International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 259-263 www.ijprajournal.com ISSN: 2249-7781

A Brief Review On: In Situ Polymeric Approaches For Intra Nasal Drug Delivery

Nalina C[1], Arun Chandran[2], Ganesh N S[3], Vineeth Chandy[4].
Dept. of pharmaceutics, T. John college of pharmacy, Bangalore-560083.

Date Of Submission: 20-03-2021 Date Of Acceptance: 05-04-2021

ABSTRACT: Nasal route isanalternative tooralandparentral route, because ofcertainlimitations andadvantagesof nasal route such as bypass thefirstpass metabolism, bypass the stomach enzymatic action, bypass the BBB, large surface area, rich blood capillaries, offers both local and systemic effects. The system exists in liquid form at room temperature 25^0C and on exposure to biological stimuli (temperature, pH, and presence of ions) covert as gel called as phase transition (sol-gel conversion). The in-situ gel under room temperature follows Newtonian law but after conversion to sol-gel follows non-newtonian. There are different triggering polymeric approaches with examples which is responsible for conversion of sol-gel. Themain triggering approaches are temperature induced, pH induced and ionic triggering system. Applications of in-situ nasal gel are high permeability, controlled and extended drug delivery system, increased residential time, onset of action, brain targeting for neuro degenerative diseases and improved patient compliance over other dosage forms.

KEYWORDS: Nasal drug delivery, in-situ gel, polymer triggering, etc.

I. INTRODUCTION

Traditionally oral drug delivery is the most desirable route for the drug administration. But with the severity of patient where can parenteral route is chosen which is invasive. To this problem novel drug delivery system can be used such astransmucosal route of drug delivery(i.e. the mucosal lining of the nasal,rectal, vaginal, ocular, oral cavity).[1]

Usually, the treatment for local diseases, such as rhinitis, sinusitis and nasal congestion has not been administered through the nasal mucosal route. However, over the last few decades, intranasal (IN) delivery has been got much more attention as a promising route of drug administration for systemic and local action. Currently, it is being recognized for the delivery of therapeutic drug moiety including biopharmaceuticals, and for topical nasal treatments such as antihistamines and corticosteroids, and also for systemic delivery of analgesics, sedatives, hormones, vaccines, and cardiovascular drugs by means of the nasal mucosa. This is because of the anatomy and physiology of the nasal passage, such as the highly vascularized epithelium, ready accessibility, large surface area, permeable endothelial membrane, high total blood flow, and the prevention of first-pass metabolism. INadministration is a "needleless" and non-invasive method of drug delivery through the nose to the brain, and hence an alternative for systemic drug delivery. Therapy through IN administration has been an is a form of treatment in the ayurvedic system of asian medicine, and is called as "Nasya Karma". Drug delivery through the nose is uncomplicated and convenient, and can include the delivery of solutions, suspensions, powders, in situ gel, and ointments.[2]

Here, the review study is on insitu nasal gel. Development of in situnasal gel has got considerable results over the past few years. In this system formulation will be in liquid form at room temperature but it becomes gel form when comes in contact with biological stimuli such as nasal temperature, change in pH and presence of ions. The in-situ gel formation is aided by polymers i.e. both natural and synthetic polymers. It forms a very strong gel. it can be easily applied in liquid form to the site of administration, so it swells up to form a strong gel which prolong the residential time of dosage form.[3]

Advantages:[4,5]

1. Reduced frequency of administration.
2. Offers both local and systemic action
3. Improved patient compliance and comfort.
4. It can administer to unconscious patients
5. It offers non-invasivness and self-administration.
6. Extend drug delivery and sustain drug delivery can be attained
7. It prolongs the residential time.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 259-263 www.ijprajournal.com ISSN: 2249-7781

8. Better bioavailability and minimal side effects
9. Can achieve the targeted drug delivery.

Disadvantages:[4,5]

1. It is too susceptible to stability problems due to chemical degradation.
2. It requires high level of fluid.

Properties of nasal in-situ gel:[6]

1. It should offer a long residence time.
2. It should be low viscous
3. Free-flowing provides for reproducible administration to the nasal cavity.
4. The nasal in-situ gel follows the phase transition mechanism and shear forces in nasal cavity wall

Approaches of in-situ gelling system:[7]

Different approaches for an in-situ gelling system,

A) Stimuli Responsive In-situ gelling system
1. Temperature induced in-situ gelling system
2. pH induced in-situ gelling system

B) Osmotically induced In-situ gelling system

C) Chemically induced In-situ gelling system
1. Ionic cross linking.
2. Enzymatic cross linking.
3. Photo polymerization.

D) In-situ formation based on the physical mechanism.

A. Stimuli responsive In-situ gelling system[4,7,8]

Physical or chemical modifications in response to external modification in the environmental conditions.

1. Temperature induced in-situ gel system:

Temperature is the most largely used stimulus in environmentally responsive polymer systems. The modification intemperature is not only easy to modulate, but also easy to applicable both in vivo and in vitro. In this system, gelation is created due to body temperature and there is no requirement of external heat. These gel systems are liquid at room temperature i.e.20-25^{0}C and leads to gelling when comes in contact with body fluids (35-37^{0}C), due to an elevation in temperature (fig.2).

There are three types of temperature induced gelling systems. Namely,

- Negatively thermo sensitive induced gel system

Eg: Poly (N-isopropylacrylamide)

- Positively thermo sensitive induced gel system

Eg: polyacrylic acid

- Thermo reversible induced gel system

Eg: Poloxamer, Tetronics.

- Thermo sensitive or temperature sensitive in-situ gel leads to sol-gel phase transition at a critical temperature, particularly at the lower critical solution temperature (LCST) or upper critical solution temperature (UCST). LCST polymers creates a hydrophilic-to-hydrophobic transition with elevated temperature. UCST polymers creates a hydrophobic-to-hydrophilic transition with elevated temperature
- LCST polymer Eg: poly (N-isopropyl acrylamide), poly (N, N-dimethyl acrylamide), poly (vinyl ether), poly (N-vinylalkylamide), polyphosphazene derivatives, and poly (ethylene oxide)-b-poly (propylene oxide).
- UCST polymer Eg: Polyacrylic acid

2. pH induced in-situgel system:[4,7,9]

The pH is one more important body environment-sensitive factor for drug delivery, because the modification in pH occurs at particular sites or pathologic body conditions, such as stomach, intestine, endosomes, vagina, blood vessels, lysosomes, and tumour extracellular sites. Polymers of this class involves an acidic or basic group that either accept or release protons when they are introduced to different environmental pH.Hence, it's called as pH sensitive polymers.Polyelectrolytes are also called as polymers with a large number of ionizable group. The pH is the main factor, which can be conducted through pH-responsive materials. Gelling of the solution is marked by a modification in pH. At pH 4.4 the formulation is free from it's free flowing solution that leads to coagulation when the pH is increased by the body fluid to pH 7.4. The polymers that allows pH-induced gelation are cellulose and its derivatives polyvinyl acetate, polyethylene glycol. There is a requirement of external pH raising, as the external pH raises, leads to swelling of hydrogel raises in case of weakly acidic groups, but reduces when polymer contains weakly (basic) groups.

Eg: Anionic pH-sensitive polymers are:

- Poly (acrylic acid), (Carbopol),
- Polyvinyl acetal diethylamino acetate solution leads to hydrogel at a neutral pH case at pH 4, with a low viscosity.
- Polymethacrylic acid, Polyethylene glycol, Cellulose acetate phthalate latex, Pseudolatexs, etc

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 259-263 www.ijprajournal.com ISSN: 2249-7781

A) Osmotically induced In-situ gelling system [4,7,10]

In this system, gelling of the solution is induced by modification in ionic strength. Here, the gelling system depends on the osmotic gradient across the surface of the gel. The aqueous solution of polymer leads to a clear solution that form a clear gel in the presence of cation such as mono or divalent cations. The polymers of gellan gum, and alginate1 allows for osmotically induced gelation.

B) **Chemically induced In-situ gelling system:**[4,7]

In this system, the gel is formed by chemical reaction. There are three different types of chemical reaction that forms in-situ gel. They are:

- Ionic cross linking
- Enzymatic cross-linking
- Photo polymerization

1. **Ionic cross linking:** Ionic sensitive polymers such as carrageenan, gellan gum, pectin, sodium alginate leads to phase changes with the presence of different kind off ions mainly like K^+, Ca^{2+}, Na^+ ions. These polymers are classified as ion sensitive polymer materials. For example, Alginic acid leads to phase transition in the presence of divalent cations (Ca^{2+}) due to interaction with a guluronic acid blocks the alginic chains.[11]
2. **Enzymatic cross-linking:** In-situ gel formation catalysed by natural enzymes has not been studied widely but this kind off system has got some uses over other polymer approaches.[12]

For example: An enzymatic action shows effectively under physiologic conditions without the harmful chemicals such as monomers and initiators.

3. **Photo polymerization:** Photo-polymerization is mainly categorized for in-situ formation of biomaterial. A solution of monomers or reactive macromers and initiators will be injected to a tissue site and with the use of electromagnetic radiation the gel is formed. The polymers such as Acrylate and or similar monomers and macromers, they rapidly cause for photo-polymerization in the presence of suitable photo-initiators. Mostly long wavelength ultraviolet and visible wavelength are used. Short wavelength ultraviolet is not used due to its limited penetration to tissues and biologically harmful. A ketone, like 2,2 dimethoxy-2-phenyl-acetophenone is categorised as the initiator for ultraviolet photo-polymerisation.Camphorqinone and ethyl eosin initiators are categorised for visible light system.[4,7]

C) In-situ formation based on the physical mechanism: [7,12,13]

There are two different types of mechanisms, namely.

- Swelling
- Diffusion

1. **Swelling:**In-situ gel formation also arises when water absorbed by the material from the surrounding environment condition and expands to give desired space. The materials like myverol 18-19 (glycerol monooleate), that involves polar lipid which swells in water to form lyotropic liquid crystalline phase structures. It has got some bioadhesive properties and will be degraded in vivo by enzymatic process.
2. **Diffusion:**This method allows for diffusion of solvent from polymer solution into surrounding tissue and that achieves in precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been studied to be useful solvent for this kind off system.

Polymers used for In-situ gelling system:

A) Polymer categorised for pH-sensitive In-situ gelling system: [4,14,15]

a) Carbopol:

Carbopol polymers have got magnificent water sorption characteristic. Carbopol polymer will be swelled in water up to 1000 times by its original volume and 10 times to its diameter that leads to gel formation when they experience to pH environment off about 4.0-6.0 which is caused by $pK_a$of polymers i.e. 6.0 0.5. Carbopol polymers are high relative molecular weight, it is a cross-linked polyacrylic acid derivatives and have got mucoadhesive

property. When cellulose added then there is a decrease in polymer concentration and improvement in gelling property. Carbopol 934 and Carbopol 981 both are mainly categorised as gelling agents. The mucoadhesive property is caused by electrostatic interaction or hydrophobic interaction, hydrogen bonding. Its considered as an acidic molecule. The formation of coil caused by dissociation of carboxylic group of molecules, when Carbopol polymers are dispersed in water. As

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 259-263 www.ijprajournal.com ISSN: 2249-7781

they are pH-sensitive polymers, an elevation in the pH of the solution achieves in swelling of the polymers. The gelling effect is initialised by two stage, solution was neutralised by added sodium hydroxide.

B) Polymer categorised for temperature-sensitive In-situ gelling system: [16,17,18,19]

Poloxamer:

Poloxamers are water-soluble tri-block copolymer which involves two polyethylene oxide and polypropylene oxide core in an ABA configuration. Poloxamer is also called as Pluronic. Poloxamer have got excellent thermal mounting property and increases the residence time of the drug. Poloxamer has got two action, gelling agent and solubilising agent. Poloxamer provides colorless and transparent gel. Poloxamers are available in different molecular weights, which is depending on the ratio and distribution of hydrophilic and hydrophobic chain, that gives different gelling properties. It involves central polypropylene oxide surrounded by polyethylene oxide. At room temperature (25^0C), it performs like a viscous liquid and there is a sol-gel phase transition which leads to a transparent gel that caused by increased temperature about 37^0C. It gives a small micellarsubunit in solution and there is a increase in temperature, achieves in increased viscosity that results in swelling to make large micellar cross-linked network at a lower temperature.

C) **Polymer categorised for ion-sensitive In-situ gelling system:[20]**

Gellangum:

Gellangum polymer is considered as an anionic deacetylated exocellular polysaccharide which was obtained by pseudomonas elodea with a tetra saccharide repeating unit of one α-L rhamnose, one β-D-glucuronic acid, and two β-D-glucuronic acid residues. Gellan gum have got properties of both temperature-dependent and cation induced. The gelation action was initiated by the formation of double-helical junction zones and follow-up by the aggregation of the double-helical segments to give a three-dimensional network by complexation with cation and hydrogen bonding with water.

Applications of In-situ nasal gel over other formulations:

1. Montelukast sodium was formulated as in-situ nasal gel for effective asthma treatment over nasal spray formulation in which in-situ nasal formulation offered and achieved for controlled drug delivery.[21]
2. Thermo-reversible in-situ nasal gel of Phenylephrine HCLfor allergic rhinitiswas developed over nasal drop or spray formulation, where thermo-reversible in-situ nasal gel will result in increased residential, contact time of dosage form time and prolong the action for good therapeutic action.[22]
3. Thermo-reversible in-situ nasal gel of Naratriptan HCL for acute migraine treatment was developed over oral dosage forms in which thermo-reversible in-situ nasal gel provides wide range of advantages like rapid on set of action, can achieve targeted drug delivery, bypass first pass metabolism, high surface area provides high drug absorption and better bioavailability.[23]
4. Thermo-reversible in-situ nasal gel of Geniposide for neuro-degenerative diseases was developed over other dosage forms in which thermo-reversible in-situ gel achieved as targeted drug delivery, brain is targeted through nasal mucosa where formulation bypass the BBB and improved bioavailability. Here in-situ formulation provides both local and systemic action.[19]

II. CONCLUSION:

The present review concluded that 'In-situ nasal gel' system emerged as one of the novel polymeric approach for drug delivery. The nasal route and in-situ system advantages explored like improved drug delivery, non-invasiveness, bypass the first pass metabolism, offered for both local and systemic action, nasal route also bypass the BBB and improved patient compliance. Briefed about properties of in-situ nasal gel. Exploration of different triggering polymeric approaches with examples. Briefing of application of in-situ nasal gel over other formulations.

REFERENCES:

[1]. R. P. Patel, M. J. Patel, and A. Patel An overview of resealed erythrocytesdrug deliver: a review J of pharmRes. 2009;2(6):1008-12.

[2]. Singh Devendra, Kumar Manish, Singh Talever, L. R. Singh, Singh Dashrath. Resealed Erythrocytes as a Carrier for Drug Targeting: a review. Inter J of Pharma and Bio Archi. 2011;2(5):1357-73.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 2 Mar-Apr 2021, pp: 259-263 www.ijprajournal.com ISSN: 2249-7781

[3]. Nisha Patel, Gajanan Shinde and Rajesh KS. Ophthalmic In situ gel, A genesis journal Pharmagene., 2014; 2(4): 29-33.
[4]. SnehalNikode, Gauri Dixit, and Kanchan Upadhya. In-situ gel applicationa and uses of polymers, WJPPS., 2016;5(7):1-6.
[5]. Jothi M, Harikumar SL and Geeta Aggarwal, In-situ ophthalmic gels for the treatment of eye diseases, International Journal of Pharmaceutical Sciences and Research, 2012; 3: 1891-1904.
[6]. Rajas NJ, Kavitha K, Gounder T, Mani T, In-Situ ophthalmic gels a developing trend, Int J Pharm Sci Rev and Res, 2011; 7: 8-14.
[7]. Sabale Anjali, Kulkarni Abijeet, Sabale Ajay, Nasal in-situ gel novel approach for nasal drug delivery, JDDT, 2020; 10(2):5-8.
[8]. N TN, R DM. An Overview on In-Situ Nasal Gel for Drug Delivery. 2019;11(7):695124.
[9]. Chand P, Gnanarajan G, Kothiyal P. In situ gel : A Review. Indian J Pharm Biol Res (IJPBR). 2016;4(2):11–9.
[10]. J.U.Kute, A. B. Darekar RBS. in Situ Gel-Novel Approach for Nasal Delivery. World J Pharm Pharm Sci. 2014; 3(i):187–203.
[11]. Qiu Y, Park K, Environment-sensitive hydrogels for drug Delivery. Adv Drug Deliv Rev., 2001; 53: 321-39.
[12]. Kaur P, Garg T, Rath G, Goyal AK. In situ nasal gel drug delivery: A novel approach for brain targeting through the mucosal membrane. Artif Cells, Nanomedicine Biotechnol. 2016; 44(4):1167–76.
[13]. Prasanth V V, Grace D, Parambi T, Vinod B, Mathew ST, Sheri PS. in-Situ Nasal Gels – an Update. 2016; 5(11):591–612.
[14]. Davies N.M., Farr S.J., Hadgraft J., Kellaway L.W. Evaluation of mucoadhesive polymers in ocular drug delivery. I. Viscous solutions, Pharm. Res., 1991; 8(8):1039–1043.
[15]. Ban MM, Chakote VR, Dhembre GN, Rajguru JR, Joshi DA. inSitu Gel for Nasal Drug Delivery Original Research Article inSitu Gel for Nasal Drug Delivery. 2018; (March).
[16]. Calfrs J, Edsman K, Peterson R. Rheological evaluation of Poloxamer as an in-situ gel for ophthalmic use. Eur J Pharm Sci., 2000; 6: 105.
[17]. Calonge M, The treatment of dry eye, SurvOphthalmol, 2011; 45: 227-239.
[18]. Shinde J V, Mali KK, Dias RJ, Havaldar VD, Mahajan NS. Insitu Mucoadhesive Nasal Gels of Metoclopramide Hydrochloride :Preformulation and Formulation Studies. J Pharm Res. 2008; 1(1):88–96.
[19]. Wang Y, Jiang S, Wang H, Bie H. A mucoadhesive, thermoreversible in situ nasal gel of geniposide for neurodegenerative diseases. PLoS One. 2017; 12(12):1–17
[20]. Salunke SR, Patil SB. Ion activated in situ gel of gellan gum containing salbutamol sulphate for nasal administration. Int JBiolMacromol [Internet]. 2016; 87(February):41–7. Available from: http://dx.doi.org/10.1016/j.ijbiomac.2016.02.044
[21]. SumithDurgapal, Mahendra Rana, Sayantan Mukhopadhyay, Amita Joshi Rana, Laxmi Goswami, Sumit Joshi. Formulation and evalution of in-situ nasal gel of montelukast sodium for effective treatment of asthma. Int J of Pharm Sci and Research. 2017; 11(10): 1-5.
[22]. ephrine HCL for allergic rhinitis. Am J PharmTech Res. 2016; 6(3): 1-5.
[23]. Santosh ShelkePankaj Verma, Neha Prashar, Vikash Kumar, Hema Chaudhary. Nasal in-situ gel of Phenyl, Sadhana Shahi, Sunil S. Jalalpure, Dinesh Dhamecha, Shengule. Formulation and evaluation of thermoreversible mucoadhesive in-situ gel for intranasal delivery of naratriptan HCL. JDDST. 2015; 238-244.