CHAPTER - 1

INTRODUCTION
Since long, work has been in progress to find methods of directing drugs and other therapeutic molecules to specific sites in the body in order to achieve tissue-specific treatment of various conditions and reduce the adverse effects of the drug. Paul Ehrlich in 1906 started the development for targeted drug delivery when he envisaged a drug delivery mechanism that would target drugs directly to diseased cells. Since then, numerous attempts have been made to device clinically effective drug delivery system(s). Many carriers were utilized to carry drug at the target (organ/tissue), which include immunoglobulins, serum proteins, synthetic polymers, lipid vesicles (liposomes), microspheres, erythrocytes, reverse micelle, niosomes, pharmacosomes etc (Gregoriadis 1977; Goldberg 1983; Poznansky and Juliano 1984; Poste et al 1983). Amongst these carriers, few were reached to the stage of clinical trials, where liposomes show significant potential for the effective drug delivery to the site of action.

Alec D. Bangham in early 1960s brought the potentiality of liposomes as carriers for a variety of drugs that include traditional small molecular weight drugs, therapeutic proteins, and diagnostic agents (Bangham et al 1974; Vemuri and Rhodes 1995). Liposomes are members of a family of vesicular structures, which can vary, widely in their physico-chemical properties. Basically, these vesicular structures contain one or more lipid bilayers surrounding an aqueous core. The backbone of the bilayers consists of phospholipids. Most commonly, Phosphatidylcholine (PC), a neutral lipid has been used to prepare liposomes. The size, number of bilayers, bilayers charges and bilayers rigidity of liposomes are the critical parameters controlling the fate of liposomes in vitro and in vivo. Many methods have been used to prepare different types of liposomes whether unilamellar, oligolamellar or multilamellar. The diameter of these vesicles can range from 25 nm to 50 μm. Charged phospholipids like phosphatidylglycerol (PG) or phosphatidylserine (PS) or other charged amphipathic molecules (like cholesterylhemisuccinate or stearylamine) are often included in the bilayers. The physical stability of liposomes tends to be improved by the presence of these charge-inducing agents in the bilayers because electrostatic repulsion forces hamper close contact between neighboring vesicles. Bilayers rigidity depends strongly on selected bilayer components. In general, long
(chain length C₁₄) and saturated acyl chains in bilayers of phosphatidylcholine give so called gel-like structure at body temperature; the bilayers are relatively rigid. At different temperatures, phosphatidylcholine membranes can exist in different phase transitions from one phase to another and can be detected by physical techniques as the temperature is increased. The most consistently observed of these phase transitions is the one occurring at the highest temperature, in which the membrane passes from a tightly ordered 'gel' or 'solid' phase, to a liquid-crystal phase at raised temperatures where the freedom of movement of individual molecules is higher. Above the transition temperature (Tc) a lower rigidity of the bilayer is found; the "fluid state". Phosphatidylcholine isolated from natural sources contains unsaturated fatty acids and their Tc value lie below 37°C, giving rather loosely packed fluid state bilayers at body temperature. Gel like liposomes tend to be less prone to leakage of liposomes-encapsulated drugs than liposomes with fluid like structures. Bilayers with a low rigidity (fluid bilayers) can be "rigidified" by inclusion of cholesterol. In general, hydrophilic drugs (Gregoriadis 1976) are located in the aqueous phase inside the liposomes, either in between the subsequent bilayers or in the core. Lipophilic drug (Stamp and Juliano 1979) are associated within the bilayers. Liposomes offer advantages over other drug carrier systems because of their relatively low toxicity and their high versatility in terms of physico-chemical properties. The limited stability during storage of certain types of liposomes may, on the other hand, pose problems. Initially, liposomes were considered to deliver drugs via parenteral route particularly for the selective delivery of anticancer, antifungal and antibiotics (Gregoradis 1993). Only since last decade, liposomes have been considered for other routes of delivery like oral (Sveinsson and Holbrook 1993; Sveinsson and Mezei 1992), Pulmonary (Schreier et al 1993), (Conley et al 1997), Ophthalmic (Velpandian et al 1999) and dermal/ transdermal (Touitou et al 1994; Singh and Vyas 1996; Hsiu-Ying and Hui-Min 1996; Trafny et al 1999; Hwang et al 1997 and Fresta and Punglisi 1997) routes. Recently, clinical evaluation has also demonstrated that the liposomal drug delivery improves the drug retention in the skin layers and thereby, showed better therapeutic efficiency of the drugs for the treatment of topical diseases (Patel et. al. 2001).
Liposomes have shown great potential as a topical drug delivery. Topical route is often found to be inefficient and unreliable because of the inability of the drug to penetrate through the stratum corneum and reach an effective concentration in viable epidermis (e.g. methotrexate) or due to rapid penetration of drug reaching systemic circulation (which results toxicity) (e.g. corticosteroids). This shortcoming limits the treatment of a number of dermatological diseases and disorders such as cutaneous tumors, eczema, infections, and psoriasis by topical application of therapeutic agents. Concerted efforts during last decade made liposomes as potential carriers and reservoirs for controlled release of drugs within various layers of skin (Egbaria et al 1990; Moghimi Patel. 1993; Sharma et al 1993; Schreier Bouwstra 1994).

Recently, it has become apparent that liposomes may offer special advantage as a topical delivery system due to following reasons:

❖ They can entrap both hydrophilic and lipophilic drugs in their respective layers.
❖ They can deliver active ingredient into the skin, which conventional vehicles fail due to inability to penetrate the horny layer.
❖ They can readily penetrate the skin but result in a decrease in systemic absorption compared to that resulting from topical application using conventional vehicles.
❖ They can be deposited into the stratum corneum and act as a reservoir for the supply of encapsulated drug.

Amongst various skin diseases, Herpes is of great concern today because of the advent of AIDS. It is a viral disease caused by Herpes simplex (type 1 & 2) and Varicella Zoster viruses. Herpes simplex type 1 commonly causes herpes labialis and keratitis and Herpes simplex type 2 usually causes herpes simplex genitalis. The infection is characterized by the appearance of single or multiple clusters of small vesicles, filled with clear fluid, on slightly raised inflammatory bases on the skin or mucous membranes. Herpes zoster caused by the varicella-zoster virus, is an acute CNS infection involving primarily the dorsal root ganglia and characterized by vesicular eruption and neuralgic pain in the cutaneous areas supplied by peripheral sensory nerves arising in the affected root ganglia.
Antiviral drugs that have been commonly used to treat these infections are idoxuridine and acyclovir. Idoxuridine is a synthetic pyrimidine nucleoside used in the topical treatment of Herpes simplex keratitis and cutaneous forms of Herpes simplex and zoster. It may produce irritation and hypersensitivity reactions when applied to the skin. Intravenous administration of idoxuridine may cause bone marrow depression and liver damage. Its topical penetration through skin is reported to be poor (Martindale 1996a).

Acyclovir, a synthetic analogue of guanine, is a drug of choice for the treatment and prophylaxis of infections due to herpes simplex or varicella-zoster viruses. Generally, it is well tolerated but when administered intravenously as its sodium salt, it may cause local reactions at the injection site with inflammation and phlebitis. Other adverse effects following i.v. administration includes increased values of liver enzymes, hematological changes, skin rashes, nausea, vomiting, and headache. Encephalopathic changes including lethargy, confusion, tremors, and seizures have also been reported (Martindale 1996b).

Oral administration of drug causes adverse effects such as nausea, vomiting, diarrhea, headache and skin rashes. It is only 15 to 30% absorbed from the GIT. A dose of 200 mg given every 4 hours by mouth is reported to produce steady-state plasma concentration of 0.29 to 0.59 μg/ml and that of a dose of 400 mg achieves 0.6 to 1.2 μg/ml, which has been attained when an i.v. infusion equivalent to 5 mg/kg body weight is given to adults over a period of one hour. Thus, it can be emphasized that oral administration of the drug does not have profound effect because of its poor gastro-intestinal absorption. It requires high frequency of doses that ultimately add to the GIT disturbances. Similarly, Topical absorption of acyclovir is poor and its application to intact skin may produce stinging and burning sensation or erythema (Martindale 1996b).

No doubt, drugs idoxuridine and acyclovir which are quite effective to treat Herpes simplex but their various systemic and GIT untoward effects compel us to target them to the site of infection i.e. epidermis and ganglia, by improving their topical absorption without any stinging and burning effects and facilitate them with reservoir for the prolonged supply of drugs.
The aim of the present investigation was to develop topical liposomal formulations of acyclovir (ACY) and idoxuridine (IDU) and evaluate these developed products in vitro and clinically in the treatment of Herpes simplex (HSV) (type 1 & type 2).

For this purpose, the research envisaged is as follows:

- Encapsulation of selected drug within liposomes by different methods.
- Optimization of the products method utilizing model-dependent optimization technique.
- Characterization of liposomes with respect to size, shape, lamellarity, drug entrappment efficiency etc.
- Drug retention studies of developed liposomal formulation to check their stability for a reasonable period of time. If necessary, improve vesicular stability of liposomes by modifying their physical characteristics, i.e., permeability of the bilayers of phospholipids or by surface hydrophobic interaction of bovine serum albumin (BSA).
- Incorporation of liposomes into suitable dermatological base.
- Controlled Clinical evaluation of the developed formulations to justify the role of developed formulations in HSV patients.
REFERENCES


