Introduction

Target oriented drug delivery systems are the areas of the major interest in the modern pharmaceutical research. The selective drug delivery to the target tissues increases the therapeutic efficacy of the drug and reduces its undesirable effect to non target tissues. The concept of drug targeting or site specific drug delivery was introduced first time by Paul Elrich in 1909, when he reported ‘magic bullet’ to deliver a drug to the desired site of action without affecting the non target organs or tissues (Juliano, 1980) by associating the drug with a pharmacologically “inactive carrier” capable of conveying the drug selectively towards its target cells. Drug targeting is defined as the ability to direct a therapeutic agent specifically to the desired site of action with little or no interaction with non target tissues (Bremier, 1987). The main goal of a site specific drug delivery system is not only to increase the selectivity and drug therapeutic index, but also to reduce the toxicity of the drug. (Widder et al.,1982). Vanlerbeghe et al. (1972) first reported the niosomes as a feature of cosmetic industry. These non ionic surfactant vesicles can entrap both hydrophilic and lipophilic drugs, either in aqueous layer or in the vesicular membrane made of lipid materials, which can be used to prolong the circulation of the entrapped drugs. Due to the presence of non ionic surfactant and the lipid, there is a better targeting of drug(s) to tumor, liver and brain. Thus, they are useful in targeting of the drug for treating cancers, parasitic, viral and other microbial diseases more effectively. These non-ionic surfactant based vesicles (niosomes) are regarded either as a inexpensive alternative of non-biological origin to liposomes or perhaps as a carrier system of drug physically similar to liposome in vivo, with specific properties to attain different drug distribution and release characteristics.

Salient-feature for site specific drug delivery (Tomilinson, 1991):

1. To reach previously inaccessible domains e.g. intracellular site, bacteria, viruses, parasites etc.
2. Exclusive drug delivery to the specific cells or diseased site in the body.
3. Reduction in the drug dose and side effects.
4. To control the rate and frequency of drug delivery at the pharmacological receptor.
5. To protect the drug and the body from one another until it reaches at the desired site of action.

**Niosomes as targeted drug carriers:**

The concept of carriers to deliver drugs to target organs has been widely been discussed (Gregoriadis, 1981). In the early 1960, (Bangham et al., 1965, Bangham and Horne, 1964) described liposomes, the phospholipids vesicles as the drug carriers. The liposomes exhibit certain disadvantages such as chemical instability, high cost and variable purity of lipids, which militates against their adoption as drug delivery vehicle. Alternatives to phospholipids are thus of interest from the technical viewpoint which could allow a wider study of the influence of chemical composition on the biological fate of vesicles.

Many synthetic amphiphiles form vesicles (Fendler, 1982) but most of them are ionic and relatively toxic and hence are unsuitable for use as drug carriers. Niosomes are the vesicles consisting of non ionic surfactants and was introduced by Handjani-vila et al., in 1979. One of the reasons for preparing niosomes is the higher chemical stability of the surfactants than that of phospholipids, being used in the preparation of liposomes. Due to the presence of ester bonds, phospholipids are easily hydrolyzed (Kemps and Crommelin, 1988) leading to phosphoryl migration at low pH.

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Rheumatoid arthritis (RA) is a chronic, inflammatory condition of unknown etiology that affects about 1% of general population (Feldmann *et. al.*, 1996) and is the most common cause of chronic inflammatory synovitis (Watson-Clark *et al.*, 1998). Although spontaneous remission can occur, it often progresses to chronic state associated with significant functional disability (Geletka and Clair, 2003). A number of drugs are used in the treatment of RA over the past 10-20 years. An ideal therapy in RA should ameliorate disease, prevent the development of extra-articular complications such as vasculitis,
serositis and lung fibrosis and prevent premature death (Rabinovich, 2000), however there is still an urgent need for a more effective drugs with reduced side effects (Corvo et al., 2002). Non steroidal anti inflammatory drugs (NSAIDs) have been used extensively for treatment of RA owing to their quick onset of analgesic effects and mild anti-inflammatory properties despite various side effects like ulceration of gastrointestinal tract and kidney toxicity with systemic administration (Jung-AhLee and Kavanaugh, 2003, Srinath et al., 2000). Presently, the treatment of RA frequently includes the use of NSAIDs such as Ketoprofen.

Ketoprofen, a non-steroidal anti-inflammatory drug (NSAID) is selected as the model drug which is useful in patients with allergic hypersensitivity to aspirin and other NSAIDs. Its plasma half life is 0.5–2h, which calls upon frequent administration.

**Advantages of niosomes**

1) Niosomes entrap solute in a manner analogous to liposomes.

2) Niosomes are osmotically active and stable and increase the stability of entrapped drug.

3) Handling and storage of surfactants require no special conditions.

4) Niosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities.

5) Niosomes exhibit flexibility in their structural characteristic (Composition, fluidity, size) and can be designed according to the desired situation.

6) Niosomes improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.

7) They can be made to reach the site of action by oral, parenteral and topical routes.

8) They allow their surface for attachment of hydrophilic group and hence hydrophilic moieties can be interpreted in bilayer to bring about changes in the *in vivo* behavior of niosomes.

9) Niosomal dispersion in aqueous phase can be emulsified in non aqueous phase to Regulate release rate of the drug and administer normal vesicles in external non-aqueous phase.
Literature Review –

1. Dubey Subodh et al., (2010), were prepared the niosome based on liposome technology. The basic process of preparation was the same i.e. hydration by aqueous phase of the lipid phase which may be either a pure surfactant or a mixture of surfactant with cholesterol. After preparing niosomal dispersion, unentrapped drug was separated by dialysis centrifugation or gel filtration. A method of in-vitro release rate study includes the use of dialysis tubing.

2. Shyamala Bhaskaran et al., (2009), was prepared Niosomes containing salbutamol sulphate using Span 60 as the surfactant, by employing different techniques namely, thin film hydration, hand shaking, ether injection, lipid layer hydration and trans membrane pH gradient method. The drug encapsulation efficiency varied from 62 % to 87 %. Transmembrane pH gradient method was found to be most satisfactory which released 78.4 % of drug in 24 h.

3. Ajay B. Solankia et al., (2010), was worked to optimize the composition of niosomes containing aceclofenac for transdermal application, with a view to improve permeation of drug during an extended period of time. Niosomes was prepared by thin film hydration technique. This study demonstrates that niosomal gel formulations may offer promise as a transdermal delivery of aceclofenac to improve efficiency and better patient compliance.

4. Saeid Daneshamouz et al., (2005), in this work author sought to determine whether vesicles (liposomes/niosomes) were able to enhance finasteride concentration in the dermis layer, including the pilosebaceous units (PSU). Niosome was prepared by the film hydration technique. Determination of finasteride content by HPLC showed 80-97% drug entrapment efficiency in the vesicles.
5. **S. Srinivas, et al., (2010)**, in this work author was studied with aimed to develope and optimized the niosomal formulation of aceclofenac in order to improve its bioavailability. In evaluation study the effect of the varying composition of non ionic surfactant and cholesterol on the properties such as encapsulation efficiency, particle size and drug release was studied.

6. **D.J. Kerr et al., (1988)**, in this study Adriamycin has been trapped within vesicles prepared from a monoalkyl triglycerol ether and its activity compared with adriamycin solution in human lung tumour cells grown in monolayer and spheroid culture and in tumour xenografted nude mice.

7. **V sankar et al., (2010)**, was tried to stabilize niosomal drug delivery system without affecting its properties of merits have resulted in the development of the promising drug carrier, proniosomes. Proniosomes is dry formulation using suitable carrier coated with non ionic surfactants and can be converted into niosomes immediately before use by hydration.

8. **Azmin et al., (1985)** used nonionic surfactant vesicles using lipophilic surfactants like Span-40, Span-60 and Span-80 entrapped with methotrexate showed improved performance. This vesicle was also found to be osmotically stable.

9. **Chandra Parakash et al., (1993)** made nonionic surfactant vesicles using lipophilic surfactants like Span-40, Span-60 and Span-80 entrapped with Methotrexate. The tissue distribution of methotrexate was improved after entrapping with niosomes, which were osmotically stable.

10. **Fendler et al., (1982)** published his work on ionic amphiphiles which were found to be toxic.

11. **Naresh et al., (1993)** were producing the number of non ionic surfactants used to prepare vesicles and series of Spans and Tweens to produce the stable niosomes.
12. Parthasarathi et al., (1994) was also producing number of non ionic surfactants to prepare vesicles viz. poly glycerol alkyl ether and series of Spans and Tweens.

13. Feldmann et al., (1996) was studied that the rheumatoid arthritis (RA) is a chronic, inflammatory condition of unknown etiology that affects about 1% of general population.

14. Rabinovich et al., (2000) were studied the therapy in rheumatoid arthritis should ameliorate disease, prevent the development of extra-articular complications such as vasculitis, serositis and lung fibrosis and prevent premature death.

15. Corvo et al., (2002) was founded in their study that there is still an urgent need for more effective drugs with reduced side effects in the treatments of rheumatoid arthritis.

16. Jung-AhLee et al., (2003) was studied that the Non steroidal anti inflammatory drugs (NSAIDs) have been used extensively for treatment of RA owing to their quick onset of analgesic effects and mild anti-inflammatory properties despite various side effects like ulceration of gastrointestinal tract with systemic administration

17. Srinath et al., (2000) was studied that the Non steroidal anti inflammatory drugs (NSAIDs) producing the serious side effect like kidney toxicity with systemic administration

18. Yatvin et al., (1980) was studied that that pH sensitive liposomes got released selectively at low pH.

19. Uchegbu et al., (1998) was studied the various non-ionic surfactant are used in the preparation of niosomes. The nature of two major constituents of the surfactants i.e.,
hydrophilic head group and a hydrophobic tail is very important which plays a crucial role in the formation of the niosomal microstructures.

20. Uchegbu et al., (2000), was studied the nature of the surfactants i.e., hydrophilic head group and a hydrophobic tail was very important which plays a crucial role in the formation of the niosomal microstructures.

21. Yoshioka et al., (1994), was studied the parameter like hydrophilic-lipophilic balance (HLB) was a good indicator of the vesicle forming ability of any surfactant. With sorbitan esters (Spans), HLB values between 4 and 8 were found to be compatible with vesicle formation.

22. Weiner et al., (1989), were classifying the niosomes as a function of the number of bilayer (e.g. MLV, SUV) or as a function of size. (e.g. LUV, SUV) or as a function of the method of preparation (e.g. REV, DRV).

23. Bangham et al., (1974), was studied about the Multilamellar vesicles are the most widely used niosomes. It was simple to make and are mechanically stable upon storage for long periods. These vesicles are highly suited as drug carrier for lipophilic compounds.

24. Yoshioka et al., (1994), was studied the mean size of niosomes increases with increase in the hydrophilic-lipophilic balance (HLB) from Span 85 (HLB 1.8) to Span 20 (HLB 8.6) because of decrease in surface free energy and hence increasing hydrophobicity of surfactant.

25. Yoshioka et al., (1992) was reported linear correlation between concentration of lipid and entrapment efficiency. The phase transition temperature (Tc) of surfactant also effects entrapment efficiency i.e. Span 60 (having higher Tc) provides the highest entrapment.
26. Yoshioka et al., (1994), was found that the inclusion of cholesterol in niosomes increases its hydrodynamic diameter and entrapment efficiency.

27. Hofland et al., (1992), was found that the Cholesterol has a decreasing effect on gel-liquid transition temperature, at which rapid efflux of vesicle content occurs. It converts a well defined gel-liquid transition temperature of a pure surfactant to gel-liquid transition range

28. Khandare et al., (1994), was studied the methods of preparation of niosomes such as hand shaking, ether injection and sonication (developed on the basis of liposome production technique).

29. Carter et al., (1989), were found that the hand shaking method form vesicles with greater diameter [0.35 – 13µm] as compared to those prepared by ether injection method [50-1000nm].

30. Parthasarathy et al., (1994), was prepared the niosomes by remote loading method show greater entrapment efficiency and slower release of drug.

31. Park et al., (1992), was found the membrane stability was increased by imparting charge to the niosomes.

32. Grit et al., (1993), had described the different variables that influence the hydrolysis reactions of phosphatidyl choline, the major phospholipids, in the most niosomal preparations and the charge inducing phospholipids phosphatidyl glycerol. Apart from pH, other experimental conditions like temperature, ionic strength, buffer species, and ultra sonication were reported to influence hydrolysis reactions.

33. Zuidam et al., (1993), was reported that nosome of different lipid composition could be steam sterilized without substantial hydrolytic or oxidative degradation.
34. Kirby et al., (1980). Was found that the erythrocytes donate cholesterol to niosomes particularly to cholesterol-free and cholesterol poor niosomes, maintaining their integrity in body as well as keeping them less vulnerable to destabilization.

35. Parthasarathi et al., (1994), was studied the Niosomes, similar to liposomes assume spherical shapes. Its diameter can be determined using light microscope.

36. Naresh et al., (1993), was found that the drug remaining entrapped in niosomes was determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100.

37. Yoshida et al., (1992), studied that the intercalation of cholesterol in the bilayers decreases the entrapment volume and thus entrapment efficiency. As the concentration of cholesterol increases, entrapment efficiency decreases.

38. Chandraprakash et al., (1990), was found that the entrapment efficiency increases with increase in the concentration and lipophilicity of surfactant.

39. Hofland et al., (1992), was studied in-vitro transdermal delivery of estradiol entrapped within niosomes. The studies on adjuvant activity of niosomes were performed on the BALB/C humoral response to bovine serum albumin after intraperitoneal and subcutaneous administration.

40. Roks et al., (1983, was founded that the vesicle systems are more or less thermodynamically unstable, proximity and regular orientation of surface active molecules at interface has been exploited to increase stability by controlled polymerization of vesicle forming non-ionic surfactant bearing a polymerisable residue.
Objective of the present work

Ketoprofen (NSAID) is available in various dosage form like tablet, capsule, Transdermal Patches etc. Dose of ketoprofen is 75 mg orally 3 times in a day or 50 mg Orally 4 times in a day. The recommended maximum is 300 mg/day. Ketoprofen Extended-release: 200 mg orally once daily. It has short biological half life (0.5-2 hrs) which calls for frequent administration. Ketoprofen has various side effects like gastritis, kidney toxicity, peptic ulcer and bleeding when taken in tablet dosage form for long period.

One Percent of total world population is affected by rheumatoid arthritis. Treatment of Rheumatoid arthritis is consisting of combination therapy of Disease-modifying anti-rheumatic drug (DMARD) along with Steroids or NSAID. 90% treatments of rheumatoid arthritis consist of combination therapy of DMARD with NSAID.

Hence there is a need of development of Novel Drug Delivery System which produce site specific drug delivery of ketoprofen which is cost effective and have several advantage over other dosage form like low dose, reduce dosing, unavailability of free drug and reduce gastric irritation.

In the present investigation, an attempt has been make to prepare a niosomal formulation of the ketoprofen in order to release the drug at a controlled rate at targeted site of inflammation.
Work Plan & Methodology –

1. Review of literature related to Drug Profile, excipients profile and Formulation development.

   a) Thin Layer Chromatography
   b) I.R. Spectroscopy
   c) Solubility & Other parameter as per mention in I.P.

3. Preparation of different formulation by varying the concentration of surfactant.

4. Optimization of formulation
   Formulation shall be optomized on the basis of rotation speed of rotary evaporator, surfactant concentration, composition of bilayers etc.

5. Preparation of different batches of optimized formula.

   a) Microscopic study of niosomal shape.
   b) Morphology.
   c) Determination of drug entrapment efficiency

7. In Vivo & In vitro Study of formulation
   a) The \textit{in vivo} anti-inflammatory studies is carried out by carrageenan induced rat hind paw oedema method.
   b) In-vitro Study is carry out by using dialysis membrane.

8. Stability study of Formulation as per ICH Guideline.