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NANOGEL: A PROMISING DRUG CARRIER

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Abstract: Pharmaceutical researchers are always in quest of a better drug delivery system for the best performance in bioavailability, technological and process outputs. Decades of significant work has already developed several drug carriers for this purpose. Nanogel, considered as the next-generation delivery system, is currently at the forefront of research. It has been shown that nanogel is a suitable carrier for the delivery of a vaccine, hormones, and proteins. Due to the benefits over conventional dosage form. The present review is aimed to update the reader on nanogel properties, synthesis methods, evaluation tests, and applications. Nanogel has safer to be a better option to encapsulate hydrophilic as well as hydrophobic drugs to achieve a controlled or sustained release. The nanosize provides high penetration property as well as stimuli-responsive delivery, hence it is preferred for targeted drug delivery with minimum side effects in cancer therapy and CNS treatment. Nanogels are widely recognized as enticing drug delivery systems due to their high bioavailability and biodegradability.

***Index Terms*- Nanogel, Hydrogel, Nano Carrier, Microgel, Drug Delivery System, skin penetration, targeted drug delivery.**

I. INTRODUCTION

Although the delivery of therapeutic agents has progressed, still some barriers remain, which pay close attention to the development of new technologies such as 'Nanoparticulate drug' [1]. The particle size of nanoparticles lies between 1-1000nm [2]. It includes various approaches as solid lipid nanoparticles [3], nanospheres [4] liposomes [5], etc. which impart effective drug delivery. Though all these methods have proven promising, simultaneously they cover various problems such as – cost, complex preparation method, minimum drug loading capacity, various adverse effects, low stability, fast elimination, and exposure to organic solvents [6]. 'Nanogels 'can be defined as the Nano-sized particulates prepared by physical or chemical cross-linked polymer at nano-size networks that swell in a suitable solvent. Firstly the term "nanogel"(NanoGelTM) has been developed to describe cross-linked polyionic and nonionic polymer for polynucleotide delivery [7, 8]. Nanogel systems are 3D hydrogel particles in the sub-micron size [9] which are formed by physical or chemical polymer intercrossing [10, 11]. The advantage of polymer intercrossing is enhanced fluid absorption and maintaining structural integrity by avoiding dissolution [12]. There are several benefits of nanogel compared to other delivery systems which customize nanogel as next-generation drug delivery systems and those benefits are tunable size, easy preparation, swelling property, biocompatibility, hydrophilicity, and stimuli dependant delivery (temperature, pH, light, biological agent) [13], controlled delivery based on-site, drug protection against harsh circumstances [14], high biocompatibility, sustained drug release, minimum toxicity [15]. Different researches were conducted on nano-drug carriers, which strengthened their multifunctional properties of them [16- 18]. The use of Nanogels has been touched the sector of drug delivery, proteins, imaging labels, Deoxyribonucleic acid (DNA), metallic nanoparticles, Ribonucleic acid (RNA) [19], genes [20], growth factors [21], etc. The spontaneous interaction of these agents with the polymer matrix is done by electrostatic, covalent, and/or hydrophobic interactions that

impart stability to nanostructures [22, 23]. It is used for targeted drug delivery by swelling mechanisms as they can swell in aqueous media and control the drug release at the targeted site [24]. For targeted drug delivery, nanogels are modified by chemical conjugation between the active molecule and surface of nanogel [25]. As nanogel easily enters a cell, it became the ideal candidate for the intracellular delivery of the desired moiety [26]. It remains in circulation for a longer duration due to its hydrophilic property which is not taken through mononuclear phagocytes. Nanogel synthesis includes synthetic as well as natural polymer [21]. Polymers such as poly (N-isopropyl acrylamide) [27], poly (ethylene glycol) [28, 29], poly (ethylenimine) [30]. Degradation of natural polymer produces a nontoxic product to the body it seems to be highly biocompatible than synthetic [21].

II. ADVANTAGES OF NANOGEL

The advantages of nanogel [31-34] are enlisted in Table 1.

table 1. advantages of nanogels

ADVANTAGES OF NANOGELS
• Less premature leakage. • Nano size impart high permeation • Feasible to hydrophilic as well as hydrophobic drugs • Highly biocompatible and relatively biodegradable • BBB crossing ability. • Parenteral as well as mucosal delivery is easy. • Stimuli-responsive targeted delivery is possible • Good transportability.

III. LIMITATIONS

Nanogel is an expensive method to remove solvent and surfactant completely at the end of the process [8]. Adverse reactions due to traces of surfactant may occur. Drug-loading shown by nanogel possesses limited efficiency.

IV. PROPERTIES OF NANOGELS [1, 8, 35]

Biocompatibility and degradability:
This property makes the nanogel a highly promising delivery system
Swelling property in aqueous media:
Rapid swelling/de-swelling is important for novel drug delivery.
Higher drug loading capacity:
It depends on the polymeric functional moiety. The functional groups interfere with the drug loading and release phenomenon. They have a vital role in targeted drug delivery due to the presence of functional moiety that forms conjugate with a target as a drug or antibody. The polymeric functional groups introduce interactions in the gel network which enhance drug loading.
Particle size:
It is the most beneficial property as it imparts permeation property even to cross BBB. It avoids fast renal excretion and uptake through the reticuloendothelial system.
Solubility:
Nanogels can solubilize hydrophobic moiety as well as diagnostic agents in networks of gel.
Electromobility:
Nanogel synthesis can be done without harmful and energy-consuming conditions.
Colloidal stability:
Nanogels or polymeric micellar Nanogel systems are highly stable than surfactant micelles and tend to have minimum critical micellular concentrations, a longer retention time of loaded drugs, and slower dissociation rates.

Non-immunologic response:
This dosage form doesn't impart any immunological response.
Others:
Hydrophilic, solutes with charge, and hydrophobic drugs are given by nanogel. Various factors affect the properties of nanogel such as groups on the polymeric network, concentration of surfactant, type, and density of cross-link of gel.

V. CLASSIFICATION OF NANOGELS

The classification of nanogel [1] is given in Figure 1.

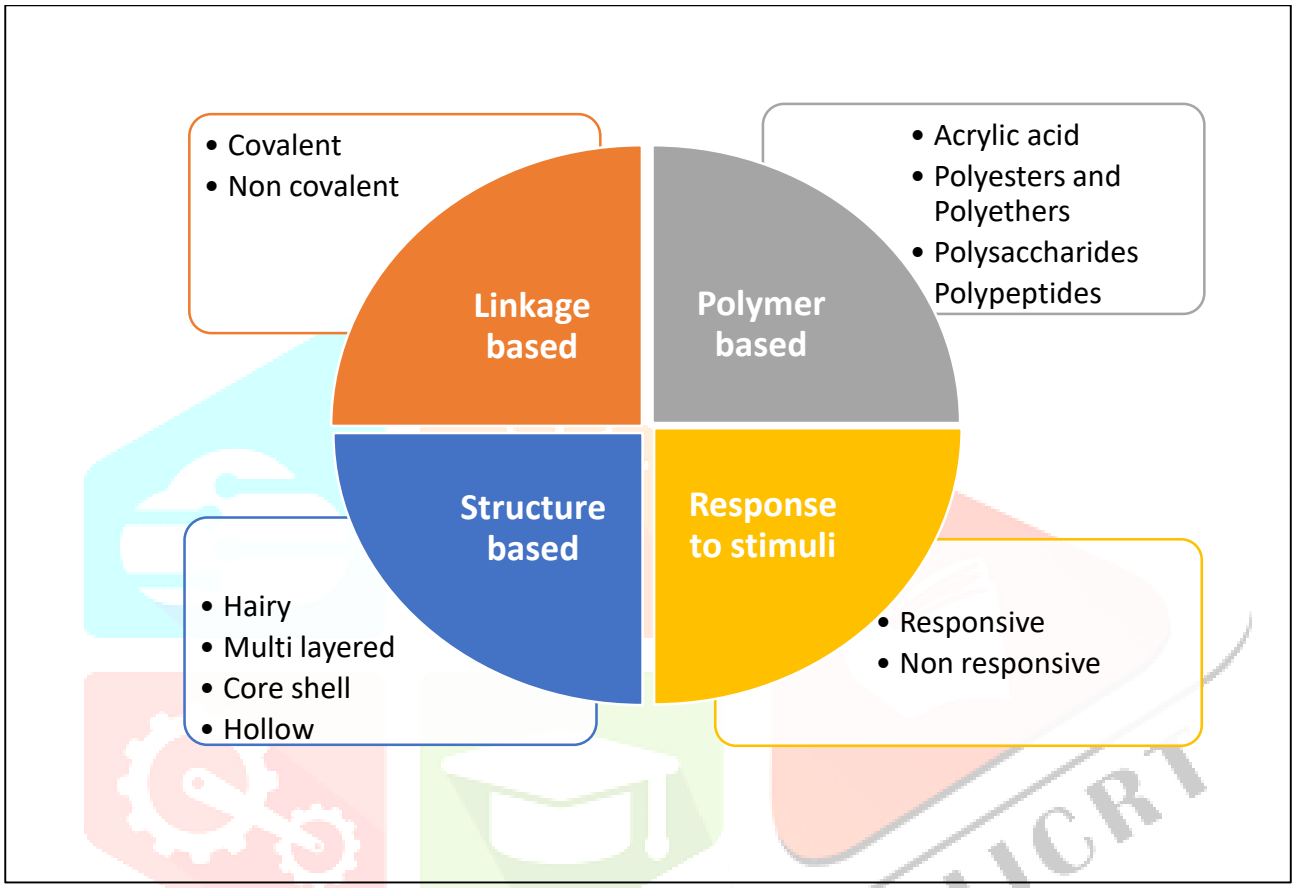

fig. 1: classification of nanogel.

VI. MECHANISM OF DRUG RELEASE

Drug release through nanogel is mainly affected by polymer(s) property. Drug release through nanogel based on some basic mechanisms: 1) pH-responsive, 2) diffusion, 3) Photochemical internalization and isomerization 4) displacement by counter ions in the external media, or 5) triggered drug release by external stimuli sources such as a magnetic field and light [1]. Some of them are explained below in detail.

4.1 pH-Responsive mechanism

It includes pH dependant drug release from nanogel. The drug release occurs according to physiological ph. The simple fact behind this mechanism is the polymer used for the preparation contains pH-sensitive functional moiety that deionizes in the polymeric gel. E.g. Insulin delivery through dextron nano particulates loaded nanogel possessing catalytic activity. It includes polymers with pH dependant swelling property [35, 36].

4.2 Diffusion mechanism

As the drug passes from the polymer matrix it shows drug release in a controlled manner. A homogenous mixture of polymer and drug is considered a matrix system in this mechanism. e.g. Doxorubicin drug releases from puronic block. It is simple and used for several nanomedicines [31, 35].

4.3 Photochemical internalization and Isomerization

On explosion to light, the bonds with restricted rotation follow conformational changes, and this phenomenon is known as photoisomerization. The photosensitive nanogel oxidizes compartment walls of a cell by producing singlet oxygen and reactive oxygen which affects the release of therapeutic agents in the cytoplasm [35, 37].

V. SYNTHESIS OF NANOGELS

Modified Pullulan technique

Cholesterol pullulan nanogel prepared using cholesterol in dimethyl sulfoxide with pyridine. In this method, cholesterol is surrogated with Pullulan, and by allowing the cholesterol isocyanate in dimethyl sulfoxide to react with pyridine a nanogel is prepared. Freeze-drying is the last step in this process and is done in an aqueous phase. In osteological treatments, nanogel after the freeze-drying technique is treated with W-9peptide, TNF-alpha, and Rankl antagonist. This method is preferred globally to evaluate nanogel efficiency in cancer therapy and Alzheimer's disease [10, 35].

Inverse (mini) emulsion polymerization technique

In the water in oil polymerization technique, aqueous droplets act as the internal phase dispersed uniformly in a continuous media using surfactant having oil solubility that imparts stability to the system e.g A Fluorescent dye Rhodamine B nanogels prepared at ambient temperatures. For stable inverse emulsion, a mechanical stirrer is preferred. Centrifugation is used for purification at the final step. The precipitate is washed with organic solvents. By controlling the amount of surfactant and cross-linking agents stirring speed, one can control the particle size. [35, 36].

Membrane emulsification technique

It includes a membrane of uniform pore size from which the dispersed phase is allowed to pass, which gives a microgel with specific membrane morphology while the external phase passes the membrane. The prepared nanogel collected the desired container. Various types of the emulsion can be prepared with this method by controlling parameters [32].

Precipitation polymerization

The easiest way to synthesize NGs is precipitation polymerization. In this technique, a homogenous solution of monomers/polymers in a specific medium [37]. Initiators, chemical compounds are added to initiate crosslinking. The solid particles are formed by polymeric chain growth became nucleation centers and initiate precipitation. Allow the process to proceed until the desired particle size obtain [38]. Centrifugation, as well as dialysis, is done for the separation and purification of the product. Produced particle size range in nanoscale 100to 600nm [39]. Narrow polydispersity is difficult to obtain [40]. The problem associated with this technique is agglomeration which occurs due to large free energy associated with the surface than bulk product and to decrease the energy they agglomerate [41]. To avoid this issue stabilizers are added which are mainly surfactant and their concentration kept below CMC [38].

Antisolvent liquid precipitation

It is also known as nanoprecipitation corresponds to the wet method for smaller solid particles preparation. The process includes Precursor dissolved in a suitable solvent and another solvent so-called antisolvent added rapidly in that [43, 44]. Selected antisolvent should miscible to solvent with less solubility towards precursor and this property imparts precursor supersaturation which leads nucleation. As the growth of the particle ends it leads to colloidal stability [45]. Process parameters are controlled to form nanogel. To avoid Ostwald ripening mechanism stabilizer added to the mixture [46, 47]. Hydrophobic anticancer drugs are preferred for this method with the nanoprecipitation method [48]. Drugs with hydrophobic property and the precursor dissolved in an organic liquid. Then water is added to the solution which tends to form supersaturation and precipitation, in this water plays the role of antisolvent. There is large research is done for functional carriers [38].

Spray drying/crosslinking

This method utilizes a volatile/semivolatile solvent to form a solution of a polymeric precursor the nebulizers well as electrosprayers used to produce small droplets from this solution. Then the volatile solvent allows evaporating [49]. Various parameters are fixed to obtain particles of the desired size. [50]. Nano precipitation and spray drying are two effective methods used to produce encapsulated drugs. The drug with polymer is

added to a volatile solvent and then allow to form droplets. Rapid evaporation forms an encapsulated drug. The precursor dissolved in solvent allowed to spray within the spray crosslinking method. The crosslinker gets surrounded by the sprayed polymeric solution. Rapid evaporation avoids agglomeration alginate nanogel is prepared using this method [51], in this process Ca^{2+}acts as a crosslinker solution which is surrounded by a sodium alginate solution. This method mainly depends on the ionic interaction [42].

Miscellaneous methods

Some methods like electrospinning, photolithography, and microfluidics techniques are preferred for NGs preparation [40, 52]. Newly developed technique nanostructure templating prepares core-shell as well as nanocapsules which depend on the nanostructure used. It includes the surface of the nano template crosslinked with the nanogel template later. Examples of nano templates such as liposomes, metal and metal oxide nanostructures, carbon nanostructures, and NGs of multi functionalities [42].

VI. CHARACTERIZATIONS OF NANOGELS

TEM analysis

TEM is used for morphological studies. In this, the nanogel loaded with drug dissolved in water, and then dropped on a grid with the copper coat. Washing of the grid done with 1 µL Milli-Q water. In a desiccator (at room temperature) with calcium chloride, the sample allowed to dry. TEM pictures show a better result with DigitalMicrographTM as well as Soft Imaging Viewer software [53].

Differential scanning calorimetry (DSC) studies

TA Instruments calorimeter (DSC 2920) is used to detect Glass transition temperatures (*T*G). For temperature dependant analysis of polymer, copolymer temperature is maintained between temperature 0- 200. with a heating rate of ten deg/min with the flow of nitrogen. The midpoint criterion is used for *T*g assignation [54].

Zeta potential

It is done by zeta sizer by allowing nanogel addition to 50 ml double distilled water with 0.02 M NaCl of ionic strength. 30 min shaking is done with sample and pH maintained at 7.4 [55].

Particle size and Polydispersity Index (PDI)

Malvern Mastersizer 2000 MS is used for the mean size of the desired nanogel [7]. Photon correlation dependent particle size analyzer used for mean particle size and polydispersity index (PDI) determination of nanogel [55].

FTIR studies

It is used to determine copolymeric nano hydrogel spectra. Using Attenuated Total Reflectance (ATR) the spectrums were collected [54].

Nuclear magnetic resonance (1H NMR) studies

The NMR spectra are used to determine copolymer composition. CDCL3is used as a solvent for the determination of spectra in the specified instrument (250 MHz) at temperature 20; chloroform with $\delta = 7.26$ taken as a reference to measure chemical shift [54].

UV–vis spectroscopy studies:

It detects the pH-sensitive group incorporation into the polymer backbone [54].

Quasielastic light scattering (QLS) measurements

For the determination of particle size with the distribution of particle size, QLS is preferred. At an angle of 90◦ light scattering spectrophotometer is used. A correlator - Brookhaven BI-9000AT 522 Chanel digital is used to measure intensity correlation function, having Argon-ion laser with water-cooling operated at 514.5nm as a light source. For the dried sample, it is dispersed in water and acetone for 24hr and temperature at 25, all measurements were taken. The size distributions analysis by CONTIN analysis is preferred for the distribution of size [54].

Appearance

For the colour, clarity, and presence of any particle, nanogels are inspected visually. Using a calibrated digital pH meter pH measurement was carried out. Glass electrode and the reference electrode dipped completely in the gel system that covers the electrodes [7]

Spreadability

The Spreadability of nanogel is tested using a wooden block having a pulley at one end. "Slip-Drag" is the simple basis of this method. In this method, a glass slide is put on the block. And the sample of prepared nanogel about 0.1 g is taken on the ground slide. By allowing 1kg weight on top of two slides after fixing gel between slides. Allow the gel to form a uniform layer. After removing the excess gel from the ends pull the plate. The time to cover the desired distance is recorded. Lesser the time better the spreadability.

Formula to calculate spreadability,

$$S = M.L/T$$

Here, S, M, T, L represents spreadability, weight applied, Time is taken, and Length of a glass slide respectively [7].

Extrudability

The force to remove material from the test-tube is recorded. This is applied to determine the shear applied in the rheogram according to a shear rate enhancing the yield value as well as allowing plug flow. Here, the basic fact behind this is the percent quantity of nanogel extruded from the aluminum tube by applying weight in grams.

Extrudability = weight Applied for eject the nanogel from tube (in g)/ Area (in cm2). [7]

Rheological Studies

A rheology study was done by Brookfield viscometer. It is done by dipping the spindle in gel until the gel surface gets touched by a notch [7].

VII. APPLICATIONS

Some of the applications of nanogels are mentioned in Table 2.

table 2: applications of nanogel

Application	Property of nanogel	Studied Drugs
Anti-inflammatory	High permeation	Methotrexate[1], ketoprofen[4]
Antimicrobial drugs	Enhanced antimicrobial activity	Berberine[1]
Antipyretic	Thermoresponsive delivery[34]	
Autoimmune disease	High bioavailability	Mycophenolic acid[8]
Anti-Cancer drug	Stimuli-responsive delivery	5flurouracil[1]
CNS targeting	Tunable size	Doxorubicin[1]
Diabetes	Stimuli-responsive delivery	Insulin[4]
Macromolecule delivery	High penetration	Oligonucleotides[1]
Neurodegenerative	Tunable size	Oligonucleotides[4]
Ophthalmic	pH-responsive release	Pilocarpine[4]
Skin disease	High penetration	Clindamycin, neomycin[34]
Stop bleeding	Biodegradable gel[4]	
Theranostic agent	Tunable delivery, high drug loading,	Doxorubicin[1]
Wound healing	Greater retention time[34]	

VIII. SMART NANOGEL

The smart nanogel drug delivery is based on the simple fact -"the right treatment, at the right time, at the right dose, to the right patient," by using a smart nanogel approach, where the desired drug is delivered with a carrier which shows selective release at the targeted site. It is preferred in cancer chemotherapy, in which a certain receptor of overexpressed cells plays an important role. The drug delivery system usually depends on stimuli response at the targeted site, by stimuli cleavage bonds.it possesses a high exchange rate due to high surface area and hence preferred over another bulk hydrogel **[42, 56]**.

IX. CONCLUSION

Nanogel appears to be an innovative and promising drug delivery system. The goal of research in this area is to empower targeted drug delivery. Cancer treatment and brain targeting delivery are vital approaches of nanogel. Due to strong control on properties, nanogel can be modified as per the need for drug treatment. As the nanogel possesses various benefits compared to conventional dosage form, it is the preferred drug delivery system. It acts as an excellent carrier for various drug moieties due to high drug loading capacity and controlled release based on stimuli response. Nanogel has a high exchange rate as compared to bulk hydrogel due to the high surface/volume ratio. Furthermore recent research on the characterization of nanogel predicts the *in vivo* release through nanogel.

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