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# Application of Niosomes as a Targeted Drug Delivery System.

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## Abstract:

Over the past several years, treatment of infectious diseases had been undergone a revolutionary shift. With the advancement of biotechnology and genetic engineering various numbers of diseases specific biological molecules have been developed and also the effective delivery of these biology molecules has been made. Niosomes (The non-ionic surfactant vesicles), considered as a Novel Drug Delivery System, can improve the solubility and stability of natural pharmaceutical molecules. They are biodegradable, relatively non toxic, an alternative to liposome. They are established to provide targeting and controlled release of natural pharmaceutical compounds. It is a non-invasive route of application, produce controlled effect maintaining sustained concentration of drug in plasma for longer period of time, and hence providing high patient's compliance. This article also presents an overview of the techniques of preparation of niosomes, types of niosomes, Formulation of Econazole Niosomes.

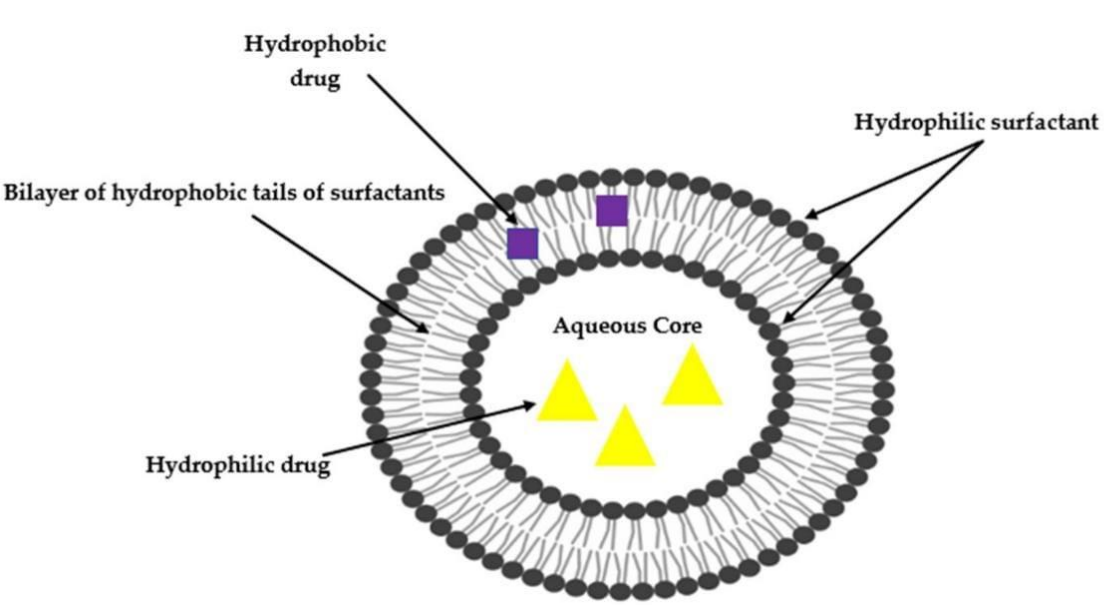
Keyword: Niosomes, Multilamellar vesicles, Cholesterol, Econazole, Immunogenic.

## Introduction:

The concept of targeted drug delivery is developed to maintain the concentration of drug in the tissues while reducing the relative concentration of the medication in the remaining tissues. The drug is localised on the targeted site. Hence, Surrounding tissues are not affected by the drug leading to get maximum efficacy of the medicine and loss of drug does not happen due to localization of drug. Different carrier have been used for targeting of drug, such as serum proteins, synthetic polymers, liposome, microspheres, erythrocytes and niosomes.[1]

Niosomes are one of the best among these carriers. They are obtained on hydration are microscopic lamellar structure formed upon combining non-ionic surfactant of the alkyl Or dialkyl polyglycerol ether class with

cholesterol.[2] The amphiphiles involved when producing niosomes include Spans® [3-4] and/or Tweens® [4-5] and/or ethoxylated alcohols and/or sucrose esters that are stablized by the addition of cholesterol and small amounts of ionic materials such as diacetyl phosphate Or chitosan[6-7].Niosomes, like other bilayer vehicular drug delivery system, can entrap and shuttle both lipophilic and hydrophilic payloads in either the bilayer membrane or aqueous layer, respectively [8-9]. Studies have suggested that niosomes are more stable than liposome [10], and the presence of non-ionic surfactants facilitates prolonged circulation of the carriers, potentially enhancing therapy and targeting delivery to specific organs such as brain, liver and tumours [11-12] A schematic representation of a niosomes.




Niosomes offers many advantage over conventional drugs delivery system in terms of flexibility for drug delivery system and the capability to entrap hydrophilic and hydrophobic drugs. Niosomes entrap solutes and API of different solubility, delivery them via many different routes of administration: oral, pulmonary, ocular, parenteral and topical [13].

## Advantages of niosomes:

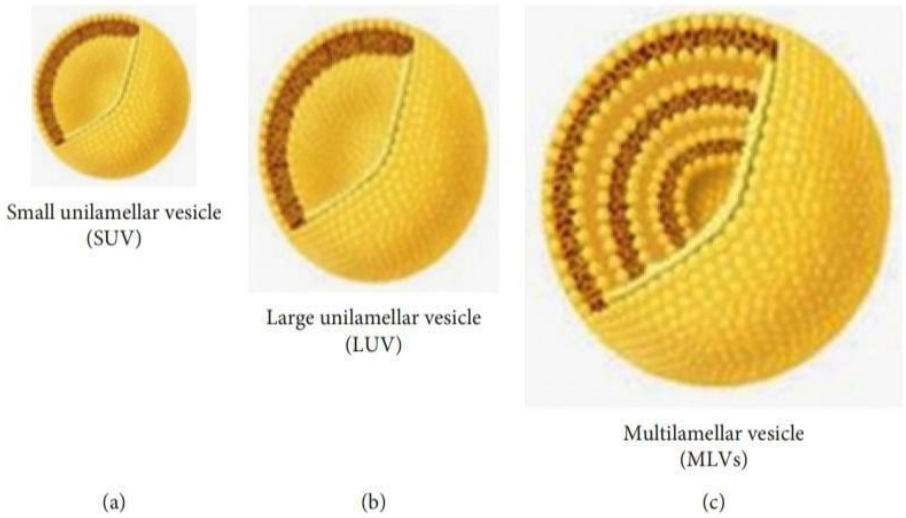
1. Niosomes are patient compliance, biodegradable, biocompatible, non-immunogenic, and low toxicity.
2. They are osmotically active and have long storing period.
3. They perform as a pool to release medication in a steady, organised, and sustained mode.
4. They provide accommodations for drug molecules with a varied sort of solubility of medication, for example hydrophilic and lipophilic in addition to amphiphilc medication moieties.
5. Niosomes can rise the stability of the encapsulated medication.
6. Niosomes can improve the skin penetration of medications.
7. Niosomes have the capability to overcome BBB and access drug delivery to the brain.

8. They improve the therapeutic performance of the drug by surface modification and restricting effects to target cells, thereby reducing the clearance of the medication.
9. Niosomes can expand the oral bioavailability of medication.
10. Surface modification is very simple due to functional groups on their hydrophilic heads.

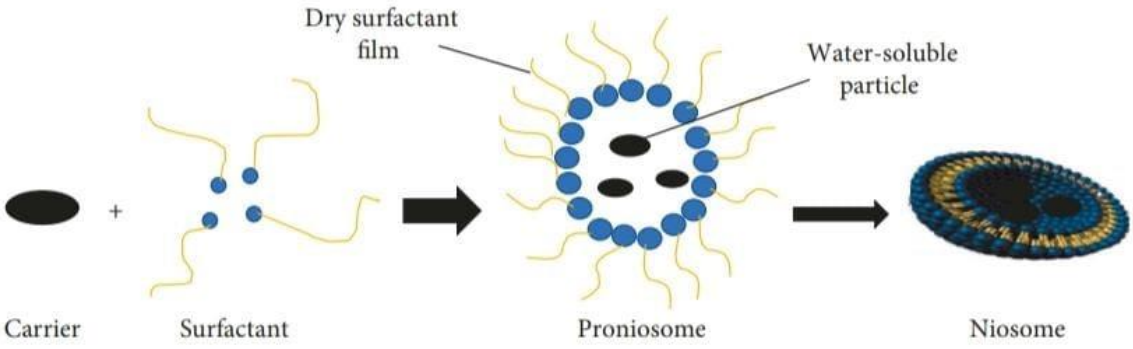
# Various Types Of Niosomes:

Based on the vesicles size, niosomes can be divided into three groups.

1. The small unilamellar vesicles (SUV, size= 0.025-0.05µm).
2. Multilamellar vesicles (MLV, size =>0.05µm).
3. Large unilamellar vesicles (LUV, size=>0.10µm).




Schematic Typical vesicles size of niosomes.



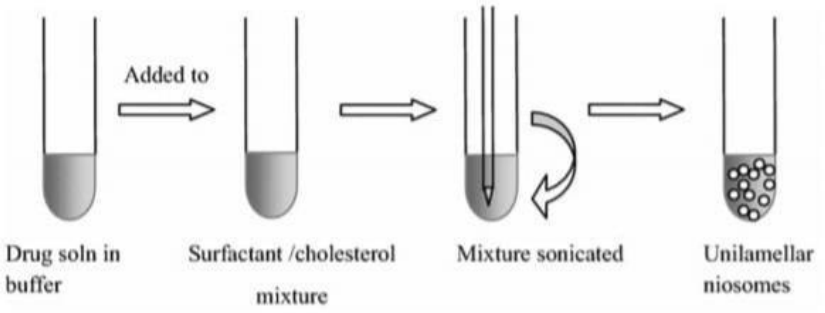

Schematic Proniosome and niosomes formation process.

# Method of preparation:

Niosomes are prepared by different methods based on the sizes of the visible and their distribution, number of double layers, Entrapment efficacy of the aqueous phase and permeability of vesicle membrane.

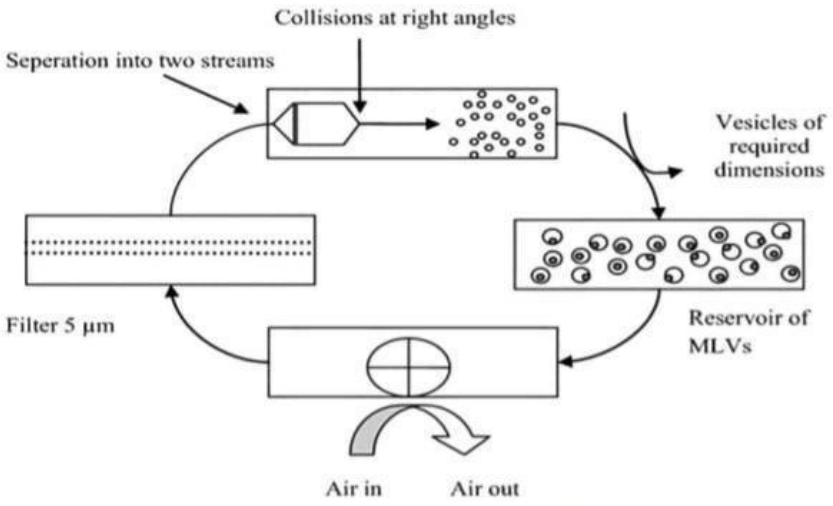
## Preparation of small unilamellar vesicle.

**Sonication:** The aqueous phase containing drug is added to the mixture of surfactant and cholesterol scintillation vial [14]. The mixture is homogenised using a Sonic probe at 60 degree Celsius for 3 minutes. The vesicles are small and uniform in size.




Schematic diagram of the preparation of niosomes via sonication [24]

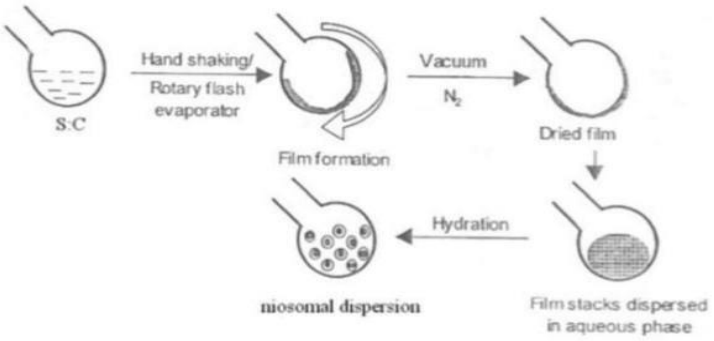
**Micro fluidization:** Two fluidized streams move forward through precisely defined micro channel and interact at ultra high velocity is within the interaction chamber.[15] Here, a common gateway is arranged such that the energy supplied to the system remains within the area of new niosomes formation. The result is Greater uniformity, small size and better reproductibility.




Schematic diagram of the preparation of niosomes via micro-fluidization[25]

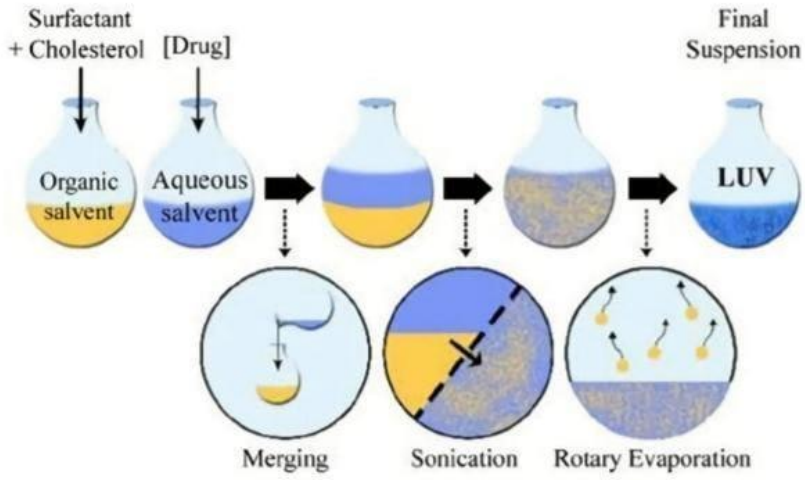
## Preparation of multilamellar vesicles.

**Hand Shaking Method:** In hand shaking method, surfactant and cholesterol are dissolved in volatile organic solvent such as diethyl ether, chloroform or methanol in a Rotary evaporator leaving a thin layer of solid mixture deposited on the wall of the flask.[14] The dried layer is hydrated with aqueous phase containing drug at normal temperature we gentle agitation.



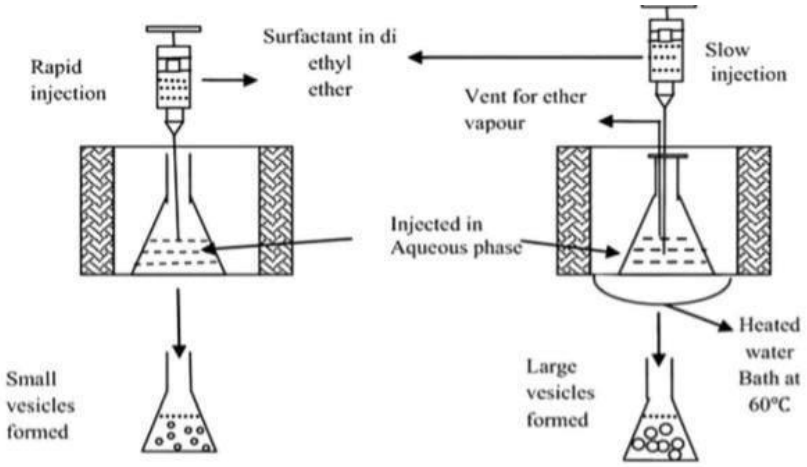

## Preparation of large unilamellar vesicles.

**Reverse phase evaporation technique:** In this method, cholesterol and surfactant are dissolved in a mixture of ether and chloroform[16]. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4 to 5 degree Celsius. The clear gel is formed is further sonicated after the addition of small amount of phosphate buffered saline. The organic phase is removed at 40°c under low pressure. The resulting viscus niosomes suspension is diluted with phosphate buffered saline and heated in a water bath at 60°c for 10 minutes to yield niosomes.




Schematic diagram of the preparation of niosomes via reverse phase method [26]

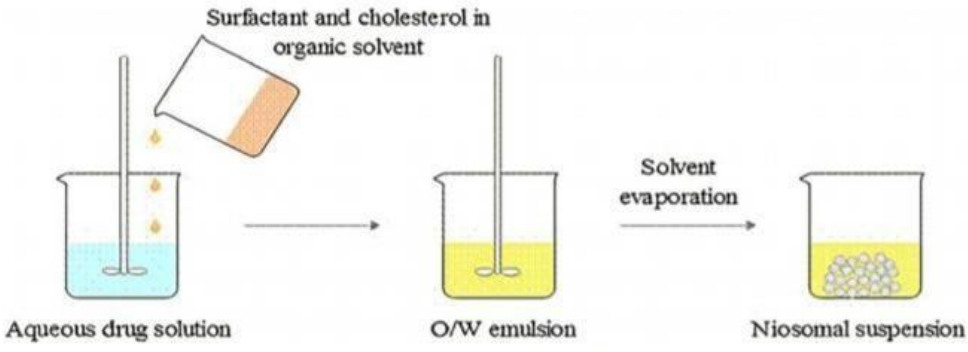
**Ether injection method:** The Ether injection method is essentially based on slow injection of niosomal ingredients in ether through a 14-gauge needle at the rate of approximately 0.25 ml /minute into a preheated aqueous phase minted at 60 degree Celsius. [14-17] The probable reason behind the formation of large unilamellar vesicles is that the slow vaporization of solvent results in an ether gradient extending towards the interface of aqueous- nonaqueous interface. The former may be responsible for the formation of bilayer structure. The disadvantages of this method are there a small amount of ether is frequently present in the vesicles suspension and is difficult to remove.




Schematic diagram of the preparation of niosomes via ether injection method [25]

## Miscellaneous Techniques

**Emulsion formation:** In initial step in this technique is the formation of an oil-in-water (o/w) emulsion from an organic solution of surfactant, cholesterol and an aqueous solution of the payload.[18] The organic solvent is than evaporated resulting in the formation of Niosomes dispersed in the aqueous phase.




Schematic diagram of the preparation of niosomes via emulsion method [27]

Niosomes Manufacture Using Micelles: Niosomes may also be developed from a mixed of micellar solution with the aid of enzymes. A mixture micellar solution of hexadecyl diglycerol (C16 G2), polyoxyethylene cholesteryl sebacetate diester (PCSD) and dicalcium hydrogen phosphate converts to a niosomes depression when incubated with esterase enzyme substrate. The PCSD is cleaved by the esterase to yield polyoxyethylene, sebacic acid and cholesterol, and cholesterol in combination with C16G2 and DCP then yields C16G2 niosomes.[19-20].

Lipid Injection: The lipid injection approach does not make use of expensive organic phases and is considered green. A mixture of lipids and surfactant are initially melted then subsequently injected into a highly agitated hot aqueous solution of payload. [21-22-23].

## Econazole Niosomes

Econazole is a imidazole antifungal agent used in the treatment of candida infections, fungal infections. Econazole niosomes was prepared by thin film hydration technique by varying the cholesterol and surfactant ratios as 1:1, 1:2, 1:3, 1:4 Each formulation was analyzed for drug releases.

## Steps involve in Formulation of Econazole Niosomes:

1. Cholesterol and span 80 is weighed accurately and were dissolved in chloroform-methanol mixture (1:1 v/v) in 100ml of RVF.
2. The weighed quality of drug is added to solvents mixture.
3. From the liquid phase the solvent mixture is removed by evaporation at 60°c.
4. A thin layer of was obtained on the walls of the flash which is rotating at the speed of 150rpm.
5. The solvent is completely removed by the help of vacum.
6. The dried lipid flim was obtained and was moisten with 5ml of phosphate buffer saline of pH 7.4 at a temp. of 60°C for one hour unit the formation of Niosomes.
7. The ratios of the formulation were 1:1, 1:2, 1:3, 1:4 of cholesterol: span 80. Batch code were A1 to A4.
8. Removal of unentrapped [28] drug from Niosomes by dialysis method.

The suspension of niosomes was placed on 3cm×8cm long dialysis bag. The dialysis bag was placed in 250ml of beaker having phosphate buffer saline of pH 7.4 with uniform stirring with the help of magnetic stirrer. Fresh buffer was added every 3 hours in Dialysis of 24 hours. [28-29]

Size analysis: By optical microscopy.

A drop on niosomes suspension was put on the glass slide and it was diluted. A cover slip was placed over the diluted niosomes suspension [30] and analysed the average vesicles size and shape by an ordinary optical microscopy using recablirated ocular eye piece micrometer [30].

The study of In-vitro release of niosomal formulation and analysis by U.V. method.

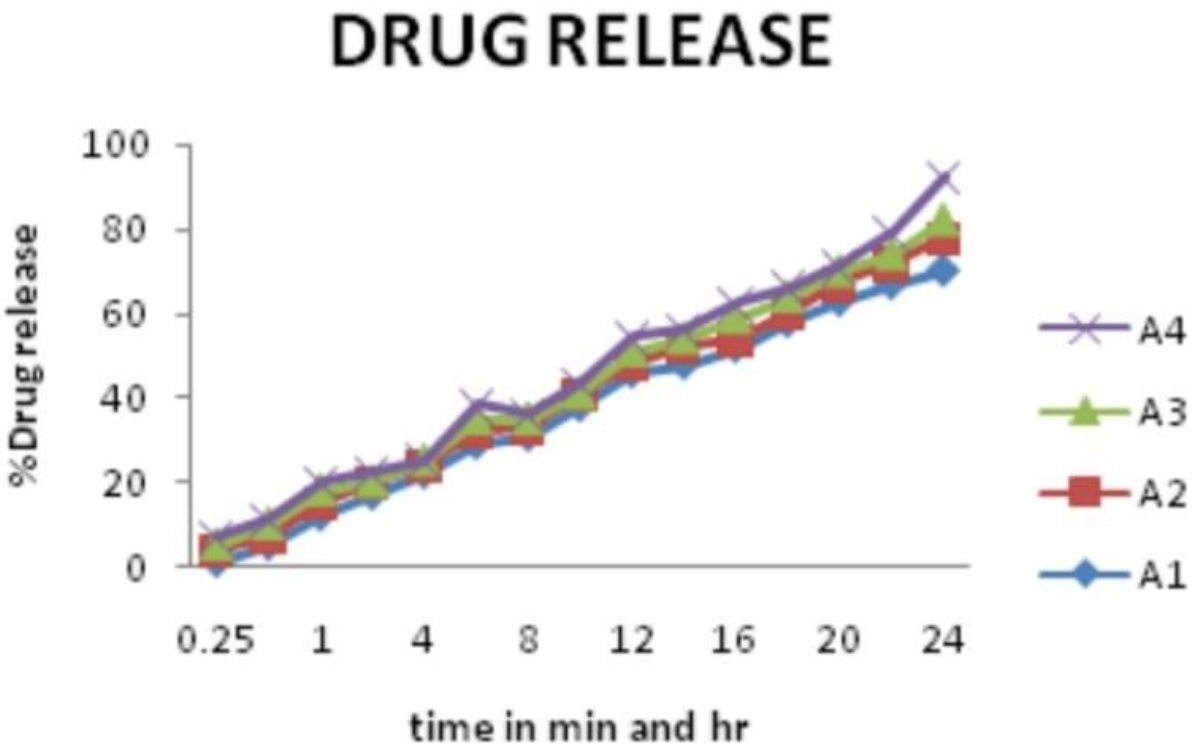
For the study of In-vitro release of niosomes formulation the niosomal preparation was taken in a dialysis membrane have a 5 cm in length and it was suspended in a beaker having 200ml of diffusion medium (Phosphate buffer saline pH 7.4). The temperature of medium was maintained at 37± 0.5°c [31] and was stirred at a constant speed by the help of magnetic stirrer. The sample of 2ml was withdrawn at every 24 hours for 8 days and replaced the diffusion medium, so that the volume of diffusion medium was maintained constant at 200 ml. The samples was analyzed by spectrophotometrically at 424nm. The release was compared with a market Econazole gel.

| Formulation code | Chole:span80 | Percentage entrapped drug | %Drug release |
|---|---|---|---|
| A1 | 1:1 | 62.5% | 70.10% |
| A2 | 1:2 | 71% | 77.89% |
| A3 | 1:3 | 88.23% | 82.18% |
| A4 | 1:4 | 98% | 92.10% |

Percentage Entrapped Drug & Percentage Drug Release

The In-vitro release was found to be bi-phasic as the release was controlled by the dialysis membrane and the lipid bilayer. Incorporation of cholesterol affected the release rate of the encapsulated drug.

Kinetics of drug release: The optimum formulation A4 was subjected to graphically treatment to assess the kinetics of drug release. A graphically representation of concentration versus time showed linearity in optimized formulation of Econazole Niosomes. Hence it follows zero order kinetics. This plot (Higuchi's plot) confirms that the release is diffusion mediated.




## Conclusion:

Recent advancement in the field of scientific research have resulted in the endorsement of small molecules such as proteins and vaccine as a major class of therapeutic agents. These, however, pose numerous drug-associated challenges such as poor bioavailability, physical and chemical instability and suitable route of drug delivery. Niosomes provide a promising carrier system in comparison with ionic drug carriers, which are relative toxic and unsuitable An effort was made to formulate the Econazole Niosomes incorporate the Niosomes into the gel. The graphically representation shows that A4 formulation was optimized one and found to follow zero order release. Researches are still going on to develop a suitable technology for large production because it is a promising targeted drug delivery system.

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