. This test was conducted in triplicate, and the average values were calculated. Extrudability is then determined using the formula:

Extrudability = Weight applied to extrude Emulgel from tube (in gm) / Area (in cm^2) [38]

Stability studies: The aluminum collapsible tubes containing the emulgels were subjected to stability testing under various conditions: 5°C, 25°C/60% RH, and 30°C/75% RH, and 40°C/65% RH for three months. Samples were taken out every 15 days to assess their physical characteristics, pH, rheological properties, drug content, and drug release profiles [39].

Skin irritation test: The mixture was applied to the cleanly shaven skin of rats, and any negative effects, such as changes in skin shape and color, were monitored for up to 24 hours. Eight rats were used for the investigation. The test was considered successful if no irritation was observed. If skin irritation symptoms appeared in more than two rats, the test was repeated [40].

***In-vitro* release kinetics:** The in vitro drug release testing of the Emulgel was conducted using dialysis in a modified diffusion cell setup. A dialysis membrane, pre-soaked in phosphate buffer pH 5.5 for nine to twelve hours, was carefully clamped to one end of a hollow glass tube. A uniform layer of Emulgel was applied to the dialysis membrane, and a beaker filled with 50 milliliters of phosphate buffer served as the receptor compartment. The receptor and donor compartments remained in contact throughout the experiment. The entire assembly was placed on a magnetic stirrer, maintaining the cell temperature at 37°C by continuously stirring the solution in the receptor compartment with a magnetic bead. Concurrently, a similar blank set served as a control. At specified intervals, samples (5 ml) were withdrawn and replaced with fresh dissolution media of the same volume. The samples were then subjected to spectrophotometric analysis to determine the cumulative percentage of drug release over time [41].

FUTURE PROSPECTS:

Pickering emulsions have gained popularity among researchers in recent years due to their increased stability and eco-friendliness compared to traditional emulsions. This interest has also spurred the rapid development of related products. For example, margarine production and consumption in China are rising annually. Unfortunately, margarine often contains trans fats, found in partially hydrogenated vegetable oil, which is linked to increased risks of diabetes, cancer, heart disease, and other health issues. Therefore, finding high-quality, affordable alternatives is crucial, and Pickering emulsions offer a very promising solution. Pickering emulsions can be tailored to exhibit desirable characteristics like improved rheology, digestibility, and freeze-thaw stability by modifying colloidal particles or creating new ones. These properties make them suitable for a broader range

of food applications. Despite their potential, several challenges remain. The real-world food production environment is more complex and variable, making it difficult to maintain the stability of Pickering emulsions. Most research to date has been conducted in laboratory settings, with few studies transitioning to commercial or industrial scales. To fully realize the economic benefits of Pickering emulsions in the food industry, future research should focus on enhancing their stability during food manufacturing and exploring more eco-friendly and efficient production methods.

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