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Review Paper

A Review: Formulation approaches for targeted drug delivery of drugs for Rheumatoid Arthritis

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Abstract

The aim of the present review article is focus on current status of Rheumatoid arthritis and to present various novel approaches for development of formulations and the techniques without inherent of side effects of antiarthritic drugs such NSAID. Rheumatoid arthritis is an auto immune disorder which followed by inflammation and disorder in function also causes depression. By using anti-inflammatory drugs and immunosuppressants together it can be treated. These drugs possess high fatal risk as they have not targeted to the receptor site and thus it shows severe adverse effects. Due to low bioavailability of these drugs, the drug candidates are potentially used in too high doses which causes adverse effects. In order to overcome these adverse effects, to increase the bioavailability and also to induce sustain release targeted drug delivery system may considered to be useful. By using the targeted drug delivery system, specificity of drugs increases, which increases bioavailability and the dose of administered drug get reduced.

Keywords: Rheumatoid arthritis, anti-inflammatory drugs, bioavailability, targeted drug delivery system.

Introduction

Rheumatoid arthritis (RA) is a prolonged and the inflammation occurs throughout the body and the cause of the disease is not known. The disease was associated with severe effect on psychosocial and economical. The symptoms of rheumatoid arthritis was synovitis and whole body inflammation., at this stage if it was not treated it leads to severe life threatening effects like cartilage damage and disability also the quality of life was reduced[1].

The primary symptoms are unclear because the environmental factors, hormones, genetics plays a major role. If the immune response was triggered, the immune system produces auto antibodies and cytokines which cause inflammation thus pannus was formed. This pannus destroys the bone and cartilage. As the bones and joints got damaged it initiates the release of inflammatory mediators which leads to complex process and causes the systemic complications[2].

RA risk was more twice with person who has first degree RA. Also there is a relation with harmones. It was more in females compared to men and the rate of onset of disease increases in pregnancy. Environment steer like exposure to chemical and smoking increases the chances of autoimmunity which leads to inflammation. Now-a-days improvement in diagnosis and treatment leads to use of the biological agents, which causes target release of specific drugs. The treatment with a combination of conventional disease modifying anti-rheumatic drugs with biological agent reduces drastically the symptoms, changes in erosions and finally reduction of disease[3].

Rheumatologist examine clinically, uses laboratory data and radiographic analysis for evaluation or diagnose the patient. Changes in C-reactive protein and Erythrocyte Sedimentation Rate (ESR) was changed, serum concentration are used to diagnose but it is not sufficient to diagnose the disease activity[4].

The image of normal joint and joint with rheumatoid arthritis was shown in Figure-1 and Figure-2 respectively[1].

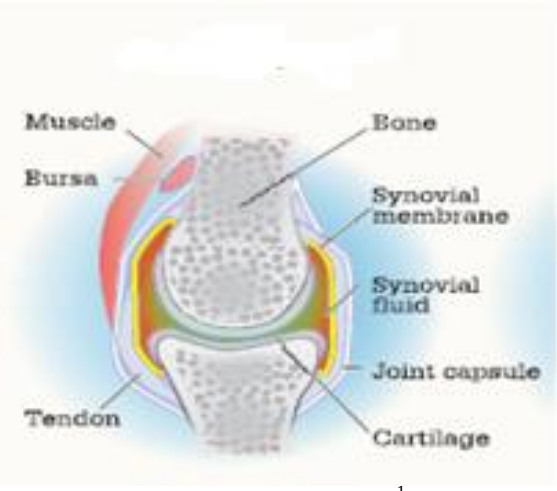

Figure-1: Normal Joint[1].

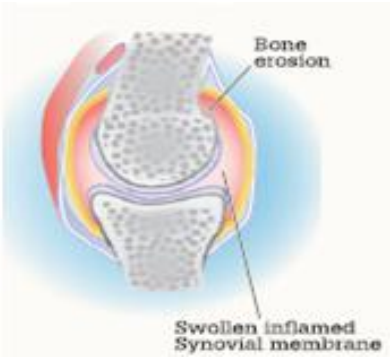

Figure-2: Joint With Rheumatoid Arthritis[1].

Diagnosis of rheumatoid arthritis

Patient history is necessary to diagnose RA. Physical examination, lab parameters, assessments like disease activity, functional status, radiographic analysis was used to confirm the diagnosis. Multiple joints were affected in RA. In RA both joints were affected and small distal joints are also commonly affected. Symptoms of RA were the joints become warm, tender, erythromtus with puffy nature as blood flow was increased and infiltration in synovial joints were occurred. This inflammation was generally recognized during physical examination as bogginess. The common sign of RA was morning stiffness which lasts for 30 minutes also pain and stiffness were occurred in joints as early symptoms. Systemic features like weakness, anorexia, fatigue and low grade fever were also accompanied which was recognised as the prodromal phase[5]. Diagnosis of rheumatoid arthritis was given in Table-1[2].

Treatment and management strategies

Various treatment procedures were available to enhance patient mobility and functionality. RA on treatment slows down, also prevents progression of disease and destruction of joints[6].

Classification of antirheumatic drugs[7]: NSAIDS: Aceclofenac, Diclofenac, Ibuprofen, Lornoxicam, etc., Disease modifying antirheumatic drugs: a. Immunosupressants :Methotrexate, Azathioprine, Cyclosporine. b. Sulfasilazine. c. Chloroquine or Hydroxychloroquine. d. Lefulonamide. e. Gold rod thiomalate, Auranofin. f. D-pencillamine.

Biologic response modifiers: a. TNF α inhibitors- Etanarcept, Infliximab, Adalimumab. b. IL-1 antagonists – Anakinra.

Adjuvant drugs: Corticosteroids – Prednisolone.

Treatment with NSAIDs

To lessen pain NSAIDS were widely used, but they are not considered as first line treatment because of the less effectiveness also it does not modify disease on long term use and its adverse effects.

Treatment of RA includes anti-inflammatory in combination with immunosuppressants. Though RA was treated with NSAIDs and disease modifying anti-rheumatic drugs, their use causes severe life threatening reactions and impaired immune function due to targeting non-specifically.

NSAIDs like aspirin and salicylates which are used in the treatment of RA act as anti-inflammatory by decreasing the cyclo-oxygenase activity and thus prostaglandins, which are the mediators of inflammation was not produced.

So, NSAIDs was used in combination therapy for RA treatment. But the long term use of NSAIDs has side effects like GI and cardiovascular complexity along with renal function impairment.

New drug development is costly and time consuming .thus old drugs were improved for safety efficacy ratio by using various methods like dose titration, individualizing the drug therapy and therapeutic drug monitoring. Even controlled drug delivery, sustain delivery and targeted drug delivery also used to improve the safety of drugs. So, NSAIDs adverse effects can be reduced by controlled release, site specific release and also by targeted delivery.

By the use of targeted drug delivery, specificity of drugs was increased and thus side effects were reduced by administering the drugs at low dose. Targeted drug delivery system increases the bioavailability and thus causes sustained release. Thus drugs degradation was reduced and even the alteration of its transport across the biological membrane can also be achieved. Thus targeted drug delivery leads to change in the pharmacokinetic activity of a drug. Thus the drugs can be delivered at selective site through TDDS compared to conventional dosage forms.

Novel formulations

Liposomes: These are lipid vesicles which contains water. It contains lipids like phospholipids or amphiphilic substances and cholesterol. Liposomes enclose hydrophilic molecules or their membranes contains lipophilic molecules. Skin surface adsorbs liposomes or it may undergo fusion, which increases the force necessary to permeate the molecule and thus increases skin penetration of the drug.

But the lopsomal fusion on dermal surface does not applicable for maco molecules. Before fusion liposomes can also penetrated to subcutaneous and thus drugs are released there, which causes localisation of drug in different layers of skin. It is useful in the case, when localisation or targeting of drug in subcutaneous is needed. With this system, it does not allow the drug to penetrate deeply in to the tissues of the dermis and thus does not allow for systemic circulation[7,8].

Table-1: Diagnosis of Rheumatoid Arthritis[2].

Disease	Patient history	Physical exams	Tests
Rheumatoid arthritis	• Duration of pain is for 6 weeks • 30 minutes of morning stiffness • Fatigue and anorexia symptoms	• Inflammation in synovial joints • Destruction of joints • Manifestations appeared extra articularly	Radiologic • X-ray and MRI shows erosions • Presence of C-reactive protein

Preparation of liposomes

Methods of preparation: Basic steps in the preparation of liposomes: i. Drying lipids from organic media. ii. Dispersion of lipid in aqueous solvent. iii. Purification of obtained liposome. iv. Evaluating the final product.

Various methods involved in the preparation of liposomes: i. Physical dispersion method. ii. Dispersion of solvent method. iii. Removal of detergent method.

Physical method: The following are types of mechanical dispersion methods: i. Membrane extrution method, ii. Micro emulsification method, iii. Freeze thraw method, iv. Film hydration by hand shaking or freeze drying.

Solvent dispersion method: i. Solvent vaporization method, ii. Reverse phase evaporation, iii. Ethanol injection.

Removal of detergent method: i. Chromatography of gel permeation, ii. Removal detergent from micelles, iii. Dialysis.

Niosomes: i. Liposomes formulated with non-ionic surfactant are niosomes. ii. Skin penetration depends on, iii. Penetrating activity of surfactant, iv. Accumulation of vesicle on the dermal surface, v. Penetration to subcutaneous (SC) layer.

The penetration depends on vesicle and lipids used, physicochemical properties of the drug. Transdermal loss of water and thus acts on the lipid layer in the intracellular domain by use of large amounts of surfactants and thus overcomes the barrier effect of the SC layer. So, niosomes are extensively used for dermal and transdermal preparations[7].

Preparation of niosomes: i. Ether Injection Method, ii. Film Method, iii. Sonication, iv. Method of Handjani–Vila, v. Reverse Phase Evaporation, vi. Heating Method, vii. Post-Preparation Processes.

Transfersomes: These are elastic vesicles which can be deformed highly. Transferosomes are first generation that had elastic vesicle which has phospholipids and edge activator. Liposomes having diameter of 200 to 400nm found difficult to pass through skin. But transfersomes reach deeper into the dermal tissues and thus easily enter into systemic circulation with its high deformable and elastic nature. Comparing liposomes and transfersomes in an in-vitro, it was found that transfersomes has high skin penetration capability than liposomes as it cannot have deformation ability like transfersomes[9,10].

Preparation of transferosomes: i. Hydration thin film method. ii. Modified hand shaking method.

Ethosomes: Like liposomes, ethosomes also contain phospholipids also it contains high amounts of alcohol. Ethosomes can easily penetrate deep into the skin layer and thus reach systemic circulation rapidly. Alcohol acts as an penetration enhancer also it disrupts the lipid intracellular structure of skin. Ethosomes has an advantage of high loading capacity of drug and more stability[11].

Methods of preparation of ethosomes: Two conventional methods for the preparation of ethosomes: i. 1. Hot Method, ii. Cold method.

Nano drug delivery: Nano structured lipid carriers and Solid lipid nanoparticles were extremely used to administer drug transdermally. SLNs contain solid as oil phase and thus water in oil emulsions are prepared from these solids as lipids. SLNs has some disadvantages like low capacity to load the drug, risk of gellifying, leakage of drug during storage, to overcome this NLCs are prepared as new generation lipids. As NLCs are prepared with various solid lipids mixed with liquid oils and thus these NLCs has low risk of toxicity. Lipid particles of NLCs has small size which ensures close contact with skin and thus increases skin penetration of drug. These nanoparticles can be prepared by using biologically degradable and non-degradable polymers[12,13].

Preparation methods for SLN and NLC: i. Homogenization Method, Hot homogenization, Cold Homogenization. ii. Solvent emulsification-diffusion method. iii. High-speed homogenization followed by ultrasonication method, iv. Solvent evaporation method, v. Spray drying method, vi. Double emulsion method, vii. Microemulsion based method, viii. Supercritical fluid method, ix. Precipitation technique, x. Film-ultrasound dispersion.

Transdermal patches: These are drug carriers which contain adhesive layer, provides a film contact with skin. Systemic circulation of drug can be accessed with controlled release. Two types of transdermal patches are there – i. membrane or reservoir type, ii. matrix type.

In reservoir type drug is present in adhesive layer and membrane controls the rate of drug release. In matrix type, drug is dispersed in polymer matrix. In matrix type, if it is not self adhesive, another layer is added for adhesive purpose. In TDDS, the components used should be chemically stable, compatible with the skin and should be appropriate for use in combination[14,15].

Methods of preparation: i. Solvent evaporation technique, ii. Solvent casting technique.

Polymers: In the field of drug delivery, polymers get importance with the use of polymers, dosage forms can be produced with.

Localized delivery: In this the dosage form can be applied directly at the place where the drug action is necessary and thus the drug cannot enter into systemic circulation and hence dose is reduced, so it is mainly useful for toxic drugs which has various side effects and adverse effects.

Sustained delivery: In this, by the use of polymers drug is released over long periods and thus reduces the frequency of dose administration. This increases patient compliance for chronic medication.

Stabilization: Polymers protect the drug from the environment which it get exposed physiologically and thus stability increases in-vivo. This technology is widely used to deliver the labile drugs like proteins[16].

Biodegradable polymers

Natural polymers: **Gelatin:** It is a natural polymer, produced by denaturing collgen. It is biodegradable, biocompatible and has low antigenicity, thus widely used in medical and pharmaceutical applications[17].

Collagen: It is a protein naturally obtained from mammal. It has good biocompatibility, biodegradable up on implantation and low antigenicity, thus widely applied in pharmaceutical purposes[17].

Alginate: It is a polysaccharide which exists in linear obtained naturally. It is obtained from bacteria, algae, seaweed[17].

Dextran: Dextran is anatural polymer linked by 1-6 glucoyranoside with glucose. It is available in two forms-dextran 40 and dextran 70 [17].

Chitosan: It consists of glucosamine and N-acetyl glucosamine. By degradation of chitin of exoskeleton, it is obtained .it is non-toxic, biocompatible, biodegradable[17].

Starch: It is synthesised from plants and biodegradable[17].

Synthetic Polymers

Polylactic acid (PLA): PLA is a polymer which is biodegradable synthesised by lactic acid monomer polymerisation. It is widely used as sutures, drug delivery devices, dialysis[18].

Polyglycolic acid (PGA): It has excellent fiber- forming properties. It is low soluble and has high melting point, thus widely used in drug delivery[18].

Polyhydroxybutyrate (PHB): It is a biopolymer, present in living organisms. It is non toxic and biodegradable[18].

Polydioxanone (PDS): It has glass transition temperature of -10-0^0 C and made by polymerisation of P-dioxanone monomer due to the presence of ether oxygen, dosage forms prepared with it shows increased flexibility[18].

Polyamide: They are referred as nylons and are synthetic alphatic polyamides. These are aliphatic and are semi crystalline and thermoplastic in nature[18].

Conclusion

RA is a major problem with potential physical, psycological and economical consequences. Females are the most common sufferes of rheumatoid arthritis. Medical treatment of RA causes relief from joint pain, controlled symptoms, physical function restoration. Though rheumatoid arthritis is treated with NSAIDS, DMARDS, in conventional dosage forms they causes serious adverse effects as it targets nonspecifically. It also impairs functions of immune system. So in order to reduce the side effects which is caused due to non-targeting, drug targeting is preferred. With novel formulations like targeted drug delivery system like liposomes, niosomes, transferosomes, transdermal drug delivery etc., rheumatoid arthritis can be treated effectively with less side effects.

Future scope: This present article will give a way for providing information for development of successful formulations of antiarrythmic drugs. Formulating drugs in the form of targeted drug delivery system like liposomes, solid lipid nanoparticles etc., will bring site specific action with less dose, less side effects and enhanced bioavailability**.**

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