NIOSOMES AS PROMISING VEHICLE FOR NOVEL DRUG DELIVERY SYSTEM: RECENT REVIEW

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ABSTRACT
Niosomes are non-ionic surfactant vesicles obtained on hydration of synthetic nonionic surfactants, with or without incorporation of cholesterol or other lipids. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. Niosomes are promising vehicle for drug delivery and being non-ionic, it is less toxic and improves the therapeutic index of drug by restricting its action to target cells. This systemic review article deals with preparation methods, characterizations, factors affecting release kinetic, advantages, and applications of niosomes.

KEYWORDS: Niosomes, Cholesterol, Ampiphilic, Lipophilic Drugs.

INTRODUCTION
At present no available drug delivery system achieves the site specific delivery with controlled release kinetics of drug in predictable manner. Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Since then, number of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc(1). Among different carriers liposomes and niosomes are well documented drug delivery. 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 nontarget tissue(2).

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(3). In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate(4). Schematic representation of a drug targeting through its linkage to niosome via antibody is shown in figure 1.
Figure 1: Niosome structure

ADVANTAGES OF NIOSOMES:

- The first report of non-ionic surfactant vesicles came from the cosmetic applications devised by L’Oreal\textsuperscript{4}. The application of vesicular (lipid vesicles and non-ionic surfactant vesicles) systems in cosmetics and for therapeutic purpose may offer several advantages:

- The vesicle suspension is water–based vehicle. This offers high patient compliance in comparison with oily dosage forms.

- They possess an infrastructure consisting of hydrophilic, amphiphilic and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities.

- The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.

- The vesicles may act as a depot, releasing the drug in a controlled manner.

- Other advantages of niosomes include:

  - They are osmotically active and stable, as well as they increase the stability of entrapped drug.

  - Handling and storage of surfactants requires no special conditions.

  - They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.

  - They can be made to reach the site of action by oral, parenteral as well as topical routes.

  - The surfactants are biodegradable, biocompatible and non-immunogenic.

  - 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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Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase.

**COMPARISON OF NIOSOMES VS LIPOSOMES:**

a) 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.

b) Differences in characteristics exist between liposomes and niosomes, especially since niosomes are prepared from uncharged single-chain surfactant and cholesterol whereas liposomes are prepared from double-chain phospholipids (neutral or charged)\(^5\). Handjani-Vila et al \(^6\) were first to report the formation of vesicular system on hydration of mixture of cholesterol and a single-alkyl chain non-ionic surfactant.

c) Niosomes behave in-vivo like liposomes, prolonging the circulation of entrapped drug and altering its organ distribution and metabolic stability\(^7\). 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 \(^8\). Such vesicular drug carrier systems alter the plasma clearance kinetics, tissue distribution, metabolism and cellular interaction of the drug \(^7,9\). They can be expected to target the drug to its desired site of action and/or to control its release \(^10\).

As with liposomes, the properties of niosomes depends both on the composition of the bilayer and on method of their production\(^11\). It was observed by Baillie et al \(^10\) that the intercalation of cholesterol in the bilayers decreases the entrapment volume during formulation and thus entrapment efficiency. As the concentration of cholesterol increases, entrapment efficiency decreases. The entrapment efficiency increases with increase in the concentration and lipophilicity of surfactant\(^12\). Chandraprakash et al \(^12\) made Methotrexate loaded non-ionic surfactant vesicles using lipophilic surfactants like Span 40, Span 60 and Span 80 and found that Span 60 (HLB = 4.7) gave highest percent entrapment while Span 85 (HLB = 9.8) gave least entrapment. They also observed that as HLB value of surfactant decreased, the mean size was reduced.

**METHOD OF PREPARATION**

A. Ether injection method \(^13,14\)
This method provides a means of making niosomes by slowly introducing a solution of surfactant dissolved in diethyl ether into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14-gauge needle into an aqueous solution of material. Vaporization of ether leads to formation of single layered vesicles. Depending upon the conditions used, the diameter of the vesicle range from 50 to 1000 nm.

**B. Hand shaking method (Thin film hydration technique)**

The mixture of vesicles forming ingredients like surfactant and cholesterol are dissolved in a volatile organic solvent (diethyl ether, chloroform or methanol) in a round bottom flask. The organic solvent is removed at room temperature (20°C) using rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask. The dried surfactant film can be rehydrated with aqueous phase at 0-60°C with gentle agitation. This process forms typical multilamellar niosomes.

Thermosensitive niosomes were prepared by Raja Naresh et al. by evaporating the organic solvent at 60°C and leaving a thin film of lipid on the wall of rotary flash evaporator. The aqueous phase containing drug was added slowly with intermittent shaking of flask at room temperature followed by sonication.

**C. Sonication**

A typical method of production of the vesicles is by sonication of solution as described by Cable. In this method an aliquot of drug solution in buffer is added to the surfactant/cholesterol mixture in a 10-ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield niosomes.

**D. Micro fluidization**

Micro fluidization is a recent technique used to prepare unilamellar vesicles of defined size distribution. This method is based on submerged jet principle in which two fluidized streams interact at ultra high velocities, in precisely defined micro channels within the interaction chamber. The impingement of thin liquid sheet along a common front is arranged such that the energy supplied to the system remains within the area of niosomes formation. The result is a greater uniformity, smaller size and better reproducibility of niosomes formed.

**E. Multiple membrane extrusion method**

Polycarbonate membranes, which are placed in series for upto 8 passages. It is a good method for controlling nosome size. Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded through
F. Reverse Phase Evaporation Technique (REV)\(^{15}\)

Cholesterol and surfactant (1:1) are dissolved in a mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-5°C. The clear gel formed is further sonicated after the addition of a small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min to yield niosomes. Raja Naresh et al\(^{15}\) have reported the preparation of Diclofenac Sodium niosomes using Tween 85 by this method.

G. Trans membrane pH gradient (inside acidic) Drug Uptake Process (remote Loading)\(^{17}\)

Surfactant and cholesterol are dissolved in chloroform. The solvent is then evaporated under reduced pressure to get a thin film on the wall of the round bottom flask. The film is hydrated with 300 mM citric acid (pH 4.0) by vortex mixing. The multilamellar vesicles are frozen and thawed 3 times and later sonicated. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexed. The pH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. This mixture is later heated at 60°C for 10 minutes to give niosomes.

H. The “Bubble” Method\(^{18}\)

It is a novel technique for the one step preparation of liposomes and niosomes without the use of organic solvents. The bubbling unit consists of round-bottomed flask with three necks positioned in water bath to control the temperature. Water-cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through the third neck. Cholesterol and surfactant are dispersed together in this buffer (pH 7.4) at 70°C, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards “bubbled” at 70°C using nitrogen gas.

I. Formation of niosomes from proniosomes\(^{19}\)

Another method of producing niosomes is to coat a water-soluble carrier such as sorbitol with surfactant. The result of the coating process is a dry formulation. In which each water-soluble particle is covered with a thin film of dry surfactant. This preparation is termed “Proniosomes”. The niosomes are recognized by the addition of aqueous phase at T > Tm and brief agitation. T=Temperature. Tm = mean phase transition temperature.
Blazek-Walsh A.I. et al (19) have reported the formulation of niosomes from maltodextrin based proniosomes. This provides rapid reconstitution of niosomes with minimal residual carrier. Slurry of maltodextrin and surfactant was dried to form a free flowing powder, which could be rehydrated by addition of warm water. Table 1 shows in brief example of some drugs incorporated into niosomes using different methods.

Table 1: Drugs incorporated into niosomes by various methods

<table>
<thead>
<tr>
<th>Method of preparation</th>
<th>Drug incorporated</th>
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<tbody>
<tr>
<td><strong>Ether Injection</strong></td>
<td>Sodium stibogluconate (18,20)</td>
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<tr>
<td></td>
<td>Doxorubicin (21)</td>
</tr>
<tr>
<td><strong>Hand Shaking</strong></td>
<td>Methotrexate (12)</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin (21)</td>
</tr>
<tr>
<td><strong>Sonication</strong></td>
<td>9-desglycinamide</td>
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<tr>
<td></td>
<td>8-arginine</td>
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<tr>
<td></td>
<td>Vasopressin</td>
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<td></td>
<td>Oestradiol (5,19)</td>
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SEPARATION OF UNENTRAPPED DRUG:
The removal of unentrapped solute from the vesicles can be accomplished by various techniques, which include:

1. **Dialysis** (18)
The aqueous niosomal dispersion is dialyzed in a dialysis tubing against phosphate buffer or normal saline or glucose solution.

2. **Gel Filtration** (22,23)
The unentrapped drug is removed by gel filtration of niosomal dispersion through a Sephadex-G-50 column and elution with phosphate buffered saline or normal saline.

3. **Centrifugation** (24,25)
The niosomal suspension is centrifuged and the supernatant is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from unentrapped drug.

CHARACTERIZATION OF NIOSOMES

a) **Entrapment efficiency**

After preparing niosomal dispersion, unentrapped drug is separated by dialysis (18), centrifugation (22,23), or gel filtration (11) as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and analysing the resultant solution by appropriate assay method for the drug. Where,
Entrapment efficiency (EF) = (Amount entrapped total amount) x 100

b) Vesicle diameter
Niosomes, similar to liposomes, assume spherical shape and so their diameter can be determined using light microscopy, photon correlation microscopy and freeze fracture electron microscopy. Freeze thawing \(^{(16)}\) (keeping vesicles suspension at –20°C for 24 hrs and then heating to ambient temperature) of niosomes increases the vesicle diameter, which might be attributed to fusion of vesicles during the cycle.

C) In-Vitro Release
A method of in-vitro release rate study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipetted into a bag made up of the tubing and sealed. The bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C or 37°C. At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method \(^{(22)}\).

FACTORS AFFECTING VESICLES SIZE, ENTRAPMENT EFFICIENCY AND RELEASE CHARACTERISTICS:

a) Drug
Entrapment of drug in niosomes increases vesicle size, probably by interaction of solute with surfactant head groups, increasing the charge and mutual repulsion of the surfactant bilayers, thereby increasing vesicle size\(^{(23,25)}\). In polyoxyethylene glycol (PEG) coated vesicles, some drug is entrapped in the long PEG chains, thus reducing the tendency to increase the size\(^{(24)}\). The hydrophilic lipophilic balance of the drug affects degree of entrapment.

b) Amount and type of surfactant
The mean size of niosomes increases proportionally with increase in the HLB of surfactants like Span 85 (HLB 1.8) to Span 20 (HLB 8.6) because the surface free energy decreases with an increase in hydrophobicity of surfactant \(^{(22)}\). The bilayers of the vesicles are either in the so-called liquid state or in gel state, depending on the temperature, the type of lipid or surfactant and the presence of other components such as cholesterol. In the gel state, alkyl chains are present in a well-ordered structure, and in the liquid state, the structure of the bilayers is more disordered. The surfactants and lipids are characterized by the gel-liquid phase transition temperature (TC)\(^{(22)}\). Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e. Span 60 having higher TC, provides better entrapment.

c) Cholesterol content and charge
Inclusion of cholesterol in niosomes increases its hydrodynamic diameter and entrapment efficiency\(^{(22)}\). In general, the action of cholesterol is two folds; on one hand, cholesterol increases the chain order of liquid-state bilayers and on the other, cholesterol decreases the chain order of gel state bilayers. At a high cholesterol concentration, the gel state is transformed to a liquid-ordered phase\(^{(25)}\).

An increase in cholesterol content of the bilayers resulted in a decrease in the release rate of encapsulated material and therefore an increase of the rigidity of the bilayers obtained\(^{(25,27,28)}\). Presence of charge tends to increase the interlamellar distance between successive bilayers in multilamellar vesicle structure and leads to greater overall entrapped volume.

d) Methods of preparation

Methods of preparation of niosomes such as hand shaking, ether injection and sonication have been reviewed by Khandare et al \(^{(16)}\). Hand shaking method forms vesicles with greater diameter (0.35-13nm) compared to the ether injection method (50-1000nm)\(^{(16)}\).

Small sized niosomes can be produced by Reverse Phase Evaporation (REV) method\(^{(15,29)}\). Microfluidization \(^{(16)}\) method gives greater uniformity and small size vesicles. Parthasarthi et al \(^{(29)}\) prepared niosomes by trans membrane pH gradient (inside acidic) drug uptake process. Niosomes obtained by this method showed greater entrapment efficiency and better retention of drug.

e) Resistance to osmotic stress

Addition of a hypertonic salt solution to a suspension of niosomes brings about reduction in diameter. In hypotonic salt solution, there is initial slow release with slight swelling of vesicles probably due to inhibition of eluting fluid from vesicles, followed by faster release, which may be due to mechanical loosening of vesicles structure under osmotic stress\(^{(3,30)}\).

NIOSOMES AS DRUG CARRIERS

A number of workers have reported the preparation, characterization and use of niosomes as drug carriers. Niosomes containing anti-cancer drugs, if suitably designed, will be expected to accumulate within tumors in a similar manner to liposomes. The niosomal encapsulation of Methotrexate and Doxorubicin increases drug delivery to the tumor and tumoricidal activity of the drug. Doxorubicin niosomes possessing muramic acid and triglycerol surfaces were not taken up significantly by liver. The triglycerol niosomes accumulated in the tumor and muramic acid vesicles accumulated in the spleen. Those vesicles with polyoxyethylene surface were rapidly taken up by the liver and accumulated to a lesser extent in tumor. Baillie et al \(^{(14)}\) investigated the encapsulation and retention of entrapped solute 5,6-carboxy fluorescence (CF) in niosomes.
They observed that stable vesicles could not be formed in the absence of cholesterol but were more permeable to entrapped solute. The physical characteristics of the vesicles were found to be dependent on the method of production.

Carter et al (20) reported that multiple dosing with sodium stibogluconate loaded niosomes was found to be effective against parasites in the liver, spleen and bone marrow as compared to simple solution of sodium stibogluconate.

Azmin et al (7) reported the preparation and oral as well as intravenous administration of Methotrexate loaded niosomes in mice. They observed significant prolongation of plasma levels and high uptake of Methotrexate in liver from niosomes as compared to free drug solution. Chandraprakash et al (31) reported the formation and pharmacokinetic evaluation of Methotrexate niosomes in tumor bearing mice.

Cable et al (32) modified the surface of niosomes by incorporating polyethylene alkyl ether in the bilayered structure. They compared the release pattern and plasma level of Doxorubicin in niosomes and Doxorubicin mixed with empty niosomes and observed a sustained and higher plasma level of doxorubicin from niosomes in mice. D’ Souza et al (33) studied absorption of Ciprofloxacin and Norfloxacin when administered as niosome encapsulated inclusion complexes. Namdeo et al (35) reported the formulation and evaluation of Indomethacin loaded niosomes and showed that therapeutic effectiveness increased and simultaneously toxic side effect reduced as compared with free Indomethacin in pawedema bearing rats.

Parthasarthi et al (29) prepared niosomes of vincristine sulfate which had lesser toxicity and improved anticancer activity. Jagtap and Inamdar (35) prepared niosomes of Pentoxifylline and studied the in-vivobronchodilatory activity in guinea pigs. The entrapment efficiency was found to be 9.26 ± 1.93% giving a sustained release of drug over a period of 24 hrs.

Raja Naresh et al (15) reported the anti-inflammatory activity of niosome encapsulated Diclofenac sodium in arthritic rats. It was found that the niosomal formulation prepared by employing a 1:1 combination of Tween 85 elicited a better consistent anti-inflammatory activity for more that 72 hrs after administration of single dose.

APPLICATIONS

Niosomal drug delivery is potentially applicable to many pharmacological agents for their action against various diseases. Some of their therapeutic applications are discussed below.

1) Targeting of bioactive agents

a) To reticulo-endothelial system (RES)
The cells of RES preferentially take up the vesicles. The uptake of niosomes by the cells is also by 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\(^{(3)}\).

b) To organs other than RES

It has been suggested that carrier system can be directed to specific sites in the body by use of antibodies\(^{(36)}\). Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier \(^{(37)}\). Many cells possess the intrinsic ability to recognize and bind particular carbohydrate determinants and this can be exploited to direct carriers system to particular cells.

2) Neoplasia

Doxorubicin, the anthracyclic antibiotic with broad spectrum anti tumor activity, shows a dose dependant irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S-180 tumor increased their life span and decreased the rate of proliferation of sarcoma \(^{(38)}\). Niosomal entrapment increased the half-life of the drug, prolonged its circulation and altered its metabolism. Intravenous administration of methotrexate entrapped in niosomes to S-180 tumor bearing mice resulted in total regression of tumor and also higher plasma level and slower elimination \(^{(31,39)}\).

3) Leishmaniasis

Niosomes can be used for targeting of drug in the treatment of diseases in which the infecting organism resides in the organ of reticulo-endothelial system. Leishmaniasis is such a disease in which parasite invades cells of liver and spleen. The commonly prescribed drugs are antimonials, which are related to arsenic, and at high concentration they damage the heart, liver and kidney. The study of antimony distribution in mice, performed by Hunter et al \(^{(40)}\) showed high liver level after intravenous administration of the carriers forms of the drug. Baillie et al \(^{(14)}\) reported increased sodium stibogluconate efficacy of niosomal formulation and that the effect of two doses given on successive days was additive.

4) Delivery of peptide drugs

Yoshida et al \(^{(28)}\) investigated oral delivery of 9-desglycinamide, 8-arginine vasopressin entrapped in niosomes in an in-vitro intestinal loop model and reported that stability of peptide increased significantly.

5) Immunological application of niosomes
Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and Alexander (41) have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability.

6) Niosomes as carriers for Hemoglobin.
Niosomes can be used as a carrier for hemoglobin. Niosomal suspension shows a visible spectrum superimposable onto that of free hemoglobin. Vesicles are permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin (42,43).

7) Transdermal delivery of drugs by niosomes
Slow penetration of drug through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes. Jayraman et al (44) has studied the topical delivery of erythromycin from various formulations including niosomes or hairless mouse. From the studies, and confocal microscopy, it was seen that non-ionic vesicles could be formulated to target pilosebaceous glands.

8) Other Applications
a) Sustained Release
Azmin et al (7) suggested the role of liver as a depot for methotrexate after niosomes are taken up by the liver cells. Sustained release action of niosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via niosomal encapsulation.

b) 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 (18,40). 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.

CONCLUSION
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 thought to be better candidates drug delivery as compared to liposomes due to various factors like cost, stability etc. Various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parenteral, etc.

REFERENCES

13. Rogerson A., Cummings J., Willmott N. and Florence A.T. The distribution of
doxorubicin in mice following administration in niosomes. J Pharm Pharmacol. 1988;
14. Baillie A.J., Coombs G.H. and Dolan T.F. Non-ionic surfactant vesicles, niosomes, as
delivery system for the anti-leishmanial drug, sodium stribogluconate
activity of Niosome encapsulated diclofenac sodium with Tween -85 in Arthritic rats.
The Eastern Pharmacist. 1994; 37: 61-64.
302.
18. Chauhan S. and Luurence M.J. The preparation of polyoxyethylene containing non-ionic
19. Blazek-Walsh A.I. and Rhodes D.G. Pharm. Res. SEM imaging predicts quality of
carrier system characteristics and the ability to clear parasites from the liver, spleen and
bone marrow in Leishmania donovani infected BALB/c mice. J.Pharm. Pharmcol. 1989;
41(2): 87-91.
22. Yoshioka T., Sternberg B. and Florence A.T. Preparation and properties of vesicles
(niosomes) of sobitan monoesters (Span 20, 40, 60, and 80) and a sorbitan triester (Span
23. Gayatri Devi S., Venkatesh P. and Udupa N. Niosomal sumatriptan succinate for nasal
1999; 185: 23-35.
25. B.L. Silver Ed., The Physical Chemistry of Membranes, Alan & Unwin and Soloman
26. Stafford S., Baillie A.J. and Florence A.T. Drug effects on the size of chemically defined


