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Preparation of Mefenamic Acid Loaded Ethosomes by Hot Method

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Abstract

TThe aim of the present investigation is to prepare mefenamic acid loaded ethosomes by hot method. Three formulations were prepared by altering drug to phospholipid ratio. The obtained vesicles were examined under trinocular microscope. The presence of large and small unilamellar vesicles indicates the formation of ethosomes.

INTRODUCTION

Transdermal drug delivery system can be used as an alternative delivery of drug into the systemic circulation.In order to increase the number of drugs administered via transdermal route, novel drug delivery systems have to be designed. These systems include use of physical means, such as iontophoresis, sonophoresis, microneedles, etc. and chemical means like penetration enhancers and biochemical means using liposomes, niosomes, transferosomes and ethosomes also have been reported to enhance permeability of drug through the stratum corneum. The vesicles have been well known for their importance in cellular communication and particle transportation for many years. Researchers have understood the properties of vesicles structure for use in better drug delivery within their cavities, which would to tag the vesicle for cell specificity. One of the major advances in vesicle research was the finding a vesicle derivatives, known as an ethosomes1,2

Ethosomes

They are mainly used for the delivery of drugs through transdermal route. Drug can be entrapped in ethosomes which have various physicochemical characteristics i.e. hydrophilic, lipophilic, or amphiphilic. Ethosomes are soft, malleable vesicles used for delivery of drugs to reach the deep skin layers and/or the systemic circulation. The size range of ethosomes may vary from tens of nano meters to microns(μ). Ethosomes are the modified forms of liposomes that are high in ethanol content3,4.

Ethosomes composition

Ethosomes are vesicular carrier comprising of hydro alcoholic or hydro/alcoholic/glycolic phospholipid in which the concentration of alcohols or their combination is relatively high. Ethosomal drug delivery can be modulated by altering alcohol:water or alcohol:polyol:water ratio. Phospholipids are most often used especially phosphatidylcholines which are amphopathic molecules in which a glycerol bridge links a pair of hydrophobic acyl hydrocarbon chains with a hydrophilic polar head group. Phosphatidylcholines contrast markedly with other amphipathic molecules in that bilayer sheets are formed in Preference to micellar structures because the double fatty acid chains give the molecule an overall tubular shape, more suitable for aggregation in planar sheets than in other aggregate structure5,6.

Phosphatidyl choline

Also known as lecithin, can be derived from both natural and synthetic sources. They are readily extracted from egg yolk and soya bean but less readily from bovine heart and spinal cord. They are often used as the principal phospholipids in liposomes for a wide range of application because of their low cost relative to other Phospholipids, their neutral charge, and their chemical inertness. Lecithin from plant sources has a high level of poly unsaturation in the fatty acyl chains, while that from mammalian sources contains a higher proportion of fully saturated chains7.

Phospholipids

Natural phospholipids have two hydrocarbon chains that are linked to a phosphate-containing polar head group. In phosphoglycerides the linkage of fatty acid to head group is via a bridge region consisting of the three carbon glycerol. In sphingolipids, the lipid sphingosine forms one of the hydrocarbon chains and it links directly to the phosphate. Phospholipids can possess fatty acid of different chain length and unsaturation and may have different hydrophilic species linked to phosphate, according to which individual members of the phospholipids category are classified8.

Phosphatidyl ethanolamine (PE)

PE has a similar head group as Phosphatidylcholines and the presence of hydrogen's directly attached to the nitrogen of ethanolamine permits interactions of adjacent molecules in the membrane by hydrogen bonding. At low or neutral pH, the amino group is protonated, giving a neutral molecule, which prefers to form hexagonal II phase inverted micelles to lamellar structures when above the main phase transition temperature9.

Phosphatidyl glycerol (PG)

PG possess a permanent negative charge over the normal physiological pH range. In addition, it is directly isolated from natural sources & readily prepared semi synthetically from other lipids by the action of phospholipase D in the presence of glycerol10.

Phosphatidyl serine (PS)

PS is linked to the phosphate via its hydroxyl group, leaving the carboxyl and amino functions both free and ionized to from a neutral zwitter ion. The net charge of the PS head group is therefore negative as a result of the charge on the phosphate. Membranes containing PS show a marked sensitivity to calcium, which interacts directly with the carboxyl functions on the head groups, causing PS molecules to aggregate within the membrane resulting in a condensed phase separate from that of the bulk lipids. Calcium also causes bridging interactions between PS on membranes of different liposomes, so that aggregation of these liposomes, in which packing defects have been introduced, often results in fusion. However, it has been reported that the presence of PS in membranes helps to stabilize them during freeze-drying in the presence of sugars11.

Phosphatidic acid (PA)

Absence of any substitution on the phosphate in PA confers a very strong negative charge to the molecule. Dispersions of PA alone in water have a pH of between 2 and 3, and rapid neutralization with acid can cause membrane reorganization, under the influence of electrostatic effect to produce unilamellar vesicles.

Sphingo myelin(SM)

SM is found to varying extents in the erythrocyte plasma membranes of a number of mammalian species and completely replaces PC in sheep red cells. It is also readily extracted from nervous tissue. It is a neutral molecule with the same phosphocholine head group as PC. SMs have hydrocarbon chains often markedly different in length and with a degree of unsaturation giving rise to transitition between 20˚C and 40˚C. Membrane packing is tighter than for PC by virtue of the extra hydrogen bonding made possible in the bridge region by the presence of the amide hydrogen, which participates in interaction between adjacent sphingomyelin molecules, and probably also with cholesterol12.

Lyso-phospholipids

Lipids described above other then lyso- phospholipids can lose a fatty acid chain by either chemical or enzymatic hydrolysis to give single chain amphiphiles. While they do not from membranes themselves. They are often present in membranes as impurities either of the starting components or as a result of degradation during storage. In high concentrations lysophospholipids can disrupt membranes and they can be highly toxic for cells and whole organisms. Membrane disruption with LPC only occurs when there is an imbalance in chains in the membrane relative to the head groups. The action of phospholipaseA converting PC to LPC and fatty acid does lead to perturbations until the fatty acid has been removed from the membrane where upon increase in permeability13

Mefenamic acid(MA) is a NSAID which is an anthranilic acid derivative. It is available as tablets, capsules and suspensions. The available dose for this drug is 250mg thrice a day. MA has a wide range of gastrointestinal disorders, like gastrointestinal bleeding and gastric upset. MA is classified as class II drug on the basis of biopharmaceutical classification system, because of its poor solubility over the pH range of 1.2-7.5.The biological half life of MA is 2-4 h. Because of short half life frequent administration of drug is required which leads to chances of missing the dose of the drug. It also acts by blocking COX1 and COX2 receptors. The major adverse effects includes blood and bone marrow problems, blood in the urine, blurred vision, breathing problems, bronchospasm, confusion, convulsions, depression, diarrhea ,difficulty sleeping, ear pain, eye or eyesight problems, feeling dizzy, feeling drowsy, feeling nervous and fluid retention. Hence to minimize the adverse effects associated with cyclooxygenase blockade such as GI Bleeding and cardiovascular problems there is need to develop site specific

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drug delivery system for mefenamic acid 14.

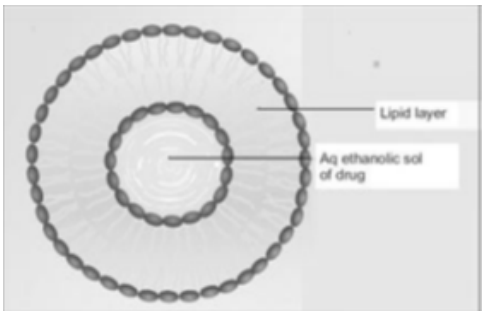


Figure 1: Representation of ethosome contents

The ethosomal system is composed of, high concentration of alcohol, phospholipid and water. The high concentration of ethanol makes ethosomes unique because ethanol causes disturbance of skin lipid bilayer organization, hence when incorporated into a vesicle membrane, it enhances the vesicles' ability to penetrate the stratum corneum15.

METHOD OF PREPARATION

Hot method

In this method, phospholipid is dispersed in water by heating in a water bath at 40°C until a colloidal solution is obtained. In a separate vessel ethanol and propylene glycol are mixed and heated to 40°C. Once both mixtures reach 40°C, the organic phase is added to the aqueous one. The drug is dissolved in water or ethanol depending on its hydrophilic/hydrophobic properties. The vesicle size of ethosomal formulation can be decreased to the desired extent using probe sonication or extrusion method. Three formulations were prepared by altering drug to phospholipid ratio16.

Optimization of stirring speed (rpm)

Process parameters such as stirring speed were optimized. Three formulations were prepared by varying stirring speed.

Table 1: Optimization of stirring speed

Stirring speed	Observation
300 rpm	The mixing of formulation ingredients was uneven.
500 rpm	There was even formation of spherical vesicles.
700 rpm	The formed vesicles were broken and incomplete.

From the literature it was observed that 500 rpm was the optimized stirring speed required for the preparation of ethosomes.

Optimization of heating temperature:

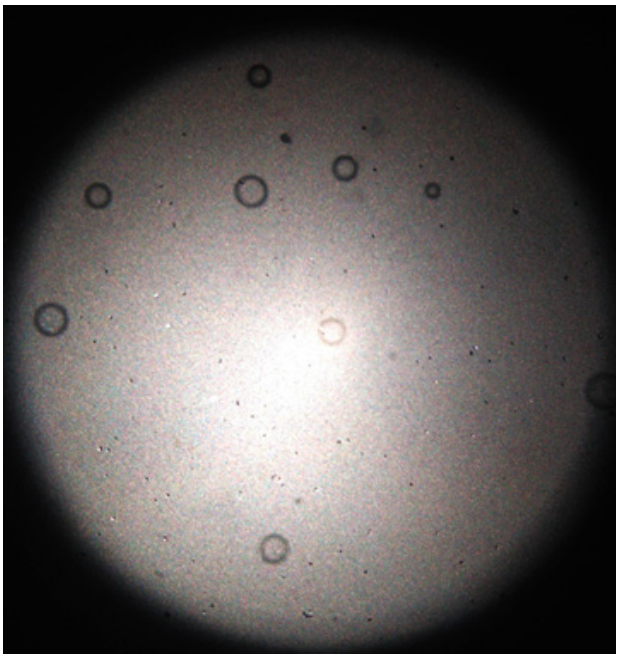
Table 2: Optimization of heating temperature

Heating temperature	Observation
30°c 40oc 50°c	less number of vesicles formed There was even formation of ethosomal vesicles. Vesicles were crushed

From the results it was observed that 40oc was the optimized heating temperature required for the preparation of ethosomes because the phospholipid dissolves in water at that particular temperature.

Visualization of vesicles

Vesicles are visualized by Transmission electron microscopy (TEM) and scanning electron microscopy (SEM).



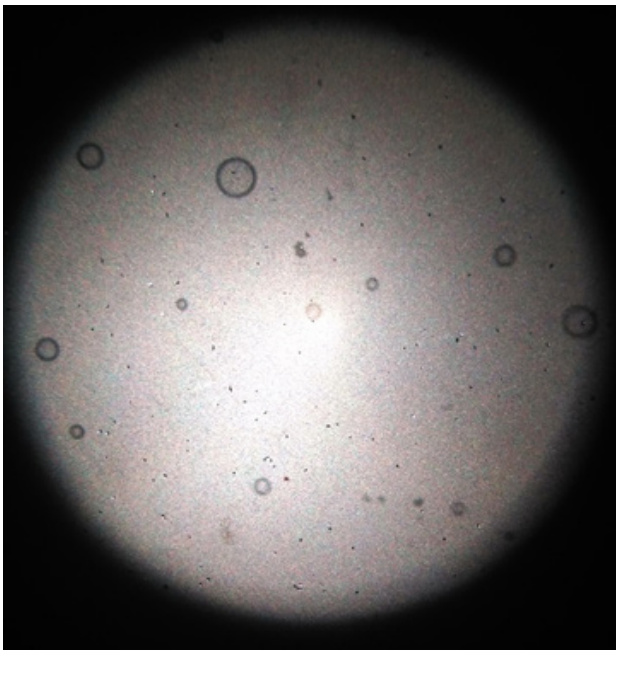


Figure2:- photomicrographic images of F1 formulation of Mefenamic acid loaded ethosomes prepared by hot method

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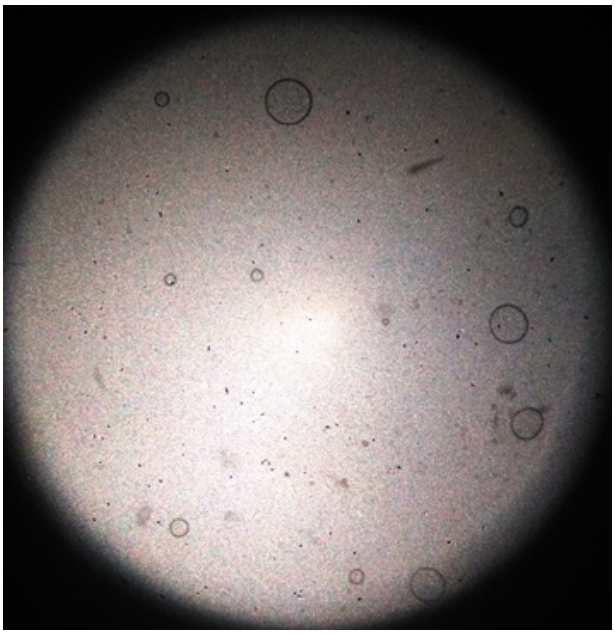

Figure3: Photomicrographic images of F2 formulation of Mefenamic acid loaded ethosomes prepared by hot method

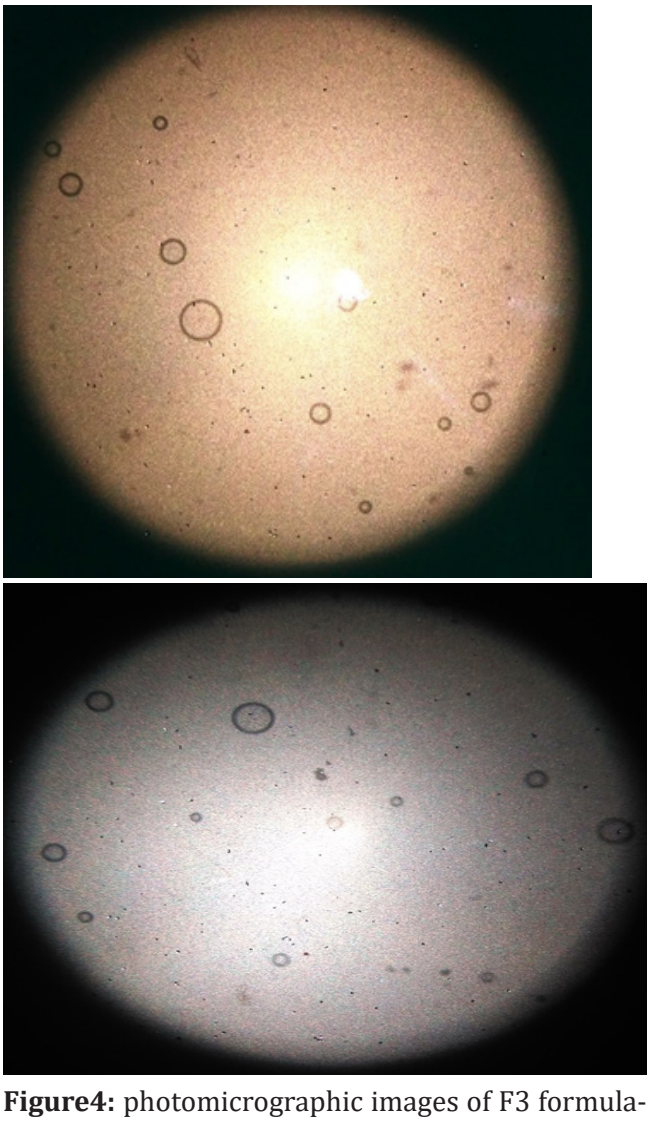

Figure4: photomicrographic images of F3 formulation of Mefenamic acid loaded ethosomes prepared by hot method.

Conclusions

Mefenamic acid loaded ethosomes were successfully prepared by hot method. Three formulations were prepared by altering drug to phospholipid ratio. Process parameters such as stirring speed and hydration temperature were optimized. Further studies has to be performed to know the entrapment efficiency, stability and drug release.

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