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Nasal *in situ* gels as a drug delivery system: An overview of literature and clinical studies

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ABSTRACT: There are various ways to deliver drugs and each one has its ups and downs depending on the purpose of use and the patients themselves. And among these drug delivery systems, the intranasal path stands out as one of the more exciting and challenging ones. Despite being perhaps the most commonly used path of delivery, the oral route is subject to facing various roadblocks in terms of efficacy and bioavailability, requiring a certain amount of dosage and synergy from the active pharmaceutical ingredient that is being used to be effective. When said active pharmaceutical ingredient is ineffective via the oral route, has to be given in small doses, or has to enter circulation quickly to manifest its effects, it inevitably falls out of favor. In its place, the intranasal route can act as a viable substitute. Although there are several methods to formulate intranasal drugs, naturally, the intranasal route possesses advantages and disadvantages of its own. Thus, *in situ* gel systems have emerged as a favorable preference among these formulation methods. Possessing the upsides of not only gels but solutions as well, the *in situ* gel systems effectively address and solve some of the disadvantages posed by intranasal drug delivery systems. This review article aims to provide a general understanding of intranasal drug delivery systems and *in situ* gels, both separately and together as a combination, while underlining the importance of each and also providing examples from existing literature to display their range of applications.

KEYWORDS: Drug delivery system; *in situ* gel; intranasal; nasal; pharmaceutical; polymer.

1. INTRODUCTION

There are multiple reasons to investigate a different way to deliver nasal drugs, rather than using the traditional methods. The nasal route provides convenience; it is easy to use, has a rapid onset of action, and does not experience gastrointestinal degradation or first-pass metabolization. It tends to have high bioavailability thanks to the small molecule size of the drugs made for it, and even when that's not the case its bioavailability can be increased, making the nasal route extremely preferable [1,2].

The nasal cavity has a limited capacity and displays low membrane permeability for hydrophilic molecules. Additionally, there is mucociliary clearance, the cleaning of the airways through the interaction of the ciliary beating and nasal mucus. This pushed the researchers and drug developers to find a way to exploit the bioadhesive agents, as well as the permeation enhancers, to develop a drug delivery system that can improve the existing conditions by enhancing the absorption of the drug, extend the area of effect of the drug and improve the bioavailability of polar compounds. Due to their characteristics, *in situ* gelling formulations can change from a solution to a gel upon intranasal delivery, as a result of physiological variables (e.g. pH, ion concentration, temperature). Thus, these dosage forms may be delivered simply as solutions, guaranteeing precision in the dose provided. In contrast, gel formation upon contact with the nasal epithelium is necessary to ensure sufficient contact time and thus better bioavailability [3-7].

2. INTRANASAL DRUG DELIVERY SYSTEMS

Nowadays the oral and parenteral routes are no longer considered the first choice as long as there are alternatives present. They owe this to their overall qualities, being less dependable and effective in some cases. This can be seen especially well with drugs containing molecules that have diminishing attributes, such as being exposed to a significant elimination from the first-pass effect, displaying low and/or limited stability in gastrointestinal fluids, or having poor intestinal absorption. Such drugs make the primary candidates for

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intranasal delivery. Although the intranasal route has been available for a considerable amount of time, it has mostly been used to provide symptomatic relief and to treat or prevent topical illnesses of the nose. Now that their properties are being understood more clearly it is possible to see that the intranasal route can offer a lot. For example, it can overcome the obstacles posed by the blood-brain barrier, which leads to direct drug delivery to the central nervous system. Similarly, the overall traits and features of the nose and the nasal cavity (e.g., their potential to provide a rapid onset of action and drug absorption) also increase the interest to explore this route of administration [4, 8-12].

2.1. Physiology of the nose

The nose is one of the most important organs of the human body. It is not only the most protruding part of the face and easily noticeable, the main organ of the olfactory system that serves the sense of smell, as well as the first organ of the respiratory system. The nasal cavity has a depth between 120-140 millimeters, a volume between 16-19 milliliters, and a surface area of approximately 160 cm^2 [13]. The nose has various functions. These are primarily allowing the entry of air into the body, warming up and humidifying the air that has entered, filtering the unwanted presence in the respired air, providing resistance for the airways, establishing the sense of smell, and acting as one of the first barriers of immunological defenses of the body [14].

There are three regions in the nose. These are the turbinate, vestibular, and olfactory regions (Figure 1). The turbinate regions make up a relatively large vascular portion of the nose, consisting of inferior, middle, and superior regions. It is made up of three types of cells, these being basal cells, ciliated cells, and non-ciliated cells, accompanied by mucosal secretions. Additionally, it possesses a pseudostratified columnar epithelium lining. Non-motile microvilli increase the surface area and cover ciliated and non-ciliated cells making them ideal for the absorption of drugs. Ciliated cells play an especially important role in transporting mucus for mucociliary clearance, as they are covered with approximately 100 motile cilia. Entry to the mucociliary area means clearance from the nasal cavity, and thus limited access to the site of absorption. The vestibular region, on the other hand, is located in the anterior part of the nose and makes up the nasal cavity's narrowest part. The majority of this area is covered by vibrissae and can filter out incoming particles [14, 15].

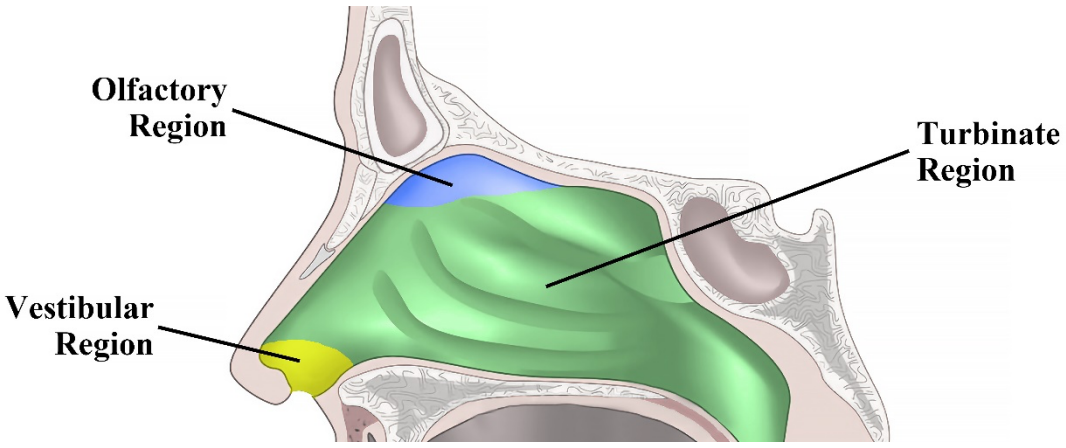

Figure 1. Regions of the nose (image was edited in Adobe Photoshop 2022) (Modified from Ref. [16])

The first stage of any nasal drug's absorption is its passage through the mucosa. It is possible to see the effects of the size of the particles of active pharmaceutical ingredients during the passage through the mucosa; while fine particles pass through without any issues, it may be relatively more difficult for larger particles to do the same. Mucus, itself, has the ability to potentially bind to solutes due to its mucin content. Additionally, changes in the environment or the physiology of the host can lead to changes in the structure of the mucus. All of these factors influence the diffusion process as a whole. But once the drug successfully passes through the mucus, it will be subjected to one of the various mechanisms of absorption. The most common of these mechanisms are transcellular and paracellular routes. The former takes place thanks to simple diffusion, whereas the latter is a method of transportation through the transcytosis carried out by vesicle carriers and movement that occurs between the cells [14, 17].

The transcellular route is mostly involved with the transportation of lipophilic drugs, which exhibit a rate dependency on their lipophilicity attribute, thus making use of the lipoidal route. The paracellular route on the other hand is rather slow and passive and deals with water-soluble compounds. It is affected by intranasal absorption and also the molecular weight of water-soluble compounds. It is known that the bioavailability of these drugs has been found to be quite poor when the molecular weights were over 1000

Daltons. Drugs can also enter cellular membranes via active transport via carrier-mediated means or tight junction openings. Possible metabolism before reaching the systemic circulation and insufficient residence time inside the nasal cavity are known obstacles to absorption [14, 18].

Permeation enhancers are used regularly, to increase the bioavailability and permeation of many drugs that are highly soluble in water and possess poor permeability and inadequate bioavailability, especially across the nasal epithelia. These permeation enhancers are widely considered to modify the phospholipid bilayer to show an effect, which in return alters the permeability of the epithelial cell layer [14, 19].

There are a variety of enhancers that increase absorption and permeation. Carbapol and chitosan are biomaterials that induce their effect by opening tight junctions. Bestatin and amastatia are enzyme inhibitors that induce their effect by inhibiting involved enzymes. Bile salts like sodium deoxycholate and sodium glycocholate may inhibit enzymes, shows mucolytic activity, and open tight junctions, being slightly similar to cyclodextrins and derivatives like α-, β- and γ-cyclodextrin, which open tight junctions and disrupt the membrane. Fatty acids like lysophosphatidylcholine and surfactants like sodium lauryl sulfate and saponin, on the other hand, may only disrupt the membrane [14, 20].

2.2. Advantages of nasal drug delivery systems

- Vascularised mucosa creates a large surface area and allows rapid drug absorption.
- Rapid onset of action.
- Easy and non-invasive administration.
- Convenience for patients who are undergoing long-term therapy.
- No requirement for a complex formulation.
- Lower doses are usually sufficient.
- Fewer side effects due to lower doses.
- Lower risk of overdosing.
- Drugs have the potential to be directly transported into the central nervous system and systemic circulation.
- No degradation in the gastrointestinal tract.
- Bypasses the first-pass metabolism.
- High bioavailability with small molecule size (<1000 Daltons).
- Option to increase bioavailability with large molecule size (>1000 Daltons) via absorption enhancers.
- Acts as a viable alternative for drugs the display poor stability in fluids [21].

2.3. Disadvantages of nasal drug delivery systems

- Delivery effect including formulation drug distribution and deposition, the viscosity of the formulation.
- Regular defense mechanisms present inside the nose may affect the permeability of the drug.
- Large interspecies variability for studies.
- Inconvenience due to possible nasal irritation.
- The smaller surface of absorption in comparison to the gastrointestinal tract.
- Possible irritation of the nasal mucosa by drugs.
- The restricted volume of delivery in the nasal cavity.
- Difficulty in delivering compounds with high molecular weight or low lipophilicity.
- Pathological conditions may induce negative effects [21].

3. *IN SITU* GELS

In situ gels are systems of suspensions or solutions that can undergo a sol-to-gel transformation, which is often set off by a stimulus, like an ion presence, pH, or temperature. In other words, they enter the body as a solution and change into a gel. There are quite a lot of upsides to using *in situ* gels. Thanks to their properties, they can be used for controlled and sustained release forms of drugs. They don't have to be used frequently, which effectively decreases the dosing frequency of the drug, while also allowing for higher patient compliance and comfort. Because of their increased bioavailability due to their route of distribution, *in situ* gels also don't have to be given in larger doses, contributing to less overall toxicity. They are easy to administer and can even be administered to unconscious patients. They can be designed to be bioadhesive, which helps facilitate the targeting of the drug and allows for non-invasiveness [22].

Of course, there are also limitations involved with *in situ* gels as well. There can potentially be stability issues, especially when they are in solution form as they then tend to be generally more susceptible to

degradation. Their administration might restrict regular activities like eating and drinking, making it less convenient for patients. If the active pharmaceutical ingredient is hydrophobic, then the homogeneity and the amount of the drug that is loaded will be limited. They also tend to possess a lower amount of mechanical strength, which contributes to possible premature dissolution or may cause the hydrogel to flow away from the site of application.

Regardless, a lot of variables are at play for each drug that is being formulated. If the advantages of *in situ* gels outweigh their limitations, they become a favorable option. When that is the case, it should be kept in mind that the type of polymer used for sol-gel conversion affects the type of system that is going to be obtained in the end [23, 24].

3.1. Thermo-responsive systems

Thermo-responsive systems make use of polymers that are affected by the changes in the surrounding temperature. The variations in the temperature are quite easy to apply both *in vivo* and *in vitro*. Additionally, it is also easy to manage them. This makes temperature as a stimulus the most commonly used polymer system in *in situ* gels and their formulations. Despite being in liquid form at 20-25°C, they go through gelation around 35-37°C, meaning that they can change form when in contact with body fluids. Three types of thermo-responsive systems are in existence [25-27].

Thermo-responsive hydrogels can swell with increasing temperature. When that is the case, they are considered to be positively thermo-responsive systems. If the opposite is the case and the hydrogel is shrinking with increasing temperature, then it is considered to be negatively thermo-responsive. Additionally, there is a third type, namely the thermally reversible type. These are hydrogels that display a lower critical solution temperature. Akin to negatively thermo-responsive systems, they deswell and shrink in aqueous solutions with increasing temperature. However, this is a reversible process for them, as they can swell once again and expand if cooled down to temperatures below the lower critical solution temperature [24, 28-30].

3.2. Ion-responsive systems

Ion-responsive systems utilize polymers that can start the gelling of the solutions by responding to the changes in the ionic strength in the surrounding chemical environment. In these systems, the rate of gelation is presumably dependent on the surface osmotic gradient of the gel [2, 24, 31, 32].

3.3. pH-triggered systems

pH-triggered systems make use of hydrogels that are sensitive to variations in pH, meaning that they will swell or deswell as a result of the changing pH in their environment. The polymers that are used are thus also required to be pH-sensitive. Polyelectrolytes are known to be widely used for these systems. They can be found inside the formulation and increase the pH externally. As a result, the hydrogel begins to swell and ultimately creates an *in situ* gel. Their qualities make pH-sensitive systems desirable for various purposes. For example, they can be utilized to sort multiple solutions following pH and how the solutions react to them [33-36].

3.4. Polymers used as gelling agents and their properties

The polymers that are used change depending on what kind of system is wanted, or rather, the polymer that is used for the sol-to-gel conversion determines what type of system it's going to be. Even so, there are several qualities that the polymers should possess, regardless of the system type. In accordance with these, an ideal polymer should;

- have the ability to adhere to the mucus membrane,
- be able to influence tear behavior,
- possess an acceptable optical clarity,
- not add any additional toxic effects,
- display pseudo-plastic behavior,
- be able to decrease the viscosity and increase the shear rate.

Some of the excipients and APIs that have been used in the literature are provided below (Table 1).

Table 1. Some of the excipients and APIs used in nasal *in situ* gel drug delivery systems.

API	Excipients	Refs
Sumatriptan	Poloxamer 407, Carbopol 934P	[37]
Voriconazole	Deacetylated gellan gum, Clove oil, Soybean lecithin, Tween 80	[38]
Almotriptan	Poloxamer 407, Poloxamer 188	[39]
Metoclopramide	Poloxamer 407, Polyethylene glycol, Hydroxypropyl cellulose, Carbopol 934P, Chitosan, Polyvinyl alcohol	[40]
Midazolam	Gellan gum, Carbopol 934P	[41]
Levodopa	Poloxamer 407, Chitosan	[42]
Budesonide	Poloxamer 407, Propylene glycol	[43]
Lorazepam	Gellan gum, Carbopol 934P	[44]
Timolol	Poloxamer 407, Hydroxypropyl methyl cellulose	[45]
Buspirone	Carbopol 974P, Sodium alginate, Poloxamer 407, Hydroxypropyl methylcellulose, Methylcellulose	[46]
Naratriptan	Poloxamer 407, Carbopol 934P, Polyvinylpyrrolidone K30	[47]
Fluticasone	Gellan gum, Pectin, Tween 80	[48]
Ketorolac	Chitosan, Pectin, Hydroxypropyl methylcellulose	[49]
Terbutaline	Chitosan, Pectin, Poloxamer 407	[50]
Donepezil	Poloxamer 407, Gellan gum	[51]
Lamotrigine	Gellan gum, Xanthan gum, Polyethylen glycol	[52]
Fexofenadine	Poloxamer 407, Chitosan, Hydroxypropyl-β-cyclodextrin	[53]
Zolmitriptan	Chitosan, Sodium alginate, Hydroxypropyl methylcellulose	[54]
Ciprofloxacin	Poloxamer 407, Propylene glycol	[55]
Mometasone	Gellan gum, Xanthan gum	[56]
Selegiline	Poloxamer 407, Propylene glycol	[57]
Repaglinide	Poloxamer 188, Gellan Gum, Propylene glycol	[58]

3.4.1. Carbopol®

Carbopol® is mostly used in pH-triggered systems as a sol-gel converting polymer. It is a polyacrylic acid polymer and as the pH is raised above its pK of around 5.5, it exhibits a sol-to-gel transition in an aqueous solution. Its acidic nature, however, may stimulate the targeted tissues when its concentration rises in the vehicle. An appropriate viscosity-enhancing polymer is often used in the formulation to increase viscosity without affecting the *in situ* gelling characteristics or overall rheological behaviors while also decreasing the Carbopol® concentration at the same time. It is preferred in pH-triggered systems [34, 59-61].

3.4.2. Chitosan

Chitosan is obtained from chitin and can be categorized as the latter's hydrolyzed polysaccharide derivative. It can be seen in abundance in nature and is considered a biopolymer. It is also biodegradable, non-toxic, and biocompatible. It can remain in its dissolved state in aqueous solutions for up to a pH of 6.2. Its gelling can occur at either temperature or pH, so when used as a sol-gel conversion polymer it is preferred in thermo-responsive and pH-triggered systems [24, 62-66].

3.4.3. Gellan Gum

Gellan gum is produced by *Sphingomonas elodea*. It can be categorized as an anionic exopolysaccharide. It begins to turn into gel form when exposed to physiological cation concentrations, such as those seen in bodily fluids like the nose fluid. As a result, the pH, volume, and ionic makeup of the surrounding nasal fluids have a significant influence on the gellan gum's ability to transport drugs. Despite its mucoadhesive qualities, which are based on relatively weak interactions like hydrogen bonds and Van der Waals forces, they are nevertheless insufficient to extend the mucosal residence duration. They are used commonly in ion-responsive systems [67- 69].

3.4.4. Poloxamer

Poloxamers are nonionic poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) copolymers. In some solvents, they are known to form structures with gel-like features, depending on the surrounding temperature and concentration. Otherwise, they form clear and thermoreversible gels at high concentrations and micelles at low concentrations. Poloxamers are available under different brand names as well; these are Pluronic® and Lutrol®. Poloxamer 407 and Poloxamer 188 can be seen extensively in existing literature, owing to their low toxicity, good biocompatibility, good compatibility with various drugs and excipients, and easy gel preparation. They have low mucoadhesiveness, thus they are often paired with more bioadhesive polymers to make them more effective. Poloxamer combinations with hyaluronic acid, chitosan, alginate, and hydroxypropyl methylcellulose are good examples of these pairings. They are used commonly in temperature-triggered systems [62, 70-76].

4. COMMON CHARACTERIZATION PARAMETERS

Different characterization methods are used to determine and evaluate various qualities of *in situ* gel nasal drug delivery systems. Depending on the results, it is possible to properly assess whether the end product is at a desirable level of quality if changes should be made to the formulation, or if any lacking properties need to be addressed. The characterization techniques vary greatly between different drugs and even when they are produced in the same delivery system, the tests need to be done differently due to the changing active pharmaceutical ingredients. Even then, it is possible to see several characterization factors being investigated commonly for most of the *in situ* gel nasal drug delivery systems.

4.1. Gelation temperature

Gelation refers to the production of a gel from a system of an active pharmaceutical ingredient and polymers. Gelation temperature refers to the specific temperature at which this phenomenon occurs. It can be determined by preparing the formulation, taking a certain amount from it, and heating it with the help of a magnetic stirrer, where the heat will be increased consistently over time whereas the stirring speed will be kept constant at the same level. The temperature at which gelation is observed (e.g. when the magnetic stirrer is stopped due to gelation) is the gelation temperature [33, 77].

4.2. Mucoadhesive strength

Mucoadhesion refers to the attracting forces that are between mucosal surface and material, this usually being a biological material. Mucoadhesive strength, on the other hand, refers to the ability of mucous membranes to successfully adhere to materials. The determination of mucoadhesive strength is carried out by texture analyzing machines (e.g. CT3 Texture Analyzer, TA.XTPLUS Texture Analyzer). Nasal mucosa from a selected *in vitro* subject is obtained and put into contact with the formulation that was prepared. Afterward, mucoadhesion per square centimeter is calculated [33, 77, 78].

4.3. Rheological studies

Rheology is the study of a material's flow behavior under circumstances in which they flow rather than deform elastically or plastically. On the continuum mechanical scale, it is similarly concerned with developing predictions for mechanical behavior based on the nanostructure or microstructure of the materials. Among the parameters that can be examined under rheological studies are shear stress and viscosity. Shear stress is the drag force caused by the fluid moving over the surface horizontally. It is determined by the fluid's gradient of velocity when it is close to the surface. Its magnitude is inversely related to the cube of the radius and directly proportional to fluid flow and viscosity. Viscosity, on the other hand, is the measurement of the resistance of a fluid to deforming under shear force. It defines the internal flow resistance of fluid and may be compared to the friction forces that exist inside a flowing fluid. The shear stress to strain rate ratio is another way to describe viscosity. These parameters and their corresponding values can be obtained via rheometers and can be used to make evaluations on further parameters like consistency index or flow behavior [33, 77, 79].

4.4. Texture profile analysis

Texture profile analysis helps evaluate the mechanical properties of *in situ* gels. These parameters for hydrogels include hardness, elasticity, compressibility, cohesiveness, and adhesiveness. Hardness is the force required to attain a given deformation. Compressibility is the work required to deform the product during the first compression of the probe. Adhesiveness is the work necessary to overcome the attractive forces between the surface of the sample and the surface of the probe. Cohesiveness is the ratio of the area under the force-

time curve produced on the second compression cycle to that produced on the first compression cycle, where successive compressions are separated by a defined recovery period, and elasticity is defined as the ratio of the time required to achieve maximum structural deformation on the second compression cycle to that on the first compression cycle, where successive compressions are separated by a defined recovery period. Various software is used for the collection and calculation of the data [80-82].

5. CLINICAL STUDIES

Chelladurai et al. prepared an *in situ* gel formulation of ketorolac tromethamine. Chitosan and pectin were used as the main polymers in the gelling system. The purpose was to increase the release duration of ketorolac tromethamine and extend the residence duration in the nasal mucosa. In the irritancy test performed on mice, it was observed that the formulation showed non-irritant properties in the nasal mucosa. It was also compared with the oral solution and intraperitoneal injection in the anti-inflammatory efficacy test on Wister rats. As a result, it has been proven that the anti-inflammatory activity of the *in situ* gel formulation was higher than the other formulations [49].

Ravi et al. developed an alternative drug for Parkinson's disease. For this purpose, Rasagiline mesylate was used as an active ingredient, and Poloxamer 407 as a mucoadhesive polymer. The study aimed to increase oral bioavailability and improve the passage of early substances into brain tissue. The studies have shown that the mucoadhesive gel of rasagiline mesylate displayed a much higher bioavailability, about 4-6 folds greater than that of the oral formulation. Accordingly, pharmacokinetic studies were conducted on New Zealand rabbits. The produced *in situ* gel form of rasagiline maleate was proven to be a viable alternative to existing oral formulations of the same active ingredient. Additionally, the obtained *in situ* gel of rasagiline maleate did not irritate the nasal mucosa of the rats that were used in the study. Moreover, it was shown to be capable of reaching the brain tissues through intranasal administration [83].

Zaki et al. prepared an *in situ* gel form of metoclopramide HCl, an antiemetic active substance, using Poloxamer 407. This study aimed to ensure that the formulation stayed longer in the nasal mucosa, to eliminate the problem of bad taste in oral use, to provide ease of use, and to reduce the mucociliary transport time. In mucoadhesion tests performed in rats, the formulation could remain in the nasal mucosa for a long time. The bioavailability of *in situ* gel formulation and oral solution formulations were compared in tests performed with New Zealand rabbits. As a result, the bioavailability of the *in situ* gel formulation was found to be significantly higher [84].

A nasal *in situ* gel containing mometasone furoate, a corticosteroid, was prepared by Cao et al. Xanthan gum and gellan gum were used for the gelling system. The aim of this study was to achieve higher success in reducing the symptoms of allergic rhinitis by prolonging the nasal residence time of mometasone furoate. In *in vivo* studies with Wistar rats, a suspension formulation containing mometasone furoate and an *in situ* gel formulation containing the same active ingredient were compared. As a result of the studies, it was observed that the *in situ* formulation was suitable for the intended purpose. In another *in vivo* study in rats, it was observed that the *in situ* gel formulation did not cause irritation. This study has proven promising results for the delivery of mometasone furoate as a nasal *in situ* gel [85].

An *in situ* gel containing paenol was prepared by Chu et al. Its absorption from the nasal mucosa was investigated in the treatment of allergic rhinitis. The main polymer used for *in situ* gel formation was Poloxamer 407. The nasal mucosa ciliotoxicity of the *in situ* gel formulation was investigated using the toad palate model and no toxic effects were observed. Guinea pigs were used for *in vivo* experiments. Experiments were also performed with physiological saline and Rhinocort® nasal spray to compare the effect of the nasal *in situ* gel formulation. It was observed that the *in situ* gel formulation showed significant improvement in the nasal mucosa. At the same time, IgE and LTE4 levels and the number of eosinophils were significantly reduced. These results showed that nasal *in situ* gel containing paenol can be used as an alternative in the treatment of allergic rhinitis [86].

Ved et al. prepared a nasal *in situ* gel formulation of zidovudine. The aim of this study was to increase the absorption of zidovudine and its transportation to the brain tissues. Poloxamer 407 was used as the main polymer in this formulation. New Zealand rabbits were used in *in vivo* pharmacokinetic studies. The rabbits were divided into groups and given intravenous, nasal solution, and nasal *in situ* gel applications. It was observed that the concentration of *in situ* gel was higher in cerebrospinal fluid and brain tissue, but lower in plasma compared to intravenous administration. It was observed that the residence time of the formulation in the nasal mucosa was prolonged with the use of nasal *in situ* gel. According to all of these results, it was concluded that the nasal *in situ* gel formulation of zidovudine could be used as an alternative [87].

A nasal *in situ* gel formulation containing Radix Bupleuri was prepared by Chen et al. In this formulation, Poloxamer 407 was used as the main polymer for gelling, and the antipyretic efficacy of Radix

Bupleuri in the form of nasal *in situ* gel was investigated. New Zealand rabbits were used to investigate this activity. The nasal solution was applied to one group to be compared with nasal *in situ* gel. Longer-lasting effects and higher efficacy were observed in the *in situ* gel formulation. The siliotoxicity of the *in situ* gel formulation was investigated in the toad palate model. As a result, no serious nasal toxicity was observed [88].

Bhandwalkar et al. prepared a nasal *in situ* gel containing venflaxin hydrochloride, an antidepressant. This study aimed to increase the bioavailability by prolonging the duration in the nasal mucosa and decreasing the mucociliary clearance of venflaxin hydrochloride. The main polymer used for gelling was Lutrol F127. *In vivo* pharmacokinetic studies were performed on rats. In order to compare the nasal *in situ* gel effectiveness, rats were divided into groups and oral solution and saline were given to the groups. After the formulations were administered, the rats were forced to swim. The immobility times of the rats were observed. As the concentration of venflaxin increased, it was expected that the rats would experience an excess of immobility times. As a result of the experiment, it was observed that rats that were administered nasal *in situ* gel remained immobile for longer, hence the targeted goal was achieved with the *in situ* gel formulation [89].

In a study by Khan et al., a nasal *in situ* gel formulation containing ropinirole used in Parkinson's disease was prepared. The aim was to increase bioavailability and reduce gastrointestinal disorders compared to oral administration. A gelling system was created using chitosan (as the main polymer) and hydroxypropyl methylcellulose. *In vivo* bioavailability and clearance studies were performed using Wistar rats. In clearance studies, rats were divided into groups. While *in situ* gel was given to one group, a control solution was applied to the other group. When the two formulations were compared, it was observed that the *in situ* gel formulation could stay in the nasal mucosa two times longer. In bioavailability studies, rats were divided into groups and given a nasal solution labeled with 99mTc, the intravenous formulation, and the nasal *in situ* gel. It was observed that the *in situ* gel formulation had a faster effect and higher concentration in the brain. In addition, increased bioavailability was demonstrated compared to the oral formulation [90].

With the use of cubosomes, Ahirrao et al. attempted to enhance resveratrol transport to the brain via the transnasal route. Cubosomes were created using glycerol monooleate and Lutrol F127, and a 32 complete factorial design was used for optimization. The best cubosomal batch was physically stabilized with Poloxamer 407 and then transformed into a thermoreversible *in situ* gel. The cubosomal *in situ* gel's resveratrol released over time and under regulated conditions, according to the *in vitro* release tests. The cubosomal *in situ* gel showed greater mucosal permeability, a higher concentration, and better distribution to the brain than the drug solution delivered intranasally or orally, according to ex-vivo permeation and *in vivo* biodistribution experiments. It was concluded that the cubosomal *in situ* gel shows promise and may be a useful drug delivery strategy for the treatment of brain disorders via the nasal route, but more clinical trials were required to assess the risk/benefit ratio [91].

The goal of Wang et al. was to create a thermoreversible and mucoadhesive *in situ* nasal gel containing geniposide for the treatment of neurodegenerative disorders. Combining poloxamers, hydroxypropyl methylcellulose, and borneol as a permeation enhancer allowed for the gel's optimization. The drug content, *in vitro* and ex vivo release kinetics, pH, clarity, gel strength, mucoadhesive strength, and gelation temperature were assessed. When compared to oral delivery, the optimized gel displayed controlled release of geniposide and showed higher permeability and potential for compliance. Their study came to the conclusion that this was a promising approach and more animal studies on the *in situ* nasal gel of geniposide are possible [92].

Mathure et al. aimed to create an *in situ* nasal gel comprising nanostructured lipid carriers (NLCs) loaded with rizatriptan for effective intranasal drug delivery to the brain. The 189 nm particle size, high drug encapsulation efficiency, and 83.9% drug release after 24 hours were all characteristics of the optimized NLCs. The liquid gelling technique used to create the *in situ* gel from the rizatriptan-loaded NLCs demonstrated high mucoadhesive strength, effective brain targeting, and no evidence of toxicity to nasal mucosa in the ex vivo study. According to their findings, the lipid carrier-loaded *in situ* gel has the potential to administer rizatriptan intranasally for the treatment of neurological conditions including migraines [93].

In the study of Vasantha et al., mucoadhesive *in situ* nasal gel formulations of loratadine and chlorpheniramine maleate were developed and evaluated for improved drug bioavailability compared to conventional dosage forms. On the nasal absorption of the pharmaceuticals from *in situ* nasal gels comprising various polymeric combinations, the effects of various permeation enhancers were examined. The three most effective enhancers, oleic acid, sodium taurocholate and Pluronic F127, greatly increased drug flux. According to *in vitro* studies, the *in situ* gels have enhanced stability and release profiles, making them a promising drug delivery system for loratadine [94].

An *in situ* mucoadhesive gel filled with darunavir was developed by Nair et al. and tested for brain targeting through the intranasal route in order to increase the efficacy of antiretroviral treatment in NeuroAIDS. The experiment's properties were adjusted using a complete factorial design, and the gel's improved formulation showed preferable rheological characteristics, prolonged drug release, and increased

permeability across the nasal mucosa. An *in vivo* pharmacokinetic study in rats revealed significantly higher drug concentrations in the brain after nasal application, compared to the intravenous route. It was concluded that Darunavir was effectively targeted by the gel to the brain via the nasal route, offering a viable treatment option for NeuroAIDS [95].

Dawre et al. aimed to to improve nasal penetration via dispersion in a thermoreversible in-situ gel. Vitamin D3-loaded PLGA microspheres were developed in their study, and optimized using the Box Behnken Design. The microspheres were uniform and colloidally stable, and the gel had a strong mucoadhesive property, a viscosity of 35698–5032 cps, and a gelation temperature of 35–37 °C. The microspheres scattered in the gel released 69% of vitamin-D3 for up to one week, which was better than the oily solution, according to *in vitro* dissolution experiments. The gel exhibited 2.5 times greater penetration than microspheres and solution, according to ex vivo permeation experiments, which raises the possibility that it may be used as a drug delivery system for vitamin D3 when administered nasally [96].

In another study, Rao et al. developed a thermoreversible *in situ* nasal gel for the anti-Parkinson drug ropinirole, aiming to tackle the limited bioavailability caused by the first-pass metabolism as well as the swallowing difficulties caused by the drug. The gel displayed mucoadhesion, which prolonged nasal residence duration, and the gelation time was less than the mucociliary clearance time. In contrast to plain ropinirole, the nasal gel formulations demonstrated high ex vivo drug release and a protective impact on nasal mucosa. Nasal application of the gel increased its bioavailability in the brain by a factor of five when compared to intravenous administration. The study concluded that the developed *in situ* nasal gel was a viable drug delivery alternative for people with Parkinson's disease [97].

6. CONCLUSION

Conventional and more traditional drug delivery systems face numerous problems and possess different disadvantages, some of which make them less efficient and thus less desirable for use. In this regard, nasal *in situ* gel drug delivery devices have drawn more and more interest as a potentially effective and efficient method of drug administration. These systems are characterized by a phase transition from a sol to a gel state following nasal administration. This facilitates sustained drug release and prolongs the time the drug spends in the nasal cavity, resulting in improved bioavailability and therapeutic effectiveness. They provide a non-intrusive, patient-friendly method of medication delivery, since there is no need for particular training for administration, unlike invasive ways, making it a practical alternative for patients, especially those who are unable to endure invasive treatments. This non-invasiveness and patient-friendliness may increase patient adherence and compliance, improving therapy results.

The capacity of nasal *in situ* gel drug delivery systems to directly target the central nervous system while bypassing the blood-brain barrier is another benefit they offer. With this ability, drugs can reach the brain directly and quickly through the olfactory area of the nasal cavity. This makes them a potentially desirable alternative for the treatment of central nervous system conditions. The therapeutic efficacy and bioavailability of drugs can also be improved. In order to provide for prolonged release and better absorption, the formulations can gel upon contact with the nasal mucosa, extending the drug's residence time in the nasal cavity. As a result, the risks of adverse effects and enzymatic degradation are reduced while the stability and shelf-life are improved. In summary, the creation of efficient and effective drug delivery systems can be made possible by nasal *in situ* gel drug delivery systems, making them well worth the many types of research that have been dedicated to them.

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