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NANOCARRIERS: A NOVEL TREATMENT APPROACH FOR ARTHRITIS

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ABSTRACT: Arthritis is a major cause of disability conventionally treated for long term with nonsteroidal anti-inflammatory drugs and corticosteroids. NSAIDs are nonselective inhibitors of cyclooxygenase and cause GI toxicity, antiplatelet effects, cardiotoxicity, renal toxicity and anaphylactic reactions in selected patients. Corticosteroids have multiple side effects, including gastrointestinal bleeding, upset stomach, thinning of bones, high blood pressure, cataracts, and increased infections. The currently available dosage forms of NSAIDs and steroids possess inherent risk of adverse effects in many different tissues in patients. The most satisfactory delivery system that overcomes the difficulties cited above shall be capable of delivering appropriate concentration of drug at site of action without involvement of other tissue and organs. This review focuses on current trends of development of drug delivery system in particular carriers, with enhanced localization to the target site and sustained drug release. The most prominent advantage of nanoscaled drug carriers such as liposomes, transferosomes, and niosomes over conventional drug delivery systems is the option to improve selective delivery of drugs to the site of action and sustained release.

INTRODUCTION: Arthritis is a major cause of disability particularly in older individuals. More than 30 percent of females have some degree of osteoarthritis after the age of 65. The symptoms and signs of arthritis include pain, stiffness, swelling, muscle weakness, and limitation of movement of the joints. Arthritis can be categorized into two major groups: degenerative and inflammatory.

Osteoarthritis is the most common type of degenerative arthritis.

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It is the most common joint affliction, and its prevalence increases dramatically with age. This is a chronic disease of the joint cartilage and bone; often result from "wear and tear" of a joint, but there are other causes also such as congenital defects, trauma and metabolic disorders.

Inflammatory arthritis such as rheumatoid arthritis (RA) is a systemic illness with inflammation. Rheumatoid arthritis (RA) is a chronic and progressive autoimmune disorder which is characterized by a chronic inflammation of the joint synovium and severe joint destruction [1, 2].

Inflammation is linked to the body's immune system attacking the tissue that lines the joints. In RA the synovial lining expands because of macrophage assembling [3]. Inflammation is caused by release of chemicals from and migrating cells and tissues such as prostaglandins (PGs),

leukotrienes (LTs), bradykinin, histamine, platelet-activating factor (PAF) and interleukin [1, 4, 5].

Non-steroidal anti-inflammatory drugs and corticosteroids are most widely used and effective Drugs for treatment of Arthritis. Non-steroidal anti-inflammatory drugs (NSAIDs) that act by inhibiting cyclooxygenase and the formation of prostaglandins, are known to cause GI toxicity, leading to peptic ulcers, unwanted antiplatelet effects (nonselective inhibitors of cyclooxygenase), cardiotoxicity, renal toxicity and anaphylactic reactions in selected patients.

Corticosteroids have multiple side effects, including upset stomach, gastrointestinal bleeding and high blood pressure, thinning of bones, cataracts, and increased infections. The use of Indomethacin as a drug is limited for rheumatoid arthritis due to its side effects such as ulceration of the kidney and central nervous system (CNS) toxicity. The risks are most pronounced when steroids are taken for long periods of time or at high doses, therefore Close supervision by a physician is essential [6].

The currently available dosage forms of NSAIDS and Steroids like tablet, capsules are not able to prevent above mentioned adverse effects of these drugs. The intravenously administered drugs are distributed throughout the whole body and rapidly cleared, therefore a high and frequent dosing is necessary to achieve an effective concentration of drug at inflamed target sites. Moreover, the activity of drug in many different tissues increases the risk of side effects in patients. Therefore, the need is to develop a drug delivery system in particular carriers, with enhanced localization to the target site and sustained drug release. Several attempts have been made in past to address this issue but each has its own limitations.

Topical delivery of Antiarthritic drugs: Topical delivery of drugs has many advantages such as avoidance of hepatic first-pass metabolism., improved patient compliance and ease of access, provide a means to quickly terminate dosing sustained therapeutic drug levels, possible self – administration, non-invasive (no needles or injections needed), avoids food related Interaction, reduction of doses as compared to oral dosage forms and intravenous therapy.

Topical route allows drug to diffuse out of its vehicle onto the surface tissues of skin. In fact, ease of applicability makes this route more comfortable for the patient which results in better patient compliance.

Penetration of drugs from trans-epidermal route is fairly fast, but slower than intestinal tract absorption. There is no significant obstacle to penetration, once the drug permeates through stratum corneum of epidermis of skin [7]. Topical NSAIDs have been reported to have reduced incidences of systemic side effects like gastric bleeding and peptic ulcer [7].

The feasibility of topical route over parenteral route in treatment of RA has been evaluated in several studies. Topical methotrexate gel prepared with poloxamer 407 polymer have been observed to produce sustained and higher drug levels in muscle tissues beneath the site of administration [7]. For the purpose to enhance the skin permeability of ketoprofen, various topical formulations have been formulated; one such formulation includes topical Oleo Hydrogel Ketoprofen preparation with enhanced skin permeability.

So far most of the analgesics and anti-inflammatory drugs used for the treatment of RA, are administered mainly by transdermal route [8]. Currently anti-inflammatory drugs are mainly delivered by transdermal iontophoresis [9, 10]. New drug application (NDA) of Alza corporation for iontophoretic fentanyl containing transdermal analgesic have been approved by US FDA. Iontophoresis is a special method of applying drug to and pushing it through the skin to reach the blood vessels and surrounding deeper tissues by electric transmission. A significant amount of Piroxicam was retained in the skin after transdermal iontophoresis from piroxicam [10].

In order to increase penetration and a prolonged release, lipid nano/submicron emulsion can be used as a vehicle for topical delivery of drugs [11].

Drug targeting approach: Most of the current therapies for RA do not achieve target specificity an to reach effective drug concentrations in affected joint tissues, high dose of drug must be administered, which may lead to significant adverse systemic side effects.

Reduction in drug doses may exhibit lesser toxicity but may lead to decreased therapeutic efficacy. To overcome this problem, approaches that can specifically target the therapeutic agent to affected joints offer unique promise.

Various approaches for targeted drug delivery have been widely used in previous studies. In inflammatory diseases several circumstances are known to activate the cellular immune response. An increased presence of immune-related cells like macrophages is common in the inflamed area. In general, macrophages which are produced by the spleen leading to an inflammatory response are the primary target cells in this drug targeting approach. Although selective targeting to those immune-related cells to organs different from liver and spleen is challenging however, essential for the success of a potential anti-inflammatory therapy [12].

The nanoscaled drug carriers improve selective delivery of drugs to the site of action, so-called drug targeting which can be either passive or active targeting. Passive targeting can be achieved without further integration of a specific targeting moiety on the particle surface. Systemically administered particles with a hydrophobic surface are recognized by the reticuloendothelial system (RES), mainly liver and spleen, and taken up by macrophages in the bloodstream which leads to fast removal from the systemic circulation [13].

It has been shown that microspheres and nanoparticles can be efficiently taken up by macrophages, and mainly by phagocytosis [14, 15]. Thus, particle uptake into those immune-related cells or the disruption of the epithelium [16] could allow the selective accumulation of the nanocarrier-based drug delivery system in the desired area. Promising results have been observed with the targeting of liposomes in arthritis and represents an important step forward towards enhancement of efficiency of drug delivery.

Targeting of macrophages by nanoparticulate systems has been proved as a powerful approach for the treatment of autoimmune blood disorders, as well as Rheumatoid Arthritis [17,18]. Passive targeting can be achieved in inflammatory diseases due to immune response and to achieve efficient uptake, related particle properties like size and surface charge play a key role [19].

Novel Drug Carrier Systems for Arthritis:

Liposomes: Liposomes are spherical vesicles made of phospholipid bilayer comparable to mammalian cell membrane. Liposomes contain an aqueous compartment which can carry molecules that are protected from the external environment.The different types of liposomes include small unilamellar vesicles made of a single bilayer, large unilamellar vesicles and multi-lamellar vesicles that contain several bilayers in a concentric manner. Methods of forming liposomes include dispersing phospholipids in aqueous medium, sonication, high pressure extrusion , detergent dialysis etc [19].

Liposomes due to their biphasic characteristic and variability in design and composition, offer a dynamic and adaptable technique for enhancing drug solubility.

The systemic use of liposomes has drawbacks such as rupturing and rapid clearance from the blood, thereby release of drugs at undesirable sites .Liposomes still face major deficiencies including: lack of control over drug release rate; sufficient loading of drugs for which pH and ion gradients do not apply and lack of means to override biological barriers [19].

Easy oxidation of phosphatidylcholine (lecithin), the main membrane component, is the limitation of the introduction of liposomes to the medicinal practice on a large scale. Unsatisfying chemical stability of lecithin has an adverse influence on drug and liposome stability. Liposomes may decompose during storage leading to leakage of the encapsulated drug [20].

There are several advantages of using liposomes in transdermal therapy-

- They may adsorb and fuse with skin surface, the collapse of Formulation on tissues increases the driving force for permeation of liberated drug molecules and hence increase penetration [21, 22].
- They provide a reservoir of drug from which the slow release of drug allow the drug content within Arthritic tissues to increase [23].

- Through transdermal route, a lower systemic blood levels is reached as the drug is localized within skin membrane

Liposomes include easy encapsulation of hydrophilic drugs into their core compartment and hydrophobic drugs into their lipid bilayer, excellent biocompatibility, ability to penetrate effectively into cell membranes, delivery of drugs into the cell compartments and diversity in modifying the surface properties by altering or introducing new components into the lipid bilayer [24, 25].

For transdermal absorption of NSAIDs at the localized site of action, liposomes may be a useful tool. With the use of Fourier Transform infrared, Nuclear Magnetic Resonance and Surface Plasma Resonance, it has been demonstrated that NSAIDs have a strong affinity to form ionic and hydrophobic associations with zwitter ionic phospholipids and specifically Phosphatidyl-cholines and this association is pH dependent usually at pH 3.5 but there is no significant change at neutral pH (Lenard *et al*, 2012). Therefore pH dependent partition of potent anti-inflammatory drugs into phospholipids may result in change in hydrophobicity, fluidity, permeability, biochemical properties and stability [25].

Caldwell *et al* 2004, formulated a liposomal suspension of Diclofenac sodium. A single topical application of Diclofenac Liposomal Suspension has shown concentrations of diclofenac in transudate within 6 hours and significantly attenuated carrageenan-induced local production of Prostaglandin . Results of this study suggest that DLS is readily absorbed transdermally and may be efficacious for reducing subcutaneous inflammation [26].

In another study, Diclofenac sodium loaded liposomes were prepared by thin film hydration technique using soya lecithin, cholesterol followed by sonication and then incorporation into 1% carbopol gel. The Particle size, Polydispersity index and zeta potential of Liposomes were found to be 230 nm, 0.247 and -41 respectively and the entrapment efficiency was found to be 62%.

The cumulative amount of drug permeated in 24 hour form the liposomal gel formulation was found to be 1176.7 µg/cm [27].

From the drug entrapment efficiency study of ketoprofen liposomal gel formulation conducted by Mansoori *et al* in 2012, maximum drug encapsulation of 97.51% was observed in Formulation, in which lipid and cholesterol were used in ratio of 1:2. Therefore, it can be interpreted that, in liposome preparation, was found to acts as fluidity buffer and provided stability and rigidity to liposome.

The marketed gel of Ketoprofen released approximately 92% of drug within 24 hour, whereas the liposomal formulations showed 87% drug release respectively in 24 hour. Liposomal formulations showed sustained drug release compared to normal gel, also an increase in release rate was observed after 12 hour [28].

Puglia *et al* in 2004 attempted to prepare LUV dispersions containing indomethacin by extrusion method using dipalmitoyl-L-alpha-phosphatidylcholine and cholesterol and observed a high percentage of entrapped drug (approximately 84%). Furthermore, in-vivo findings revealed that the anti-inflammatory effect was more prolonged when indomethacin was delivered from a liposomal gel formulation rather than from a gel formulation without liposomes.

In particular, the indomethacin-loaded gel formulation LUV-A showed a sustained release, possibly related to an interaction between LUV lipids and stratum corneum lipid structure. The anti-inflammatory effect was also found to be more prolonged when indomethacin was delivered from a liposomal gel formulation rather than from a gel formulation without liposomes [29]. Therefore the selection of lipids for the formulation can be considered critical as it can certainly effect the drug permeation and duration of anti-inflammatory effects.

Piroxicam liposomes were prepared by Canto *et al* in 1999 by thin film hydration technique using Phospholipids and cholesterol. Liposomes were characterized by electron transmission microscopy, and the mean structure diameter was found to be 278 nm. The encapsulation efficiency obtained was 12.73%. The topical anti-inflammatory effect was evaluated in vivo by the cotton pellet granuloma method.

Inhibition of inflammation by free piroxicam and piroxicam encapsulated in liposomes gel the inhibition of inflammation was observed to be 21.1%, and 47.4%, respectively. These results showed that the encapsulation of piroxicam produced an increase of topical anti-inflammatory effect. In addition it was also observed that, anti-inflammatory effect can be achieved using lower drug concentrations when formulated as liposomal gel [29].

In a study, liposomal gel of Dex-ibuprofen was prepared by rotary evaporation followed by sonication using Phosphatidylcholine and cholesterol (Wasankar *et al* in 2012). Particle size of 5.40 µm and entrapment efficiency of 61% was achieved. The Formulation showed sustained drug delivery for 12 hours [30].

In the study, Phosphatidylcholine and cholesterol ratios were varied and it was observed that, ratio of Phosphatidylcholine and cholesterol significantly affect the entrapment efficiency of drug in liposomes.

Prednisolone proliposome formulations were prepared using thin film hydration technique by varying the lipid phase composition lecithin/cholesterol. Proliposome formulations were characterized for drug content, entrapment efficiency, surface charge, surface morphology, FTIR studies and stability studies. Topical proliposomal gels were prepared by incorporation of proliposome into structured vehicle carbopol (2%).

Alternatively, hydrogels containing prednisolone were prepared and their drug release properties were investigated. Pharmacodynamic activity was also determined for optimized proliposomal gel and was compared with commercial marketed gel. A spherical shape of reconstituted prednisolone liposome with an average vesicle about 2-6µm was observed in photomicrographs. The percentage entrapment of drug was increased with increase in phospholipid composition in the range of 85-98%.

Proliposomal gel showed prolonged release of prednisolone than the Hydrogels as well as anti-inflammatory activity proliposomal gel showed maximum percentage of inhibition of edema 60% when compared to commercial marketed gel 55% [31]. The lipid phase composition was observed to have a strong impact on vesicle size and entrapment efficiency.

In a study, liposome preparation was prepared consisting of a combination of a Methyl Prednisolone, phospholipid and cholesterol. Phospholipids were a combination of hydrogenated soybean phosphatidylcholine (HSPC), poly-ethylene glycol coated distearoyl phosphatidyl ethanolamine (PEG-DSPE) and cholesterol. HSPC/ Cholesterol/PEG-DSPE-2000 at mole ratio of 55:40:5. In the work, methyl prednisolone derivative encapsulated in a liposome was essentially retained in said liposome for 6 months; liposomes were uniformly sized to a selected size range between 70-100 nm, preferably about 80nm (AU 2005/281351A1).

The lipids mixture forming the liposome can be selected to achieve a specified degree of fluidity or rigidity, to control the stability of the liposome in serum and to control the rate of release of the entrapped agent in the liposome. Charge-inducing lipids, such as phosphatidylglycerol can be incorporated into the liposome bilayer to decrease vesicle-vesicle fusion and to increase interaction with cells, while cholesterol and sphingomyelin can be included in formulations in order to decrease permeability and leakage of encapsulated drugs.

At neutral pH buffers can decrease hydrolysis. Addition of an antioxidant, such as sodium ascorbate can decrease oxidation etc. A preferred formulation according to one invention was that comprising phosphatidylcholine (PC) such as egg PC (EPC) or hydrogenated soy PC (HSPC) as a the liposome forming lipid (US 2008/0003276 A1).

Transferosomes: These are ultradeformable vesicle, elastic in nature which can squeeze itself through a pore which is many times smaller (1/10th) than its size owing to its elasticity. These are applied in a non-occluded method to the skin and have been shown to permeate through the stratum corneum lipid lamellar regions as a result of the hydration or osmotic force in the skin. Transfersomes are made up of a phospholipid component along with a surfactant mixture (Sodium Cholate, Spans and Tweens).

The ratio and total amount of surfactants which acts as edge activator controls the flexibility of the vesicle. The unique property of this type of drug carrier system lies in the fact that it can accommodate hydrophilic, lipophilic as well as amphiphilic drugs. These ultradeformable drug carriers trespass the intact skin spontaneously, probably under the influence of the naturally occurring, transcutaneous hydration gradient. The `moisture seeking' (hydrotaxis) of transfersomes permits the carrier to bring more than 50% of the epicutaneously administered drug across the skin barrier [33].

It is evident from the studies carried out by Gregor *et al* in 2001, where transferosomes of diclofenac Na were prepared using soya phosphotidylcholine by suspending lipids in aqueous phase containing drug and thereafter sonication, size achieved was in the range of 100-200 nm diclofenac association with ultradeformable carriers have a longer effect and reach 10-times higher concentrations in the tissues under the skin in comparison with the drug from a commercial hydrogel.

In rats, a single epicutaneous application of 2 mg of diclofenac per kg bodyweight in highly deformable carriers produced at least 4 times higher drug concentration in the treated muscles than a drug-loaded hydrogel [32].

In another study on Ibuprofen transferosomes by Irfan *et al* in 2001, the best formulations were observed with the use of Span 80 and Tween 80 where vesicle size was found to be 962 nm and 2250 nm respectively, and zeta potential (negatively charged) for Span 80 and Tween 80 was found to be -16.1 and -17.5 respectively.

The %EE of ibuprofen in the vesicles was 47.8 and the elasticity of both increases with increase in surfactant conc. and were found to be 34.4 and 26.5, *in vitro* skin permeation studies were carried by human cadaver skin using Franz diffusion cell, and drug release after 24 hrs and flux was found 2.5824 and 1.9672 μg/cm^2/hr respectively.

Fourier Transform Infrared Spectroscopy (FT-IR) and Differential Scanning Calorimetry (DSC) analysis indicated that the application of transfersomes significantly disrupted the stratum corneum lipid [33].

Ketoprofen transfersome formulation has been marketing approval by the Swiss regulatory agency (Swiss Medic) in 2007; the product is under the trademark Diractin of IDEA AG (Munich)

U.S. Pat. No. 6,165,500 (Idea AG) describes an adaptable bilayer vesicle comprising a phospholipid combined with edge activators which include alcohols and surfactants such as cholates or polyoxyethylene ethers. These ultradeformable particles are termed Transferosomes® and are suitable for delivering hydrophilic and lipophilic agents through the hydrophilic pores in the skin.

Transferosomes® ranging from 200 to 600 nm in size physically appear as milky emulsions. For dermal delivery applications, a particle sizes in the range of 100 to 200 nm is preferred.

Studies with phospholipid vesicles with differing phosphatidylcholine (PC) content suggest that those with high phosphatidylcholine content and high content of lysophosphatidylcholine (lysoPC) can penetrate into the stratum corneum, probably due the action of lysoPC as an edge activator and increasing the elasticity of the vesicles. Hence, liquid-state elastic vesicles are able to penetrate the skin more readily than gel-state vesicles and this may enhance drug penetration. Elastic vesicles of size 100 to 150 nm in diameter have been prepared from polyoxyethylenelaurate ester PEG-8 laurate (HLB number 7) and egg phosphatidylcholine [34, 35].

A pharmaceutical preparation was prepared which comprises of a bilayer membrane vesicles suspended in a liquid medium. The components were bilayer forming lipid, an amphipathic analgesic drug and a surfactant capable of self-aggregation in the suspension medium, surfactant selected were preferably nonionic such as polyethyleneglycol-sorbitan-long fatty chain ester, a polyethylene glycol-long fatty chain ester or –ether and a polyhydroxyethylen-long fatty chain ester (EP 1551370 B1).

Niosomes: Niosomes are vesicles of microscopic lamellar structures formed by admixture of nonionic surfactant of the alkyl or dialkylpolyglycerol ether class and cholesterol with subsequent hydration in aqueous media Non-ionic surfactant acts as a penetration enhancer and hence can overcome the barrier of stratum corneum [36].

Niosomes can entrap both hydrophilic and lipophilic drugs, either in aqueous layer or in vesicular membrane made of lipid materials. It is reported to attain better stability than liposomes. Proniosomes are dry formulations of surfactant-coated carrier, which when needed, rehydrated by brief agitation in hot water. These are considered superior drug delivery system because of low cost, greater stability, non-toxic, biocompatible, biodegradable and non-immunogenic, as it is nonionic in nature [36].

Niosomes were first described in U.S. Pat. No. 4,217,344 (L'Oreal) which suggested the use of vesicles of 100 to 1000 nm in diameter. Examples include the use of mixtures of oleth-10 and oleth-2 together with glycerol which form "milky dispersions". Subsequently, the more readily available sorbitan fatty acid esters with an HLB of 4-8 were found to be compatible with niosome vesicle formation, these materials are biodegradable, cheap and non-toxic and have been extensively applied in the cosmetic and pharmaceutical fields

The effect of type of surfactant on the characteristics of niosomes is significant as evident from the work of Ammar *et al* in 2007, which showed that Ketorolac niosomes formed from Span 60 and Tween 20 exhibited a very high encapsulation efficiency owing to almost complete inclusion of the highly lipophilic portion of the drug within the lipid bilayer of the niosomes. The niosomal formulation using span 60 showed an entrapment efficiency of 98.9% and a vesicle size of 6.6 micron whereas for those made using tween 20, the entrapment efficiency of 99% and vesicle size of 27.5 micron was observed [39].

In another study, a novel elastic bilayer vesicle (niosomes) entrapping diclofenac diethyl ammonium was prepared for topical use. This eighteen bilayer vesicular formulations comprised of DPPC, tween 61 or span 60 mixed with cholesterol in solvent ethanol at 25% (v/v) and prepared by chloroform film method with sonication (Mansoroi *et al*, 2004).

Niosomes made using tween 61 gave no sedimentation, no layer separation, unchanged particle sizes of about 200 nm. The entrapment efficiency of the drug in the conventional and elastic tween 61 niosomes was found to be 65% and 93%, respectively and demonstrated the enhancement of transdermal absorption through rat skin as well as enhanced *in vivo* anti-inflammatory effect [36].

The ketoprofen niosomal gel prepared by slurry method using span 40, cholesterol and malt dextrin(carrier) followed by probe sonication, shows 54.82% percentage drug entrapment and mean vesicle diameter of 4.92 micrometer. The cumulative amount of drug permeation of ketoprofen from niosomal gel was found to be 403.65 μgcm^{-2} and from plain gel was 346.48 μgcm^{-2}. The steady state transdermal flux from niosomal gel was found to be significantly higher 50.81 $\mu gcm^{-2}h^{-1}$ than from the plain gel i.e. 38.12 $\mu gcm^{-2}h^{-1}$ [37, 38].

Piroxicam niosomes prepared with coacervation method using span 20, span 40, span 60, span 80, cholesterol, lecithin, span 40 and span 60 showed better percentage entrapment that is, 90.4 and 94.8% respectively. Niosomes prepared using span 60 were smaller in size, demonstrated higher entrapment efficiency and higher surface area as compared to that of span 40. Maximum flux achieved was 35.61 $g/cm^2/h$ from the Niosomes, and thus an enhancement of 7.39 times drug permeation was achieved for transdermal system based on proniosomal gel as compared to control gel [39].

Celecoxib proniosomes using surfactant (Span 40 and Span 60), alcohol (ethanol or isopropyl alcohol) and CXB (100 mg) solution, in a ratio 5:5:4 w/w/w. The gel formulation was made using hydroxypropyl methyl cellulose (HPMC 4% w/v in ethanol) with entrapment efficiency 93.8% and mean size 317-449 nm [40]. The non-ionic surfactants span 40 and span 60 give least leaky niosomes and have highest phase transition temperature. Soya lecithin is preferred over egg lecithin because the former gives vesicles of larger size, possibly due to differences in the intrinsic composition of soya and egg derived lecithin [41].

Preparations with a white semi-solid appearance were obtained with span and cholesterol while incorporation of lecithin results in a gel-like appearance. The types of alcohol affect the size of niosomal vesicles as well; ethanol gave the largest

and isopropanol gave the smallest. The larger size with ethanol may be due to the slower phase separation because of its greater solubility in water.

The smaller size with isopropanol may be due to its branched chain. In proniosomal formulation the entire drug may be intercalated within the bilayers as opposed to the aqueous spaces in the gel. This result was consistent with the entrapment efficiency of, ketorolac and oestradiol in Span 40 and 60 proniosomes. The cholesterol content contributed to an increase in the hydrophobicity, with subsequent reduction of vesicle size thereby also reducing the entrapment efficiency [41].

Celecoxib loaded niosomes were prepared and characterized *in vitro*, *ex-vivo* and *in vivo* by Kaur *et al* in 2007, the niosomal gel provided 6.5 times higher drug deposition as compared to carbopol gel. The ratio of muscle to plasma concentration was 2.16µg/g and 0.34µg/ml and produced significant reduction of rat paw edema as compared to conventional gel indicating better skin permeation and deposition of celecoxib from niosomes. The results demonstrated that niosomal gel formulation possess great potential for enhanced skin accumulation, prolonging drug release and improving the site specificity of celecoxib [41].

The lecithin-free proniosomes tenoxicam prepared from Tween 20 and cholesterol in ration of 9:1 has proved to be stable with high entrapment and release efficiencies. The investigated tenoxicam loaded proniosomal formula proved to be non-irritant, with significantly higher anti-inflammatory and analgesic effects compared to that of the oral market tenoxicam tablets [42]. The lecithin free formulation has shown greater stability profile.

CONCLUSION: The orally and intravenously administered drugs for arthritis are distributed throughout the whole body and rapidly cleared, therefore a high and frequent dosing is necessary to achieve an effective concentration of drug at inflamed target sites.

The high and frequent dosing increases the risk of adverse effects in patients. Thus, we need to develop a drug delivery system which can provide sustained drug release for a prolonged period and avoid side effects.

Several advancements have been made in recent past to address the issue of side effects in chronic therapy of Arthritis. Formulation approaches like liposome, PEG liposome, polymeric micelles, solid lipid nanoparticles, polymeric vesicles etc. have been explored to achieve a limited success.

Liposomes still face major deficiencies including lack of control over drug release rate, insufficient loading of drugs for which pH and ion gradients do not apply and lack of means to override biological barriers. Surface modification of liposomes by the inclusion of hydrophilic components (e.g., carbohydrates, glycolipids or polymers) to form long-circulating liposomes cause changes in the pharmacokinetic pattern seen for unmodified (classical) liposomes. Problem associated with polymeric carriers is that they are less biocompatible and more toxic as compared to liposomes and selection of polymers and their use for drug delivery must be carried out with caution.

Phagocytic cells i.e. macrophages and neutrophils, play important role in induction and maintenance of inflammation. Strategies to optimize the drug delivery within a localized arthritic tissue and the uptake of anti-inflammatory drugs to these cells need to be quantified. Systemically administered particles with a hydrophobic surface are recognized by the reticuloendothelial system (RES), mainly liver and spleen, and taken up by macrophages in the bloodstream which leads to fast removal from the systemic circulation.

In general, macrophages which are produced by the spleen leading to an inflammatory response are the primary target cells in this drug targeting approach.

Although selective targeting to those immune-related cells to organs different from liver and spleen is challenging, however it is essential for the success of a potential anti-inflammatory therapy.

In inflammatory diseases, several circumstances are known to activate the cellular immune response. An increased presence of immune-related cells like macrophages is common in the inflamed area. Tabata *et al* (1996) has shown that microspheres and nanoparticles can be efficiently taken up by macrophages, mainly by phagocytosis.

Thus, particle uptake into those immune-related cells or the disruption of the epithelium could allow the selective accumulation of the nanocarrier-based drug delivery system in the desired area. Therefore, passive targeting can be achieved in inflammatory diseases due to immune response. To reach efficient uptake into those immune-related cells, particle properties like size and surface charge play a key role. .

Drug carriers can provide better permeation through skin and a reservoir for sustained drug release for control of inflammation for a prolonged period. Modification of carrier composition or surface can enhance the drug penetration and affinity to the target site. Topical delivery of drugs in the form of Liposomal, Transferosomal of Niosomal gels can be a suitable treatment strategy to achieve better absorption through skin as well as a sustained therapeutic effect and also to minimize the side effects associated with oral and invasive therapies.

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