ORIGINAL ARTICLE

INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: www.ijrps.com

The Advantages of In situ Gel from Every Different Formulation

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Article History:

Received on: 08 Sep 2020
Revised on: 01 Oct 2020
Accepted on: 10 Oct 2020

Keywords:

In situ Gel,
Formulation,
Gel Forming Agent

ABSTRACT

The in situ gel system is one of the polymer-based solutions that show the sol phase transition to gel. In addition to being used to improve bioavailability, this gel is also used to make the drug increase the residence time in the area of use, so that it can provide maximum effectiveness via enhancing of per cent permeation, The use of in situ gel, usually used in ocular administration of drugs, for the treatment of cancer, administration of drugs in the vaginal, rectal, topical, oral, and any route administration. There are many formulations of in situ gel formation that are used for medicinal preparations for many purposes, with different lengths of stay. Searching for articles is done online, browsing the PubMed and Google scholar site with the keyword "Formulation In situ Gel". The fourty articles used, there were 40 in situ gel formulations with gelling agents and also different uses. The purpose of this article review is to look at the superiority of in situ gel formulations and to compare various in situ gel formulations studied from 40 articles used, so that it can be seen which formulation is most often used and has a good effect on drugs preparations.

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ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11i4.3845

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INTRODUCTION

The in situ gel system is a polymer-based solution that demonstrates the transition of the sole phase to the gel, where the formation of an in situ gel system is used to overcome low bioavailability. In-situ forming gels show sol-to-gel transitions in response to one or two or even more combinations of stimuli, including UV irradiation, temperature, and pH changes, solvent exchange (Al-Tahami and Singh, 2007). Based on stimuli, in situ gel can be divided into in situ gel activated ions (Rupenthal *et al.*, 2011), thermosensitive and sensitive to pH from all three in situ the gel in situ thermosensitive gel has a higher safety (Kawase *et al.*, 2010). In situ, this thermosensitive gel will undergo the process of transitioning from sole to gel during heating or cooling; it can occur due to changes in intermolecular (Ruel-Gariépy and Leroux, 2004).

As for ion-activated gel in situ can perform cross-binding found in tear fluid to form eye surface gel. So it can extend the retention of time precursors and can lead to increased bioavailability (Greaves *et al.*, 1990). The drug with in situ gel supply can be made with various formulations; it is by the purpose of use, it depend on route of administration. As in the formulation of the polymer, the eye can be divided

into three groups

1. Polymer Viscosity Enhancer, That simply increases the viscosity of the formulation, resulting in decreased lacrimal drainage and increased bioavailability.
2. Mucoadhesive polymers, That interacts with ocular mucin, therefore increasing the concentration of wisdom with ocular tissue.
3. In situ gel forming polymer, WHO undergoes a sol-to-gel phase transition after exposure to physiological conditions present in the eye. The latter group is the most profitable when compared to preformed.

Method

The method used in this article review is the collection of data related to in situ gel obtained from some literature and obtained through searches on the PubMed site. The reference obtained is a research article in English with the number of articles search results on PubMed as many as 60 articles and obtained 40 articles meet the desired criteria. Where the inclusion criteria in this article review are that the article used should discuss the formulation of in situ gel, included in international journals, and published from 2010 to 2020.

Results

In situ gel-forming polymer delivery system is one of the solutions used to make drug administration controlled, sustainable, and achieve effectiveness, reliability, and drug products that are much better safety. Many biodegradable polymers used for gel in situ formulations include gum gel, alginate acid, xyloglucan, pectin, chitosan, poly (DL-lactic acid), poly (DL-lactide-co-glycolate), and polycatechism, some polymers allow it to be used as a gel-forming agent namely Nafion-zirconia. In situ gel can be for oral, ocular, rectal route, vaginal, injection, intraperitoneal, and so on, depending on the purpose of use (Nirmal *et al.*, 2010).

Here is a table of gel-forming agents used in each formulation of 40 reference articles Table 1. As below

Chitosan Combination Gel Forming Agent Formulation

In situ gel formation system is one of the solutions to make the drug can diffuse well for a long time. Research conducted by Kolawole *et al*., in 2019 discusses the shape of in situ gel using chitosan/β-glycerophosphate, the active substance mitomycin–C formulated for the treatment of bladder cancer. Research shows the results of a mixture of chitosan/β-glycerophosphate formulations form in situ gel quickly, as well as having superior retention against urine washing, thus providing a controlled release in mitomycin-C for 6 (Kolawole *et al.*, 2019). Subsequent combination formulations of chitosan (CT) and sodium tripolyphosphate (TPP) for the use of ocular, vaginal, orthodontic, and locally used model drugs. Showing the results of both combinations, poloxamer – CT and poloxamer – TPP showed a decrease in the rate of dissolution and superior release characteristics with three different drugs, namely metoprolol, doxycycline, and flufenamat. Chitin can increase the acidity of P407 and can also increase the strength and mucoadhesive of poloxamer gel. At the same time, TPP contains $Na_2H_2PO_4$ high levels that can neutralize the acidity of the chitosan solution when mixing. So that in the form of in situ gel for the drug supply to be used, it can be adjusted to the pH required by mixing Pluronic with TPP (Ur-Rehman *et al.*, 2011). The formulation of in situ anionic polysaccharide gel (gellan gum, xanthan gum, carrageenan, and alginate) into an uncharged polymer system (HPMC) shows results, physically entangled polymer tissue that is beneficial for eye use, as it makes polymers able to easily decompile at blinking, thus preventing induced lacrimation, which is usually triggered by a more vicious system. As for gellan gum and carrageenan, formulations show the most preferred characteristics of phase transitions, rheological properties, and textures increased viscosity at the time of contact with tear fluid cations thus providing extended stay time on the cornea and also reducing nasolacrimal drainage (Rupenthal *et al.*, 2011). Polymer formulations do not cause het-cam irritants so they can be classified as safe for in vivo use. As for the system with gellan gum, xanthan gum, and carrageenan formulations shows highly preferred characteristics, as it can dry out at an almost constant rate with >80% remaining radioactivity corresponding to miotic studies in vivo (Rupenthal *et al.*, 2011).

Gel Forming Agent Formulation Gel Combination Gellan Gum

The use of in situ gel-forming using gum gel can be used for drugs for vaginal use purposes, wherein research conducted by Patel, and Patel in 2015, obtained test results from gum gellan formulations combined with the active substance clindamycin, showing improved texture characteristic results seen from rheological results. The addition of HPMC to the formulation is useful to reduce the sole at the gel transition temperature, as well as also used to affect the mucoadhesive (Kurniawansyah *et al.*, 2018).

Table 1: Gel Forming Agent Used

Compounds Used in Testing	Testing Methods Used	Purpose of Use Area	Description	Reference
Gellan gum, alginate-acid, xyloglucan, pectin, chitosan, poly (DL- lactate acid), poly (DL-lactida-co-glikolide) dan poly-caprolactone	Diffusion method and otassium Bromide ellet method	The oral, ocular, rectal route, vaginal, injection, and intraperitoneal	Formulations can be used	(Nirmal *et al.*, 2010)
Chitosan /β-glycerophosphate	Bottle intervention method	Bladder	Formulations can be used	(Kolawole *et al.*, 2019)
Chitin (CT) and Sodium Tripolyphosphate (TPP)	Calorimetric differential scanning (DSC), tube inversion, and gravimetry methods	Administration of ocular, vaginal, orthodontic, and local parenteral drugs.	Formulations can be used	(Ur-Rehman *et al.*, 2011)
Gellan Gum Dan Hydroxyethylcellulose	New rheology methods and synergistic methods of rheumatism	Ophthalmic	Formulations can be used	(Destruel *et al.*, 2020)
Gellan Gum dan Hydroxypropyl Methyl Cellulose (HPMC)	modified physical balance method	Nasal treatment	Formulations can be used	(Salunke and Patil, 2016)
Ofloxacin	Method HPLC-MS / MS	Ophthalmic	Formulations can be used	(Li *et al.*, 2013)
Carbopol 940 and HPMC	Cup-Plate Method, Ultracentrifugation Method, and Ultraviolet Spectrophotometric (UV) Method	Ocular administration of the drug	Formulations can be used	(Pandurangan *et al.*, 2016)
gellan gum dan Carbopol 934P	Methode HPLC, method RP-HPLC, Methode hemolytic dan sessile droplet method using Theta Optical Goniometer	Eye Treatment	Formulations can be used	(Ranch *et al.*, 2019)
Poloxamer 407 and Methyl Cellulose	Bottle Intervention Method	Ocular administration of the drug (eye drops)	Formulations can be used	(Wei *et al.*, 2020)
Poloxamer-407	Thermo-gelling property	Eye treatment	Formulations can be used	(Bhowmik *et al.*, 2013)
Cellulose nanocrystals (CNC)	Toxicity assay of in vitro gel, Rheological analysis	Administration of ocular model drugs	Formulations can be used	(Orasugh *et al.*, 2019)
Poloxamer 338 (P338) dan Poloxamer 407 (P407)	Analytical methods and Bioanalytic Methods	Intramuscular injection	Formulations can be used	(Van Hemelryck *et al.*, 2019)

Continued on next page

Table 1 continued

Pluronic F127 dan Pluronic F68	Inversion Botle Method, Differential Scanning Calorimetry, Rheological Measurements, and Dynamic Light Scattering.	Eye treatment	Formulations can be used, but luronic F68 is much weaker in gel formation than Pluronic F68	(Khateb *et al.*, 2016)
Pluronic/Gelrite®	Differential scanning calorimetry (DSC), Biocompatibility study, Kinetic analysis of lidocaine release date from in situ gel	Cervical and vaginal tissue	Formulations can be used	(Ellah *et al.*, 2018)
Gellan Gum dan Sodium Hyaluronate	Method HPLC	Nasal treatment	Requires the development of further formulations that take into account the optimization of precipitation patterns in the early phases of formulation development	(Nižić *et al.*, 2019)
sodium carboxymethylcellulose (CMC) and sodium alginate (ALG)	HPLC Method and In Vitro Methods	Eye Treatment	Formulations can be used	(Abdelkader *et al.*, 2014)
Pluronic ® F-127 dan HPMC	nanoprecipitation method, the tube inversion method	Eye Treatment	Formulations can be used	(Morsi *et al.*, 2016)
Pluronic® F127 dan F68	gradient flow method, HPLC method, Tube Inversion Method	Oral	Formulations can be used	(Li *et al.*, 2020)
Pluronic ® F127 dan Pluronic ® F68	desolation method, surface method	Ophthalmic	Formulations can be used	(Zhang *et al.*, 2014)
alginate / pectin	Method HPLC, dan gentamicin content method	Wound area	Formulations can be used	(Cicco *et al.*, 2014)
poloxamer (PM) dan methylcellulose (MC)	open-end tube method and ultraviolet spectroscopy	Subgingival	Formulations can be used	(Rajendran *et al.*, 2017)
SAIB-PLA	HPLC method, and trapezoid method	Injection	Formulations can be used	(Geng *et al.*, 2016)

While in the subsequent formulation of gellan gum combined with hydroxyethyl cellulose for the manufacture of ophthalmic gel in situ combination of phenylephrine hydrochloride with tropicamide, the results showed high stay time on the surface of the eye, i.e. >3 hours, providing better therapeutic effects, reduced side effects due to decreased absorption at the systemic level (Destruel *et al.*, 2020). In situ sulfate salbutamol gel uses gellan gum formulation and hydroxypropyl methylcellulose (HPMC) as in situ gel-forming agent. The results of the formulation study have a pH of the range of nasal cavities, as well as optimal viscosity for nasal administration. Forming effective gelation, viscosity, drug content, medicinal release properties, and good mucoadhesive strength. For histopathology examination does not detect any damage during ex vivo permeation studies, and increases efficacy in sulfate salbutamol therapy (Salunke and Patil, 2016).

Carbopol Combination Gel Forming Agent Formulation

The in situ formulation ofloxacin gel obtained by dispersing Carbopol 974P, and HPMC E4M, showed the results of ophthalmic gel ofloxacin in situ could not significantly reduce systemic absorption of the drug at the same dose as the ophthalmic solution administered to the (Li *et al.*, 2013).

SLN formulations of in situ gels are composed of Carbopol 940 polymers and methylcellulose (HPMC) that release continuously to reduce the frequency of dosage and maintain more prolonged therapeutic effects. Besides, the combination formulation of carbopol with HPMC for sinomenine hydrochloride (SIN) in situ gel is also used for the treatment of uveitis and shows good potential for its. Pandurangan *et al.* research, in 2016 showed results that the in situ formulations of SLN gel produced good ZOI at the time of microbial testing did not cause eye irritation in the rabbit's eyes at the time of (Pandurangan *et al.*, 2016).

The formulation of gellan gum and Carbopol 934P for the delivery of eye drugs shows the result of improved characteristic gelation (synergistic effect) of in situ gel. Then when optimized in situ gel clear, isotonic, pH 4.7 and shows pseudoplastic flow, high in vitro gel-forming capacity, low contact angle, accepted hardness (51018 gm), compressibility (64617), and stickiness value (74 grams) for eye application.

The results of testing on the rabbit's eyes showed safety in the in situ formulations of this gel in human use and shows the contact time on the eyes reaches 3 (Ranch *et al.*, 2019).

Poloxamer (PM) Combination Gel Forming Agent Formulation

The formulation of in situ gel-forming using poloxamer 407 and methylcellulose obtained the result that the in situ gel-forming occurs at gelation temperature, which corresponds to the release rate. Based on the results of pharmacokinetic studies in vivo shows that gels in situ are superior to increasing the concentration of the drug in (Wei *et al.*, 2020). Poloxamer-407 was successfully formulated as a thermoreversible in situ ophthalmic gel-forming vehicle. XG and GG (3:7) are used to modify non-gellable poloxamer solutions into gel solutions. The solution is liquid at 25^0C and forms gelation below body temperature. The temperature of the gel, viscosity, and swelling properties of the gel solution in situ are not affected by the merging of the drug. Studies of the release of in vitro drugs show modified poloxamer solutions release the drug at a slower rate in comparison to those who are not XG-GG. From an in vivo study, it found that formulations developed from 16% of MPS showed increased bioavailable through longer precursor stay times and decreased frequency of administration, resulting in better patient admissions. Based on observation, it is concluded that gel-forming eye drops containing poloxamer-407 with XG – GG (3:7) may be a better alternative than conventional eye drops.

Successful utilization of CNC has a positive impact on PM properties, and their application in ODDS has been proven. CNC derivatives at low percentages have been shown to have a positive influence on poloxamer glass temperature 407 (PM). CNC hydrophilic reduces the interaction between molecules H_2O and poloxamer 407. The reinforcing properties of CNC through H bonding in situ nanocomposite gels lead to increased gel strength along with the continued release of loaded drugs when compared to pure PM gels. All formulations reveal that the diffusion of Fickian controls the mechanism of release of the drug. Nanocomposites containing the highest weight of CNC (M4) have shown the best performance with non-toxic (Orasugh *et al.*, 2019).

The in situ gel formulation uses different polymers, namely poloxamer 188, poloxamer 407, gellan gum, and Carbopol 934P, for in situ gel in the treatment of periodontal diseases. From the results of the study obtained results that there was an increase of each polymer, stable does not show any meaningful changes, and there is a continuous release of the drug for 6 hours, to treat periodontal. In situ formulations of poloxamer gel 388 and poloxamer 407 for intramuscular injection use showed results that

poloxamer in situ formed the gel for about 6 hours as well as having a continuous release of the drug in the short term observed in mice for up to 24 hours (Van Hemelryck *et al.*, 2019).

Formulations of poloxamer (PM) and methylcellulose (MC) are used for the delivery of simvastatin in situ gel (SMV), the result of research showing that PM 25% and MC 25% can form an ideal thermosensitive injectable gel at a temperature of 37^0C used for subgingival on SMV drug delivery, as well as indicating the release of a controlled drug within ten days (Rajendran *et al.*, 2017).

Pluronic Combination Gel Forming Agent Formulation

The next in situ gel formation formulation uses Pluronic F-127. From the formulation obtained results Of Tsol-gel Pluronic F-127 increased by 20% with the addition of THA, Pluronic F-68, and PEG 8000, unaffected by the addition of chitosan, good physical properties (the rheological properties of slow-release kinetics, Tsol-gel suitable) has improved stay time, enhanced bioavailability and absorption of THA by the brain so that it can be used as an intranasal formulation for THA. The formulation of in situ gel with the combination of Pluronic F68 with Pluronic F217 can be used as an eye medicine, based on research results written by Al Khateb, *et al*. in 2016 that conducted irritation tests on snail mucosa and cowed corneal erosion studies that showed results did not cause significant irritation. This study obtained results that Pluronic non-gelling formulation F68 is much weaker compared to Pluronic F127 (Khateb *et al.*, 2016).

The in-lidocaine HCl in-dual responsive gel consisting of PF-127 and Gelrite® demonstrates optimal sol-to-gel transitions in response to physiological temperature and ionic strength. The optimal F5 formulation shows control of the desired release of the drug over time and biocompatibility with cervical and vaginal tissue. Clinical evaluation of the optimal F5 formulation of the placebo demonstrates the ease of self-administration by the patient, thereby significantly reducing pain scores through the installation of an IUD. These results suggest that our responsive double in situ gel is a superior alternative to previously reported formulations with good patient acceptance and better pain management (Ellah *et al.*, 2018).

Hydrochloric thiothixene (HT) is one of the drugs for the treatment of various psychosis diseases. HT injection in the formation of in situ gel is assisted by the addition of polylactic acid (PLA) with bio gradable benzyl benzoate, from such formulations shows the result that the injection of HT gel has a long-term period of drug release for several weeks and histocompatibility both signs there is a remarkable inflammatory. As for the in situ formulations of fluticasone gel for nasal use, used gellan gum and sodium hyaluronate as gel-forming agents. From the formulation shows that this formulation has an absorption in sound design. Still, from this study, it has not been determined whether the formulation is sufficiently feasible to use, as further formulation development should be carried out that takes into account the optimization of the deposition pattern in the initial phase of formulation development (Nižić *et al.*, 2019).

CMC Combination Gel Forming Agent Formulation

The gel-forming fluid is transformed into a gel shape when added to simulated gastric fluid (pH 1.2). The gel immediately floats in the gastric environment and indicates the release of a controlled drug for 12 hours. Preparation and evaluation of oral controlled discharge that can float floating PRG systems with the administration of gastric-specific drugs that control the release of drugs for the treatment. In situ gel-forming formulations using sodium carboxymethylcellulose (CMC) and sodium alginate (ALG) for the drug naltrexone hydrochloride (NTX) eye treatment, showing superior mucoadhesive properties in cow conjunctiva, chemical and physical stability ends at three months under accelerated storage conditions 30^0C/ 75%RH as good conjunctiva tolerability with minimal irritation (Abdelkader *et al.*, 2014).

Pluronic Combination Gel Forming Agent Formulation

The research conducted by Morsi, *et al*. in 2016 on the formation of in situ gel for increased ocular availability of ketorolac tromethamine and to extend the precursor stay time of the drug for the treatment of eye inflammation after surgery. Pluronic ®F-127 and HPMC are used as gel-forming agents. From the results of the formulation, the addition of eudragit nanodispersion showing high trap efficiency, small particle size, and continuous release of drugs incorporated into the gel in situ using Pluronic gel-forming agents ®F-127 and HPMC resulted in optimal gel-forming capacity and mucoadhesive properties, relatively high bioavailability when compared to acular ® commercial eye drops. Thus, this formulation is considered to have the potential of delivery of eye drugs for the treatment of post operative inflammation, as well as can improve patient compliance because of it formulation can (Morsi *et al.*, 2016).

Other formulations used are Pluronic®F127 and

F68, as a gel in situ forming agents in treatment to treat oral mucositis pain. Pluronic formulations® F127 and F68 were also added as well as Carbopol® or Noveon® to improve mucoadhesive. From the results of the study obtained Pluronic results® reached gelation temperature at 22.5-42^{0}C, experienced an increase in mucoadhesive without reducing gelation temperature and also the level of the drug, also found lower pH so that it can be used as an interpretation of in vivo results for the future (Li *et al.*, 2020).

O luronic formulations® F127 and F68 are also used to optimize and evaluate ophthalmic in situ thermoresponsive gels containing curcumin-containing albumin nanoparticles (Cur-BSA-NPs-Gel). From the combination of formulations obtained results showing that Cur-BSA-NPs-Gel has achieved a special continuous release effect, combining albumin nanoparticles gives minimal effect on the gel structure. Cur-BSA-NPs-Gel tested on the rabbit's eyes showed that the formulation was safe for the introduction of ophthalmic (Zhang *et al.*, 2014). While the formulation that combines Pluronic ® F127, Pluronic ® F68, and Carbopol 940 on Pluronic-based thermoresponsive diclofenac F127 sodium ophthalmic in situ gel (DS in situ gel), shows results that Pluronic F127 can decrease sol-gel transition at product temperature. At the same time, Pluronic F68 can increase sol-gel at transition temperatures, and for Carbopol 940 does not affect sol-gel transition temperature, it can affect the transparency, pH, and gel-forming capacity of the product.

Alginate Combination Gel Forming Agent Formulation

In de Cicco *et al*. research, 2014 explained the formulation of in situ gel using alginate - pectin added gentamicin sulfate (GS) and administered locally to treat wounds. Research shows results that nano spray drying technology has been successfully applied, resulting in a stable alginate-pectin nanoparticle powder. The powder will then be able to jellify quickly in the wound cavity and absorb the fluid present in the wound because the formulation of the powder forms in situ gel it will show the right stickiness to facilitate the wound to dry (Cicco *et al.*, 2014).

Formulation of gel formation for the administration of rectal nimesulide, using sodium alginate gel-forming agents (Alginate-Na) and HPMC with the addition of poloxamer 407, nimesulide, PEG which is used to modify the temperature of gelation and the release properties of the drug, and obtained the result of an increase in gelation temperature at the time of the addition of nimesulide as well as PEG, where PEG also increases the rate of release of the drug, while for polymer mucoadhesive lower gelation temperature, does not cause irritation of mucosa at a dose of 20mg / Kg, and it produces a much higher initial serum.

SAIB-PLA Combination Gel Forming Agent Formulation

The in-situ gel formulation, which uses SAIB-PLA as a gel-forming agent for continuous ivermectin release, shows the results of the study, at the time the concentration of IVM was increased from 1% - 2%, the cumulative release was 2.4 to 2.9 and 3.1 to 3.7 times from 1%. Thus, show a slow in vitro release rate with a burst release of 10.46% and 80% where the cumulative release is within 80 days. As for pharmacokinetic results show the concentration of effective blood on the gel can be maintained up to 110 to 120% (Geng *et al.*, 2016).

CONCLUSION

The results of the review of the article, conducted to 40 different articles, can be concluded that there is the use of different gel in situ forming agents from each formulation, as well as for medicinal purposes. And when viewed from the results of the 40 articles reviewed, the formulations listed can mostly be used as a safe gel in situ formulations. And judging by the results of the study to 40 articles obtained, it can be concluded that the gel-forming agent is qualified for use, can improve the bioavailability of the drug used, extend the duration of stay of the drug precursor in the destination area of use so that with extended time can improve the patient's adherence in the use of the drug, safe, does not cause toxicity.

ACKNOWLEDGEMENT

We acknowledge all parties involved in the preparation of this review, especially for DRPMI UNPAD.

F unding Support

Neither party funded this review.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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