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An overview on nanogel based drug delivery system

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Abstract
Nanogel are nanoparticles composed of a hydrogel that is high cross-linked physically and chemically with hydrophilic polymer chain. Particle size range of nanogel is varies from 20-200nm. The basic things which help to make nanogel as an effectively drug delivery system, that is the nanogel based ingredients have exalted loading capacity, biodegradability and biocompatibility. They have a massive drug loading capacity and it shows superior permeation capacities due to its smaller size. The route of administration are various types, they are oral, nasal, parenteral, pulmonary, intra-ocular and topical. Biomedical and Pharmaceutical application of nanogel have been explored for tissue regeneration, surgical device, wound healing, rectal, vaginal, implementation and peroral, ocular and transdermal drug delivery. Nanogel are the neoteric drug delivery system that can make-out an integral part in denoting many issues related to old and modern courses of treatment such as nonspecific effect and poor stability. Nanogel are on of the way in nanotechnology which has been most confine in successful drug delivery inside the body and in addition topical treatment. So, nanogel make a good position in medical science, in future it is use for the treatment of diabetes, bone regulation, inflammation and cancer, etc.

Keywords: nanogel, nanoparticles, hydrogel, biodegradability, biocompatibility, pharmaceutical applications

Introduction
Drug delivery is the approaches, formulations, technologies, and systems to administering a pharmaceutical compound to achieve a therapeutic effect in human or animals. There are various methods are present in drug delivery. They are – oral, topical, parenteral, inhalation and trans-mucosal (Nasal, sublingual, buccal, vaginal, ocular rectal) etc. The drug delivery systems can be decided into two part

1. Conventional drug delivery system.
2. Novel drug delivery systems.

Nanoparticles are basically microscopic in character which composed of biodegradable polymers which offers to fulfilling the stringent requirements placed on these delivery systems, such as ability to be transferred into an aerosol, stability against forces generated during biocompatibility, targeting of specific sites, predetermined release of the drug,aerosolization and degradation [1]
Over the last few years nanogel have been emerged as an effective prover to carrying and releasing drug to the patients. Nanogel comes under the nanomedicines which is the pure combination of medicine and nanotechnology. Nanogel are basically a nanosized hydrogen in essence a polymer based gel, which is assemble of cross linking polymer chains to form macromolecular chain. Particle size range of nanogel is varies from 20-200nm [2]. Nanogel are superior drug delivery system, which make a important role in pointing out many issues related to old and modern courses of treatment like poor stability and nano specific effects [3]. Nanogel have some good characteristics such as drug loading ability, high stability, biologic consistence, good permeation capability and can be responsive to environmental stimuli [4]. In nanotechnology nanogel is one of the valuable technique which has been most prevalent in additional topical treatment and successful medication delivery inside the body [5].

Routes of Administration: [6]
- Oral
- Parenteral
- Topical
- Nasal
- Pulmonary
- Intra-ocular

Classification [2, 6]
Nanogel are mainly classified into two major ways.
The first classification is based on their responsive behaviour. They are

1. In the case of non-responsive Nanogels
2. Stimuli-responsive nanogels

In the case of non-responsive Nanogels
Absorbing water they swell simply.

Stimuli-responsive nanogels
Exposure to environmental changes such as PH, temperature, ionic strength and magnetic field these factors are depends upon swelling. The second classification is based on the type of linkages present in the network chains of gel structure, polymeric gels divided into 4 types, such as, Physical cross-linked gels, Micellar Nanogels, Hybrid nanogel and Liposome modified nanogel

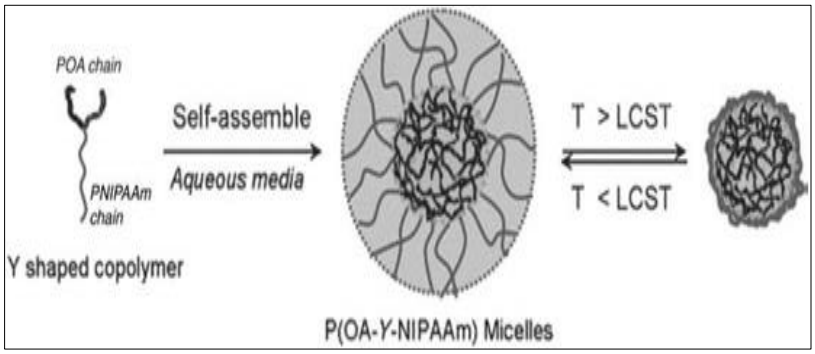

Fig 1: Y- shaped copolymer self-assembly to give micelle structures

Table 1: Other side Nanogel also classified according to their structure. They are:

Type of Nanogel	Network structure	Example
Multilayer nanogels	Cross-linked by dispersion polymerization	Poly (NIPAM-co-AA-co-rhodamine) nanogel with layer-by-layer assembly of polyelectrolytes
Hollow nanogel	Interpenetrating polymer network	Poly (acrylicacid) (PAA) network and poly(N-isopropylacrylamid) (PNIPAM) network (PNIPAM/PAA IPN hollow nanogels)
Simple nanogel	Cross-linked by self-aggregation pH and temperature responsive semi-interpenetrating polymer network	Cholesterol-bearing pullulan nanoge,cholesterol-bearing enzymatically synthetized amphiphilic glycogen
Hairy nanogel	Cross-linked by RAFT aqueous dispersion polymerization	Core-shell nanogel containing linear poly(ethylene glycol) and/or nonlinear polymer with oligo(ethylene glycol) side chains
Core-shell nanogels	Magnetic particles encapsulated by the synthetized polymer gel	Poly(acrylamide) or poly(acrylamide-vinyl amine) (shell) with magnetic core (Fe3O4 nanoparticles)
Functionalized nanogels	Cross-linked by three-step cross-linking	Diblock copolymer of poly(ethylene oxide)-b-poly(methacrylic acid) (PEG-b-PMA) with folate targeting group

Properties of Nanogel

There are different properties present in nanogel they are described bellow:

Biocompatibility and Degradability

Nanogel is made up of either natural or synthetic polymer [7]. Nanogel based drugs or drug delivery system is extremely biodegradable and biocompatible due to this characteristic. It have highly advantageous field now days. Nanogel as an effectively drug delivery system because of nanogel based ingredients have high loading capacity, biodegradability and biocompatibility [6].

Higher Drug Loading Capacity

Like other Nano delivery system, Nanogel are able to higher loading capacity than conventional dosage forms [8]**.** The properties of higher drug loading capacity of nanogel depends on the presence of functional groups in polymeric unit. Presence of functional group of polymeric chains contribute toward establishing hydrogen bonding or Vander Waals forces of interaction within the gel network and thus facilitate the drug carrying efficiency [5]. Other side, the properties of higher drug loading capacity of nanogel is mainly due to the swelling property which allows the formulation to absorb large quantity of water.

Loading takes place through 3 methods:

1. Physical entrapment
2. Covalent attachment of bioactive molecules which leads to the formation dense drug – loaded core.
3. Self- assembly.

Other than above fenomenon some other factors are also make valuable role in high loading capacity such as the possible interaction between the drug, composition, molecular weight, employed polymer and the different functional groups in each polymeric unit [7, 10].

Solubility

Due to good solubility properties nanogels are able to solubilize hydrophobic drugs and diagnostic agents in their core or networks of gel [6]. Sometimes addition of hydrophobic molecules can be solubilized into hydrophobic domains present in some nanogels.

Ex – Prostaglandin E2 was solubilized in nanogels of cholesterol-modified pullulan [11].

Colloidal Stability

Nanogel always apropensity of aggregation that compromises the colloidal stability [7]. They also have a high water content that assure good dispersion stability [12]. Polymeric micellar Nanogel or nanogel system maintain superior stability above the surfactant micelles and slower rates of dissociation,longer critical micelle concentration and longer retention of loaded drug.

Electromobility

Sonication, homogenisation or employing energy these are the critical criteria for encapsulating bio macro molecules but nanogel could be prepared without this things [6]

Swelling Property in Aquous Media

The most advantageous characteristics of nanogel is their instantaneous swelling/de-swelling properties. NanogelsNanogels are very small and soft nanomaterials that's why it have the potency to swelling of an aqueous medium. ItIt is considered to be the fundamental property influencing the mechanism of action followes by this drug delivery system. It depends on---

1. The structure of nanogel
2. Environmental parameter [2]

Permeability and Particle Size

Due to tiny manipulation in particle size, surface charge and

hydrophobicity nanogel gives good performance in permeability. The Particle size range of nanogel is varies from 20-200 nm. For this small size range or diameter nanogel are effective in avoiding the rapid renal exclusion but are small enough to avoid the uptake by the reticuloendothelial system. More specifically, it can cross the Blood Brain Barrier (BBB) [13].

Non- Immunological Response

The nanogel based drug delivery system are don't produce any immunological responses [6].

Advantages of Nanogel [9, 14, 15, 16, 17].

1. Highly biodegradable, which is crucial to avoid accumulation of nanogel material in the bodily organs thereby leading to toxicity and adverse effects.
2. High biocompatible, makes nanogel a very promising approach to drug delivery system.
3. Good permeation capacities due to extreme small size.
4. High drug loading capacity.
5. Capacity to cross Blood Brain Barier (BBB).
6. Non-immunological response.
7. Good transport characteristics.
8. Applied to both hydrophilic and hydrophobic drug and charged solutes.
9. Rapid responsiveness to environmental changes such as PH and temperature.
10. Avoid rapid phagocytic clearance.
11. By tuning crosslinking densities drug release can be regulated.
12. Ability to encapsulate a variety of compounds.
13. Avoid rapid renal excretion.
14. Reaching small capillaries penetrate tissues through paracellular and transcellular pathway.
15. Nanogels are administered via a variety of routes including oral, pulmonary, nasal, parenteral, intra-ocular and topical routes of administration.

Disadvantage [6, 14, 18, 19, 20].

1. Surfactant or monomer traces may remain and can impart adverse effect.
2. Expensive technique to completely remove the solvent sand surfactants at the end of preparation process.
3. Some fraction of particles are in the micrometre range.
4. Scale up is not easy due to mean size and weight.

Synthesis of Nanogel

Modified pullulan technique: Pullulan is one of the polysaccharide polymers obtained from the fermentation medium of the black yeast, such as Aureobasidium pullulan, it consist of maltotriose units, also known as alpha-1,4; alpha-2,6-glucan.

Example – Another example is Cholesterol based pullulan nanogel. Here, pullulan was substitute with 1.4 cholesterol and the nanogel is fabricated by simply reacting cholesterol isocynate in dimethyl sulfoxide and pyridine. This mixture was freeze dried and in aqueous phase it formed nanogel which further formed a complex with W-9 pectide, a TNF-alpha and RANKL antagonist for delivery of osteological disorder [21].

Free radical cross linking polymerization technique: By free radical crosslinking of a vinyl-containing florescent prepolymer, photo cross linked bio degradable photo luminescent polymers (PBPLPs) nanogel can be prepared and they can be used for drug delivery and cell imagine. A new era of nanobiomaterialscan be developed by the development of PBPLPs nanogel for drug delivery and cell imaging [22].

Photolithographic technique

Photolithographic technique, photochemical reaction for activation and subsequent reaction have been explored in strive of producing 3D hydrogel particles and nanogels for drug delivery [23].

It has been explore to Produced 3D hydrogen particles and microgel or nanogel rings for drug delivery. Photo lithography is consist of five steps. They are

a. The UV cross-likable polymer, which possesses low surface energy. As a substrate is released on the pre-baked photo resist – coated water.
b. It involves molding the polymer into patterns on the silioon wafer by pressing the quartz template onto the polymer and exposed it to the intense UV light.
c. The particles with a thin residual interconnecting film layer are uncovered by removing the quartz template.
d. This residual thin layer is removed by a plasma containing oxygen that oxidizes it.
e. The fabricated particles are directly collected by dissolution of the substrate in water of bufter.

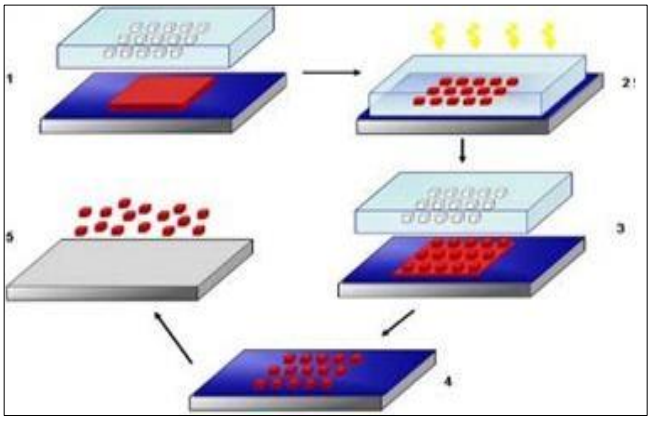

Fig 2: Schematic diagram of five steps involved in photolithography (Glangchai *et al*., 2008).

The photolithography method is essential to the blooming of techniques for surface treatment of new material or stamps for replica molds to authorise the liberate of molded gel from stamps or replica molds. (Jung *et al*; 2008) [6].

Micromolding method

This method are similar to photolithographic technique. Micromolding is a set of fabrication technique for replicating microstructures in polymers using molds (also commonly known as tools or masters) to define features. TheThe three most common micromolding technique are – injection molding, hot embossing and casting.They can minimize the need to use costly lithographic equipment and clean room facilities [2]. The resulting mixture was deposited onto plasma-cleaned hydrophilic PDMS patterns and then photocross linked via exposure to UV light. The resulting cell-laden microgels were removed, hydrated, and then harvested. They were also molded into various shapes including square prisms, disks, and strings [23].

Water-In-Oil (W/O) Heterogeneous Emulsion Methods
W/O emulsion methods involve generally two steps: emulsification of aqueous droplets of water soluble biopolymers in continuous oil phase with an aid of oil-soluble surfactants and cross linking of biopolymers with water-soluble cross linkers [24].

Inverse (mini) emulsion method
A W/O emulsion is formed from a mixture consisting of aqueous biopolymer droplets and a continuous oil phase using either a homogenizer or a high-speed mechanical stirrer.
Resulting aqueous droplets of biopolymers are then crosslinked with appropriate crosslinking agents. Then crosslinked microgel particles are prepared as dispersion in organic solvent purified by precipitation, centrifugation, washing with organic solvents such as isopropanol, and lyophilization. The size of the prepared microgel particles can be controlled by amount of surfactants and crosslinking agents as well as stirring speed during the formation of inverse emulsion.

Emulsion polymerization technique
Emulsion polymerization is a polymerization process with different applications on the academic scale and industry.It involves emulsification of hydrophobic monomers by oil- in-water emulsifier, then reaction initiation with either an oil-soluble initiator(e.g,- 2,2-azobisisobutyronitrile(AIBN) or a water soluble initiator (e.g,- potassium persulfate($K^2S^2O^8$) in the present of stabilizer which may be nonionic, ionic or protective colloid to disperse hydrophobic monomer through aqueous solution [25].

Inverse miniemulsion polymerization technique
Inverse miniemulsion polymerization is a heterogeneous water-in-oil (w/o) polymerization process, which can be applied to the synthesis of hydrophilic and water- soluble polymeric particles [26]. Inverse miniemulsion polymerization was investigated for the synthesis of welldefined nanogels. ForFor inverse emulsion process stable dispersion are formed by mechanical stirring and by sonication for inverse miniemulsion polymerization [27].

Reverse microemulsion polymerization technique
Microemulsion are thermodynamacally stable, optically transparent, isotropic dispersion of aqueous and hydrocarbon liquids stabilized by an interfacial film of surfactants molecules. The The microemulsion polymerization process is a multiskilled methods to acquire nanoparticles range between 10-100 nm with a very homogeneous particle size distribution [28].
Example: Lithium loaded polyacylic acid (PAA) nanogels were formulated by reverse microemulsion polymerization technique [29].

Mechanism of Drug Released From Nanogel

1. Diffusion
Diffusion is the net movement of anything (for example, atom, ions, molecules) from a region of higher concentration to a region of lower concentration. Diffusion is driven by a gradient in concentration [30].
Example: The diffusional release of doxorubicin from stable hydrogel nanoparticles based on pluronic block copolymer. This release mechanism is simple and has been successfully employed in various nanomedicines.

2. Nanogel degradation
To trigger the release of encapsulated molecules like Rhodamine 6G, Doxorubicin, an anticancer drug etc. the degradation of these nanogel happened.
Example---The release of Doxorubicin was significantly increased due to glycol chitosan nanoparticles sensitivity to pH stimuli due to grafting of diethylaminopropyl group [31].

3. Displacement by ion present in environment
Many research works are going on to develop a nanogel which can release it's biological agents in the response of environmental conditions at the specific site of action. Eg: Water soluble polymers like POEOMA nanogel are biodegraded in aqueous medium in the presence of glutathione tripeptide, which is commonly found in cells. [32, 34].

4. There are some other mechanism also such as, pH responsive mechanism, Photo chemical internalization and photoisomerisation [35, 36].

Application of Nanogel
Nanogel drug delivery system hold great potential to overcome some of the barriers in the delivery. Nanogel revolutionize the field of curative medicine. In short duration nanogel based drug delivery system create a magnificent achievement in terms of application.
The different application of nanogel are:

Cancer
Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. In cancer chemotherapy nanogel delivered drug are create a good role.
Cancer treatment involves targeted delivery of drugs with expected low toxicities to surrounding tissues and high therapeutic efficacy [6]. Many polymeric nanogel are Use for cancer therapy. Engulfing of chemotherapeutic drugs into the nanogel not only increase bio- availability, also enhance permeability and retention [5]. Nanogel were use in the treatment of cancer and as carriers of the following low-molecular weight drugs: doxorubicin, 5-flurouracil, temozolomide, cisplatin, neocarzinostatin, Adriamycin etc [13]. Self-organizing nanogel like Doxorubicin formulated by acetylated chondroitin sulphate use for cure cancer. Other side reducible heparin with disulfide linkage nanogel used in internalization of heparin for apoptotic death of melanoma cells.
Specific targeting nanogel of doxorubicin loaded acetylated hyaluronic acid use in cancer treatment [2].

Table 2

Nanogel constitution	Types of nanogel	Drug use	Application
Acetylated chondroitin sulphate	Self-assembled by hydrophobic interaction	Doxorubicin	Cervical cancer
Poly(N-isopropylacrylamide-co-metacrylic acid-co-N,N'-	Temperature- and pH-responsive	Cisplatin	Brest cancer therapy

methylenbisacrylamide-co-O-(methacryl)-O'-methylpolyethylene glycol)	nanogel		
Disulphide cross-linked heparin nanogel	Reducible nanogel	Heparin	Induction of apoptosis of melanoma cells
Poly(N-isopropylacrylamide-co-polyethylenimine-co-N,N'-methylenebisacrylamide)	Temperature- and pH- responsive nanogel	5-flurouracil	Mastocarcinoma therapy
Self-assembly pullulan-based nanogel with folic substituents	pH-responsive	Doxorubicin	Cervical cancer
Poly(N-isopropylacrylamide-co-butylacrylate-co-N,N'-methylenebisacrylamide)	pH-responsive	Methotrexate	Breast cancer, lung cancer, leukemia and lymphoma
Poly (acrylic acid-co-N,N'-methylenebisacrylamide) filled with hydroxypropylcellulose	Temperature- and pH-responsive nanoge	Temozolomidine	Melanoma

Stopping bleeding

A nanogel composed of protein molecules in solution has been use to stop bleeding even in severe gashes. The proteins have mechanism of self-assemble on the nanoscale in to a biodegradable gel [37].

Neurodegenerative

For the treatment of neurodegenerative disorders nanogel is a promising system for delivery of ODN (godexynucleotides) to the brain. Nanogel or encapsulate with spontaneously negatively charged ODN results in formation of stable aqueous dispersion of polyelectrolyte complex weith particle size less than 100 nm which can effectively transported across the Blood Brain Barier (BBB) [6]. Currently, neurodegenerative disorders like Parkinson's disease and Alzheimer's disease don't have any specific treatment, therefore, when oligonucleotides showed a potential to be used as a diagnostic or therapeutic tool for these diseases, they became the focus of many studies [2].

Nasal drug delivery

For the vaccine purpose nanogel are delivered via nasal route, this is a new approach to control the disease progression. Nanogel are effectively taken up by nasal mucosa and therefore, may possibly be Use as efficient transport and delivery system for therapeutics through nasal mucosa [38]. The advantages of nanogel is reduced mucociliary due to elevated viscosity, reduction in taste impart due to reduced postnasal drip towards nasopharynx, reduced irritation due to soothing/emollient excipients and target delivery to mucosa for better absorption [39].

Diabetes

Nowadays diabetes becomes more and more prevalent in world's populations, revolutionized approaches are being considered for its treatment. An injectable nanogel network that response to glucose levels in the blood and releases particular amount of insulin according to the formulation, containing a network of oppositely charged nanoparticles [2]. It accommodate a mixture of oppositely charged nanoparticles that attract each other, for the result the gels are get together and stops the nanoparticles drifting away once in the body [6].

Ophthalmic

Polyvinyl pyrrolidone – poly (acrylic acid) (PVP/PAAc) nanogel is Ph sensitive and prepared by γ – radiation – induced polymerization. It used for encapsulate pilocarpine in order to remain an adequate concentration of the pilocarpine at the site of action for prolonged of time [40].

Example – Dexamethasone containing eye drop was prepared by solvent evaporation or emulsification method using 2-hydroxypropyl-γ-clclodextrin (HP γ CD) medium containing γ-CD nanogel for sustain release [3].

Anti-inflammatory action

Nanogel have an ideal application dermatology and cosmetology as topical delivery system of non-steroidal anti-inflammatory drug (NSAID) and for the treatment of allergic contact dermatitis and psoriatic plague. Nanogel are the most valuable formulation which can overcome the major limitation to topical delivery systems, which is the relatively short contact time between active drugs and the application site [2]. 3-acetyl-11-keto-β-boswellic acid (AKBA) loaded nanoparticles are use to prepared the treatment of inflammation. AKBAAKBA is most potent pentacyclic triterpenic acid present in gum of boswellia serrata for antiinflammatory activity [41]. Two anti-inflammatory drugs, Spantide-2 and Ketoprofen drugs which are effective against allergic contact dermatitis and psoriatic plague were applied topically along with nanogel [6].

Local anesthetics

A local anesthetic (LA) is a medication that causes absence of pain sensation. In the context of surgery, a local anesthetic creates an absence of pain in a specific location of the body without a loss of consciousness, as opposed to a general anesthetic. Nanogel are one of the better option due to the lesser pain during injection and longer blood circulation time [42].

Example: A delivery system of procaine hydrochloride, which is an amino ester local anesthetic, loaded into methacrylic acid ethyl acrylate nanogel via hydrophobic and hydrogen bonds exhibited a high release rate at high pH.

The mechanism of release is based on the deprotonation of the acid on the nanogel which leads to an increase in the osmotic pressure and the swelling of the whole system, which increases the porosity, thus promoting the release of the procaine hydrochloride [43].

Transdermal drug delivery

In drug administration Transdermal route is one of the advantages over other routes in that it bypasses first pass effect, improves the efficiency of drugs, provides steady state drug concentration in plasma and increases patient compliance.

Example: As the oral administration of aceclofenac causes a number of side effects like ulcers and transdermal delivery, gastric bleeding of the drug, was studied as an alternative, and showed better permeability and stability [44].

Bone regeneration

F of or the successful regeneration of bones, biodegradable cell scaffold should release lithium as well as other medicament slowly and locally. Bone growth can be increased by lithium, hence, lithium nanogel, synthesized by

micro-emulsion polymerization of polyacrylic acid and incorporated into the biodegradable polyhydroxybutyrate matrix, are formulated for the controlled release of lithium into bone tissue [45, 46].

Vaginal drug delivery

The vaginal nanogel contain antibacterial drugs which is used to prevent various vaginal infection [47]. Researchers are initiate that certain vaginal nanogel have antiretroviral drugs, which decreases the risk of HIV infection among women.Vaginal drug can also use for the treatment of vaginal irritation, discharge and others sexual problems [48]. Otherside the Tenofovir vaginal gel has been investigated in the prophylaxis of HIV [49].

Conclusion

Nanogel based drug delivery is one of the most innovative as well as promising approach towards the various treatment of many diseases. In current and common treatment approaches there are some issues such as stability issue, nonspecific issue and some side effects are there as well. But in nanogel based drug delivery the chances of these types of issue are very less. As we have discussed in this paper, nanogel is a very promising approach due to its high bio compatibility and high biodegradability nature. Many researches are going on to improve the design of the nanogel, specific target characteristics for the treatment of various diseases such as cancer, diabetes etc. At last we are hoping that in near future "Nanogel based drug delivery" will take the center stage.

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