Review on Recent Advances in In-Situ Gel: Drug Delivery System for Nasal and Various Routes

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***Abstract*: The study was conducted to explore in depth the in-situ gel nasal drug delivery system since these systems have higher systemic bioavailability via the nose route as compared to the oral route of administration. Many medications now have higher systemic absorption via the nasal route as compared to oral administration. The nose is also seen to be anappealing route for needle-free immunisation and systemic medication administration, particularly when quick absorption and action are required. Because of the high permeability of the nasal epithelium, fast drug absorption through this membrane, and avidity of first pass metabolism, nasal delivery is a viable alternative to oral or parenteral administration for several drugs. The study was conducted to explore in depth the in-situ gel nasal drug delivery system since these systems have higher systemic bioavailability via the nose route as compared to the oral route of administration. Many medications now have higher systemic absorption via the nasal route as compared to oral administration. The nose is also seen to be an appealing route for needle-free immunisation and systemic medication administration, particularly when quick absorption and action are required. Because of the high permeability of the nasal epithelium, fast drug absorption through this membrane, and avidity of first pass metabolism, nasal delivery is a viable alternative to oral or parenteral administration for several drugs.**

***Keywords*: In-situ gel, nasal mucosa, Bioavailability, novel dosage form, first pass metabolism.**

INTRODUCTION:

The most unremarkably used route of administration for general impact is oral administration. except for some drug the general impact wasn't in fascinating condition because of oral bioavailability and promoted for the search of simpler route for general delivery [1].Usually the bodily cavity is employed for the treatment of native diseases they're inflammation, migraine, cold, pain and nasal congestion. In recent years it's been tried that several medicine achieved higher general bioavailability through nasal route [2] .The various formulations utilized by nasal route square measure nasal gel, spray, powders, etc. Transmucosal route of drug delivery (i.e. the tissue layer lining of the nasal, rectal, vaginal, ocular, oral cavity) nasal tissue layer is that the major route of administration to attain quicker and better level of drug absorption[1] .This is because of the anatomy and physiology of nasal passage that's porous epithelial tissue membrane, giant extent, high total blood flow, the shunning of 1st pass metabolism and pronto accessibility[3][4] .In-situ could be a Latin term which suggests _In its original place or in position'. unaltered gel could be a variety of indefinite quantity type during which the medicinal drug is in resolution type before administration into the body, once administered it undergoes gelation to make a gel[5]. because of its accessibility, nasal drug administration is taken into account as another route for circulation rather than blood vessel administration[6] Nasal drug delivery conjointly provides how to the brain that circumvents the barrier as a result of the sense modality receptor cells square measure in-tuned with central system directly [7] .The nasal route is a horny not just for delivery of vaccines because of giant extent and low chemical action activity however conjointly it improves the patient compliance and reduce the assembly value compared to epithelial duct production[8]. Due to their high permeableness the nasal route show solely smaller relative molecular mass medicine the absorption are going tobe additional. for giant relative molecular mass medicine or deliquescent medicine show low bioavailability or no absorption because of the less pervious to the peptidase medicine within the nasal membrane therefore the medicine cleared quickly before reaching the blood stream that's the drug doesn't meet up with the tissue layer barrier [9] .Penetration enhancers like surfactants, gall salts and phospholipids will increase the drug penetration however in website of clinical use the toxicity check tried that the permeation enhancers has some limitation due their irreversible damage[10,11] .Even though the amount of challenges for the researchers to beat some disadvantages in typical nasal merchandise and to create effort for the new nasal formulation.

Gel

Gel is that the state that exists between solid and liquid section. The solid part contains a 3 dimensional network of inter-linked molecules that immobilizes the liquid section.

In-Situ Gel Delivery System

In situ gelation could be a method of gel formation at the positioning of action once the formulation has been applied at the positioning. Insitu gel development based mostly upon liquid resolution of drug formulation and reborn into semi-solid mucoadhesive key depot. It permits the drug should be delivered during a liquid type or resolution type. [12-13]

Advantages of In-Situ Gel Nasal Formulation

- Increased residence time of drug in nasal cavity.

- Decreased frequency of drug administration.
- Results in rapid absorption and onset of effect.
- Avoids degradation of drug in gastrointestinal tract resulting from acidic or enzymatic degradation.
- Low dose required.
- Minimized local and systemic side effects.
- Improved bio-ability of drug.
- Direct transport into systemic circulation and CNS, is possible.,
- Offers lower risk of overdose of CNS acting drug
- Improved patient compliance.[14-17]

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.
- Nasal in-situ gel should have long residence time.
- The nasal in-situ gel follows phase transition mechanism and to stand with the shear forces in the nasal cavity wall.[18]
- Advantages of nasal drug delivery
- Rapid drug absorption
- Non-invasive
- Easy administration
- Good bioavailability
- Improved patient compliance and convenience.
- Large surface area for drug absorption
- Rapid action
- Less side effects
- The nasal drug is used when the drug which are not suitable for oral route.
- Crosses blood brain barrier.
- First pass metabolism is avoided. [19]

Disadvantages for nasal drug delivery:

- Removal of drug is not possible in nasal cavity.
- Less number of drugs is given by nasal route.
- Nasal irritant drugs are not given through this route.
- Less than 25-200µl volume of drugs given by this route.
- Lower molecular weight drugs are only given by this route.
- Frequently use of this route causes mucosal damage.
- The drug absorption may cause allergic problems.
- The reached amount of drug may vary in different regions (brain, spinal cord). Profile of an _ideal‘ drug candidate fornasal delivery: [20]

An ideal nasal drug candidate should possess the following attributes:

- Appropriate aqueous solubility to provide the desired dose in a 25–150 ml volume of formulation administration pernostril.
- Appropriate nasal absorption properties.

- No nasal irritation from the drug.
- A suitable clinical rationale for nasal dosage forms, e.g. rapid onset of action.
- Low dose. Generally, below 25 mg per dose.
- No toxic nasal metabolites.
- No offensive odors/aroma associated with the drug.
- Suitable stability characteristics.

Anatomy and Physiology of Nose.

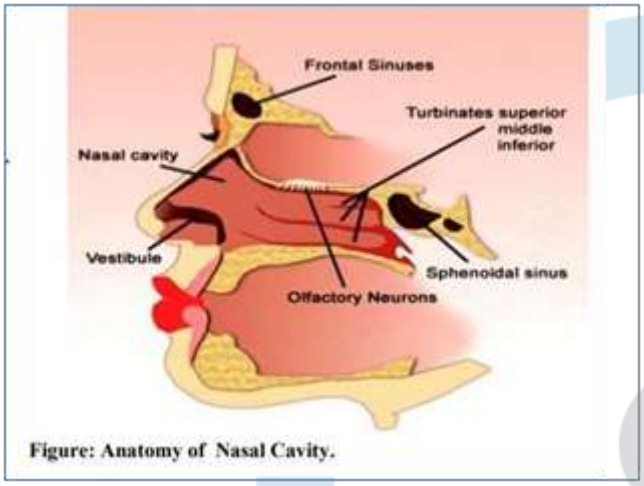

Figure: Anatomy of Nasal Cavity.

The nose is divided into two cavities by presence of septum between them and it extends posterior to the nasal pharynx. The surface area of nasal is about 150 cm2 and the volume of nasal cavity is approximately 15 ml. Nose has three regions they are vestibular, respiratory and olfactory .The most anterior part of the nasal cavity is vestibule; it opens through the nostril breathing and olfactory plays a major role of human nose in transportation of drugs to the brain. But for systemic drug delivery the respiratory region is important .The respiratory epithelium consists of basal cells, mucus containing goblet cells, ciliated columnarand non- ciliated columnar cells. These cells facilitate active transport processes such as exchange of water, ions between the cellsand cilia motility .The cilia are a hair like microvilli which is 300 in numbers. They provide large surface area for the drug absorption and the movement of cilia is like a wave and it helps to transport the particles to the pharynx for ingestion. Below the epithelium the blood vessels, nerves, serous glands, secretory glands are found. There is a presence of capillaries network whichis responsible for drug absorption. The epithelium covered by a mucus layer is renewed every 10 to 15 minutes. The pH of the mucus secretion ranges from 5.5 to 6.5 and for children it ranges from 5.0 to 6.7. The mucus layer entrapped the particles which are cleaned by the cilia and they cleared within 20 minutes.[21]

Principle involved in in-situ gelling:

The principle involved in in-situ gelling of nasal formulation is that the nasal fluid is absorbed by the nasal formulation after administration and forms gel in the nasal cavity. The formation of nasal gel avoids the foreign body sensation. The bioadhesive properties of the gels are used for maintaining contact between gel and mucosa. It acts as release controlling matrix and acts as sustained delivery system. Cilia present backwards help to remove the obstacle if there is any interference present in the propulsion phase. After the formation of gel, dissolution and mucociliary removal occurs. So there is no need to remove the dosage form after it has been depleted of drug. [22]

Blood Supply to Nasal Cavity:

Nasal vasculature is richly supplied with blood to fulfill the basic functions of the nasal cavity such as heating and humidification, olfaction, mucociliary clearance and immunological functions. Blood supply comes from branches of both the internal and external carotid artery including branches of the facial artery and maxillary artery.
The named arteries of the nose are,

•Sphenopalatine artery, a branch of maxillary artery.

•Anteriorethmoidal artery, a branch of ophthalmic artery.

Branches of the facial artery supplying the vestibule of the nasal cavity. The lamina propria in the nasal mucosa is rich in blood vessels. They differ from the vasculature in the tracheobronchial tree in three ways. First is venous sinusoid in the nose. Second is arteriovenous anastomosis in the nose. Third are the nasal vasculature shows cyclical changes of congestion giving rise to the nasal cycle. Porosity of the endothelial basement membrane has been described as a characteristic of nasal blood vessels. The capillaries just below the surface epithelium and surrounding the glands are well suited for rapid movement of fluid through the vascular wall.

[23]

In-situ gel formulation:

There are many mechanisms for formulating in-situ gels are discussed as follows:

Stimuli response in situ gelling system:

Thermally triggered system: Under this mechanism, in-situ gel is formed by using polymer that changes from solution to gel by changing physiological temperature of the body. When the temperature increases the biomaterials used to form in- situ gel leads to transition from sol to gel and produce in- situ gel. pH triggered systems: In-situ gel is also prepared by changing pH of the gel based on physiological stimuli and here pH sensitive polymers were used. If the polymer contains weakly acidic groups the swelling of hydro gel increases as the external pH increasesbut it decreases if the polymer contains weakly basic groups.
Osmotically induced in situ gelling system: In this method, gelling of the instilled solution is triggered by change in the ionic strength. The rate of gelation is depends on the osmotic gradient across the surface of the gel. The aqueous polymer solution forms a clear gel in the presence as the mono or divalent cations. The polymers are induced gelation are gellan gum, hyaluronic acid and alginates etc.

Chemically induced in situ gel system:

Ionic cross linking: Some ion sensitive to polysaccharides such as carrageenan, Gellan gum, pectin, sodium alginate undergo phase transition in the presence of various ions such as K+ , Ca2+, Mg2+, Na+ . These polysaccharides fall into the class of ion- sensitive ones
Enzymatic cross linking In situ: formation catalyzed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. For example, an enzymatic process operates efficiently under physiological conditions without need for potentially harmful chemicals such as monomers and initiators.
Photo-polymerization: In situ photo-polymerization has been used in biomedical applications for over more than decade. A solution of monomers or reactive macromere and initiator can be injected into a tissues site and the application of electromagneticradiation used to form gel. Acrylate or similar polymerizable functional groups are typically used as the polymerizable groups on theindividual monomers and macromere because they rapidly undergo photo polymerization in the presence of suitable photo initiator. Photopolymerizable 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 prolonged period of time.[24,25]

Mechanism of nasal drug delivery:

The first step involved in the absorption of drug in nasal cavity is crossing the mucus membrane, because small, uncharged particles were passing through the mucus easily. But charged large molecule does not pass easily through the mucus membrane. The protein present in the mucus layer is Mucin, which binds with the solutes that delays the diffusion and structural changes in the mucus layer are also possible because of environmental changes (i.e. pH, temperature, etc.) [26].During the drug passage in mucus there are several mechanisms for absorption n across the mucosa thus includes simple diffusion, Para cellular transport between cell and transcytosis by vesicle carriers. The restrictions to the drug absorption are essential for metabolism before reaching the systemic circulation and limited residence time in the cavity. Several mechanisms have been proposed but the following two mechanisms have been considered predominantly. The first mechanism is known as paracellular route which involves an aqueous route for transportation. This is slow and passive route. There is log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The drugs with a molecular weight greater than 1000 Daltons are having poor bioavailability[27] .The second mechanism is known as trans cellular route which involves transportation throughthe lipoid route and it is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. The drugs cross the cell membrane by active transport through carrier mediated or opening of tight junctions [28]

Factors Affecting Nasal Drug Absorption:

Factors influencing absorption are related to nasal physiology, physicochemical characteristics of drugs and formulation aspects.

Biological Factors:

- Structural features
- Biochemical changes
- Physiological factors
- Blood flow
- Nasal secretions
- pH of the nasal cavity
- Mucociliary clearance and ciliary beat frequency
- Pathological conditions
- Environmental factors

- Temperature
- Humidity

Physicochemical Properties of Drugs:

- Molecular weight
- Size
- Solubility
- Lipophilicity
- pKa and Partition coefficient

Physicochemical Properties of Formulation:

- Dosage form
- Viscosity
- pH and mucosal irritancy
- Device Related Factors:
- Particle size of the droplet/powder
- Size and pattern of disposion.[29,30]

Evaluation of In situ Gel:

In situ gels may be evaluated and characterized for the following parameters,

Clarity:

The clarity of formulated solution was determined by visual inspection under black and white background.

Texture Analysis:

The firmness, consistency and cohesiveness of formulation are assessed using texture analyzer which mainly indicates the syringe ability of sol so the formulation can be easily administered in vivo.

Gelation Point:

It is temperature at which the liquid phase makes a transition to gel. A gelation temperature range suitable for thermoreversible nasal gel would be 30 to 36°C. Gelation point was considered as the temperature where formulations would not flow when test tubes were tilted to 90° angle as the temperature was gradually increased.

pH of the Gels:

The pH of each batch was measured using pH meter which was calibrated using buffers of pH 4 and pH 8 before the measurements.

Content Uniformity:

Weighed amount of the formulation was dissolved in medium and after suitable dilution the absorbance was measured using UV/visible spectrophotometer. The amount of the drug present in the formulation was calculated by measuring the absorbance of a standard solution of known concentration of drug prepared in distilled water.

Rheological Studies:

Viscosity of the prepared formulations was measured by using Brookfield Viscometer. The gel under study was placed in the small sample holder and the spindle was lowered perpendicularly into it. The spindle was rotated at varying speeds and the suitable speed was selected.

Gel Strength:

This parameter can be evaluated using a Rheometer. Depending on the mechanism of the gelling of gelling agent used, a specified amount of gel is prepared in a beaker from the sol form. This gel containing beaker is raised at a certain rate so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface.

Measurement of Gel Strength:

Formulated gels were placed in the test tubes and gelled in a thermostat at 37°C. The apparatus for measuring gel strength was then placed onto the in situ gel. The time taken by the apparatus to sink to a depth of 5 cm through the prepared gel was measured for each formulation. Weights that detached the two vials using the following equation, Detachment stress (dynes /cm2) = mg /A where m is the weight added to balance in grams, g is the acceleration due to gravity taken as 980 cm/sec2 , A is the area of the tissue exposed and is equal to $\pi r2$ (r is the radius of the circular hole in the aluminium cap).

In vitro Nasal Diffusion Cell:

The nasal diffusion cell was fabricated in glass. Drug release from gel was tested with nasal diffusion cell using dialysis membrane (mol.wt.12, 000-14,000 kDa) with permeation area of 0.785 cm2 .20ml of diffusion medium was added to the acceptorchamber. Gel containing drug equivalent to its dose was placed in donor compartment. At predetermined time points, 1ml sample was withdrawn from the acceptor compartment replacing the sampled volume with diffusion medium after each sampling. The samples were suitably diluted and measured spectrophotometrically. The concentration of drug was determined from a previously constructed calibration curve.

Fourier Transform Infrared Spectroscopy and Thermal Analysis:

During gelation process the nature of interacting forces can be evaluated using this technique by employing KBr pellet method. Thermogravimetric analysis can be conducted for in situ forming polymeric systems to quantitate the percentage of water in hydrogel. DSC is used to observe if there are any changes in thermograms as compared with the pure ingredients used thus indicating the interactions. [31,32,33]

Recent Advances in the Development of In Situ Gelling Drug Delivery Systems for Non-Parenteral Administration Routes:

1. Ocular Route

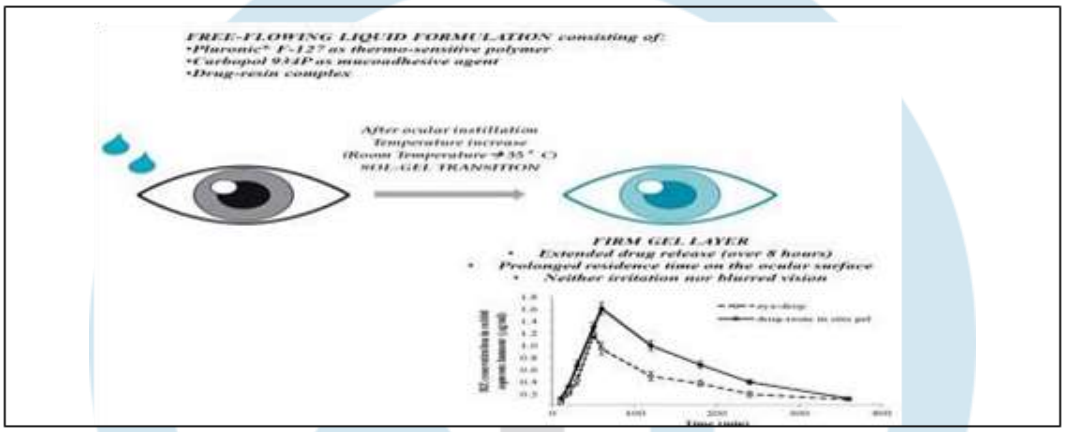

Figure: Drug–resin thermo-sensitive in situ gelling system for ophthalmic use: After instillation, an increase in temperature is responsible for the transition of the polymeric liquid formulation loaded with brinzolamide (BZ) into a mucoadhesive gel layer on the ocular surface. The graph represents the concentration–time profiles of BZ in the rabbit aqueous humor: BZ amount in the aqueous humor is significantly higher when BZ is instilled as drug–resin in situ gel than as eye drops. Such results demonstrate that the drug–resin in situ gel is responsible for a higher BZ absorption into the eye: the formation of a gel in the conjunctival cul- de-sac guarantees a prolonged residence time in the pre-corneal area and provides sustained BZ release[34-42]

2. Nasal route:

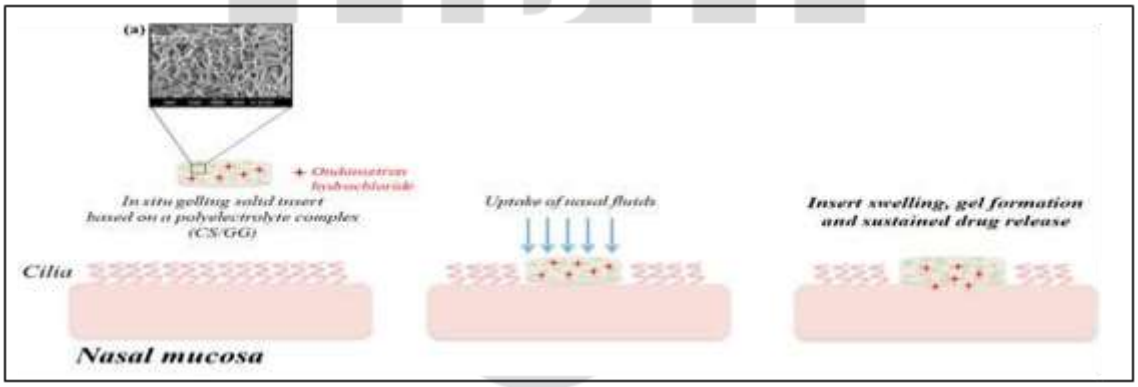

Figure: In situ gelation of a solid nasal insert loaded with ondansetron hydrochloride, prepared by freeze-drying of an aqueous polymeric solution consisting of chitosan (CS) and gellan gum (GG); (a) scanning electron micrograph of the freeze-dried insert (Adapted from [56], ELSEVIER, 2016). Upon contact with the nasal mucosa, the porous structure of the insert allows rapid hydration of the cross-linked polymeric matrix and the consequent formation of a gel that guarantees a controlled drug release (Adapted with permission from [47], ELSEVIER, 2016). [43-57]

3. Buccal Route

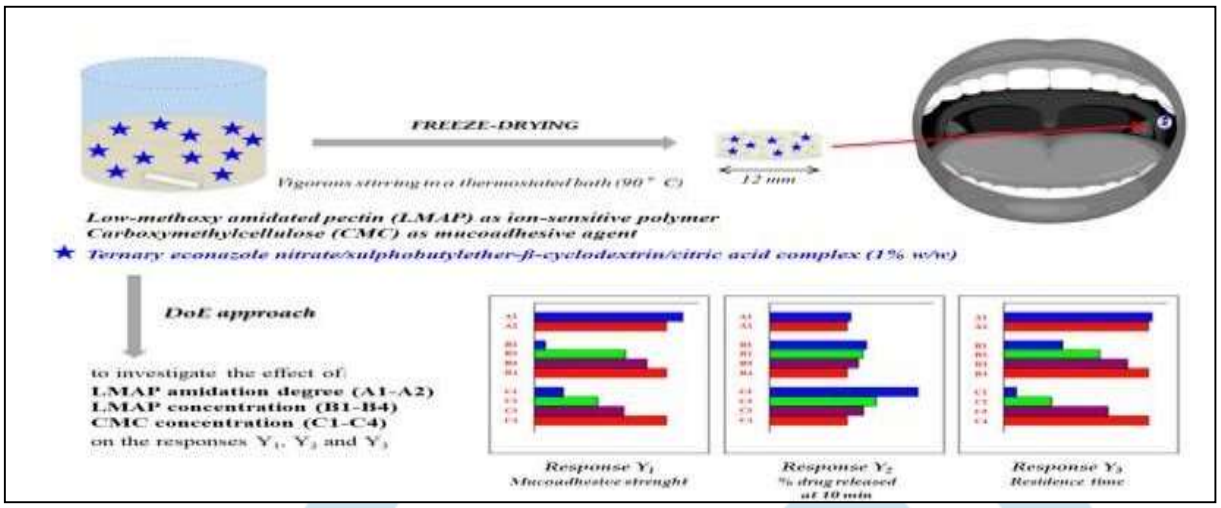

Figure: Schematic representation of the preparation method and the application of lyophilized wafers for the local delivery of econazole nitrate in the treatment of oral candidiasis: Low-methyl-ester-amidated pectin (LMAP) is able to gel upon contact with saliva ions, while carboxymethylcellulose (CMC) ensures mucoadhesive properties. In the attempt to optimize the formulation, a DoE (Design of Experiments) approach was used to individuate the factors whose variation could influence the wafer performance in terms of mucoadhesive strength (response Y1), % drug released at 10 min (response Y2) and in situ residence time (response Y3). In a screening design, the authors selected LMAP amidation degree, LMAP and CMC concentrations as the critical independent variables. The variation of LMAP amidation degree (A1–A2) did not influence any of the considered response, while an increase in both LMAP (B1–B4) and CMC (C1–C4) concentrations significantly increased the responses Y1 and Y3. A central composite design was then considered with the aim of optimizing the formulation (Adapted with permission from [63], ELSEVIER,2015. [57-63]

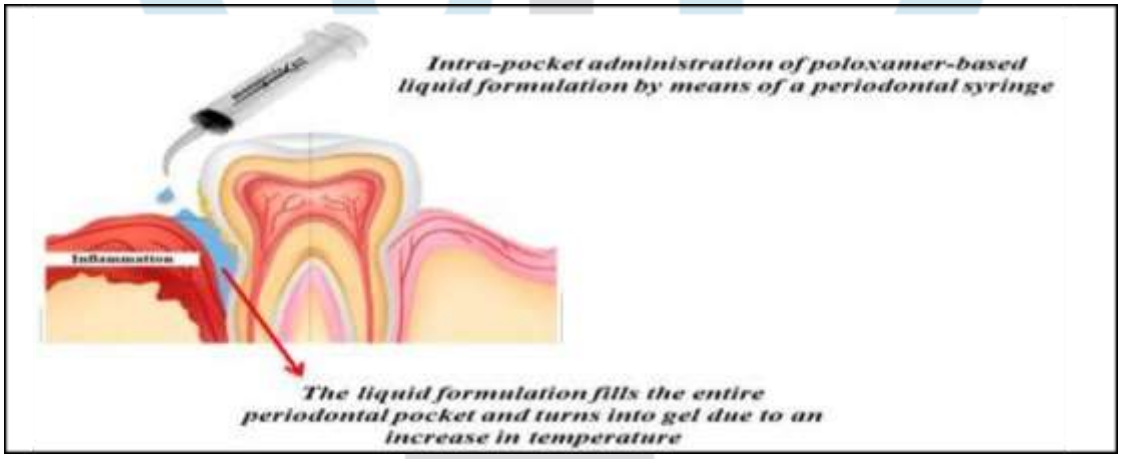

Fig: Rationale for the use of thermo-sensitive in situ gelling system for topical intra-pocket delivery of anti-inflammatory and/or antimicrobial compounds in the treatment of periodontitis.[62]

4. Vaginal Route

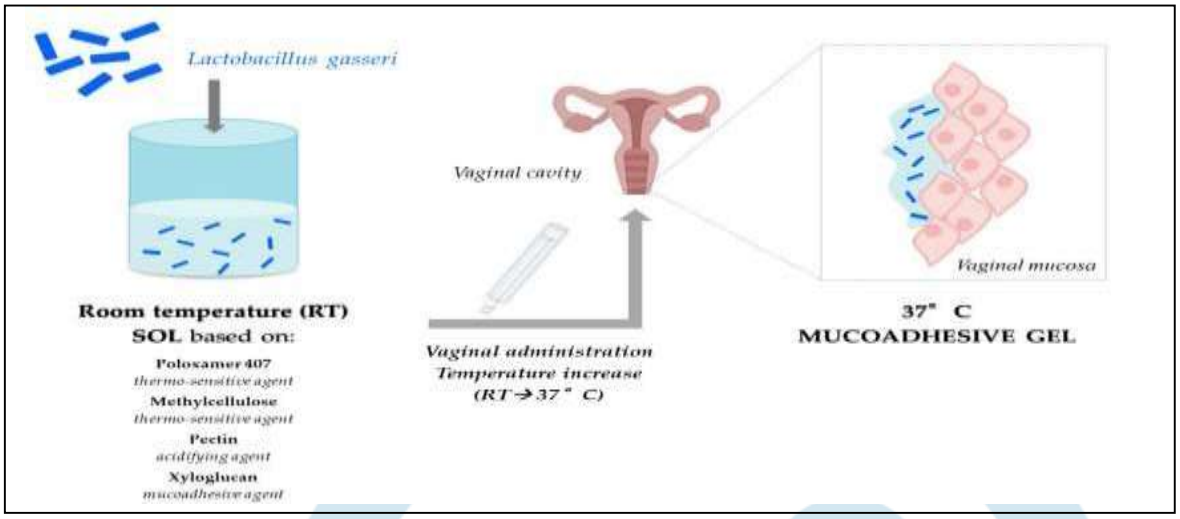

Figure. Rationale for the development of a vaginal formulation intended for the treatment of candidosis recurrences: An increase in temperature (from room to body temperature) is responsible for the transition of a polymeric solution loaded with Lactobacillus gasseri into a mucoadhesive gel after vaginal administration [64-73]

5. Intravesical Route

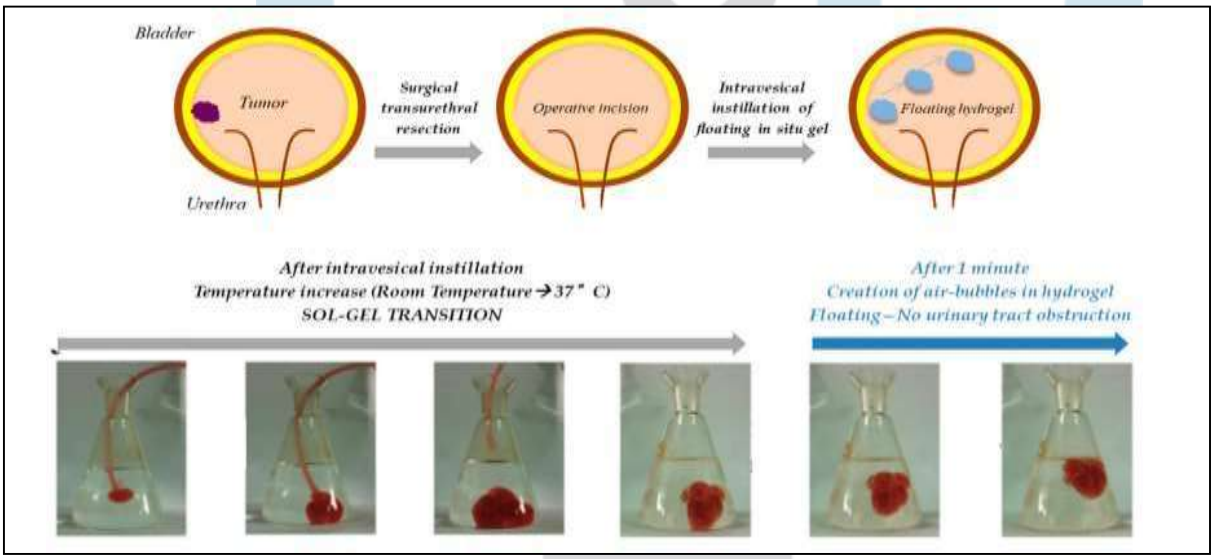

Figure: Schematic representation of the management procedure for the treatment of bladder cancer; it involves the surgical transurethral resection, followed by the intravesical instillation of chemotherapeutic-loaded floating in situ gel, using P407 as thermo-reversible agent. The strategy proposed by Lin and co-workers aimed to avoid the obstruction of the urinary tract (Adapted with permission from [82] [74-82]

Conclusion:

Although nasal medication delivery systems provide a variety of formulations such as solution, spray, and powder, nasal gel preparations have proven to be more successful in terms of enhanced residence duration, higher bioavailability, and rapid beginning of action. According to the table, the impact of the polymer employed in formulation offers adequate gelation, but drug release decreases with greater polymer content and drug loading. The most often utilised permeation enhancer in nasal gel preparation is beta cyclodextrin. Additives used in nasal gel preparation are also very important because they provide the safety of formulations by preventing microbial attack with preservatives, increasing solubility with solubilizing agents, preventing dryness with humectants, reducing the risk of oxidation with antioxidants, and improving the taste.

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