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AN OVERVIEW OF *IN SITU* GEL

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ABSTRACT:

In situ gel system has emerged as one of the best novel drug delivery system, it used for the sustained and controlled release of the drugs. *In situ* gelling agent is a polymeric formulation that are in sol-state prior to administration and its undergo gelation in to a body under physiological conditions and it has various factors to trigger the sol-gel transition such as temperature rise, pH change and the presence of ions. To formulate an *in situ* gel drug delivery system, various types of natural and synthetic polymers are used. They are ease of administer, have a resistance time, sustained drug release at a site of administration and increase patient compliance. Most drugs are inherently not long lasting in the body and its require several dose to attain the desired blood concentration to provide therapeutic activity. To overcome this there is increasing interest in sustained release drug delivery system. The evaluation tests are pH, Clarity, Viscosity, Gelatine temperature and time, gelling strength, in-vitro drug release study were conducted for the developed formulation. The characterization of drug and excipients were performed by FTIR and UV spectroscopy.

Key words:- *In situ* gel, Retention time, Gellan, Sodium alginate, Transition temperature.

INTRODUCTION[11]:

Oral drug delivery system has been popular most widely utilized route of administration among all the route due to many advantages it exhibits such as good patient compliance, ease of administration and safety of administration. An ideal drug delivery system should be a capable of delivering a sufficient amount of drug over an extended period of time to provide optimal therapeutic activity. In situ gel system has emerged as one of the best novel drug delivery system, it used for the sustained and controlled release of the drugs. *In situ* gelling agent is a polymeric formulation that are in sol-state prior to administration and its undergo gelation in to a body under physiological conditions and it has various factors to trigger the sol-gel transition such as temperature rise, pH change and the presence of ions. To formulate an *in situ* gel drug delivery system, various types of natural and synthetic polymers are used. They are ease of administer, have a resistance time, sustained drug release at a site of administration and increase patient compliance. Most drugs are inherently not long lasting in the body and its require several dose to attain the desired blood concentration to provide therapeutic activity. To overcome this there is increasing interest in sustained release drug delivery system.

ADVANTAGES:

- Controlled and sustained release of the drug[11].
- Ease of drug administration[11].
- It can be administered to unconscious patients[11].
- More patient compliance and comfort[11].
- Minimizing the dose frequency and drug toxicity[11].
- Increasing bio availability[11].
- Use of natural polymers provide bio-compatibility[11].
- Natural polymers have inherent properties of bio-compatibility, bio-degradability and biologically recognizable moieties that support cellular activities[11].
- Synthetic polymer has well defined structures that can be modified to yield tolerable degradability and functionality[11].
- *In situ* gel can also be engineered to exhibit bio-adhesiveness to facilitate drug targeting through mucus membrane, for non -invasive drug administration[11].
- To provide sustained and controlled drug delivery[11].
- To increase ocular bio-availability of the drug by increasing corneal contact time[21].
- Drug effect is prolonged hence frequent installation of the drug is not required[21].
- For patient compliance and enhance therapeutic performance of the drug[21].
- Generally, more comfortable than insoluble or soluble insertion[21].
- System provides ease of administration[21].

DISADVANTAGE[11]:

- It requires high level of fluids.
- The solution form of the drug is more susceptible for degradation.
- The chance of stability problems due to chemical degradation.
- After placing the drug eating and drinking may become restricted up too few hours.
- The quantity and homogeneity of drugs loading into hydrogels may be limited, particularly for hydrophobic drugs.
- Only drugs with small dose requirement can be given.
- Lower mechanical strength, may result into premature dissolution or flow away of the hydrogel from a targeted local site.

Ideal characteristics[14]:

- It should be compatible and not risky.
- It must be pseudo plasticity.
- Good tolerance and optical clarity is more ideal for the preparation of *in situ* gels.
- It must influence the tear behaviour.
- Prerequisites of *in situ* gelling system are, viscosity and gelling capacity.
- When it applied in solutions or suspensions are capable of undergoing rapid sol-gel transitions.
- It is triggered by the external stimulus temperature, pH.
- The polymer can minimize the viscosity by the increasing the cutting speed.

CLASSIFICATION OF IN SITU GELLING SYSTEM[9]:

They are classified into 2 two types:

1) Natural polymer
   E.g.:- Alginic acid, Pectin, Xyloglucan, Sodium alginate, Gellan gum, Xanthum gum
2) Synthetic polymer
   E.g.:- HPMC, MC, CAP, PAA, Poloxamers, Poly acrylic acid.

NATURAL POLYMERS:

SODIUM ALGINATE[5]:

It is natural origin polymer, chemically sodium alginate is a alginic acid salt and it consists of β-D mannuronic acid and α- glucuronic acid residues linked by 1,4- glucosidic linkages.

It is bio-degradable and non-toxic nature.

It is water soluble polymer is useful in sustained release liquid preparation for oral administration act as a stabilizing agent, viscosity is an increasing agent.

PECTIN:

It is found to be the presence of calcium ions, when it is administered orally, divalent cations induce gel formation in the stomach[7].

It is a polysaccharide in which the polymer backbone mainly comprises α-1,4 D-galacturonic acid residues, low methoxy pectin (degree of esterification <50%) readily forms a gels in the presence of free calcium ions, they crosslink the galacturonic acid chains it is described by egg box model[6].

Gelation of pectin will occur in the presence of hydrogen ions, a source of divalent ions, calcium ions are required to produce the gel that suits for this delivery system[6].

Divalent cation presents in stomach, that carries the transition of pectin to gel state when it is administered orally[6].

XYLOGLUCAN[8]:

Xyloglucan has a backbone of β1-4 linked glucose residues, which are substituted with 1-6 linked xylose side chain. The xylose residue these are often capped with a galactose residue.

GELLAN GUM[20]:

It is an anionic deacetylate exocellular polysaccharide secreted by pseudomonas elodea its current gelation is temperature dependent or cation induced.

This gelation involve the formation of double helical junction zones followed by aggregation of the double helical segment to form 3D network by complexation with cation and sodium citrate complex.

In oral administration the calcium ions are released in acidic environment of stomach lead to gelation of gellan, thus forms an *in situ* gel e.g.: Theophylline.

XANTHAN GUM[20]:

It is high molecular weight extra cellular polysaccharide produced by the fermentation of xanthomoans campestris and it is a gram negative bacteria.

This primary structure is cellulose derivative contains a cellulosic backbone (β-D-glucose residues) and tri saccharide side chains β-D-mannose, β-D glucuronic acid, α-D mannose, they are attached with an alternative glucose residues of the chain.

SYNTHETIC OR SEMI-SYNTHETIC POLYMERS[2]:

HYDROXY PROPYL METHYL CELLUOSE:

It is a biocompatible, thermos reversible, mucoadhesive polymer. It is often used in ophthalmic preparation, mainly as a viscosity enhancer and gelling property.

It is a type of cellulose either due to its high swelling ability or thermal gelation property. It plays an important role in aqueous formation for topical treatment of the eye.

HPMC also used in combination with other polymer especially carbopol, enhancing the solution's viscosity while reducing the solution's acidity.

HPMC is most widely used for the preparation of *in situ* gel because of its viscosity enhancing property.

POLOXAMERS[11]:

It has an excellent thermal setting properties and increasing drug resistance time. Poloxamers are commercially called as pluronic and it was used in thermos sensitive *in situ* gels.

Pluronic F127 is the most commonly used poloxamer polymer in pharmaceuticals due to its colourless and transparent gel forming property.

A copolymer of pluronic F127 poly (acrylic acid) was used as a vehicle for the formulation of *in situ* gels due to its prolonged resistance time and better bioavailability of the ocular drugs.

POLY LACTIC -CO-GLYCOLIC ACID (PLGA):

PLGA has been used extensively for the drug delivery due to its biodegradable and bio compatible nature and different drug delivery have been prepared including ophthalmic delivery.

It is a synthetic copolymer of poly lactic acid (PLA) and poly glycolic acid(PGA). It also used in tissue engineering applications because of its long clinical experience.

MECHANISM OF ACTION[1]:

To increase the retention time of the dosage form in the stomach, Floating dosage forms are included. These are commonly used(FDDS) Floating drug delivery system. It has a lesser bulk density than the Gastric fluids. So they remain floating on the stomach without affecting the gastric emptying rate for a prolonged period of time.

The *in situ* gels are aqueous in liquid solutions before the administration. Then converts to gel under physiological conditions. *In situ* gels formation are ionic cross linkage, pH change and temperature modulation.

Polymer solutions such as Gellan, pectin and sodium alginate. It contains divalent ions and complexed with sodium citrate. The sodium citrate is break down in the acidic environment of stomach to release the free Divalent ions(ca^{+2}). so, it causes the *in situ* gelation.

While the system is floating on the stomach, the drug is released slowly at the desired rate. After the drug releases the residual system is emptied from the stomach besides minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, minimal level of the floating force(F) is also required to keep the dosage form reliably Buoyant on the surface of the meal.

OCULAR[30]:

Sol-to gel formation, the transition in the ocular Cul-de-sac to form viscoelastic gel. This provides a response to environmental changes. Polymers are used to exhibit the reversible phase transitions (sol-to gel). And the pseudo plastic polymers are used to minimize the inference with blinking. Liquid dosage forms are suitable to administered into the eyes, up to the physiological conditions it changes into gel phase. so, it increases precorneal residence time of the delivery system.

Polymers that have been used includes:

Poly sacharides (alginate, gellan, xylogellan)

Polyesters (PLA, PLGA)

Polyethers (PEG, PPG-PEG) polaxamers.

Mixed polyesters, Polyethers (PEG-PLGA-PEG).

NASAL[29]:

First step absorption of drug in the nasal cavity crossing the mucus membrane. The protein present in mucus layer is Mucin, it binds with the solutes that delays the diffusion.

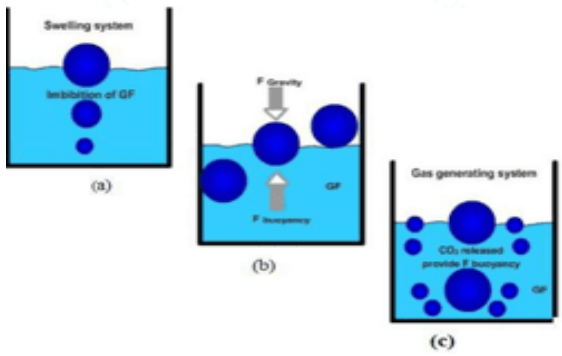
Absorption across mucosa includes:

1.Simple diffusion

2.Paraceluular transport between the cell and trans cytosine by vesicle carriers.

TWO MECHANISMS INCLUDE:

1. Para cellular route:
   - It involves an aqueous route for transportation.
   - Slow and passive route.



2. Transcellular route:
   - Transportation occurs through the lipid route.
   - It is responsible for the transport of lipophilic drug.
   - The drugs cross the cell membrane by active transport through carrier mediated or opening of tight junctions.

EVALUATION:

1.PHYSICAL APPEARENCE[20]:

In situ gel should be clear and free of any particulate matter. The clarity of gelling solution was examined by visual inspection under black and white background.

2.pH[28]:

pH was measured by using a calibrated digital pH meter. The formulation was taken in beaker and add 1ml of NaOH dropwise with continuous stirring.

3.GEL STRENGTH[3]:

The gel state was determined by using Rheometer. Its depending on the mechanism of the gelling of gelling agent used, an amount of gel is prepared in a beaker it forms a sol form. This gel containing beaker is raised at a certain rate, so pushing a probe slowly through the gel.

The changes are measured as a function of depth of immersion of the probe below the gel surface.

4. GELLING CAPACITY[3]:

Gelling capacity was determined by placing a drop of the formulation in a vial containing 2ml of freshly prepared simulated tear fluid (ocular drug delivery) and visually observed. The time taken for its gelling was recorded.

5. VISCOSITY[31]:

Measurement of viscosity was determined by using a Brookfield digital viscometer by using spindle number 1 at 20 rpm measurement was done for three times.

6. SOL-GEL TRANSITION TEMPERATURE:

In vitro gelation was demonstrated by using USP II dissolution apparatus. The dissolution apparatus containing 900ml of 0.1N HCL in 1000 ml of beaker and the pH was adjusted 1.2 and the temperature was maintained at 37±0.5°c when the formulation was cooling in contact with 0.1N HCL it gets converted from sol to gel and the time was noted.

7. DRUG CONTENT ESTIMATION[27]:

Approximately, 10 ml of formulation was taken in 100 ml volumetric flask and add 0.1N HCL and sonicated for 30 minutes, volume was adjusted to 100ml and contents are filter with the help of what Mann filter paper and 10ml of sample was withdrawn and diluted to 100ml with 0.1 N HCL and finally measure the absorbance by using UV-visible spectrophotometer.

8. IN VITRO FLOATING STUDY[27]:

The floating lag time is defined as time taken by the gel to reach the top from bottom of the dissolution flask. The floating time was determined by visual inspection in a USP (TYPE 2) dissolution test apparatus containing 900ml of 0.1N HCL at 37°c and 10ml of formulation were transferred. Time taken by the formulation to reach the top surface of the medium and the time during which the formulation constantly floating on the surface of dissolution medium was measured.

9. IN VITRO DRUG RELEASE STUDIES[27]:

The dissolution studies were performed by using a USP type II method. 900 ml of 0.1 N HCL were taken in the dissolution apparatus and the temperature, pH was maintained at a range of 37.C and 1.2 respectively. The stirring rate was adjusted to 50 rpm and this speed was believed to stimulated mild *in vitro* agitation and also slow enough to avoid the breaking of the gelled formulation. At the determined time intervals 10ml sample were withdrawn and replaced by same volume (10 ml) of fresh dissolution medium,

filtered through whatsmann filter paper and it was diluted, assayed at maximum absorbance of 205nm using UV visible spectrophotometer.

APPLICATION[11]:

Recent advances in *in situ* gels have made it possible to exploit the Change in physiological uniqueness in different regions.

Gastrointestinal tract is used as per the patient convenience and compliance.

Oral delivery:

- It is the most suitable route and the common form of drug delivery system[13].
- In oral route the drugs are observed through the GIT with major absorption from stomach and intestine[12].
- pH sensitive hydro gel has greater role in local drug delivery of GI tract Hydro gels are made up of variety of cross linked elements poly ethyl glycol and poly acrylic acid[14].
- The formation of gellan and sodium alginate both contains complex calcium ions that under goes a gelation process by releasing these ions in acidic environment of the stomach[14].

OCULAR DELIVERY:

- Ophthalmic/ocular drug delivery is one of the most interesting and challenging process faced by pharmaceutical scientist[15].
- The natural polymers used are alginic acid, inulin, xyloglucan[14].
- It is an isolated organ, and quite difficult to study the delivery point[15].
- The disadvantage of the conventional drug delivery system can be improved by the *in situ* gel based drug delivery system[14].

- In this system various ophthalmic compound such as anti-inflammatory & anti-microbial agent are used to relieve intra ocular intolerance in glucoma[14].
- Penetration enhancers (preservatives, chelating agent, surfactants) are used to develop the corneal drug penetration[14].
- Viscosity enhancers were used in the *in situ* gel formulations to improve bio availability[14].

GASTRO RETENTIVE DRUG DELIVRY SYSTEM:

- Formation of *in situ gel is* due to different stimuli like pH change, temperature modulation and solvent exchange[1]. Gastro retentive in situ oral gel system belongs to the floating system majorly used for the antacid drug delivery. e.g.: Metformin[22].
- The ingredients are mixed with the gel that undergoes gelation in stomach due to change of pH[22].
- In GRDDS, the drugs can be retained in the stomach, improving the oral delivery of drugs[19].
- Gellan gum& sodium alginate are used as a polymer[22].
- Calcium carbonate, calcium chloride & sodium citrate is used as cross linkers[22].
- It provides control drug delivery in the stomach. This low density gel formation provides gastro retention to prolong the contact time and slows drug release[1].
- *In situ* gelling system can produce sustained release formation of an oral liquid formulation[1].

NASAL DELIVERY:

- In nasal *in situ* gel, xanthan gum and gellan gum are used[16].
- Nasal route is a natural choice for the topical administration of drug intended for the treatment of local disorder affecting the nose para-nasal sinuses such as allergic or infectious rhinitis, sinusitis rhino-sinusitis and nasal epithelium lesions[16].
- Nasal delivery is an alternative to oral or parenteral administration due to certain limitation such as absorption of drug, drug targeting to particular organ can cause a problem through oral route[17].
- In nasal drug delivery system, *in situ* gel formulations have been used for both local and systemic drug delivery[18]. These route have been successfully used for bypassing the blood brain barrier drug delivery molecule to the CNS[17].
- Lag time related to oral drug delivery can be reduces by this route and produces non-invasiveness, self-medication, patient compliance& patient comfort[17].

RECTAL DELIVERY:

- Solid dispersion of ibuprofen in combination with poloxamer 407, HPMCES and sodium alginate is known to have a better effect than solid suppository and produces high plasma concentration and bio-availability[23].
- In this dosage from, drugs remain long time in the rectum without being ejected for ensuring maximal absorption of the drug[24].
- In this formulation, it improves local effect or enhance drug absorption[24].
- These are successfully conducted for improving rectal absorption of drugs[24].
- A conventional solid suppository melts or softens in the rectal area at normal temperature[10].
- These suppository does not produce pain or leak from the anus[10].
- It has several disadvantages[10];

Patient discomfort
Low patient compliance
Anal leakage.

CONCLUSION:

Most of the drugs are inherently not long lasting in the body and it require several dose to attain the desired blood concentration to provide therapeutic concentration. So, it creates incompliance among the patient. To overcome this problem, there is increasing interest in sustained release drug delivery. *In situ* gel system have an ability to provide the sustained and controlled drug release of drug and the plasma therapeutic concentration of a drug can be maintained over a long period of time and the patient compliance can be improved.

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