A REVIEW ON EVALUATION OF ACECLOFENAC NIOSOMES PREPARED BY VARIOUS TECHNIQUES

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ABSTRACT
Aceclofenac belongs to non-steroidal anti-inflammatory drug (NSAID) is considered to be the first-line drug in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The drug is having narrow therapeutic index, short biological half-life (about 4 h) as well as two third (70-80%) of dose is excreted by renal transport and it makes aceclofenac dosing frequency more than once a day. Niosomes are multilamellar vesicular structure of nonionic surfactants, similar to liposomes and are composed of non-ionic surfactant instead of phospholipids which are the components of liposomes. So, niosome or non-ionic surfactant vesicles are now widely studied as an alternative tool to liposome. The present work was to investigate the influence of various preparation techniques on formulation of aceclofenac niosomes by using span and cholesterol by ether injection method, ethanol injection method, sonication method followed by evaluating the parameters such as drug content, entrapment efficiency, particle size, shape and in-vitro drug release and drug release kinetics.

KEYWORDS: Aceclofenac, Niosome, Span, Cholesterol.

INTRODUCTION
Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with non target tissue. The concept of targeted drug delivery is designed for attempting to concentrate the drug in the tissues of interest while reducing the relative concentration of the medication in the remaining tissues. As a result, drug is localized on the targeted site. Hence, surrounding tissues are not affected by the drug. In addition, loss of drug does not happen due to localization of drug, leading to
get maximum efficacy of the medication. Niosomes are one of the best among these carriers. Structurally, niosomes are similar to liposomes and also are equiactive in drug delivery potential but high chemical stability and economy makes niosomes superior than liposomes. Both consist of bilayer, which is made up of non-ionic surfactant in the case of niosomes and phospholipids in case of liposomes. Niosomes are microscopic lamellar structures of size range between 10 to 1000 nm and consists of biodegradable, nonimmunogenic and biocompatible surfactants. The niosomes are amphiphilic in nature, which allows entrapment of hydrophilic drug in the core cavity and hydrophobic drugs in the non-polar region present within the bilayer hence both hydrophilic and hydrophobic drugs can be incorporated into niosomes. Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. In Niosomes, the vesicles forming amphiphile is anon-ionic surfactant such as Span –60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetylphosphate.

Various types of surfactants have been reported to form vesicles, and have the capacity to entrap and retain the hydrophilic and hydrophobic solute particles. Niosomes mainly contain two types of components, nonionic surfactant and the additives. The non-ionic surfactants form the vesicular layer and the additives used in noisome preparation are cholesterol and the charged molecules. The presence of the steroidal system (cholesterol) improves the rigidity of the bilayer and is important component of the cell membrane and their presence in membrane affects bilayer fluidity and permeability. This carrier system protects the drug molecules from the premature degradation and inactivation due to unwanted immunological and pharmacological effects. In recent years, niosomes have been extensively studied for their potential to serve as a carrier for the delivery of drugs, antigens, hormones and other bioactive agents. Besides this, niosome has been used to solve the problem of insolubility, instability and rapid degradation of drug.

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span 60 and cholesterol followed by evaluating the parameters such as drug content, entrapment efficiency, particle size, shape and in-vitro drug release and drug release kinetics.

**Importance of niosomes**
Niosomes have better patient compliance and better therapeutic effect than conventional oily formulations. Niosomes can be utilized in the delivery of wide variety of drugs as it has capability to entrap hydrophilic, lipophilic as well as amphiphilic drugs. Niosomes show controlled and sustained release of drugs due to depot formation. Shape, size, composition, fluidity of niosomes drug can be controlled as and when required. Niosomes show a greater bioavailability than conventional dosage forms. Niosomes had been effectively used in targeting drugs to various organs. Niosomes are more stable than liposomes. Niosomes can increase the permeation of drugs through the skin. Niosomes can be administrated via various routes like oral, parenteral and topical etc. Niosomes are biodegradable, biocompatible and nonimmunogenic to the body. Handling, storage and transportation of the niosomes is easy.

Oral bioavailability of the drug can be improved using niosome. It can protect the drugs from biological enzymes and acid thereby increasing the stability of the drugs. No tissue irritation and damage are caused by penetration enhancers in the ocular drug delivery system.

**Types of Niosomes**
The niosomes are classified 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). The various types of niosomes are described below.

1. **Multilamellar vesicles (mlv)**
   It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 μm diameter. Multilamellar vesicles are the most widely used niosomes. These vesicles are highly suited as drug carrier for lipophilic compounds.

2. **Large unilamellar vesicles (luv)**
   Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.
3. Small unilamellar vesicles (suv)

These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French presse extrusion electrostatic stabilization is the inclusion of dicetylphosphate in 5(6)-carboxyfluorescein (CF) loaded Span 60 based niosomes.

Niosomes in comparison with liposomes

Niosomes are now widely studied as an alternative to liposomes, which exhibit certain disadvantages such as –they are expensive, their ingredients like phospholipids are chemically unstable because of their predisposition to oxidative degradation, they require special storage and handling and purity of natural phospholipids is variable. Niosomes are prepared from uncharged single-chain surfactant and cholesterol whereas liposomes are prepared from double chain phospholipids (neutral or charged). Niosomes behave in-vivo like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability. Encapsulation of various anti neoplastic agents in these carrier vesicles has been shown to decrease drug induced toxic side effects, while maintaining, or in some instances, increasing the anti-tumor efficacy. Such vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug. They can be expected to target the drug to its desired site of action and/or to control its release.

METHODOLOGY

Niosomes mainly contains following types of components.

Non-ionic Surfactants: The non-ionic surfactants orient themselves in bilayer lattices where the polar or hydrophobic heads align facing aqueous bulk (media) while the hydrophobic head or hydrocarbon segments align in such a way that the interaction with the aqueous media would be minimized. To attain thermodynamic stability, every bilayer folds over itself as continuous membrane i.e. forms vesicles so that hydrocarbon/water interface remains no more exposed. Mainly following types of non-ionic surfactants are used for the formation of niosomes.

Alkyl Ethers: L’Oreal described some surfactants for the preparation of niosomes containing drugs/chemicals as Surfactant-I (molecular weight (MW 473) is C16monoalkyl glycerol ether with average of three glycerol units. Surfactant-II (MW 972) is diglycerol ether with average of the seven glycerol units. Surfactant III (MW 393) is ester linked surfactant. Other
than alkyl glycerol, alkyl glycosides and alkyl ethers bearing polyhydroxyl head groups are also used in formulation of niosomes.

Alkyl Esters: Sorbitan esters are most preferred surfactant used for the preparation of niosomes amongst this category of surfactants. Vesicles prepared by the polyoxyethylene sorbitan monolaurate are relatively soluble than other surfactant vesicles. For example polyoxyethylene (polysorbate 60) has been utilized for encapsulation of diclofenac sodium. 11) A mixture of polyoxyethylene-10-stearylether: glyceryl laurate: cholesterol (27: 15: 57) has been used in transdermal delivery of cyclosporine-A.

Alkyl Amides: Alkyl amide (e.g. galactosides and glucosides) have been utilized to produce niosomal vesicles.

Fatty Acid and Amino Acid Compounds: Long chain fatty acids and amino acid moieties have also been used in some niosomes preparation.

Cholesterol Steroids are important components of the cell membrane and their presence in membrane affect the bilayer fluidity and permeability. Cholesterol is a steroid derivative, which is mainly used for the formulation of niosomes. Although it may not show any role in the formation of bilayer, its importance in formation of niosomes and manipulation of layer characteristics can not be discarded. In general, incorporation of cholesterol affects properties of niosomes like membrane permeability, rigidity, encapsulation efficiency, ease of rehydration of freeze dried niosomes and their toxicity. It prevents the vesicle aggregation by the inclusion of molecules that stabilize the system against the formation of aggregates by repulsive steric or electrostatic forces that leads to the transition from the gel to the liquid phase in niosome systems. As a result of this, the noisome becomes less leaky in nature.

Charged Molecule Some charged molecules are added to niosomes to increase stability of niosomes by electrostatic repulsion which prevents coalescence. The negatively charged molecules used are diacetyl phosphate (DCP) and phosphotidic acid. Similarly, stearylamine (STR) and stearyl pyridinium chloride are the well known positively charged molecules used in niosomal preparations. These charged molecules are used mainly to prevent aggregation of niosomes. Only 2.5—5 mol percentage concentration of charged molecules is tolerable because high concentration can inhibit the niosome formation.
Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Few of their therapeutic applications are as follows.

Targeting of bioactive agents: To reticulo-endothelial system (RES) 15. The vesicles occupy preferentially to the cells of RES. It is due to circulating serum factors known as opsonins, which mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver. To organs other than reticulo-endothelial system (RES): By use of antibodies, carrier system can be directed to specific sites in the body. Immunoglobulins seem to have affection to the lipid surface, thus providing a convenient means for targeting of drug carrier. Many cells have the intrinsic ability to recognize and bind particular carbohydrate determinants and this property can be used to direct carriers system to particular cells.

Delivery of peptide drugs: Niosomal entrapped oral delivery of 9-desglycinamide, 8-arginine vasopressin was examined in an in-vitro intestinal loop model and reported that stability of peptide increased significantly 18. Immunological applications of niosomes. For studying the nature of the immune response provoked by antigens niosomes have been used. Niosomes have been reported as potent adjuvant in terms of immunological selectivity, low toxicity and stability. Niosome as a carrier for Hemoglobin: Niosomal suspension shows a visible spectrum superimposable on to that of free hemoglobin so can be used as a carrier for hemoglobin. Vesicles are also permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin.

Transdermal delivery of drugs by niosomes: An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes as slow penetration of drug through skin is the major drawback of transdermal route of delivery for other dosage forms. The topical delivery of erythromycin from various formulations including niosomes has studied on hair less mouse and from the studies and confocal microscopy, it was found that nonionic vesicles could be formulated to target pilosebaceous glands. Diagnostic imaging with niosomes: Niosomal system can be used as diagnostic agents. Conjugated niosomal formulation of gadobenate dimeglumine with [N-palmitoylglucosamine (NPG)], PEG4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging. Ophthalmic drug delivery: From ocular dosage form like ophthalmic solution, suspension and ointment it is difficult to achieve
excellent bioavailability of drug due to the tear production, impermeability of corneal epithelium, non-productive absorption and transientresidence time. But niosomal and liposomal delivery systems can be used to achieve good bioavailability of drug. Bioadhesive-coated niosomal formulation of acetazolamide prepared from span 60, cholesterol stearylamine or dicetyl phosphate exhibits more tendencies for reduction of intraocular pressure as compared to marketed formulation (Dorzolamide). Localized Drug Action: Drug delivery through Niosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration. Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduces its systemic toxic effects e.g. Antimonials encapsulated within niosomes are taken up by mononuclear cells resulting in localization of drug, increase in potency and hence decrease both in dose and toxicity 24. The evolution of niosomal drug delivery technology is still at an infancy stage, but this type of drug delivery system has shown promise in cancer chemotherapy and anti-leishmanial therapy.

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Methods of preparation

Modified ether injection method
In this method cholesterol (100 mg) and span 60 (surfactant 100 mg) at 1:1 ratio were dissolved in 10 ml of chloroform and was injected slowly at a rate of 0.25 ml/min through 16 gauges needle into 15 ml of hydrating solution phosphate buffer pH 7.4 containing aceclofenac (100 mg) as the aqueous phase and the solution was stirred on magnetic stirrer by maintaining the temperature at 60°C.

Ethanol injection method
The ethanol injection method was similar to modified ether injection method where instead of chloroform, ethanol was used as an organic solution for dissolving the cholesterol and span 60. It has been reported that small unilamellar vesicles can be prepared by this method

Sonication method
The aqueous phase phosphate buffer solution pH 7.4 containing aceclofenac (100 mg) was added to the chloroform containing mixture of span 60 and cholesterol at 1:1 ratio in a scintillation vial and was subjected to bath sonication, maintained the temperature at 60°C for three minutes to produce small and uniform size niosomes.

Thin film hydration method
In this method cholesterol (100 mg) and span 60 (100 mg) at 1:1 ratio were dissolved in chloroform and the solvent was evaporated at room temperature, using rotary vacuum evaporator. The thin layer of cholesterol and surfactant mixture was formed on the round bottom flask. The aqueous phase phosphate buffer solution Ph 7.4 (15 ml) containing aceclofenac was added to the round bottom flask at 70°C and shaken for about 15 min which results in good dispersion of the mixture and the noisome were formed.
Reverse phase evaporation method
In this method cholesterol and span 60 at 1:1 ratio were dissolved in 10ml of chloroform. An aqueous phase phosphate buffer solution pH 7.4 (5 ml) containing drug was added to the above organic solution and the resulting two phases were sonicated at 50°C for 5 min. The emulsion was formed, from which the organic solvent was removed slowly at 40°C under low pressure using a rotary vacuum evaporator until the thin film was formed around inside the flask wall. The resulting film was hydrated with 10ml of phosphate buffer solution pH 7.4 to produce niosomal suspension and kept on water bath at 60°C for 10 min to yield niosomes.

RESULT AND DISCUSSION
It is obvious that niosome appears to be a well preferred drug delivery system over liposome as niosome being stable and economic. Also niosomes have great drug delivery potential for targeted delivery of anti-cancer, anti-infective agents. Drug delivery potential of niosome can enhance by using novel concepts like proniosomes, discomes and aspasome. Niosomes also serve better aid in diagnostic imaging and as a vaccine adjuvant. Thus these areas need further exploration and research so as to bring out commercially available niosomal preparation. The concept of incorporating the drug into liposomes or niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Niosomes represent a promising drug delivery module. They present a Structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multi environmental structure. Niosomes are thoughts to be better candidates drug delivery as compared to liposomes due to various factors like cost, stability etc. Various types of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral. Niosomes are formations of vesicles by hydrating mixture of cholesterol and nonionic surfactants. Different novel approaches used for delivering these drugs include liposomes, microspheres, nanotechnology, micro emulsions, antibody-loaded drug delivery, magnetic microcapsules, implantable pumps and niosomes. Niosomes and liposomes are equiactive in drug delivery potential and both increase drug efficacy as compared with that of free drug. Niosomes are preferred over liposomes because the former exhibit high chemical stability and economy. The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages. They improve the therapeutic performance of the drug molecules by delayed clearance from
the circulation, protecting the drug from biological environment and restricting effects to target cells.

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REFERENCE