A REVIEW: IN SITU NASAL DRUG DELIVERY

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ABSTRACT: In the nasal cavity, nasal mucosa had a high blood perfusion rate, due to this the absorption of the drug is high as compared to another route, as well as has increased good bioavailability of drug at the systemic circulation. To improve the nasal retention time of in-situ gel with nasal mucosa we have to use bio-compatible mucoadhesive polymer. In situ gel nasal drug delivery system is the type of mucoadhesive drug delivery system. When the drug is administered through the nasal route then the first-pass metabolism gets reduced, had less enzymatic reaction occurrence, and prevents gastrointestinal tract Ulceration. Drug release kinetic can be controlled by the Gelation strength of the formulation and viscosity of the in-situ gel formulation, so in-situ gel nasal drug delivery is also called a controlled and sustained drug delivery system. In-situ gels are prepared by various types of phenomenon and techniques that depend upon the different types of polymers used in the formulation.

Introduction
The gel is the state which exists between solid and liquid phase. The solid component comprises a three-dimensional network of inter-linked molecules that immobilizes the liquid phase [1]. In-Situ Gel Delivery System In situ gelation is a process of gel formation at the site of action after the formulation has been applied at the site. In-situ gel phenomenon based upon liquid solution of drug formulation and converted into the semi-solid mucoadhesive key depot. It permits the drug must be delivered in a liquid form or solution form [2].

Advantages of In-Situ Gel Nasal Formulation
The increased residence time of the drug in the nasal cavity.
Decreased frequency of drug administration.
Results in rapid absorption and onset of effect.
Avoids degradation of the drug in the gastrointestinal tract resulting from acidic or enzymatic degradation.
Low dose required.
Minimized local and systemic side effects.
Improved bio-ability of the drug.
Direct transport into systemic circulation and CNS, is possible.,
Offers lower risk of an overdose of CNS acting drug
Improved patient compliance [3],[4],[5]

Properties of Nasal In-Situ Gel
It should be low viscous It should be free-flowing to allow for reproducible administration to the nasal cavity, as droplet mist or as a spray.

The nasal in-situ gel should have a long residence time.
The nasal in-situ gel follows the phase transition mechanism and to understand with the shear forces in the nasal cavity wall.
[6],[7] Nasal Drug Delivery Intranasal route is considered for the drugs that are ineffective orally and are used chronically where rapid entry into the Circulation is desired and they require small doses [8]. The absorption of drugs from the nasal mucosa most probably takes place via the aqueous channels of the Membrane. Therefore, as long as the drug is in the form of a solution and the molecular size is small, the drug will be absorbed rapidly via the aqueous path of the membrane [9].
The absorption from the nasal cavity decreases as the molecular size increases. Nasal conciliary clearance is one of the most important limiting factors for nasal drug delivery. It severely limits the time allowed for drug absorption to occur. However, mucoadhesive preparations had been developed to increase the contact time between the dosage form and mucosal layers of nasal cavities [10],[11].

Factors that affect the rate and extent of absorption of drugs via the nasal route are as follows:

- The rate of nasal secretion.
- Ciliary movement.
- Vascularity of the nose.
- Metabolism of drugs in the nasal cavity.
- Volume that can be delivered into the nasal cavity is restricted 25 to 200 µl.
• Diseases affecting nasal mucous membrane. 3. Various Approaches of In-Situ Gelation To cause sol to gel phase transition on the nasal surface the following type of systems are recognized:
  • pH Triggered system
  • Temperature-dependent system
  • Ion activated the system
  • Induced photo polymerization gelation (UV Induced gelation)
  • Solvent exchange induced gelation [12],[13],[14],[15]

**pH Triggered system:** - the entire pH-sensitive polymer contains acidic or basic groups that either accept or release proton in response to in environmental pH. In the case of anionic groups swelling of gel increases as the external pH increases, but decrease if polymer contains cationic groups [16].

**Temperature-dependent system:** - Temperature-sensitive gels are classified into two types first negatively thermo sensitive and second positively thermo sensitive.

CST is a critical solution temperature at which temperature gelation occurs.

a) **Negatively thermo sensitive:** - Negative temperature sensitive gel had a lower critical solution temperature (LCST) and contract upon heating above the LCST.

b) **Positively thermo sensitive:** - Positive temperature sensitive gel had an upper critical solution temperature (UCST) [17], [18], [19].

c) **Ion activated system:** - In situ formation is based on chemical reactions, following chemical reactions cause gelation, undergoes in situ gelling in the presence of mono- and divalent captions, including Ca 2+, Mg 2+ , K +, and Na + . Alginic acid undergoes gelation in presence of divalent/polyvalent captions [20], [21].

d) **Induced photo polymerization gelation:** - Photo polymerization is commonly used for in-situ formation of biomaterials. A solution of monomers or reactive micromere and initiator can be injected into a tissue site and application of electromagnetic radiation used to form a gel. The photoreaction provides a rapid polymerization rate at physiological temperature. The photo polymerization systems when introduced to the desired site via injection get photo cured in situ with the help of fiber optic cables and then release the drug for a prolonged period [22],[23].

Polymer Used in in situ Gel Drug Delivery System For achieving better drug product effectiveness, reliability we select appropriate polymer for the formulation. Material that shows sol to gel transition in the aqueous solution used in in-situ gelation [24]. Some examples of polymers that is capable of in-situ gelation such as poloxamer, pluronic, various copolymers such as PEO-PLLA and PEG-PLGA-PEG. Pectin, generate, cellulose cephalate latex, gellan gum, alginate, matrigel, carbopol, chitin. The gel formation is induced by temperature change poloxamer, cellulose acetophalte latex, carbopol gelation induced by pH change [25].

**Evaluation**

**Clarity:** The clarity of in situ gel was examined by visually under dark background.

**pH of the gel:** The normal range of nasal mucosal pH is 6.2 to 7.0 pH. The advisable pH of the nasal formulation is in the range of 5.5 to 7. For determining the pH of the formulation of nasal in situ gel, taken 1 ml quantity of each formulation was transferred into a different beaker and diluted it with distilled water up to 25 ml and then pH of each formulation was determined by using a pH meter (model no CL 54 ) [26],[27].

**Drug content:** 1 ml of the formulation was taken in 10 ml volumetric flask and then it was diluted with 10 ml of distilled water then volume adjusted to 10 ml, 1 ml from this solution again diluted with distilled water up to 10 ml. After this absorbance of the prepared solution was measured at a particular wavelength of the drug by using U.V visible spectrophotometer [28], [29], [30].

**Viscosity measurement:** The viscosity of nasal in situ gel was measured by using (cone and plate viscometer) programmable Brookfield dv2nd model viscometer. The viscometer was equipped with the temperature control unit and the sample was equilibrated for 10 min before the measurement. The viscosity of nasal in situ gel was recorded at various temperatures from 4°C to 40 °C respectively against increasing the shear rate [31], [32].

**Measurement of gelation temperature:** The gelation temperature was described by the miller & Donovan technique. In this phase transition occurred from liquid phase to a gel phase. In this 2 ml insitu gel transferred to test tube and placed
into water bath then the temperature of water bath increased slowly and constantly. Gel was allowed to equilibrate for 5 minute at each setting, and then formulation was examined for gelation. When the meniscus would no longer move upon tilting to 90°, this is known as a gelation temperature [33], [34].

**Determination Of Mucoadhesive Strength:** Mucoadhesive strength is known as the force to detach the in situ gel formulation from nasal mucosal tissue, for determining the mucoadhesive strength we use modified special chemical balance. A small section of nasal mucosa of goat was cut & tied or fixed on 2 glass vial with the help of rubber band or thread and stored it at 37°C ±2°C for 10 minute and then 50mg of gel was placed on first vial and it placed below the height adjustable balance, while on another hand second vial was fixed in inverted position to the underside of the same balance after this height both vial were adjusted and come in intimate contact for 5 minute to ensure the contact between nasal mucosal tissue and the in situ gel formulation. Then weight was put off on the other side of balance, until vials got detached, it expressed as the strength or stress in dyne/cm² [35], [36], [37].

**Stress is calculated by the formula:**

\[ \text{Detachment Stress (dyne/cm}^2) = M \times G \div A \]

Where

- \( M \) = wt required for detachment of two vials in gm
- \( G \) = acceleration due to gravity
- \( A \) = Area of tissue exposed.

**Figure:**

Modified Balance, B Weights, C Glass Vial, E, F Membrane, G Height Adjustable Pan.

In vitro Diffusion Study of In situ Gel: Franz having capacity 2.4 diameter and 15 ml diffusion cell was used for in vitro diffusion study of in situ gel. Dialysis (.22µm pore size) or cellophane membrane (12000-18000 mol wt) with diffusion area .8cm² used. 60 ml of phosphate buffer (6.4- 6.6pH) was prepared and membrane was soaked with phosphate buffer (6.4- 6.6 pH), after this temperature was maintained at 37°C±0.5°C, after this phosphate buffer placed into the acceptor chamber and gel containing drug equivalent to 10 mg was placed in donor chamber, at predetermined time point, 1ml sample was withdrawn from acceptor chamber and replacing the sampled volume with same amount of phosphate buffer, for a period of 300 minute, after each sampling, the samples were suitably diluted and measured spectrophotometrically at specific wavelength of drug. The concentration of drug was determined with the help of previous calibration curve [38], [39].

**In vitro Permeation Study of In situ Gel:** To check permeation of drug and capacity of permeation enhancer which was added in formulation. Fresh nasal tissue section of goat obtains from slaughter house. Tissue was inserted in the diffusion cell. Gel containing drug equivalent to 10 mg was placed in donor chamber, at predetermined time point, 1ml sample was withdrawn from acceptor chamber and replacing the sampled volume with same amount of phosphate buffer, for a period of 300 minute, after each sampling, the sample were suitably diluted and measured spectrophotometrically at specific wavelength of drug [40].

**Permeability coefficient calculated from the slope of the graph:**

\[ P = \text{Slope} \times \text{Vd} \div s \]

\( Vd \) = volume of the donor solution
\( S \) = surface area of tissue
\( P \) = permeability coefficient.

D.S.C (Differential Scanning Calorimetry), X Ray Diffraction and FTIR (Fourier Transform Infra –Red Spectroscopy) Studies: used for drug and polymer interaction, compatibility and to check matrix formation [41].

**CONCLUSION**

Used of biodegradable, water soluble, thermo sensitive, pH sensitive polymer for the nasal in situ gel formulations can make them more acceptable and excellent drug delivery system. Exploitation of polymeric in situ gels for controlled release of various drugs, good stability and biocompatibility, bioavailability of drug characteristics makes the nasal in situ gel dosage forms very reliable. Nasal in situ gel enhanced the nasal residence time due to its viscosity and mucoadhesive strength. For optimum formulation can be achieved with better rheological properties, gelation time, gelation temperature, pH, mucoadhesive strength, and in vitro release and permeation studies.

**References:**


