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Review Article

IN-SITU GELLING SYSTEM – POTENTIAL TOOL FOR IMPROVING THERAPEUTIC EFFECTS OF DRUGS

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ABSTRACT

In-situ forming polymeric gelling systems has become prominent among novel drug delivery system (NDDS) in recent years due to advantages such as sustained and prolonged drug action, improved patient compliance and reduced frequency of administration of the drug in comparison to conventional drug delivery system (DDS). This is a type of mucoadhesive DDS where the polymeric formulation is in sol form before administration and once comes in contact with body fluids; it undergoes gelation to form a gel. Use of various natural, biocompatible, biodegradable as well as water soluble polymers such as chitosan, glycoginic acid, poly-caprolactone, gellan gum, xyloglucan, poly-D,L-lactic acid, pluronic F127, carbopol, poly-D, L-lactide-co-glycolide and pectin makes this DDS more acceptable. *In-situ* gels can be fabricated by various methods in combination with different drugs and polymers for both local and systemic therapy where each drug shows its own therapeutic effects at the targeted site of action. This review presents the current developments and importance of various drugs formulated as *in-situ* polymeric gelling systems and its corresponding improvement in therapeutic effects.

Keywords: *In-situ* gel, Pluronic, Carbopol, β-cylcodextrin, Celecoxib.

INTRODUCTION

In-situ is a Latin word which means 'In its original place or in position'. There are many mechanisms which triggers the formulation of *in-situ* gels such as solvent exchange, ultra violet irradiation, ionic cross linkage, temperature modification, pH change and ionization. Studies are performed through various routes like oral, rectal, ocular, injectable, vaginal, nasal, parental and intraperitoneal. With the increased demand in techniques and recent developments in the field of polymer sciences various stimuli sensitive hydrogels like pH and temperature sensitive hydrogels are developed, which are used as chemotherapeutic agents to tumour regions. Prolonged and sustained release of the drug, reproducible, excellent stability, biocompatible and accurate quantities of administration makes the *in-situ* gel system more reliable. *In-situ* gel formulation applied for targeted delivery via ophthalmic, rectal, vaginal, nasal mucosa avoids the hepatic first-pass metabolism, especially for the proteins and peptides [1]. Enormous research works are being carried out for various category of drug, to prove the significance of *in-situ* gelling systems. This review paper highlights on the contribution of various researchers worked on the different *in-situ* gelling polymers, to improve the therapeutic effect of drugs. The categories of drugs discussed here includes anti-microbial, anti-tumour, anti-glaucoma, anti-asthma, anti-ulcer, anti-diabetic and drugs used for CNS disorders.

Anti-microbial effects

A range of the drugs with antimicrobial effects such as Ciproflaxin, Amoxillin, Linezolid, etc., have been investigated by various scientists through different routes of *in-situ* gelling action, employing various biodegradable polymers. These systems were identified with improved drug targeting, sustained drug release and enhanced bioavailability. The polymers used and their significant results are shown in table 1.

Table 1: List of Anti-microbial drugs developed as *in-situ* gel drug delivery system

S. No.	Drugs	Polymer	Route	Result
1.	Ciproflaxin	Carbopol 940P, pluronicF-127, gellan gum, 1.5% HPMC	Ophthalmic	Drug release for about 6 h [2]
2.	Amoxillin	Sodium alginate, calcium chloride, sodium bicarbonate, sodium citrate, HPMC-K100	Incorporated directly to stomach	Drug release was found to be 6 to 10 h [3]
3.	Linezolid	Hydroxyl propyl guar, hydroxy ethyl cellulose, carbopol, sodium alginate, xanthum	Ocular	Sustained release over a period of about 6 h [4]
4.	Itraconazole	Poloxamer 407, 188, HPMC	Vaginal	Improved treatment of vaginal candidiasis [5]
5.	Gatifloxacin	Sodium alginate, HPMC	Ocular	Sustained drug release of about 8 h [6]
6.	Clotrimazole	Carbopol 934P, gellan gum, HPMC	Oral	Zero order release kinetics with the sustained release for 8 h [7]
7.	Doxycycline hyclate	Poloxamer 188, gellan gum, HPMC, sodium alginate	Ocular	Controlled release for about 24 h [8]
8.	Moxifloxacin hydrochloride	HPMC, sodium alginate	Ocular	Drug release for about 10 h [9]
9.	Metronidazole	Pluronic F68, F127	Vaginal	Treats bacterial vaginosis [10]
10.	Sesbania grandiflora	Pluronic F127, chitosan	—	An increase in the viscosity at a temperature of about 37°C to form gel and provide sustained release [11]
11.	Ofloxacin	Carbopol, HPMC	Ophthalmic	Sustained release for a period for 8 h [12]
12.	Levofloxacin	Gelrite	Ophthalmic	Drug release of about 90.2% [13]

Anti-tumour effect

An ophthalmic *in-situ* gelling formulation of 5-Flurouracil with the polymers sodium alginate and poly lactic acid (PLA) made as nanoparticles for the treatment of conjuctival squamous cell carcinoma. The Nanoparticles with gel matrix-embedded drug showed increased retention time due to the higher 5-Flurouracil level in aqueous humour [14]. An injectable mucoadhesive *in-situ* gel of Paclitaxel was designed with chitosan and glycerol monooleate. This formulation resulted in a sustained drug delivery and drug targeting [15].

In-situ gel for rectal administration of Oxaliptalin with Pluronic-poly(acrylic acid)(PAA) polymer was formulated for treating colorectal cancer where pluronic and PAA were proved to be non-toxic. The formulation showed increased C_{max} and higher AUC (0 to 12 h) than the orally administered dosage form [16]. Anti-tumor efficacy and sustained release behaviour was obtained when Doxorubicin hydrochloride was encapsulated with graphene oxide [17]. An ophthalmic delivery of Matrine with alginate, gelrite, gelrite/ alginate was formulated which was found to have enhanced ocular retention [18].

Anti-inflammatory effects

Certain anti-inflammatory drugs like Radix bupleri, Diclofenac sodium, Curcumin, etc., were used in formulating *in-situ* gels by various methods. Different routes has been chosen for delivery of these drugs to show the improvement in their activity and bioavailability which are shown in table 2.

Table 2: Anti-inflammatory drugs formulated as *in-situ* gelling system

S. No.	Drug	Polymer	Route	Result
1.	Radix bupleri	Gellan gum	Nasal	The *in-situ* gel had a greater effect (longer anti pyretic effect) than the *in-situ* solution [19].
2.	Diclofenac sodium	Carbopol, sodium alginate, HPMC	Ophthalmic	Drug release prolonged for 8 h [20].
3.	Curcumin	Capryol 90, solutol HS15, transcutol HP	Nasal	Direct drug transport of nose-to-brain is better in nasal route than intravenous route [21].
4.	Bupivacaine hydrochloride	Poly(D,Llactide), poly(D,L-lactide-co-glycolide)(PLGA)	Parenteral	Prolonged analgesic effect of the drug in gel condition [22].
5.	Ketorolac tromethamine	Methyl cellulose	Ophthalmic	Gelation tempature at 32^{o}C and sustained drug release upto 9 h [23].
6.	Acetomenophen	Polycarbophil, polaxamer F188, 407	Rectal	*In-situ* gelling liquid suppository and mucoadhesive gels found to be more effective and convenient method for rectal delivery [24].
7.	Indomethacine	Gelrite	Ocular	Drug release upto 8 h [25].
8.	Nimesulide	Sodium alginate, polaxamer, Poly Ethylene Glycol , HPMC	Rectal	Addition of PEG resulted in satisfactory drug release rate and rectal retention [26].
9.	Paracetamol	Xyloglucan	Oral	Over a period of 6 h diffusion-controlled drug release was found [27].

Anti-glaucoma effect

Ocular delivery of Timolol maleate with carbopol and chitosan showed sustained release behaviour over period of 24 h [28]. For treating glaucoma an ophthalmic administration system of S(-)-Satropene along with formic acid, acetonitrile and phemotolamine was developed. After instillation, within 1 h the bio availability of S(-)-Satropene in aqueous humor increased to the maximum level with Cmax of 1.508±0.297gml^{-1}. This *in-situ* gel formulation exhibited 3.2 fold greater C_{max} and 2.2 fold greater AUC0−3 h ($p < 0.05$) [29].

Pilocarpine, used in the treatment of glaucoma, formulated with xyloglucan and pluronic F127 showed a sustained drug release of about 6 h. Here, the ratio of xyloglucan to pluronic was about 1.5%:25% (w/w) [30]. *In-vitro* release study of Forskolin, an anti-glaucoma agent with poloxamer showed efficient release of drug for more than the period of 5 h when administered ocularly. *In-vivo* results indicated that intra-ocular pressure lowering efficacy of the gel was about 31% for 12 h where as only 18% observed in eye suspension [31]. For treating precorneal loss, an ophthalmic administration of Dexamethasone with gellan gum was used which resulted in the sustained drug release upto 7 h [32].

Drugs for chronic diseases

In-situ gel for rectal administration of Meveberine hydrochloride was formulated with hydroxyl propyl methylcellulose (HPMC), methyl cellulose, polyvinyl pyrrolidone and poloxamer188/407 for treating irritable bowel syndrome. *Ex-vivo* antispasmodic activity was studied and compared with the conventional drug. Sustained release of drug for 8 h is observed for the gels [33]. Nasal administration of *in-situ* gel of Scopolamine hydrobromide along with gellan gum was used to treat motion sickness. The symptoms of motion sickness were decreased by nasal administration of 100 µg/kg of Scopolamine hydrobromide [34].

Drugs for CNS disorder

Central Nervous System disorders are categorized into various types which include alzheimers disease, cerebral malaria, schizophrenia, migrane, etc., and they are treated with drugs obtained from natural and synthetic sources. The detailed description of different *in-situ* gelling formulations of drugs using novel polymers for treating various disorders is shown in table 3.

Table 3: Drugs for CNS disorders formulated as *in-situ* gelling system

S. No.	Drug	Polymer	Diseases	Result
1.	Rivastigmine	N-stearoyl L-alanine methyl ester (SAM)	Alzheimers disease	Drug with SAM showed a prolonged therapeutic efficacy for 11 days [35].
2.	Artemether	Pluronic, hydroxyl propyl β-cyclodextrin, HPMC	Cerebral malaria	Better stability for 90 days [36].
3.	Huperazine A	Triethanol amine and chloral hydrate	Alzheimers disease	The AUC brain 0 to 6 h/AUC plasma 0 to 6 h was found to be ($p<0.05$) 96.5% [37]
4.	Midazolam hydrochloride	Pluronic F127, carbopol 934P and HPMC	Epileptic seizure	Increased bioavailability of the drug is obtained in the *in-situ* formulation [38]
5.	Eletriptan hydrobromide	Poloxamer 407(17%), carbopol 934 (0.3%)	Migraine and head ache	Increased bioavailability of about 86.27% was obtained and permeation rate was found to be more (480 min) [39]
6.	Sumatriptan succinate	Pluronic F127, carbopol 974	Headache and migraine.	Controlled drug release with higher permeability rate of 250 min [40]

Anti-ulcer drugs

Oral administration of Famotidine was formulated with calcium chloride and sodium alginate resulted in extraordinary formation of gel in stomach region and sustained the release of drug [41]. Similarly, oral administration of the drug Cimetidine with gellan gum, sodium alginate and xyloglucan was also used for treating ulcer. In release studies each formulation followed time dependent drug release kinetics for a period of 6 h [42].

Anti-diabetic drugs

To treat diabetes and to remove toxins, *in-situ* gel of Paracetamol and Ambroxol was formulated with pectin. The bioavailabilities of these drugs when released from gels formulated at the two pH limits didn't show any notable difference. This signifies that in the fasting state the normal variations of gastric acidity did not affect the bioavailability of these drugs. An ocular delivery of Ambroxol *in-situ* gel was formulated with the polymers pectin, sorbital, polyhydric acid. Sustained release was obtained with pectin (1 or 1.5%) and sorbitol (10%) [43].

Drugs to treat asthma

An oral administration of Theophylline *in-situ* gel was formulated with sodium alginate and 2-1% w/v concentration of alginate to treat asthma. When administered in rats, it showed increased bioavailability of the drug [44]. Salbutamol sulphate *in-situ* gel was formulated with carbopol 934P, HPMC to treat chronic diseases. The optimized formulation containing 0.25% Salbutamol sulphate, 0.4% carbopol, 1% HPMC, 0.9% NaCl, 0.02% benzalkonium chloride, 0.1% sodium metabisulphate showed a sustained drug release for 8 h [45].

Other category of drugs

Ocular administration of the anti-hypertensive drug Diltiazem hydrochloride as floating *in-situ* gel was formulated with HPMC, sodium alginate, calcium chloride, sodium methyl paraben. Formulation containing Diltiazem HCl-300 mg, HPMC-0.5%w/v, sodium alginate-2.5% w/v, calcium carbonate-2%w/v and sodium methyl paraben-180 mg showed significant floating efficacy. Thus, the optimized formulation *in-situ* gel proved to be an alternate for conventional dosage form [46].

Prilocaine hydrochloride, which is used as an anaesthetic for dental administration, was formulated as *in-situ* gel with the polymers chitosan and HPMC. This formulation showed good gelation at pH 7.4 [47]. Metoclopromide hydrochloride *in-situ* gel was formulated with polymers guar gum, sodium alginate and calcium carbonate which produced a better anti-emetic effect in the stomach. Release of drug content from this formulation was observed upto 8 h which showed that guar gum is responsible for controlled release of drug for longer period than sodium alginate due to its viscous nature [48].

An *in-situ* oral formulation of the drug Dexomethorphan, an anti-tussive agent was formulated along with sodium citrate, calcium chloride, sodium alginate and chitosan. The release pattern of this formulation in both the intestinal and gastric condition showed sustained release [49]. Ophthalmic *in-situ* gelling system of the drug Peurarin, an anti- angiogenic agent with the polymers Polaxamer 407,188 and carbopol was formulated which showed diffusion-controlled *in-vitro* drug release for about 8 h [50]. More recently, the fourth generation fluoroquinolone antibiotic Moxifloxacin was successfully developed as ophthalmic insitu gel for commercial applications, to overcome the drawbacks associated with its eye drops. [51] The specific relevance of insitu gelling system for ophthalmic delivery of various drugs has been extensively studied in this field [52].

CONCLUSION

Each drug having its own therapeutic effects can be administered through various routes as *in-situ* gels. These gels are more capable of sustained release and hence used widely nowadays. *In-situ* gelling systems have transformed as conventional drug delivery systems because of its controlled delivery and convenient application. *In-situ* gel dosage forms are very reliable due to sustained and prolonged drug release and good stability. The contact time of the drug in the target should be longer to increase the efficacy of the drug which will lengthen the residence time of the gel along with improved systemic absorption and trim down the need for frequent administration leading to enhanced patient compliance.

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