POLYMERIC LIPOSPHERE DRUG DELIVERY SYSTEM: REVIEW ON PREPARATION METHODS AND DISEASE MANAGEMENT

Abstract

The biggest and most accessible organ of the body is the skin. Topical medication delivery has become more and more popular among people as the prevalence of dermatological problems, desire for drug targeting, and patient compliance have all grown. The stratum corneum, the top layer of the epidermis, blocks the penetration of most pharmaceuticals, making drug administration over the skin a difficulty for researchers. To administer the medications topically, a variety of techniques have been utilised, including the use of chemical permeation enhancers and physical techniques including sonophoresis, iontophoresis, electroporation, microneedles, etc. There are certain restrictions and disadvantages to these approaches to topical administration of drugs. Therefore, new techniques based on nano delivery system such as liposphere gels has been developed for the treatment of disease like osteoarthritis which is common in old age people.

Keywords: Drug targeting, liposphere, topical medication, solvent evaporation, modified-release solid dosage forms, bioavailability, etc.

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I. INTRODUCTION

Liposphere formulations are created through a combination of solvent evaporation and melt dispersion techniques. In the solvent evaporation method, the primary goal is to minimize the exposure of thermolabile compounds, such as proteins and nucleic acids, to high temperatures. This technique relies on the evaporation of an organic solvent in which lipids are dissolved. The lipidic matrix is initially dissolved in an organic solvent like ethyl acetate while maintaining the temperature at approximately 50°C. Subsequently, it is emulsified with an external aqueous phase, followed by agitation at 500 rpm using a mechanical stirrer. The particle size is primarily controlled by the composition of the formulation. By introducing cationic or anionic lipids such as stearyl amine, phosphatidyl ethanol amine, stearic acid, or phosphatidyl acid, it is possible to produce cationic or anionic lipospheres. This concept is applied to enhance the bioavailability of diclofenac sodium.[1]

1. Cetyl Alcohol

- **Empirical Formula:** $C_{16}H_{34}O$
  Used in pharmaceutical manufacture, cetyl alcohol is a mixture of solid aliphatic alcohols made up mostly of commercially accessible grades of cetyl alcohol, which are available in mixtures of 60–70% cetyl alcohol and 20–30% stearyl alcohol, with related alcohols making up the remaining percentage.
- **Functional category:** Coating agent; emulsifying agent; stiffening agent.
- **Description:** Cetyl alcohol occurs as waxy, white flakes, granules, cubes, or casting. It has faint characteristic odour and bland taste.
- **Solubility:** Almost insoluble; freely soluble in ether and 95% ethanol, with solubility rising with warmth.

2. **Application in Pharmaceutical Formulation or Technology:** Cetyl alcohol finds extensive applications in cosmetics and pharmaceutical formulations, including but not limited to suppositories, modified-release solid dosage forms, emulsions, lotions, creams, and ointments. In the case of suppositories, cetyl alcohol serves to elevate the base's melting point. It also plays a role in modified-release dosage forms by potentially forming a permeable barrier coating. When it comes to lotions, creams, and ointments, cetyl alcohol is employed for its emollient properties, water-absorptive capabilities, and emulsifying attributes. Its use contributes to improved stability, enhanced texture, and increased consistency of these formulations. The emollient qualities stem from the absorption and retention of cetyl alcohol within the epidermis, where it not only lubricates and softens the skin but also imparts a distinctive "velvety" texture.[2]

3. **Stearic Acid:** Stearic acid, with its 18-carbon chain and IUPAC name octadecanoic acid, is a saturated fatty acid. It exists as a solid with a waxy texture and follows the chemical formula CH3(CH2)16CO2H. Its derivatives and salts are referred to as stearates. Among saturated fatty acids, stearic acid is the most prevalent, with palmitic acid (a C16 compound) being another common example. Its versatile applications leverage its bifunctional nature, featuring a polar head group for binding with metal cations and a nonpolar chain that imparts solubility in organic solvents. This unique combination makes it valuable as a surfactant and softening agent. Stearic acid undergoes typical reactions

associated with saturated carboxylic acids, including reduction to form stearyl alcohol and esterification with various alcohols. Isolating pure stearic acid from complex mixtures is challenging and typically involves methods like crystallization, vacuum distillation, or chromatography of the acid or its appropriate derivatives. Pure stearic acid exhibits the usual chemical behaviors of carboxylic acids. It is a colorless, waxy solid with limited solubility in water. Stearic acid's soap-like properties enable it to penetrate the skin and provide emollient, skin-softening effects..[3]

4. Ethyl Acetate

- Molecular formula: $C_4H_8O_2$
- Description: This colourless liquid has a characteristic sweet smell.
- Classifications: Ester, Solvent.
- Use: Due to its affordable price, low toxicity, and pleasant smell, ethyl acetate is mostly employed as a solvent and diluent. Mixtures containing ethyl acetate are frequently utilized in extractions and column chromatography in the laboratory. Because it is easily hydrolyzed and trans esterified, ethyl acetate is not frequently chosen as a reaction solvent. At just 77 °C, ethyl acetate has a low boiling point and is very volatile. Because of these characteristics, it can be eliminated from a sample by boiling it in a hot water bath and using compressed air for ventilation.

II. GEL

A gel is a solid substance that resembles jelly and can range in consistency from soft and fragile to strong and rigid. Gels are described as a significantly diluted cross-linked system that, in its steady-state, shows no flow. Gels are primarily liquids by weight, but because of a three-dimensional cross-linked network inside the liquid, they behave like solids. The fluid's crosslinks are what give a gel its hardness and help with sticky tack. Gels can be thought of as a dispersion of liquid molecules within solids, where the liquid is the discontinuous phase and the solid is the continuous phase. Gel is a water-soluble, non-greasy liquid lubricant that can be used to suspend or dissolve a range of dermatological treatments administered topically. There are numerous benefits of administering medications topically for both local and systemic treatment. Topical administration has the potential to improve patient compliance and significantly reduce systemic adverse effects in the treatment of musculoskeletal disorders and skin diseases.

Gels are semirigid systems where a three-dimensional network of interlacing particles or solvated macromolecules of the dispersed phase limit the mobility of the dispersing medium. There could be a significant amount of chemical or physical cross-linking. The semisolid condition results from increased viscosity brought on by the interlacing and ensuing internal friction. Gel can be made up of matted, twisted strands that are frequently coiled together by greater van der Waals pressures to create crystalline and amorphous areas in different parts of the system, such as carboxymethylcellulose, tragacanth, and CARBOPOL NF934. Certain gel systems exhibit a color as transparent as water, while others have a muddy appearance due to the possibility of partially or partially dispersed components forming clumps that scatter light. [4]

The gelling agents typically have a concentration of between 0.5 and 2.0%, which is less than 10%. As to the USP, gels are semisolid systems comprised of suspensions comprising of large organic molecules interpenetrated by a liquid or small inorganic particles. When the gel mass is made up of a collection of tiny, distinct particles, it is categorized as a two-phase system. Organic macromolecules are evenly spread throughout a liquid to create single phase gels; the dispersed macromolecules and liquid do not appear to have any boundaries. Natural gums (mucilage) or artificial macromolecules can be used to create single phase gels. Although it can also be alcoholic or oleaginous, the continuous phase is often watery. Crystal clear and sparkly gels are the most appealing to consumers. The majority of gels function as absorption bases, are greaseless, soluble in water, and washable in water. Over a broad temperature range, the gel should also hold onto its viscosity and characteristics. The pH and the presence of electrolytes have an impact on gel swelling. Elastic contraction of the polymeric molecules is assumed to be the cause of separation of a solvent phase.[5]

1. **Technique of Preparation of Gel:** Gels were formulated by dispersing 1% w/w Carbopol NF 934 in distilled water and subjecting it to high-speed mechanical stirring. Subsequently, the dispersion was neutralized to a pH of 7.4 using 1% w/w triethanolamine. To remove any entrapped air within the gel, the gels were left undisturbed overnight.

2. **Carbopol NF934:** Carbopol polymers are cross-linked polymers derived from acrylic acid, incorporating polyalkenyl ethers or divinyl glycol. These polymers originate from primary polymer particles with an average diameter ranging from approximately 0.2 to 6 μm. Carbopol, along with pemulen and Noveon polymers, belongs to the category of cross-linked polymers. When exposed to a pH range of 4.0 to 6.0, they have the remarkable ability to swell in water, expanding up to 1000 times their original volume and increasing in diameter by up to 10 times. This swelling is attributed to the ionization of the carboxylate groups within the polymer, resulting in repulsion between the negative charges. The Carbopol family of resins is often generically referred to as "carbomer." These resins are characterized by their high molecular weight and are crosslinked with allyl pentaerythritol. They are acrylic acid-based and have been modified with C10-C30 alkyl acrylates. Carbomer resins are typically in the form of fluffy, white, dry powders with low moisture content (maximum 2%) and a pKa value of approximately 6.0±0.5. The pH levels of 0.5% and 1.0% aqueous dispersions fall within the ranges of 2.7-3.5 and 2.5-3.0, respectively. Carbomer resins encompass a wide range of viscosities, spanning from 0 to 80,000 cps.[6,7]

III. OSTEOARTHRITIS

A joint serves as the point of articulation or connection between two or more bones. These joints can be categorized into different types based on their degree of movement. Fibrous joints lack mobility, while cartilaginous joints offer limited movement, and synovial joints provide extensive mobility. Inflammatory conditions affecting joints can lead to arthritis. Diseases of synovial joints involve various tissues, including the synovial membrane, hyaline cartilage, and bone. Osteoarthritis is a chronic degenerative disorder influenced by various factors, characterized by the gradual loss of articular cartilage, the development of bone hypertrophy at joint margins, subchondral sclerosis, and various

biochemical and morphological changes within the synovial membrane and joint capsule. In later stages, pathological changes may include the softening, ulceration, and localized deterioration of articular cartilage, along with the potential occurrence of synovial inflammation.. [9]

Clinical symptoms typically manifest as pain during extended activity and stiffness in the morning. It's called degenerative arthritis, and it usually affects the spine, hands, feet, and big weight-bearing joints like the knees and hips. Osteoarthritis can be localized, widespread, or erosive. Primary osteoarthritis is osteoarthritis for which there is no recognized etiology. The main cause of primary osteoarthritis is aging. Another illness or ailment is the cause of secondary osteoarthritis. The second most prevalent inflammatory joint issue is osteoarthritis.10. One of the earliest and most prevalent types of arthritis is osteoarthritis, a degenerative joint disease. It is typified by moderate to severe pain in the hands and joints, including the feet, knees, hips, and back. The majority of people with osteoarthritis are 45 years of age and older. Females are more vulnerable to the illness. The illness results in the degeneration of joint cartilage. When the buffer between bones is destroyed, bone against bone friction results, which hurts and eventually limits movement. The symptoms include restricted or complete loss of motion, joint soreness or aching (usually during activity or prolonged periods of pressure on weight-bearing joints), and other symptoms.[11]

1. **Management of Osteoarthritis:** Osteoarthritis management entails managing pain, preserving and enhancing the affected joints' range of motion and stability, and minimizing functional impairment.

2. **Non-Pharmacological Management:** Pain and impairment can be effectively reduced by education, weight loss, lower extremity strengthening exercises for 20 to 30 minutes each day, strengthening of the quadriceps, active range of motion of the hip, knee, and ankle, graded elastic band use, and pool therapy.[12]

3. **Pharmacological Management:**

   - **Symptom Modifying Drugs:** Acetaminophen is often effective in osteoarthritis associated with fewer adverse reactions than NSAIDs and suggested as a starting point for osteoarthritis treatment. Salicylates and conventional NSAIDs are only prescribed to people who are unable to receive sufficient pain relief from paracetamol. Because COX-2 inhibitors are more gastrointestinal tolerable, they may be used. For the alleviation of pain, celecoxib, etoricoxib at a dose of 60 mg/day, and valdecoxib at a dose of 10 mg/day are just as effective as non-selective NSAIDs. On the other hand, new research calls into question the security of COX-2 inhibitors. When misoprostol is used in conjunction with NSAIDs for certain patients who need long-term treatment, stomach ulcers may be avoided.[13]

     Analgesia produced by the combination of opioids (codeine) and paracetamol is superior than that of paracetamol alone. Patients with chronic pain who receive tramadol treatment see a statistically significant, clinically meaningful, long-lasting relief in their pain, stiffness, physical function, and sleep. The combination of 37.5 mg of Tramadol and 325 mg of Acetaminophen is also safe and helpful in treating

osteoarthritis pain. Topical analgesics, such as 0.025% capsaicin cream and other topical NSAIDs, are thought to be suitable for treating mild cases of pain, helping individuals who are unable to tolerate systemic medication, or treating a single problematic joint. One theory about capsaicin's mode of action is that it releases substance P by selectively stimulating unmyelinated type C afferent neurons. This type of release reversibly depletes the body's supply of substance P, a neurotransmitter involved in peripheral pain perception.[14]

- **Symptomatic Slow Acting Drugs for OA (SYSADOA):** N-acetyl glucosamine and D-glucuronic acid repeat as disaccharide units to form the linear polymer known as hyaluronic acid (HA). Although they are now only thought to be medications that modulate symptoms, they are frequently cited as possible medicines that alter structure. By directly buffering synovial nerve endings, they have anti-inflammatory, short-term lubricating, analgesic, and stimulating effects on synovial lining cells that result in proper hyaluronic acid synthesis. Its repeated intraarticular injections may have a similar therapeutic benefit to NSAIDs. [15]

- **Nutraceuticals:** Glucosamine sulfate and chondroitin sulfate are nutritional supplements. More substrates are supplied by chondroitin sulphate to aid in the development of a robust joint matrix. Chondroitin sulphate taken orally can gradually lessen symptoms and eventually eliminate the need for NSAIDs.

- **Structure Modifying OA Drugs (SMOADS) /Chondroprotective:** Tissue metalloproteinases are inhibited by tetracyclines. Their capacity to bind zinc and calcium ions explains this. It has been demonstrated that minocycline and doxycycline block the action of collagenase in articular cartilage, prevent cell death and loss of proteoglycan cells, and prevent the deposition of type X-collagen matrix.

- **Topical Analgesic:** These are voltren gels that are applied directly to the painful area.

  - **Factors causing Osteoarthritis[16]:** The disease's onset and course are brought on by a myriad of circumstances. A few risk variables are age, sex, and joint injuries from accidents, jobs, or sports. hereditary Plus-size, crystal in joint fluid or cartilage, chondrocalcinosis, bone density, and joint location.
  - **Diagnosis of Osteoarthritis [17]:** A person needs to see a doctor for a diagnosis. Following a comprehensive discussion of symptoms and a physical examination, the doctor might additionally advise X-rays to confirm the disease's presence.
  - **Treatment options:[18]** The treatment options for osteoarthritis, include:
    - Engaging in joint and muscle exercises aimed at enhancing flexibility and strength.ϖ Implementing weight reduction measures to alleviate stress on weight-bearing joints
    - ϖ Utilizing anti-inflammatory medications to manage degenerative joint disorders.
    - ϖ Applying heat and cold therapies for relief.
    - ϖ Considering synovectomy, which involves surgically removing inflamed synovial tissue

- ϖ Exploring osteotomy, a procedure that involves restructuring bones to redirect stresses away from diseased areas toward healthier tissue.
- ϖ Evaluating partial knee replacements (unicompartmental knee), which replace only the affected portion of the joint
- ϖ Assessing total knee replacement surgery, typically employed in cases of severe osteoarthritis, as well as high tibial osteotomy and joint fusion as potential treatment options.ϖ

IV. CONCLUSION

The aim of this review was to investigate the properties of gelling, particularly in the context of microemulsion lecithin gels. Throughout the review, lecithin nanocarrier-based gels were compared to traditional gels, with a focus on the fluid characteristics of nanocarriers. Various aspects were assessed, including their practical applications and characterization. It was found that liposomal gels and lecithin microemulsion gels exhibited greater suitability for topical use compared to liposomal dispersions and microemulsions..

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