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Insitu Gelling Systems: Novelty towards Controlled And Sustained Drug Delivery

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ABSTRACT:
Controlled and sustainable drug release is always being one of the most interesting and challenging tasks for the pharmaceutical scientists. This interest led to the researches over the advantages of the insitu gelling phenomena such as reduced frequency of administration, improved patient compliance, therapeutic effectiveness, safety and efficacy. The main aim of the review is to explore the grounds of insitu gelling drug delivery systems, major focus is based on the current applications and also on-going researches on the insitu gels. The review includes approaches of insitu drug delivery systems, polymeric systems used in the phenomena, evaluation and characterisation of insitu gel system, recent advances/applications of insitu gels. Review further concluded by the view that insitu gels are one of the the most successful formulation with respect to the controlled and sustained drug delivery in comparision to conventional drug delivery systems.

Keywords: Insitu Gelling, Controlled, Sustained, Polymers,Swelling, Solvent exchange.

I. INTRODUCTION:

Over last three decades pharmaceutical researches found quite likely to be interested in controlled and sustained release drug delivery. Overlapping their interest development of insitu gels is taking place, as it bears the quality of controlled as well as sustained release very efficiently. Currently many marketed formulations are available of insitu gels targeting at specific site or area. The aim of using insitu gel formulation is its unbeatable advantages over the other conventional drug delivery as by using the insitu gels, we can carry advantages like reduced frequency of administration, improved patient compliance, therapeutic effectiveness, safety and efficacy. Insitu gel formulation is being considered as an best alternative for achieving systematic drug other than parentral or oral route of administration. The novelty of insitu gel system solely depends upon the ease and convenience of administration, deliverance of accurate dose as well as to prolong the residence time of drug in contact with mucosa. The formation of insitu gel majorly depends on one or combination of different stimuli like pH change, temperature modulation, and solvent exchange. Representation of smart polymeric system would be promising means of delivering of drugs, these polymer undergo sol-gel transition once administered. Nowadays the use of natural and synthetic polymers is being investigated for controlled and sustained release formulation.

The review attempts to discuss the parameters and strategies of this drug delivery systems including consideration of physico chemical to formulation factors. Also approaches of insitu drug delivery system, smart polymeric systems, evaluation and characterisation of insitu gel and recent advances or application of the gels is being discussed.

APPROACHES TO INSITU GEL DRUG DELIVERY:

There is certain broadly defined mechanism used for triggering the insitu gel formation of biomaterials:

1. Insitu formation based on physiological stimuli:

Thermally triggered system: They are the temperature sensitive hydrogels, most commonly studied class of environment sensitive polymer system in drug delivery research. The way of using the biomaterials whose transitions from sol-gel state is triggered by increase in temperature is an attractive way to approach insitu gelation. Temperature at which gelation occurs is known as Critical Solution Temperature (CST). Thermally triggered system majorly classified into:

a. Positively thermo sensitive: Hydrogels having upper critical solution temperature (UCST).Such hydrogels contracts upon cooling below this UCST.

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Eg: Poly (acrylic acid)(PAA), Poly(acrylamide)(PAAm), Poly(acrylamidecobutyl methacrylate).

b. Negatively thermo sensitive: They have lower critical solution temperature (LCST).Such hydrogels contracts upon heating above LCST. Eg: poly (N-isopropyl acrylamide) (PNIPAAm).

c. Thermo reversible gels: They are mostly prepared from Pluronics and Tetronics.

TABLE:1

Type of polymer	Phase transition temperature in aqueous solution
LCST Behaviour	
PNIPAM	30-34*Celsious
Poly(N,N-diethylacrylamide)	32-34*Celsious
Poly(methyl vinyl)ether	37*Celsious
PEO-bPPO	20-85*Celsious
Poly(GVGVP)	28-30*Celsious

Above the mentioned temperature sol converts to gel state.

TABLE 2:

Type of polymer	Phase transition temperature in aqueous solution
UCST Behaviour	
PAAm/PAAc IPN	25*Celsious

Below the above mentioned temperature sol converts to gel state

pH triggered system: All pH sensitive polymers contain acidic or basic groups that either accept or release protons in response to changes in environmental pH. Swelling of hydrogels increases as external pH increases when we talk about weakly acidic groups but decreases in the case of weakly basic groups.

Eg: PMMA, PEG, CAP Latex, Pseudolatex etc.

2. Insitu formation based on Physical mechanism:

Insitu formation based on physical mechanism deals with two important processes:

a. Swelling: Occurance of insitu formation when absorption of water take place by material from surrounding enviornment and expand to cover desired space. Example of one suitable substance is Myverol 18-99 (glycerol mono oleate), which is a polar lipid that swells in waterto form lytrotropic liquid crystalline phase structures.

b. Solvent exchange diffusion: The method shows the involvment of the diffusion of solvent from polymer solution into surrounding tissue and result in precipitation or solidification of polymer matrix.Example of polymer which shows best results by this system is N- methyl pyrrolidone(NMP).

3. Insitu formation based on Chemical reaction:

Gelation causing chemical reaction are:

a. Ion activated system: This system deals with the phenomena of phase transition in the presence of various ions. Some of the polysaccharides fall into the class of ion sensitive ones , while K-carrageenan forms rigid brittle gels in reply of small amount of K+ . Gellan gum commercially available as Gelrite, is an anionic polysaccharide that undergoes insitu gelling in the presence of mono and divalent cations.Likewisealginic acid also undergoes gelation in the presence of divalent and polyvalent cations.

b. Enzyme activated syatem: It is being said that natural enzymes play role of catalyser in insitu formation but it has not been investigated widely but seem to have advantages over chemical and photochemical approaches.

Intelligent stimuli responsive delivery system using hydrogels that can release insulin have been investigated.The adjustment of the amount of enzyme also provides a convenient mechanism for controlling the rate of gel formation, which allows mixtures to be injected before gel formation.

c. Photo Ploymerisation: It is the commonly used process for the insitu formation of biomaterials. Photo polymerised systems when introduced to the desired site via injection get photocuredinsitu with the help of fiber optic cables and then released the drug for prolonged period of time.Furthermore, the systems are easily placed in complex shaped volumes leading to an implant formation.

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Majorly used polymers in insitu drug delivery:

TABLE 1:

Name of Polymer	Type of polymer	Major Use
Gellan Gum(Gelrite or Kelcogel)	An anionic deacetylatedexocellularpolyascch aride secreted by Pseudomonas elodea with a tetrasaccharide repeating unit of one alpha rhamnose, one beta glucoronic acid residues.	Majorly used in oral administration as calcium ions are released in acidic environment of stomach leading to gelation of gellan thus forming a gel in situ.
Alginic acid	It is a linear block co-polymer polysaccharide consisting of beta mannuronic acid and alpha-L-glucuronic acid residues joined by 1,4-glycosidic linkages.	Alginic acid can be chosen as a vehicle for opthalmic formulation since it exhibits favourable biological properties and posses ability to gel in eye(at lachrymal fluid pH).
Pectin	They are a family of polysaccharides in which the polymer backbone mainly comparises alpha-(1-4)-D-galacturonic acid and residues.	When it is administered orally divalent cations present in the stomach carry out the transition of pectin to gel.
Chitosan	It is a biodegradable thermosensitive, polycationic polymer obtained by alkaline deacetylation of chitin.	It is a biocompatible pH dependent cationic polymer which remain dissolved in aqueous solution upto a pH 6.2.
Xyloglucan	It is a polysaccharide derived from tamarind seeds and is composed of (1,4)-beta-D-glucan backbone chain, which has (1,6) alpha xylose branches that are partially substituted by (1-2)-beta galactoxylose.	Xyloglucan gels have potentially been used for oral, intraperitoneal, ocular and rectal drug delivery.
Carbopol	A well known pH dependent polymer, used in combination with HPMC to impart viscosity to the preparation.	Based on this formulation and evaluation of ocular delivery system of indomethacin for the treatment of uveitis carried out which provide excellent results.

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Smart Polymers Used: Smart polymers majorly called as Synthetic polymers are the popular choice mainly for parentral formulation. The trend in drug delivery technology has been towards biodegradable polymers such as poly(lactic acid), poly (lactide-coglycoside), poly(decalactone) has been the subjects of most extensive recent investigations.

The feasibility of lactide/giycolide polymers as excipients for controlled release of bioactive agents is well proven. These materials have been subjected to extensive animal and human trials without the evidence of any harmful side effects. Various other polymers like triblock polymer system composed of poly(D-L-lactide)-block-poly(ethylene glycol)-block poly(DL lactide) are also majorly use for injectable in situ formulation.

CHARACTERIZATION AND EVALUATION PARAMETERS OF INSITU GEL:

Characterization of insitu gel forming system have been broadly done in two ways;

1. Based on mechanism of gelation:
a. pH sensitive gels
b. Gel sensitive to electrical current
c. Thermosensitive gels
d. Enzyme sensitive
e. Presence of ions

2. Based on route of administration(Applicability of insitu drug delivery system)
a. Insitu forming polymeric systems for oral administration.
b. Insitu forming polymeric systems for ocular delivery.
c. Insitu forming polymeric systems for rectal and vaginal delivery.
d. Insitu forming polymeric systems for injectable drug delivery.
e. Insitu forming polymeric systems for nasal drug delivery.

Evaluation parameters for insitu gels are:

1. Clarity: The clarity of formulated solution was determined by visual inspection under the white or black background.

2. Viscosity and rheology: These properties of the polymeric formulation either in solution or in gel made with artificial tissue fluid were determined with Brookfield rheometer and Ostwald's viscometer.

3. Determination of mucoadhesive force: This can be determined by modified balance method or Tensilometer.

4. Gel Strength: This parameter can be evaluated using a rheometer, depending on the mechanism of the gelling of gelling agent used , a specified amount og gel is prepared in a beaker from the sol form. This gel containing beaker is raised at a certain rate, so pushing a probe slowly through the gel.
The changes in the load on the probe can be measured as a function of depth of immersion of the probe below the gel surface.

5. Sol-Gel transition temperature and gelling time: Sol-Gel transition temperature is the temperature at which the phase transition of sol meniscus is first noted when kept in a sample tube at specific temperature and then heated at a specific rate.
Gel formation is indicated by the lack of movement of meniscus on tilting the tube . Gelling time is the time for first detection of gelation

6. Texture Analysis: The firmness, consistency and cohesiveness of formulation are assessed using texture analyser which mainly indicates the syringeability of sol so the formulation can be easily administered invivo. Higher values of adhesiveness of gels are needed to maintain an intimate contactwith surfaces like tissues.

7. Fourier transform infra red spectroscopy and thermal analysis: During the gelation process, the nature of interacting forces can be evaluated using this technique by employing potassium bromide pelletemethod.Differential Scanning Calorimetry is used to observe if there are any changes in thermograms as compared with pure ingredients used and thus indicating the interactions.

8. Invitro drug release studies: For insitu gel formulation ,invitro drug release can be carried out by using the plastic dialysis cell.

The cell is made of two half cells, donor compartment and receptor compartment seprated by cellulose membrane.The sol form of the formulationis placed in the donor compartment.Theassembeled cell is then shaken horizontally in an incubator. The total volume of the receptor solution can be removed at intervals with the fresh media. This receptor solution is analysed for the drug release using analytical technique.

COMMERCIAL APPLICATIONS OF INSITU GELS:

1. Timoptic-XE: It is a timolol maleate opthalmic gel formulation of Merck and Co. Inc, supplied as a sterile, isotonic, buffered, aqueous gel forming solution of timolol maleate.

2. ReGel: depot technology: it is one of the Macromeds proprietary drug delivery system and

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based on triblock copolymer technique.hGHD-I is a novel injectible depot formulation of growth harmone (hGH).

3. Cytoryn: This is one of the Macromed'sproducts,whuch is novel, peritumoral, injectible depot formulationof interleukin-2 (IL-2) for canacer immunotherapy using Regel drug delivery system.

SOME OF THE STUDIES INVESTIGATING THE INSITU DRUG DELIVERY IS SHOWN IN TABLE 3:

Name of Drug	Type of Polymer used	Administration route	Inference
Theophylline	Gellan Gum	Oral	Four to Five fold increase in bioavailability in rats and three foldincrease in rabbits as compared to commercial formulation.
Doxorubicin	Human serum albumin and tartaric acid derivatives	Injectible	Sustained delivery of anticancer drug for a long /specified period.
Paracetamol and Ambroxol	Pectin	Oral	Sustained Oral Delivery.
Metoclopramide Hydrochloride	Poloxamer 407 and polyethylene glycol	Nasal	Ease of administration,accuracy of Dosing, Prolonged nasal residence and improved drug bioavailability.
Cinnarizine	4% of sodium alginate with 0.5% of calcium carbonate	Oral	Formulation having sustained action for 12 hours.
Sumatriptan	Pluronic F127 and Carbopol 934P	Nasal	Prolonging nasal residence time and nasal absorption.
Timolol Maleate	Carbopol and Chitosan	Ocular	Therapeutically efficacous and showed a diffusion controlled type of release behaviour.
Clarithromycin and Metronidazole Benzoate	Sodium Alginate and Calcium Carbonate	Oral	Sustained Oral Delivery
Itraconazole(1%w/w)	Poloxamer and carbopol 934	Oral topical gel (Mucoadhesivebuccal gel)	Increase in buccal residence time and patient comfort.
Salbutamol Sulphate	Carbopol 934 and HPMC	Nasal	Sustained Release and higher bioavailability.

RECENT ADVANCES:

One of the challenges faced by a today's pharmaceutical era is on coming up with efficient treatment options that are readily acceptable to physicians and patients.Delivery system must also contribute to a better therapeutic effects if they are going to provide a viable alternatives to pharmaceuticals currently delivered by other routes.Insitu gelling formulation overcome all the challenges as discussed above in a very safe and efficacous manner.

Recently various Biodegradable polymers are being used for formulation of insitu gels but there are fabrication problems, difficult process ability, burst effect and irreproducible drug release kinetics. Natural polymers somehow satisfy the ideal characteristics but when it comes to batch to batch reproducibility, synthetic polymers satisfy the needs.

The recent advancement of biotechnologies has lead to development of laible macromolecular therapeutic agents that require

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complex formulation of their efficient administration N-stearoyl L alanine (m) ethyl easters when mixed with vegetable oil and a biocompatible solvent led to the formation of injectible ,insitu forming organ gel.

II. CONCLUSION:

The primary requirement of a sucessful controlled release product focuses on increasing patient compliance which insitu gel offer,majorly for this purpose insitu gelling is being considered as a most successful novel approach towards controlled and sustained release drug delivery systems. Also characteristics like good stsbility, biocompatibility make insitu formulation a reliable approach, acceptance of delivery system of the specific formulation become easier.

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