

NANO GEL: A NOVEL APPROACH FOR TRANSDERMAL DRUG DELIVERY

Abstract

The advancement of nanotechnology opens up a wide range of possibilities for illness prevention and therapy. The development of a nano-sized particle drug delivery method addressed the issues by improving absorption, lowering toxicity, and allowing for controlled drug release. This chapter examines recent developments in the field of 'nanogel,' which is defined as a nanoparticle made up of hydrogel that is cross-linked by a hydrophilic polymer network. The benefits of designing nanogel system, their composition, method of preparation and their characterization are described briefly. Furthermore, the applicability of nanogel in various disease and its available marketed formulations have been summarized.

Keywords: Nanotechnology, Nanogel, Nanoparticles, controlled release, Topical drug delivery.

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I. INTRODUCTION

Nanotechnology is a novel technique to develop a smart drug delivery and manufacturing of drug that is nanomedicine approach which includes design, synthesis and characterizing the materials or molecules of nanometer scale.^[1-3] The development of nanosized particulate drug delivery shows extended release of doses, more precise drug targeting and distribution, increased safety and biocompatibility.^[4-6]

There are various nano technological based formulations for an advanced drug delivery system are lipid based nanoparticles, protein based nanoparticles, nanocrystals, nanosuspensions, nanoemulsions, nanosuspensions, nanodiamonds, carbon nanotubes and nanogels. Above all the nanogels are introduced in the market for its maximum advantages over other drug delivery approaches.^[7,8]

II. NANO GEL

Nanogels are nanoparticles made up of a hydrogel with a cross-linked hydrophilic polymer network structure that ranges from 20 to 200 nm in size. Nanogels are structurally spherical shaped nanometer sized which can range from 10s-100s of nm i.e., upto about 700nm.^[9-11]

The idea of 'nanogel' was initially presented by Hoar and Schulman in 1942 and the term 'nanogel' was first begat by Schulman and colleagues in 1959.^[12] They are characterized as an clear, thermodynamically steady, isotropic combination of oil, water, surfactant and as often as possible the blend with co-surfactant.^[13,14]

The polymers found in nanogels absorb water from the aqueous environment around them and exhibit a protracted release time after swelling. Due to their hydrophilic nature, nanogels have the potential to be used in medicine to deliver controlled, targeted, and prolonged medication release.^[15-19]

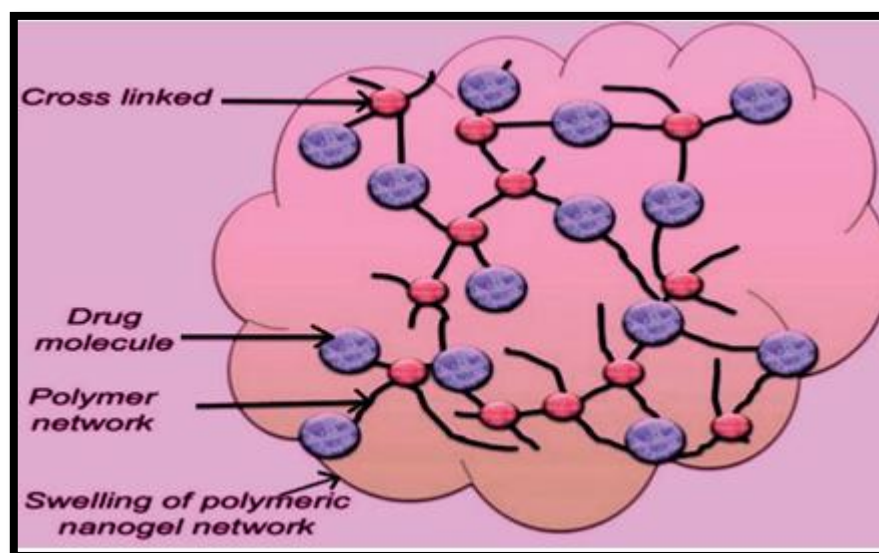


Figure 1: Structure of Nanogel

Swollen crosslinked polymer nanoparticles known as hydrophilic nanogels hold promise as promising nanocarriers for next-generation therapies. However, these nanogels are restricted in their capacity to effectively encapsulate and distribute hydrophobic medicines because of their general hydrophilic nature. In order to increase the therapeutic potential of traditional nanogels, amphiphilic nanogels with a hydrophilic polymer matrix and embedded hydrophobic groups are now being developed.^[20,23] The routes of administration for nanogel are Oral, Pulmonary, Nasal, Parenteral, Intra-ocular, and Topical.

III. ADVANTAGES:[24-28]

1. Good colloidal stability.
2. Controlled release of drug and have a better targeting site of interest.
3. Due to their high water absorptivity, they swell in the presence of aqueous environments.
4. High drug loading capacity by various methods like physical entrapment, covalent attachment and controlled self-assembly.
5. Reduced particle size, larger the surface area and hydrophobicity remarkably gives improved permeability.
6. Electromobility and non- immunologic response.
7. Nanogels respond quickly to environmental stimuli such as pH, temperature, light, magnetic field, etc.
8. Low amount of both hydrophobic and hydrophilic drug can be formulated in nanogel formulation.
9. Reduced toxicity and improved bioavailability.
10. Nanogels can easily cross BBB as well as physiological barrier like skin.
11. They are easy to apply, have flexible fabrication and enhanced patient compliance.
12. Excellent transport characteristics.
13. Better permeation via biological membranes due to extremely small size.
14. By tuning crosslinking densities drug release can be regulated

IV. LIMITATIONS ^[24-28]

1. If any traces of polymers or surfactant remain in the body they can impart toxicity. The removal of surfactant and polymers at the end of the preparation process is also expensive.
2. Complete removal of the solvent and surfactants requires expensive techniques.
3. Traces of the surfactants or monomers may be left and can cause toxicity.
4. Manufacturing variance, wherein the typical properties of nanogels are possible only within a certain range of sizes.

V. CLASSIFICATION

1. Based on response towards a stimuli

- **Non-responsive nanogel**
- **Stimuli responsive nanogel**
 - pH responsive
 - Temperature responsive

- Light responsive
- Magnetic field responsive
- Ionic strength responsive, etc.

2. Based on type of linkage present in the network chains

- **Physically cross-linked**
 - Liposomal modified
 - Micellar
 - Hybrid
- **Chemically cross-linked**

VI. COMPOSITION OF NANO GEL

The nanogel formulation generally consists of nanocarrier system containing drug with polymers, co-polymers, crosslinkers, stabilizers, etc.

Table 1: Composition of Nanogel

Sr. No	Agents to be used in the Nanogel formulation	Examples
1.	Polymers	Natural polymers: Collagen, fibrin, hyaluronic acid, chitosan, alginate, starch, etc. Synthetic polymers: Polyethyleneimine, poly(lactic-co-glycolic acid), polyNIPAM, polyacrylates, polystyrenes, poly(ϵ -caprolactone) Carbopol, HPMC etc.
2.	Co-polymers	Polyvinyl alcohol, polyvinyl pyrrolidone, polyethylene glycol, polyacrylic acid, poly (glycolic acid), polyethylene oxide, polypropylene oxide, etc.
3.	Cross-linking agents	Poly(ethylene glycol)dimethylacrylate, sodium tripolyphosphate, different acrylic acids, etc.
4.	Stabilizers	Poloxamer F68, Pluronic F127, polysorbates, etc.

VII. METHOD OF PREPARATION OF NANO GEL

The most commonly used method for the preparation of nanogel are listed and described in brief as below:

1. **Ionic gelation method:** The ionic gelation method entails a number of procedures that result in the formation of gel spheres. External ionic gelation method involves the cross-linker which forms a layer over the polymer solution whereas in internal ionic gelation method, the polymer solution embodies the cross-linker. The external ionic gelation

method is widely used because it results in formation of thin films having smoother surface, stiffness, more matrix power, more drug encapsulation, slower drug release and higher permeability.^[33,34]

2. **Emulsion polymerization:** This approach can be classified into two types of continuous phases: a) Aqueous phase, b) Organic phase. Nucleation, particle development, and polymerization are the three steps of the process. In this method the hydrophobic monomer is emulsified in a dispersion media and the surfactant concentration is added till it exceeds its critical micellar concentration (CMC), thus there is formation of micelles. The initiator is added to start polymerization and the micelle grows by continuous adding of monomers.^[33-38]
3. **Solvent emulsification/ Emulsion solvent evaporation technique:** In this approach, the drug and polymer are produced in an organic solvent, then added to an aqueous continuous phase including stabiliser and stirred continuously at room temperature until nanoemulsions form and the surplus solvent is removed.
4. **Emulsion solvent diffusion method:** The weighed amount of drug, polymer, and stabiliser is dissolved in solvent with constant stirring and ultrasonically processed. The gelling agent is added to water in an aqueous phase and heated continuously with stirring. The o/w nanoemulsion is generated by adding the drug phase dropwise to the aqueous phase and homogenising at 5000-8000 rpm for 1 hour. To improve efficiency, a penetration enhancer is added, and the pH is changed..^[38,39]
5. **Coacervation/ precipitation polymerization:** The formation of nanogel by precipitation polymerization method by physicochemical properties of polymers used in the preparation. As chitosan is insoluble in alkaline solution, it gets precipitated when it comes in contact at alkaline pH. The compressed nozzle spray is used to adjust the particle size of polymer-containing drugs.
6. **Emulsion cross linking:** The reactive functional medicines, polymer, and cross-linking agent are all cross-linked in this process, resulting in a nanogel. The w/o emulsion is made by dispersing a polymer-containing water solution into the oil phase, then stabilising and hardening the droplets with appropriate surfactants and cross-linking agents. The nanospheres are then rinsed in organic solvents and dried.
7. **Emulsion droplet coalescence method:** It is a slight modification to both the emulsion cross-linking and precipitation method. Along with the cross-linking, the emulsion also induces the precipitation which coalescence the polymer droplets. The other emulsion was prepared containing drug in the same polymer at alkaline pH. Both emulsions are to be mixed by excessive pace homogenization method. Whereas the droplets of polymer containing drug collides and coalescence which precipitates the small particles from the solution. The obtained particles are further centrifuged, washed and dried.
8. **Desolvation method:** For the desolvation technique, high molecular weight polymers such as gelatin are employed. The gelatin must be dissolved in double distilled water with constant stirring while it is heated. It is then allowed to stand for 10 minutes at room temperature before being treated with a sufficient amount of a desolvating agent, such as

ethanol, to precipitate out the high molecular weight polymer instantly. The supernant is then discarded, and the precipitated polymer is dissolved in double distilled water containing drug and crosslinking agent and agitated at constant temperature for 8 hours at 500-1000 rpm. The pH of the resultant solution is then adjusted before being centrifuged and rinsed.

9. Micro-emulsion template method: The three-dimensional nanogels for drug delivery are prepared by use of photolithography. It involves replica molds for molding gels. This method occurs in five steps:

- On pre-baked photo resist coated water, a UV cross linkable polymer is used as a substrate.
- Molding of polymer in predetermined patterns by pressing of quartz template on polymer.
- Removal of the quartz template to reveal the thin film layer.
- Oxidation of layer.
- Dissolution of substrate and collection of fabricated particles.

Others: Modified pullulan polymerization, reverse micro emulsion polymerization, inverse polymerization, free radical cross linking polymerization, and nanogel by direct or reverse RAFT polymerization are among the various approaches.^[38-40]

Table 2: Methods of Preparation and its Composition ^[35-38]

Method of preparation of nanogel	Composition
Ionic gelation	Chitosan, TPP
Emulsion polymerization	NIPAM, MBA, Acc
Solvent emulsion/ evaporation method	PEI, PEG
Precipitation polymerization	PNIPAM
Microemulsion template method	Carbopol 940, Propylene glycol
Dispersion polymerization	PEG, Oligo (ethylene glycol) (methyl) acrylates

VIII. DRUG LOADING TECHNIQUES:[39,40]

The following methods can be used to load the drug into the nanogel:

1. Covalent conjugation
2. Physical entrapment
3. Self- assembly

IX. MECHANISM OF DRUG RELEASE IN NANO GEL

The drug release from nanogel occurs by various mechanisms such as

pH Responsive Mechanism

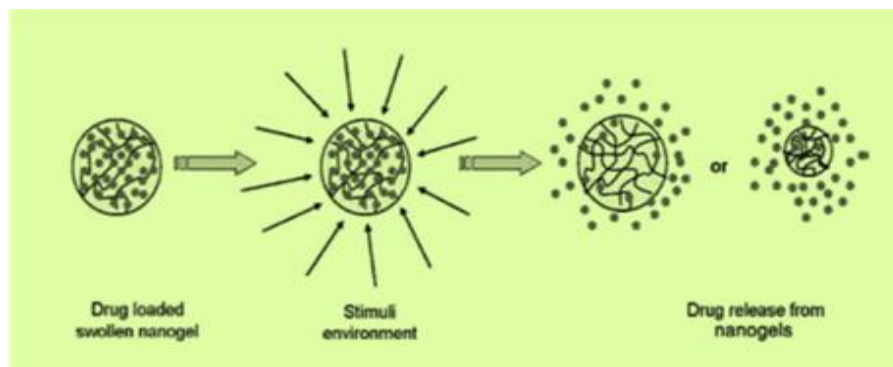


Figure 2: Release Mechanism of Nanogel

The release of drug from the nanogel can be possibly used for the anticancer drug delivery agent, where the acidic tumor environment triggers the release of drug from the system by disintegrating or swelling of polymer in a nanogel system. Because of the pH-sensitive glycol chitosan nanoparticles and the grafted diethylaminopropyl groups, the doxorubicin release was dramatically increased.^[42-48]

- 1. Volume transition and thermo sensitive mechanism:** Polymers having thermosensitive characteristics, such as Poly (N-isopropylacrylamide), have been utilised to release the medication indomethacin at temperatures higher than the lower critical solution temperature, causing the nanogel to decrease in volume. This technique, which can be successfully employed for gene delivery, can also be exploited for drug release at body temperature by superficial modification of polyethyleneimine with pluronic.^[45,46]
- 2. Diffusion of the drug from nanogel:** The strength of drug binding with the micelle core and the polymer chain binding in the micelle structure can both influence drug release from the delivery system via diffusion. Doxorubicin involves the diffusional release process. The release is controlled by addition of anionic and cationic polyelectrolyte, resulting in increased polymeric size and doxorubicin starts to release with sudden initial outburst.^[42-46]
- 3. Drug release by Photochemical internalization and photo isomerisation:** Singlet oxygen and the reactive oxygen is produced by exciting photosensitizers loading nanogels which effects the release in to the cytoplasm.^[48,49]
- 4. Displacement of ions present in the environment:** Due to the inclusion of glutathione tripeptide, which is usually prevalent in cells, the water soluble polymer POEOMA nanogels are biodegradable in aqueous environments.^[49]

X. TECHNIQUES USED TO CHARACTERIZE NANO GEL

- 1. Gelling property, gelation temperature and time:** Gelling property of the nanogel can be determined visually. Gelation time is measured by the time taken to completely conversion of nano formulation system from sol to gel at an optimum temperature.
- 2. Spreadability:** The spreadability of nanogel can be measured by taking amount of formulation between two slides of 5cm² and left for 1 min.
- 3. Viscosity:** It is measured using the Brookfield viscometer. The viscometer spindle was immersed into 100 mL of sample, then rotated with different speeds of 6, 12, 30, and 60 rpm at room temperature. The viscosity values at each speed were recorded to describe the rheological properties of the prepared mucoadhesive nanogel.
- 4. pH measurement:** The nanogel should be dispersed in water and measure using digital pH meter.
- 5. Particle size and Zeta potential measurement:** The sample is diluted with purified water IP before the particle size measurement, and the zeta potential, mean particle size, and polydispersity index are determined with a Zeta sizer. The polydispersity index (PDI) and z-average obtained using polystyrene cells of 10mm at 25°C.
- 6. Percent drug entrapment:** The accurately weighed amount of nanogel was taken for the centrifugation, the supernant layer is removed and the settled layer is to be dissolved in a suitable solvent and analyzed using UV spectroscopy. The supernant is analyzed for the entrapped drug and percent drug entrapment can be calculated using the equation,

$$\% \text{ Drug entrapment (PDE)} = \frac{\text{Total drug} - \text{free drug}}{\text{total drug}} \times 100$$

- 7. Swelling ratio:** The swelling ratio can be carried out using gravimetric method. The weighed amount of nanogel is continuously mixed with deionized water using Remi-Shaker CM 101. The centrifugation of above solution is done and the swollen samples are thus weighed by removal of excess surface water by moistened filter paper.

The swelling ratio is calculated as:

$$\frac{W_s - W_d}{W_d},$$

Where, W_s is a weight of swollen nanogel and W_d is weight of freeze died nanogel respectively.

- 8. Drug content:** The nanogel was weighed and dissolved into solvent and it is sonicated to dissolve completely. The filtrate is diluted with solvent after being filtered with Whatmann filter paper. The aliquot is scanned using UV spectrophotometer.

9. **Surface morphology:** Scanning electron microscopy (SEM) and Transmission electron microscopy (TEM) can be used to determine structural and morphological characteristics. The both techniques identify the particle size range and structural formation of the nanogel respectively.
10. **In- vitro drug diffusion study:** The Franz diffusion cell is used to investigate in-vitro diffusion. The nanogel is put in a donor compartment and the phosphate buffer solution in receptor compartment and stirred under 100 rpm at 32 °C. Different aliquots at prefixed time intervals are withdrawn and analysed by UV spectrophotometer to determine the diffusion of drug.
11. **Stability study:** The accelerated stability study of optimized nanogel is performed according to the ICH Q1A (R2) guidelines. The study is performed at 25±2 °C and 60±5% RH in environmental stability chamber over three months to assess stability.
12. **Applications of nanogel formulation:**^[58-73] The nanogel formulation provides significant role in treatment of various disease which improves the effectiveness and safety of certain hydrophobic drugs, anti-cancer drugs, anti-fungal, etc. They can be useful for many drug delivery systems such as oral, topical, pulmonary as well as parenteral. These formulations have an ability to deliver the drug at specific site in a controlled manner. It is also useful for encapsulating the lipophilic drugs and proteins. They have wide applications due to its flexibility.
13. **In cancer:** Nanogels used for the anti-cancer drug delivery involves the targeted approach only to the tumor tissues rather than the surrounding, resulting to low toxicities with high therapeutic efficacy.^[58-61]

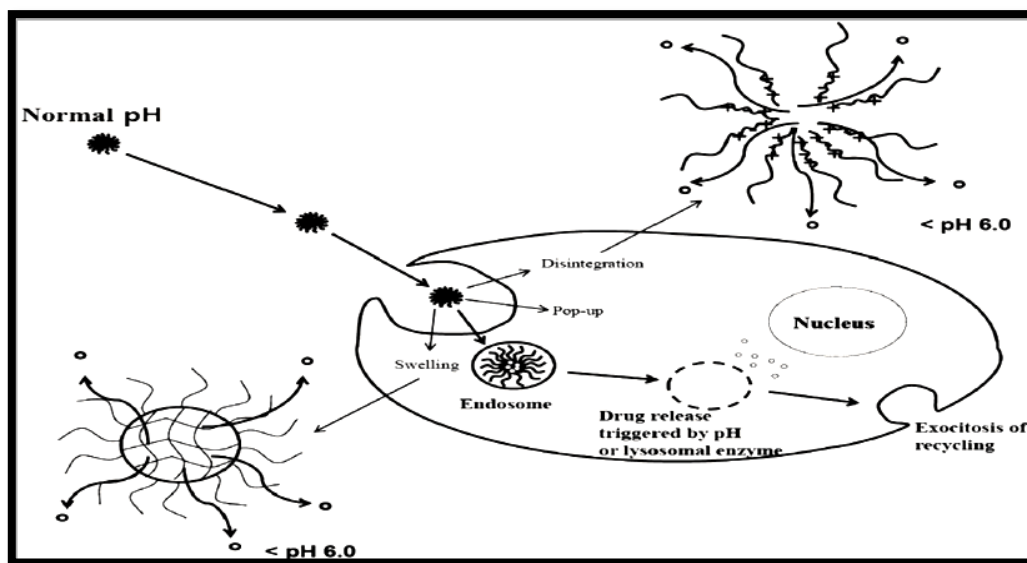


Figure 3: Drug release from nanogel in tumor environment

They can be used in treatment for brain cancer, lung cancer, ovarian cancer, skin cancer as well as breast cancer. The 10-hydroxycamptothecin (HCPT) loaded nanogel prepared via facile diffusion method showed high drug loading efficiency, prolonged

residence time, rapid release and improved tissue penetration. When compared to free HCPT, it also had a higher cytotoxicity against human T24 bladder cancer cells.^[64] pH responsible biocompatible nanogel of doxorubicin to treat osteosarcoma in MG 63 cancer cells gave targeted drug delivery. In-situ thermosensitive nanogel of poly(N-isopropylacrylamide) gelatinized 5-fluorouracil.^[70-73]

The cytotoxicity study of anti-cancer containing nanogel formulations are done to conform the effectiveness of the drug delivery to tumor tissues. They are carried out by utilising various cancer cell lines and by MTT assay procedures.^[56,57]

- 14. In autoimmune disease:** With mycophenolic acid, oligomers of lactic acid – poly (ethylene glycol) that were terminated with cyclodextrin, the loading liposomes were easily solubilized. Irgacure 2959 photo initiator and an acrylate are end group. It is then exposed to ultraviolet light to create photosynthesis. The PEG oligomers are polymerized. The term "nanogel" refers to a higher level of systemic accumulation as a result of their In-vivo, they have more intrinsic abilities and bind to immune cells than free fluorescent tracer and allow for a high degree of localization. Mycophenolic acid concentration by means of these kinds there will be an increase in patient numbers as a result of the drug delivery system compliance, as well as delaying the onset of kidney damage a common lupus complication.
- 15. Anti-inflammatory action:** The nanogels were made with carbopol and hydroxypropylmethyl cellulose (HPMC) in the required viscosity. Similar to another polymer, chitosan and poly –(Lactide – co – glycolic acid) is a bilayering agent. Oleic acid was used to modify the nanoparticles and the surface. Two anti-inflammatory drugs, for example, spantide II and Drugs containing ketoprofen are effective in the treatment of allergic reactions. In order to prepare dermatitis and psoriatic plaque, nanogel and topically applied The findings reveal that Percutaneous absorption is increased by nanogel deeper skin layers for the treatment of these two drugs of various inflammatory skin diseases.^[63]
- 16. For targeted protein and peptide delivery:** The targeted delivery for protein and peptide have stability issues in various environmental conditions such as pH, temperature which can be overcome by nanogel formulation. The fabrication of dextran-based nanogels for haemoglobin loading revealed a strong affinity for oxygen.^[66]
- 17. Vaccine delivery:** Vaccination is based on the induction of an antigen-specific immune response. Nanogels have an advantage over conventional vaccines in that they can protect vaccine antigens from enzymatic degradation. The vaccine delivery can help target specifically. Surface modification can significantly improve by nanogels with antibodies and other ligands.^[69]
- 18. Ophthalmic delivery:** To prolong time at site of action for drug pilocarpine was encapsulated by preparing the pH sensitive nanogel containing polyvinyl pyrrolidone-poly (acrylic acid) by γ radiation induced polymerization of acrylic acid in an aqueous solution of PVP as a template polymer.^[67]

- 19. Genetic material delivery:** Nanogels are now being utilised to deliver antisense oligodeoxynucleotides, siRNA, and DNA to treat disorders such as cancer, viral infections, and autoimmune diseases.^[68]
- 20. As theranostic agents:** The octeoride-conjugated fluorescent PEGylated nanogel for delivery at a specific site. As a result of the higher cellular absorption, theranostic drugs have a greater potential for use.
- 21. As imaging agents:** The swell or shrink property depending on surrounding environment and the encapsulation give silver and gold particles imaging to a large extent. Also useful for MRI and Optical imaging.^[62]

Other applicability of nanogel includes organ targeting, as therapeutic carriers, in diabetes, in stopping bleeding, etc.^[72]

There are various nanogel formulations that are marketed^[25]. They are listed in following table 3.

Table 3: Various marketed formulations of Nanogel

Product Name	Applications
Skin-perfecting, brightening nanogel	It brightens and moisturises the skin and also provides skin protection.
NBF Gingival gel	It's a gel made with nano-biofusion technology.
Muc-Off Nano Gel	It's designed to keep disc brake pads and paintwork safe.
HA nanogel	Reduces risk of decay and an excellent alternative to toothpaste.
Acnesol Nanogel	Reduces the acne and spots.
Zyflexnanogel	Relaxes muscles and erase body pain.
Sane care nanogel	It aids in the reduction of accumulated fat deposits on the arms, legs, thighs, belly, and double chin.
Augen Nanogel Eye-care Gel	It's an eye care gel with a high level of penetration.

XI. CONCLUSION

The nanogel system can be helpful to achieve controlled and sustained delivery of both hydrophobic and hydrophilic nature of drug due to its nano sized particle and having easy encapsulation property. Nanogel formulation is a novel and better technique that may also be utilised as a carrier to treat cancer, diabetes, and neurological diseases, among other conditions. They also reduce pharmacological adverse effects, which leads to enhanced treatment efficacy and patient compliance. Various nanogel formulations are already in market, but the future goal of nanogel can be improved by modification in designing of nanogel which can enable high selective uptake to specific cells, particularly in cancer. Thus

the further development of nanogel will bring out the new approach in novel drug delivery system.

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