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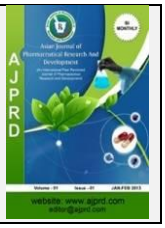

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Review Article

In Situ Mucoadhesive Nasal Gel: A Novel Approach for Enhanced Drug Delivery

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A B S T R A C T

In situ mucoadhesive nasal gels have emerged as a novel and effective approach for enhancing drug delivery through the nasal route, offering significant advantages over conventional dosage forms such as drops and sprays. The nasal cavity provides a highly vascularized surface, rapid onset of action, and avoidance of first-pass metabolism, making it an attractive pathway for both local and systemic drug delivery. However, rapid mucociliary clearance and limited residence time restrict the efficiency of traditional formulations. In situ gel systems address these limitations by undergoing a sol-to-gel transition upon exposure to physiological conditions such as temperature, pH, or ionic strength, forming a viscous gel that remains in contact with the nasal mucosa. The addition of mucoadhesive polymers further enhances retention by promoting strong interactions with mucin, thereby prolonging residence time and improving drug absorption. These systems utilize a combination of natural and synthetic polymers, along with suitable excipients, to achieve optimal gelation, stability, and controlled drug release. As a result, in situ mucoadhesive nasal gels offer improved bioavailability, sustained release, and reduced dosing frequency, leading to better patient compliance. They are particularly promising for the delivery of peptides, proteins, vaccines, and drugs targeting the central nervous system via the nose-to-brain pathway. Recent advancements, including nanoparticle-loaded gels and stimuli-responsive systems, have further expanded their therapeutic potential. Despite certain formulation and regulatory challenges, these systems represent a versatile and promising platform for advanced drug delivery applications.

Keywords: -Nasal Gel, mucoadhesive,Nasal drug delivery, Controlled drug release, Biocompatible polymers

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INTRODUCTION

The nasal route is now commonly used for delivery of medicines, not only for local effects but also for systemic effects, because of its particular anatomical and physiological characteristics. The nasal cavity has the following features: a large surface area, a rich blood supply and a highly permeable epithelial membrane. These features allow medicines to enter the bloodstream quickly after administration through this route, resulting in a quicker response to treatment. Because the nasal route avoids first-pass metabolism by the liver, it has the potential to increase the bioavailability of drugs that are broken down extensively when given by mouth. Also, due to the location of the olfactory region, it provides an alternative pathway for drugs to reach the brain, thus allowing for nose-to-brain delivery of drugs. This route is especially beneficial for treating certain neurological illnesses including Parkinson's disease, Alzheimer's disease and epilepsy. The advantages of using the nasal route of drug delivery include: ease of use; no degradation in the gastrointestinal tract; and a better chance of patient compliance(1,2) .However, although there are several advantages to using the nasal route of drug delivery, there are some limitations associated with the use of conventional nasal products, such as drops or sprays, that negatively impact their therapeutic benefit. One of the major challenges with using the nasal route of drug delivery is that the mechanism for clearing the nasal passages (the mucociliary clearance mechanism) will fully eliminate a given formulation from the nasal cavity within approximately 15 to 20 minutes. This short time span limits both the time that the drug has to reside in the nasal cavity and the drug's chances to be absorbed into the systemic circulation via the nasal route. Neuroplasticity is defined as

the ability of the human brain to reorganize itself by creating new neural connections throughout one's life. This is particularly seen in the early stages of human development, particularly during childhood. Research has shown that there is a direct effect of environmental stimulation and learning on the thickness of the cortex and dendrites. Functional magnetic resonance imaging studies have also shown that there is a significant degree of neuroplasticity in the human brain even in adults, which helps in healing and learning. The neuroplasticity model is particularly important for the fields of educational psychology and rehabilitation medicine. (3, 4)

The limitations that have been seen with traditional nasal drug delivery systems have created a need to design advanced drug delivery systems that can effectively counteract drug clearance, improve drug permeation, and provide sustained therapeutic responses. Various approaches, such as in situ gelling systems, mucoadhesive systems, nanoparticles, and lipid-based systems, have been explored for addressing these issues. Among these approaches, mucoadhesive in situ nasal gel systems have attracted significant attention due to their potential to undergo a sol-to-gel transition, thereby increasing their residence time in the nasal cavity. The mucoadhesive properties of these systems have also been found to increase their residence time in the nasal cavity, thereby increasing drug absorption. Additionally, these systems have been found to increase drug release, thereby reducing the frequency of drug administration. Advanced drug delivery systems have also been found to increase drug transport across biological barriers, such as the blood-brain barrier, which is difficult to achieve with traditional drug delivery systems. Various approaches, such as using permeation enhancers, enzyme inhibitors, and nanoparticles, have been found to increase drug permeability. These systems are particularly advantageous for the administration of biopharmaceuticals, which include peptides, proteins, and vaccines. In addition, the progress achieved in polymer science and formulation techniques has enabled the development of smart drug delivery systems that can respond to various physiological changes, including temperature, pH, and ionic strength. Thus, the development of advanced nasal drug delivery systems is a promising approach for achieving the best results from drug therapy and expanding the potential for intranasal drug administration.(5,4)

In situ gels are smart drug delivery systems with the ability to change phase from a low-viscosity liquid (sol) to a semi-solid gel in response to physiological conditions such as temperature, pH, or ionic strength. This property enables the system to be easily administered as a liquid into the nasal cavity and then rapidly form a gel upon contact with the target site. The gelation of the system is facilitated by the presence of smart polymers such as poloxamers, which are thermosensitive; carbopol, which is pH-sensitive; or gellan gum, which is ion-activated. On the other hand, the term "mucoadhesion" is used to describe the ability of a material to adhere to the mucus layer on the surface of biological membranes through physical and chemical interactions such as hydrogen bonding, electrostatic attraction, and interpenetration of chains. Mucoadhesive polymers such as chitosan, alginate, and hydroxypropyl methylcellulose form a strong bond with the mucus layer.(3,2)

The rationale for using in situ gelation with mucoadhesive properties stems from addressing the major drawbacks of traditional nasal drug delivery systems. The limitations of traditional drug delivery systems are related to fast mucociliary clearance rates and residence time. Although in situ gelation systems offer a sustained drug release profile through gelation, mucoadhesive properties are known to significantly increase the retention time of a drug delivery system. This approach has been found to increase drug absorption, bioavailability, and release of drugs over a prolonged period. Moreover, it has been found to reduce the frequency of drug administration. This approach has been found to be highly advantageous for drugs that need to adhere to the nasal tissues for a prolonged period. Peptide, protein, and central nervous system drugs are examples of such drugs. Therefore, in situ mucoadhesive nasal gel systems have been found to be a highly promising approach in modern drug delivery systems(1,3).

Anatomy and Physiology of the Nasal Cavity

The nasal cavity has three distinct anatomical areas that play a significant role in drug delivery. They are the vestibular region, respiratory region, and olfactory region. The vestibular region, located at the front of the nasal cavity, is covered with stratified squamous epithelium. Additionally, it contains nasal hairs that function as a barrier to filter out drug particles from entering this region. This region does not play a significant role in drug absorption due to its small surface area. The respiratory region covers a larger area of the nasal cavity. It is covered with pseudostratified columnar epithelium that contains goblet cells. The goblet cells produce mucus. This region is rich in capillaries. It plays a significant role in drug absorption due to its large surface area. The olfactory region covers a small area at the back of the nasal cavity. It contains olfactory epithelium. This region plays a significant role in smelling. However, it plays a significant role in drug delivery to the brain through the olfactory nerve.(6)

The nasal cavity is also characterized by an extensive blood supply, mainly from branches of both the external and internal carotid arteries. The blood supply is in the form of a dense vascular bed located below the epithelial lining. The extensive blood supply is responsible for the rapid absorption of the drug into the systemic circulation. Moreover, the nasal cavity is also characterized by a relatively large surface area for absorption, estimated at about 150-200 cm^2. The large surface area is mainly due to the presence of microvilli in the respiratory epithelium. However, other factors may also affect the surface area for absorption. The presence of mucociliary clearance and mucus renewal may affect the surface area available for absorption. Thus, the nasal cavity is an important route for both local and systemic drug delivery owing to its extensive blood supply and large surface area for absorption. (7).

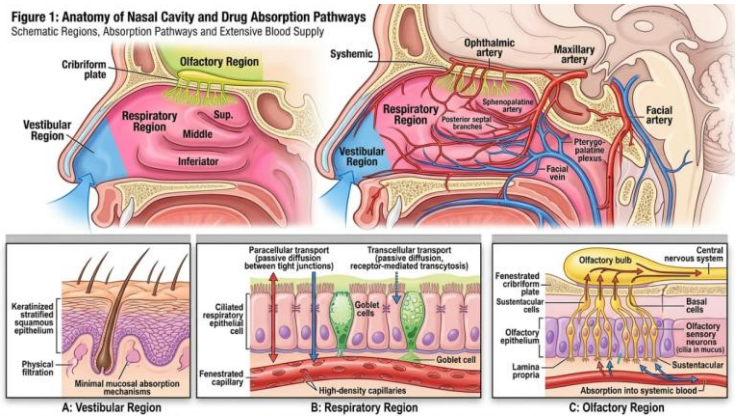

Figure 1: Anatomy of Nasal Cavity and Drug Absorption Pathways

Mucociliary clearance is one of the major physiological protective mechanisms of the nasal passage that has been identified to be of significant importance in limiting the effectiveness of intranasally administered drugs. The nasal mucosa is covered with ciliated epithelial cells and is covered with a two-layered mucus system, which consists of a low-viscosity sol layer and a high-viscosity gel layer. The cilia beat in a coordinated fashion to push the mucus layer towards the nasopharynx, thus removing particles, pathogens, and other drug substances from the nasal passage. Mucociliary clearance is completed within a period of 15 to 20 minutes. Thus, only a small amount of the administered dose is left at the site of absorption. Overcoming the problem of mucociliary clearance is a major challenge for the effective delivery of conventional nasal dosage forms such as drops and sprays. Thus, there is a need for the use of mucoadhesive or in situ gelling systems. (8,9)

Drug absorption in the nasal mucosa is mediated by two main pathways: the transcellular (intracellular) pathway and the paracellular (intercellular) pathway. In the transcellular pathway, lipophilic drug molecules pass through cell membranes, making this pathway the most important for drug absorption. In contrast, the paracellular pathway facilitates the transport of hydrophilic drug molecules through the junctions between epithelial cells. However, this pathway is quite restrictive, limiting drug absorption. Other biological barriers that influence drug permeation in the nasal mucosa include the mucus barrier, which restricts drug diffusion; enzymatic degradation, which affects peptides and proteins; and tight junctions, which restrict drug molecules. In addition, pathological changes such as inflammation or congestion may influence drug permeation. These barriers emphasize the requirement for advanced drug delivery systems, such as permeation enhancers, to facilitate drug delivery through the nasal route. (10)

Concept and Mechanism of In Situ Mucoadhesive Gels

In situ mucoadhesive nasal gels are a type of advanced drug delivery system that is introduced into the body as a low viscosity liquid. However, upon contact with physiological conditions at the target site, it changes its physical form to a semi-solid gel. The expression “in situ” is used to define the gel formation at the point of application and not prior to its application. The formulation of these gels is normally done using stimulus-responsive polymers that can be responsive to particular stimuli such as temperature, pH, or concentration of ions. Moreover, the use of mucoadhesive polymers has the effect of attaching the gel to the mucosal surface of the nose, thereby increasing the residence time for the absorption of the drug. As a result, in situ mucoadhesive nasal gels have been identified as an effective means of improving the efficiency of nasal drug delivery systems. (11,12).

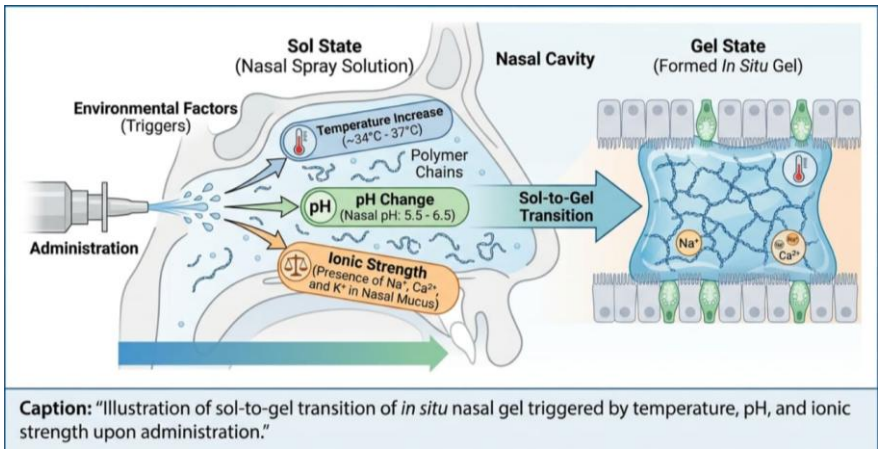

Figure 2: Mechanism of In Situ Gel Formation in Nasal Cavity

The working principle of such systems is based on sol-to-gel transformation as well as mucoadhesive properties. When administered intranasally, the liquid formulation comes in contact with physiological stimuli such as a change in temperature from room temperature to nasal cavity temperature, i.e., 32-34°C, a change in pH, or cations such as calcium ions. This triggers gelation. During gelation, the viscosity of the formulation increases, thereby reducing clearance from the nasal passages. At the same time, mucoadhesive polymers interact with mucin through hydrogen bonding, electrostatic interactions, as well as polymer interpenetration, thereby resulting in mucoadhesion. This prevents clearance as well as creates a drug reservoir that enables sustained release of drugs. (13,14)

Temperature-triggered systems:

Temperature-sensitive in situ gels are known to have a sol-to-gel transition with a change in temperature, usually from room temperature to physiological nasal temperature, i.e., between 32°C to 34°C. Thermoresponsive polymers are usually used to make such in situ gels. Poloxamers, such as pluronic F127, are known to have reversible gelation properties. At lower temperatures, the hydrated polymer chains are in a free-flowing state. However, at higher temperatures, dehydration of the hydrophobic segments of the polymer occurs, resulting in micelle formation. This allows for a gel to form in the nasal passages, thereby increasing residence time for a sustained release. (15)

PH-triggered systems:

pH-sensitive in situ gels are those gels that make use of pH changes in the environment to initiate gelation. pH-sensitive gels are usually prepared using polymers like carbopol, which exist in a sol state at acidic pH. However, they undergo gelation at a pH close to the nasal environment, which is slightly alkaline. In the nasal environment, the pH is around 5.5-6.5. If the pH is too low, the polymer chains exist in a coiled state due to the protonation of the carboxyl groups. However, when the pH is raised to the nasal environment pH, the polymer chains get ionized, which causes them to uncoil, thus increasing the viscosity. Therefore, the pH sensitivity causes the gel to form when the drug is administered.(16)

Ion-activated systems:

Ion-activated in situ gels consist of polymers that gelate in the presence of ions. In this category, divalent ions like calcium ions, which are present in nasal fluids, play a crucial role. Polymers like gellan gum, alginate, pectin, etc., are used for ion-activated in situ gels. In solution form, the polymers exist as a system with low viscosity. However, when they come in contact with ions present in the nasal environment, cross-linking between the polymer chains takes place, resulting in the gelation of the system. In the case of alginate or gellan gum, the presence of calcium ions causes the cross-linking between the polymer chains, resulting in the gelation of the system. Ion-activated gelation increases the viscosity and mucoadhesive character of the system, thus extending the residence time.(17)

Mucoadhesion is a significant mechanism for the prolongation of the residence period of drug formulations in the nasal cavity. In this regard, the mucoadhesive potential is a significant parameter for the enhancement of the efficiency of nasal drug delivery systems. It is the ability of a polymer to interact with the mucus present on the nasal epithelium by means of different physicochemical interactions. In the presence of mucoadhesion, when a drug formulation is administered nasally, the formulation comes in close contact with the nasal epithelium, thus resisting the natural clearance mechanism. In the presence of mucoadhesion, the drug formulation is retained for a longer period on the nasal epithelium, thus providing sufficient time for the release of the drug.(16,17,18)

In addition, mucoadhesion not only extends residence time but also allows for a sustained release of drugs. This is due to the mucoadhesive properties that allow for a drug reservoir at the site of absorption. This close contact between the drug formulation and the mucus membrane enables a drug to diffuse through it. This allows for a better permeation of drugs, particularly those with poor absorption characteristics. In addition, mucoadhesive polymers have been found to have a hydrating effect on nasal tissues. This enables them to swell, thereby increasing viscosity. This effect is particularly important for drugs that need to have a prolonged period of contact with the nasal tissues. This includes peptides, proteins, and drugs that need to target the central nervous system. Overall, mucoadhesive properties are a significant aspect that has been incorporated into in situ nasal gels to ensure that drugs are not cleared rapidly from the site of administration. (19,20)

Mucoadhesion: Mechanism and Theoretical Aspects

It is a complex process that involves interaction between the mucoadhesive polymer and the mucous layer present on the nasal epithelium, which in turn leads to prolonged contact at the target site. The mucoadhesive interaction occurs in two stages: contact and consolidation stages. The contact stage is the first stage in which mucoadhesive formulation is in close proximity to the mucous membrane. In this stage, it is important to have proper wetting and spreading of the mucoadhesive formulation over the mucous membrane for mucoadhesive interaction to take place effectively. In this stage, concentration, viscosity, and surface tension have a significant effect on mucoadhesive interaction. Proper contact is important to have polymer chains in a favorable position for interaction with mucin.(21)

The consolidation phase follows the initial phase of contact. In this phase, adhesive bonding between the polymer and the mucus layer is enhanced. During consolidation, interpenetration of the polymer chains occurs with the glycoprotein network of the mucin. This results in the formation of physical and chemical bonds between the two. The interpenetration of the chains depends on several factors, such as flexibility of the chains, molecular weight, and presence of sufficient groups to facilitate bonding. This phase results in a stable adhesive bond between the formulation and the tissue. This helps in retaining the formulation in the nasal cavity. The two phases of mucoadhesion ensure an effective adhesive bond.(22)

Diffusion theory:

The theory of diffusion explains the mechanism of mucoadhesion, which is based on the interpenetration of

chains from a polymer and glycoprotein chains found in mucus, known as mucin. In this theory, when a mucoadhesive polymer is brought into contact with mucus, chains from the polymer, as well as chains from mucus, interpenetrate, leading to a semi-permanent bond. The extent of interpenetration is affected by chain flexibility, molecular weight, concentration, and time. Thus, the higher the extent of interpenetration, the higher the strength of mucoadhesive. This theory is significant for hydrophilic polymers, especially when they have the capability of forming an entangled network.(23,24)

Electronic theory:

The electronic theory is based on the idea of the transfer of electrons between the mucoadhesive polymer and the mucus layer. The theory states that when two materials with different electronic structures are brought into contact with each other, there is a possibility of the transfer of electrons from one material to another. This leads to the formation of an electrical double layer on the surface of the materials, which generates attractive forces between the materials. The polymers with charged functional groups, such as the cationic polymer chitosan or the anionic polymer carbopol, may react with the oppositely charged sites on the mucin surface and generate electrostatic attraction.(25,24)

Adsorption theory:

Based on the adsorption theory, mucoadhesion occurs as a result of the formation of secondary chemical bonds between the polymer and the mucus layer. This includes hydrogen bonding, van der Waals' forces, and hydrophobic bonding. Although these types of bonding are not very strong, their cumulative effect can be very strong. The presence of hydroxyl, carboxyl, and amine groups in the polymer chain enhances the ability of a polymer to bond with glycoproteins in the mucus layer.(26)

Wetting theory:

The wetting theory is mainly applicable to liquid or low viscosity mucoadhesive systems. The wetting theory is based on the concept that the extent of contact between the formulation and mucus is related to the surface tension of the formulation. A formulation with low contact angle has greater wetting or spreading properties. Thus, the greater the wetting or spreading of the formulation, the greater the extent of contact with the mucosal surface, thereby enhancing the adhesion. Thus, wetting is an important aspect of mucoadhesion, particularly at the initial stage of contact.(27,28)

Fracture theory:

In fracture theory, mucoadhesion is explained on the basis of the mechanical strength required for detaching a formed mucoadhesive bond. In this theory, emphasis is placed on the force required for detaching a polymer from a mucous membrane. Fracture theory is used to measure the strength of a mucoadhesive bond. In this theory, the strength of a formed bond is determined by several parameters, such as the stiffness of a polymer, cross-linking, and interaction with mucus. A higher force for detaching a bond is a measure of strong mucoadhesion, which is used to test a mucoadhesive product.(29,30)

Polymers and Excipients Used

Natural and synthetic polymers are the main constituents of in situ mucoadhesive nasal gel systems. These are responsible for gelation and adhesion, which are essential for drug delivery. Among natural polymers, chitosan, alginate, and pectin are widely used because of their excellent biocompatibility, biodegradability, and low toxicity. Chitosan, a cationic natural polymer, has excellent mucoadhesive properties due to electrostatic interaction with negatively charged mucin. Chitosan has been found to improve drug permeability by temporarily disrupting tight junctions. Alginate and pectin, on the contrary, are anionic natural polymers that exhibit excellent ion-induced gelation properties when they come into contact with divalent cations, such as Ca2+ ions, present in nasal fluid(31,32). These polymers, therefore, are used for sustained drug delivery. Synthetic and semi-synthetic polymers, such as carbopol, hydroxypropylmethyl cellulose (HPMC), and poloxamer, are used because they are easier to control. Among them, carbopol is known for its excellent mucoadhesive and pH-sensitive gelation properties. HPMC is used as a viscosity enhancer. Poloxamer, a thermosensitive synthetic polymer, is used for sol-to-gel transitions at physiological temperatures, making them ideal for in situ gels. A mixture of all these polymers is used to achieve an optimum balance. (33,34,35)

Table 1: Polymers Used in In Situ Mucoadhesive Nasal Gels

Polymer Type	Polymer Name	Mechanism of Gelation	Mucoadhesive Property	Role in Formulation
Natural Polymer	Chitosan	pH-sensitive	High (cationic interaction with mucin)	Enhances permeability and mucoadhesion
	Sodium Alginate	Ion-activated (Ca^{2+} ions)	Moderate to high	Forms gel in presence of ions
	Pectin	Ion-activated	Moderate	Gel formation with divalent ions
Semi-synthetic Polymer	HPMC (Hydroxypropyl methylcellulose)	Viscosity-based (no true gelation)	Moderate	Viscosity enhancer and stabilizer
	Carbopol (Carbomer)	pH-triggered	Very high	Strong mucoadhesive and gel-forming agent
Synthetic Polymer	Poloxamer (Pluronic F127)	Temperature-sensitive	Low to moderate	Thermoreversible gelation
	Polyvinyl Alcohol (PVA)	Temperature/chemical crosslinking	Low	Film-forming and stabilizing agent
Other Functional Polymers	Gellan Gum	Ion-activated	Moderate	Forms gel in nasal ionic environment
	Xanthan Gum	Viscosity-based	Moderate	Enhances consistency and stability

Besides polymers, other excipients play a supporting yet critical role in the enhancement of the efficiency of nasal gel drug delivery systems. Penetration enhancers, including surfactants and bile salts, are used to increase the drug concentration by adjusting the permeability of the epithelium. Preservatives, including methylparaben and propylparaben, are added to ensure microbiological stability. In addition, a buffer is added to the formulation to maintain the pH at a level that is compatible with the nasal environment (36,37). In the development of nasal gel drug delivery systems, the polymers used for the formulation should have the ideal characteristics for the efficient performance of the drug. The polymers should be non-toxic, non-irritating, and capable of interacting with the nasal environment. The polymers used for the formulation of nasal gel drug delivery systems should have good mucoadhesive characteristics, gelation characteristics at the pH of the nasal environment, viscosity for easy administration and efficient gelation at the site of application, controlled release characteristics, chemical stability, economic viability, and availability. The selection of the polymers for the formulation of nasal gel drug delivery systems is critical for the efficient development of the drug.(38,39)

Formulation Development and Preparation Methods

The selection of drug and excipients is a critical step in the development of in situ mucoadhesive nasal gel formulations, as it directly influences the efficacy, stability, and patient acceptability of the system. The drug candidate should ideally possess suitable physicochemical properties such as adequate solubility, low molecular weight, and good permeability to ensure efficient absorption across the nasal mucosa; drugs requiring rapid onset or targeting systemic or central nervous system effects are particularly suitable for this route(40,41). Additionally, the drug should be stable within the nasal pH range and resistant to enzymatic degradation or may require protective strategies. Excipients are selected based on their functional roles, including polymers for gelation and mucoadhesion (e.g., thermosensitive, pH-sensitive, or ion-activated polymers), penetration enhancers to improve drug absorption, preservatives to ensure microbial stability, and buffers to maintain physiological pH. Compatibility between the drug and excipients must be ensured to avoid instability or reduced efficacy. Overall, careful and rational selection of both drug and excipients is essential to achieve optimal gelation behavior, prolonged residence time, controlled drug release, and enhanced therapeutic performance. (42,43)

Cold method (thermosensitive gels):

The cold method is the most commonly used approach for the development of thermosensitive in situ gels, especially those containing polymers. In the cold method, the polymer is slowly added to cold water, usually between 4°C and 8°C, under stirring. The addition is done slowly to ensure proper hydration of the polymer. The cold water is essential for the dissolution of the polymer since the polymer will be in a liquid state at the cold temperatures. After the polymer is fully dissolved, the other components are added under stirring. The solution is stored under refrigeration until a clear solution is formed. Once the solution is administered to the nasal cavity, the solution changes from sol to gel form as the temperature increases to the normal range.(44,45)

Dispersion method:

The dispersion method uses a mixture of polymers and other excipients in an aqueous medium for in situ gel formation. In this method, a specific amount of a polymer, such as carbopol or HPMC, is slowly added to an aqueous medium containing distilled water under constant stirring. This helps in the prevention of aggregation of the polymers. The dispersion of the polymers in an aqueous medium swell properly, which may take several hours. This helps in attaining a suitable viscosity. After proper hydration of the polymers, a solution or dispersion of a drug in an appropriate solvent is mixed with the polymer. Other excipients, such as preservatives, buffers, and enhancers, are then added to enhance the formulation. The mixture is stirred properly to obtain a solution. This method is used for pH-sensitive gels, where gel formation is triggered by exposure to a suitable pH in the nasal passage.(46,47)

Ion-activation method:

The ion activation method is used for the preparation of in situ gels that gel in the presence of certain ions. The polymers used for the preparation of gellan gum, sodium alginate, or pectin gels are dissolved in deionized water with constant stirring. Gentle heating is done to ensure the dissolution of the polymers. In order to prevent gel formation during the preparation of the gels, complexing agents or chelating agents such as sodium citrate can be added to the solution. The drug and other additives can be added to the solution under controlled conditions. When the gel is introduced into the nasal cavity, it comes into contact with physiological ions present in the nasal fluid. Ionic cross-linking of the polymers occurs to form a three-dimensional gel matrix. The advantages of using the ion activation method for the preparation of gellan gum gels include its controlled gelation mechanism, which improves mucoadhesion, increases the residence time, and provides sustained drug release.(48,49)

Optimization strategies for in situ mucoadhesive nasal gels are of prime importance in order to obtain an optimal balance of gelation characteristics, mucoadhesive properties, drug release, and patient acceptability. A scientific approach is usually used in which experimental design methods, such as factorial design or response surface methodology (RSM), are used to evaluate the effect of critical formulation factors, such as concentration of polymers, amount of drugs, and ratios of excipients. Factors such as gelation temperature (in thermosensitive gels), pH, viscosity, and mucoadhesive strength are critically optimized to ensure that the formulation remains a free-flowing liquid in order to be easily administered and instantly forms a stable gel in the presence of nasal secretions. The concentration and type of polymers used are of particular interest since they directly influence the gel strength, adhesive properties, and release characteristics of drugs. Furthermore, optimization of penetration enhancers and preservatives used in formulations is of particular interest in order to maximize drug absorption without causing irritation or toxicity.(48)

Further optimization of the formulation includes in vitro and ex vivo evaluation of parameters such as drug release profile, permeation through nasal mucosae, and dwell time. Rheological tests are conducted to check the fluidity of the formulation, which should be suitable for administration and should possess a gel-like character. Stability tests are conducted under various environmental conditions to check the stability of the formulation. Sensory properties of the formulation are also taken into consideration to ensure patient compliance. In all, optimization of a formulation involves a combination of formulation, statistical analysis, and evaluation of a formulation to obtain an effective and patient-friendly nasal drug delivery system.(49)

Evaluation Parameters of In Situ Mucoadhesive Nasal Gels

Evaluation of in situ mucoadhesive nasal gels is important in order to evaluate their quality, efficacy, and effectiveness. Some important parameters that are to be evaluated during the development stage are pH, viscosity, and gelation behavior. The pH of the nasal gel should lie in the range of 4.5 to 6.5 to prevent irritation and to ensure nasal mucosa compatibility. The viscosity is also to be evaluated to ascertain that it is sufficiently low to enable easy administration and also increases upon gelation. Gelation behavior, including gelation temperature, gelation time, and gel strength, is also to be evaluated to ascertain that it occurs rapidly in order to enable proper delivery. These parameters are important in order to ascertain that the nasal gel is retained in the nasal cavity for proper delivery.(50,49)

Mucoadhesive strength and residence time are important parameters affecting the retention of the formulation in the nasal cavity. The mucoadhesive strength is normally measured using texture analyzers or modified balance techniques, which determine the force required to remove the formulation from the mucosa surface. The residence time study is normally done using ex vivo nasal mucosa tissues to determine the time for which the formulation remains attached to the mucosa surface. In vitro studies for drug release are done using diffusion cells to determine the rate and extent of drug release from the gel formulation, whereas ex vivo permeation studies using animal nasal mucosa tissues, such as sheep or goat nasal mucosa, help in understanding the permeation behavior of the drug from the gel formulation.(50,46)

Rheological behavior is another significant parameter, which helps in understanding the flow characteristics of the formulation. Ideally, a pseudoplastic or shear-thinning fluid is desirable, which would allow for easy administration under shear stress (e.g., during spraying) and would have higher viscosities at rest, providing better retention. In some cases, oscillatory tests may be performed on the formulations to determine their gel strength. Stability studies are performed on the formulations to check for their physical, chemical, as well as microbiological stability under different storage conditions, such as varying temperatures and humidity. These tests ensure that parameters such as drug content, pH, viscosity, appearance, etc., remain constant over time. These tests provide a comprehensive understanding of the formulation, which is essential for nasal drug delivery.(51,52)

Drug Absorption, Advantages, and Applications

The drug absorption from in situ mucoadhesive nasal gels takes place mainly through two routes, namely, transcellular and paracellular pathways. In the transcellular pathway, drug molecules are absorbed by passing through the cell membranes. However, this pathway is generally favored by lipophilic, low molecular weight compounds, as they are capable of diffusing through the cell membranes. In the paracellular pathway, hydrophilic drug molecules are absorbed by passing through the spaces between adjacent epithelial cell membranes. However, this pathway is restricted by the tight junctions between epithelial cell membranes. The use of mucoadhesive and permeation enhancers helps in increasing drug absorption from in situ gels. These polymers are known to temporarily alter the permeability of epithelial membranes, thus increasing drug absorption. All these pathways combine to make in situ gels a highly efficient drug delivery system.(53,54,55)

The in situ mucoadhesive nasal gels have numerous advantages over conventional dosage forms. They enhance bioavailability by avoiding first-pass effects. The bioavailability of drugs from in situ mucoadhesive gels is significantly enhanced by extending the residence period of the formulation in the absorption area. In addition, the dosage forms exhibit controlled release of drugs. This helps in minimizing fluctuations in the concentration of drugs. The dosage forms are of wide applicability. They are particularly used in central nervous system (CNS) drug delivery. In CNS drug delivery, in situ mucoadhesive gels play a major role in directly delivering drugs to the brain via olfactory and trigeminal pathways, bypassing the blood–brain barrier. In situ mucoadhesive gels are particularly used in peptide, protein, vaccine, and hormonal therapies. These types of drugs are normally degraded in the gastrointestinal tract. In addition, they normally exhibit poor bioavailability.(56,57)

Recent Advances and Challenges

Significant improvements in in situ mucoadhesive nasal gel systems in recent years have greatly improved their performance and expanded their scope of application. One of the notable improvements in in situ gel systems is the use of nanoparticle-loaded gels. In this system, drugs are incorporated in nanoparticles such as polymeric nanoparticles, solid lipid nanoparticles, or nanosponges before loading them in gel systems(58). This system helps in stabilizing drugs, enhances permeability, and allows for controlled and targeted release of drugs. In addition, nanoemulsion and liposome-based in situ gels are also notable improvements in in situ gel systems. This system helps in dissolving poorly soluble drugs and enhances their absorption. Liposomes, in particular, are biocompatible and can be used to dissolve both hydrophilic and lipophilic drugs. Another notable improvement in in situ gel systems is the use of smart or stimuli-responsive gels. In this system, gels respond to physiological stimuli such as temperature, pH, or ionic strength. This system has been very promising, especially in nose-to-brain delivery and in the delivery of sensitive biomolecules.(59).

Table 2: Research Studies on In Situ Mucoadhesive Nasal Gels

Drug	Polymer Used	Type of Gelation	Key Findings	Application
Sumatriptan	Poloxamer + Carbopol	Temperature + pH-sensitive	Improved bioavailability and rapid onset	Migraine treatment
Insulin	Chitosan + β-glycerophosphate	Temperature-sensitive	Enhanced nasal absorption and permeability	Diabetes management
Ondansetron	Poloxamer + HPMC	Thermosensitive	Prolonged residence time and sustained release	Antiemetic therapy
Midazolam	Chitosan	pH-sensitive	Enhanced brain targeting via nasal route	CNS delivery
Fluconazole	Carbopol + HPMC	pH-triggered	Sustained drug release and improved retention	Antifungal therapy
Propranolol	Gellan gum	Ion-activated	Increased nasal residence time	Antihypertensive
Leuprolide	Poloxamer + Carbopol	Temperature-sensitive	Improved systemic absorption	Hormonal therapy
Rizatriptan	Chitosan + Poloxamer	Dual mechanism	Enhanced permeability and faster onset	Migraine
Metoclopramid	Carbopol + Sodium alginate	pH + ion-activated	Better mucoadhesion and controlled release	Antiemetic
Donepezil	Poloxamer + Chitosan	Thermosensitive	Improved brain delivery efficiency	Alzheimer's disease

However, despite these promising advances, a number of hurdles remain to be overcome for the application and commercialization of in situ mucoadhesive nasal gels. Irritation and toxicity in the nose are significant hurdles, especially with prolonged use and the presence of penetration enhancers and preservatives. The drug loading potential of nasal products is limited because of the limited volume that can be administered intranasally, which is a significant constraint for the application of this route for drugs that require a larger dose. Physiological variability among individuals, including the effect of mucociliary clearance, the composition of mucus, and the presence of diseases like rhinitis, may affect drug absorption, thus making the outcome variable. Finally, regulatory hurdles are a significant constraint for the application of these products, especially for complex products like nanoparticle-loaded gels.(60,59)

Future Perspectives

The future of in situ mucoadhesive nasal gel systems appears very promising, considering the development of new trends in this area. One of the trends in the development of in situ mucoadhesive nasal gel systems involves artificial intelligence (AI) formulation and advanced targeted drug delivery. In addition, the use of advanced technologies in the development of in situ mucoadhesive nasal gel systems will enhance their effectiveness in targeted drug delivery. This will be achieved by incorporating ligand-functionalized nanoparticles and receptor-mediated transport. The development of multifunctional and stimuli-responsive polymers appears to be a major breakthrough in the development of in situ mucoadhesive nasal gel systems. This will be achieved by using stimuli-responsive polymers, which will be used to control the release of drugs..

From a clinical standpoint, in situ mucoadhesive nasal gels possess considerable potential for clinical translation to marketable products owing to their non-invasive character, patient compliance, and ability to carry a variety of drugs. In spite of this, challenges need to be overcome in terms of large-scale manufacture, reproducibility, stability, and regulatory hurdles. In conclusion, in situ mucoadhesive nasal gels offer a novel and potent drug delivery system, which can overcome the shortcomings of conventional nasal drug delivery. The potential of in situ mucoadhesive nasal gels to enhance bioavailability, offer sustained release, and target specific sites of action signifies their importance in contemporary pharmaceutics, which can influence future therapeutic approaches.

CONCLUSION

In situ mucoadhesive nasal gels have proven to be a promising and innovative method for increasing drug delivery through the nasal route. By incorporating the benefits of in situ gelation as well as mucoadhesion, it has been possible to effectively circumvent the limitations of traditional nasal drug delivery systems, such as rapid mucociliary clearance. The use of stimuli-responsive polymers allows for gelation to occur in physiological conditions, with mucoadhesion allowing for a prolonged residence time at the site of absorption. This allows for a significant increase in drug bioavailability. Moreover, the versatility of these systems allows for the potential delivery of a wide range of therapeutic agents, including small molecules, peptides, proteins, and vaccines, especially for nose-to-brain targeting for CNS disorders. Recent developments, including the potential for the incorporation of nanoparticles and smart polymers, have further increased the potential for these systems. However, the issues concerning the optimization of the formulation, nasal irritation, physiological conditions, and regulatory requirements must be addressed. In conclusion, in situ mucoadhesive nasal gels have a significant potential for the efficient drug delivery system, which is patient-friendly. Further research and development in this area are expected to result in the successful clinical translation and commercialization of the nasal gels in the near future.

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