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Formulation and Evaluation of Alendronate-Loaded Nano Emulsion for Osteoporosis Management

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ABSTRACT

Reduced bone mineral density and an elevated risk of fracture are the hallmarks of osteoporosis, a common skeletal condition. Although alendronate, a bisphosphonate, is frequently used to treat osteoporosis, oral administration of this medication is linked to gastrointestinal adverse effects and limited absorption. The objective of this research is to create and assess a nanoemulsion loaded with alendronate in order to improve drug permeability, bioavailability. Nanoemulsions' small droplet size, great solubility, and enhanced stability make them a promising medication delivery method. In order to maximize the properties of the nanoemulsion, the formulation procedure entails choosing the right oil, surfactant, and co-surfactant. The created nanoemulsion is assessed according to its stability, zeta potential, pH, viscosity, and particle size. Ex vivo and in vitro investigations evaluate the effectiveness of skin penetration and medication release characteristics.

This nanoemulsion-based approach has the potential to improve osteoporosis care, lessen side effects, and increase patient adherence by addressing the drawbacks of traditional oral alendronate therapy. The results of the study help create new, patient-friendly drug delivery strategies for the treatment of osteoporosis.

KEYWORDS: *Osteoporosis, Alendronate, Nanoemulsion, Drug Delivery, Bioavailability, Bone Health*

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1. INTRODUCTION

A skeletal condition called osteoporosis is on the rise globally and is associated with a decline in a reduction in bone micro-architecture degradation and an increase in bone mineral density, which raises the risk of fracture. This fracture is followed by a rise in morbidity, death, and the high cost to the person Epidemiologic investigations conducted worldwide have reported a prevalence of 18.3% (23.1 in women and 11.7 in males) [3]. Countries and continents have different prevalence rates. The range is 8.0% in Oceania to 26.9% in Africa; it ranges from 4.1% in the Netherlands to 52.0% in Turkey [4]. According to the National Osteoporosis Foundation, 43.4 million Americans have low bone mass, 10.2 million individuals have osteoporosis, and 16.5% of women have it compared to 5.1% of men. By 2030, According to estimates, 71 million adults will have poor bone mass and osteoporosis [4]. Because of decreased bone mineralization or microarchitecture, decreased bone strength, and decreased bone mass, osteoporosis is a bone condition that puts a person at increased risk for fracture. This illness is generally asymptomatic and goes undiagnosed until a low stress fracture of the hip, spine, proximal humerus, pelvis, and/or wrist occurs, necessitating hospitalization [5][6].

Additionally, researchers predict that by 2020, the number of Americans with osteoporosis will rise from roughly 10 million to over 14 million [7]. Although osteoporosis is thought to mostly affect women, one in five Americans has been diagnosed with osteoporosis or low bone mineral density [7], indicating that men are also impacted by this condition. Osteoporosis is frequently associated with bedridden individuals, which is risky, in addition to being linked to the majority of fractures in the elderly.

Figure 1 Overview of Osteoporosis

The increased understanding of bone morphology and the true cause of osteoporosis has led to the development and discovery of highly advanced therapy options in the recent few years. Additionally covered in this article will be the epidemiology, diagnosis, screening, and therapy of osteoporosis prevention; specifics of pertinent professional guidelines and procedures; pharmaceutical and non-pharmacologic therapies; and what is known as the "cost-utility" of those treatments.

Age and sex hormone deficiencies are also associated with primary osteoporosis. According to assessments of bone structure, age-related osteoporosis is caused by the continuous deterioration of the bone's trabeculae. Moreover, postmenopausal populations experience higher proportionate bone loss due to lower estrogen levels. In men, testosterone is neutralized by sex-hormone-binding protein.

Vitamin D and sex hormones are known to have a harmful impact on calcium metabolism in the aforementioned illnesses. For instance, it has been discovered that Cushing's syndrome causes excessive glucocorticoid production, which speeds up bone loss. Furthermore, the majority of inflammatory disease conditions, such as rheumatoid arthritis, have been linked to secondary osteoporosis and may necessitate long-term glucocorticoid medication [9]. Most notably, it is thought that glucocorticoids are primarily responsible for drug-induced osteoporosis [10]. Following around three to six months of glucocorticoid medication, BMD has been seen to decrease quickly. Glucocorticoid-induced osteoporosis (GIO) can be prevented and treated with the help of the ACR's comprehensive guidelines [11].

1.1. Alendronate's Drug Profile

Menopausal osteoporosis, osteoporosis linked to glucocorticoid usage, and Paget's disease in males are all treated and prevented using alendronate. Additionally, alendronate requires a dose modification below the creatinine clearance threshold of 35 milliliters per minute. A major study found that alendronate is a safe medication for haemodialysis patients. Alendronate has also been shown in another trial to be a safe and effective treatment for osteoporosis in women with impaired renal function.

1.1.1. Classification of Chemicals and Pharmacology

Alendronate is classified as a member of the bisphosphonate drug class. Alendronate sodium's elemental name is 4-Amino-1-hydroxybutylidene disposophobic acid, which makes up its chemical formulation. In its pharmacological form, this drug is known as alendronate sodium. Since alendronate is a member of the nitrogen-containing bisphosphonate group, its ability to inhibit osteoclast activity is more potent than that of non-nitrogen-containing bisphosphonates.

1.1.2. The Action Mechanism

Alendronate works by inhibiting the process of osteoclast-mediated bone resorption. This amino bisphosphonate reduces bone turnover by inhibiting osteoclast activity. This suppression results in the inhibition of the mevalonate pathway, which is essential for osteoclast survival and function. Alendronate primarily aids in maintaining or raising BMD by reducing bone resorption. [12]

1.1.3. Pharmacokinetics

while taken orally, alendronate has a relatively poor bioavailability (about 0.6% while fasting). In addition to water, it may also be further hindered in its absorption by other foods and drinks. About half of the medication attaches to bone surfaces after absorption, with the kidneys excreting the other portion unaltered. Because alendronate acts for a long time at the site of incorporation, it has a long terminal elimination half-life in bone.

1.2. Alendronate Transdermal Drug Delivery Systems (TDDS)

Bypassing gastrointestinal issues and increasing bioavailability, TDDS provides a non-invasive method. The medication alendronate has been delivered transdermal in a number of methods.

A. Transdermal Patches: Katsumi and colleagues created a brand-new alendronate transdermal patch. The patch had adequate penetration through both human and rat skin, with a bioavailability of roughly 8.3% in rats (oral dose produced a bioavailability of 1.7%). Pharmacological analysis verified that bone loss in osteoporotic animals was prevented and that plasma calcium levels in hypercalcaemic rats were effectively reduced. Butylhydroxytoluene reduced skin irritation without sacrificing effectiveness while increasing antioxidant incorporation.

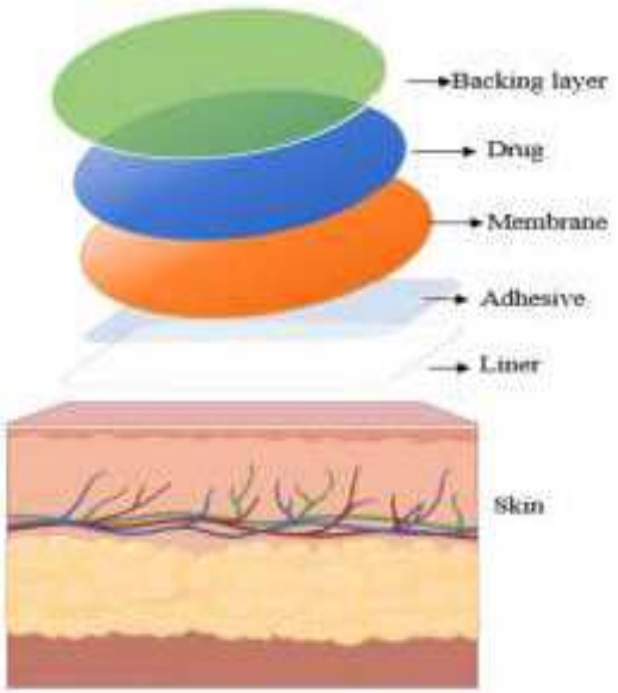

Figure 2 Key Components of Transdermal Drug Delivery Systems (TDDS).

B. Niosomal Formulations: To increase skin permeability and maintain drug release, Abo-Zour et al. created an alendronate-loaded noisome. The respective noise particle sizes and zeta potentials ranged from 99.6 to 464.3 nm and -27.6 to -42.27 mV, respectively. Which were integrated into polyvinyl pyrrolidone (PVP) and poly(vinyl alcohol) (PVA) microneedle arrays. These formulations demonstrated promise as a transdermal delivery strategy and demonstrated sustained release of alendronate in vitro [14].

C. Microneedle Arrays: Katsumi et al. also explored self-dissolving microneedle arrays for alendronate delivery. The drug is released into dermal layers after insertion into the skin using these microneedles, which consist of biodegradable polymers that can dissolve on skin insertion. Efficient transdermal delivery without significant skin irritation was obtained with this method, which has the potential for osteoporosis treatment.

1.2.1. Evaluation of Transdermal Alendronate Systems:

There have been several studies (performed to assess the effectiveness of various transdermal systems of alendronate) with regard to the skin permeation parameters, drug release profiles and overall efficacy. Below are examples of key findings:

1.2.2. Skin Penetration Studies in Vitro and Ex Vivo

Using both in vitro and ex vivo models, numerous research have investigated the capacity of different transdermal methods to distribute alendronate through epidermal layers. For example, one study discovered that Alendronate and a chemical penetration enhancer (DMSO) were combined to create transdermal patches, which demonstrated the viability of such systems for long-term bisphosphonate delivery by increasing the cumulative drug flux through human skin.

1.2.3. Comparison of Transdermal Delivery vs. Oral Administration

Multiple research projects examined the pharmacokinetic outcomes of trans dermally delivered alendronate and oral alendronate administration. A study showed transdermal patches could deliver drugs through the skin at levels matching oral dose results but reduce whole-body side effects. The transdermal system offered the benefit of avoiding the gastrointestinal tract, which is critical for reducing adverse effects such as esophageal irritation [15].

1.3. Nanoemulsion

Isotropic, thermodynamically stable, transparent (or translucent) systems of water, oil, and surfactants, nano emulsions typically have droplets between 10 and 100 nm in size [16]. Because of its stable structure, simple fabrication method, and high drug molecule dissolving capabilities by spontaneous emulsification procedures, the drug delivery technology has potential. The method can be widely used in oral drug delivery systems to increase the bioavailability and solubility of these lipophilic medicines [17]. The investigation of nanoemulsions for transdermal administration has exploded recently [18].

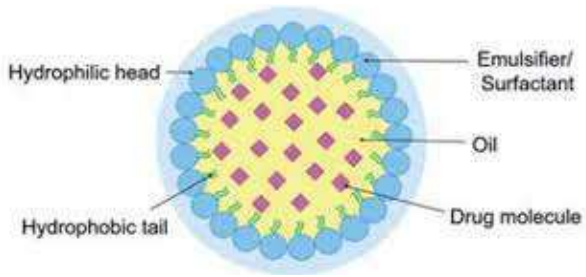

Figure 3 Nanoparticle's as A Tropical agent.

Nano emulsion preparation can be divided into two groups of methods: high-energy methods and low-energy methods. High-energy methods are energy intensive methods and typically require power density input of 107e109 W/kg1. In contrast, low-energy methods only require power density input of 103e105 W/kg.1 We first describe some examples of each kind of method and then discuss the advantages and disadvantages of both types of methods. Nano emulsions are a specific type of colloidal emulsion, or mini emulsion, which are often referred to by their "nano" label in more recent times, replacing the older "colloidal" terminology [19]. The term "nano" refers to objects that are between 1 nm and 100 nm in size. Although there is some debate about whether to measure the radius or diameter of a spherical droplet, emulsions with droplet sizes between 100 nm and 1,000 nm are typically considered submicron emulsions, not nano emulsions. In any case, emulsions at the nanoscale often show unique physical properties that make them particularly interesting and useful in ways that traditional, larger-scale emulsion systems can't achieve. These properties open up new possibilities for various applications in industries like pharmaceuticals, food, and cosmetics, among others.

1.3.1. Nanoemulsion.Composition

The drug's nature and therapeutic needs are taken into consideration while choosing the nanoemulsion's constituent parts:

- Oil Phase: Serves as a solubilizer for medications that are lipophilic. Isopropyl myristate, medium-chain triglycerides, and natural oils like coconut or jojoba oil are all well-liked oils.
- Surfactants: Lower interfacial tension to stabilize nanoemulsion droplets. These are widely used nonionic surfactants, as Span 20 and Tween 80 (Polysorbate).
- Co-Surfactants: Ethanol, polyethylene glycol, or propylene glycol are used to further reduce droplet size and stabilize the nanoemulsion.
- Aqueous Phase: The continuous phase is often formed by water or an appropriate buffer.

2. Material & Method

High-energy methods, low-energy methods, and hybrid methods that integrate both approaches are the three types of production processes used by nanoemulsion manufacturers. The intended droplet size, stability, enclosed materials, and industrial viability all influence the technique selection.

2.1. High-Shear Stirring

- Uses mechanical stirring at high speeds to create macroemulsions containing nanoemulsifiers.
- Acts as an initial step in combined methods before applying further energy-intensive processes.
- Generates large droplets that require additional processing to achieve nano-scale sizes.

2.2. Ultrasonic Emulsification

- Utilizes high-frequency ultrasonic waves to break down droplets into nanoscale sizes.
- Effective in reducing droplet size distribution and improving emulsion stability.
- Requires specialized ultrasonic equipment and controlled processing conditions.

2.3. High-Pressure Homogenization (HPH)

- Forces the emulsion through a narrow orifice at extremely high pressure (100-200 MPa).
- Generates uniform nano-sized droplets with high stability.
- Often used in pharmaceutical and food industries due to its efficiency.

2.4. Microfluidics

- Uses precisely controlled microchannels to create monodispersed nanoemulsions.
- Offers superior control over droplet size and distribution.
- Applied in drug delivery and advanced material synthesis.

2.5. Membrane Emulsification

- Forces the dispersed phase through a porous membrane to create controlled droplets.
- Produces highly uniform emulsions with minimal energy input.
- Suitable for applications requiring precise control over droplet size.

2.6. Low-Energy Methods

Low-energy methods rely on the intrinsic physicochemical properties of surfactants and phase transitions rather than mechanical force. These techniques are preferred for their mild processing conditions, lower energy consumption, and ability to preserve encapsulated bioactive molecules.

A. Phase Inversion Temperature (PIT) Method

- Relies on temperature-induced changes in surfactant solubility to create nanoemulsions.
- A temperature shift causes phase inversion, resulting in nano-sized droplets.
- Commonly used in cosmetic and pharmaceutical formulations.

B. Emulsion Inversion Point (EIP) Method

- Involves gradual compositional changes that lead to phase inversion.
- Generates smaller and more stable droplets compared to traditional emulsification.
- Effective for producing nanoemulsions with high stability.

C. Spontaneous Emulsification

- Occurs in nonequilibrium systems when two immiscible phases rapidly mix.
- Relies on diffusion and interfacial tension to form nano-sized droplets.
- Requires minimal energy input and is widely used in drug delivery applications.

2.7. Hybrid Methods

- Hybrid techniques **combine high-energy and low-energy methods** to optimize nanoemulsion formation. These approaches offer enhanced efficiency, improved stability, and better control over droplet size distribution.

A. Combined High-Shear Stirring and Ultrasonic Emulsification

- Uses high-shear stirring to form macroemulsions, followed by ultrasonic emulsification for nanoscale droplet formation.
- Improves efficiency and reduces energy consumption compared to pure high-energy methods.

B. High-Shear Stirring with High-Pressure Homogenization

- Initial mechanical stirring forms a coarse emulsion, which is later refined using high-pressure homogenization.
- Ensures high stability and uniform droplet size distribution.

C. PIT Method with High-Pressure Homogenization

- The phase inversion process creates pre-emulsions, which are further processed under high pressure.
- Enhances stability and improves encapsulation

2.8. Early High-Energy Approaches

Early nanoemulsion production was limited to high-energy methods, primarily high-shear stirring and ultrasonic emulsification. High-pressure homogenizers were later developed to improve efficiency. These methods provided excellent emulsification but required significant energy input and could degrade sensitive compounds.

2.9. Transition to Low-Energy Methods

Recent research has focused on low-energy methods due to their advantages, including:

- **Reduced energy consumption**, making them more cost-effective for industrial production.
- **Minimal impact on encapsulated molecules**, preserving bioactivity and stability.
- **Scalability for pharmaceutical, food, and cosmetic industries**.

2.10. Current Trends in Hybrid Methods

Hybrid approaches are now gaining traction as they offer the best of both worlds—the stability of high-energy methods and the efficiency of low-energy methods. Advances in membrane emulsification, microfluidics, and temperature-controlled phase transitions are leading to the development of next-generation Nano emulsions with improved functionality and industrial feasibility.

3. Results:

The efficiency and development of three main strategies— high-energy, low-energy, and hybrid methods—are highlighted by the examination of nanoemulsion production techniques. The following are the main conclusions:

A. High-Energy Techniques: Accuracy and Effectiveness at a Price

Methods including membrane emulsification, high-shear stirring, high-pressure homogenization, ultrasonic emulsification, and microfluidics efficiently decrease droplet size and improve stability. These techniques are dependable for large-scale manufacturing yet resource-intensive due to their high energy input and need for specialized equipment.

B. Low-Energy Techniques: Economical and Kind to Bioactive Substances

Energy-efficient substitutes include the Phase Inversion Temperature (PIT), Emulsion Inversion Point (EIP), and Spontaneous Emulsification techniques. In sectors including food, cosmetics, and medicines, these methods facilitate better scalability, lower production costs, and protect delicate components.

C. Hybrid Approaches: Enhancing Sustainability and Performance

Combination techniques (such as PIT with high-pressure homogenization or high-shear stirring followed by ultrasonic emulsification) offer improved control over droplet size and stability. These techniques are becoming more and more common for industrial applications because they strike a compromise between energy efficiency and nanoemulsion quality.

The Development of Nanoemulsion Technology:

Low-energy and hybrid approaches are preferred in recent developments because of their reduced energy needs, affordability, and capacity to preserve the integrity of encapsulated molecules. The advancement of membrane-based and microfluidic emulsification methods is opening the door to more accurate and environmentally friendly nanoemulsion manufacturing.

A careful selection of nanoemulsion preparation techniques is necessary for the formulation and assessment of alendronate-loaded nanoemulsions for the treatment of osteoporosis in order to provide the best possible drug delivery, stability, and bioavailability. The results of the examination of techniques for producing nanoemulsions emphasize how crucial it is to select a method that is suitable for energy efficiency, droplet size control, and the integrity of molecules that are encapsulated.

Choosing the Nanoemulsion Method to Formulate Alendronate

The absorption and bioavailability of alendronate sodium, a bisphosphonate medication with poor gastrointestinal absorption, can be enhanced by high-energy techniques like high-pressure homogenization and ultrasonic emulsification, which can produce tiny, homogeneous droplets.

Low-energy techniques are perfect for encapsulating bioactive molecules because they maintain the stability of the medicine and inhibit degradation. This is especially true of Phase Inversion Temperature (PIT) and Emulsion Inversion Point (EIP).

Hybrid approaches could provide an optimal balance by utilizing high-shear stirring for primary emulsification, followed by ultrasonic or high-pressure homogenization for finer droplet formation, ensuring enhanced stability and prolonged drug release.

Effect on the Management of Osteoporosis By providing a steady, sustained-release formulation, alendronate sodium delivered via nanoemulsion can increase bioavailability, lessen gastrointestinal side effects, and increase patient compliance.

Higher medication effectiveness at lower dosages can result from improved gastrointestinal absorption caused by smaller droplet sizes (usually less than 100 nm).

The medication is shielded from deterioration by encapsulation in nanoemulsions, guaranteeing its therapeutic efficacy in the treatment of osteoporosis.

4. Discussion

The formulation and evaluation of Alendronate-loaded nanoemulsions for osteoporosis management require a strategic selection of nanoemulsion preparation methods to ensure optimal drug delivery, stability, and bioavailability. The findings from the analysis of nanoemulsion production methods highlight the importance of choosing an appropriate technique based on energy efficiency, droplet size control, and the integrity of encapsulated molecules.

Selection of Nanoemulsion Method for Alendronate Formulation

- High-energy methods such as high-pressure homogenization and ultrasonic emulsification can generate small, uniform droplets, improving the absorption and bioavailability of Alendronate sodium, a bisphosphonate drug known for its poor gastrointestinal absorption.
- Low-energy methods, particularly Phase Inversion Temperature (PIT) and Emulsion Inversion Point (EIP), offer advantages by preserving the drug's stability and preventing degradation, making them ideal for encapsulating bioactive molecules.
- Hybrid approaches could provide an optimal balance by utilizing high-shear stirring for primary emulsification, followed by ultrasonic or high-pressure homogenization for finer droplet formation, ensuring enhanced stability and prolonged drug release.

Impact on Osteoporosis Management

- Nanoemulsion-based delivery of Alendronate sodium can enhance bioavailability, reduce gastrointestinal side effects, and improve patient compliance by offering a stable, sustained-release formulation.
- Smaller droplet sizes (typically <100 nm) can promote better absorption in the gastrointestinal tract, leading to higher drug efficiency at lower doses.
- Encapsulation within nanoemulsions protects the drug from degradation, ensuring its therapeutic effectiveness for osteoporosis management.

5. Challenges and Considerations

- **Surfactant selection and concentration** play a crucial role in nanoemulsion stability. Excessive surfactant levels can cause toxicity, whereas insufficient surfactant concentrations may lead to phase separation
- **Manufacturing scalability and cost-effectiveness** must be considered for large-scale production, making low-energy methods more attractive for pharmaceutical applications.
- **Long-term stability studies** are required to evaluate the shelf-life, particle size retention, and drug release profile over extended periods.

Conclusion

An effective method for increasing bioavailability, boosting stability, and minimizing adverse effects linked to traditional formulations is the creation of an alendronate-loaded nanoemulsion for the treatment of

osteoporosis. The drug's effectiveness and delivery performance are greatly impacted by the methods used to prepare the nanoemulsion. Drug stability is ensured via low-energy techniques (PIT, EIP, and spontaneous emulsification), which are economical, scalable, and gentle.

Superior control over droplet size is offered by high-energy techniques (such as Ultrasonic Emulsification and High-Pressure Homogenization), which can improve drug absorption.

By combining the benefits of both approaches, hybrid approaches can provide enhanced stability, drug protection, and controlled release.

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