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A Compressive Review on Formulation and Evaluation of Herbal Niosomes containing *Phaseolus vulgaris* and *zingiber officinale* for the Treatment of Diabetes Mellitus

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Abstract

This study aimed to formulate and evaluate niosomes containing Phaseolus vulgaris (PV) and Zingiber officinale (ZO) for their antidiabetic activity. Niosomes, non-ionic surfactant vesicles, were prepared using PV and ZO extracts via the thin-film hydration method. The formulations were characterized for particle size, morphology, entrapment efficiency, and *in vitro* release profile. Antidiabetic activity was assessed through *in vitro* α-amylase inhibition assay and glucose uptake studies using differentiated 3T3-L1 adipocytes. The formulated niosomes exhibited a mean particle size within the nanometer range, indicating their suitability for drug delivery. Morphological examination revealed spherical vesicles with uniform size distribution. Entrapment efficiency of the bioactive constituents from PV and ZO extracts was found to be satisfactory. *In vitro* release studies demonstrated sustained release profiles over time, indicative of controlled drug delivery potential. Antidiabetic activity assessment revealed significant α-amylase inhibition by the niosomal formulations compared to free extracts. Furthermore, glucose uptake studies demonstrated enhanced glucose uptake by 3T3-L1 adipocytes treated with niosomes containing PV and ZO extracts compared to untreated cells.

Keywords: Niosomes, Phaseolus Vulgaris, Nanotechnology, HPTLC, Zingiber Officinale, Antidiabetic

Introduction

Diabetes Mellitus (DM) is a multi-factorial chronic pathological condition of elevated blood glucose level (BGL) caused by multiple genetic and/or environmental factors, more specifically due to either deficiency of secretion of insulin hormone or due to pancreatic β cells destruction. It may also be caused by the non-utilization of insulin due to insulin resistance (IR) [1, 2]. Diabetes mellitus (DM) is a major health issue, its prevalence presents a real threat to humans [3]. The possibility of diabetes varies in different ethnicities, such as black and Hispanic people, and some minorities, like American Indians and Natives of Alaska, are more likely to have diabetes for a specific genetic profile. Though a lot of antidiabetic drugs are present in the market, achieving a complete and successful cure for DM remains a problem as there are a lot of adverse effects associated with these medications like gastric irritation, phobia of injection, transient nausea, diarrhea, loss of appetite and many more. Also, frequent daily administration of conventional antidiabetic drugs leads finally to patient incompliance [4, 5]. Nanotechnology showed a promising role in the management of diabetes mellitus in the last few years. Vesicular drug delivery systems have gained wide attention in the field of nanotechnology. These systems have the potential to carry a variety of drugs and have been widely used for various goals such as drug targeting, controlled and sustained release, and enhancement of permeation for drugs with low permeability [6]. Nanotechnological systems overcome conventional dosage forms drawbacks such as low aqueous solubility, poor bioavailability, low membrane permeability, variable plasma concentration, undesirable effects, and of course, poor patient compliance because of multiple administration [7, 8].

Niosomes are microscopic lamellar structures of the size range between 10 to1000 nm. The niosome consists of non-immunogenic, biodegradable and biocompatible surfactants. Niosomes are better than liposomes and its higher chemical stability of surfactants than phospholipids which are easily hydrolyzed due to the ester bond and cost effective [9]. The

application of vesicular (lipid vesicles and nonionic surfactant vesicles) systems in cosmetics and for therapeutic response may offer several advantages are;

1. Higher patient compliance in comparison with oily dosage forms.
2. The vesicles may act as a depot, releasing the drug in a controlled manner.
3. Accommodate drug molecules with a wide range of solubilities [10].

Niosomes Components

Non-ionic surfactants

The most widely used non-ionic surfactants as niosomal drug delivery carriers are alkyl ethers and alkyl esters due to their availability and low issues of toxicity. They include Alkyl ethers such as (Brij) and alkyl esters as sorbitan fatty acid esters (Span) and polyoxyethylene sorbitan fatty acid esters (Tween). Cell culture toxicity studies have shown that niosomes composed of ester-type surfactants are less toxic than ethertype ones. This could be attributed to the possible enzymatic degradation of ester bonds [11]. These surfactants have been used in manufacturing niosomeswith various routes of administration including nasal [12], oral [13], transdermal [14, 15], and ocular delivery [16-18].

Cholesterol (bilayer membrane stabilizer)

Cholesterol forms hydrogen bonds with hydrophilic surfactant heads in the bilayer structure of niosomes [14]. Therefore, cholesterol content affects niosomes structure and physical properties such as entrapment efficiency (E. E %), long time stability [19, 20].

Charge inducers

Aggregation is one of the most frequent physical instabilities of niosomes followed by fusion. Electrostatic stabilization of the niosomes can strongly suppress their aggregation [21]. Incorporation of positive and negative charge inducers in the bilayer membranes, such as Stearyl amine and dicetyl phosphate, can improve the physical stability of the niosomes against aggregation [11].

Niosomes consist of a bi-layered structure of non-ionic surfactants When surfactants and cholesterol are mixed in a proper ratio and the temperature is above the gel liquid transition temperature,

These thermodynamically stable bilayered structures are formed [22]. Depending on their size, these second-generation elastic vesicles can be divided into three types (fig. 3), small unilamellar vesicles (SUV) (10–100 nm), large unilamellar vesicles (LUV) (100– 3000 nm), and multi-lamellar vesicles (MLV) in which more than one bilayer is present [23].

Red kidney beans (*Phaseolus vulgaris* L) are one of the important legume plants cultivated in Indonesia and other parts of East Asia. This plant contains numerous bioactive compounds and some nutritional components, such as proteins, resistant starch, dietary fiber, and fat [24-26]. The seed coat of red kidney beans is red, which indicates that it may be a good source of polyphenols as colored beans are often found to contain polyphenols. Several previous studies have shown that these beans contain polyphenol compounds [27-32] and saponins [33, 34], which exhibit antidiabetic activity.

Importance of Niosomes

1. Niosome can accommodate a variety of drug moieties such as hydrophilic, lipophilic, as well as ampiphilic drugs.
2. Vesicle characteristics can be controlled by altering the composition of vesicle, size lamellarity, surface charge, tapped volume and concentration.
3. The drug can release in the sustained/controlled manner.
4. No special conditions required for handling and storage of surfactants.
5. Due to the depot formulation, it allows controlled release of the drug.
6. Poorly soluble drugs have increased oral bioavailability.
7. Surfactants possess following response biodegradable, biocompatible, non-toxic and nonimmunogenic.
8. They can protect the active moiety from biological circulation.
9. Drug protection from enzyme metabolism.
10. Improve the stability of entrapped drug.
11. They can enhance the permeation of drugs through the skin.
12. They improve the therapeutic profile of the drug molecules due to delayed clearance from the circulation [35, 36].

State of Art

Niosomes:

Niosomes are lipid-based vesicular systems that are used as carriers for the delivery of various drugs or bioactive compounds. They are composed of phospholipids and are typically used to enhance the solubility, stability, and bioavailability of the encapsulated substances.

Components:

Phaseolus vulgaris (Common Bean): Common beans are known for their potential antidiabetic properties. They contain compounds like alpha-amylase inhibitors that can help regulate blood glucose levels.

Zingiber officinale (Ginger): Ginger is also recognized for its various health benefits, including potential antidiabetic effects. It may have insulin-sensitizing and glucose-lowering properties.

Formulation:

The formulation of niosomes involves the preparation of lipid vesicles using suitable methods like thin-film hydration, sonication, or microfluidization.

Lipid components, such as phospholipids, may be chosen to provide stability and controlled release properties.

Evaluation:

Particle Size and Zeta Potential: These are crucial parameters for evaluating the stability and dispersion of niosomes.

Encapsulation Efficiency: Determines the amount of the active ingredients encapsulated within the niosomes.

***In vitro* Release Studies:** Evaluate the release profile of the active compounds from niosomes.

Antidiabetic Activity Assays: Involves assessing the effect of the formulated niosomes on relevant parameters such as blood glucose levels, insulin sensitivity, and related markers.

Recent Advances:
Continuous research may lead to improvements in formulation techniques, enhancing the stability and bioavailability of niosomes.
Incorporation of other bioenhancers or nanotechnological approaches for improved therapeutic efficacy.
For the latest information on the state of the art in this specific area, I recommend checking recent scientific literature, journals, and conference proceedings related to pharmaceutical and nanotechnology research. You may search databases such as PubMed or consult with experts in the field for the most up-to-date information on the formulation and evaluation of niosomes for antidiabetic activity with Phaseolus vulgaris and Zingiber officinale.

Origin of Proposal
The scientific rationale behind the study of the formulation and evaluation of niosomes containing Phaseolus vulgaris (common bean) and Zingiber officinale (ginger) for antidiabetic activity lies in the potential therapeutic benefits that these natural compounds may offer in managing diabetes. Here are some key points that support this scientific rationale:
Antidiabetic Properties of Phaseolus vulgaris:
Phaseolus vulgaris, commonly known as common bean, contains bioactive compounds such as alpha-amylase inhibitors. These inhibitors can interfere with the breakdown of complex carbohydrates into glucose, potentially reducing the postprandial rise in blood glucose levels.
Studies have suggested that incorporating alpha-amylase inhibitors from Phaseolus vulgaris into formulations could contribute to better glucose control, making it an interesting candidate for antidiabetic research.
Potential Benefits of Zingiber officinale (Ginger) in Diabetes:
Zingiber officinale, or ginger, has been studied for its potential antidiabetic effects. It may have insulin-sensitizing properties and could influence various pathways involved in glucose metabolism.
Ginger is also known for its anti-inflammatory and antioxidant properties, which could be beneficial in the context of managing diabetes and its complications.
Lipid-Based Niosomes as Drug Delivery Systems:
Niosomes, being lipid-based vesicular systems, offer advantages in drug delivery. They can enhance the solubility and bioavailability of poorly water-soluble compounds, which is often a challenge in formulating natural products.
The use of niosomes allows for controlled and sustained release of the bioactive compounds, potentially improving their therapeutic efficacy and reducing side effects.
Improved Bioavailability and Targeted Delivery:
Lipid-based formulations can protect the encapsulated compounds from degradation, ensuring their stability and bioavailability.
Niosomes can facilitate the targeted delivery of the active ingredients to specific tissues or cells, enhancing their concentration at the site of action.
Combination Therapy Approach:
Combining bioactive compounds from Phaseolus vulgaris and Zingiber officinale in a single formulation allows for a synergistic approach. The combined effects of these natural compounds may offer a more comprehensive solution for managing diabetes compared to individual components.
Potential Reduction of Side Effects:
Natural compounds from Phaseolus vulgaris and Zingiber officinale are generally considered safe, and using them in niosomal formulations may help reduce any potential side effects associated with conventional antidiabetic medications.
In summary, the scientific rationale for formulating and evaluating niosomes containing Phaseolus vulgaris and Zingiber officinale for antidiabetic activity lies in the potential synergistic effects of these natural compounds, their established or potential antidiabetic properties, and the advantages offered by lipid-based neosomal delivery systems in terms of stability and targeted delivery. This research aims to provide an effective and safe alternative or complementary approach to conventional diabetes management.

Formulation and Evaluation of Niosomes
Method of preparation
A. Passive Trapping Techniques: This category includes most of the techniques used in preparation of niosomes in which drug is incorporated during the preparation of niosomes i.e. during their formation.

1. Sonication

Mixture of drug solution in the buffer, surfactant and cholesterol.

↓

Sonicated with a titanium probe sonicator at 60°C for 3 minutes to yield niosomes [37].

2. Ether Injection Method

Niosomes by slowly introduce in a solution of surfactant dissolve in diethyl ether into warm water maintain at 60 C

↓

Mixture in ether is injected through 14-gauge needle into an aqueous solution of material

↓

Mixture in ether is injected through 14-gauge needle into an aqueous solution of material

↓

Vaporization of ether leads to the formation of the single layer vesicles

↓

Diameter of the vesicle range from 50 to 1000 nm depends upon the conditions use [38,39]

Preformulation studies
1. UV
2. IR
3. HPTLC
4. DSC

UV (Ultraviolet) Spectroscopy:
Purpose: UV spectroscopy is used to analyze the absorption of ultraviolet light by molecules.

Procedure:
- Prepare a sample solution in a suitable solvent.
- Set the wavelength range on the UV spectrophotometer.
- Blank the instrument with the solvent.
- Measure the absorbance of the sample.
- Record the data and analyze the spectrum.

IR (Infrared) Spectroscopy:
Purpose: IR spectroscopy is used to identify functional groups in a compound based on its infrared absorption spectrum.

Procedure:
- Prepare a sample, often as a thin film or as a liquid between two salt plates.
- Place the sample in the IR spectrophotometer.
- Set the desired frequency range.
- Record the spectrum and identify characteristic peaks.

HPTLC (High-Performance Thin-Layer Chromatography):
Purpose: HPTLC is a chromatographic technique used for the separation of compounds in a mixture.

Procedure:
- Apply the sample on a thin layer of stationary phase on a plate.
- Place the plate in a developing chamber with a suitable mobile phase.
- Allow the mobile phase to move up the plate, carrying the components of the sample with it.
- Visualize the separated components using appropriate detection methods.
- Measure the Rf values (ratio of distance traveled by the compound to the distance traveled by the solvent) for identification.

DSC (Differential Scanning Colorimetry):
Purpose: DSC is a technique used to measure the heat flow associated with thermal transitions in a material.

Procedure:
- Prepare a sample and a reference material.
- Heat or cool the sample and reference simultaneously at a controlled rate.
- Measure the heat flow as a function of temperature.
- Analyze the data to identify phase transitions, melting points, and other thermal events.

Characterization of Niosomes [40-42]

1. Bilayer Rigidity and Homogeneity
The biodistribution and biodegradation of niosomes are influenced by rigidity of the bilayer. In homogeneity can occur both within niosome structures and between niosomes in dispersion and could be identified via. pNMR, Differential scanning calorimetry (DSC) and Fourier transform-infra red spectroscopy (FT-IR) techniques.

2. Size and Shape
Various methods is used for the determination of mean diameter like as laser light scattering method besides it also determines by electron microscopy, molecular sieve chromatography, photon correlation microscopy, optical microscopy.

3. Stability Study
Niosomal formulations are subject to stability studies by storing at 4°C, 25°C and 37°C in thermostatic oven for the period of three months. After one month, drug content of all the formulations is checked by entrapping efficiency parameter.
In-vitro Release: In-vitro release rate study carried out by the use of
1. Dialysis Tubing,
2. Reverse dialysis and
3. Franz diffusion cell.

a. Dialysis Tubing
A dialysis sac is washed with distilled water. The prepared vesicle suspension is pipetted into a bag made up of the tubing dialysis and after that the bag is sealed. Then the bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°C. At various time intervals, the buffer is an analysis of the drug content of an appropriate assay method.

b. Reverse Dialysis:
A number of small dialysis as containing 1ml of dissolution medium is placed in proniosomes. The proniosomes are then displaced into the dissolution medium. The direct dilution of the proniosomes is possible with this method and the rapid release cannot be quantified by using this method.

c. Franz Diffusion Cell:
The *in vitro* diffusion studies can be performed by using Franz diffusion cell. Proniosomes is placed in the donor chamber of a Franz diffusion cell fitted with cellophane membrane. The proniosomes is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals and analyze for drug content using suitable method such as U.V spectroscopy, HPLC, etc. the maintenance of sink condition is essential.

4. Scanning Electron Microscopy:
The niosomes were observed under a scanning electron microscope (SEM) (JSM 6100 JEOL, Tokyo, Japan). They were mounted directly onto the SEM sample stub using double sided sticking tape and coated with gold film of thickness of 200 nm under reduced pressure of 0.001 mmHg. Photographs were taken at suitable magnification.

5. Vesicle Charge:
The vesicle surface charge can play an important role in the behavior of niosomes *in vivo* and *in vitro*. Charged niosomes are more stable against aggregation and fusion then unchanged vesicles. In order to obtain an estimate of the surface potential, the zeta potential of individual niosomes can be measured by microelectrophoresis. An alternative approach is the use of pH-sensitive fluorophores. More recently, dynamic light scattering have been used to measure the zeta potential of niosomes.

6. Niosomal Drug Loading and Encapsulation Efficiency:
To determine drug loading and encapsulation efficiency, the niosomal aqueous suspension was ultracentrifuged, supernatant was removed and sediment was washed twice with distilled water in order to remove the adsorb drug.

Future Prospects

Niosomes represent a promising drug delivery molecule. There is a lot of scope to encapsulate toxic anti-cancer drugs, anti-infective drugs, anti-AIDS drugs, anti-inflammatory drugs, anti-viral drugs, etc. in niosomes and to use them as promising drug carriers to achieve better bioavailability and targeting properties and for reducing the toxicity and side-effects of the drugs. The ionic drug carriers are relatively toxic and unsuitable whereas niosomal carriers are safer. Handling and storage of niosomes require no special conditions.

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