Review Article

Solid Lipid Nanoparticle Loaded Mucoadhesive Thermoreversible Nasal *in situ* Gel for Brain Targeting

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ABSTRACT

The formulation and evaluation of solid lipid nanoparticles (SLNs) incorporated into mucoadhesive thermoreversible nasal in situ gels present a novel strategy for enhancing brain-targeted drug delivery. This review focuses on the development of this innovative system, highlighting the dual advantages of SLNs and mucoadhesive thermoreversible gels in optimizing therapeutic efficacy for central nervous system (CNS) disorders. We discuss the selection of suitable lipids, surfactants, and gelling agents, emphasizing their role in achieving desired physicochemical properties, such as particle size, stability, and drug release profiles. The mucoadhesive properties of the in situ gel facilitate prolonged retention in the nasal cavity, while the thermoreversible nature allows for easy application and enhanced patient compliance. The article also addresses the evaluation methodologies for assessing in vitro drug release, permeation studies, and in vivo brain targeting efficiency, providing insights into the mechanisms of action. Challenges related to formulation stability, toxicity, and regulatory considerations are critically examined, along with potential solutions. Finally, this review outlines future perspectives in the field, aiming to underscore the significance of SLN-loaded mucoadhesive thermoreversible nasal in situ gels as a promising avenue for targeted CNS therapies.

Keywords: Solid lipid nanoparticles, In situ gel, brain targeting, CNS.

INTRODUCTION

Targeted delivery of pharmaceutical compounds remains a significant challenge, and it is a major focus in the research conducted by pharmaceutical scientists. The advancement of colloidal drug delivery systems, including nanoparticles, liposomes, and micelles, represents a novel approach to enhancing drug administration. A nanoparticle serves as the foundational element in the construction of nanostructures, existing in a scale that is smaller than common objects governed by Newtonian physics but larger than individual atoms or simple molecules, which are influenced by quantum mechanics [1].

Solid lipid nanoparticles (SLNs) are spherical, biodegradable nano-dispersions typically ranging from 10 to 1000 nm in average diameter. These nanoparticles consist of a colloidal solid lipid core matrix that is emulsified and stabilized within an aqueous environment by surfactants. Lipophilic drugs can be effectively solubilized within the lipid core of this nanocarrier [2,3]. SLNs exhibit distinct characteristics and numerous benefits compared to traditional dosage forms, including reduced particle size, an increased surface area, and high drug entrapment efficiency (EE).

In situ gelation refers to the process of gel formation at the site of action after the formulation is applied. This phenomenon involves the transformation of a liquid drug formulation into a semi-solid, mucoadhesive depot. It allows for the delivery of the drug in a liquid or solution form [4-6].

The delivery of medications to the central nervous system (CNS) is primarily regulated by the blood-brain barrier (BBB), a protective structure that restricts the passage of foreign substances from the bloodstream into the brain's extracellular fluid. Current treatments for neurological disorders, which affect millions worldwide, are only partially effective and often lead to severe systemic side effects. Additionally, certain drugs struggle to penetrate the BBB due to their physicochemical properties, resulting in sub-therapeutic concentrations within target tissues. In this context, the intranasal route, with its unique anatomical advantages, presents a promising pathway for drug delivery to the brain. Nanoparticle-based systems have demonstrated significant efficacy in overcoming the challenges associated with the intranasal route, facilitating drug accumulation in the brain while minimizing systemic exposure. This review discusses recent advancements in the use of polymeric, lipidic, and inorganic nanoparticles, as well as drug nanocrystals, for the intranasal delivery of medications to the brain, along with a comprehensive overview of the benefits and limitations of this approach [7].

SOLID LIPID NANOPARTICLES [8]

Solid lipid nanoparticles are nearly spherical, biodegradable nano-dispersions with an average diameter ranging from 1 to 1000 nm.They comprise a colloidal solid lipid core matrix that is emulsified and stabilized in an aqueous medium through surfactants.

ADVANTAGES

- Manipulating particle size and surface characteristics of

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nanoparticles allows for both passive and active drug targeting following parenteral administration.

• Targeting ligands can be conjugated to the surface of the particles to enable site-specific targeting.

• Magnetic guidance can facilitate targeted delivery.

• SLNs have a relatively high drug loading capacity.

• The release characteristics and degradation rates can be controlled by altering the matrix components.

• SLNs can be utilized via various administration routes, including oral, nasal, parenteral, and intraocular.

• The use of biodegradable, physiological lipids reduces the risk of acute and chronic toxicity and eliminates the need for organic solvents during manufacturing[9].

• They enhance the bioavailability of poorly water-soluble compounds[10].

• Lyophilization can be performed on SLNs.

• They avoid the use of organic solvents.

DISADVANTAGES

• The small size and large surface area can lead to particle aggregation.

• Handling of the particles can be challenging.

• There may be limitations in drug loading and potential for burst release.

• Unexpected dynamics in polymeric transitions can occur.

PROPERTIES OF SOLID LIPID NANOPARTICLES[11]

SLNs are spherical, biodegradable nano-dispersions with an average diameter ranging from 1 to 1000 nm. They consist of a colloidal solid lipid core matrix that is emulsified and stabilized in an aqueous medium by surfactants. Nanoparticles derived from solid lipids are garnering significant attention as innovative colloidal drug carriers for intranasal applications, offering a promising alternative to traditional particulate carrier systems. This system comprises spherical solid lipid particles in the nanometer range, dispersed in either water or an aqueous surfactant solution. Typically, they feature a solid hydrophobic core encapsulated by a monolayer of phospholipids. The drug is incorporated within the solid, high-melting fat matrix, with the hydrophobic chains of phospholipids integrated into this lipid core. These nanoparticles have the potential to transport both lipophilic and hydrophilic drugs or diagnostics.

SLNs exhibit several notable characteristics, including low toxicity, a large surface area, prolonged drug release, and enhanced cellular uptake compared to conventional colloidal carriers. They also have the ability to improve the solubility and bioavailability of drugs. The release profile of the drug from SLNs is influenced by the type of matrix used and the positioning of the drug within the formulation. SLNs made from biodegradable and biocompatible materials can accommodate both hydrophilic and lipophilic bioactive compounds, making them a promising option for controlled and targeted drug delivery. The hydrophobic solid core of SLNs is coated with a monolayer of phospholipids, and the drug is typically dispersed or dissolved within this core.

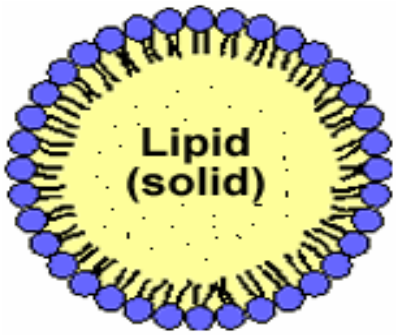

Figure 1: Structure of solid lipid nanoparticle (SLN)

COMPOSITION OF SLNs

The key components required for the fabrication of solid lipid nanoparticles (SLNs) comprise lipids and surfactants/stabilizers, as well as co-surfactants, preservatives, cryoprotectants, and charge modifiers. (Table 1). Surfactants play a crucial role in stabilizing the SLN structure by reducing the interfacial tension between the aqueous environment and the hydrophobic surface of the lipid core [11]

Table 1: composition of SLN

Sl no	Ingredient	Examples
1	Lipid component	Beeswax, Stearic acid, Glyceryl stearate (-mono, and -tri)
2	Surfactant/Emulsifiers	Phosphatidyl choline, Soy and Egg lecithin, Poloxamer, Poloxamine, Polysorbate 80
3	Co-surfactant	Sodium dodecyl sulphate, Taurocholate sodium salt, Butanol
4	Preservative	Tween 80,Thiomersal
5	Cryoprotectant	Gelatin, Glucose, Mannose, Maltose, Lactose, Sorbitol, Mannitol, Glycine, Polyvinyl alcohol, Polyvinyl pyrrolidone
6	Charge modifiers	Dipalmitoyl phosphatidyl choline, Stearylamine, Dicetylphosphate, Dimyristoyl phophatidyl glycerol

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PREPARATION OF SOLID LIPID NANOPARTICLE

High shear homogenization

High shear homogenization methods are frequently utilized for producing solid lipid nanodispersions[13,14]. Both methods are widely used and easy to manage; however, the quality of the dispersion can be negatively affected by the presence of microparticles. The high-speed homogenization method is utilized to create SLNs through melt emulsification. Olbrich et al. examined the effects of various process parameters, such as emulsification time, stirring rate, and cooling conditions, on particle size and zeta potential. The lipids studied included trimyristin, tripalmitin, and a blend of mono-, di-, and triglycerides (Witepsol W35, Witepsol H35) with glycerol behenate and poloxamer 188 serving as steric stabilizers at a concentration of 0.5% w/w. For Witepsol W35 dispersions, the optimal SLN quality was achieved after stirring for 8 minutes at 20,000 rpm, followed by 10 minutes of cooling and stirring at 5,000 rpm at room temperature. Conversely, the ideal conditions for Dynasan116 dispersions involved 10 minutes of emulsification at 25,000 rpm and 5 minutes of cooling at 5,000 rpm in cool water (approximately 16°C)[12]. While higher stirring rates did not significantly affect particle size, they did slightly enhance the polydispersity index.

Hot Homogenization

Hot homogenization is performed at temperatures above the lipid's melting point, similar to the homogenization process used for emulsions.A pre-emulsion is formed by high-shear mixing the drug-loaded lipid melt with the aqueous emulsifier phase at the same temperature. The quality of this pre-emulsion significantly influences the final product's quality, and it is essential to achieve droplet sizes in the micrometer range. High-pressure homogenization of the pre-emulsion occurs above the lipid melting point. Generally, smaller particle sizes are obtained at higher processing temperatures due to the reduced viscosity of the lipid phase[15]. However, this may also lead to accelerated degradation of both the drug and the carrier. Optimal products are typically achieved after several passes (usually 3-5) through a high-pressure homogenizer (HPH). High-pressure processing inevitably raises the temperature of the sample (approximately 10°C at 500 bar)[16]. In most cases, 3-5 homogenization cycles at pressures ranging from 500 to 1500 bar are adequate. Increased homogenization can result in larger particle sizes due to particle coalescence, which occurs due to the high kinetic energy of the particles.

Cold Homogenization

Cold homogenization is performed using solid lipids, making it analogous to milling a suspension under elevated pressure. To maintain the solid state of the lipid during the process, effective temperature control is essential[16]. This technique was developed to address several issues associated with hot homogenization, including: accelerated degradation of the drug due to temperature, partitioning and subsequent loss of the drug into the aqueous phase during homogenization, along with the unpredictable polymorphic transitions of the lipid resulting from the intricate crystallization processes of the nanoemulsion, can lead to various modifications or supercooled melts. The initial preparatory step mirrors that of the hot homogenization process, involving the solubilization or dispersion of the drug in the lipid melt. However, subsequent steps differ: the drug-laden melt is rapidly cooled (using dry ice or liquid nitrogen) to enhance homogeneous drug distribution within the lipid matrix. This cooling process pulverizes the drug-containing solid lipid into microparticles using ball or mortar milling, resulting in typical particle sizes ranging from 50 to 100 microns. Chilled processing further aids particle milling by increasing the lipid's brittleness. The solid lipid nanoparticles (SLNs) are subsequently dispersed in a chilled emulsifier solution and undergo high-pressure homogenization at or below room temperature, with careful temperature control to address the usual temperature increase that occurs during high-pressure processing. However, in comparison to hot homogenization, cold homogenization typically results in larger particle sizes and a wider size distribution[17].While this method reduces thermal exposure, it cannot entirely eliminate it due to the initial melting of the lipid/drug mixture.

Ultrasonication or High-Speed Homogenization

Solid lipid nanoparticles (SLNs) can also be prepared using high-speed stirring or ultrasonication [18,19]. One significant advantage of these methods is that the equipment used is commonly available in most laboratories. However, a drawback of this approach is the broader particle size distribution, which can extend into the micrometer range, leading to physical instability such as particle growth during storage. Additionally, potential metal contamination from ultrasonication poses a substantial concern. To create a stable formulation, various research groups have explored combining high-speed stirring with ultrasonication, particularly at elevated temperatures.

SLNs Prepared by Solvent Emulsification/Evaporation

For producing nanoparticle dispersions through precipitation in oil-in-water (o/w) emulsions, the lipophilic material is dissolved in a water-immiscible organic solvent (such as cyclohexane), which is then emulsified in an aqueous phase[20]. As the solvent evaporates, nanoparticle dispersion is formed through lipid precipitation in the aqueous medium. The mean diameter of the particles was determined to be 25 nm when cholesterol acetate was utilized as the model drug, with a blend of lecithin and sodium glycocholate functioning as the emulsifier.The reproducibility of these results was confirmed by Siekmann and Westesen, who successfully produced cholesterol acetate nanoparticles with a mean size of 29 nm[21].

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Microemulsion-Based SLN Preparations

Gasco and colleagues developed SLN preparation techniques that utilize the dilution of microemulsions[22]. These microemulsions are formed by stirring a clear mixture at temperatures between 65 and 70°C, typically comprising a low melting fatty acid (like stearic acid), an emulsifier (such as polysorbate 20, polysorbate 60, soy phosphatidylcholine, and sodium taurodeoxycholate), co-emulsifiers (like sodium monooctylphosphate), and water. The hot microemulsion is then dispersed in cold water (2-30°C) under continuous stirring. The typical volume ratios of the hot microemulsion to cold water range from 1:25 to 1:50. The dilution process is critically influenced by the composition of the microemulsion. According to the literature, the droplet structure is already present in the microemulsion, thus requiring no additional energy to achieve submicron particle sizes[23,24]. In comparison to the methods used for producing polymer nanoparticles described by French scientists, various mechanisms can be considered. For example, Fessi produced polymer particles through the dilution of polymer solutions in water. De Labouret et al. reported that the particle size is greatly affected by the speed of the distribution processes[25]. Nanoparticles were produced only with solvents that rapidly disperse into the aqueous phase, such as acetone, whereas more lipophilic solvents were linked to larger particle sizes. The hydrophilic co-solvents in the microemulsion may play a similar role in the formation of lipid nanoparticles as acetone does in the formation of polymer nanoparticles[26].

SLN Preparation Using Supercritical Fluid

The preparation of solid lipid nanoparticles (SLNs) using supercritical fluids is a relatively novel technique that offers the advantage of solvent-free processing[27,28].This platform technology includes several variations for producing powders and nanoparticles. One method involves the rapid expansion of supercritical carbon dioxide solutions (RESS), with carbon dioxide (99.99%) being a favorable solvent for this approach[29].

Spray Drying Method

Spray drying serves as an alternative to lyophilization for converting an aqueous SLN dispersion into a final drug product and is more cost-effective than lyophilization. However, this method may lead to particle aggregation due to the effects of high temperatures, shear forces, and partial melting of the particles. Freitas and Mullera recommend using lipids with melting points greater than 70°C for optimal spray drying[30]. The best results are achieved with an SLN concentration of 1% in a solution of trehalose in water or a 20% trehalose concentration in ethanol-water mixtures (10/90 v/v).

Double Emulsion Method

To prepare hydrophilic drug-loaded SLNs, a novel technique based on solvent emulsification-evaporation has been utilized[31]. In this method, the drug is encapsulated with a stabilizer to prevent its partitioning into the external water phase during the solvent evaporation process within a water-in-oil-in-water (w/o/w) double emulsion.

EVALUATIONS OF SLN

Measurement of Particle Size and Zeta Potential

Photon correlation spectroscopy (PCS) and laser diffraction (LD) are the most effective techniques for routine particle size measurements. The Coulter method is infrequently employed for SLN particle size assessment due to challenges in measuring small nanoparticles and the need for electrolytes that may destabilize colloidal dispersions. PCS, also known as dynamic light scattering, measures the fluctuations in light intensity caused by particle movement, covering a size range from a few nanometers to approximately 3 microns. While PCS is suitable for characterizing nanoparticles, it cannot detect larger microparticles, which can be evaluated using LD measurements[32].

Zeta potential is a critical characteristic of SLNs, as a high zeta potential is expected to facilitate the deaggregation of particles, barring other complicating factors such as steric stabilizers or hydrophilic surface attachments. Zeta potential is typically measured using a zetameter.

Dynamic Light Scattering (DLS)

Dynamic light scattering (DLS), also referred to as PCS or quasi-elastic light scattering (QELS), measures variations in light intensity scattered on the microsecond time scale. These variations arise from the interference of light scattered by individual particles influenced by Brownian motion, and are quantified through the compilation of an autocorrelation function. This function is fitted to an exponential model or its modifications, with the corresponding decay constant(s) related to the diffusion coefficient(s). Assuming spherical size, low concentration, and known viscosity of the suspending medium, particle size can be calculated from this coefficient. The advantages of DLS include rapid analysis, no requirement for calibration, and sensitivity to submicrometer particles.

Static Light Scattering/Fraunhofer Diffraction

Static light scattering (SLS) is an ensemble technique that involves collecting the scattering pattern from a particle solution and fitting it to fundamental electromagnetic equations where size is the main variable. This method is both quick and robust, although it requires more stringent cleanliness compared to DLS and prior knowledge of the particles' optical properties.

Acoustic Methods

Acoustic spectroscopy, another ensemble approach, assesses the attenuation of sound waves to determine size by fitting physically relevant equations. Additionally, it can detect the oscillating electric field generated by charged particles moving under acoustic energy, providing insights into their surface charge.

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Nuclear Magnetic Resonance (NMR)

Nuclear magnetic resonance (NMR) is capable of determining both the size and qualitative nature of nanoparticles. The selectivity offered by chemical shifts, combined with sensitivity to molecular mobility, provides valuable information regarding the physicochemical state of components within the nanoparticles.

Electron Microscopy

Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) offer direct visualization of nanoparticles, with SEM being more effective for morphological examinations. TEM has a lower limit for size detection, serves as a validation for other methods, and provides essential structural information, although one must consider the small statistical sample size and the impact of vacuum on the particles[33].

Atomic Force Microscopy (AFM)

In atomic force microscopy (AFM), a probe tip with atomic-scale sharpness is scanned across a sample to create a topological map based on the forces between the tip and the surface. The probe can either contact the sample (contact mode) or hover just above it (non-contact mode), with the nature of the employed force distinguishing among the various sub-techniques. This approach allows for ultrahigh resolution and the ability to map samples based on properties beyond size, such as colloidal attraction or resistance to deformation, making AFM a valuable characterization tool.

X-ray Diffraction and Differential Scanning Calorimetry (DSC)

Powder X-ray diffraction utilizes the geometric scattering of radiation from crystal planes in a solid to assess the presence or absence of crystallinity, thus allowing the degree of crystallinity to be evaluated. Differential scanning calorimetry (DSC) can also be employed to determine the nature and specification of crystallinity within nanoparticles by measuring glass and melting point temperatures along with their associated enthalpies[34].

***In Vitro* Drug Release**

In vitro drug release can be performed using dialysis tubing, where the solid lipid nanoparticle dispersion is placed in pre-washed dialysis tubing that can be hermetically sealed. The dialysis sac is then placed in a suitable dissolution medium at room temperature; samples are periodically withdrawn from the dissolution medium, centrifuged, and analyzed for drug content using an appropriate analytical method[34]. In the reverse dialysis technique, several small dialysis sacs containing 1 mL of dissolution medium are immersed in the SLN dispersion, allowing the SLNs to disperse into the medium.

NASAL IN SITU GEL

In situ gelation refers to the process of gel formation at the site of action after the formulation is applied. This phenomenon involves the transformation of a liquid drug formulation into a semi-solid, mucoadhesive depot. It allows for the delivery of the drug in a liquid or solution form

Advantages of In-Situ Gel Nasal Formulation

- Prolonged residence time of the drug in the nasal cavity.
- Reduced frequency of drug administration.
- Facilitates rapid absorption and quick onset of action.
- Prevents drug degradation in the gastrointestinal tract caused by acidic or enzymatic conditions.
- Requires a lower dosage.
- Minimizes local and systemic side effects.
- Enhances the bioavailability of the drug.
- Enables direct transport into systemic circulation and the central nervous system (CNS).
- Lowers the risk of overdose for CNS-active drugs.
- Improves patient compliance[35-38]

Properties of Nasal In-Situ Gel

- It should have low viscosity.
- It must be free-flowing to ensure consistent administration to the nasal cavity, either as a droplet mist or a spray.
- The nasal in-situ gel should have an extended residence time.
- It operates based on a phase transition mechanism and must withstand the shear forces exerted by the nasal cavity walls[39-42]

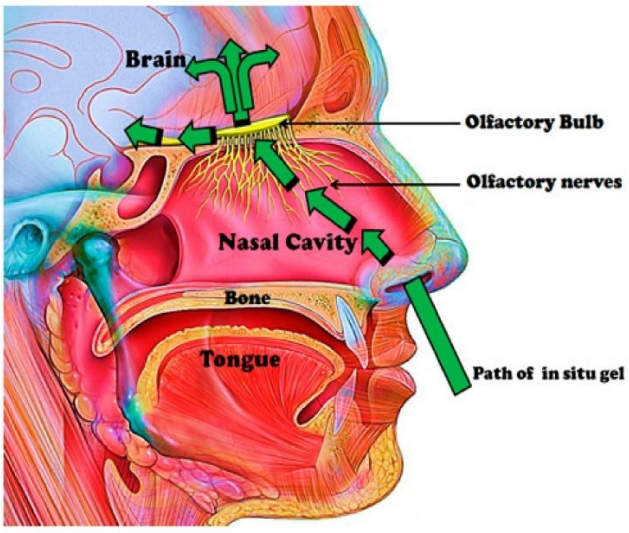

Figure 2: Anatomical components involved in the transport of substances from the nose to the brain[52]

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MUCOADHESIVE IN SITU GELLING SYSTEM

Bioadhesion refers to the adhesion of a polymer to a biological substrate. When this adhesion specifically occurs with the mucus layer lining the mucosal surfaces, it is termed mucoadhesion. Mucoadhesive controlled release systems can enhance drug effectiveness by maintaining the drug concentration within therapeutic ranges, reducing dilution by body fluids, and enabling targeted localization of the drug at specific sites. Moreover, mucoadhesion increases the affinity and duration of contact between the drug-loaded polymer and the mucosal surface. The combined effects of enhanced drug absorption and reduced excretion rate (due to prolonged residence time) contribute to increased bioavailability with smaller doses and less frequent administration[43]

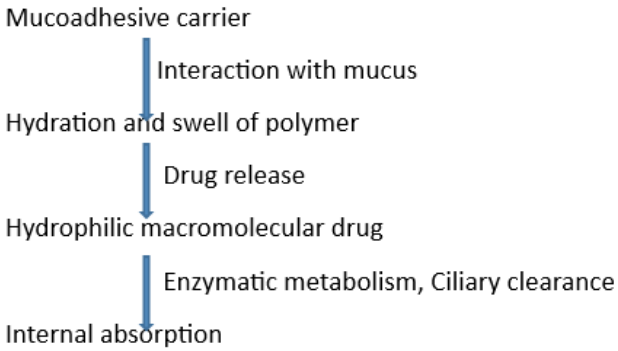

Figure 3: Schematic representation of the mucoadhesive drug delivery system.

IDEAL MUCOADHESIVE POLYMER PROPERTIES:

1. The polymer must be significantly loaded with the active compound.
2. It should swell in the aqueous biological environment at the site of absorption.
3. It must effectively interact with mucus or its components for sufficient adhesion.
4. It should permit controlled release of the active compound upon swelling.
5. It should be excreted unchanged or be biologically degraded into inactive, non-toxic oligomers.
6. The polymer must possess a sufficient number of hydrogen-bonding chemical groups.
7. It must have a high molecular weight.
8. The polymer should exhibit high chain flexibility.
9. It should possess surface tension conducive to spreading into the mucus layer[44]

MECHANISM OF MUCOADHESION

Mucoadhesion requires the polymer to spread over the substrate, facilitating close contact and increasing the surface area for interaction, which promotes the diffusion of polymer chains into the mucus. A balance of attractive and repulsive forces exists, and for mucoadhesion, the attractive forces must prevail. Each step is influenced by the characteristics of the dosage form and its method of administration. For instance, a partially hydrated polymer can be attracted to the substrate due to the presence of surface water.

As defined, mucoadhesion refers to the bond formed between the drug and an appropriate carrier with the mucous membrane. It is a complex phenomenon involving processes such as wetting, adsorption, and interpenetration of polymer chains. The mechanism of mucoadhesion can generally be divided into two stages[44]:

- The contact stage
- The interaction stage

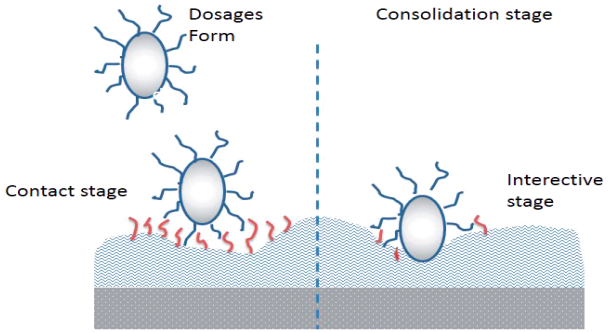

Figure 4: Mechanism of Mucoadhesion. The mucoadhesion occurs in two stages.

Mechanism of Mucoadhesion[45]

Mucoadhesion occurs in two stages:

(A) Contact Stage: This stage involves the close interaction between a bioadhesive and a membrane, characterized by wetting or swelling phenomena.

(B) Interactive Stage: This stage includes the penetration of the bioadhesive into the tissue or the surface of the mucous membrane, referred to as interpenetration.

Contact

This stage is defined by the interaction between the mucoadhesive and the mucous membrane, where the formulation spreads and swells, leading to deeper contact with the mucus layer. In some instances, the deposition of the formulation is aided by the aerodynamics of the specific organ where it is administered, such as the nasal route. When a particle approaches the mucosal surface, it encounters both repulsive forces (e.g., osmotic pressure, electrostatic repulsion) and attractive forces (e.g., van der Waals forces, electrostatic attraction). Therefore, the particle must overcome these repulsive barriers.

Consolidation

In the consolidation step (Figure:4), the mucoadhesive materials become activated upon contact with moisture. The presence of moisture plasticizes the system, allowing the mucoadhesive molecules to detach and form connections through weak van der Waals and hydrogen bonds. There are two primary theories explaining the

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consolidation step: the diffusion theory and the dehydration theory.

Diffusion Theory: According to this theory, the mucoadhesive molecules and the glycoproteins in the mucus interact through interpenetration of their chains, forming secondary bonds. For this interaction to occur, the mucoadhesive device must possess features that promote both chemical and mechanical interactions. For example, molecules containing hydrogen bond-forming groups (–OH, –COOH), having anionic surface charges, high molecular weight, flexible chains, and surface-active properties can enhance spreadability throughout the mucus layer, thus exhibiting mucoadhesive properties.

Dehydration Theory: This theory posits that materials capable of gelling readily in an aqueous environment can cause dehydration of the mucus when in contact, due to osmotic pressure differences. The concentration gradient draws water into the formulation until osmotic balance is achieved. This process promotes a mixture of the formulation and mucus, potentially increasing contact time with the mucous membrane. Thus, the motion of water facilitates the consolidation of the adhesive bond, rather than the elucidation of macromolecular chains. However, the dehydration theory does not apply to solid formulations or highly hydrated forms.

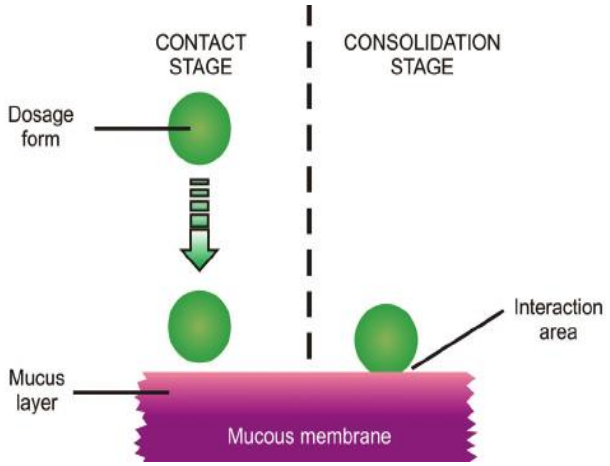

Figure 5: A Schematic Diagram of the Dehydration Theory of Mucoadhesion

THERMO REVERSIBLE IN SITU GELLING SYSTEM

Thermo-reversible in situ forming gel systems are fluid at ambient temperatures and transition to gel-like properties at body temperature. This system does not necessitate an external heat source beyond body temperature to initiate gelation[46]. Poloxamers are triblock copolymers made up of a hydrophobic polypropylene oxide (PPO) central block, which is flanked by two hydrophilic polyethylene oxide (PEO) blocks.

Advantages of Thermoreversible In Situ Gel

- Extended residence time.
- Reduced irritation.
- Enhanced patient compliance.
- Accurate dosing due to prevention of drug leakage.
- Improved bioavailability.
- Targeted delivery to the mucosa for better absorption.
- Sustained and controlled drug delivery.

Thermoreversible Polymers [46]

The gelation process is reversible and characterized by a sol-gel transition temperature (T_sol-gel). Below T_sol-gel, poloxamer aqueous solutions remain fluid, whereas above this temperature, the solution transforms into a semi-solid state. This sol-gel transition is referred to as curing. However, if the cured polymer is subsequently heated further, it may lead to polymer degradation. Curing primarily involves the formation of covalent cross-links between polymer chains, resulting in a macromolecular network[46]

Theory

Several polymers exhibit significant changes in their physical properties, such as solubility and viscosity, with increasing temperature; the resulting sol-gel transition occurs at a lower critical solution temperature (LCST) and is characterized by minimal heat production and absence of by-products. Consider the free energy of association (G) between polymer chains:

G=H-T*S

Where, H is the enthalpy term, S the entropy term and T temperature.

An increase in temperature beyond a critical point results in a larger T * S value compared to the positive enthalpy term (H), leading to a negative G that favors polymer association: chain-chain interactions (hydrophobic effects, hydrogen bonding) dominate over chain-water hydrogen bonding. Various theories regarding the formation of thermoreversible gels have been proposed, with individual polymers adhering to distinct theories of gel formation.

EVALUATIONS OF NASAL IN SITU GEL

pH

The pH of each formulation was measured using a digital pH meter, which was calibrated with pH 4 and pH 7 standards prior to use. The pH values were recorded immediately after preparation, with each measurement performed in triplicate[46]

Drug Content

The drug content was assessed by transferring 1 mL of the formulation into a 100 mL volumetric flask. This was then dissolved thoroughly in ethanol, and the volume was adjusted to 100 mL with additional ethanol. From this solution, 1 mL was taken and transferred into a 10 mL volumetric flask, where the final volume was also made up to 10 mL with ethanol. The absorbance of the resulting solution was measured at 274 nm using a UV-visible

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spectrophotometer. The percentage of drug content in the formulation was then calculated based on the absorbance values obtained.[47]

Viscosity

The rheological properties of the prepared gel were evaluated using a Brookfield Viscometer (Model DV-2+PRO) equipped with spindle number 62. The viscosities of the formulations were measured at two different pH levels: the formulation's pH and pH 7.4, while varying the shear rate.

Gelation Temperature

To determine the gelation temperature, a formulation equivalent to 10 mg was placed in a test tube and immersed in a water bath. The water bath temperature was gradually increased, allowing the sample to equilibrate for 5 minutes at each new setting. Gelation was observed when the meniscus remained stationary upon tilting the tube at an angle of 90° [48]

Gelling Capacity

The gelling capacities of the formulations were assessed by adding one drop of the prepared formulation into a vial containing 2 mL of freshly prepared simulated nasal fluid (SNF). Gelation was assessed visually by recording the time it took for gel formation and the duration required for the gel to dissolve [49]

Gel Strength

A sample of 25 mL of the gel was placed in a 50 mL graduated cylinder. A weight of 14.33 g was placed on the surface of the gel, and gel strength, an indication of the nasal gel's performance at physiological temperature, was measured by recording the time in seconds needed for the weight to penetrate 5 cm into the gel. All measurements were performed in triplicate (n=3) using an apparatus designed for assessing gel strength at both room temperature and 37°C [50].

Mucoadhesive Strength

The mucoadhesive strength of the formulation was evaluated using a method described previously. A section of goat nasal mucosa was obtained immediately after the animal was sacrificed at a local slaughterhouse. Two cylindrical glass vials, each 2 cm in diameter, were used in conjunction with a modified balance instrument. The goat nasal mucosa was secured to one end of both vials, which were then attached for 2 minutes. Water was added dropwise to the balance container until the two vials separated. The amount of water required was recorded, and the mucoadhesive strength of the formulation was expressed as detachment stress in dyne/cm², calculated using the formula:

Mucoadhesive strength (dyne/cm2) = n×g/A (m = Weight required for detachment of two vials in grams**,** g = Acceleration due to gravity (980 cm/s2),

A = The area of nasal mucosa exposed), (Figure: 2).

***In Vitro* Drug Release Studies**

The in vitro release study of the formulated in situ gel was conducted using a diffusion cell with an egg membrane as the biological barrier. A diffusion cell with an inner diameter of 1.4 cm was employed. One mL of the formulation was added to the donor compartment, and 100 mL of freshly prepared simulated nasal electrolyte solution (containing 0.745 g of sodium chloride and 0.129 g of potassium chloride) was used in the receptor compartment. Calcium chloride dihydrate 0.005 g, and distilled water up to 100 mL) was added to the receptor compartment. Egg membranes were positioned between the donor and receptor compartments. The assembly was placed on a thermostatically controlled magnetic stirrer, maintaining the medium temperature at 37°C ± 0.5°C. At predetermined intervals (30 min, 1, 2, 3, 4, 5, 6, 7, and 8 h), 2 mL of sample was withdrawn from the receiver compartment, and an equal volume of fresh medium was replaced. The samples were diluted to 10 mL with simulated nasal fluid and analyzed using UV spectrophotometry at 274 nm[50]

***In Vitro* Permeation Study**

In vitro permeation studies were conducted using natural membranes to simulate in vivo permeation patterns. Fresh goat nasal mucosa was employed due to its large respiratory area and ease of collection. The mucosal tissue was extracted from the nasal cavity of a goat and positioned on a diffusion cell with a permeation area of 0.786 cm².The acceptor chamber of the diffusion cell (designed in the laboratory) was filled with simulated nasal fluid (SNF) containing 7.45 mg/mL NaCl, 1.29 mg/mL KCl, and 0.32 mg/mL $CaCl_2 \cdot 2H_2O$. A 0.5 mL aliquot (equivalent to 10 mg) of the formulation was placed in the donor compartment. At specified time intervals (30 min, 1, 2, 3, 4, 5, 6, 7, and 8 h), 1 mL of sample was withdrawn from the acceptor compartment, and replaced with fresh simulated nasal fluid. The samples were then diluted appropriately, and their absorbance was measured at 274 nm. The permeability coefficient (p) was determined using the formula below:

Where dQ/dt is the flux or permeability rate (mg/h), Co is the initial concentration in the donor compartment, and A is the effective surface area of nasal mucosa.

Accelerated Stability Study

Stability studies were performed following ICH guidelines at 40°C ± 2°C and 75% ± 5% relative humidity to assess the physical and chemical stability of the developed in situ nasal gel. A sufficient quantity of the pH-sensitive in situ gel was stored in screw-capped vials under various stability conditions.[51]

CONCLUSION

In summary, the development and assessment of solid lipid nanoparticles (SLNs) incorporated into mucoadhesive thermoreversible nasal in situ gels represent a promising strategy for enhancing the delivery of therapeutic agents to

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the brain. This innovative drug delivery system offers numerous benefits, including increased bioavailability, extended residence time in the nasal cavity, and the potential to bypass the blood-brain barrier. The addition of SLNs not only improves the solubility and stability of lipophilic drugs but also allows for controlled release, thereby enhancing therapeutic effectiveness.

Furthermore, the mucoadhesive characteristics of the in situ gel improve interaction with the nasal mucosa, leading to better absorption and retention of the formulation. The thermoreversible quality of the gel facilitates easy administration and transitions from a liquid to a gel at body temperature, ensuring patient comfort.

Future research should concentrate on optimizing the formulation parameters and conducting thorough in vivo studies to assess the pharmacokinetics and biodistribution of the drug. Overall, this approach has significant potential to advance brain-targeted therapies, especially for neurological disorders, and deserves further investigation to fully explore its clinical applications.

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