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# NANOGELS; AN ADVANCED TECHNOLOGY OF TARGET DRUG DELIVERY SYSTEM: NEW PARADIGM

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**Abstract:**

*Nanogels are the advanced technology in pharmaceutical sciences which has been most popular in effective drug delivery inside the body as well as topical treatment. Nanogels are promising and innovative formulation to deliver the drug at target site, hence it becomes a part of "Target Drug Delivery System". Nanogels are composed of nanoparticles having physically or chemically crossed linked hydrogel porous structure that can be used as highly efficient and biodegradable carriers for the transport of drugs in controlled drug delivery. Nanogels have great potential in the Chemotherapy, Gene silencing therapy, Organ targeting and Delivery of bioactive substances. The main areas of the target for the nanogels have been tumors of brain, liver, skin etc. The formulations improve the effectiveness and safety of certain composition, which have been confirmed from in vivo study in animal models. In this article, we have discussed the basic mechanism of action of nanogels in vivo. And the possibility of using the nanosystems in improving the current therapies, diagnosis as well as clinical trial progress.*

**Keywords:** *Nanogel, Nanoparticle, Nanocarrier, Drug Release, Stimuli responsive, Degradation, In vivo mechanism, Evaluation parameters.*

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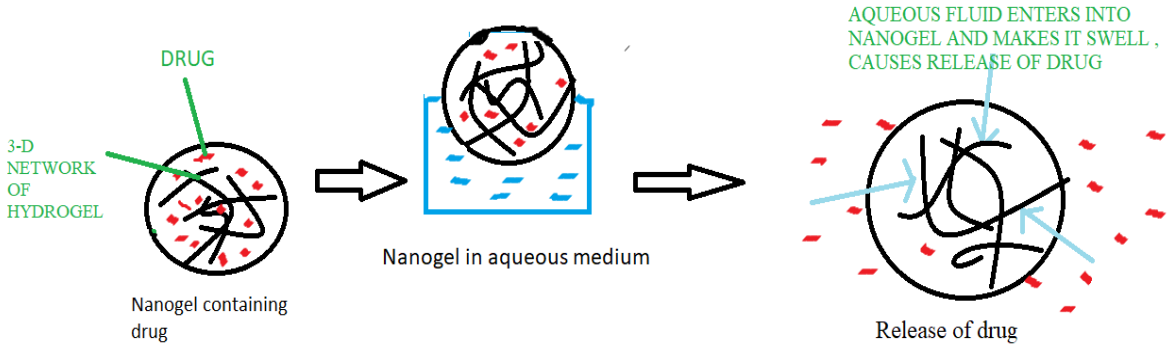
## INTRODUCTION:

Nanogels are three- dimensional hydrogel materials in the size range of nanometers formed by cross linked chemical or physical polymers network having capability of swelling/ de-swelling with high capacity to hold great amount of water, without actually dissolving into the aqueous medium. Nanogels are composed of some nanoparticles having size range 1-100 nm, where the actual size of nanogels lies between 20-200nm in diameter. The significance of nano-sized microgel and hydrogel has arisen due to specific delivery system anticipation. Wide variety of polymer system and the easy alteration of their physico-chemical characteristics have given advantage for versatile form of nanogel formulations. Recent studies at clinical level have shown promising value of nanogels. Nanogels have revolutionized the field of gene therapy, since delivery of gene has now become possible within cellular organelles for gene silencing therapy systems. [1-5]

## DRUG RELEASE FROM NANOGEL:

Nanocarrier contain drug/cargo ( Nanogel) when comes in contact with aqueous medium get swells as it containing hydrogels having capacity to absorb great amount of water and this may lead to release the drug at the disease site from the nanogels.




**Properties Of Nanogels: [6-11]**

There are following properties of nanogels-

- **Biocompatibility and Degradability:** Nanogel based drug delivery system is highly biocompatible and biodegradable; due to this characteristics it is highly suitable for the patients.
- **Swelling Property in Aqueous Media:** The most beneficial feature of Nanogels is their rapid swelling/de – swelling characteristics.
- **Higher Drug Loading Capacity:** Drug loading capacities of nanogels depend on the functional group present in the polymeric unit. These functional groups have an effect on drug carrying and drug releasing properties, and some functional groups have the potential to conjugate with drugs/antibodies for targeting applications. These functional groups of polymeric chains contribute toward establishing hydrogen bonding or Vander Waals forces of interactions within the gel network and thus facilitate the drug carrying efficiency. Moreover, the presence of functional groups at interface with drug/protein molecules is also responsible for higher loading.
- **Particle Size:** Nanogels ranges in size of 20 to 200 nm in diameter and therefore effective in avoiding the rapid renal exclusion but are small enough to avoid the uptake by the reticule endothelial system. Good permeation capabilities due to extreme small size. More specifically, it can cross the blood brain barrier.
- **Solubility:** Nanogels are able to solubilize hydrophobic drugs and diagnostic agents in their core or networks of gel.
- **Electro mobility:** Nanogels could be prepared without employing energy or harsh conditions such as sonication or homogenization, which is critical for encapsulating bio-macromolecules.
- **Colloidal Stability:** Nanogels have better stability over the surfactant micelle concentrations, slower rate of dissociation, and longer retention of loaded drugs.

- **Non Immunologic Response**: This type of drug delivery system usually does not produce any immunological responses.

**Routes of administeration:**

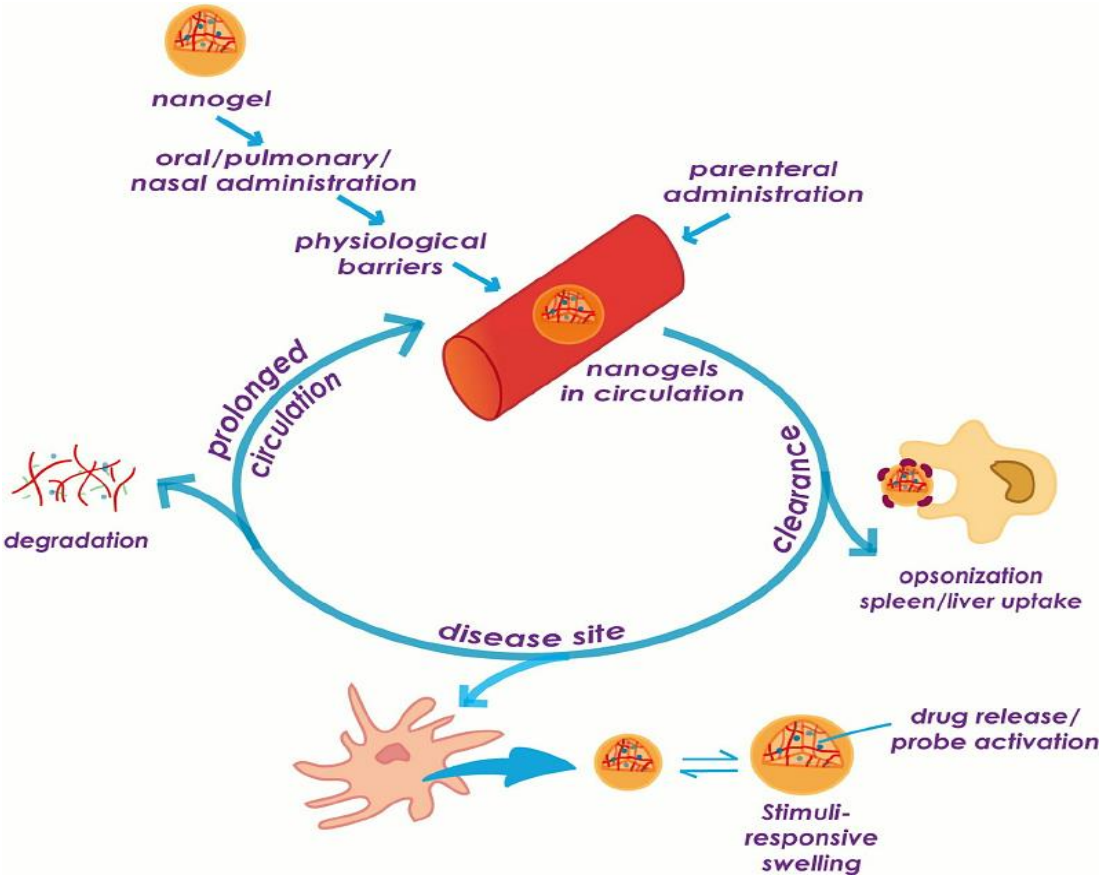
1. Topical
2. Nasal
3. Pulmonary
4. Parenteral
5. Intraocular
6. Oral

**Mechanism of nanogels:**

As we know nanogels are part of target drug delivery systems, it reaches the target site by passing many physiological barriers in case of any route of administration (oral, pulmonary, nasal, topical) except intravenous route.

After crossing the physiological barriers, it enters blood circulation where it diffuses into the blood and undergoes into opsonisation and clearance via spleen and liver.

After extravasation from the blood compartment, it reaches the disease site where the drug is released from the nanogel by drug release mechanism and is uptake by various monocytes and macrophages. After this, nanocarrier undergoes degradation, as degradability is the most important step in the mechanism of action of nanogel because in vivo, degradation of nanocarrier is necessary to reduce the toxicity created by the accumulation of the nanocarriers in the body. [12-14]



**MECHANISM ACTION:**

**Advantages Of Nanogels: [15]**

- The biodegradation of drugs is prevented, when administered in the form of nanogels.
- Size and other related physical properties of nanogels are easily maintained as per the desired delivery of drug.
- The amount of drug in formulation is reduced further leading to decrease in dose of the drug.
- The toxicity of drug is controlled, also the bioavailability of drug is enhanced.
- Nanogels containing drugs can be administered in the body without any adverse or side effects and also nanogels can be administered topically.
- The high permeability of nanogels allows them to cross the blood brain barrier and other barriers like skin.

**Disadvantages of nanogels:**

- Solvent and surfactant is not easily removed at the end of preparation, so it may be some more expensive.
- Sometimes traces of surfactants can cause toxicity.

**Evaluation parameters:**

Evaluation parameters are used to evaluate the particle size, zeta potential, drug diffusion, permeation studies, entrapment efficiency of formulated nanogel.

- Particle size analysis: - By using particle size analyzer (Malvern instrument), we can analyze the particle size of the prepared nanogel particulate systems. For this purpose nanogel particulate systems are suspended in ultra-pure water and particle size analysis is performed.
- FTIR spectroscopy:- For this purpose, samples are prepared by mixing the prepared grounded formulations with potassium bromide and is placed on disc slit and then the IR spectra is recorded.[16]
- Entrapment efficiency: - In this, a small portion of the nanodispersion is centrifuged at 10,000 rpm for 1 hour using Microcentrifuge. The supernatant is removed and amount of unincorporated is measured using spectrophotometer.
- Rheological measurements: - The rheological measurements can be performed on the Brookfield Rheometer RVDV Pro 11. All the measurements are carried out at room temperature 25+/-100C.
- Experimental design: - In this study, a 32 factorial study is used to optimize the nanogel.
- In vitro drug release: - A calibrated USP type-2 dissolution apparatus is used in order to perform the dissolution studies of drug loaded formulations at pH. 1.2 and 6.8 respectively. 900ml of each solution was used as a medium while maintaining the temperature at (37+/-0.20C) and paddles speed at 50 rpm. After specified time interval 5ml of the sample are taken and replaced it with the same quantity of fresh medium. The cumulative drug released is calculated by measuring the absorbance with the help of UV spectrophotometer at 332nm.[17]

**Application of nanogels:**

Nanogel based drug delivery formulations improve the efficacy and safety of certain anti-cancer drugs and many other drugs, due to their chemical composition, which have been confirmed from *in vivo* study in animal models. [18-28]

- **Nanogel in Cancer –** Nanogel in cancer is used for the specific targeted drug delivery with low toxicities and high therapeutic efficacy. A single particle can carry hundreds of drug molecules that concentrate in the tumor, increasing the efficacy of the drug combination while decreasing its toxicity. The initial use of this delivery system will be a drug known as IMM-01. A multi-pronged treatment for metastatic cancer, it contains two agents: Interleukin-2 (IL-2) and an inhibitor of tissue growth factor (TGF beta). IL-2 amplifies the body's immune system, while the TGF-beta inhibitor dampens the cancer cell's ability to hide from the immune system." Fahmy" however, designed a unique biodegradable gel that can contain both drugs and then release them in the tumor. Nanogels technology assures all these advantages as listed below.

| S.No. | Polymer | Type of nanogel | Remarks |
|---|---|---|---|
| 1. | Acetylated chondroitin sulfate | Self-organizing nanogel | Doxorubicin loaded |
| 2. | Cross linked polyethyleneimine and PEG/pluronic | Biodegradable nanogel | 5'-triphosphorylated ribavirin reduced toxicity |
| 3. | Glycol chitosan grafted with 3-diethylaminopropyl groups | pH-responsive | Doxorubicin uptake accelerated |
| 4. | Cholesterol bearing pullulan with modified amino group | Nanogel quantum dot hybrid | Probe for bioimaging |
| 5. | Acetylated hyaluronic acid | Specific targeting nanogel | Doxorubicin loaded nanogel |
| 6. | Heparin pluronic nanogel | Self-assembled nanogel | RNaseA enzyme delivery internalized in cells. |
| 7. | Pullulan/folate-pheophorbide | Self-quenching polysaccharide based | Minimal phototoxicity of pheophorbide |

- **Nanogel as NSAIDS –** To prepare the nanogel**,** Carbopol and Hydroxypropylmethyl cellulose (HPMC) with the desired viscosity should be used. Another polymer like chitosan and poly-(Lactide – co – glycolic acid) used to prepare bi-layered nanoparticles and surface was modified with oleic acid. e.g. two anti – inflammatory drugs spantide II and ketoprofen drugs effective against allergic contact dermatitis and psoriatic plaque have been prepared in nanogel and applied topically. The results show that nanogel increases the absorption through permeation of these two drugs deeper skin layers for the treatment of various skin inflammatory disorders.
- **Nanogel as an Autoimmune Disease –** Nanogels are fabricated by remotely loading liposomes with mycophenolic acid (MPA) solubilized within cyclodextrin, oligomers of lactic acid – poly(ethylene glycol) that were terminated with an acrylate end group and Irgacure 2959 photo initiator. Particles are then exposed to ultraviolet light to induce photo polymerization of the PEG oligomers. The Nanogels are attractive because of their intrinsic abilities to enable greater systemic accumulation of their cargo and to bind more immune cells in vivo than free fluorescent tracer, and permits high localized concentrations of MPA.
- **Nanogel in Haemostatic –** A protein molecule which is in solution has been used for the formation of nanogel, has been used to stop bleeding, even in severe cases. The proteins have mechanism of self – assemble on the nanoscale in to a biodegradable gel.
- **Nanogel in Ophthalmic –** Polyvinyl pyrollidone (PVP) – poly acrylic acid (PAA) nanogel is pH sensitive and prepared by γ – radiation induced polymerization. It is used to encapsulate pilocarpine in order to maintain an adequate concentration of the pilocarpine at the site of action for long period of time.
- **Nanogel in Gene Delivery –** Controlled delivery of plasmid DNA by using the polymer Di – acrylated pluronic 127 and glycidyl methacrylated chitoolgosaccharides and making photo crosslinking nanogel. Potential in gene therapy by using the polymer poly (2 – (N, N – diethylaminoethyl) methacrylate) PEGlyted macroRAFT agent for making one step PEGlylated cationic nanogel. Used in Endosomal escape of SiRNA by using the polymer Dextran hydroxyl ethyl ammonium chloride for making nanogels with photochemical internalization. SiRNA delivery to HCT – 116 cells by using the polymer thiol functionalized hyaluronic acid for making specific target and degradable nanogel.
- **Nanogel in Diabetics-** An injectable Nano-Network that responds to Glucose and Releases Insulin has been developed. It contains a mixture of oppositely charged nanoparticles that attract each other. This keeps the gel together and stops the nanoparticles drifting away once in the body. To make the nanogel respond to increased acidity dextran, a modified polysaccharide, was used. Each nanoparticle in the gel holds spheres of dextran loaded with insulin and an enzyme that converts glucose into gluconic acid. Glucose molecules can easily enter and diffuse through the gel. Thus when levels are high, lots of glucose passes through the gel and triggers release of the enzyme that converts it to gluconic acid. This increases acidity, which triggers the release of the insulin. There is still some work to do before the gel is ready for human trials (www. medical newstoday. com/articles/ 260664. php, accessed 19th June 2013).

**Clinical Trial Status For Nanogels: [29-33]**

The first phase of clinical trials for a possible new treatment for cancer is in the works for a Yale University created immunotherapy drug delivery system that can carry multiple drugs inside a miniscule particle in 2016. Developed in the lab of associate professor "Tarek Fahmy", the nanogel delivery system can be employed for multiple combinations of drugs for different cancers and even some immune disorders. The system is intended to deliver multiple drugs with different chemical properties. Nanogels have already been employed as DDS in vivo and in clinical trials, primarily for cancer therapy. In mice with subcutaneous fibrosarcoma, subcutaneous injections of recombinant murine interleukin-12 (IL-12) encapsulated in CHP nanogels, via incubation at room temperature, led to a prolonged elevation of IL-12 in the sera and resulted in significant growth retardation of the tumor (Shimizu et al., 2008). Clinical trial of Cholesteryl pullulan (CHP) nanogels has shown tremendous potential in delivering peptides. The CHP-HER-2 vaccine was administered to nine patients biweekly dosing of 300µg with booster doses. The vaccine was well tolerated with some skin sensitivity at site of subcutaneous injection. All the patients showed CD4+ and CD8+ T- cell response suggesting better therapeutic activity (Dorwal et al., 2012). CHP angels have further proved their prospects for clinical trials by reducing cytotoxicity of nervous system cells by showing increase in binding capacity to Aβ oligomer in treating Alzheimer's disorder, (Lee et al., 2009). It has also been clinically investigated for bone loss disorder and it proved its worth by reducing the dosage of W9 peptide by only two times a day than tedious eight time dosage of drug which was clinically impossible. Recent prospects in diabetes management by optical sensitive insulin loaded silver nanoparticle nanogel of poly (4- vinylphenylboronic acid-co-2-(dimethylamine) ethyl acrylate) have been designed opening new era in the field of clinical trials (Wu et al., 2010). Development of antibiotic conjugated nanogels and their in-vivo application have given promising approach towards phase 1 clinical trial (Vinogradov, 2014).

**Current status and future perspective of nanogels:**

The recombinant murine interleukin – 12 (IL – 12) encapsulated in CHP angels, via incubation at room temperature and injected in mice with subcutaneous fibro sarcoma leads delayed release & retardation the growth of tumour.

Nanogels have been primarily used for cancer therapy. Cholesteryl pullulan angel has shown in clinical trials for delivery of peptidase. The Cholesteryl – HER – 2 vaccine was administered to nine patients with 300µg with booster doses twice a week. From this shown that skin sensitivity at the site of S.C injection & CD4+ & CD8+ T- cell shows the better therapeutic efficacy. Cholesterol pullulan angels show the reduce the toxicity to the nervous system cells and increase the binding capacity to AB oligomer in treating Alzheimer's disease.

Recently the new development of controlled diabetes by optical sensitive insulin loaded silver nanoparticle nanogel of poly (4 – vinyl phenyl boronic acid – co – 2 – (dimethylamine) ethyl acrylate) has been designed. Now a day's nanogel is conjugated with antibiotics for the specific drug delivery and conducted at the single cell level.

In future the mechanism of blood brain barrier and cytosolic destination over and Endosomal or nuclear are necessary to study for the specific and targeting drug delivery. It is obvious that researchers focus primarily on finding new nanogel structures with more and more capabilities: improved design to upload/release bioactive substances over a specified period of time and targeting properties to enable highly selective uptake into the desired organs. At that point in the near future, nanogels as bio actives delivery carriers would improve the efficiency of medical care and benefit of the patients. [34-36]

## CONCLUSION:

Nanogels are promising and innovative drug delivery system that can play a vital role by addressing the problems associated with old and modern therapeutics such as nonspecific effects and poor stability. Future design and development of effective nanogel based drug delivery system for in vivo application requires a high degree of control over properties. Nanogels appear to be excellent candidates for brain delivery. One future goal of research in this area should be the improved design of microgel/nanogel with specific targeting residues to enable highly selective uptake into particular cells. This will be especially important for the targeting of cancer cells, thereby reducing non-specific uptake into healthy cells.

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