DRUG DISCOVERY

A curcumin loaded niosomes as novel drug delivery system by ether injection method

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ABSTRACT

Curcumin is a natural chemical which is produced by a plant called *Curcuma longa* species. Curcumin has been shown to be an antioxidant, anti-inflammatory, anti-viral, anti-bacterial, anti-fungal and anti-cancer activity. But the chemical structure of curcumin shows poor stability, low solubility and rapid degradation. To overcome this problem a novel niosomal drug delivery system was developed. Niosome vesicles are composed of cholesterol and non-ionic surfactants, in which both amphiphilic and lipophilic drugs can be encapsulated. It is a novel drug delivery in which the drug delivers to its target site. These are similar to liposomes but show more advantages over them. This article shows improving Stability, Solubility, its advantages and disadvantages, Methodology, characterization and evaluation of curcumin by niosomal formulation. In this study drug content was found to be 8.04mg/ml, Entrapment efficiency was found to be 95.2% and the percentage of drug release was 34.5% at 4th hour.

Keywords: Niosomes, Ether Injection Method, Novel Drug Delivery System, Curcumin

1. INTRODUCTION

Curcumin is a yellow pigment obtained from *Curcuma longa*; in spice turmeric, this is the main active compound. For spice and food-coloring agents, curcumin is used commonly. Due to its potent therapeutic qualities, curcumin is now used in the medical field (Rahman and Arisanty, 2015). Many therapeutic benefits of curcumin have been demonstrated, including its anticancer, anti-inflammatory, antioxidant, antimicrobial, anti-rheumatic and hepatoprotective effects (Alleman et al., 1998). Curcumin's oral administration has been restricted primarily because of its poor solubility in water at physiologically acidic pH levels. In addition, curcumin has poor absorption and quick metabolism, which results in low bioavailability and makes it susceptible to degradation in an alkaline environment. Consequently, it is essential to identify a different method of delivery for curcumin than oral dosing. Transdermal administration of curcumin is one of the best and most practical methods because it contains numerous benefits (Akbari et al., 2020).

Niosomes, a type of surfactant-based colloidal drug carrier, have been promoted as an effective formulation for transferring larger doses of medication via the skin and being able to release the drug at controlled rates for systemic

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absorption (Akbari et al., 2020). Niosomes size that ranges from 10 to 1000 nm. Niosomes have a bilayer structure which is amphiphilic in nature, which allows them to deliver hydrophilic drugs in the aqueous core and lipophilic drugs in the surfactant-based bilayer (Singh, 2013). Because they can encapsulate a variety of drugs with the intent to increase their stability and efficacy, niosomes can be used as an alternative to liposomes and polymersomes (Ge et al., 2019). Surfactants don't need to be handled or stored under any specific circumstances (Khan and Irchhaiya, 2016).

Components of Niosomes

Niosomes Mainly composed of Non-ionic surfactant and Cholesterol.

Non-ionic Surfactant

A non-ionic surfactant has a hydrophilic head group and a hydrophobic tail. The size of the niosome grows as the HLB value and consequently, the alkyl chain increases. As a result, HLB values 14–17 is inappropriate for niosome formulation. The highest entrapment efficiency is at HLB value 8. The non-ionic surfactant is ether-linked, a Di-alkyl chain surfactant, Sorbitan ester (Sanklecha et al., 2018).

Cholesterol

To provide non-ionic surfactants rigidity, cholesterol, a waxy steroid metabolite, is typically added. It is also known that cholesterol prevents leaks by preventing the transition from the gel to the liquid phase (Sanklecha et al., 2018).

Advantages of Niosomes

A sustained or controlled release of the drug is achievable. Surfactants exhibit biodegradable, biocompatible, non-toxic and non-immunogenic. Enhance the drug's stability while entrapped. Niosomes are amphiphilic in nature which can entrap both hydrophilic and lipophilic drugs. Low production cost and high chemical stability. These niosomes are more stable than the liposomes. They have great bioavailability when compared to conventional dosage form (Kaur and Kumar, 2018; Bhardwaj et al., 2020; Verma and Utreja, 2019).

Disadvantages of Niosomes

Niosomal delivery systems have several benefits; however, stability is a concern because the medication may hydrolyze in an aqueous suspension of niosomes. Niosome aggregation development and drug leakage from the entrapment site are other potential issues (Bhardwaj et al., 2020).

Methods of preparation

For formulating the niosomes so many methods are available they are:

1. Hand shaking method (Thin-film hydration method)
2. The bubble method
3. Ether injection method
4. Sonication method
5. Reverse phase Evaporation method

Hand-Shaking technique (Thin Film-Hydration method)

A thin film hydration method was prepared for forming nanosized vesicles for topical application. For the preparation of niosomes, weigh the required quantity of drug, cholesterol and non-ionic surfactant. This was dissolved in a volatile organic solvent (diethyl ether, Chloroform or methanol) in a clean round bottom flask. This mixture was kept in a rotary vacuum evaporator at room temperature to remove the organic solvent. This will lead to a thin film formation on the wall of the flask. After this, the film was dehydrated with an aqueous phase at 0-60°C with gentle stirring. This will lead to the form of multilamellar niosomes (Singh, 2013).

The bubble method

The bubble method was prepared in a round bottom flask which consists of three necks. This was kept in a water bath to control the temperature. Nitrogen is supplied through the third neck and the first and second necks include a water-cooled reflux and thermometer. In the buffer (PH 7.4), cholesterol and surfactant are dispersed simultaneously, the dispersion is mixed for 15 seconds

with a high shear homogenizer and then the dispersion is immediately "bubbled" at 70°C using nitrogen gas to produce niosomes (Sharma et al., 2018).

Ether Injection Process

The Ether injection process is done by slowly injecting the niosomal ingredients into the ether through a 14-gauge needle at an approximate rate into the aqueous phase which is pre heated at 60°C (Shirsand and Keshavshetti, 2019). Ether vaporization leads to the formation of vesicles, whose diameter can range from 50 to 1000 nm depending on the conditions (Singh, 2013).

Sonication Method

The Sonication method was prepared by adding a drug solution to the buffer. This was added in a 10ml glass vial which contains a surfactant/ Cholesterol mixture. This mixture was subjected to probe sonication for 3 min at 60°C (Xu et al., 2016).

Reverse Phase Evaporation Method

The Reverse phase evaporation method was prepared with two phases in organic phase cholesterol and surfactant (1:1) was dissolved in the mixture of ether and chloroform. In the second phase (aqueous phase) the drug was added. Then the organic phase was added to the aqueous phase and was sonicated at 4-5°C. After the clear gel formation, it was subjected to further sonication. To this, a small quantity of Phosphate buffer was added. At low pressure of 40°C the organic phase was removed. Then the formed suspension was diluted with a phosphate buffer and heated at 60°C for 10 min in a water bath. This will lead to forming the niosomes (Shirsand and Keshavshetti, 2019).

2. METHODOLOGY

Preparation of Curcumin Niosomes by ether injection method

Curcumin niosomes were prepared by ether injection method. A fixed amount of Non-ionic surfactant was taken along with Cholesterol and dissolved in 6 ml of diethyl ether which is mixed with 2 ml of ethanol containing the weighed amount of the drug. Then the releasing solution was slowly injected using a micro syringe at a rate of 1 ml/min into 10 ml hydrating phosphate buffer solution. Then the solution was stirred continuously using a magnetic stirrer and the temperature was maintained at 60-65°C. As the lipid solution was injected slowly into the aqueous phase the difference in temperature between the two phases causes rapid vaporization of ether resulting in the formation of niosomes.

Table 1 Materials

Ingredients	Quantity
Curcumin	100mg
Span-20	100mg
Ethanol	2ml
Diethyl Ether	6ml
Buffer	10ml

Characteristics

Particle Size

The particle size of niosomes was measured by using dynamic light scattering (DLS) and morphology was examined by TEM (Transmission electron microscopy) (Rungphanichkul et al., 2011)

Vesicle size and size distribution analysis

The vesicle size and size determination were determined by laser light scattering method with particle size analyzer (Mujariya et al., 2011).

Morphology

Using cryo preparation equipment, the niosome dispersion was rapidly frozen in liquid propane. At -150° C, the frozen sample was broken up in the freezer replicating equipment. Platinum was evaporated at an angle of 45° C to simulate the fracture surface.

Carbon was then added to strengthen the replica. It was cleaned with acetone and water and then put on a 150-mesh copper grid. With the use of a transmission electron microscope, the vesicles were examined

Stability Studies

For stability study, the niosomes were stored in sealed airtight containers at different temperatures. The niosomal sample was collected at regular intervals that is, 0, 1, 2 and 3 months and surface characteristics and color change this sample was observed and analyzed by UV spectrophotometer (Sharma et al., 2018).

Evaluation

Drug Content

1 ml of suspension was taken into 10 ml of volumetric flask and made up to the volume with 9 ml of methanol. Shake for 15-20 min and check absorbance in the UV spectrophotometer.

$$\text{Drug content} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Entrapment Efficiency

Take 1ml of suspension and dissolve in 9 ml of 7.4 PH buffer. Sample was poured into the centrifuge tube and kept for ultracentrifugation for 45 min at 17000 rpm. The supernatant was collected and absorbance was determined by UV spectrophotometer.

$$\%\text{Entrapment efficiency} = \frac{\text{Total drug added} - \text{un entrapped drug}}{\text{Total drug added}} \times 100$$

Diffusion Study

The diffusion Study was conducted in Franz diffusion cell. This contains a donor and receptor chamber. The preparation is placed in the donor chamber and in between the chamber membrane was placed. The samples are retrieved from the medium with suitable intervals and were analyzed by UV and percentage drug release is estimated.

3. RESULTS AND DISCUSSION

Optical Microscopy

The Niosomes are observed under a projection microscope. The vesicles are obtained like Uni-lamellar and multi-lamellar structure (Figure 1).

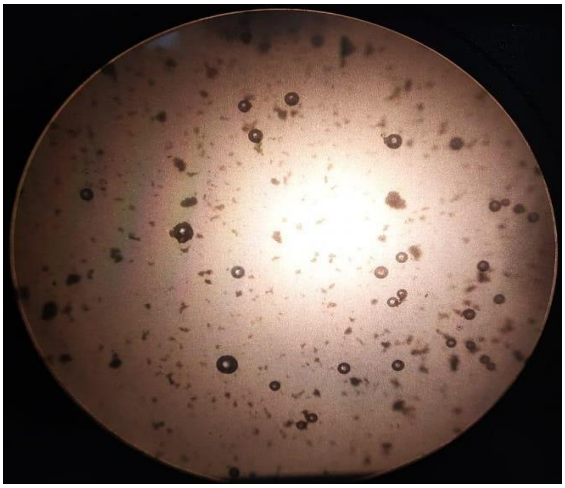

Figure 1 Vesicles of Curcumin Niosomes

Drug content was found to be 8.04 mg/ml and the entrapment efficiency was found to be 95.2%. The diffusion studies were done by Franz diffusion cell by taking 7.4 phosphate buffers. The amount of drug release was done in a period of 5 hours and the percentage of drug release was 34.5% at 4th hour (Figure 2).

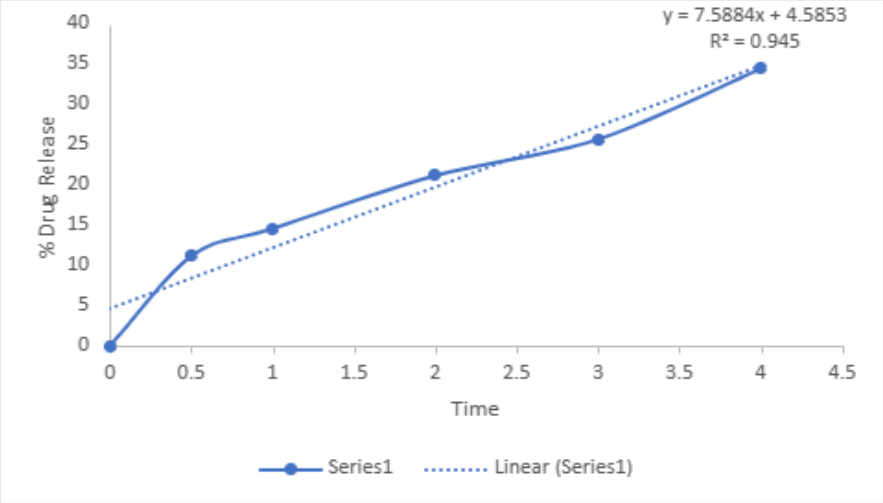

Figure 2 In vitro drug release of the formulation

4. CONCLUSION

Curcumin is low soluble and low stable and shows toxicity when consumed orally due to that niosomal formulation was developed. These niosomes are biochemically stable and have high entrapment efficiency and this can encapsulate the poorly soluble drugs. These are the effective alternative methods of curcumin for both transdermal as well as topical drug delivery. In this study, the curcumin loaded niosomes were successfully prepared by ether injection method and it showed sustained and prolonged release of drug and 34.5% of drug was released at 4th hour.

Informed consent

Not applicable.

Ethical approval

Not applicable.

Conflicts of interests

The authors declare that there are no conflicts of interests.

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The study has not received any external funding.

Data and materials availability

All data associated with this study are present in the paper.

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