EXPERT OPINION

Advancement in stimuli triggered *in situ* gelling delivery for local and systemic route

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Introduction: Current research efforts focused on the design and evaluation of drug delivery systems that are easy to administer require decreased administration frequency, and provide sustained drug release in order to increase clinical efficacy and compliance of the patients. The gel forming smart polymeric formulations offer numerous applications resemble sustained and prolonged action in contrast to conventional drug delivery systems.

Areas covered: Article summarizes type of bioactive, sol–gel triggering factors, dose, rationales, and polymers involved in gelation with respect to their route of administration. A lot of work has been done with smart polymeric gelling system taking the advantage of stimuli (temperature and pH) triggered sol–gel phase-transition in the administered area that have great prospective in biomedical and pharmaceutical applications, particularly in target-specific controlled drug delivery systems.

Expert opinion: Although the principle of gelation is so attractive, key issues remain to be solved which include (i) variability of the drug release, (ii) avoidance of burst release in case of depot formulation, and (iii) issues related to toxicity. Unfortunately, till now area concerning the detailed processes of the gelling formation is still not much explored. Despite this proclamation, many efforts are made in industry and institutions to improve concerned approaches. New materials and approaches enter the preclinical and clinical phases and one can be sure that this strategy will gain further clinical importance within the next years. Thus, this review article will assuredly serve as an informative tool for the innovators working in the concern area.

Keywords: *in situ*, smart polymers, sustained delivery, triggering factor

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1. Introduction

Widespread research has promoted the evolution of newer polymeric drug delivery system. The development of gelling system has received considerable attention over the past decade. This interest has been evolved by advantages shown by polymeric delivery system such as ease of administration and reduced frequency of administration, improved patient compliance and comfort, sustained and controlled delivery system [1].

In situ forming polymeric formulations drug delivery systems is in sol form before administration in the body, but once administered, undergoes gelation *in situ* to form a gel. The formulation of gel depends upon factors like temperature modulation, pH changes, presence of ions and ultra-violet irradiation, from which drug gets released in a sustained and controlled manner (**Figure 1**). The *in situ* gel exhibited the expected viscosity, drug content, and sustained drug release along with ease of administration and reduced frequency of administration, improving patient compliance and comfort [2,3].

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Article highlights.

- Exploiting smart polymeric gels for controlled release of bioactive provides a number of advantages over conventional dosage forms.
- Stimuli triggered sol–gel phase-transition of polymers in the administered area have great prospective particularly in target-specific controlled drug delivery systems.
- The foremost impediments of these systems are the variability in the shape of the formed gel, suppression of the burst release and toxicity of the matrix forming materials and solvents used.
- Article highlighted the useful finding in relevant area of last 2 to 3 years with respect to their route of administration.
- Subcutaneous and intramuscular sol–gel implants of anti-diabetic, anti-inflammatory, and anti-neoplastic bioactives are amazingly untouched and have a great scope ahead.

This box summarizes key points contained in this article.

One of the main reasons for the great success of this delivery system is that it can be delivered through various routes for either local or systemic effect in the body. On the other hand, incorporation of novel drug delivery approaches like liposomes, nanoparticles, microsphere, pegylation, nanoemulsion, microemulsion etc. again make this delivery system more promising [4,5]. Hence, in this review article we have highlighted the recent findings of different bioactive which takes the advantage of this delivery system by different routes of administration and at the same time this article also highlighted the beneficial effect of this amalgamation.

2. Ophthalmic/topical gelling system

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scientists. Rapid elimination of the eye drops administered often results in a short duration of the therapeutic effect making a frequent dosing regimen necessary [6,7]. The polymers, which carry on sol–gel phase transition and thus modify drug release owning to external stimuli, are the most investigated by this route. In this series, Ma W.D. *et al.*, 2008, developed the Pluronic F127-g-poly acrylic acid (Pluronic-g-PAA) copolymers were used as gelling vehicle for ophthalmic specific delivery system [8]. The release rates of the drug from such copolymer gels were mainly dependent on the gel dissolution. The gelation essentially be actual by temperature aid, such as Pluronic and ethyl (hydroxyethyl) cellulose. Suited to its unique thermo-reversible gelation characteristics, Pluronic F127 became one of the most extensively investigated temperature-responsive materials by this route. In their report, they have shown that the release effect of Gatifloxacin (GTX) in rabbit's conjunctivae sac was investigated with the aid of above-mentioned polymer. The level of GTX in rabbit's conjunctivae sac after instillation of 0.2% GTX gel containing 4.0% (w/v) copolymer significantly prolongs the drug resident time and thus improves bioavailability in comparison with 0.2% GTX eye drops without polymer. The rate of released drug from such copolymer gels was mainly dependent on the gel dissolution. The formulations have been prepared to overcome their lower bioavailability and precornial retention time. Pluronic-g-PAA copolymer may significantly prolong the drug resident time and thus improve bioavailability [9]. Another mode of sol–gel transition other than thermo responsive is pH-triggered gelation, which has become popular in recent years. The pH-triggered gelation of Ofloxacin is an example in the same context, in which Polyacrylic acid (CarbopolÒ 940) was used as the gelling agent in combination with hydroxypropylmethylcellulose (Methocel E50LV) which acted as a viscosity-enhancing agent. The formulation was liquid at the formulated pH (6.0) and underwent rapid gelation upon raising the pH to 7.4. Ofloxacin, a broad-spectrum antibacterial agent used in the treatment of ocular infections, was or successfully formulated as pH-triggered gel-forming eye drops (0.3%, w/v). The vile bioavailability and analeptic response exhibited by conventional ophthalmic solutions appropriate to runway precorneal elimination of the drug may be overcome by the use of gel-forming systems that are dropped into the eye and instilled as undergo a sol–gel transition in the cul-de-sac [10]. The developed formulation is a viable alternative to conventional eye drops by virtue of its ability to enhance bioavailability through its longer precorneal residence time and ability to sustain drug release [11].

Baicalin was successfully formulated in pH-triggered *in situ* gelling system using Carbopol® 974P (0.3%, w/v) as a pH-triggered gelling agent in combination with HPMC E4M (0.6%, w/v) as a viscosity-enhancing agent [12]. Baicalin has been reported to have anti-inflammatory and anti-cataract effects on eye tissues, but it has a low bioavailability partly due to its poor stability of Baicalin, the special anatomic structure, and efficient protective mechanism of eyes. It was found that the gelling system can flow easily under non-physiological condition (25°C, pH 5.8) and undergo rapid gelation under physiological condition (35°C, pH 6.8). *In situ* gelling system can support sustained drug release over an 8-hr period, and the release mechanism *in vitro* was dependent on two simultaneous processes, water migration into the *in situ* gelling system and drug diffusion. Stability data recorded over a 3-month period under (4 ± 1)°C, room temperature (25 ± 1)°C, and accelerated temperature (45 ± 1)°C condition indicated that the formulation was stable. And the formulation caused no irritation to rabbit eye tissues. Aqueous humor pharmacokinetic parameters (**Figure 2**) show that the AUC value of optimized formulation (F1-3) was much higher than that of the control solution, which were 6.1-fold vs. the control group ($p < 0.01$), and the C_{max} value of formulation F1-3 vs. the control solution was 3.6-fold ($p < 0.05$). The T_{max} value and $t_{1/2}$ value of formulation F1-3 were higher than those of control solution, which were

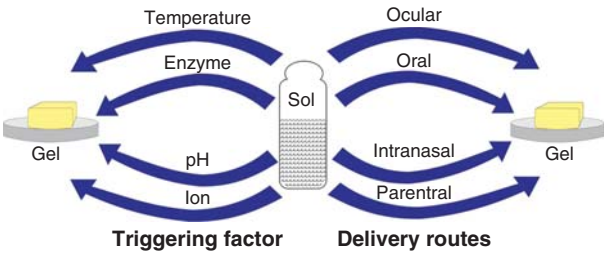

Figure 1. *In situ* gelling system showing the transition of sol–gel depending upon the triggering factors and delivery route.

2.6-fold. Both the *in vitro* and *in vivo* results indicated that the *in situ* pH-triggered gelling system is a viable alternative to conventional eye drops by virtue of its ability to enhance bioavailability through its longer precorneal residence time and the ability to sustain drug release. More importantly, it was a suitable medium for baicalin, the pH-sensitive drug, to be used as novel ophthalmic delivery system. Some other bioactives facing the same conventional problems of poor bioavailability by this route have been extensively studied in recent years. Their remarkable findings including polymer involved mode of transition, dose, and application of ophthalmic Gelling System as summarized in **Table 1**.

3. Intra nasal gelling system

The nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption [13]. This is due to the large surface area, porous endothelial membrane, high total blood flow, avoidance of first-pass metabolism, and ready accessibility [14,15]. Nasal delivery of *gelling* systems for different categories of bioactives have been studied in recent past, especially opioids, antihistaminics and antihypertensive [16-18]. Taking the advantage of this delivery system, intranasal gelling system of Sumatriptan using thermo reversible polymer Pluronic F127 (PF127) and mucoadhesivepolymer Carbopol 934P (C934P) formulations were optimized which bypassed the poor bioavailability of Sumatriptan which previously showed the low bioavailability of 15% in clinical trials [19]. Another important intranasal gelling system utilizing antimicrobial Ketamine Hydrochloride has been developed with Methylcellulose gel (3%) which resulted in the most prolonged nasal clearance whereas Carbopol 934P aqueous gel (0.2°C) had the largest rapid clearance. Among the polymers studied, the cellulose derivatives (3% methylcellulose) appear to possess the best combination for desirable characteristics through present route.

The intranasal delivery of Norwalk virus-like particles (NV VLPs) in a dry powder vaccine containing the inert mucoadhesive polymer, GelSite (an *Aloe vera* L.-derived, inert polysaccharide polymer), induces robust systemic and mucosal immunity in animal models [20]. A potential limitation to intranasal immunization is the rapid mucociliary clearance of vaccine components from the nasal cavity. Nasal mucociliary clearance in healthy humans is known to occur in less than 10 min. In nasal clearance studies using rabbits, greater than 90% clearance of control solutions from the nasal cavity was observed in 1 hr, with a half time of 24 min [21]. In this study it was found that a formulation of immune stimulating complexes (ISCOMs) could extend the clearance time to half times over 1 hr, due to mucoadhesive characteristics. These types of observations emphasize to examine the mucoadhesive and *in situ* gelling properties of GelVac powder that contains GelSite and has been proposed for use with mucosally delivered vaccines. Lissette *et al.*, presented evidence for *in situ* gelation of the dry powder when it contacts nasal epithelia. Their team conclude from the studies that the dry powder formulation stabilizes the norovirus VLP antigen; GelSite does not have immunostimulatory (adjuvant) activity itself; and that the superior immunogenicity of dry powder formulations containing GelSite compared to a control because of the delay in mucociliary clearance of the latter thereby prolongs VLP antigen exposure to immune effector sites. Some of the Intranasal Gelling systems are listed in **Table 2**.

4. Oral gelling system

Among oral dosage form, liquid dosage forms are more prone to low bioavailability because of their quick transit from the gastrointestinal tract (GIT). Strategy of liquid gelling system can be successfully augmented sustained release profile for an oral liquid formulation considerably [22]. Buccal drug delivery is a promising area for continued research with the aim of efficient systemic and local delivery of orally inefficient drugs. Buccal route is the most commonly employed route for a drug administered, which are susceptible to drug degradation, and for hepatic metabolism [23]. Local delivery of drugs to the tissue of the buccal cavity has a number of applications if delivered through gelling systems including the treatment of toothache periodontal diseases, dental caries, bacterial and fungal infections. Most of the oral-controlled drug delivery systems rely on diffusion, dissolution, or combination of both mechanisms to release the drug in a controlled manner to the GIT [24,25]. Some of the oral Gelling Systems are summarized in **Table 3**.

The pH-triggered formulations prepared for oral gelling system shows the sustained delivery of the bioactives which remarkably increases the bioavailability of the drug. *In situ* gelling system developed by Kuboa *et al.,* 2004, involved the principle of gelation having solutions containing calcium ions in complexed form, which on release in the acidic environment of the stomach caused gelation of the pectin. The bioavailability of Ambroxol Hydrochloride gels containing an identical dose shows an increased bioavailability of 64% and a sustained release of drug over a period of at least 6 h when compared with the commercially available formulation [26-28].

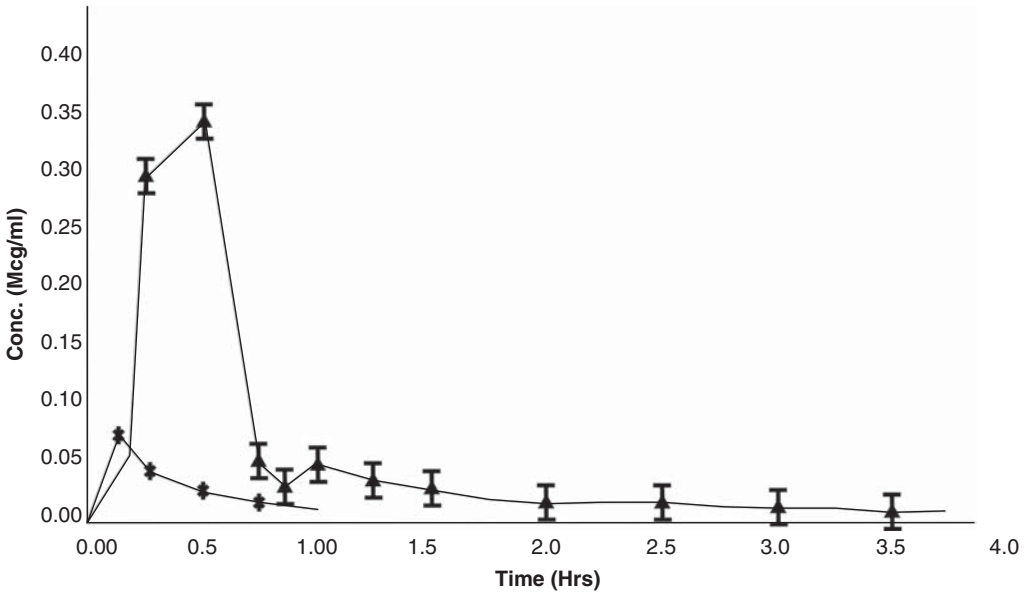

Figure 2. Aqueous humor baicalin concentration–time proles following a 100 μL topical dose in conscious rabbits (n = 3).
▲: Formulation F1-3; ×: The control solution.
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Kunihiko and team investigated the potential of an *in situ* gelling xyloglucan/pectin mixture for the oral administration of paracetamol. The formulations have been optimized to produce gelling and rheological properties suitable for oral administration and the *in vitro*/*in vivo* drug release characteristics have been examined. Xyloglucan solutions, 1.0, 1.5 and 2.0% (w/w), were mixed with various concentrations of pectin between 0 and 1.25% (w/w) and the flow behavior assessed visually after 10 min at 37°C. The 1.0% (w/w) xyloglucan solution formed a soft gel in the absence of added pectin, but failed to gel when pectin was present in the solutions at concentrations greater than 0.25% (w/w); 1.5 and 2.0% (w/w) xyloglucan solutions formed soft gels at pectin concentrations of between 0 and 0.75% (w/w); and a stronger gel in the presence of 0.75% (w/w) pectin; further addition of pectin, however, inhibited gelation. Formulations of 1.5 and 2.0% (w/w) xyloglucan/0.75% (w/w) pectin were selected for further study. Although *in vitro* drug release from the xyloglucan and xyloglucan/pectin mixtures was similar, the 2.0% (w/w) xyloglucan/0.75% (w/w) pectin solution had a significantly higher viscosity, which may be a disadvantage in swallowing the formulation during oral administration. In view of this, researchers chose to conduct *in vivo* experiments on the 1.5% (w/w) xyloglucan/0.75% (w/w) pectin mixture, which has a satisfactory gel strength and drug release characteristics. Measurement of plasma levels of paracetamol, after oral administration to rats, of a solution containing 1.5% (w/w) xyloglucan and 0.75% (w/w) pectin showed that a more sustained release and higher drug bioavailability was achieved from the gels formed by the *in situ* gelation of this formulation compared to that of a 1.5% (w/w) xyloglucan solution; 0.75% (w/w) solutions of pectin did not form gels under these conditions. The release profiles of paracetamol from gels formed from above selected formulations (**Figure 3**) are compared. At the completion of the release experiments (6 h) the gels were removed and weighed; the amounts of gels remaining were 77.0 ± 4.4% for the xyloglucan/pectin formulation compared to 34.0 ± 13.9% for the xyloglucan formulation (n = 6). The significantly slower erosion of the gel formed from the xyloglucan/pectin mixture is a consequence of its much greater gel strength and gives rise to the more sustained release of drug observed in **Figure 2** [29].

5. Parenteral gelling system

The parenteral route is the most effective and common form of delivery for active drug substances with poor bioavailability and the drugs with a narrow therapeutic index. However, parenteral administration of drug is often critical and associated with problems such as limited number of acceptable excipients, stringent requirements of aseptic production process, safety issues, and patient noncompliance [30]. In spite of these limitations, lots of research has been done in recent years regarding injectable systems capable of forming polymeric matrices *in situ*. This approach is highlighted as an attractive approach for minimally invasive and patient-friendly implantation of prosthesis and drug depots, avoiding the risk of burst release, and major surgeries. Furthermore, the list of biocompatible materials suitable for injectable gels is quite short and hence an intense research is being carried out for synthesizing new polymers and gelling modulators for designing adequate combinations for existing approved polymeric materials. The

Table 1. Ophthalmic *in situ* gelling system.

Drug	Polymer	Triggering factor	Dose	Duration of release	Problem	Improvement	Ref.
Cyclosporine A (CsA)	Polysorbate 80, Carbomer	Electrolyte-triggered gelling system	0.05%	32 h	Ocular inflammation	Preventing cornea allograft rejection	[41]
Timolol maleate, and brinzolamide	Mucoadhesive polymer, collagen	On contrast sensitivity	0.5% (TM+BA)		Variation in intraocular pressure (IOP)	Improved hypotensive effect	[42]
Timolol maleate	Poly(N-isopropylacrylamide)–chitosan (PNIPAAm–CS)	Thermo responsive gelation	0.5 mg/mL	12 h	Poor bioavailability and therapeutic response	Improves the bio-availability by reducing IOP*	[43]
Pilocarpine hydrochloride	Carbopol(PAA) polymer, pluronic	Phase transition temperature mediated	0.5%	Up to 6 h	Poor stability	Improved bioavailability	[44]
Timolol maleate	Pluronic F127	Thermo responsive gelation	0.5%	Up to 4 h	Poor bioavailability	Bioavailability increased upto 2.5 fold	[45]
Ofloxacin	Carbopol; Hydroxypropylmethylcellulose	pH-triggered gelling system	0.3% w/v	8 h	High tear fluid turnover and dynamics cause rapid precorneal elimination of the drug	provided sustained release of the drug which increases the bioavailability	[11]
Pilocarpine	Poly(ethylene glycol)	Cross linking hydrogels	0.5%	24 h	Reduced bioavailability	PEG hydrogels possess the viscoelastic, retention, and sust ained delivery of drug	[46]
Timolol maleate	Carbopol/Chitosan	pH- triggered gelling system	0.3–0.5%	24 h	Poor bioavailability due to nasolacrimal drainage of the drug	Carbopol-chitosan based formulation showed a fickian (diffusion-controlled)	[47]
Methotrexate	Synthesized co- polymerized N -isopropylacrylamide (NIPAM) and butylacrylate (BA)	Thermo responsive gelation	25 mg/mL	Up to 12 h	The use of Methotrexate is greatly limited due to its toxicity	Activated nanogel of Methotrexate reduces the toxicity and improves the bioavailability	[48]
Fluconazole	Poloxamer, Chitosan	Thermo responsive gelation	1.0%	Up to 6 h	Antifungal subconjunctival and intracameral injections are uncomfortable and may cause complications such as cataracts	*In situ* gelling are viable alternatives to enhance ocular bioavailability	[49]
Selegiline	Pluronic F127, Alginate	Thermo responsive gelation	0.25 mg	Up to 48 h	Sol–gel transition temperature(24.1 to 30.4°C)	Controlled-release transdermal system, sustained permeation	[50]

*Intra Ocular Pressure.

Table 1. Ophthalmic *in situ* gelling system (continued).

Drug	Polymer	Triggering factor	Dose	Duration of release	Problem	Improvement	Ref.
Diclofenac sodium	Pluronic F127	Thermo responsive gelation	0.1% w/v	Up to 12 h	Rapid precorneal elimination by protective mechanisms of the eye	Increase biovailability in aqueous humor significantly	[51]
Platelet lysate	Chondroitin sulphate sodium (CS) & Hydroxypropylmethyl cellulose (HPMC)	Thermo responsive gelation	–	Up to 24 h	Decreased production of tears or reduced corneal sensitivity	Enhanced cell growth & stimulating cell proliferation	[52]
Baicalin	Carbopol 974P (0.3%, w/v) with Hydroxypropylmethylcellulose E4M (0.6%, w/v)	pH-triggered gelling system	100 µL	Up to 8 h	Rapid clearance and reduced bioavailability	AUC and C max values 6.1-fold and 3.6-fold higher than control	[53]
Pilocarpine	Carrageenan	Ion- activated gelation	20 µl	2 h	Fast clearance and Poor AUC	2.5-fold higher bioavailability than aqueous solution	[54]

*Intra Ocular Pressure.

most studied synthetic polymers used for parenteral route are copolymers of poly (ethylene oxide) (PEO) and poly (propylene oxide) (PPO) (PEO– PPO– PEO; known as Poloxamers) and copolymers of poly (N-isopropyl acrylamide) (PNIPAAM). However, the use of these systems is limited because they are not biodegradable and hence block copolymers of PEG and poly (lactide-co-glycolide) (PLGA) were proposed as alternative and biodegradable materials. Among the natural polymers that exhibit gelation upon temperature change, particularly chitosan-based systems or derivatives have been studied in detail in the past decade.

Abashzadeh *et al.* prepared the *in situ* gel forming system of Triptorelin acetate as a model peptide using chitosan or its water-soluble derivatives as controlled delivery system for triptorelin acetate. In their studies, they reported the sustained *in vitro* release of triptorelin acetate to 192 h and at the same time suppressed the serum testosterone level *in vivo* in male rats up to 88% for a period of 35 days similar to standard marketed Diphereline SR microspheres. Release of prepared *in situ* gelling system is also compared with physical hydrogel composed of chitosan derivatives and opened ring polyvinyl pyrrolidone (OR-PVP). One more physical hydrogel which is composed of sodium carboxymethyl chitosan (NaCMCh) was also compared with *in situ* delivery system with respect to drug release. Physical hydrogel showed first-order release kinetics and delivered up to 100% of the peptide within 96 h without any burst. *In situ* gel forming system followed a biphasic pattern with an initial release phase of about 70% in 48 h and followed by sustained release of up to 100% within 192 h. Diphereline SR followed a biphasic pattern, showing an initial burst release of about 30% on the first day which was followed by sustained release of up to 45% within 2 weeks. The initial burst might be due to the presence of drug on the surface of the particles and the sustained release, which is a characteristic of microspheres (**Figure 4**). The *in situ* system delivered the active ingredients within the 196 h while the therapeutic effect prolonged up to 35 days. It seems that rapid swelling properties of the chitosan/OR-PVP hydrogels and availability of water as medium of release is responsible for short *in vitro* delivery period (192 h) while there was not such amount of available water *in situ* so the system swelled very slowly and consequently active ingredient was delivered in longer period.

Similarly injectable implant of vancomycin in combination with Pluronic F127 and αCD is explored which forms thermoresponsive supramolecular gels [31]. Pluronic F127 in the presence of αCD has been examined as a way to design syringeable gel formulations able to sustain drug release while using the lowest proportion of both components. Formulated gels sustained the release of vancomycin for several days being active against *S. aureus in vitro* cultures. However, formation of supramolecular system with combination of Pluronic F127 with αCD behave viscoelastic but syringeable gels when the concentration of αCD is equal to or above 5% enables the decrease of Pluronic concentration up to 6.5%

Table 2. Intra nasal *in situ* gelling system triggered mostly by "Thermo responsive" and "Ion-activated gelation".

Drug	Polymer	Triggering factor	Dose	Duration of release	Problem	Improvement	Ref.
Insulin (FITC)*	N-[(2-hydroxy-3-trimethyl-ammonium) propyl] chitosan chloride (HTCC) and poly (ethylene glycol) (PEG)	Thermo responsive gelation	13.7%	4 – 5 h	Poor absorption and bioavailability	Hydrogel formulation decreased the blood glucose concentration	[55]
Insulin	Chitosan (CS), Glutaraldehyde (GA)	Thermo responsive gelation	< 0.01%	24 h	Poor absorption and bioavailability	Nasal delivery of insulin using chitosan solutions increases trans-mucosal absorption	[56]
Mometasone furoate (MF)	Xanthan gum	Ion- activated gelation	20 μg/body	24 h	Rapid elimination of the instilled drug from the nasal cavity by mucociliary b eating	Allergic rhinitis, viscosity-enhancing (usually polymers), provide the prolonged contact between the drug and the absorptive sites in the nasal cavity	[57]
Atenolol	Poloxamers 407		3 mg/L	480 min	Low permeability and high solubility; Class III‡	Micro particles were compacted into tablets, which represent a simple dosage form for buccal/sublingual administration	[58]
Dummy	Chitosan, poly(ethylene glycol)	Thermo responsive gelation	13.7%	–	Photolytic enzymes in nasal secretions impact upon the bioavailability of proteins and peptides	Increased viscosity and rheological synergy of the resulting mucus/mucoadhesive system effects prolonged residence at the site of action	[59]
Vaccines	Trimethyl chitosan (TMC), Hyaluronic acid (HA)	Ion-activated gelation	25–250 μL)		Purified proteins show reduced immunogenicity compared to inactivated pathogen	Co-formulated in micro- or nanoparticles, foreign proteins are much more effective in eliciting immune responses	[60]

*Fluorescein isothiocyanate (FITC)-labeled insulin.
‡According to the Biopharmaceutical Classification System.

Table 3. Oral *in situ* gelling system.

Drug	Polymer	Triggering factor	Dose	Duration of release	Problem	Improvement	Ref.
Ambroxol hydrochloride	Pectin	Ion-activated gelation	1.0 and 1.5% w/v	6 h	Poor bioavailability	Sustained release	[26]
Diclofenac sodium	Gelatin grafted N - isopropy acryla-mide (NIPAAm)	Thermo-responsive (34.6–34.8°C)	10 mg	30 h	Poor bioavailability	The reversible on/off-switching behavior of the micro-spheres sustained the release of drug	[61]
Bupivacaine 9-anthracene carboxylate	9-Anthracene carboxylic acid	pH triggered	34 – 36 mg	Up to 30 h	Incomplete precipitation of the drug salt	The initial fast release was followed by a substantial sustained release	[62]
Cimetidine	Xyloglucan, sodium alginate	Thermo responsive gelation	300 mg	6 h	Poor bioavailability	Sustained release and increased bioavailability	[63]
Paraquat, Gramoxone INTEON®	Alginate, paraquat	Ion-activated gelation	12.5 ± 6 (µg/mL)	24 h	Acute toxicity	Reduce the acute oral toxicity of the formulation	[64]
Theophylline	Calcium alginate or aluminum alginate	Ion-activated gelation	29.5 ± 1.5 mg	8 h	Large fluctuations in plasma concentrations	Sustain the release of theophylline from alginate matrices	[65]
Theophylline	Sodium alginate	Ion-activated gelation	10 mg	8 h	Poor bioavailability	Bioavailability of theophylline increased by 1.3–2-fold	[66]
Leuprolide acetate	Poly(D, L -lactide-co-glycolide) PLGA	pH triggered	25 mg	Stable up to 150 days	Instability and poor bioavailability	Chemically more stable	[67]
Paracetamol, Ambroxol	Pectin gel	Ion-activated gelation	10 mg		Poor bioavailability	Sustained release following oral administration	[68]

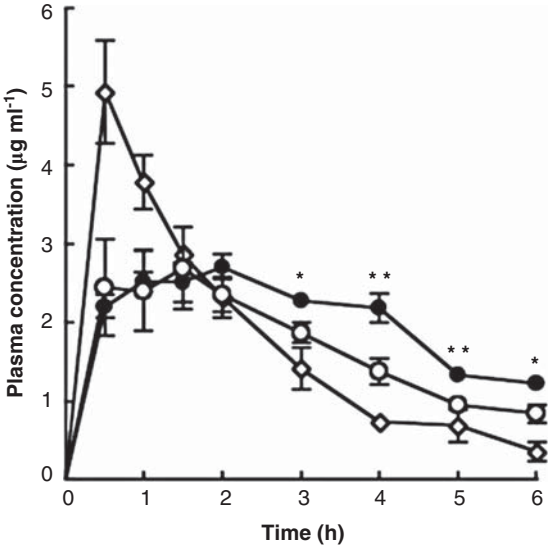

Figure 3. Plasma concentrations of paracetamol in rats after oral administration of (◇) 0.75% (w/w) pectin, (¤) 1.5% (w/w) xyloglucan, and (•) 1.5% (w/w) xyloglucan/0.75% (w/w) pectin solutions. Each value is the mean ± S.E. of 3–6 determinations.

*$p < 0.05$.

**$p < 0.01$, compared with 1.5% (w/w) xyloglucan.

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while keeping high storage and loss moduli. This was achieved by an optimum molar concentration of Pluronic: αCD (αCD: EO molar ratios 0.070 and 0.097 at 20°C) and were the most physically stable as observed by Simoes *et al*. Some of the parenteral gelling systems developed in recent years are summarized in **Table 4**.

6. Smart polymers involved in gelation (Figure 5)

6.1 Pectin

Pectins are a family of polysaccharides, in which the polymer backbone mainly comprises α-(1-4)-D-galacturonic acid residues. Although the gelation of pectin will occur in the presence of H^+ ions, a source of divalent ions, generally calcium ions is required to produce the gels that are suitable as vehicles for drug delivery.

6.2 Xyloglucan

Xyloglucan is a polysaccharide derived from tamarind seeds and is composed of a (1-4)-β-D-glucan backbone chain, which has (1-6)-α-D xylose branches that are partially substituted by (1-2)-β-D-galactoxylose.

6.3 Xanthum gum

Xanthum gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium *Xanthomonas campestris*. Cellulose derivative contains a cellulosic backbone (β- D-glucose residues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronic acid-α-D-mannose attached with alternate glucose residues of the main chain.

6.4 Gellan gum

Gellan gum (commercially available as Gelrite TM or Kelcogel TM) is an anionic deacetylated exocellular polysaccharide secreted by *Pseudomonas elodea* with a tetrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid, and two β-D-glucuronic acid residues.

6.5 Chitosan

Chitosan is a biodegradable, thermo-sensitive, polycationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell. Chitosan is a biocompatible pH-dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2 [32,33].

6.6 Carbopol

Carbopol is a well-known pH-dependent polymer, which stays in solution form at acidic pH but forms a low viscosity gel at alkaline pH. HPMC is used in combination with carbopol to impart the viscosity to carbopol solution, while reducing the acidity of the solution.

6.7 Pluronic F-127

Poloxamers or pluronic (marketed by BASF Corporation) are the series of commercially available difunctional triblock copolymers of non-ionic nature. They consist of a central block of relatively hydrophobic polypropylene oxide surrounded on both sides by the blocks of relatively hydrophilic poly ethylene oxide.

Apart from these above-mentioned polymers some polar lipids and surfactants are also exploited for *in situ* gelation. In this series Phelps *et al*. reported subcutaneous injection of naltrexone to sustain its release. Precursor formulations were obtained by combining BRIJ 97 with propylene glycol. Water uptake followed second-order kinetics, and after 2 – 4 h all precursor formulations were transformed into hexagonal phases. Drug release was prolonged by the precursor formulations (compared to a drug solution in PBS), and followed pseudo-first order kinetics regardless of naltrexone concentration. The release from BRIJ-80 was significantly higher than that from BRIJ-95 after 48 h, and both precursor formulations were significantly less cytotoxic than sodium lauryl sulfate at the same concentration (up to 50 μg/mL). These results suggest the potential of BRIJ-based *in situ* formulations for sustained naltrexone release [34]. In another study, Chang *et al.* reported the use of monoglyceride containing drug induced low viscous injectable sustained release formulations of chlorpheniramine maleate (CPM) and propranolol (PPL) HCl. In their study, they concluded that low viscous formulation of both drugs gets transformed into highly viscous cubic phase upon contact with aqueous media. And when transformed into the cubic phase the drug release

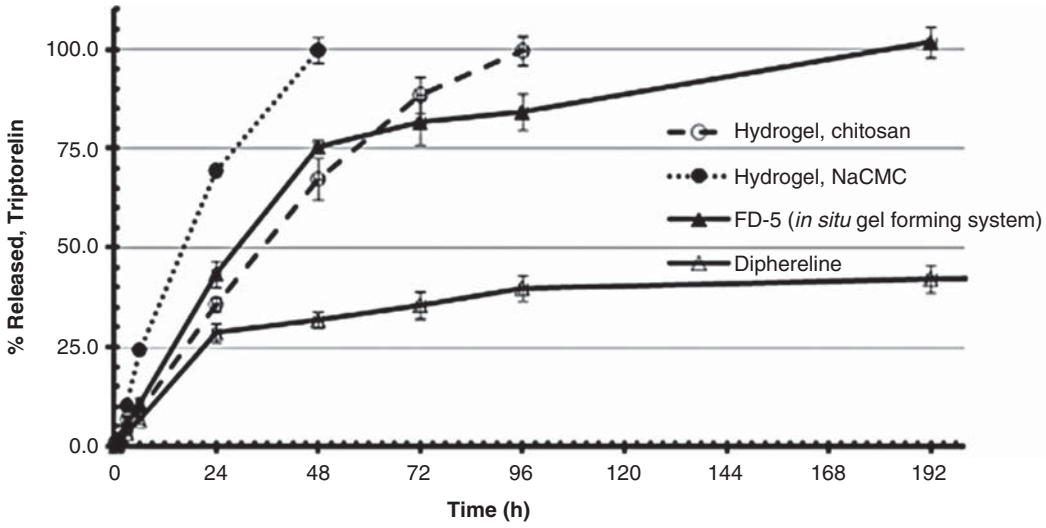

Figure 4. Comparison of release prole of Triptorelin acetate from prepared physical hydrogels composed of NaCMCh or Chitosan/OR-PVP, *in situ* gelling system (FD-5) and Diphereline.
Reproduced from [61] with permission of Elsevier.

decreased with increasing monoglyceride content and decreasing drug content [35]. A recent finding was explored by Nakai *et al.*, showing the effect of salt-induced HA nanogel, which contains a hyaluronic acid-based anionic nanogel formed by self-assembly of cholesteryl-group-bearing HA designed for protein delivery. The HA nanogel spontaneously binds various types of proteins without denaturation, such as recombinant human growth hormone, erythropoietin, exendin-4, and lysozyme which prove to be a very simple method for sustained release of proteins [36].

7. Value addition of gelling system through novel approaches

Much research effort in developing novel drug delivery system has been focused on controlled release and sustained release dosage forms. A well-designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a particular drug [37].

Novel drug delivery systems (NDDS) have many benefits, which include improved therapy by increasing the efficacy and duration of drug activity, increased patient compliance through decreased dosing frequency and convenient routes of administration and improved targeting for a specific site to reduce unwanted side effects [38].

Researchers developing new drugs pursue novel delivery technologies for enhanced products with the objectives of improving drug safety, increasing efficacy, site specificity, and enhancing the profitability. The current challenge of drug delivery is liberation of drug agents at the right time in a safe and reproducible manner to a specific target site [39].

Several applications of *in situ* gelling system used in improving the drug delivery are sustained and controlled drug delivery system, cell encapsulation, tissue repair, improving bioavailability, good stability and biocompatibility, improved patient compliance and comfort, Hydrogel used as biosensor, penetration enhancer, gene delivery, nutritional supplement, antioxidant, Antibiotic, anti-inflammatory action, membrane development, polymer stability, and sustained release [40]. Some of the novel drug deliveries through *in situ* gelling systems are summarized in **Table 5**.

8. Conclusion

The gel forming polymeric formulations offer several advantages like sustained and prolonged action in comparison to conventional drug delivery systems. This interest has been evolved by advantages shown by polymeric delivery system such as ease of administration and reduced frequency of administration, improved patient compliance and comfort, sustained and controlled delivery system. This review attempts to discuss the newer developments and strategies for this drug delivery including physiological factors, physiochemical factors, and different routes (oral, nasal, parenteral, ocular, and topical) and formulation factors to be considered in the development of *in situ* drug delivery system. Novel drug delivery systems have several advantages over conventional multidose therapy. Much research effort in developing novel drug delivery system has been focused on controlled release and sustained release dosage forms. Now considerable efforts are being made to deliver the drug in such a manner to get optimum benefits. The primary requirement of a successful controlled release product focuses on increasing patient compliance, good stability, and biocompatibility characteristics making the gel forms very reliable. Use of biodegradable and water-soluble

Table 4. Parenteral *in situ* gelling system.

Drug	Polymer	Triggering factor	Route	Dose	Duration of release	Problem	Improvement	Ref.
Rifampicin	Sodium alginate	Ion- activated gelation	Pulmonary injection	–	Up to 21 days	Untargeted distribution cause adverse effects	2-fold Prolonged drug release compared to plain microspheres	[69]
Triptorelin	Chitosan	Thermo responsive gelation	Subcutaneously	180 μg	Up to 192 h	Conventional formulation have less sustained effect	Suppressed the serum testosterone (up to 88% for a period of 35 days)	[70]
Leucine Isoleucine	Poloxamer- Alginate	Thermo responsive gelation	Periocular delivery	0.03 μmol	72 h	Intraocular administration of neurotrophic factors delay irreversible degeneration of (RGCs) *	Induces BDNF & GDNF[‡] level up to 72 days	[71] [72]
Doxorubicin	oligo(b-amino ester urethane) OAEU	Thermo responsive gelation and pH- triggered gelation	Subcutaneous delivery	0.5 mL	10 days	Shows poor bioavailability and short duration of action	OAEU[§] hydrogel was noncytotoxic and biodegradable and extend the release of the drug	[73]
Model protein	Elastin-like polypeptides (ELPs)	Thermo responsive gelation	Intratumoral injection	–	7 days	Normally Surgical implantation is required for sustained release	Injectable biomaterial to pervade tumors to maximize tumor coverage and retention time	[74]
Metoprolol, Doxycycline & Fufenamic acid	Polaxamer containing Chitosan & sodium tripolyphosphate	Ionotropic gelation	*In vitro* (passed through 27/23G needle)	–	–	–	Enhance the strength and mucoadhesiveness of formulation and hence give prolog release	[75]
Drug-free	N-methyl-2-pyrrolodone (NMP)	Electricalconducti-vity-based (pH 7.4 PBS)	–	–	110 min	Optimizing the organogel	Sustained-release drug delivery	[76]
l-alanine	L-alanine	Thermo responsive gelation	Sub cutaneous	–	–	Poor bioavailability	Sustained drug delivery	[77]

*Retinal ganglion cells (RGC).
[‡]BDNF (brain-derived growth factor) & GDNF (glial cell line-derived neurotrophic factor).
[§]Oligo(b-amino ester urethane) (OAEU).
[¶]chitosan–b –glycerophosphate.
[#]oxidized dextran.
[**]N-carboxyethyl chitosan.
[‡‡]*In situ* forming parenteral drug delivery systems.
[§§]Diethylaminopropyl-amine-poly(vinyl alcohol)-g-poly(lactide-co-glycolide).
[¶¶]Diethylaminoethyl-amine-poly(vinyl alcohol)-g-poly(lactide-co-glycolide).

Table 4. Parenteral *in situ* gelling system (continued).

Drug	Polymer	Triggering factor	Route	Dose	Duration of release	Problem	Improvement	Ref.
Drug free	Chitosan, mannitol	Thermo responsive gelation	Subcutaneous	–	–	Challenges in sterility and storage	More stable and sterilized	[78]
Drug free	Chitosan (C–GP)[¶]	Thermo responsive gelation	–	–	–	Limited use for parenteral administration as they are not biodegradable	Sustain the release of macromolecules over a period of several hours to a few days	[79]
Dextran	Odex[#], CEC**	pH and Thermo responsive gelation	–	–	–	Cell toxicity	Tests revealed that the hydrogels were non-cytotoxic	[80]
Paclitaxel	Pluronic-F127	Thermo reversible gelation	Subcutaneous	250 mg	12 h	PTX has a narrow therapeutic window and short elimination half-life, thus requiring higher doses	Targeted cytotoxicity, and controlled release of a drug without systemic toxicities	[81]
Chemokines	Ethylene–vinyl–acetate	Crosslinking gelation	Intramuscularly	50 mg	72 h	Limited effort has been made in using *in situ* crosslinking hydrogels for immunotherapeutic purposes migration	Porous gels are able to internalize pDNA–siRNA carrying microparticles leading to efficient gene silencing	[82]
Ellagic acid	Chitosan, propylene glycol	Thermo responsive gelation	Subcutaneous route	50 mg/kg body weight	360 h	Poor bioavailability due to poor biopharmaceutical properties	Sustained release	[83]
Doxorubicin and Paclitaxel combined therapy	Glycol chitosan & Benzaldehyde terminated poly (ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol)	pH triggered gelation	Intratumoral	20 mg/kg	12 days	Nonspecific uptake of antitumor drugs to target healthy organs when dosed by intravenous injection	Localization and prolongation of survival time in comparison with the single drug therapy	[84]

*Retinal ganglion cells (RGC).
[‡]BDNF (brain-derived growth factor) & GDNF (glial cell line-derived neurotrophic factor).
[§]Oligo(b-amino ester urethane) (OAEU).
[¶]chitosan–b –glycerophosphate.
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Table 4. Parenteral *in situ* gelling system (continued).

Drug	Polymer	Triggering factor	Route	Dose	Duration of release	Problem	Improvement	Ref.
Ethosuximide	Chitosan	Thermo responsive gelation	Subcutaneous	10 mg/mL	20 days	Drug release is below 24 h in conventional formulations	Reduced burst release and release rate with excellent cytotoxic action	[85]
Heparin and Dextran	Tyramine	Enzyme mediated gelation	*In vitro*	2 m g/mL	21 days	–	Injectable hydrogels are promising scaffolds for cartilage regeneration	[86]
Insulin (ISFPD‡‡)	**(DEAPA–PVAL-g-PLGA§§), DEAEA-PVAL-g-PLGA¶¶ and DMAPA-PVAL-g-PLGA‡**	**Ion- activated gelation**	***In vitro***	**2% insulin solution**	**Up to 2 weeks**	**Unstable in gastrointestinal tract and low permeability across biological membrane**	**Formulation is stable thus suitable for storage and showed sustained release, best suited for parenteral depot formulation**	[87]
Naltrexone hydrochloride and vitamin B12	**Triblock copolymer of PLGA–PEG1000–PLGA and Triblock copolymer of PLGA–PEG1500–PLGA**	**Thermo responsive gelation**	***In vitro***	**–-**	**4 weeks**	**Fluctuations in the plasma concentration**	**Control the release and reduce fluctuation**	[88,89]

*Retinal ganglion cells (RGC).
‡BDNF (brain-derived growth factor) & GDNF (glial cell line-derived neurotrophic factor).
§Oligo(b-amino ester urethane) (OAEU).
¶chitosan–b –glycerophosphate.
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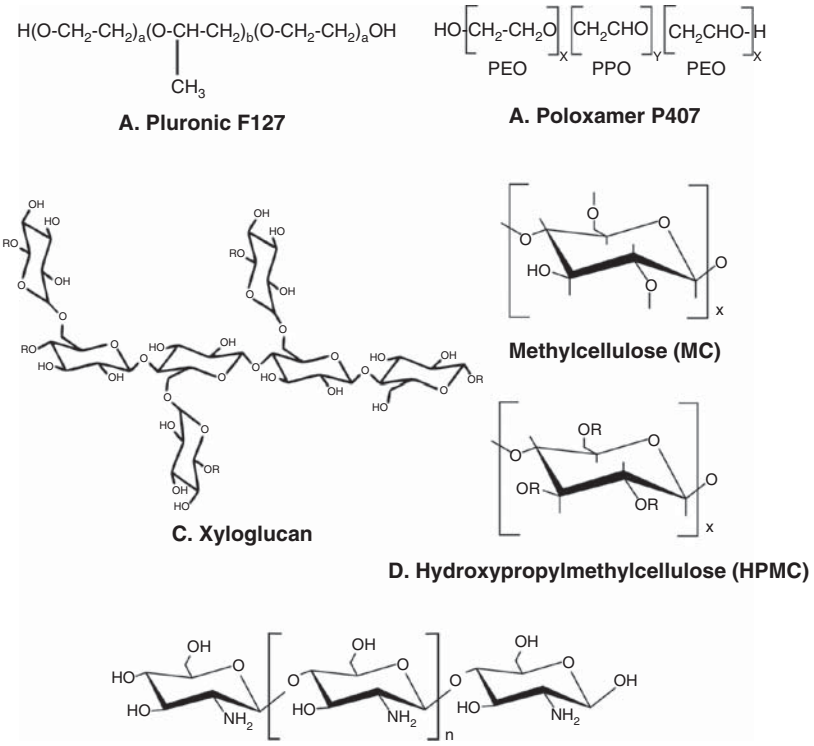

Figure 5. **A.** Pluronic F127: polyoxyethylene-polyoxypropylene triblock copolymer of general formula E106 P70 E106, with an average molar mass of 13,000. **B.** Polaxomer P407: Chemical structure of the P407 poloxamer, which contains between 95 and 105 monomeric ethyleneoxide (x) subunits and 54 to 60 propyleneoxide (y) sub-units. **C.** Xyloglucan: Xyloglucan (**B**) is β-(1,4)-d-glucan, like cellulose. **D.** Hydroxypropylmethylcellulose: Methylcellulose solutions transform into opaque gels between 40 and 50°C, and HPMC shows phase transition between 75 and 90°C (NaCl decreases the transition temperature of methylcellulose solutions to 32–34°C). **E.** Chitosan: Chemical structure of chitosan. **F.** Ethylhydroxyethylcellulose (EHEC): These solutions completely changed their thermal behavior. These systems underwent sol–gel phase transition upon heating from room temperature to 30 – 40°C, resulting in the formation of stiff and clear gels. **G.** Alginic acid: Alginic acid is a linear polymer based on two monomeric units, β -D-mannuronic acid and α -L-guluronic acid. **H**. Corbopol: The carboxyl groups provided by the acrylic acid backbone of the polymer. **I.** Gellan gum: Chemical structure of low acyl gellan gum.

polymers for the gel formulation can make them more acceptable and excellent drug delivery system.

9. Expert opinion

One of the challenges facing today's pharmaceutical industry centers on coming up with efficient treatment options that are readily acceptable to physicians and patients and in this series gel formulations remain an exigent drug delivery systems. Utilizing controlled release of various drugs by the use of polymeric gels provides a number of advantages over conventional dosage forms. Gel dosage forms are more prominent because of their sustained and prolonged release of the drug with improved stability and biocompatibility characteristics. The gelling systems are more popular and acceptable delivery systems due to the use of biodegradable and water-soluble polymers in their preparation.

Gels administered by oral, ocular, rectal, vaginal, and parenteral routes make this system more versatile. The use of different polymeric material for different routes of administration makes it more prominent. Pectin, gellan gum, xyloglucan, and alginic acid are the natural polymers used for forming oral drug delivery systems. The potential of orally administered gelling pectin and gellan gum formulation for the sustained delivery of different bioactive have been reported in recent past. However, among these two much of the interest in the pharmaceutical application of gellan gum has concentrated on its application for ophthalmic drug delivery because drug release from gellan gum gels is sustained due to greater precorneal residence times of the viscous gels compared with conventional ophthalmic drops. In continuation with the same, Alginic acid can be chosen as a vehicle for ophthalmic formulations, since it exhibits favorable biological properties such as biodegradability and nontoxicity. Alginic acid is also a polymer of choice for ophthalmic preparation not only based on its ability to conversion into gel in the eye, but also because of its mucoadhesive properties and prolonged precorneal residence time.

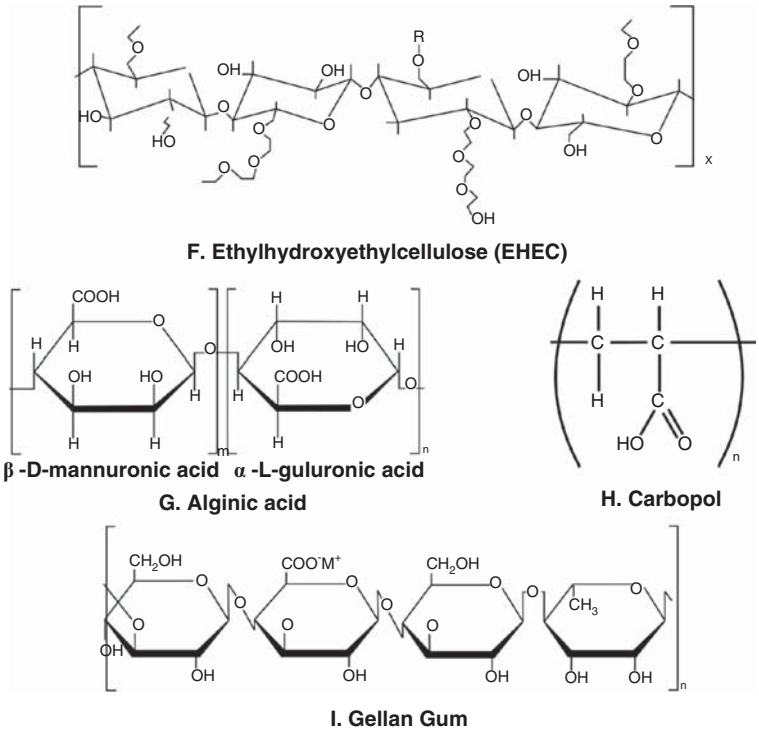

Figure 5. (continued). A. Pluronic F127: polyoxyethylene-polyoxypropylene triblock copolymer of general formula E106 P70 E106, with an average molar mass of 13,000. **B.** Polaxomer P407: Chemical structure of the P407 poloxamer, which contains between 95 and 105 monomeric ethyleneoxide (x) subunits and 54 to 60 propyleneoxide (y) sub-units. **C.** Xyloglucan: Xyloglucan (**B**) is β-(1,4)-d-glucan, like cellulose. **D.** Hydroxypropylmethylcellulose: Methylcellulose solutions transform into opaque gels between 40 and 50°C, and HPMC shows phase transition between 75 and 90°C (NaCl decreases the transition temperature of methylcellulose solutions to 32–34°C). **E.** Chitosan: Chemical structure of chitosan. **F.** Ethylhydroxyethylcellulose (EHEC): These solutions completely changed their thermal behavior. These systems underwent sol–gel phase transition upon heating from room temperature to 30 – 40°C, resulting in the formation of stiff and clear gels. **G.** Alginic acid: Alginic acid is a linear polymer based on two monomeric units, β -D-mannuronic acid and α -L-guluronic acid. **H**. Corbopol: The carboxyl groups provided by the acrylic acid backbone of the polymer. **I.** Gellan gum: Chemical structure of low acyl gellan gum.

Synthetic polymers along with their block copolymers are also gaining recognition in the past decade for the formulation of temperature and pH-sensitive gelling system. Among them, some of broadly used synthetic polymers are poly (N -substituted acryl amide)-based block copolymers, poloxamers and their derivatives, poly (ethylene glycol)-polyester block copolymers, polyelectrolyte-based block copolymers, and the polyelectrolyte-modified thermo-sensitive block copolymers.

Recently, FDA approved gelling system of Leuprolide acetate (Eligard®) and Doxycycline hyclate (Atridox®) for treatment of advanced prostate cancer and adult parodontitis, respectively. Thermally induced intratumor injection of Paclitaxel gelling system (Oncogel®) is presently in Phase II clinical trial. For the indication of schizophrenia and bipolar disorder DURET company launches the Risperidone intra muscular injection which is currently in preclinical phase.

Despite the attractive features of this delivery system and the existence of clinically used systems, serious constraints do still exist. The main obstacles in the development of gel system are the variability in the shape of the formed gel, suppression of the burst release and toxicity of the matrix forming materials and solvents used. To sum it up it can be said that an ideal forming implant should possess a low viscosity of the implant solutions to ensure a good injectability, allow a simple drug load, contain only biodegradable and biocompatible excipients, possess superior system stability, and yield a low unpredictability of drug release with a low preliminary burst.

The diminishing of discrepancy and the upgrading the system to provide a burst free, controlled drug release with unsurprising biological fate of a nontoxic carrier will be the main challenge for the future development of gelling system. Development of gelling system especially subcutaneous and intramuscular sol–gel implants of anti-diabetic, anti-inflammatory, and anti-neoplastic bioactives is amazingly untouched till date and has a great scope ahead. Many efforts are made in industry and academia to improve the current approaches. New materials and approaches enter the preclinical and

Table 5. Novel drug deliveries through *in situ* gelling system formulation.

Formulation	Polymers	Application of Formulation	Biological Activity	Mode of Transition	PH	Dose	Novel Drug Delivery	Route of Administration	Ref.
Doxorubicin liposome	Hexadecylphospho-choline (HePC)	Activity against cancer cells	Cytotoxicity activity	pH gradient method	7.5	5%	Liposome	Oral	[90]
Istaroxime liposome	Poly(ethylene glycol)	Controlled release	Inotropic agents, Vasodilator	Transmembrane pH-gradient	7.3 – 7.4	0.5 – 1.5 mg/kg/min	Liposome	Intravenous	[91]
Cefuroxime sodium-loaded microspheres	Gelatin-mucin	Enhance the rectal bioavailability	Antibiotic	Emulsification-crosslinking technique	7.4	100 mg	Microsphere	Rectal delivery	[92]
Subtilisin microsphere	Alginate	Improved dissolution time	Enzymatic activity	Emulsification, Internal gelation	7.5	3%	Microsphere	–	[93]
Alginate microsphere	Alginate	Soft tissue regeneration,	Anti-toxic	Crosslinking external gelation technique	7.4	2.5% to 4% w/v	Microsphere	Injectable	[94]
Clarithromycin	Gellan gum	Increase floating time	Antimicrobial agent	Gelation by crosslinking	1.2	0.75% w/v	Floating Tablet	-	[95]
Diallyl trisulfide microemulsion	Diallyl trisulfide	Better therapeutic effect.	Anti-toxic	Oil-free o/w gelation	1,7.4,10	30 mg/kg	Microemulsion	Intravenous (i.v.)	[96]
Chitosan nanoemulsion	Chitosan	Prolong its residence..	Antibacterial and Antitoxic	Oil-free o/w gelation	7.4	13%	Nanoemulsion	Ophthalmic	[97]
Flurbiprofen nanoemulsion	Flurbiprofen	Process in size distribution of drug	Anti-inflammatory	Oil/water (O/W) gelation	3.5	0.03% FB	Nanoemulsion	–	[98]
Camptothecin	Polyethylene glycol–poly (d,l-lactide)	Possessed high cytocompatibility	Anticancer	Thermo responsive gelation, sol–gel phase transition	6.4 – 6.8	1 mg/kg	Nanopartical	Dendritic	[99]
Trimethyl chitosan (TMC)	Hyaluronic acid (HA)	Beneficial effects of stabilization	Antibiotic	Ion- activated gelation	7.4	13%	Nanopartical	Nasal and intradermal	[60]
Superparamagnetic iron oxide	Iron oxide	Cancer therapy, excellent biocompatibility	Anti cancer	Ion-activated gelation	7.4	–	Nanopartical	–	[100]
Calcitonin	Glycol chitosan	Pulmonary peptide delivery	Anti-Hypercalcemia	Ion- activated gelation	6.7	0.5mL	Nanopartical	Pulmonary route	[101]
Teicoplanin	Polymethylmetha-cylate (PMMA)	Therapeutic inflammatory response	Systemic antibiotic	Thermo responsive gelation implant	7 or 8	200 – 400 mg	Nanopartical	Topical and intravenous	[102]

clinical phases and one can be sure that this delivery system will gain further clinical importance within the next years.

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Declaration of interest

The authors declare no conflict of interest.

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