WWW.IJRPR.COM

International Journal of Research Publication and Reviews

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

A Descriptive Review on Advances and Future Directions in Situ Gelation Systems for Nasal Drug Delivery.

Shivaji Patil, Sujit Karpe, Anand Bhagwat*, Samadhan Mali, Pankaj Vasugade, Rohan Barbole.

Sojar college of pharmacy, khandvi, barshi, India -413401
E-mail – anandbhagwat101022@gmail.com
DOI: https://doi.org/10.55248/gengpi.5.0524.1256

ABSTRACT

Recent breakthroughs in a development of in situ gelation drug delivery for intranasal routes have sparked widespread interest because of their potential to increase medication delivery. This review delves into a history and scope of in situ gelation systems, highlighting their effect and future trends. These technologies have great potential for improving nasal medication administration, overcoming obstacles, and achieving sustained release. Important advancements include the use of biocompatible polymers and novel formulation strategies to optimize medication release kinetics and improve patient compliance. The therapeutic applications of in situ gelation systems are diverse, ranging from central nervous system problems to viral infections and hormone therapy. Future research areas will concentrate on increasing formulation stability and efficacy, developing additional excipients, and addressing regulatory issues in clinical translation. Overall, recent improvements in in situ gelling drug delivery show significant potential for improving nasal medication administration, allowing for more targeted and long-term therapeutic effects.

Keywords - Nasal drug delivery, In situ gelation, Drug delivery systems, Formulation strategies, Sustained release, Therapeutic outcomes.

Introduction

Environmental variables such as pH and temperature cause aqueous polymer solutions to gel in situ. Fluids in the created tissue, organ, or bodily cavity can be administered into the body in a minimally invasive manner before solidifying or gelling. This is known as in-situ gelation. Formulation researchers are currently interested in these systems due of their structural and functional advantages. To enhance drug transport across mucosal surfaces, numerous in situ gelation techniques have been created. Composite scientists are actively focusing on these systems' structural and functional advantages. To help medications move through mucosal surfaces, in situ gelation techniques have been created. The technique has various advantages if the gel is generated under physiological conditions and retains its integrity for the specified time. In situ forming systems have been used in the literature for a growing range of biomedical applications in recent years, including medication administration, tissue healing, and cell encapsulation.

Advantages of in situ gel.

1. When in situ gel production occurs under physiological settings and retains its integrity for a set amount of time, it can provide various advantages over typical hydrogels. Before injection, they are liquid aqueous solutions, but under physiological conditionsne a gel.
2. 2. Injectable fluid systems offer the advantage of being liquid before solidifying or gelling in the target tissue, organ, or body cavity. This allows for minimally invasive injections. The majority of polymers utilized in topical gelling compositions have bioadhesive characteristics. Touching the mucosal membrane makes them easier to deliver as drops or sprays.
3. The gelled formulation's improved viscosity and bioadhesive qualities reduce mucosal shedding and promote close contact with absorbent tissue, making it appealing for both local and systemic effects. This extends the drug's absorption time.
4. 4. These injectable fluid systems can be injected into the body with little invasiveness before hardening or gelling in the desired tissue, organ, or cavity. The majority of the polymers utilized in topical gel formulations have bioadhesive characteristics.

1.2 Disadvantages of topical gel.

1. Preservatives are necessary in the preparation, because the drugs can become unstable in aqueous solutions.

2. In addition, viscous liquids and gels require advanced dosing systems.

3. Risk of inadvertent exposure of the formulation to gelling stimuli, which may cause malfunction of the drug delivery system.

4. These polymeric systems are not sensitive to changes in the metabolic states of patients.

1.3 Classification

In situ forming hydrogels are highly hydrated networks composed of a variety of hydrophilic polymers. They are divided into two categories: "permanent" or "chemical" gels and "reversible" or "physical" gels. In addition to molecular entanglements, additional factors such as ionic crosslinks, hydrogen bonds, and hydrophobic interactions hold networks together in physical gels. Chemical gels, on the other hand, are composed of networks that are covalently bonded. [1] In situ gel systems can be classed according to the sorts of stimuli that cause gelation.

Physiologically stimulated in situ gel.

• Ion-sensitive hydrogel.

• Temperature-sensitive hydrogel.

• pH-sensitive hydrogel.

• Glucose-sensitive hydrogel.

1.4.1 Ion-sensitive hydrogels.

Different ions can trigger phase transitions in polymers. Ion-sensitive polymers contain polysaccharides. In the presence of Ca^{2+}, β-carrageenan preferentially produces elastic gels, whereas κ-carrageenan forms hard, brittle gels with small quantities of K^+. Gellan gum, also known as Gelrite®, is an anionic polysaccharide that gels in the presence of mono- and divalent cations such Ca^{2+}, Mg^{2+}, K^+, and Na^+.

1.4.2 Temperature-sensitive hydrogels.

Temperature-sensitive hydrogels are the most commonly investigated type of environment-sensitive polymer systems in drug delivery research. These hydrogels can swell or shrink in response to variations in the temperature of the liquid. Hydrogels that respond to temperature changes are divided into three types: negatively thermosensitive, positively thermosensitive, and thermally reversible gels. (Peppas & others, 2000). Hydrogels sensitive to negative temperatures have a lower critical solution temperature (LCST) and contract when heated above it. (N-isopropylacrylamide) (PNIAAm) copolymers are frequently utilized for negative temperatures. The most common thermosetting gel is polyethylene oxide-b-polypropylene oxide-b-polyethylene oxide, also known as Tetronics®, Poloxamers, Pluronics®, and so on. Figure 2 shows the mechanism for pluronic gel production.

1.4.3 pH-sensitive hydrogels

All pH-sensitive polymers contain pendant basic or acidic groups that can donate or absorb protons and are resistant to changes in the pH of their surroundings. Polyelectrolytes are polymers having a high concentration of ionizable groups. When the polymer contains weakly basic (cationic) groups, hydrogel swelling diminishes when external pH rises, but increases slightly when acidic (anionic) groups are present [2].

1.5. Requirements for an ideal in situ gelation system

When using a mucoadhesive hydrogel as a drug delivery vehicle, it must not:

• be in physical-chemical interaction with the active ingredient, and not generate an adverse artificial environment that could lead to inactivation of the active compound. and degradation

• swells at the site of delivery absorption in the biological aquatic environment;

• interacts to ensure proper adhesion to mucus or its particles;

• enables a tightly controlled release of the active ingredient;

• To remain biocompatible with the underlying epithelium, the substance must be fully non-toxic, ciliotoxic, or exhibit any other irreversible alteration in the components of the cell membrane.

1.6 Mucoadhesive Drug Delivery System

Since the early 1980s, pharmaceutical specialists have been particularly interested in the use of bioadhesive polymers to extend a formulation's contact time during mucosal drug administration. "Bioadhesive" refers to a material that can interact with, attach to, or hold biological materials together for an extended period of time. The term "mucoadhesion" refers to the occurrence of sticky attachment to mucous membranes. Mucoadhesive medication

delivery methods use the bioadhesive qualities of specific polymers. They become sticky when hydrated and can be utilized to keep medications at specific absorption sites for extended periods of time. Polymers are considered to interact with the tissue surface and mucus, increasing the duration of exposure. The majority of widely used bioadhesive polymers are anionic or nonionic in nature, having active hydrophilic functional groups that create hydrogen bonds with mucus.

1.6.1 Mechanism of mucoadhesion

In general, the process of mucosal adhesion involves the following steps .

1. The polymer and mucosa are in close contact as the dosage form \disperses, wets and swells on the mucosal surface.

2. Diffusion and penetration occur between the mucoadhesive polymeric chains and the mucosal organization, forming a surrounding contact zone.

3. In addition to the mucus mask's atoms, a trap and selective synthetic bonds form between the polymer chains. For adhesion to occur, the molecules must bond across the mucus contact. These relationships can form in the following ways. [3]

Ionic bonds

- hydrogen bond
- hydrophobic bond
- covalent bond
- Vander Waal bond

1.6.2 Possible ways of mucosal administration:

Possible ways of drug administration by in situ gelling drug delivery systems are:

• nasal

• oral

• rectal

• eye

• gastrointestinal tract

• vaginal

1.7 Nasal route of drug administration

Nasal treatment is being considered in India. The medical system known as Ayurveda. Traditionally, medications have been administered through the nose canal to treat nasal congestion, sensitivity, and contamination. Subfactors Polymer-bound molecular weights Active Polymer Concentration Spatial structure. Polymer chain flexibility. Environmental pH used force. Swelling Physiological mucin turnover Mucosal illness condition. This method of drug delivery into the bloodstream is currently being explored. Mucoadhesive topical hydrogels can be extremely effective in nasal pharmacotherapy. When such gels come into contact with the mucosa, they rapidly expand and constantly release the medication as they cling to the nasal mucosa [4].

1.8 Anatomy and Physiology of the Human Nose

The medial septum separates the human nose into two symmetrical half, each of which extends behind the nasopharynx and enters into the face via the nostrils. The nasal vestibule is close to the middle zone, which is the most anterior region of the nasal cavity (see Figure 3). The olfactory area is positioned on the roof of the nasal cavity, directly behind the writing plate of the ethmoid bone (source: [5]). An adult's nasal cavity has a total volume of 15-20 ml and a surface area of around 150 cm^2, with the respiratory region accounting for approximately 85%. In humans, the surface area of the olfactory region on the roof of the respiratory region is around 2–10 cm [6].

1.9 Absorption From The Nose Epithelium

The nasal respiratory epithelium, like all other bodily epithelia, has similar absorptive pathways. Absorption occurs via four basic routes: transcellular and paracellular passive absorption, transporter-mediated transport, and transcytosis. Most medications are absorbed primarily through transcellular passive diffusion; however, the paracellular pathway may allow for the reception of big or ionized molecules [7].

1.9.1 Mechanisms of transport along the olfactory tract.

The material must pass through the olfactory epithelium before entering the olfactory tract. As mentioned earlier, the general transport processes in the olfactory epithelium are comparable to those of other epithelial types. Material can enter the cell by passive diffusion through Bowman's glands or supporting cells, or by a paracellular route through the tight junctions of supporting cells. Material can enter the peripheral region and central nervous system (CNS) through the lamina propria adjacent to the olfactory neurons (Figure 4) [8].

1.9.2 Factors influencing transport along the olfactory pathway.

The size of medication molecules influences how much is absorbed through the nasal cavity, particularly for hydrophilic medicines. Compound molecular weight has been demonstrated to have a roughly linear relationship with bioavailability in water-soluble medicines (190-70,000 daltons) and variable mass dextrans (1260-45,500 daltons). absorption Molecules having a molecular weight of less than 1000 appear to be efficiently and rapidly transferred by the nose [9,10].

Factors Influencing The Permeability Of Drugs Through The Nasal Mucosa

•Biological factors:

1. Blood supply and nerve cell regulation
2. Nasal discharge
3. Nasal circulation
4. nasal cavity pH
5. Mucociliary clearance and heart rate
6. Pathological conditions.

•Environmental factors :

1. Temperature
2. Humidity

•physical and chemical factors :

1. Molecular weight
2. Size
3. Solubility
4. Lipophilicity
5. pKa
6. Separation efficiency

• Device related :

1. Particle size of drop powder
2. Place and pattern of deposition

1.10 Motion sickness

Symptoms connected with movement or visual movement in the environment suggest motion sickness. Motion sickness can be caused by a multitude of factors, including driving, particularly on steep mountainous terrain, riding in automobiles, spaceships, boats, and elevators, and being exposed to moving sights. The vestibular system is the primary source because it feeds the vestibular nuclei, which project into the vomiting center, resulting in the characteristic symptoms of motion sickness and vomiting. [11] As a result, various medicines have been explored to treat motion sickness, including antihistamines, anticholinergics, and antidopaminergics [12]. Motion sickness involves far more complex indications and symptoms that involve extensive activity of the autonomic nervous system, particularly the sympathetic branch. Table 2 shows some of the main features.

Dimenhydrinate, an over-the-counter medication, is used to prevent motion sickness. It is identical to Benadryl® (diphenhydramine hydrochloride). Because diphenhydramine and its antagonist must dissociate in the body before dimenhydrinate can take effect, diphenhydramine acts faster and more broadly. Dimenhydrinate is a salt of diphenhydramine and 8-chlorotheophylline, a chlorinated theophylline derivative. Theophylline is closely related to

theobromine and caffeine, both weak CNS stimulants. It was thought that combining the stimulant diphenhydramine with its antiemetic effects might help to reduce the former's excessive sleepiness. Diphenhydramine-induced sedation is significantly more effective than chlorotheophylline stimulation.

Systemic nasal administration has lately gained popularity due to its advantages, such as quick absorption and avoidance of liver metabolism, and prefers to transport the drug to the brain via the olfactory region. Intranasal delivery of dimenhydrinate, which acts centrally, may be more effective than oral or subcutaneous administration [13,14].

1.11 Approaches

There are four mechanisms that trigger in situ gelation. of biomaterials.

They are:

1. In Situ Gel Formation From Physiologicaltoitings:

a) Temperature Outputs In Situ Gelation Systems

b) pH Outputs In Situ Gelation Systems

2. In situ gel formation due to ion-activatedsystem

3. In situ formation of a gel from a physicalmechanism

a) Swelling

b) Diffusion

4. In situ gelation from chemical reactions

a) Ionic crosslinking

b) Enzymatic crosslinking

c) Photopolymerization [14]

1.12 Nasal Route of Administration

The nasal cavity has emerged as an attractive route for the delivery of a large variety of drugs, from small compounds to the biological macromolecules. which including peptides, proteins and vaccines [15].

The nasal route of administration is a natural alternative for the administration of topical medications intended to treat local illnesses of the nose and paranasal sinuses, such as allergic or infectious rhinitis, sinusitis, rhinosinusitis, and nasal epithelial lesions [16, 17]. Furthermore, the nasal mucosa represents a non-invasive alternative route for systemic administration of drugs with low bioavailability. Indeed, the highly vascularized nasal epithelium has been used for rapid absorption of drugs, which typically undergo extensive first-pass metabolism and/or digestion after oral administration [17]. Furthermore, the nasal route of administration demonstrated as to be effective in delivering medications to the brain by bypassing the blood-brain barrier (BBB), which inhibits the diffusional transport mechanisms for many therapeutic agents following oral and parenteral administration. Drugs are directly and rapidly transported from the nasal cavity to central nervous system in brain (CNS) via the olfactory neuroepithelium [16,18].

Although the intranasal route of administration has various advantages in accessibility, efficiency, tolerability, and also in patient compliance, mucociliary clearance is a physiological component primarily responsible for limiting drug residence time in the nasal cavity. This self-cleaning process is responsible for the drug's quick evacuation from the nasal cavity, minimizing the time it takes for the medicine to cure local nasal disorders or reach the systemic circulation or central nervous system [15–17]. To prevent the quick drainage of medications supplied as simple water solutions and to extend their residence duration in the nasal canal, a viscosity-enhancing strategy has been proposed: intranasally gelled topical preparations appear to more successful option for the nasal fluids [15]. Such formulations are simple to administer as low-viscosity polymer solutions, ensuring excellent nasal deposition, and transform into gels upon mucosal contact. Temperature, pH, ionic strength these all are the examples of physical and chemical stimuli that can cause the sol-gel transition. In vivo polymer network development enhances drug interaction time with the site of absorption while also ensuring drug release throughout time [19].

Corticosteroids administered intranasally are the first-line therapeutic method for the local treatment of the nasal inflammatory diseases. Numbers of research groups have confirmed that the advantages of in situ gelling system for the local drug administration in the nasal route, rapid gel formation reduces the effect of the mucociliary removal, and also prevents locally acting drugs from penetrating the nasal membrane, limiting their systemic rate of absorption [20, 21] created a topical gelling formulation for corticosteroid are administration to treat chronic rhinosinusitis with the help of nasal polyps. Specifically, lipid nanoparticles (NPs) loaded with dexamethasone (DEX) were disseminated in the PEC solution and can easily injected into the region of inflammation with an appropriate nasal administration device. The sol-gel transition is caused by PEC's capacity to form gels when exposed to Ca2+ ions in the nasal mucosa. The development of such an NP-containing in situ gel was effective for long-term local anti-inflammatory effects: loading DEX

into NPs reduced DEX release from the NP contains gel, as did diffusion from the DEX-loaded NPs through the PEC gel. Polymer chain entanglement and potential interaction with the NP surface were inhibited [20]. created an in situ gelation technique including polymer and Ca2+ ions.

The authors created the in situ gelling suspension containing fluticasone that was optimized for nasal accumulation following manual injection under respiratory circumstances; the injectability of the preparation and turbinate precipitation were identified as the primary parameters determining the outcome of local treatment interactions between PEC and GG. Agents which interact with divalent cation has been utilized as gelling agents, while sodium hyaluronate is has been used as a bioactive gel structuring agent that gives the healing of mucosal surface of the wounds [19]. examined the interaction in between GG with ions in the nasal cavity, developing the in-situ gel containing mometasone furoate (MF). stressed the need of selecting a gelling agent concentration that allows for facile nasal injection while also forming a gel strong enough to sustain topical corticosteroid delivery without quick disintegration or erosion. They used thermos reversible polymers to create nasal gelation devices [22].

In this study, P407 was combined with the bioadhesive polymer Carbopol® 974P NF to create a thermos sensitive gel for prolonged release of MF for the treatment of allergic rhinitis. The poloxamer has bee tuned so that the developed in situ gelation system's sol-gel transition temperature (Tsol-gel) is lower than the human nose's temperature. An rise in the concentration of P407 causes a drop in the composition of the Tsol gel, resulting in the quick production of a gel with good structure. Demonstrated the P407 is concentration of 18% w/v which may rapidly form a gel at approximately 30°C, which ensuring the precise drug administration at room temperature. A poloxamer concentration of 15.5 wt% was chosen as the best for creating a thermosensitive system with a Tsol gel appropriate for nasal delivery [23]. Poloxamer was combined with bioadhesive polymers like HPMC, E4M or CS for the increaseing dexamethasone-21-phosphate disodium gel's adherence to the nasal mucosa. Topical gel formulations have been used to treat nasal ulcers similar to distribute corticosteroids. Gholizadeh and associates [24] produced a thermosensitive and mucoadhesive formulation are manly based on the usage of CS, which is known for the hemostatic and wound healing nature. With a addition of GP, as weakly basic organic molecule which neutralizes the pH of the CS solution, It was important to develop a formulation that could undergo a sol-gel thses transition in response for the temperature fluctuations. The CS-GP solution was treated with a tranexamic acid (TXA), as an effective and well-tolerated hemorrhage control medication. The CS-GP solution is saline at the room temperature which forms the gel at 32 ◦C in 5 minutes, making it appropriate for nasal administration. Over the last ten years, nasal injection of antiemetics and seasickness medications has employed to achieve the fast absorption into the systemic circulation and the well-vascularized, permeable nasal mucosa allows it for the rapid commencement at pharmacological site of action, which is especially significant in the treatment for the acute nausea and vomiting which is frequently linked with cancer treatment and migraines. Nasal administration has sparked particular interest in systemic drug administration because it promotes patient compliance unlike the parenteral administration, it is the painless and enables the possibility of self-medication. Furthermore, nasal administration assures a precise and consistent dose of the medicine, as nausea and vomiting promote gastric dysmotility, resulting in considerable alterations in oral absorption of the drug from the intestine [17].

Metoclopramide hydrochloride (MCP HCl) which is a strong antiemetic chemical with extremely variable oral bioavailability as (32% - 98%) due to substantial first-pass metabolism with a short duration of half-life that necessitates for the three to four doses. Per day Intranasal delivery of MCP HCl has been suggested as an effective alternative. Given the limited permeability of MCP HCl through the nasal mucosa and mucociliary action, in situ gelation systems appear to be an effective formulation technique for increasing MCP HCl's residence duration in the nasal cavity. [25] created an MCP HCl loaded muco-adhesive in situ gel which is with P407 as a thermos reversible polymer and polyethylene glycol (PEG) act as a release promoter, and C934P act as a mucoadhesive agent. The bioavailability for the MCP HCl was found in investigated in rabbits using an optimized nasal gel vs oral drug solution, it was discovered that bioavailability of MCP HCl rose dramatically changes from the 51.7% (oral drug solution) to 69.1% (nasal topical). The scientists found that the created in situ gel formulation was capable of rapidly forming a gel following delivery and retaining the drug in the nasal cavity for long enough to ensure mucosal absorption. Intranasal delivery appears to be a promising alternative to ondansetron hydrochloride (OND), is a selective 5-HT3 sretoinin receptor antagonist, for preventing nausea and vomiting during radiation, chemotherapy, or surgical procedures. [23]

We created an OND-loaded in situ gelling as nose patch by freezing a polymer solution which containing a CS-GG polyelectrolyte complex. Nausea, vomiting are the following radiation, chemotherapy, or surgical operations. [23] created an OND-loaded in situ gelling nasal patch by freezing a polymer solution made of a CS-GG polyelectrolyte complex. In situ gelation of a solid nasal insert loaded with ondansetron hydrochloride made by freeze-drying an aqueous polymer solution of chitosan (CS) and gellan gum (GG); (a) Scanning electron microscopy of a freeze-dried insert adapted from [58]. When in contact with the nasal mucosa, the separator's porous structure allows for quick hydration of the cross-linked polymer matrix, resulting in the creation of a gel and controlled drug release. Adapted from [15]. Cross-linking of cationic CS with oppositely charged GG resulted in the formation of a three-dimensional network of polymer chains in which the medication was distributed. Nasal suppositories are solid dose forms made of a spongy, hydrophilic polymer. Agents that interact with divalent cations have been utilized as gelling agents, while sodium hyaluronate has been employed as a bioactive gel structuring agent that aids in the healing of mucosal surface wounds. The interaction of GG with ions in the nasal mucosa was already examined in 2009 [19]. Who created an in situ gel containing mometasone furoate (MF). The authors of this research stressed the need of selecting a gelling agent concentration that allows for facile nasal injection while also forming a gel strong enough to sustain topical corticosteroid delivery without quick disintegration or erosion. Other authors also used thermoreversible polymers to create nasal in situ gelation devices [21].

In this study, P407 was combined with the bioadhesive polymer Carbopol® 974P NF to create a thermosensitive gel for the prolonged release of MF in the treatment of allergic rhinitis. The poloxamer concentration was tuned so that the developed in situ gelation system's sol-gel transition temperature (Tsol-gel) was lower than the human nose's physiological temperature. An rise in the concentration of P407 causes a drop in the composition of the Tsol gel, resulting in the quick production of a gel with good structure. demonstrated that a P407 concentration of 18% w/v could rapidly form a gel at approximately 30 °C, ensuring precise drug administration at ambient temperature. A poloxamer concentration of 15.5 wt% was chosen as the best for creating a thermosensitive system with a Tsol gel appropriate for nasal delivery [23]. Poloxamer was combined with bioadhesive polymers such HPMC

E4M and CS to increase dexamethasone-21-phosphate disodium gel's adherence to the nasal mucosa. Topical gel formulations have been used to treat nasal ulcers as well as to distribute corticosteroids. Gholizadeh and collaborators [24] produced a thermosensitive and mucoadhesive formulation using CS, which is known for its hemostatic and wound healing characteristics. The inclusion of GP, a weakly basic organic molecule that neutralizes the pH of the CS solution, was required to create a formulation that can undergo a sol-gel transition in response to temperature changes. The CS-GP solution was treated with tranexamic acid (TXA), an effective and well-tolerated hemorrhage control medication. The CS-GP solution is saline at room temperature and forms a gel at 32 ◦C within 5 minutes, making it appropriate for nasal administration. Over the last decade, nasal injection of antiemetics and seasickness medications has been employed to achieve fast absorption into the systemic circulation. The well-vascularized and permeable nasal mucosa allows for a rapid commencement of pharmacological action, which is especially significant in the treatment of acute nausea and vomiting that is frequently linked with cancer treatment or migraines. Nasal administration has sparked particular interest in systemic drug administration because it promotes patient compliance: unlike parenteral injection, it is painless and enables for self-medication. Furthermore, nasal administration assures a precise and consistent dose of the medicine, as nausea and vomiting promote gastric dysmotility, resulting in considerable alterations in oral absorption of the drug from the intestine [18].

Cross-linking of cationic CS with oppositely charged GG forms a three-dimensional network of polymer chains in which a medication is distributed. Nasal suppositories are solid dose forms made of a spongy, hydrophilic polymer. matrices that, following injection, absorb physiological fluids in a nasal cavity with quickly produce gels from which the drug is delivered at a regulated fashion. The extremly porous structure of an insert causes improve water penetration and consequently swelling, which is required for both the lengthy residence period in the nose and the gradual release of the medicine. Animal studies revels that the nasal implant for the development and not only ensured correct medication dosing, also enhanced the systemic absorption of the ondansetron when versus an oral medication solution [26]. Finally, nasal route of administration which has been utilized in the treatment of neurological problems; various drugs, including those for migraines, Parkinson's disease, depression, anxiety, psychosis, and epilepsy, have been combined in the both liquid and solid topical gel formulations. Luppi and colleagues [27] developed nasal contents containing chlorpromazine hydrochloride, which quickly form gels when in contact with nasal fluids, allowing the drug to penetrate the nasal mucosa for longer periods of time, reducing the number of daily doses required and eliminating peak-to-trough fluctuations, which limits the occurrence of adverse effects. Lyophilizing CS/PEC polyelectrolyte complexes with dispersed drugs resulted in such nasal implants. The scientists noted that the polycation/polyanion molar ratio had a significant impact on the insert's porosity and, as a result, water permeability. Insert swelling influencing medication bioavailability over time, as established in vitro sheep nasal mucosal permeability experiments. Several authors have studied the use of thermosensitive formulations for the intranasal delivery of migraine medications such as sumatriptan [28], risatriptan benzoate [29], and zolmitriptan [30] throughout the last decade. [31]

To transfer naratriptan hydrochloride (NH) into the brain via the olfactory lobe, they developed an in situ gelling bioadhesive formulation that containing P407 and C934. When subjected to shear stress, this formulation is formed gel at 29 °C and maintained the gel-like structure for the priod of 47 seconds (desired time). In vitro release tests revealed the drug diffusion rate with polymer chain relaxation influenced with a NH3 release (greater than 65% after 12 hours). According to these ex vivo trials, C934 served has both a mucoadhesive agent and a penetration enhancer, while the P407, is thermoreversible polymer, which was responsible for the drug's prolonged release [32].

The potential for systemic Alzheimer's disease treatment was investigated using the nasal in situ gelling formulation containing rivastigmine (RV)-loaded NLCs. To achieve maximum resistance for the mucociliary clearance, a system was created by employing the GG and poloxamer, these two polymers that are respond to distinct stimuli (ions and temperature, respectively). In vivo pharmacokinetic and pharmacodynamic tests were they used to assess the formulation's for the brain targeting potential when NLCs were delivered intranasally as an in situ gelation technique, brain RV concentration was 1.61 times greater than when administered is intravenously. Nose-to-brain transfer has also been utilized to treat AIDS dementia complex, with the central nervous system illness that arises when the human is immunodeficiency virus (HIV) infects to the brain tissue; specifically [33]. developed an in situ gelation technique using poloxamer as a thermoreversible agent to increase the intranasal zidovudine (ZVD) administration into brain. In vivo absorption and brain distribution tests in rabbits revealed that ZDV concentrations in both cerebrospinal fluid (CSF) the brain were roughly fivefold higher following the intranasal delivery of the thermosensitive device than after the intravenous injection. Recent Advances One of the pharmaceutical industry's concerns with the creation of viable treatment choices that doctors and patients can endure. Delivery methods should also help to enhance treatment outcomes since they provide potential alternatives for the medications now supplied through other channels. Topical gelling formulations are among the most complicated drug delivery methods. In situ gels are made from a variety of biodegradable polymers, however their production presents manufacturing hurdles, problematic performance, the usage of organic solvents (particularly for synthetic polymer-based systems), the bursting effect, and non-reproducible drug release kinetics. Natural polymers have the features of a perfect polymer, but batch-to-batch reproducibility is challenging, hence synthetic polymers are utilized. However, all of these issues are being addressed on a daily basis, and topical gels are emerging as a valuable tool for site-specific medication delivery.

Conclusions

The fundamental prerequisite for a successful controlled release product is to prioritize patient compliance, which topical gels do. Each medicine has a unique therapeutic effect and can be delivered in variety of ways, including topical gels. Polymeric in situ gels for controlled release of various medications have many advantages over conventional dosage forms, including long-term and sustained drug release, superior stability, and biocompatibility. The use of biodegradable and water-soluble polymers in in situ gel forms improves their acceptability and effectiveness as a delivery strategy.

Conflict of interest

All authors declare that there are is no conflicts of interest regarding with the publication of this review paper.

Funding

None

Authors' contributions

All authors conducted the acquisition of data. All authors Helped to draft the manuscript. All authors read and approved the final manuscript.

Acknowledgment

We want to express our gratitude to all the researchers and authors whose work and contributions have greatly enriched the content of this review paper. Additionally, we acknowledge the support and guidance provided by our colleagues and mentors throughout the preparation of this manuscript.

References

1. Brandl, C., Haas, C., d'Argouges, S., Fisch, T., Kufer, P., Brischwein, K., Prang, N., Bargou, R., Suzich, J., Baeuerle, P. A., & Hofmeister, R. (2007). The effect of dexamethasone on polyclonal T cell activation and redirected target cell lysis as induced by a CD19/CD3-bispecific single-chain antibody construct. Cancer immunology, immunotherapy : CII, 56(10), 1551–1563.
2. Ajazuddin, A.; Junaid, K.; Tapan, K.; Dulal, T.; Swarnlata, S.; Shailendra, S. Advancement in stimuli triggered in situ gelling delivery for local and systemic route. Expert Opin. Drug Deliv. 2012, 9, 1573–1592.
3. Ruel-Gariépy; Leroux, C. In Situ-Forming Hydrogels—Review of Temperature-Sensitive Systems. Eur. J. Pharm. Biopharm. 2004, 58, 409–426.
4. Caramella, M.; Rossi, S.; Ferrari, F.; Bonferoni, C.; Sandri, G. Mucoadhesive and thermogelling systems for vaginal drug delivery. Drug Deliv. Rev. 2015, 92, 39–52.
5. Matanovi´c, R.; Kristl, J.; Grabnar, A. Thermoresponsive Polymers: Insights into Decisive Hydrogel Characteristics, Mechanisms of Gelation, and Promising Biomedical Applications. Int. J. Pharm. 2014, 472,262–275.
6. Rossi, S.; Mori, M.; Vigani, B.; Bonferroni, M.; Sandri, G.; Riva, F.; Caramella, C.; novel dressing for the combined delivery of platelet lysate and vancomycin hydrochloride to chronic skin ulcers: Hyaluronic acid particles in alginate matrices. Eur. J. Pharm. Sci. 2018, 118, 87–95.
7. Vigani, B.; Rossi, S.; Sandri, G.; Bonferoni, C.; Milanesi, G.; Bruni, G.; Coated electrospun alginate-containing fibers as novel delivery systems for regenerative purposes. Int. J. Nanomed. 2018, 13,6531–6550.
8. Tenci, M.; Rossi, S.; Giannino, V.; Vigani, B.; Sandri, G.; Bonferoni, C.; Daglia, M.; Longo, M.; Macelloni, C.; An In Situ Gelling System for the Local Treatment of Inflammatory Bowel Disease (IBD). The Loading of Maqui (Aristotelia chilensis) Berry Extract as an Antioxidant and Anti-Inflammatory Agent. Pharmaceutics 2019, 11, 611.
9. Tenci, M.; Rossi, S.; Bonferoni, C.; Sandri, G.; Mentori, I.; Boselli, C.; Icaro Cornaglia, A.; Daglia, M.; Marchese, A.; Caramella, C.; et al. Application of DoE approach in the development of mini-capsules, based on biopolymers and manuka honey polar fraction, as powder formulation for the treament of skin ulcers. Int. J. Pharm. 2017, 516, 266–277.
10. Tenci, M.; Rossi, S.; Bonferoni, C.; Sandri, G.; Boselli, C.; Di Lorenzo, A.; Daglia, M.; Icaro Cornaglia, A.; Gioglio, L.; Perotti, C.; et al. Particulate systems based on pectin/chitosan association for the delivery of manuka honey components and platelet lysate in chronic skin ulcers. Int. J. Pharm. 2016, 509, 59–70.
11. Al-Kinani, A.; Zidan, G.; Elsaid, N.; Seyfoddin, A.; Alani, G.; Alany, G. Ophthalmic Gels: Past, Present and Future. Adv. Drug Deliv. Rev. 2018, 126, 113–126.
12. Kant A, Reddy S, Shankraiah M, Venkatesh S, Nagesh C. In situ gelation system - a review, Pharmacologyonline 2011;2: 28–44 .)
13. Karavasili, C.; Fatouros, G. Smart materials: In situ gel-forming systems for nasal delivery. Drug Discov. Today 2016, 21, 157–166.
14. Pires, A.; Fortuna, A.; Alves, G.; Falcão, A. Intranasal drug delivery: How, why and what for? J. Pharm. Pharm. Sci. 2009, 12, 288–311.
15. Fortuna, A.; Alves, G.; Serralheiro, A.; Sousa, J.; Falcão, A. Intranasal delivery of systemic-acting drugs: Small-molecules and biomacromolecules. Eur. J. Pharm. Biopharm. 2014, 88, 8–27.
16. Aderibigbe, B.A. In Situ-Based Gels for Nose to Brain Delivery for the Treatment of Neurological Diseases. Pharmaceutics 2018, 10, 40. Pharmaceutics 2020, 12, 859 26 of 29
17. Cao, S.L.; Ren, X.W.; Zhang, Q.Z.; Chen, E.; Xu, F.; Chen, J.; Liu, L.C.; Jiang, X.G. In situ gel based on gellan gum as new carrier for nasal administration of mometasone furoate. Int. J. Pharm. 2009, 365, 109–115.

18. Niži´c, L.; Ugrina, I.; Špoljari´c, D.; Saršon, V.; Kuˇcuk, M.S.; Pepi´c, I.; Hafner, A. Innovative sprayable in situ gelling fluticasone suspension: Development and optimization of nasal deposition. Int. J. Pharm. 2019, 563, 445–456.

19. Dukovski, B.J.; Planti´c, I.; Cunˇci´c, I.; Krtali´c, I.; Jureti´c, M.; Pepi´c, I.; Lovri´c, J.; Hafner, A. Lipid alginate nanoparticle-loaded in situ gelling system tailored for dexamethasone nasal delivery. Int. J. Pharm. 2017, 533, 480–487.

20. Altunta¸s, E.; Yener, G. Formulation and Evaluation of Thermoreversible In Situ Nasal Gels Containing Mometasone Furoate for Allergic Rhinitis. AAPS PharmSciTech 2017, 18, 2673–2682.

21. Pandey, P.; Cabot, P.J.; Wallwork, B.; Panizza, B.J.; Parekh, H.S. Formulation, functional evaluation and ex vivo performance of thermoresponsive soluble gels—A platform for therapeutic delivery to mucosal sinus tissue. Eur. J. Pharm. Sci. 2017, 96, 499–507.

22. Gholizadeh, H.; Messerotti, E.; Pozzoli, M.; Cheng, S.; Traini, D.; Young, P.; Kourmatzis, A.; Caramella, C.; Ong, H.X. Application of a Thermosensitive In Situ Gel of Chitosan-Based Nasal Spray Loaded with Tranexamic Acid for Localised Treatment of Nasal Wounds. AAPS PharmSciTech 2019, 20, 299.

23. Zaki, N.; Awad, G.; Mortada, N.; Abd Elhady, S. Enhanced bioavailability of metoclopramide HCl by intranasal administration of a mucoadhesive in situ gel with modulated rheological and mucociliary transport properties. Eur. J. Pharm. Sci. 2007, 32, 296–307.

24. Sonje, A.; Mahajan, H. Nasal inserts containing ondansetron hydrochloride based on Chitosan-gellan gum polyelectrolyte complex: In vitro-in vivo studies. Mater. Sci. Eng. C Mater. Biol. Appl. 2016, 64, 329–335.

25. Luppi, B.; Bigucci, F.; Abruzzo, A.; Corace, G.; Cerchiara, T.; Zecchi, V. Freeze-dried chitosan/pectin nasal inserts for antipsychotic drug delivery. Eur. J. Pharm. Biopharm. 2010, 75, 381–387.

26. Majithiya, R.; Ghosh, P.; Umrethia, M.; Murthy, R. Thermoreversible-mucoadhesive gel for nasal delivery of sumatriptan. AAPS PharmSciTech 2006, 7, E80–E86.

27. Kempwade, A.; Taranalli, A. Formulation and evaluation of thermoreversible, mucoadhesive in situ intranasal gel of rizatriptan benzoate. J. Sol. Gel Sci. Technol. 2014, 72, 43–48.

28. Kumar, A.; Garg, T.; Sarma, G.; Rath, G.; Goyal, A. Optimization of combinational intranasal drug delivery system for the management of migraine by using statistical design. Eur. J. Pharm. Sci. 2015, 70,140–151.

29. Shelke, S.; Shahi, S.; Jalalpure, S.; Dhamecha, D.; Shengule, S. Formulation and evaluation of thermoreversible mucoadhesive in-situ gel for intranasal delivery of naratriptan hydrochloride. J. Drug Deliv. Sci. Technol.2015, 29, 238–244.

30. Wavikar, P.; Pai, R.; Vavia, P. Nose to Brain Delivery of Rivastigmine by In Situ Gelling Cationic Nanostructured Lipid Carriers: Enhanced Brain Distribution and Pharmacodynamics. J. Pharm. Sci. 2017, 106, 3613–3622.

31. Ved, P.; Kim, K. Poly(ethylene oxide/propylene oxide) copolymer thermo-reversible gelling system for the enhancement of intranasal zidovudine delivery to the brain. Int. J. Pharm. 2011, 411, 1–9.

32. Sonis, S.; Elting, L.; Keefe, D.; Peterson, D.; Schubert, M.; Hauer-Jensen, M.; Bekele, B.; Raber-Durlacher, J.; Donnelly, J.; Rubenstein, E. Perspectives on cancer therapy-induced mucosal injury: Pathogenesis, measurement, epidemiology, and consequences for patients. Cancer 2004, 100, 1995–2025.

33. Puccio, A.; Ferrari, F.; Rossi, S.; Bonferroni, M.; Sandri, G.; Dacarro, C.; Grisoli, P.; Caramella, C. Comparison of functional and biological properties of chitosan and hyaluronic acid, to be used for the treatment of mucositis in cancer patients. J. Drug Deliv. Sci. Technol. 2011, 21, 241–247.

Figures

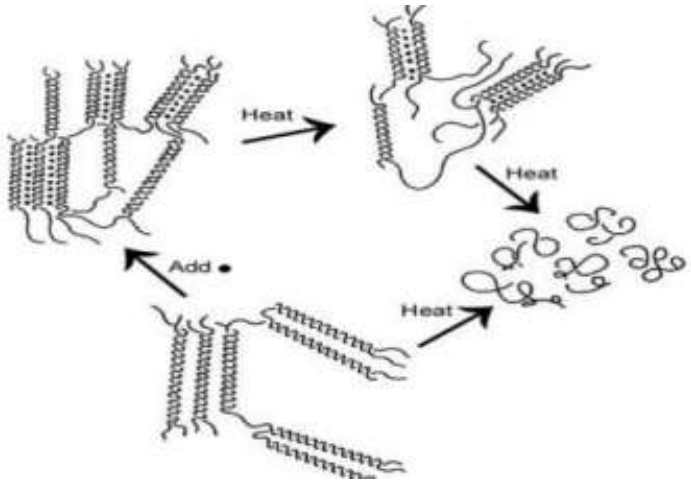

Fig . 1: Model of Gelrite® gel formation after addition of cations.

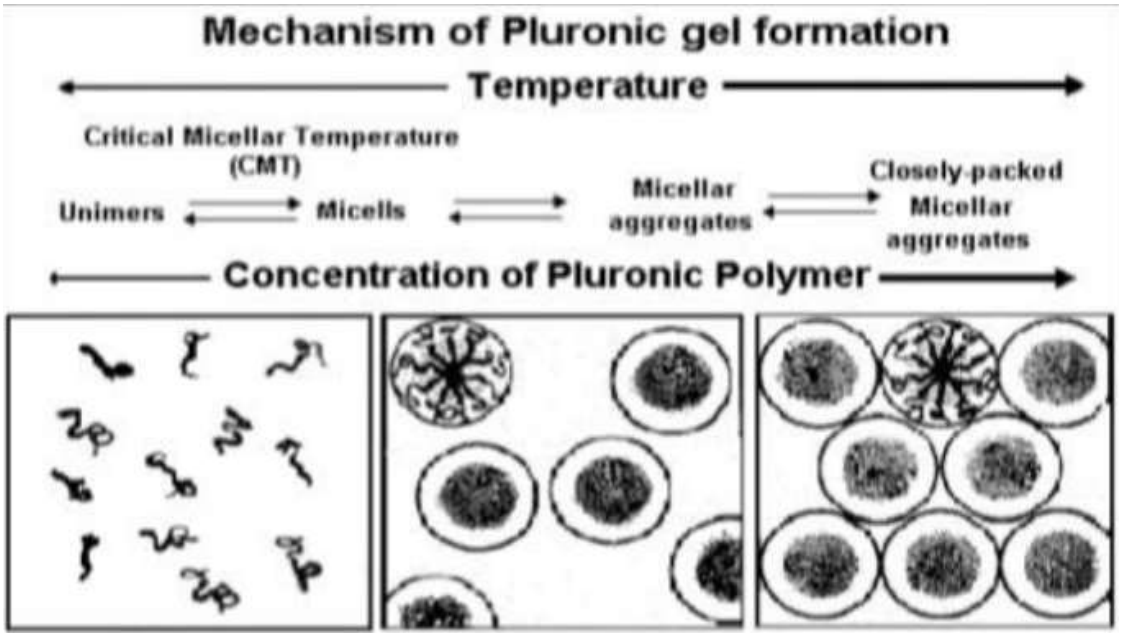

Fig. 2: Mechanism of Pluronic F127 gel1.

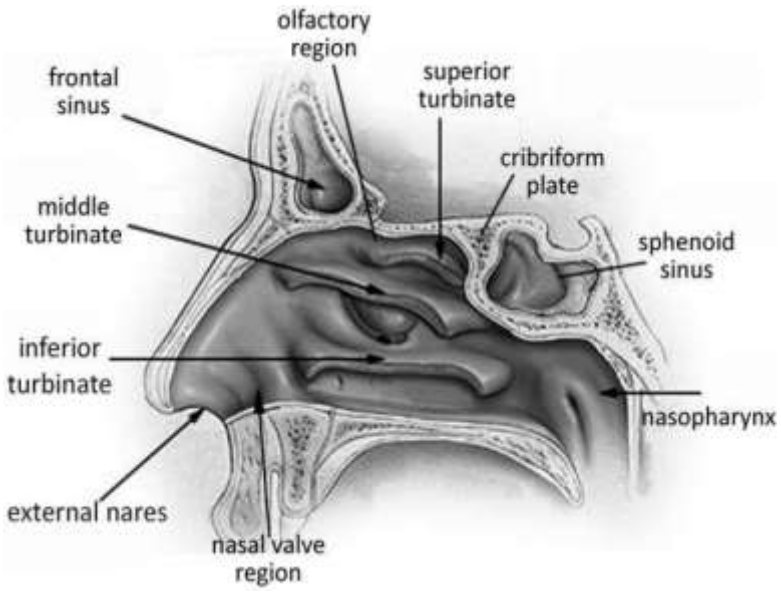

Fig. 3. Anatomy and Physiology of the Human Nose

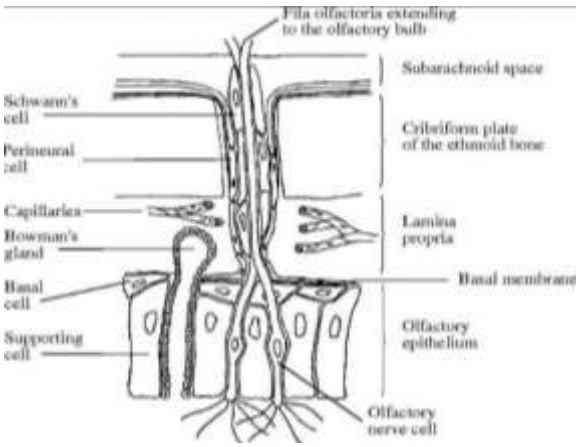

Fig. 4. Anatomical relationship between the nasal olfactory membrane and CSF in the subarachnoid space outside the olfactory bulb.

Tables

Table 1. Factors influencing mucosal adhesion

Factors	Sub-Factors
Polymer Related	Molecular Weight Concentration of active polymer Spatial Conformation Chain flexibility of polymer
Environmental	pH Applied strength Swelling
Physiology	Mucin turnover Disease state of mucus layer

Table 2. Diagnostic elements of motion sickness

Features	Epigastric awareness	Skin sign	Central nervous system features nausea syndrome
Symptoms	Epigastric discomfort Nausea Vomiting	Pallor Cold sweating Dry mouth	Headache Dizziness Drowsiness Eye strain Apathy