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Review Article

A REVIEW ON IN SITU GEL

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ABSTRACT

The current review on in situ gel was to complete the recent literature with special focus on *in situ* gelling system to increase the residence time of drug at the target site. This study has been sparked by the advantages shown by *in situ* forming polymeric delivery system such as ease of administration and reduced frequency of administration. The *in situ* gel forming polymeric formulations offer several advantages like sustained and prolonged action in comparison to conventional drug delivery system. There are various polymers which undergo in situ gel forming and potentially used for various routes of drug administration.

INTRODUCTION

Nasal Drug Delivery System

Intranasal delivery mainly offers potentially an alternative viable for various drug deliveries. It is suitable for the local and systemic delivery of diverse therapeutic compounds. Hence there have been many investigations involving the nasal cavity as a feasible site for the administration of many therapeutic agents. It is effective in the treatment of local, systemic and central nervous system sites.

- Local: The intranasal administration of medicines is the natural choice for the treatment of topical nasal disorder. In these cases, the intranasal route is the primary option for drug delivery because it allows a rapid symptom relief with fewer side effects.
- Systemic: The intranasal administration is an effective way to systemically deliver drugs as an alternative to oral and intravascular routes. Consequently, by nasal formulations, the number of drugs administered intended to achieve systemic effects has widely increased.[1]

Advantages of nasal drug delivery system

1. Hepatic first pass metabolism is avoided.
2. Rapid drug absorption and quick onset of action can be achieved.
3. The bioavailability of larger drug molecules can be improved by means of absorption enhancer or other approach.
4. The nasal bioavailability for smaller drug molecules is good.
5. Drugs possessing poor stability in G.I.T fluids are given by nasal route.[2]

Disadvantages of nasal drug delivery system

1. Nasal administration is primarily suitable only for potent drugs.
2. Drugs for continuous and frequent administration may be less suitable because of harmful long-term effects.
3. Nasal administration has also been associated with a high variability in the amount of drug absorbed.
4. Relatively inconvenient to patients when compared to oral delivery systems since there is a possibility of nasal irritational nasal cavity provides smaller absorption surface area when compared to GIT.[3]

Ideal drug candidate for nasal drug delivery

- The drug should not produce any irritation to the nasal mucosa.
- The drug should not cause any side effect.
- The drug should not contain any toxic metabolites.
- The drug should be free from any offensive odour.
- The dose should be less than 25 mg.
- The drug should possess appropriate nasal absorption property.
- Suitable clinical rationale for a nasal dosage form. [4]

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Nasal diseases

- Allergic rhinitis.
- Cerebral spinal fluid leaks.
- Sinusitis.
- Allergy. [5]

Gelling system

A gel is a soft, stable or solid-like material which consists of a least component in which on component is a liquid is present in substantial quantity.[6] Gels are a transitional state of matter containing both and other ingredients (semisolids or semi-liquids). [7] Gels consists of 3-dimentional, stable and secure component network. In gels, the polymer network is formed by the cross-linking of polymer chains either by the formation of covalent (chemical cross-linking) or noncovalent bonds (physical cross-linking).[8]

In-situ gel

In-situ gels are more desirable dosage form in which the drugs are delivered in solution form, when it is exposed to physiological condition it will convert to gel phase. [9] *In-situ* gels are in the form of solution or suspensions that undergo gelation after reaching the particular site due to contact with body fluids or physicochemical changes such as pH, temperature, ionic concentration, UV radiation, presence of specific molecules or ions, etc. [10]

In situ gels produces a constant plasma drug profile in the body by extending the release of a drug, so it is attached and absorbed in gel form and is known to prolong the life of the drug in the mucosa.[11] *In-situ* gels, potentially used for oral, buccal, subcutaneous, transdermal, intraperitoneal, ocular, nasal, rectal, vaginal and parenteral routes. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered. Various natural and synthetic polymers are used for formulation development of in situ forming drug delivery systems. [12] In the discovery phase, these gel formulations are used to increase the local and systemic exposures of potential active compounds, which is ideal for establishing animal models for various conditions quickly and cost-effective. Comprehensive research has been carried in designing of *in-situ* gels, emerged as one of the best novel drug delivery systems (NDDS).[13]

Advantages

- To decrease the wastage of drug.
- Easy for administration.
- Can be administered to unconscious and old patient.
- Controlled and sustained release of the drug.
- More patient compliance and comfort. [14]
- Minimizing the dose frequency and drug toxicity.
- Increased bioavailability.
- More flexibility in designing.
- Ease of production.[15]

Disadvantages

- Requires high level of fluids.
- The solution form of the drug is more susceptible for degradation.
- Changes of stability problems are more due to chemical degradation.
- After administration of drugs, eating and drinking is avoided for few hours.
- Only drugs with small dose requirement can be given. [16]

Importance of in-situ gelling system

- Helps for the controlled and sustained release of the drug by its special sol gel transition.
- Helps for the reduced frequency of drug administration of the drug in the body.
- Low dose of the drug is required and there will be no drug accumulation and no side effects.
- The bioavailability of the drug will be more.
- There will be increased residence time of the drug due to gel formation.
- The *in-situ* gel system decreases wastage of the drug.
- Liquid dosage form that can sustain drug release and remain in contact with cornea of eye for extended period of time is ideal.
- Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects. [17]

Polymers used in in-situ gelling system

1. **Gellan gum:** Gellan gum (commercially available as gel rite or Kelo gel) is an anionic deacetylated exocellular polysaccharide. It is secreted by pseudomonas elodea. It is a type of temperature depended or cation induced polymer. The formulation consists of gellan solution with calcium chloride and sodium citrate complex. In food industry, gellan gum is used as suspending and stabilizing agent. [18]
2. **Pectin:** Pectin is a family of polysaccharides. The polymer backbone mainly comprises of α-(1-4)-D-galacturonic acid residues. The gelation of pectin will occur in the presence of H+ ions. Gelling property of pectin depends upon the molecular size and degree of esterification. Pectin is used in this formulation because it is water soluble, so organic solvents are not used in the formulation. Divalent cations present in the stomach, carryout the transition of pectin to gel state when it is orally administered. [19]

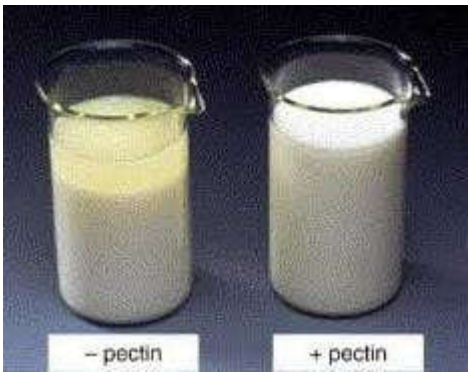

Figure 3 Pectin

3. **Xyloglucan:** It is also called tamarind gum. It is a polysaccharide derived from tamarind seeds. It is composed of (1-4)-B-D-glucan backbone chain. Xyloglucan gels have potentially been used for oral, intraperitoneal, ocular and rectal drug delivery. It is partially degraded by B-galactosidase. It has gelling ability in the presence of sugar or alcohol. [20]

4. **Alginic acid:** It is a linear block copolymer polysaccharide consisting of B-D-mannuronic acid and α-L-glucuronic acid residues joined by 1,4-glycosidic linkage. It can be chosen as a vehicle for ophthalmic formulation, since it exhibits favourable biological properties. [21]
5. **Chitosan:** It is a biodegradable, thermosensitive, polycationic polymer. It is obtained by alkaline deacetylation of chitin, is a natural component of shrimp and crab shell. It is a biocompatible pH dependent cationic polymer. [22]

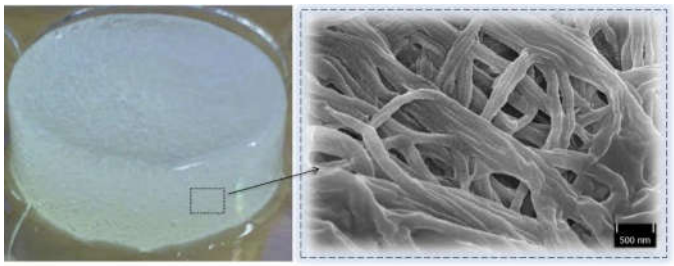

Figure 4 Chitosan and its microscopic structure

6. **Carbopol:** It is a well-known pH dependent polymer, which stays in solution form at acidic pH but form a low viscosity gel at alkaline pH. Hydroxy propyl methyl cellulose is used in combination with Carbopol to impart the viscosity to Carbopol solution. [23]

Figure 5 Carbopol

7. **Guar gum:** Guar gum is also called as guaran of naturally occurring gum which is obtained from the endosperm of the seed. Guar gum is insoluble in hydrocarbons, fats, esters, alcohols and ketones but soluble in water. It can be used as a polymer in matrix tablets which shows controlled release. [24]

METHODS

1. Cold method.
2. Hot method.

Cold method: In cold method the drug is stirred with required amount of double distilled water and kept whole night at 4°C in a refrigerator. Then *in-situ* gelling polymer should add slowly in continuous stirring. This cold method is selected when carbopol, poloxamer or chitosan is used as a gelling polymer. Considering the fact that polymeric dispersion of poloxamer remains as solution at lower temperature and gets converted into gel at higher nasal temperature because the solubility of polypropylene oxide chain of poloxamer decrease at high temperature which results in precipitation or salting out of polymer. Similarly, chitosan also requires low temperature to remain as solution at room temperature, its hydrophobicity increases with increase in temperature. [25]

Hot method: This hot method is utilized when gellan gum or pectin is used as a gelling gum or pectin is used as a gelling polymer. At higher temperature, gellan chains dissolve in water and assume a random-coil conformation with a high segmental mobility at high temperature and remains as a solution at higher temperature. Sol-gel transition occurs on cooling gellan gum solution in the presence of ions like K^+ or Ca^{2+}. Similarly, pectin also requires higher temperature for its demethoxylation, which helps in the formation of solution or dissolving of pectin. [26]

Evaluation of in situ gels

1. **Clarity:** The clarity of various formulations was determined by visual inspection under black and white background, and it was graded as follows: turbid: clear, ++; and very clear (glassy), +++. [27]
2. **pH of gels:** pH of human nasal mucosa is found to be in the range of 5-6.5. But it can tolerate about 4-7.5. pH of prepared formulation should be within the range of nasal mucosa which can tolerate in order to reduce nasal irritation. The result indicates that in all formulation pH is found to be within the tolerable. They are in the range of 6.1-6.5. [28]
3. **Gel-strength:** This parameter can be evaluated using a rheometer. Depending on the mechanism of the gelling agent used, from the solution form, a specified amount of gel is prepared in a beaker. This gel containing beaker is raised at a certain rate, 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. [29]
4. **Viscosity and rheology:** These are an important parameter for the *in-situ* gels, to be evaluated. Viscosity and rheological properties of forming drug delivery system may be assessed using bookifield rheometer or some other type of multipoint viscometers. The viscosity of this formulation should be such that no difficulties are envisaged during their administration by the patient during administration. [30]
5. **Measurement of gelation temperature and gel melting:** *In-situ* gel forming system incorporating thermoreversible polymers, the gelation temperature may be defined as that temperature at which the liquid phase makes a transition to gel. The liquid formulation is kept in a sample tube, immersed in a water bath and heated at a specific temperature and then heated at a specific rate. The samples shall then be examined for gelation, which is said to have occurred when the meniscus would no longer move upon tilting through 90°C. The gel melting temperature is a critical temperature when the gel starts flowing upon tilting through 90°C shall be recorded. Gel formation is indicated by a lack of movement of meniscus on tilting the tube. [31]
6. **Evaluation of the mucoadhesive strength:** The mucoadhesive potential of each formulation can be determined by measuring the force required to detach the formulation from nasal mucosal tissue. In brief, at the time of testing, a section of nasal tissue is secured to the upper probe using a cyanoacrylate adhesive. The upper probe was attached to precalibrated force displacement

transducer SS12LA, (BIOPAC system Inc, Santa Barbara CA) connected to the biopac MP-30 data system. The surface area of each exposed mucosal membrane was 0.785cm^2. At room temperature, fixed numbers of samples of each formulation were placed on the lower probe at 34°C. Probe with nasal tissue was lowered until the tissue get contacted the surface of the sample. Immediately, a force of 0.1M was applied for 2 min to ensure for intimate contact between the tissues and the samples. The probe was then moved upward at a constant speed of 0.15 mm/sec. [32]

7. **Sterility testing:** This testing is done with the aseptic transfer technique to avoid contamination of the environment. Sterility testing is an essential parameter for all ophthalmic preparation, and it must perform for aerobic, anaerobic bacteria and fungi by using suitable media under aseptic conditions. As per Indian Pharmacopoeia and British Pharmacopoeia, mostly direct inoculation method used to test sterility. Initially, inoculate the sample into the liquid media (thioglycolate medium and soyabean digest medium). After that, inoculate for 7-14 days at different temperatures: for thioglycolate medium (30-35°C) and soyabean digest medium (20-25°C), then identify microbial growth. [33]
8. **Antibacterial studies:** This test was conducted to find out the effectiveness of antibacterial of active antibiotic substance, the concentration data referred to as antibacterial. Finally, the result of the growth of bacteria samples could compare with standard antibacterial. [34]
9. **Stability studies:** Stability testing aimed to know the time of storage and the use of the material as per the international conference on harmonization (ICH). Place the sample in a climatic chamber at 42°C temperature and 75% RH for approximately for one month. After a few months, the sample analyzed associated clarity, pH, viscosity, drug content, rheological and *in-vitro* dissolution. The storage condition and the length of the study chosen should be sufficient to cover the storage, shipment and subsequent use. [35]
10. **Texture analysis:** The cohesiveness, consistency, firmness of *in-situ* gels assessed using a texture profile analyzer, which mainly indicates the syringe ability of solution so the formulation can be quickly administrated through *in-vivo*. [36]
11. **Gelling capacity:** By placing a drop of freshly prepared formulation with a vial containing 2ml of stimulated tear fluid and note down the time taken for gel formed or gel to dissolve in 7.4 pH phosphate buffer and it used for determination of the suitable polymer concentrations or gelling agent to form *in-situ* gelling system. [37]
12. **Gelling time:** Gelling time is the time required for the first detection of gelation, as defined in sol-gel transition temperature. [38]
13. **Drug content determination:** The vials containing the formulation were shaken for 2-3min manually and 100 ml of the preparation was transferred to 25 ml volumetric flask with a micro pipette and the final volume was made up with phosphate buffer pH 6.2. The amount of drug was determined using UV-visible spectrophotometer. [39]

CONCLUSION

The present review concludes that *in situ* gel system has emerged as one of the best novel drug delivery system. The utilization of *in situ* gels providing various advantages over conventional dosage forms. Sustained and prolonged release of drug, good stability and biocompatibility characteristics make the *in situ* gel dosage form very reliable. In recent years, there is a scope to provide an advanced technique in drug delivery. The *in situ* gelling system helps for the sustained and controlled release of the drug. Use of biodegradable and water soluble polymers for the *in situ* gel formulations can make them more acceptable and excellent drug delivery systems.

References

1. Chand P, Gnanarajan G, Kothiyal P. *Insitu* gel: A Review. Indian J Pharm Bio Res. 2016;4(2):11-19.
2. Intranasal:[Internet] cited May 2022 from https://www.slideshare.net/AlexaJacob1/intranasal-drug-delivery-system.
3. Intranasal:[Internet] cited May 2022 .Available from https://www.slideshare.net/AlexaJacob1/intranasal-drug-delivery-system.
4. Intrnasal:[Internet].Cited May 2022.Available from https://www.slideshare.net/DrSahilKumar/intranasal-route-of-drug-administration.
5. Nasal Disorders:[Internet].Cited May 2020.Available from https://www.ohsu.edu/ent/common-disorders-nose-and-sinuses.
6. Ragovina LZ, Vasibu VG, Braudo EE. Definition of the concept of the polymer gel. Polym Sci Series C. 2008; 50:85-95.
7. Whitlak DR, Weiss L, Ambragio LN. Ammonia oxidizing microorganisms for used and delivery to the gastrointestinal system. United states patent application US 16/318, 583;2019.
8. Carlfors J, Edsman K, Peterson R, Jornuig K. Rheological evaluation of gelrite *in situ* gels for ophthalmic use. Eur J Pharm Sci. 1998; 6:113-119.
9. Katarina E, Johan C, Rogaer P, Rheological evaluation of gelrite *in situ* gel for ophthalmic delivery use. Euro J Pharm Sci. 1998;113-119.
10. KUO CK, Ma PX. Ionically cross-linked alginate hydrogels as scaffolds for tissue engineering: part 1. Structure, gelation rate and mechanical properties. Biomaterials 2001; 22:511-21.
11. Bhardwaj L, Sharma PK, Malriya R. A short review on gastroretentive formulations for stomach specific drug delivery: special emphasis on floating *in situ* gel systems. Afr J Basic Appl Sci. 2011; 3:300-12.
12. Cappelo J, Crissman JW, Crissman M, Ferrai FA, Textor G, Walliso. *In situ* self-assembling protein polymers gel systems for administration, delivery and release of drugs. J control release. 1998; 53:105-117.
13. Mishra M, Kumar P, Rajawat JS, Malik R, Sharma G, Modgil A. Nanotechnology: revolutionizing the science of drug delivery. Curr Pharm Des 2018; 24:5086-107.
14. Langmaier F, Mokrejs P, Kolomaznik K, Modek M. Biodegradable packing materials from hydrolysates of collagen waste protiens. Waste management. 2008; 28:549-56.
15. Foda, N.H and S.M. Ali, 2011. Gastroretentive drug delivery systems as a potential tool for enhancing the efficiency of antibiotics: A review. Int J Pharm Biosci. 2019;2(2):94-104.
16. Bai B, Zhou J, Yinn. A comprehensive review of polyacrylamide polymer gels for conformance control. Petrol Explor Dev. 2015; 42:525-32.

17. Calfes J, Edsman K, Peterson R. Rheological evaluation of ophthalmic films for timolol maleate. Planta Indica. 2008; 4:49-50.
18. Grasdalen H, Smidsroed O. Gelation of Gellan gum. Carbohydrate polymers. 1987; 7:371-85.
19. Miyazaki S, Kawasaki N. Comparison of *in situ* gelling formulations for the oral delivery of cimetidine. Int J Pharm. 2000; 207:109.
20. Shastri DH, Patel LD. Novel alternative to ocular drug delivery system: Hydrogel. Ind J Pharm Res. 2010; 2:1-13.
21. Sechoy O, Tissie G, Sebastian C, Maurin F. A new long-acting ophthalmic formulation of carteolol containing Alginic acid. Int J Pharm. 2000; 207:109.
22. Grant G.T., Morais E.R., Peas DA. Biological interactions between polysaccharide and divalent cations: The egg box model. FEBS Lert. 1973; 32:195-198.
23. Davies NM, Farr SJ, Hadgraft J. Evaluation of mucoadhesive polymers in ocular drag delivery. Pharm Res. 1991;8(8):1039-1043
24. Kokate Ck, Purohit AP, Gokhale SB. Pharmacognosy. 14th edition. Published by Nirali Prakashan. 2008; 137:141-152.
25. Nimi N, Deepa Manohar. An overview on *in situ* nasal gel for drug delivery.
26. Mayuri MB, Vijay RC, Gunesh ND, Jeevan, Deepak. *In situ* gel for nasal drug delivery. Int J Dev Res. 2018;8(2):18763-18769.
27. HB N, Bakliwal, Pawar. *In situ* gel as new trends in controlled and sustained drug delivery system. Int J Pharma Res. 2010; 2:1398-408.
28. PK Aabib, Ashwani. Formulation and evalution of nasal *in situ* gel of sumatriptan succinate for the treatment of migraine. Int J Pharm Res. 2019; 11:202-210.
29. Miyazaki S, Suisha F, Kawasaki N. Thermally reversible xyloglucan gels as a vehicle for rectal drug delivery. J control Release. 2001; 73:205-211.
30. Srividya B, Rika M, Cardoza PD. Sustained ophthalmic delivery of ofloxacin from a pH triggered *in situ* gelling systems. J Control release. 2001; 73:205-211.
31. Miller SC, Donavan MD. Effect of poloxamer 407 gels on the miotic activity of pilocarpine nitrate in rabbits. Int J Pharm. 1982; 12:147-152.
32. Pandit NK, Kisaka J. Loss of gelation ability of Pluronic F127 in the presence of some salt. Int J Pharm. 1996; 145:129-136.
33. Jones DS, Woolfron AD, Brown AF. Design characteristics and preliminary clinical evalution of a novel mucoadhesive topical formulation containing tetracycline for the treatment of periodontal disease. J Control release. 2000; 67:357-365.
34. Aldrich DS, Bach CM, Brown W. Ophthalmic preparations. US Pharmacopeia. 2013; 39:1-21.
35. Rodriguez J. Antibacterial/Antifungal surfaces obtained by surface modification: Polymers against Microorganisms. Springen Cham. 2017; 22:95-123.
36. Bansal G, Suthar N, Kaur J, Jain A. Stability testing of herbal drugs: Challenges, regulating compliance and perspectives. Phytothec Res. 2016; 30:1046-58.
37. Moore MM, Schober TJ, Dockery P. Textural comparison of gluten free and wheat-based doughs, batters and breads. Cereal Chem. 2004; 81:567-75.
38. Mondal S, Thimmashetty MK, Prabhushankar GL. Formulation and evalution of an *in situ* gel forming ophthalmic formulation of moxifloxacin hydrochloride. Int J Pharm Invert. 2012; 2:78.
39. Asasuljarit R, Thanasachokpibull S. Optimization and evaluation of thermoresponsive diclofenac sodium ophthalmic *in situ* gels. Int J Pharm. 2011; 411:128-35.

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