REVIEW PAPER

Pharmaceutical

FLOATING CONTROLLED AND SUSTAINED IN-SITU GELLING SYSTEM: CURRENT APPROACHES

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ABSTRACT

An intensive research have been undertaken to develop drug delivery system to achieve better drug product effectiveness, reliability and safety. In situ forming polymeric delivery systems shows advantages such as ease and reduced frequency of administration, improved patient compliance and comfort. These systems are liquid at room temperature but undergo gelation when come in contact with body fluids or change in pH. The formation of gels depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation. Drug gets released in a sustained and controlled manner from the gel. Various biodegradable polymers are used for the formulation of in situ gels. These are administered by oral, ocular, rectal, vaginal, injectable and intraperitoneal routes. These systems offer sustained and prolonged action in comparison to conventional systems. Also production of such system is less complex and lowers manufacturing cost.

INTRODUCTION

Oral route of drug delivery is preferred and most patient convenient means of drug administration. But many compounds are either incompletely or ineffectively absorbed after oral administration or required dosing frequency is too short to enable once or twice-daily administration. Modified-release formulations offer an effective means to optimize the bioavailability and resulting blood concentration-time profiles of drugs that otherwise suffer from such limitations (Charman, 2002).

In situ gel forming systems have been widely investigated as vehicles for sustained drug delivery as it shows advantages like ease & reduced frequency of administration, improved patient compliance and comfort. In situ gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. Various natural and synthetic polymers such as gellan gum, alginic acid, xyloglucan, pectin, chitosan, poly (DL lactic acid), poly (DL-lactide-co-glycolide) and poly-caprolactone are used for its formulation development. (Remya, Damodharan, Venkata 2011: Dressman et al. 1990) Gastroretentive in situ gelling system increases bioavailability of drug compared to conventional liquid dosage form. The gel formed, being lighter than gastric fluids, floats over the stomach contents or adhere to gastric mucosa due to presence of bio adhesive polymer and produce gastric retention of dosage form increasing gastric residence time. (Yokel, Dickey, Goldberg 1995; Rania, Gehanne, Nahed, 2007)

APPROACHES FOR IN SITU GELLING SYSTEM

Stimuli-responsive in situ gel system:

According to Subhashis et al. (2011) these systems comprise of polymers that undergo relatively large and abrupt, physical or chemical changes in response to small changes in the external environment. These polymers might recognize a stimulus as a signal, judge the magnitude of this signal and then change their chain conformation in direct response.

Temperature induced in situ gel systems

Temperature-sensitive hydrogels are most commonly studied class of environment-sensitive polymer systems. Use of biomaterial whose transitions from sol to gel is triggered by increase in temperature is an attractive way to approach in situ formation. The ideal critical temperature range for such system is physiologic temperature and no external source of heat other than that of body is required for trigger gelation. A useful system should be tailorable to account for small differences in local temperature. Temperature-sensitive hydrogels are classified into negatively thermosensitive, positively thermosensitive and thermally reversible gels. (Kant, Reddy, Shankraiah, Venkatesh, Nagesh 2011)

pH induced in situ gel systems-

In another in situ gel system based on physiologic stimuli formation of gel is induced by pH changes. All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. The most of anionic pH-sensitive polymers are based on poly acrylic acid (PAA) or its derivatives. Likewise polyvinyl acetaldiethyl aminoacetate (AEA) solutions with a low viscosity at pH 4 form hydrogel at neutral pH condition. Drug formulated in liquid solutions have limitations like limited bioavailability and propensity. Kumar et al. (2005) found that at concentrations to cause gelation, low pH of PAA solution would cause damage to surface of eye before being neutralized by the lacrimal fluid. This problem was solved partially by combining PAA with HPMC, which resulted in pH responsive polymer mixtures that was solution at pH 4 and gel at pH 7.4. Mixtures of poly methacrylic acid and poly ethylene glycol also has been used as a pH sensitive system to achieve gelation.

Osmotically induced in situ gel systems

In this method, gelling of the solution instilled is triggered by change in the ionic strength. (Kant et al. 2011). It is assumed that the rate of gelation depend on the osmotic gradient across the surface of the gel. The aqueous polymer solution forms a clear gel in the presence of the mono or divalent cations especially Na+, Ca++ and Mg++. The polymer which shows osmotically induced gelation are gelrite or gellan gum, hyaluronic acid and alginates. (Nirmal, Bakliwal, Pawar 2010)

Chemically induced in situ gel systems:

Chemically induced systems are of following type-

Ionic crosslinking:-

Bhardwaj et al. (2000) studied that certain ion sensitive polysaccharides such as carragenan, Gellan gum (Gelrite), Pectin, Sodium Alginate undergo phase transition in presence of various ions such as K+ , Ca++, Mg++, Na+. Alginic acid undergoes gelation in presence of divalent/polyvalent cations due to the interaction with guluronic acid block in alginate chains.

Enzymatic crosslinking:

In situ formation catalysed by natural enzymes has not been investigated widely but seems to have some advantages over chemical and photochemical approaches. An enzymatic process operates efficiently under physiologic conditions without need for

potentially harmful chemicals such as monomers and initiators. Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion. (Podual, Doyle, Peppas; 2000)

Photo-polymerization:

In situ photo-polymerization has been used in biomedical applications for over more than a decade. A solution of monomers or reactive macromers and initiator can be injected into a tissues site and the application of electromagnetic radiation used to form gel (Jones, Philip, Msssersmith 2002). Acrylate or similar polymerizable functional groups are typically used because they rapidly undergo photopolymerisation in the presence of suitable photo initiator. Photopolymerizable systems when introduced to the desired site via injection get converted in situ with the help of electromagnetic radiation and then release the drug for prolonged period of time. A photo-polymerizable, biodegradable hydrogel as a tissue contacting material and controlled release carrier is reported. (Sawhney et al. ; Miyazaki et al. 1999)

In situ formation based on physical mechanism

Swelling

In situ formation may also occur when material absorbs water from surrounding environment and expand to acquire desired space. One such substance is myverol 18-99 (glycerol mono-oleate), which is polar lipid that swells in water to form lyotropic liquid crystalline phase structures. It has some bioadhesive properties and can be degraded in vivo by enzymatic action.

Diffusion

This method involves the diffusion of solvent from polymer solution into surrounding tissue and results in precipitation or solidification of polymer matrix. N-methyl pyrrolidone (NMP) has been shown to be useful solvent for such system. (Kant, Reddy, Shankrajah, Venkatesh, Nagesh 2011).

APPLICABILITY OF IN SITU POLYMERIC DRUG DELIVERY SYSTEM

Oral-delivery

Pectin, xyloglucan and gellan gum are the natural polymers used for in situ forming oral drug delivery systems. (Raina, Gehanne, Nahed 2007). The potential of such formulation using pectin for the sustained delivery of amobroxol has been reported. The main advantage of using pectin for these formulations is that it is water soluble, so organic solvents are not necessary in the formulation. (Podual 2000) In situ gelling gellan formulation as vehicle for oral delivery of theophylline is reported. It consisted of gellan solution with calcium chloride and sodium citrate complex. When administered orally, calcium ions are released in acidic environment of stomach leading to gelation of gellan. Increased bioavailability with sustained drug release profile of theophylline in rats and rabbits was observed from gellan formulations.

Ocular- Delivery

For in situ gels based ocular delivery, natural polymers such as gellan gum, alginic acid and xyloglucan are most commonly used polymers. (Pandya, Modasiya, Patel 2011) Local ophthalmic drug delivery has been used for various compounds such as antimicrobial, anti-inflammatory agents and autonomic drugs. Conventional delivery systems often result in poor bioavailability and therapeutic response because high tear fluids turn over, rapidly eliminating drug from the eye. So, to overcome bioavailability problems, ophthalmic in situ gels were developed. (Itoh, Hirayama, Takahashi, Kubo 2007) Drug release from these in situ gels is prolonged due to longer precorneal contact times of the viscous gels compared with conventional eye drops. B. Srividya et al. attempted to formulate in situ gels for ocular delivery using carbopol 940 (0.5% w/w) as polymer. (Bhimani, Patel, Patel 2007) These systems were observed to show a significant mitotic response for a period of 4 h when instilled into lower cul-de-sac of rabbit eye. (Rathore et al. 2009) The formulation and evaluation of an ophthalmic delivery system for indomethacin showed sustained release of indomethacin for a period of 8 h in vitro. (Srividya, Rita, Cardoza, Amin, 2001)

Nasal -Drug Delivery Systems

In situ gelling inserts are a new solid dosage form for the application of drugs via the nasal mucosa. They can be formed by various amorphous, water-soluble polymers and has properties such as water uptake behavior, bioadhesion potential, mechanical properties and drug release profile. Higher molecular weight polymers gave an extended release over more than 8 h under in vitro test as well as have excellent bioadhesion property. (Cao, Zhang, Shen 2007) An in situ gel system for nasal delivery of mometasone furoate was developed using gellan gum and xanthan gum as polymers. In situ gel was found to inhibit the increase in nasal symptoms as compared to marketed formulation. Intact ciliated respiratory epithelium and normal goblet cell appearance indicated from histopathology of rat nasal cavity proved that these formulations were safe for nasal administration. (Bertram, Bodmeier 2006)

Rectal and Vaginal -Delivery

In situ gels also possess a potential application for drug delivery by rectal and vaginal route. Yu-Kyoung Oh et al. investigated in situ gelling mucoadhesive vaginal vaccine delivery system. The in situ gelling mucoadhesive delivery system of hepatitis B surface antigen (HBsAg), composed of poloxamers and polycarbophil, showed the prolonged retention at the vaginal tissues. The thermosensitive and mucoadhesive polymer based vaginal vaccine delivery systems might be useful in enhancing mucosal and systemic immune responses. (Tiwaria, Goyalb, Mishraa, Vaidya 2009)

Injectable-Drug Delivery Systems

A novel, injectable, thermosensitive in situ gelling hydrogel was developed for tumor treatment. This hydrogel consisted of drug loaded chitosan solution neutralized with - glycerophosphate which is injected intratumorally. Ito et al. designed and synthesized injectable hydrogels that are formed in situ gel by cross-linking of hydrazide modified hyaluronic acid with aldehyde modified versions of cellulose derivatives such as carboxy methylcellulose, hydroxyl propyl methylcellulose and methyl cellulose. These gels were used for preventing postoperative peritoneal adhesions thus avoiding pelvic pain, bowel obstructions and infertility. (Oha, Park, Yoonc, Kimb 2003)

EVALUATION AND CHARACTERIZATIONS OF IN SITU GEL SYSTEM

The prepared in situ gel formulations were evaluated for clarity, pH measurement, viscosity, texture analysis, Sol-Gel transition temperature, gelling time, gel strength, drug content, drug polymer interaction study, thermal analysis, in vitro drug release studies and stability study.

CONCLUSION

A lot of research is ongoing in various laboratories to explore in situ gel as drug delivery systems for better patient care. The polymeric in situ gels for controlled release of various drugs provides a number of advantages over conventional dosage forms. Sustained and prolonged release of the drug, good stability and biocompatibility characteristics make the in situ gel dosage forms very reliable. Nowadays, in situ gelling system has become the alternative of conventional dosage form because of its controlled drug release, use of water soluble and biodegradable polymers, biocompatibility and better patient compliance by reducing dosing frequency.

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