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

RAMYA DEVI D*, ABHIRAMI M, BRINDHA R, GOMATHI S AND VEDHA HARI B N
Department of Pharmaceutical Technology, School of Chemical and Biotechnology, SASTRA University, Thanjavur-613 401. Tamil Nadu, India.
Email: *ramya@scht.sastra.edu

Received: 24 Apr 2013, Revised and Accepted: 28 May 2013

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 fluid; it undergoes gelation to form a gel. Use of various natural, biocompatible, biodegradable as well as water soluble polymers such as chitosan, glycolic acid, poly-caprolactone, gelan gum, xylloglucon, 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-cyclodextrin, Gelling system

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, parenteral 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 chemothapeutic 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

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drugs</th>
<th>Polymer</th>
<th>Route</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ciproflaxin</td>
<td>Carbopol 940P, pluronic F127, gelan gum, 1.5% HPMC</td>
<td>Ophthamlic</td>
<td>Drug release for about 6 h [2]</td>
</tr>
<tr>
<td>2</td>
<td>Amoxillin</td>
<td>Sodium alginate, calcium chloride, sodium bicarbonate, sodium citrate, HPMC-K100</td>
<td>Incorporated directly to stomach</td>
<td>Drug release was found to be 6 to 10 h [3]</td>
</tr>
<tr>
<td>3</td>
<td>Linezolid</td>
<td>Hydroxypropyl guar, hydroxy ethyl cellulose, carbopol, sodium alginate, xanthum</td>
<td>Ocular</td>
<td>Sustained release over a period of about 6 h [4]</td>
</tr>
<tr>
<td>5</td>
<td>Gatifloxacin</td>
<td>Sodium alginate, HPMC</td>
<td>Ocular</td>
<td>Sustained drug release of about 8 h [6]</td>
</tr>
<tr>
<td>6</td>
<td>Clotrimazole</td>
<td>Carbopol 954P, gelan gum, HPMC</td>
<td>Oral</td>
<td>Zero order release kinetics with the sustained release for 8 h [7]</td>
</tr>
<tr>
<td>7</td>
<td>Doxycycline</td>
<td>Poloxamer 188, gelan gum, HPMC, sodium alginate</td>
<td>Ocular</td>
<td>Controlled release for about 24 h [8]</td>
</tr>
<tr>
<td>8</td>
<td>Moxifloxacin</td>
<td>HPMC, sodium alginate</td>
<td>Ocular</td>
<td>Drug release for about 10 h [9]</td>
</tr>
<tr>
<td>9</td>
<td>Metronidazole</td>
<td>Pluronic F68, F127</td>
<td>Vaginal</td>
<td>Treats bacterial vaginosis [10]</td>
</tr>
<tr>
<td>10</td>
<td>Sesbania grandiflora</td>
<td>Pluronic F127, chitosan</td>
<td></td>
<td>An increase in the viscosity at a temperature of about 37°C to form gel and provide sustained release [11]</td>
</tr>
<tr>
<td>11</td>
<td>Ofloxacin</td>
<td>Carbopol, HPMC</td>
<td>Ophthamlic</td>
<td>Sustained release for a period for 8 h [12]</td>
</tr>
<tr>
<td>12</td>
<td>Levofloxacin</td>
<td>Gelrite</td>
<td>Ophthamlic</td>
<td>Drug release of about 90.2% [13]</td>
</tr>
</tbody>
</table>
Anti-tumour effect

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

In-situ gel for rectal administration of Oxaliplatin with Pluronic-poly(acrylic acid)(PAA) polymer was formulated for treating colorectal cancer where phronic and PAA were proved to be non-toxic. The formulation showed increased Cmax 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

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drug</th>
<th>Polymer</th>
<th>Route</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Radix bupleri</td>
<td>Gellan gum</td>
<td>Nasal</td>
<td>The in-situ gel had a greater effect [longer anti pyretic effect] than the in-situ solution [19].</td>
</tr>
<tr>
<td>2.</td>
<td>Diclofenac sodium</td>
<td>Carbopol, sodium alginate, HPMC</td>
<td>Ophthalmic</td>
<td>Drug release prolonged for 8 h [20].</td>
</tr>
<tr>
<td>3.</td>
<td>Curcumin</td>
<td>Capryol 90, solutol HS15, transcutol HP</td>
<td>Nasal</td>
<td>Direct drug transport of nose-to-brain is better in nasal route than intravenous route [21].</td>
</tr>
<tr>
<td>5.</td>
<td>Ketorolac tromethamine</td>
<td>Methyl cellulose</td>
<td>Ophthalmic</td>
<td>Gelation temperature at 32°C and sustained drug release upto 9 h [23].</td>
</tr>
<tr>
<td>6.</td>
<td>Acetomenophen</td>
<td>Polycarbophil, polaxamer F188, 407</td>
<td>Rectal</td>
<td>In-situ gelling liquid suppository and mucoadhesive gels found to be more effective and convenient method for rectal delivery [24].</td>
</tr>
<tr>
<td>7.</td>
<td>Indomethacin</td>
<td>Gelrite</td>
<td>Ocular</td>
<td>Drug release upto 8 h [25].</td>
</tr>
<tr>
<td>8.</td>
<td>Nimesulide</td>
<td>Sodium alginate, polaxamer, Poly Ethylene Glycol, HPMC</td>
<td>Rectal</td>
<td>Addition of PEG resulted in satisfactory drug release rate and rectal retention [26].</td>
</tr>
<tr>
<td>9.</td>
<td>Paracetamol</td>
<td>Xyloglucan</td>
<td>Oral</td>
<td>Over a period of 6 h diffusion-controlled drug release was found [27].</td>
</tr>
</tbody>
</table>

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, acetointrile and phenetolamine was developed. After instillation, within 1 h the bio availability of S(-)-Satropene in aqueous humor increased to the maximum level with Cmax of 1.50±0.297gm⁻¹. This in-situ gel formulation exhibited 3.2 fold greater Cmax and 2.2 fold greater AUC-0-3 h (p < 0.05) [29].

Pilocarpine, used in the treatment of glaucoma, formulated with xyloglucan and plronic F127 showed a sustained drug release of about 6 h. Here, the ratio of xyloglucan to plunirone was about 1.5%-25% (w/w). [30]. In vitro release study of Forskolin, an anti-glaucoma agent with polaxamer 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 preconeral loss, an ophthalmic administration of Dexamethason with gelan 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 Mebeverine hydrochloride was formulated with hydroxy propyl methylcellulose (HPMC), methyl cellulose, polyvinyl pyrrolidone and poloxamer188/407 for treating irritable bowel syndrome. Ex-vivo antisapmsodic 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 gelan 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 alzheimer disease, cerebral malaria, schizophrenia, migraine, 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

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Drug</th>
<th>Polymer</th>
<th>Diseases</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Rivastigmine</td>
<td>N-stearoyl L-alanine methyl ester (SAM)</td>
<td>Alzheimer's disease</td>
<td>Drug with SAM showed a prolonged therapeutic efficacy for 11 days [35].</td>
</tr>
<tr>
<td>2.</td>
<td>Artemether</td>
<td>Pluronic, hydroxy propyl β-cyclodextrin, HPMC</td>
<td>Cerebral disease</td>
<td>Better stability for 90 days [36].</td>
</tr>
<tr>
<td>3.</td>
<td>Huperazine A</td>
<td>Triethanol amine and chloral hydrate</td>
<td>Alzheimer's disease</td>
<td>The AUC brain 0 to 6 h/AUC plasma 0 to 6 h was found to be (p&lt;0.05) 96.5% [37].</td>
</tr>
<tr>
<td>4.</td>
<td>Midazolam hydrochloride</td>
<td>Pluronic F127, carbopol 934P and HPMC</td>
<td>Epileptic seizure</td>
<td>Increased bioavailability of the drug is obtained in the in-situ formulation [38].</td>
</tr>
<tr>
<td>5.</td>
<td>Eletriptan hydrobromide</td>
<td>Poloxamer 407(17%), carbopol 934 (0.3%)</td>
<td>Migraine and head ache</td>
<td>Increased bioavailability of about 86.27% was obtained and permeation rate was found to be more (480 min) [39].</td>
</tr>
<tr>
<td>6.</td>
<td>Sumatriptan succinate</td>
<td>Pluronic F127, carbopol 974</td>
<td>Headache and migraine.</td>
<td>Controlled drug release with higher permeability rate of 250 min [40].</td>
</tr>
</tbody>
</table>
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 xylolucan 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, sorbitol, 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 2-15% 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 Diltaizem hydrochloride as floating in-situ gel was formulated with HPMC, sodium alginate, calcium chloride, sodium methyl paraben. Formulation containing Diltaizem HCI-300 mg, HPMC 0.5%, v/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]. Metoclopramide 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 Dexamethorphan, 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 Poloxamer 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 Mofoxacin was successfully developed as ophthalmic in-situ gel for commercial applications, to overcome the drawbacks associated with its eye drops. [51] The specific relevance of in situ 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.

ACKNOWLEDGEMENT

The authors are thankful to the management of SASTRA University, Thanjavur for providing the infrastructure and facilities.

REFERENCES


