# NANO DRUG DELIVERY SYSTEM FOR EFFECTIVE TREATMENT OF RHEUMATOID ARTHRITIS

**Rohan Khandu Kamble ; Manjusha Vasantrao Kadam ; Rachita Malshette**
rohankamble1308@gmail.com
**Rachita Malshette,** Department of Pharmaceutics, Channabasweshwar Pharmacy College (Degree),Latur-413512, Maharashtra, India.
rachitamalshette09@gmail.com

## ABSTRACT

*Rheumatoid arthritis, or RA, is an autoimmune and inflammatory disease, which means that your immune system attacks healthy cells in your body by mistake, causing inflammation (painful swelling) in the affected parts of the body.RA mainly attacks the joints, usually many joints at once. RA commonly affects joints in the hands, wrists, and knees. In a joint with RA, the lining of the joint becomes inflamed, causing damage to joint tissue. This tissue damage can cause long-lasting or chronic pain, unsteadiness (lack of balance), and deformity (misshapenness).RA can also affect other tissues throughout the body and cause problems in organs such as the lungs, heart and eyes.*

## INTRODUCTION

### Definition:-

Rheumatoid arthritis is a chronic progressive disease-causing inflammation in the joints and resulting in painful deformity and immobility, especially in the fingers, wrists, feet, and ankles.

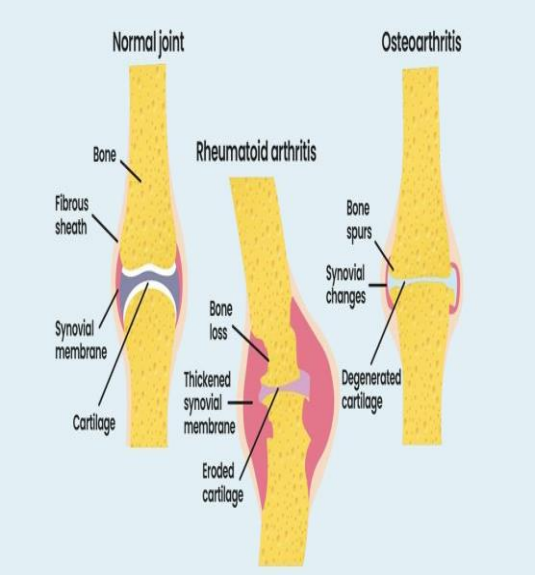


**Fig 1. Rheumatoid Arthritis**

❖ **PREVALANCE OF RHEUMATOID ARTHRITIS**

Worldwide, approximately 1% of the adult population is afflicted with RA, and about twice as many women as men suffer from the diseases. Prevalence increases with age in both sexes, with nearly 5% of women and 2% of men over 55 years of age affected. In a 1978 survey, an estimated 2.4 million adults in the United States had "symmetric polyarthritis," representing 2.4% of women and 1.4% of men in this country. The increased frequency among women is more pronounced in the United Kingdom, where

the female to male ratio is 3: 1, with prevalences of 1.6% and 0.5% among women and men, respectively. Some ethnic variation has been observed in the prevalence rates for RA, although they remain relatively constant in most white populations; the only exception is a slightly higher rate among white subjects in Finland and West Germany. Although in the United States some rheumatic diseases (scleroderma, polymyositis, and systemic lupus erythematosus) are more prevalent among blacks than whites, the overall incidence of RA is similar between the two groups; furthermore, seropositive RA appears to be clinically and radiologically similar for American whites and blacks.30 Annual incidence rates for definite RA vary from country to country. In the United States, the incidence rates between 1950 and 1974 were 22/100,000 and 48/100,000 among men and women, respectively.

## ❖ CAUSES OF RHEUMATOID ARTHRITIS-

- The cause of RA is not yet fully understood, although doctors do know that an abnormal response of the immune system plays a leading role in the inflammation and joint damage that occurs.
- No one knows for sure why the immune system goes awry, but there is scientific evidence that genes,hormones and environmental factors are involved.
- Obesity and the body's response to stressful events such as physical or emotional trauma Research also has indicated that environmental factors may play a role in one's risk for rheumatoid arthritis.
- Some include exposure to cigarette smoke, air pollution, insecticides and occupational exposures to mineral oil and silica
- Following are the some general causes of rheumatoid arthritis

### 1) Genetic

Worldwide, RAaffects approximately 1% of the adult population and occurs one in 1000 children. Studies show RA primarily affects individuals between the ages of 40–60 years and is seen more commonly in females.(1)A family history of RA increases the risk around three to five times; as of 2016, it was estimated that genetics may account for between 40 and 65% of cases of seropositive RA, but only around 20% for seronegative RA. RA is strongly associated with genes of the inherited tissue type major histocompatibility complex(MHC) antigen. HLADR4 is the major genetic factor implicated – the relative importance varies across ethnic groups.

### 2) Environmental

There are established epigenetic and environmental risk factors for RA. Smoking is an established risk factor for RA in Caucasian populations, increasing the risk three times compared to non-smokers, particularly in men, heavy smokers, and those who are rheumatoid factor positive.Modest alcohol consumption may be protective.

### 3) Other

- **Risk factors-**

  Factors that may increase your risk of rheumatoid arthritis include

- **Gender:**

Women are more likely than men to develop rheumatoid arthritis.

- **Age:**

  Rheumatoid arthritis can occur at any age, but it most commonly begins between the ages of 40 and 60.
- **Family history:**

  If a member of your family has rheumatoid arthritis, you may have an increased risk of the disease.
- **Smoking:**

  Cigarette smoking increases your risk of developing rheumatoid arthritis, particularly if you have a genetic predisposition for developing the disease. Smoking also appears to be associated with greater disease severity

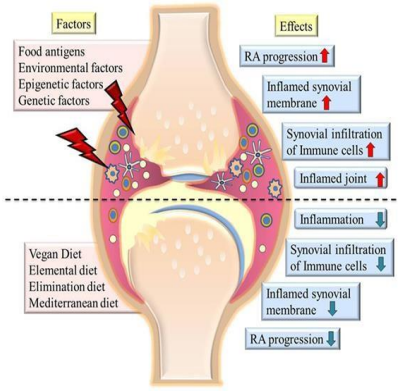


**Fig 2. Factors causing Rheumatoid Arthritis**

❖ **Symptoms RA**

- These following joint symptoms are clues to RA
- Joint pain, tenderness, swelling or stiffness for six weeks or longer
- Morning stiffness for 30 minutes or longer
- More than one joint is affected
- Small joints (wrists, certain joints of the hands and feet) are affected
- The same joints on both sides of the body are affected

Along with pain, many people experience fatigue, loss of appetite and a low-grade fever.The symptoms and effects of RA may come and go. A period of high disease activity (increases in inflammation and other symptoms) is called a flare. A flare can last for days or months. Ongoing high levels of inflammation can cause problems throughout the body. Here of some ways RA can affect organs and body system.

❖ **OBJECTIVES OF TREATMENT OF ARTHRITIS**

- To prevent or stop the inflammation.
- To relive symptoms.
- To prevent joint and organ damage.
- To improve physical function and overall well-being.
- To reduce long term complications.
- To prevent loss of functions.
- To maintain the patient's quality of life

❖ **CONVANTIONAL DRUG TREATMENT OF RHEUMATOID ARTHRITIS**

- There are three general classes of drugs commonly used in the treatment of rheumatoid arthritis:s

1. Non-steroidal anti-inflammatory agents (NSAIDs)

2. Corticosteroids
3. Disease modifying anti-rheumatic drugs (DMARDs).

**1) Non-steroidal Anti-inflammatory Agents (NSAIDs)**

The major effect of these agents is to reduce acute inflammation thereby decreasing pain and improving function. All of these drugs also have mild to moderate analgesic properties independent of their anti-inflammatory effect. It is important to note however that these drugs alone do not change the course of the disease of rheumatoid arthritis or prevent joint destruction.

Aspirin is the oldest drug of the non-steroidal class, but because of its high rate of GI toxicity, a narrow window between toxic and anti-inflammatory serum levels, and the inconvenience of multiple daily doses, aspirin's use as the initial choice of drug therapy has largely been replaced by other NSAIDs. There are a large number of NSAIDs from which to choose, and at full dosages all are potentially equally effective. Likewise, the toxicities of the currently available NSAIDs are similar. However, there is a great deal of variation in tolerance and response to a particular NSAID. These drugs were designed to decrease the gastrointestinal risk of NSAIDS, but concerns of possible increases in cardiovascular risk with these agents has led to the withdrawal of two of these drugs from the market (rofecoxib, Vioxx®; valdecoxib, Bextra®).

**2) Corticosteroids**

Corticosteroids (such as prednisone; methylprenisolone, Medrol®) have both anti-inflammatory and immunoregulatory activity. They can be given orally, intravenously, intramuscularly or can be injected directly into the joint. Corticosteroids are useful in early disease as temporary adjunctive therapy while waiting for DMARDs to exert their anti-inflammatory effects. Corticosteroids are also useful as chronic adjunctive therapy in patients with severe disease that is not well controlled on NSAIDs and DMARDs. The usual dose of predinisone is 5 to 10mg daily. Although prednisone can be started at higher doses (15 to 20mg daily), attempts should be made to taper the dose over a few weeks to less than 10mg daily. Once started, corticosteroid therapy may be difficult to discontinue and even at low doses. Some patients are very sensitive to the tapering of prednisone which may be done slowly over a few weeks.

**3) Disease modifying anti-rheumatic drugs (DMARDs).**

Although both NSAIDs and DMARD agents improve symptoms of active rheumatoid arthritis, only DMARD agents have been shown to alter the disease course and improve radiographic outcomes. DMARDs have an effect upon rheumatoid arthritis that is different and may be slower. In most cases, when the diagnosis of rheumatoid arthritis is confirmed, DMARD agents should be started. The presence of erosions or joint space narrowing on x-rays of the involved joints is a clear indication for DMARD therapy, however one should not wait for x-ray changes to occur.

❖ **DISADVANTAGES OF**

**CONVENTIONAL / TRADITIONAL DRUG TREATMENT OF RHEUMATOID ARTHRITIS**

1. Low solubility and permeability
2. Poor bioavailability
3. Degradation by gastrointestinal enzymes
4. First pass metabolism, food interactions
5. Toxicity.
6. They exhibit fluctuations in plasma drug levels and do not provide sustained effect
7. Poor patience compliance
8. Short half-life

❖ **NANOTECHNOLOGY**

➢ Nanoparticle drug delivery systems are engineered technologies that use nanoparticles for the targeted delivery and controlled release of therapeutic agents. The modern form of a drug delivery system should minimize side-effects and reduce both dosage and dosage frequency. Recently, nanoparticles have aroused attention due to their potential application for effective drug delivery.

Nanoparticles (NP) are a type of colloidal drug delivery system comprising particles with a size range from 10 to 1000 nm in diameter.

❖ **NEED OF NANOTECHNOLOGY IN RHEUMATOID ARTHRITIS**

➢ Although conventional RA treatment has made considerable progress with certain therapeutic effect, it is still compelling to develop advanced therapies to overcome the risks of dose escalation-induced defunctionalization and therapeutic tolerance. Among all the advanced therapies, nanotherapy is a rising technology that gives an innovative therapeutic platform to treat RA with minimal side effects and lower costs.

➢ Most RA therapeutic drugs are limited by poor solubility, high toxicity, large dose, non- specific administration and short cycle half-life.

➢ Nanotechnology provides opportunities for the development of new drug delivery vehicles which can improve drug properties including solubility, diffusivity, bioavailability and cycle half-life, leading to precise treatment at molecular level.

➢ Target delivery can significantly reduce the damage of off-target distribution to other organs.

➢ In addition, nanocarriers can protect therapeutic agents from rapid biodegradation, resulting in sustained drug release and extended cyclic kinetics.

❖ **VARIOUS NANOTECHNOLOGY BASED DOSAGE FORMS OF RHEUMATOID ARTHRITIS**

➢ Following are the various nanotechnology based dosage forms of rheumatoid arthritis:-

1. Solid lipd nanoparticles
2. Liposomes
3. Phytosomes
4. Niosomes
5. Nanofibers

**1) Solid lipid nanoparticles**

SLNs mainly comprise lipids that are in solid phase at theroom temperature and surfactants for emulsification, the mean diameters of which range from 50 nm to

1000 nm for colloid drug delivery applications.

2) **Liposomes**

liposomes are simple microscopic vesicles in which an aqueous volume is entirely enclosed by phospholipid bilayer.

3) **Phytosomes**

Phytosomes, also called phyto-phospholipid complexes, are the vesicular systems formed by the interaction between hydrophilic parts of phospholipids and the phyto-active components resulting in the formation of hydrogen bonds between them

4) **Niosomes**

Niosomes are microscopic lamellar structures that are formed by the admixture of the non-ionic surfactant of alkyl or dialkylpolyglycerol ether class and cholesterol with subsequent hydration in aqueous media**.**

5) **Nanofibers**

Nanofibers are fibers with diameter in the range of 1 to 100 nanometers

## ❖ NANOFIBERS IN RHEUMATOID ARTHRITIS

- Nanofibers are traditionally defined as cylindrical structures with an outer diameter below 1000nm and aspect ratio – the ratio between length and width –greater than 50.
- Nanofibers are fibers with diameter in the range of 1 to 100 nanometers.
- They are widely used in various biomedical applications such as drug delivery, gene delivery, cell therapy, cancer therapy, tissue engineering, and regenerative medicine.
- The nanofibers have been proven to be much more efficient systems for cellular and molecular applications as compared to their micro- or macro-scale counterparts, owing to their functional properties such as large surface area, high aspect ratio, superior surface properties, quantum confinement effects, and fast-absorbing ability of biomolecules, which provides abundant binding sites to cell receptors and thus allowing a strong cell- matrix interaction to take place while engineering cells, tissues, and organs [1].
- Nanofiber composites are the engineered materials composed of two or more distinct phases combined to impart new and desirable physical, chemical, and/or biological properties, which will have bulk properties significantly different form those of any of the constituent phases.
- The matrix and reinforcing phases are the two components of the nanofiber composites. The matrix phase (also called continuous phase) is the primary phase, which is usually more ductile and less hard, and the reinforcing phase (also called secondary phase or dispersed phase) is embedded within the matrix, which is usually stronger than the matrix phase, as the name implies.

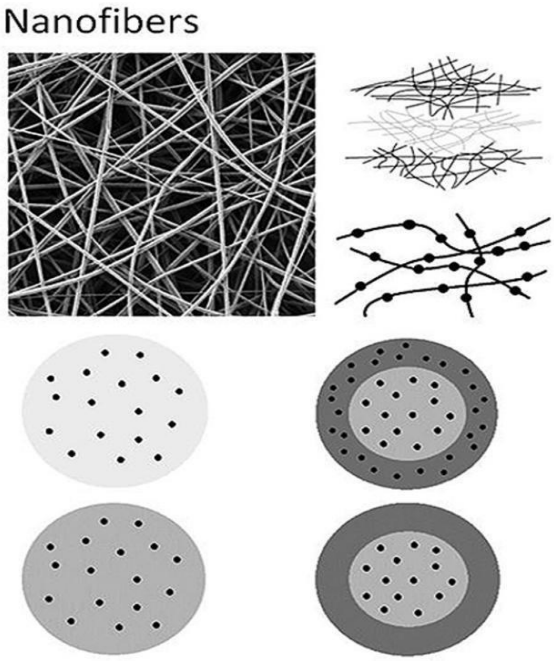


**Fig 3.Nanofibers**

❖ **Advantages of Nanofibers**

- High porosity (ca. 90%)
- High surface area (1 - 100 $m^2/g$)
- Small diameters (10 nm - 10 mm)
- Small fiber-to-fiber distance

❖ **Disadvantage**

- use on organic solvents
- limited control of pore structures

❖ **Properties of Nanofibers**

- Low density of nanofibers
- Large specific surface area of nanofibers
- Small pore size
- High porosity - good breathability
- Excellent mechanical properties in proportion to weight
- Possibility to incorporate different additives.
- Surface-to-volume ratio
- The huge surface area available on a nanofiber makes it very suitable for new technologies which require smaller and smaller environments for chemical reactions to occur.

❖ **Application of Nanofibers**

**1) Drug delivery system:**

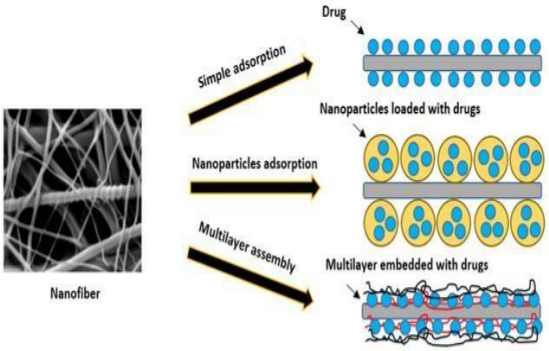


**Fig 4.Nanofibers Drug Delivery System**

- Encapsulation of the drug inside the electrospun fiber
- Improve therapeutic efficacy due to the high surface area and safety of drugs (Dissolution rate of a particulate drug increases with increasing surface area of both the drug and the corresponding carrier if needed.)

**2) Wound dressing:**

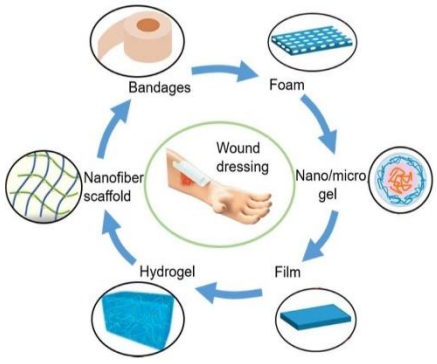

**Fig 5. Wound dressing**

- Novel polymeric composite materials that have antimicrobial properties and variable surface properties that can reduce attachment and adhesion to the wound.
- Wound dressings having antibacterial properties would be highly desirable for wounded personnel
- High surface area: Filtration, Protective clothing.
- Filter applications: Oil droplet coalescing on Nanofibers increase.
- Nano-Tex fabrics with water, cranberry juice, vegetable oil, and mustard after 30 minutes (left) and wiped off with wet paper towel (right).
- Structure: Fuel cell, Micro/Nano electronic devices
- Nanofibers can be used to greatly decrease the size of a fuel cell while increasing the electrical output.

**3) ORTHOPEDIC AND NEURAL IMPLANTS**

- Nano fibers are compatible with human tissues.
- Can create better bone & neural implants.
- Compatibility arises from similarity in body tissue and Nano structure.
- Orthopedic Nano implants - Commercially available in 5-10 years.
- Recently, researchers have found that nanofiber meshes could be used to fight against the HIV-1 virus, and be able to be used as a contraceptio

❖ **Methods of Preparation of Nanofibers**

1) Electrospinning
2) Thermal-induced phase separation
3) Drawing
4) Template Synthesis
5) SelfAssembly

**1) Electrospinning**

Electrospinning is the most commonly used method to fabricate nanofibers. The instruments necessary for electrospinning include a high voltage supplier, a capillary tube with a pipette or needle with a small diameter, and a metal collecting screen. One electrode is placed into the polymer solution and the other electrode is attached to the collector. An electric field is applied to the end of the capillary tube that contains the polymer solution held by its surface tension and forms a charge on the surface of the liquid. As the intensity of the electric field increases, the hemispherical surface of the fluid at the tip of the capillary tube elongates to form a conical shape known as the Taylor cone. A critical value is attained upon further increase in the electric field in which the repulsive electrostatic force overcomes the surface tension and the charged jet of fluid is ejected from the tip of the Taylor cone. The discharged polymer solution jet is unstable and elongates as a result, allowing the jet to become very long and thin. Charged polymer fibers solidifies with solvent evaporation. Randomly-oriented nanofibers are collected on the collector. Nanofibers can also be collected in a highly aligned fashion by using specialized collectors such as the rotating drum,metal frame, or a two-parallel plates system.]Parameters such as jet stream movement and polymer

concentration have to be controlled to produce nanofibers with uniform diameters and morphologies.

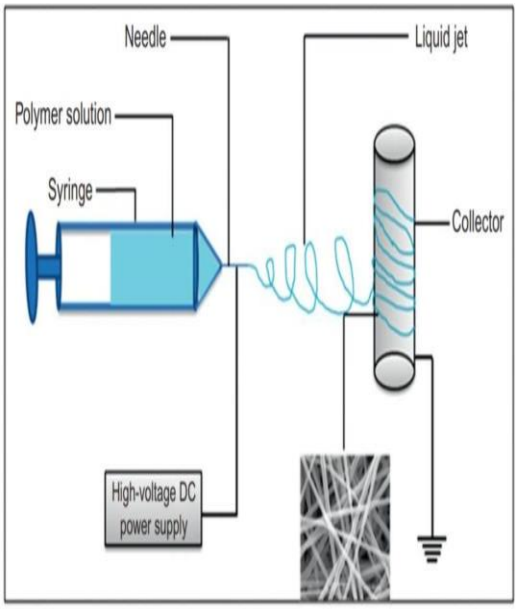


**Fig 6.Electrospinning Technique**

➢ **Key parameters of Electrospinnig**

- **Viscosity**

  Viscosity is affected by molecular weight of polymer and concentration of solution, composition of used solvents and temperature of the mixture. In a solution of low viscosity surface tension is dominant and therefore only beads or beaded fibers can be produced. Generally, with increasing viscosity the nanofibers of larger and more uniform diameter are formed.

- **Surface tension**

  High surface tension leads to instability of the jet which results in formation of droplets, beads and beaded fibers so generally low surface tension enables production of continuous uniform nanofibers.

- **Conductivity**

  Conductivity of the solution depends mainly on polymer type and solvent used. With increasing conductivity the fiber diameter decreases, low conductivity may lead to formation of beads. It has been demonstrated that addition of ionic salt (NaCl, NaH2PO4) increases conductivity of polymer solution

- **Distance between electrodes**

  Certain minimum distance should be set to allow the solvent to fully evaporate. It has been concluded that the distance between the electrodes also affects the formed nanofibers. Flatter fibers were formed from silk-like polymer with closer electrode distance.

- **Applied voltage**

  It is necessary to find optimal value of voltage for each polymer type and concentration. Generally application of higher voltage results in thinner diameter but it also leads to higher probability of formation of beads.

❖ **Materials for production of nanofibers**

**1) Polymers**

Nanofibers can be formed from many types of polymers both natural and synthetic, e.g. nanofibers from proteins,polysaccharides or nucleic acids were produced. Nanofibers formed from natural polymers are generally more biocompatible and less immunogenic, compared to the nanofibers formed from synthetic polymers. Natural polymers carry specific sequences which enable binding of cells to the formed nanofibers, they are, however, more prone to degradation/change of properties when put to inappropriate environment (special attention is needed when selecting a solvent for dissolution of polymer). Natural polymers include e.g. silk

fibroin, fibrinogen, collagen, cellulose, gelatin, chitin or chitosan. Nanofibers formed from synthetic materials offer many advantages compared to natural polymer nanofibers - their mechanical properties (strength, viscoelasticity) and degradation rate are more flexible and enable wider range of produced types of nanofibers of various structure, properties and behavior. Synthetic polymers used for formation of nanofibers are e.g. poly(ε-caprolactone), poly(lactic acid), polyglycolide, polyacrylonitrile, polyamide or polyurethane.

**2) Solvents**

Solvent used in electrospinning has a significant impact on the produced nanofibers. It is thus essential to use a solvent of properties suitable for intended use of the formed nanofibers. Solvent used for dissolution of polymer should have certain properties - good volatility, suitable boiling point and vapor pressure and the integrity of the polymer solution should be maintained. Depending on the type of solvent interaction in the system polymer-solvent may be attractive of repulsive .

The solvents are often organic and toxic which requires certain safety measures during the production and subsequent effective wash-out procedure of residual leachables (i.e. residual monomers and solvents). The safest system regarding solvent toxicity is water - polymer, however, in that case subsequent crosslinking would be inevitable for long-term release as the nanofibers would be unstable in humid environment. Nevertheless, the nanofibers prepared from water solution instable in humid environment have been used with advantage for preparation of orally dissolving web. Donepezil HCl (Alzheimer's disease medication)-loaded poly(vinyl alcohol) nanofibrous web formulation was studied in order to obtain a formulation with ultrafast release that would provide suitable way of oral administration (alternative to orally disintegrating tablets) for people with swalowing difficulties (elderly, pediatric patients etc.).[42]

| Polymer | Solvent | Active ingredients |
|---|---|---|
| Cellulose acetate | 2:1 acetone/ dimethylacetamide | Naproxen, indomethacin, Ibuprofen, sulindac |
| | | Curcumin |
| | | Vitamins A and E |
| Poly (caprolactone) | 7:3 dichloromethane/ methanol | Heparin |
| | 3:1 chloroform/ethanol | Resveratrol, gentamicin |
| Poly (ethylene oxide)/ Poly(caprolactone) blend | Chloroform | lysozyme |
| Poly (vinyl alcohol) | Deionised water | Ketoprofen |
| | | Sodium salicylate, diclofenac, naproxen, indomethacin |
| Gelatine | Gelatine in | Raspberry |

| | | |
|---|---|---|
| /poly(vinyl alcohol) blend | formic acid, poly (vinyl alcohol) in deionised water | ketone |
| Poly (lactic-co-glycolic acid) | Dichloromethane/ dimethyl formamide Dimethyl formamide | Paclitaxel |
| | | Cefoxitin sodium |
| Polyurethane | Dimethyl formamide | Itraconazole |
| | Dimethylacetamide | Ketanserin |

**Table 1. Polymers and solvent types commonly used in the preparation of electrospun drug delivery system, together with examples of the drugs which have been incorporated.**

## ❖ Conclusion

There are several anti-arthritic drugs that have been developed and are in market. But prolonged use these drugs may lead to various un- wanted side effects. Since in case of RA the treatment is usually required for the entire lifetime therefore natural products can be considered as better approach for its management. Several phytoconstituents derived from natural sources are safe and effective in RA. These phytoconstituents but suffers from various limitations like low bioavailability, less stability and requirement of higher dose. Many literature reports have confirmed the use of nano-system for delivering the phytoconstituents and therefore these limitations can be overcome, and higher drug localization can be achieved for RA treatment. Nanosystems can improve pharmacological and therapeutic proper- ties of drugs, protect the drug from degradation and are able to deliver the drug to the target site. Furthermore, safety data is required for these nanosytems is required for effective use. In future these nanocarriers can become the first choice for delivery of phytoconstituents for better management of RA .

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