WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

A Review on Proniosomal Gel

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ABSTRACT

Depending on the size and quantity of the bilayer, encapsulation and partitioning systems between hydrophobic domains allow peptidosomal drug delivery systems to entangle both hydrophilic and hydrophobic pharmaceuticals. Different routes of medication administration can now be covered by a variety of innovative drug delivery strategies that have arisen to provide either targeted or controlled distribution. The domain formulation and characterization of Proniosomal gel includes introduction, preformulation, excipient selection criteria, formulation, and preparation technique. Stability studies, labeling, documentation, packaging, and evaluation are also covered.

KEY WORDS: PRONIOSOMAL GEL

INTRODUCTION

Simply dissolve the surfactant in the least amount of water and the least amount of suitable solvent (ethanol) to create a proteosome gel. The semisolid liquid crystal products of nonionic surfactants are called proteosome gel. Proniosomal gel has a large potential to reduce pharmacological side effects and increase therapy efficacy.Proniosomes, sometimes referred to as dry niosomes, are a well-known novel drug delivery method due to its additional advantages in dosage, transport, distribution, and storage. Proniosomes are free-moving, anhydrous, water-soluble carriers coated in surfactant. Niosomal dispersions can be generated later on when proniosomes are rehydrated with warm water. Because they facilitate skin penetration and function as a drug depot for an extended period of time, promethiosomes are excellent vesicular drug delivery devices for transdermal administration.[1]

ADVANTAGES

1. Enhanced Drug Delivery: Proniosomal gels can improve the solubility and bioavailability of poorly water-soluble drugs, making them more effective in the body.

2. Prolonged Drug Release: They can provide sustained or controlled drug release, allowing for a more consistent therapeutic effect over an extended period.

3. Increased Skin Penetration: For topical applications, proniosomal gels can enhance the penetration of drugs through the skin, leading to improved therapeutic outcomes.

4. Improved Stability: Proniosomes can protect drugs from degradation and enhance their stability, which is particularly important for sensitive drugs.

5. Reduced Side Effects: Controlled release and targeted delivery can minimize potential side effects associated with high drug concentrations in the body.

DISADVANTAGES

1. Complex Formulation: Proniosomal gels can be more challenging to formulate compared to conventional dosage forms, requiring expertise in formulation and quality control.

2. Cost: The production of proniosomal gels can be more expensive compared to simpler dosage forms.

3. Potential for Instability: Proniosomal formulations may be sensitive to environmental factors such as temperature and humidity, which can affect their stability and shelf life.

4. Limited Commercial Availability: Proniosomal gels are not as commonly available as other dosage forms, limiting the variety of drugs that can be administered using this system.

5. Variable Drug Loading: The amount of drug that can be loaded into proniosomal gels may vary, and achieving high drug-loading capacity can be challenging.[2]

PREFORMULATION

In order to optimize the formulation and guarantee the stability and efficacy of proniosomal gel, a carrier system for the controlled administration of medications, preformulation experiments are crucial.

A) IDENTIFICATION AND CHARECTERIZATION OF PRONIOSOMAL GEL

Proniosomal gel is identified and characterized using a battery of tests and analysis aimed at evaluating its structural, chemical, and physical characteristics. The following are some typical procedures and methods for identifying and characterizing proniosomal gel:

1. Visual Inspection: To begin, visually inspect the proniosomal gel to check its consistency, color, and clarity. Inhomogeneity or other visual changes could be signs of instability problems.

2. Microscopy: To investigate the morphology and structure of proniosomal vesicles inside the gel, use optical or electron microscopy.

3. Particle Size Analysis: Use methods such as dynamic light scattering (DLS) or laser diffraction to ascertain the size distribution of proniosomal vesicles. This aids in evaluating the vesicles' homogeneity and size range.

4. Zeta Potential Measurement: To determine how the surface charge of the proniosomal vesicles influences stability and drug release behavior, measure their zeta potential.

5. Encapsulation Efficiency: Using spectrophotometric or separation techniques, determine how much of the active pharmaceutical ingredient (API) is encapsulated within the proniosomal vesicles.

6. Drug Content homogeneity: To guarantee consistent dosing, ascertain the homogeneity of the drug content in various proniosomal gel samples.

7. In Vitro Drug Release Studies: To determine how the API is released from the proniosomal gel over time, conduct in vitro drug release studies. This sheds light on the formulation's performance and release kinetics.

8. Rheological Characterization: Using rheological tools, examine the proniosomal gel's rheological characteristics, such as viscosity, shear-thinning behavior, and thixotropy.

9. Differential Scanning Calorimetry (DSC): DSC can be used to look into the proniosomal vesicles' thermal behavior and find any phase transitions or component interactions.

10. Fourier Transform Infrared Spectroscopy (FTIR): Use FTIR analysis to determine functional groups and evaluate the API's and lipids' chemical compatibility.

11. X-ray Diffraction (XRD): Employ XRD to analyze the crystallinity and polymorphic forms of the API within the proniosomal vesicles.

12. Nuclear Magnetic Resonance (NMR): Utilize NMR spectroscopy for structural characterization and determination of lipid components in the proniosomal formulation.

13. Stability Studies: Conduct accelerated stability testing under various conditions (e.g., temperature, humidity, and light) to assess the proniosomal gel's shelf life and storage requirements.

14. Scanning Electron Microscopy (SEM): Employ SEM to examine the surface topography and morphology of the proniosomal vesicles at a higher resolution.[11]

B) EXCIPIENT DRUG COMPATIBILITY

To guarantee the stability and effectiveness of the formulation, it is crucial to assess how well excipients work with the proniosomal gel's active pharmaceutical ingredient (API).

1. Physical Compatibility Tests: These tests assess the physical properties of the mixture, including:

a. Solubility Studies: Determine the solubility of the API in the excipient or excipient blend. If the API is insoluble in the excipient, it may lead to poor drug distribution within the proniosomal vesicles.

b. Phase Solubility Studies: Conduct phase solubility studies to identify if any excipient affects the solubility of the API. This can reveal if certain excipients enhance or reduce API solubility.

c. Melting Point and Thermal Analysis: Use differential scanning calorimetry (DSC) or thermogravimetric analysis (TGA) to study the thermal behavior of the API and excipients, looking for interactions or decomposition.

d. Particle Size and Morphology: Assess the particle size and morphology of proniosomal vesicles when excipients are added to ensure they remain within the desired range.

2. Chemical Compatibility Tests:

a. Fourier Transform Infrared Spectroscopy (FTIR): Use FTIR to analyze the functional groups and chemical structures of the API and excipients to identify potential chemical interactions.

b. Nuclear Magnetic Resonance (NMR): Employ NMR spectroscopy to study chemical interactions and verify the presence of specific chemical groups.

c. X-ray Diffraction (XRD):Examine the crystallinity and polymorphism of the API and excipients to detect any changes in the solid-state form.

d. High-Performance Liquid Chromatography (HPLC): Analyze the chemical stability of the API and its degradation products in the presence of excipients.

3. Bioavailability Studies: To determine how excipients affect the systemic absorption of the API, conduct bioavailability studies in people or animals, if at all practicable. Variations in bioavailability may be a sign of compatibility problems.

4. In Vitro Drug Release tests: To determine how the API is released from the proniosomal gel in the presence of excipients, carry out in vitro release tests. Changes in a drug's release profile may indicate compatibility issues.

5. Accelerated Stability Testing: To evaluate the proniosomal gel's long-term stability and find any compatibility problems that might develop during storage, subject it to accelerated stability settings (such as high temperature and humidity).

6. Impurity Profiling: Keep an eye out for the development of degradation products or impurities once excipients are introduced, as these may be signs of incompatibility.[12]

C) CRITERIA FOR EXCIPIENT SELECTION

To ensure the performance, stability, and safety of proniosomal gel formulations, a number of considerations must be made while selecting the appropriate excipients. Proniosomal gels are complex systems, thus the excipients that are utilized need to be compatible with the way proniosomes grow and function. The following are the main standards for choosing an excipient in proniosomal gel formulations:

1. Safety and Regulatory Approval:

Excipients should have a well-established safety profile and regulatory approval for their intended use in proniosomal gels. Ensure compliance with relevant pharmacopoeial standards and guidelines.

2. Compatibility with Proniosomal Formation:

Excipients should be compatible with the formation and stability of proniosomal vesicles. This includes not interfering with the vesicle formation process or destabilizing the vesicles.

3. Compatibility with the Active Pharmaceutical Ingredient (API):

Excipients should not adversely affect the API's stability, solubility, or release behavior. Conduct compatibility studies to ensure that the API remains stable and effective within the proniosomes.

4. Functionality:

Choose excipients that fulfill specific functions within the proniosomal gel, such as stabilizers, surfactants, or gelling agents, to support proniosome formation and drug delivery.

5. Physicochemical Properties:

Consider excipients' physicochemical properties, such as solubility, compatibility with the lipid phase, and their influence on proniosome size and vesicle stability.

6. Stability and Shelf Life:

Excipients should contribute to the stability of the proniosomal gel, preventing degradation of the API or destabilization of proniosomes over time.

7. Biocompatibility:

Ensure that excipients are biocompatible and do not cause irritation, sensitization, or adverse effects when applied to the intended site, such as the skin or mucous membranes.

8. Dosage Form and Route of Administration:

Excipients should align with the specific dosage form (gel) and the intended route of administration (e.g., topical or transdermal application).

9. Patient Acceptance:

Excipients should not negatively impact the patient's experience in terms of texture, odor, or appearance. For topical gels, this is particularly important.

10. Traceability and Supply Chain Considerations:

Ensure a reliable supply chain for excipients, including traceability of the source and quality of excipients.

11. Eco-Friendly and Sustainable Sourcing:

Consider environmental and sustainability factors when sourcing excipients for proniosomal gels, including responsible and sustainable sourcing practices.

12. Cost-Effectiveness:

Assess the cost-effectiveness of excipients, balancing the cost with their contribution to the formulation's performance and stability.

D) FORMULATION OPTIMIZATION TECHNIQUE

DOE (DESIGN OF EXPERIMENT)

Design of experiment is a powerful statistical technique for improving product / process designs and solving process /production problems

As the purpose of obtaining the most information possible about the cause and effect relationship with the largest possible sample size, DOE carefully modifies the input variables.

Experiments are frequently used in process analysis to assess which process inputs significantly affect the process output and what the goal level of input should be to obtain a desired outcome.

Design of experiments (DOE) Is also referred to as **designed experiments** or **experimental design**

WHY DOE ?

Reduce time to design/develop new products and processes

Improve performance of existing processes

Improve reliability and performance of products

Achieve product and process robustness

Perform evaluation of materials, design alternatives, setting component and system tolerance

FACTORS:

Factors are inputs to the process

Factors can be classified as either controllable or uncontrollable or uncontrollable variables.

In this case, the controllable factors are flour, flour, eggs, sugar, and oven.

Potential factors can be catogerized using the cause and effect diagram

LEVELS:

Levels represent settings of each factor in the study

Examples include the oven temperature setting, number of spoons of sugars, number of cups of flour, and number of eggs

RESPONSE

Response is output of the experiment

In the case of cake baking, the taste, consistency, and appearance of the cake are measurable outcomes potentially influenced by the factors and their respective levels

appearance of the cake are measurable outcomes potentially influenced by the factors and their respective levels [7]

FORMULATION

The proniosomal gel-making procedure Method of phase separation for escalation Proniosomal gel is commonly made with this method. 0.5 ml of alcohol is added to a 5.0 ml wide mouth glass vial that has been cleaned, dried, and filled with precisely weighed amounts of medicine, lipid, and surfactant. Using a glass rod, all the components are well blended after warming. The glass bottle's open end is covered with a lid to prevent solvent leakage. The liquid is then heated for about five minutes, or until the surfactant mixture completely dissolves, over a water bath at 60 to 70°C. Next, the aqueous phase of the 0.1% glycerol solution is added, and it is heated on a water bath until a clear solution develops.[5]

EVALUATION

Organoleptic properties

Using the membrane diffusion method, the release of fluconazole from proniosomal gels was ascertained. A glass tube of 2.5 cm in diameter and 8 cm in effective length was used to hold the proniosomal gel, which contains 25 mg of fluconazole. The tube was previously covered with a soaking osmotic cellulose membrane with a molecular weight cutoff of 12,000 Daltons, which serves as a donor compartment. As a receptor compartment, the glass tube was put in a beaker with 100 cc of phosphate buffer pH 5.5. The entire assembly was fastened such that the gel-filled tube's lower end barely brushed the diffusion medium's surface (1-2 mm deep). The media used for the receptor was kept at 37°C ± 100°C, and the medium agitated using a magnetic stirrer at a speed of 100 rpm. Periodically, 3 ml sample aliquots were removed and replenished with an equivalent volume to keep the receptor's phase's volume constant. The UV spectrophotometer was used to evaluate the obtained samples for the presence of drugs at 260 nm absorbance against a reagent.

Particle size analysis of proniosomes

A Zeta sizer 3000 PCS (Malvern Institute, England) fitted with a 5 mW helium–neon laser with an output wavelength of 633 nm was used to assess the particle size (PS) and Polydispersity Index (PDI) of proniosomes. At least 180 seconds of runtime, a 90° angle, and 25°C were used for the measurements. Prior to measurements, the proniosomal gels were suitably diluted with distilled water. The PDI was calculated as a homogeneity metric. A homogenous population is indicated by small PDI values (<0.1), whereas substantial heterogeneity is shown by PDI values >0.3.

Zeta potential analysis

Charge on drug-loaded vesicles surface was determined using zeta potential (ZP) analyzer (A Brookhaven Instrument Corp). Analysis time was kept for 60 s, and average ZP and charge on the proniosome preparation after hydration with phosphate buffer saline pH 7.4 were determined at 25°C and three runs were carried out. [7]

High-resolution transmission electron microscopy

The selected and prepared fluconazole proniosomal gel was characterized for its shape by transmission electron microscopy (JEOL Model - JEM 2100–200KV, Tokyo, Japan), using a 300 mesh carbon-coated copper grid and phosphotungstic acid (1%; w/v) as a negative stain. After being stained, the samples were allowed to dry at room temperature for 10 min for investigation.

Physical stability studies

The selected fluconazole proniosomal gel (F4) was evaluated for their stability by storing and sealing in well-closed containers in the refrigerator at 4°C ± 1°C for 6 months. The stability study was performed according to different parameters, including physical appearance, %EE, PS, and ZP.[13] The changes of %EE, PS, and ZP against storage time were monitored.[8]

Statistical analysis

Statistical analysis of the results was performed using one-way analysis of variances to determine the significance of differences between groups; $P < 0.05$ was considered statistically significant.[9]

STABILITY STUDIES

The duration of a pharmaceutical product's physical, chemical, microbiological, and pharmacokinetic features and characteristics over the course of its shelf life after manufacture is referred to as the stability study of the product. The product's shelf life is determined by the substance's reduction to 90% of its initial concentration. The term "shelf life" refers to the product's stability and is commonly used interchangeably with "expiration date." Every medicinal preparation has a different expiration date.

STABILITY TESTING METHODS

Every pharmaceutical product undergoes stability testing at different phases of the product development process. Early on, the accelerated stability studies—which are primarily conducted at high temperatures and humidity—perform the stability tests. Depending upon the aim, steps followed, the stability testing procedures have been categorized into four types and they are :-

REAL TIME STABILITY TESTING

It is typically carried out over an extended period of time to permit the product to significantly deteriorate under the advised storage conditions. The product's stability will determine how long it will be tested for.

ACCELERATED STABILITY TESTING

Higher temperatures are used, and the product's breakdown is monitored. The data is used to analyze the relative stability of different formulations or to forecast the shelf life.The accelerated stability studies are easily predicted by the Arrhenius equation:

K=Ae-Ea./RT

K= Specific rate constant

A= Frequency factor or Arrhenius factor

Ea= Energy of activation

R= Real gas constant 4.184 j/mol. K

T= Absolute temperature,

RETAINED SAMPLE STABILITY TESTING

To test for stability, a single batch is chosen and kept under observation for a full year. The shelf life is predicted in part by the stability assessments of the samples. Product shelf life predictions range from a maximum of five years to a typical three, six, nine, twelve, eighteen, twenty-four, thirty, forty, and sixty months.

CYCLIC TEMPERATURE STRESS TESTING

Using this approach, cyclic temperature stress tests are created with product knowledge to replicate possible market storage circumstances. The sampling in this experiment is said to be done in cycles of 24 hours, or what is known as the earth's 24-hour rhythm.[3]

PACKAGING AND LABELLING OF TABLETS PACKAGING: -

PACKAGING

A device or material that holds a pharmaceutical product, whether or not it comes into direct touch with the substance, is called a pharmaceutical package container. A sturdy container is necessary for pharmaceutical packaging. Medicines must be produced with precision in both their content and packaging. When medicine comes into persistent contact with heat, air, or water, it could turn fatal. Numerous kinds and classifications of packaging machines have developed and are now extensively utilized worldwide thanks to innovation and technology.

TYPES OF PACKAGES

1.PRIMARY PACKAGING .

Packages that come into direct touch with the pharmaceutical formulation are referred to as primary packaging. Protecting the formulation against mechanical, chemical, environmental, and/or other risks is the primary goal of the primary package.

2. SECONDARY PACKAGING

The secondary package is the one that is located outside of the primary package. In addition to offering extra security during storage, this packaging contains information on pharmaceutical products, such as leaflets.

3. TERTIARY PACKAGING: This is the secondary packaging's outer layer and guards against product damage. It is employed in shipping and bulk handling. Barrel, crate, container, pallets, and slip sheet are a few examples.

LABELLING

LABEL:

Label means a display of written, printed or graphic matter upon immediate container or the wrapper of a drug package.

TYPES OF LABELS

I. Manufacturer label

II. Dispensing label

MANUFACTURER LABEL

A label provided by the medicine's maker, packer, or distributor that includes drug information intended for use by physicians, pharmacists, or nurses (FDA).

LEGAL REQUIRMENTS OF A MANUFACTURER LABEL

➢ The name of preparation

➢ Strength and dosage form.

➢ Quantity.

➢ Instructions for the use.

➢ Precautions & warnings.

➢ Registration number.

➢ Batch number.

➢ Manufacturing & Expiry date.

➢ Price

➢ The name and address of pharmaceutical industry

DISPENSING LABEL

Dispensing label is defined as the label used for dispensing, bearing the name and address of the supplier, the nature of the medicine and any other prescribed directions, the name of patient and the date of dispensing.[4]

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