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A REVIEW ON NANOGEL: A NOVEL DRUG DELIVERY SYSTEM

***[1]Nidhi Raturi, [2]Popin Kumar and [3]Praveen Kumar Ashok**

*[1]Research Scholar, Gyani Inder Singh Institute of Professional Studies Dehradun (UK) India.
[2,3]Faculty, Gyani Inder Singh Institute of Professional Studies Dehradun (UK) India.

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***Corresponding Author**
Nidhi Raturi
Research Scholar, Gyani Inder Singh Institute of Professional Studies Dehradun (UK) India.

ABSTRACT

According to Centres for Disease Control and Prevention, Rheumatoid Arthritis (RA) is an autoimmune and inflammatory condition in which your immune system unintentionally assaults healthy cells in your body, leading to inflammation (painful swelling) in the body areas affected. This review was emphasized on the process of preparation, polymers used, benefits & demerits and applications of nanogel. Rational treatment aims to reduce inflammation and relieve discomfort generally. Nonsteroidal anti-inflammatory drugs (NSAIDs), which include acetylsalicylate (Aspirin), naproxen (Naprosyn), ibuprofen, and etodolac are medications that are regarded as fast-acting. Nanogels (nanosized hydrogels) are small, swelling particles formed of adaptable hydrophilic or amphiphilic polymer networks that have been mechanically or chemically cross-linked. Ionic or anionic polymer networks are also possible. Benefits of cutaneous drug delivery include sustained action, dose flexibility, less adverse effects, the potential to avoid hepatic first pass metabolism and protection against drug inactivation by gastro-intestinal pH and enzymes. Nanogels are prepared by the two processes, i) physical crosslinking, ii) chemical crosslinking- inverse polymerization method. Polymers are used in development of nanogel including albumin, pullulan, hyaluronic acid, methacrylated chondroitin sulphate, chitosan, poly (N-isopropylacrylamide), poly (N-isopropylacrylamide-co-acrylic acid) and poly (ethylene glycol)-b-poly (methacrylic acid). It concludes that development of nanogels are essential and beneficial fast efficient drug delivery and quick relief from the pain of Rheumatoid Arthritis (RA).

KEYWORDS: Rheumatoid Arthritis (RA), nanogel, topical drug delivery, nanostructures.

INTRODUCTION

According to Centres for Disease Control and Prevention, Rheumatoid Arthritis (RA) is an autoimmune and inflammatory condition in which your immune system unintentionally assaults healthy cells in your body, leading to inflammation (painful swelling) in the body areas affected. RA primarily targets joints, typically a number of joints at once. Hand, wrist, and knee joints are frequently impacted by RA. Joint tissue is harmed in a RA-affected joint because of the inflammation of the joint lining. Long-lasting or persistent pain, unsteadiness (loss of balance), and deformity can all result from this tissue damage (misshapenness) (CDC, 2022).

All of this joint degeneration results in deformities and bone erosion, which are typically excruciatingly painful for the patient (Fox & Ahmed, 2002). Rheumatoid nodules under the skin, weariness, fever, weight loss, and morning stiffness of the affected joints lasting more than 30 minutes are all common symptoms of RA. This illness typically begins between the ages of 35 and 60, with periods of remission and exacerbation. Juvenile RA (JRA), which is comparable to RA but lacks the rheumatoid factor, can also affect young children even before the age of 16 (Chaudhari et al. 2016). The prevalence of RA is estimated to be 1% globally (Picerno et al. 2015) and 1-2 percent in the West (Chopra et al. 2008).

Osteoarthritis (OA) primarily affects the distal interphalangeal (DIP) joint; the proximal interphalangeal (PIP) and metacarpophalangeal (MP) joints are impacted in RA, which can be distinguished clinically from OA (McGonagle et al. 2015). Osteoarthritis (OA) often affects the distal interphalangeal joint (DIP), while RA typically affects the proximal interphalangeal (PIP) and metacarpophalangeal (MP) joints (Staheli., 1998). As a result, osteoarthritis and RA can be distinguished clinically (Smolen et al. 2018).

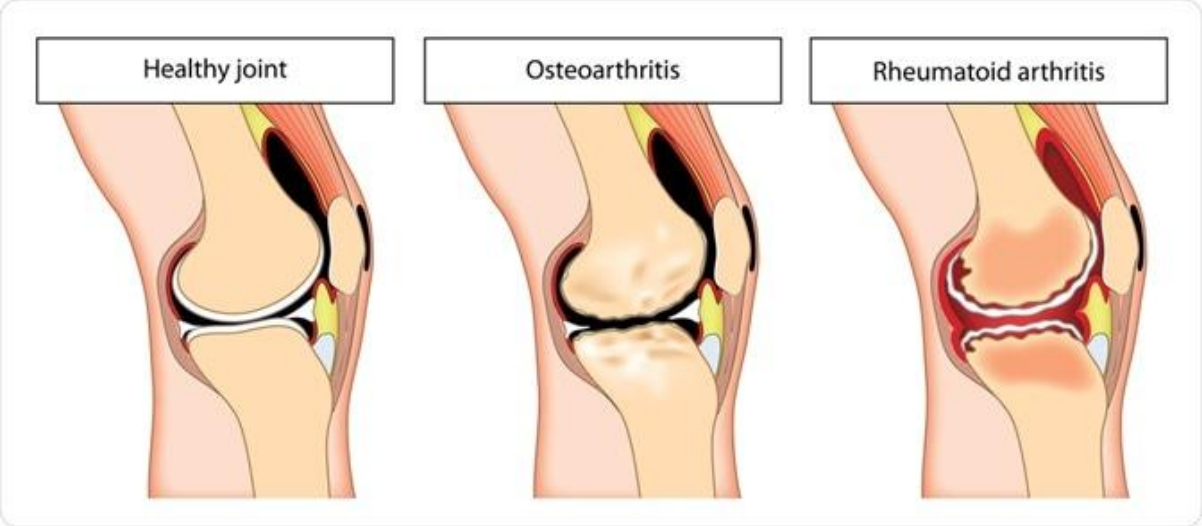

Fig 1: Depiction of Rheumatoid arthritis & Osteoarthritis.

Rational treatments of RA

First line

First-line therapy aims to reduce inflammation and relieve discomfort generally. Nonsteroidal anti-inflammatory drugs (NSAIDs), which include acetylsalicylate (Aspirin), naproxen (Naprosyn), ibuprofen (Advil and Motrin), and etodolac, are medications that are regarded as fast-acting (Lodine). Due to the suppression of prostaglandins, aspirin is an effective anti-inflammatory for RA when given at high doses. In order to stop the production of prostaglandins, prostacyclin, and thromboxanes, NSAIDs block the enzyme cyclo-oxygenase. GI bleeding, ulcers, stomach pain, and nausea are typical adverse reactions. If taken with meals, antacids, proton pump inhibitors, or misoprostol, these symptoms can be lessened (Cytotec), Celecoxib (Celebrex), an even more recent NSAID, is a selective Cox-2 inhibitor with a lower risk of GI side effects (Ong et al. 2007).

Although corticosteroids are a more effective anti-inflammatory drug than NSAIDs, they also have higher negative effects. They are therefore only recommended for brief periods at low doses, during RA exacerbations or flare-ups. Corticosteroid injections intra-articularly may be utilised to treat local inflammatory symptoms (Combe et a. 2107). They function by inhibiting phospholipid release and reducing eosinophil activity, which reduces inflammation. Bone thinning, weight gain, diabetes, and immunosuppression are a few of their adverse effects. The patient can avoid bone weakening by being advised to take calcium and vitamin D supplements. As a patient's health improves, doses can be gradually tapered off to lessen side effects (Liu et al. 2013).

Second line

Second-line therapy aims to promote remission by reducing or halting the development of joint degeneration and deformity. A medication is said to be slow-acting if it takes weeks or months to start working. Disease-modifying antirheumatic medications (DMARDs) can also lessen the possibility of getting lymphoma, which is connected to RA (Smolen et al. 2010).

The first medication in the second line is methotrexate (MTX) (also considered an anchor drug). It is a folic acid analogue that competitively prevents dihydrofolic acid (FH2) from attaching to the enzyme that transforms FH2 into folinic acid (FH4). Purine and pyrimidine metabolism is compromised, and the production of amino acids and polyamines is impeded, without FH4. Due to the immunosuppressive medicine MTX's negative effects, which include liver issues, cirrhosis, and bone marrow decline, regular blood tests are necessary (Tian & Cronstein, 2007).

A long-term RA therapeutic option is the antimalarial medication hydroxychloroquine (Plaquenil). The release of monocyte-derived proinflammatory cytokines is reduced by this medication. Issues with the GI tract, skin, and central nervous system are frequent adverse effects. When this medication is taken in excessive amounts, the eyes can be particularly affected. Patients taking this medicine are required to visit an ophthalmologist regularly (Silva et al. 2013).

Irritable bowel illness is commonly treated with sulfasalazine (Azulfidine), a DMARD. This DMARD can be utilised in conjunction with anti-inflammatory drugs to treat RA. There is no known mechanism of how this medication works to treat RA. It is believed that sulfapyridine, a decreased version of the drug following administration, may lessen interleukin (IL)-8 secretions (Volin et al. 1999).

Newer drugs

The oral drug leflunomide is metabolised to malononitrilamide, which prevents the production of ribonucleotide uridine monophosphate pyrimidine. It eases symptoms and slows RA's progression. Although it

is advised to be used in conjunction with MTX, it is also an option if a patient does not respond to MTX. There are numerous side effects, including as high blood pressure, digestive discomfort, liver damage, leukopenia, interstitial lung disease, neuropathy, rash, and bone marrow destruction (Fox et al. 1999).

The biological DMARDs, sometimes referred to as biologics, are highly efficient at halting the progression of the joint destruction brought on by RA. They are thought of as a more "direct, defined, and targeted" form of therapy. However, the issue of major side effects, like an elevated risk of infections, is present with biologics. Multiple sclerosis and lymphoma are two additional neurological conditions that can cause negative effects (Rein P, Mueller, 2017).

Supplements containing omega-3 fatty acids and fish oils are helpful for treating the acute symptoms of RA. In people with this condition, cumin has been proven to have anti-inflammatory properties. Supplementing with calcium and vitamin D can be beneficial for avoiding osteoporosis. And finally, folic acid can lessen the negative effects of MTX (Escott-Stump, 2011).

Nanogel

Nanogels (nanosized hydrogels) are small, swelling particles formed of adaptable hydrophilic or amphiphilic polymer networks that have been mechanically or chemically cross-linked. Ionic or anionic polymer networks are also possible (Vinogradov, 2010). They function as drug carriers and are constructed such that they may quickly absorb biologically active substances through the creation of biomolecular interactions such as salt bonds, hydrophobic bonds, or hydrogen bonds. By tailoring the molecular composition, size, and shape, these nanogels may easily encapsulate a variety of classes of biomolecules, ensuring the controlled release of the therapeutic molecule in vivo (Jain et al. 2010).

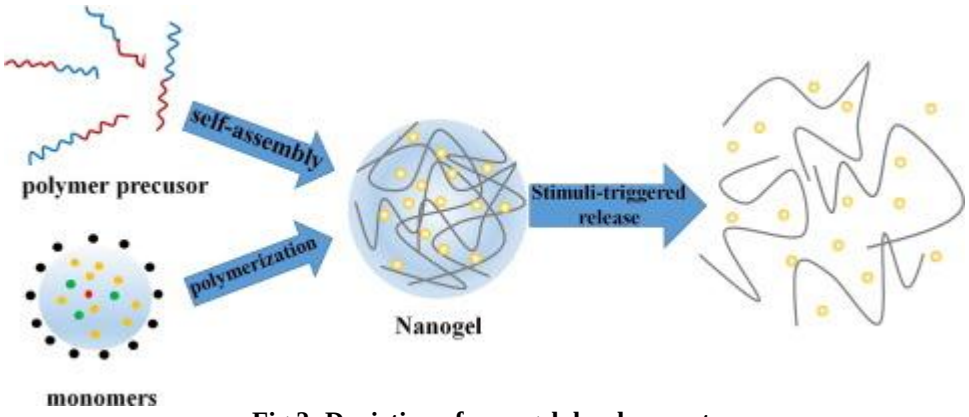

Fig 2: Depiction of nanogel development.

By permitting the creation of accidental contacts between the polymer matrix and the agents, which results in the formation of highly distributed hydrophilic particles, desired biological or drug molecules can be loaded into the nanogels. The resulting structure can offer the desired loaded biomolecule physical protection from degradation. Nanogels are a flexible structure that can be used for medication encapsulation as well as drug-controlled release at the target site (Raemdonck et al. 2009).

During the first 10 years of their development, nanogels were demonstrated to be a promising structure for systemic drug release, multifunctional nanocarrier design for theranostics, and controlled drug release at the target location (Kabanov et al. 2009).

Drug release mechanisms from nanogel

There are a number of methods that can cause a medication or biomolecule to discharge, including simple diffusion, nanogel structure degradation, changes in hydrogen ion concentration and temperature, counter ion displacement, or provoked by an external energy source.

H^+ Concentration responsive mechanism

As its name suggests, drug Unleash reacts to variations in the hydrogen ion concentration of the immediate environment. In physiological conditions with varied hydrogen ion concentration values, the release of medicines will manifest entirely differently. Therefore, the majority of discharges can come up inside the permissible hydrogen ion concentration, indicating that the discharge is mostly accomplished in a highly targeted area of the body that has that concentration of hydrogen ions. This method is based on the fact that the polymers used to create a nanogel contain practical teams that are sensitive to the concentration of hydrogen ions and deionize within them the network of compounds. Deprotonating causes the force per unit area, swelling, and consistency of to rise the substance that causes the electrostatically certain molecules to discharge (Nishcal et al. 2020).

Volume transition mechanism (heat sensitive)

Some nanogels exhibit volume phase temperature (VPTT) reactivity, which means they alter their volume in response to changes in temperature. The molecule becomes quenched and hydrous, which causes it to swell

and release the drug-loaded if the surrounding medium is below VPTT. The alternative occurs higher than VPTT, where the nanogel contracts and the substance leaks out (Lu et al. 2011). Cellular networks used to be torn apart by thermoresponsive nanogels when they expanded and gained volume. As a result, modifications were made to the thermosensitive drug-containing nanogels, such as constantly altering the polymer's magnitude in relation to achieving a lower critical temperature. An honest illustration is the biocompatible fieldtargeting capability of the chitosan and poly (N-isopropyl acrylamide) nanogel that is covertly used in the hyperthermia cancer treatment.

Photoisomerization & Photochemical internalization

The process of photoisomerization involves exposing a limited rotation bond to light, which causes various conformational changes. Covalently linked molecules are a good example; upon light irradiation, they often isomerize from a trans orientation to a cis orientation (Fomina et al. 2013). The production of two species of atomic number 8 (singlet and reactive) by photosensitizer-loaded nanogels, which are excited, can result in reactions within cellular compartment walls and have a significant impact on the release of medicinal substances into living things. Studies were released with the theme of azodextran nanogel filled with empirin. The findings demonstrated that the E-configuration of an azo cluster is produced by the photo-regulated Cis-trans transition of azobenzene. As a result, Empirin has a greater unleash profile when compared to previous Z configuration.

Impacts of Nanogel in Rheumatoid Arthritis (RA)

Traditional RA treatments often involve the administration of first-line medications such non-steroidal anti-inflammatory medicines (NSAIDs) and glucocorticosteroids (GCs), which are primarily used to relieve pain (Garg et al. 2017). Indomethacin (IND), celecoxib (CLX), etoricoxib (EXB), meloxicam (MLX), and other commonly used NSAIDs work by blocking the inflammatory COX enzyme (Kwiatkowska et al. 2017). However, long-term use of NSAIDs can cause nephrotoxicity, hypertension, myocardial infarction, and gastro-intestinal bleeding and perforation. The most significant class of anti-inflammatory medications for the treatment of pain and inflammation brought on by RS are GCs. However, long-term use of GCs may result in negative side effects include glaucoma, diabetes, osteoporosis, muscle atrophy, and suppression of the hypothalamic-pituitary-adrenal axis (Schache et al. 2002).

Second-line medications known as disease-modifying antirheumatic medicines (DMARDs) are used to manage and lessen joint deterioration. Some typical examples of DMARDs include methotrexate, sulfasalazine, clodranate, leflunomide (Krishnan et al. 2018), D-penicillinamine cyclosporine and tetracyclines (Janakiraman et al. 2018). Curcumin, capsaicin, and withanolides are a few well-known examples of herbal medicines that have been researched for reducing pain and inflammation brought on by RA (Yang et al. 2013; White et al. 2016). Transdermal medication delivery via the topical route, which is non-invasive by nature and patient-compliant due to its simplicity of use, has received more attention in recent years. Benefits of cutaneous drug delivery include sustained action, dose flexibility, less adverse effects, the potential to avoid hepatic first pass metabolism and protection against drug inactivation by gastro-intestinal pH and enzymes (Turk et al. 2002).

Preparations methods of nanogels

Nanogels are synthesized by choosing one of the 2 following mentioned methods.

1. Physical Crosslinking
2. Chemical Crosslinking

1. Physical Crosslinking

An insoluble molecule is physically incorporated into a crosslinked polymer network via the semi-interpenetration process, and the resulting nanogels can then extend the new properties of the incorporated molecule. PPY/Co-dPG nanogels were created by semi-interpenetrating poly(N-isopropylacrylamide-co-N-isopropylmethacrylamide) cross-linked dendritic polyglycerol (dPG) nanogels with polypyrrole (PPY) with photothermal convention, which may be employed for photoacoustic (PA) imaging. For PA imaging-guided photothermotherapy with NIR irradiation, PPY/Co-dPG nanogels having near infrared (NIR) responsive and hermoresponsive qualities may be employed (Theune et al. 2019).

2. Chemical Crosslinking

Chemical crosslinking is the most advanced and adaptable method for creating nanogels, as opposed to physical crosslinking. Reversible addition-fragmentation chain transfer (RAFT), click chemistry crosslinking and photo-induced crosslinking are a few examples of chemical crosslinking techniques. For the creation of biodegradable nanogels based on amino acids, amino crosslinking is frequently utilised (Kabanov & Vinogradov, 2009).

2.1 Inverse emulsion polymerization method

The constant emulsification of water-in-oil emulsifiers in the oil phase is what starts the polymerization reaction known as inverse emulsion polymerization. Numerous variables, including the surfactant, feed ratio of the monomer and crosslinker, and pH, can control the sizes of nanogels. For instance, Ashrafizadeh et al. created zwitterionic poly (AA-BA-EGDMA) nanogels utilising acrylic acid (AA), butyl acrylate (BA), and ethylene glycol dimethacrylate (EGDMA) as monomers. Peres and coworkers created poly(l-AGA) and poly(l-AGA-co-BIS) hydrogels by inverse emulsion polymerization using N, N′-methylenebis(acrylamide) (BIS) and N-acryloyl-l-glutamic acid (l-AGA), which showed that the

degree of hydrogel swelling increased with modification in pH (Wang et al. 2018).

Polymers used in preparation of nanogel

In order to create nanogels with anticancer applications, various natural polymers (Martinez et al., 2017) are used as enumerated below.

- albumin
- pullulan
- hyaluronic acid
- methacrylated chondroitin sulphate
- chitosan
- poly (N-isopropylacrylamide)
- poly (N-isopropylacrylamide-co-acrylic acid)
- poly (ethylene glycol)-b-poly (methacrylic acid)

Advantages

1. Physical characteristics like size of nanogels can be easily adjusted and maintained according to the desired delivery molecule **(**Al-Rahman et al. 2017).
2. It protects from biodegradation of drug inside the body (Goncalves et al. 2010).
3. Low amount of drug is required as well as quantity of doses is reduced.
4. Improves the bioavailability of the drug molecule and reduces the toxicity of the drugs.
5. Drugs loaded nanogels can be delivered inside the body with no adverse or side effects.
6. It can cross blood brain barrier and skin as physical barrier.
7. Nanogels do not cause any immunological reactions in the body since they are inert in the bloodstream and the internal watery environment.
8. Superior permeation ability
9. rapid reaction to changes in temperature and pH in the environment.
10. There are several different ways to give nanogels, including orally, pulmonary, nasally, parenterally, intraocularly, and topically.
11. For a number of in vivo applications, nanogel dispersions are known to have an unusually wide surface area.
12. When introduced in an aqueous media, nanogels can swell or de-swell and absorb water due to their high affinity for aqueous solutions.
13. A greater capacity for penetration.
14. Steer clear of abrupt renal exclusion. Lengthened serum half-life results from renal clearance evasion (Sultana et al. 2013).
15. Avoiding phagocytic cell clearance and reticuloendothelial system uptake allows for both passive and active medication targeting.

Disadvantages

1. The solvents and surfactants must be thoroughly removed at the end of the procedure using pricy techniques.
2. Surfactant residues can occasionally be harmful.

Applications

1. Ophthalmic

Ph-sensitive polyvinyl pyrrolidone-poly (acrylic acid) nanogel (PVP/PAAc) is made by radiation-induced polymerization. To keep an appropriate concentration of pilocarpine at the site of action for an extended period of time, it is utilised to encapsulate pilocarpine (Abd et al. 2013).

2. Bleeding prevention

Even in serious gashes, bleeding can be stopped using protein molecules that are in solution and have been used to make nanogel. The proteins have a nanoscale self-assembly mechanism that results in a biodegradable gel.

3. As NSAIDs- painkiller

The nanogels are made using Carbopol and Hydroxypropylmethylcellulose (HPMC) in the desired viscosity. Bilayered nanoparticles were created using the same polymer, chitosan, and poly (Lactide - co - glycolic acid), and their surfaces were changed with oleic acid. For instance. Two anti-inflammatory medications, spantide II and ibuprofen, were made into nanogel and administered topically to treat allergic contact dermatitis and psoriatic plaque. The findings demonstrate that the use of nanogel enhances the percutaneous absorption of these two medications into deeper skin layers for the treatment of a variety of skin inflammatory conditions (Shah et al. 2012).

4. In cancer

For the specific targeted medication delivery with low toxicities and high therapeutic efficacy in cancer, nanogel is utilised.

5. In autoimmune disorder

The loading liposomes with mycophenolic acid, oligomers of lactic acid-poly (ethylene glycol) that were ended with an acrylate end group, and Irgacure 2959 photo initiator were easily solubilized by cyclodextrin. after being subjected to UV radiation, which causes the PEG oligomers to photopolymerize (Look et al. 2013).

6. Combinational therapy

There are certain benefits to combination therapy above standard single-drug chemotherapy. First, because the medicine is taken in combination therapy at a lower level than in single administration, it can lessen the toxicity and side effects of chemotherapeutic agents. Second, several therapeutic targets would be activated simultaneously as a result of the various methods of chemotherapeutic drugs, decreasing the emergence of drug resistance (He et al. 2016).

7. Photo-chemotherapy

Since the beginning of the 20th century, light has been used in clinical settings, and phototherapies have been widely used to treat malignancies and skin conditions (such lupus). Photodynamic treatment (PDT) and photothermal therapy are the two types of phototherapies

used nowadays (PTT). PDT uses photosensitizers (PSs) to produce lethal reactive oxygen species (ROS) and cause cancer cell death, whereas PTT uses photon energy to physically heat tumours. Traditional radiotherapy and chemotherapy are inferior to phototherapies in a variety of ways, including their invasiveness, low side effects, and high selectivity (Zhu et al. 2018).

CONCLUSION

Optical sensitive insulin loaded silver nanoparticle nanogel of poly (4-vinyl phenyl boronicacid-co-2-(dimethylamine) ethyl acrylate) has recently been created to treat diabetes. Nowadays, nanogel is combined with antibiotics for precise medication delivery that takes place at the level of a single cell. Therapeutics that are hydrophilic or hydrophobic can be encapsulated in nanogels made either chemical crosslinking or physical self-assembly, including but not limited to small molecule drugs, proteins, DNA/RNA sequences, and even ultrasmall nanoparticles. The carriers' nanoscale structure gives them a precise surface area and inside volume, enhancing the stability of loaded medications and extending the time they spend in circulation in biological systems.

It concludes that development of nanogels are essential and beneficial fast efficient drug delivery and quick relief from the pain of Rheumatoid Arthritis (RA).

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Nil.

CONFLICT OF INTEREST

None.

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