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A Review on Nanogel as a Novel Drug Delivery System

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Abstract:-

Nanogels are nano-sized particles which are composed of hydrogel. These are crosslink network of hydrophilic polymers. Most of nanogels are synthesized by using synthetic polymers or biopolymers which are physically as well as chemically crosslinked.

Due to presence of hydrophilic functional group nanogel can hold more amount of water. Generally particles present in nanogels are of 10 to 200 nanometers. Nowadays nanogels are widely used for the drug delivery.

Nanogel has fascinated significant attention as one of the most flexible drug delivery systems mainly for targeted drug delivery and prolonged drug delivery of bioactive agents due to their integrate characteristic of hydrogel and nanoparticle. This review focus to provide a perception into the different roles that nanogels can play for enhance tissue regeneration, for decreasing frequent doses and increase the possibility of effective pharmacological action.

Nanogels have an intensity of drug loading capacity and it exhibit better permeation capabilities due to smaller size. They can be administered by several routes such as oral, nasal, parenteral, pulmonary, intra-ocular etc.

Nanogels can be used for the treatment of cancer, diabetes, bone regeneration and inflammation. They are the novel drug delivery systems for both hydrophilic as well as hydrophobic drugs.

Keywords:- Nanogel, hydrogel, novel drug delivery system, drug release, cancer treatment, drug administration, crosslink network

Introduction:-

Nanogels perhaps describe as highly cross linked micro-sized hydrogel systems which are likewise co-polymerized or monomers which may be ionic as well as non-ionic [1]. The word 'Nanogel' itself defined as nano-sized particles which have good swelling property in solvents [2]. They are not only used in sensing, diagnostics, and bio-engineering but also widely used as drug delivery system [3]. Due of their high stability, high drug loading capacity and better time of contact with surface of skin they are more beneficiary than other convenient or nano-sized delivery systems. And these are things which makes nanogels as a suitable or convenient transdermal drug delivery system [3]. Nanogels may be composed of naturally or synthetically occurring polymers or combination of both natural as well as synthetic polymers [4, 5]. Most often nanogels have round shaped particles but the recent development in synthetic strategies permit for the manufacturing of different shapes of nanogel [5]. Nanogels have three dimensional hydrophilic networks which have a tendency to consume water or physiological fluid in a huge amount, without changing in their internal network structure [1]. Nanogels as multifunctional polymer based drug delivery system has versatility in drug encapsulation and drug release [6]. One of the example, Doxorubicin is a chemotherapy agent firstly used against some cancers such as breast, ovary, lung, bladder, various myeloma [7]. But there is the intrinsic limitations of the traditional doxorubicin is its nonspecificity which might causes serious side effects inhibiting the use of higher concentrations of the therapeutic agent. To overcome all these adverse effects current trends are all about to develop the doxorubicin loaded composite nanogels [7]. Nowadays we are noticing that a speedy growth of interest in novel application of medicines, among most of them are focusing on diagnostic modalities and improvement of current therapies

[8]. Currently nanomedicine or novel drug delivery system is the field medicine which experiencing a period of powerful growth and credit goes to the development of many strong formulations that can be applied for different pathologies and treatments [9]. In early 1960s Wichtrele and Lim firstly introduced type of hydrophobic hydrogel/nanogel for biological uses [10]. Vaccine inventions takes place in non-communicable diseases such as cancer have developed nanogel based vaccines [11].

Routes of administration of nanogels:-

- Oral
- Nasal
- Pulmonary
- Parenteral
- Topical
- Intra-ocular

[Reference 2]

Properties of nanogels:-

1. Particle size:-

The particle size of the nanogels generally ranges between 5 to 400 nm in diameter. Because of this effectual size range plays a dtermining role in avoiding rapid renal segregation, but they are sufficient to avoid uptake by the reticuloendothelial system. They can simply cross the blood–brain barrier (BBB) due to nano-sized particles and also shows potential permeation capabilities [1, 2, 12]. Size and shape of nanogels are demonstrated by electron spectroscopy and light scattering methods [13]. The tiny size of nanogel particles make sure better surface area availability for enzyme loading as well as it is also beneficial for the interaction of the immobilized enzyme with a substrate. If the high enzyme loading occurs it enhances the catalytic activity and stability of the immobilized enzyme [14].

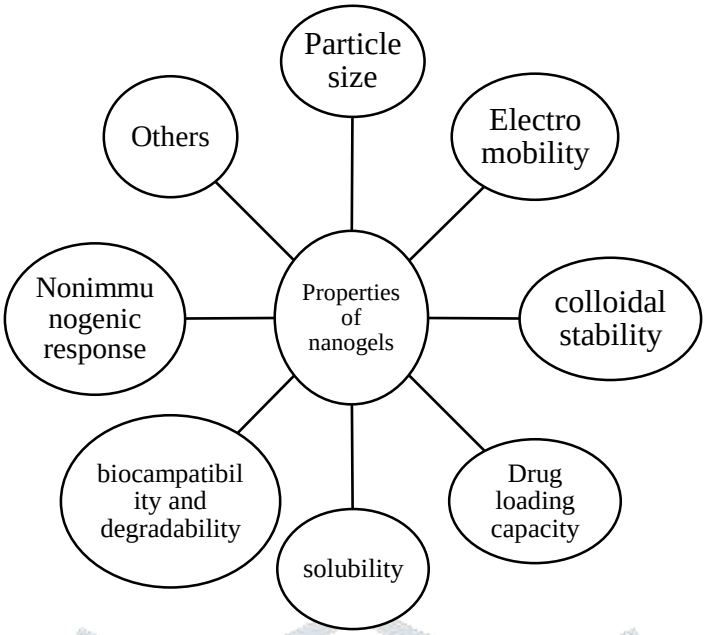

Fig: Properties of Nanogels

2. Electromobility:-

The nanogels could be comfortably synthesized without employing more energy also they can be prepared by avoiding the use of higher mechanical systems or machineries this are the main advantages of nanogels [1, 12]. In nanogels for the systematic entrapment and encapsulation of drug or therapeutical agent uncomplicated sonication and homogenization are sufficient [12].

3. Colloidal stability:-

If we do comparison in between nanogels or Polymeric micellar nanogels and the surfactant micelles we find that polymeric micellar nanogels are shows better stability over the surfactants micelles nanogels [12]. They also have the low critical micellar concentrations, a steady rate of dissociation and increase conservation of loaded drugs or bioactive molecules [1, 12].

4. High drug loading capacity:-

Due to the swelling property of nanoparticles, drug permit the huge absorption of water this is the main reason for the nanogels and other novel drug delivery system that they have the high drug loading capacity as compare to other conventional delivery systems [1]. This high drug loading capacity of nanogels mainly depends on the functional group of polymeric unit [12]. In drug transporting/carrying and drug-

releasing property functional groups plays massive role [2]. Mainly, drug loading takes place through three methods: 1. Physical entrapment 2. Covalent attachment of bioactive molecules and 3. Controlled self-assembly [1, 15].

5. Solubility:-

Nanogels are expertly solubilize the biomolecules and hydrophobic drugs in their gel structure. They can also solubilize the diagnostic agents in their network of gel [2, 12].

6. Biocompatibility and degradability:-

Nanogels are made up of natural as well as synthetic polymers [16]. Polysaccharide based polymers like dextrin, dextran, pullulan and methyl cellulose, chitosan, ethyl cellulose are used for the preparation of nanogels [1, 16, 17]. Nowadays, nanogel based delivery system is highly auspicious in the field of pharmaceutics and biotechnology because of property of highly biocompatibility and degradability [1, 12]. Mostly nanogels are found to be non-cytotoxic, although sometimes it is dose and time dependent phenomenon [18].

7. Non-immunogenic response:-

Nanogel based drug delivery system commonly does not produce any non-immunogenic response [12, 19].

8. Others:-

Nanogels have ability to give all types of drugs such as hydrophilic, hydrophilic as well as charged solutes [2, 12, 19]. Which have control and effected by temperature, pH, functional group (hydrophilic or hydrophobic) in the polymeric network, the surfactant concentration, cross linking density of gels and the type of cross linker present in the nanogels [1, 12].

Advantages of nanogels:-

1. Nanogels have high biocompatibility which makes them favorable perspective to drug delivery system [1].

2. They are biodegradable in nature so that they cannot accumulate in body organs which makes them non-toxic and there will be no adverse/ side effects [1, 20].

3. Nanogels are inert in blood and plasma, this is the reason for nanogel does not causes non-immunologic responses [1].

4. The nanosized particles are responsible for avoiding rapid renal clearance by the phagocytic cells which allow them to active and passive targeted drug delivery [2].

5. Controls the rate, time and target of the drug release in the body and this is the great advantage of this system [21].

6. They have greater drug loading capacity [20].

7. Nanogels can be administered through various routs such as oral, nasal, pulmonary, transdermal, ocular [1, 16].

8. Hydrophilic as well as hydrophobic drug can be synthesized as the nanogel drug delivery system [1, 19, 22].

9. They have magnificent transport features [20].

10. Integrating drug into the nanogel is simple, spontaneous also does not requires extra machineries as well as chemical reaction [1].

11. Design flexibility [23].

12. Nanogels shows controlled and sustained release drug mechanism so that they doesn't show side and adverse drug effects [2].

13. They can be simply escape by reticulo-endothelial system [20].

Classification of nanogels:-

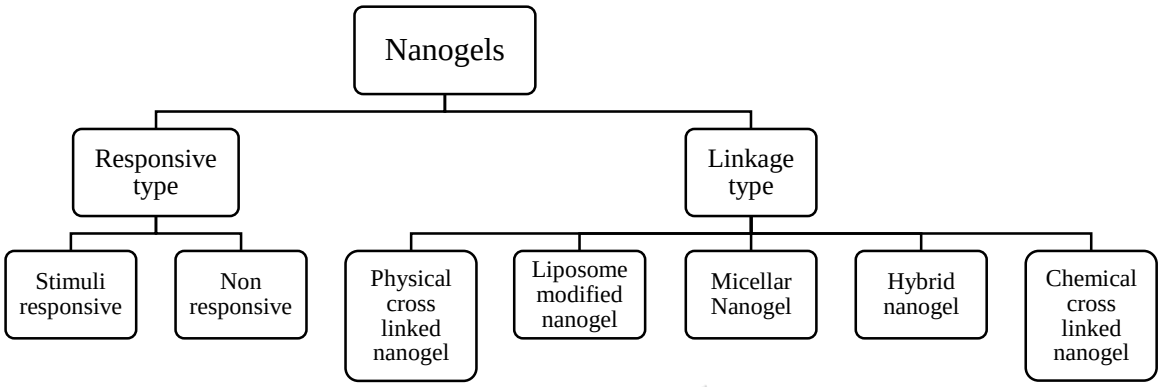

Fig: Classification of nanogels

1. Responsive type:-

It is divided into two subtypes as follows:

1.1 Nonresponsive nanogels:

They have good swelling property in solvents like water because of simple absorption process [12]. Although when they comes in contact with water, swells itself [1].

1.2 Stimuli-responsive nanogels:

They are generally effected by environment changes like temperature, pH, magnetic field, humidity, ionic strength and so on. This are the conditions where stimuli-responsive nanogels are either swell or Deswell [12]. Currently stimuli sensitive nanogels have been extensively use as smart drug delivery system for cancer treatment and controlled release delivery system [23].

Stimuli sensitive nanogels have two subtypes named as:

1. Single stimuli sensitive nanogels in which i) pH responsive nanogels and ii) temperature responsive nanogels iii) magnetic field responsive nanogels are included [24].
2. Dual stimuli sensitive nanogels in which there are also i) temperature and pH responsive nanogels ii) pH and magnetic field responsive nanogels included [24].

2. Linkage type:-

This type based on the linkage in nanogels. Further divided as follows:

2.1 Physical cross-linked nanogels:

Physical crossed linked gels also called pseudo gels. They are prepared by wander Waal's forces hydrogen bonding, electrostatic interactions and hydrophobic interaction and other weak linking forces [12]. By the association of amphiphilic blocks, self-assembly, polymeric chain aggregation and complexation of oppositely charged polymeric chains [1].

2.2 Liposome modified nanogels:

Liposomes are simply microscopic vesicles in which structure of lipid bilayer is present along with an aqueous volume which is completely enclosed by the lipid membrane [20]. Cholesterol and phospholipids are the main ingredients of liposome modified nanogels [20]. They are widely used as excellent drug carriers in various drug treatment [12]. They possess liposomes in their network structure. Liposome modified nanogels are stimuli responsive, physically crossed linked which studied as devices in transdermal delivery system because of their distinctive properties [1]. Especially liposome modified nanogels are used for the carrying various drug particles like antiviral, antibacterial, antifungal and anticancer agents [19].

2.3 Micellar nanogels:

They are sensitive nanogels synthesized by super molecular self-assembly of amphiphilic blocks and graft copolymers in aqueous medium [12]. As the micelles of micellar nanogels enters into the body, the hydrophilic shell which is made up of polymeric blocks and surrounding by hydrophobic core (this made micelles stable) interacts with the aqueous medium by forming hydrogen bonds in order to shield a hydrophobic core which is carrying the drug to its target cells.

This whole process safeguards the drug molecules from being hydrolyzed and degraded by enzymes [1]. Micellar drug delivery system has attracted the research attention because of its focus to deliver drug at prearranged rate and predetermined period of time and this is happen since use of polymeric block micelles as drug carrying vehicle (proposed in 1980) [20]. Micellar core distributes the small molecules of drug or active pharmaceutical ingredient by the process of physical entrapment [19].

2.4 Hybrid nanogels:

Due to structural formation they are very sensitive and prepared by nanosized particles which are dispersed in organic as well as inorganic medium [12]. They are stable monodispersed nanogels created by the self-aggregation of cholesterol bearing pullulan molecules [1]. Pullulan is broadly used in food, cosmetics as well as pharmaceutical industries because some of its advantages like easily modified by chemically, non-immunogenic, non-carcinogenic and nontoxic [19, 20]. This type of nanogels are able to assisting interactions with a multiple arrangements of drug molecules, DNA and proteins [19].

2.5 Chemical cross linked nanogels:

These type of nanogels are developed by covalent bonding technique [12]. As compare to physically cross linked nanogels chemically cross linked nanogels are more stable due to covalent bonding and other permanent linkage [1]. By Using various polymers and various chemical linking strategies lead the way to the manufacturing of nanogels with a variation of properties for a number of applications [1]. This type of nanogels are prepared by chain growth polymerization, addition and condensation polymerization as well as gamma and electron beam polymerization [20]. Free radical polymerization, controlled free radical polymerization and ionic and cationic polymerization are included in the chain growth polymerization [20]. And this are completed through three steps: initiation, prorogation and termination [19].

Synthesis of nanogels:-

Method used for synthesis of nanogels are listed as follows:

1. Photolithographic technique
2. Micromolding method
3. Biopolymer synthesis system
4. Water in oil (W/O) heterogeneous emulsion method
5. Inverse miniemulsion method
6. Reverse micellar method
7. Membrane emulsification method
8. Heterogeneous free radical polymerization method
9. Conversion of microscopic gel to nanogel
10. Chemical cross linking method

[Reference 12]

Applications of nanogels:-

1. **Local Anesthetics:**
   Local anesthetics are drugs which induce analgesia and give relief from pain. Local anesthetics give analgesic effect by blocking nerve impulses in nerve cell membranes by blocking Na voltage gated channels [1].

2. **Herbal nanogels:-**
   Oral and transdermal applications of herbal nanogels are possible. Oral route is a most preferable route for delivery of many clinical drugs. But when drugs give orally there are many processes are seen such as absorption, distribution, metabolism and elimination which takes time for drugs to show its effect. Apart from this oral administration also shows first pass metabolism effect, poor bioavailability, GI degradation [25]. On the other hand transdermal applications of herbal nanogel has various advantages over the other conventional drug delivery such as good patient compatibility, controlled release of drug, and it avoids first-pass metabolism effect

of the drug [25]. Curcumin based nanogel is one of the example of the herbal nanogel [26].

3. CNS delivery:-

Delivery of drugs (hydrophilic) to the brain is still challenge for the treatment of various CNS related disorders. Methotrexate loaded nanogel were prepared by using ionic gelatin method. [27]. Latest developments in studying the cell biology of BBB have opened new point of view in directing drugs to the CNS [28].

4. Protein delivery:-

Nowadays, more therapeutically active proteins have been discovered and attracted attention in specific diseases such as malignant, viral and autoimmune disease [4, 29].

5. Nanogel for bone regeneration:-

Nanogel formulations are used as injectable carriers for systemic and local administration of drugs or gene material also can be incorporated into scaffolds for exact hosting and release of the active substances (API) during the newly formed tissue growth and for the modulation of the scaffold physical properties. Systemic delivery can strongly benefit from nanogels decorated with targeting ligands capable of recognize bone cells and the mineral component, while exact localized release can also requires the nanogels to be responsive to the healing states of the bone [30].

6. Cardiovascular diseases:-

Cardiovascular diseases are the main cause of death worldwide. The cardiovascular diseases such as coronary heart disease, rheumatic and congenital heart disease, venous thromboembolism, peripheral arterial disease and cerebrovascular disease. Different factors can be lead to cardiovascular problems, from genetic issues to hypertension, diabetes or obesity. Different approaches have been studied in order to treat such diseases. Different researchers are attempting to use nanogels for drug delivery applications against this kind of diseases. For example, hypertension can treated with

many different approaches. Such as drug nanocarriers, an intranasal vaccine capable to treat hypertension and pneumococcal infections has been developed by scientists [31].

7. Anticancer therapy:-

Cancer treatment involves targeted delivery of drugs which has low toxic effects to surrounding tissues and have therapeutic efficacy [32]. Many polymeric nanogels have been used for cancer therapy. Integrating chemotherapeutic drugs into the nanogel not only increases the bioavailability but also increases permeability and retention. Nanogel are being used to deliver drugs more successfully in cancer chemotherapy. One of the example of polymeric nanogels for use in patients with breast cancer, which has FDA approved, is Genexol-PM [20]. Another example is Chitin-polymerized Doxorubicin nanogels are used for treatment of prostate, breast, lungs, and liver cancer [22].

8. Autoimmune diseases:-

A study directed, designed and tested a novel nanogel drug delivery vehicle for the immunosuppressant mycophenolic acid (MPA). Study come to an end that there is a better efficacy of nanogel based local drug delivery for lupus erythematosus as it targets antigen-presenting cells. This new drug delivery system increases the survival of the patient and delays the onset of kidney damage, a common complication of lupus [20].

9. Vaginal drug delivery:-

Vaginal nanogel carrying antibacterial drugs have been used to prevent various vaginal infections. They may also be used to decrease vaginal irritation, discharge and other sexual problems. Along with that there are some disadvantages of vaginal nanogel are that they can be contraindicated during menstruation and pregnancy. Researchers have studied that some of vaginal nanogel having antiretroviral drugs can reduce the risk of HIV infection among women. One of the example of vaginal nanogel is Tenofovir vaginal gel has been investigated in the prophylaxis of HIV [20].

10. Diabetes:-

Injectable Nano-Network which responds to Glucose and releases Insulin has been developed. In vivo experiments carried out in diabetic rats in 2012 disclose that insulin-loaded nanogels reduced the blood glucose levels by 51%. Importantly, when compared with free insulin the insulin loaded nanogels could be keep blood glucose levels stable and also avoided blood sugar variations [20].

Disadvantages:-

1. While formulating nanogels surfactants or emulsifiers are being used; they are difficult to remove after formulation [12].
2. Remaining amount of surfactants or emulsifiers may cause the toxicity [12].

Conclusions:-

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. This system plays crucial role in delivery of wide variety of medicaments and therapeutics in bacterial and microbial diseases. They possess significant characteristics and bypass problems associated with formulation like stability, absorption, and compatibility. Nanogels appear as a significant candidate in multiple targeting like brain, lungs, colon, skin, GIT and heart with enormous advantage of various routes of administration. Future design and development of effective nanogel based DDSs for in vivo applications 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 nanogels 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. More and more in vivo and in vitro study should be needed to confirm the use of this delivery system on human being.

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