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Nanostructured Lipid Carrier-Based Mucoadhesive Gel for the Management of Aphthous Stomatitis: Formulation Strategies and Evaluation Approaches

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Abstract:

- ***Background***

Aphthous stomatitis is a recurrent inflammatory disorder of the oral mucosa associated with painful ulcers that affect normal activities such as eating and speaking. Conventional oral formulations show limited effectiveness because they are rapidly removed from the oral cavity. Nanostructured lipid carrier (NLC)-based mucoadhesive gels have emerged as a promising strategy for improving drug retention, stability, and localized therapeutic action.

- ***Aim***

The aim of the present study was to formulate and optimize a Lycopene and Coenzyme Q10-loaded NLC mucoadhesive gel for the treatment of aphthous stomatitis and to evaluate its physicochemical and therapeutic properties.

Keywords: *Aphthous Stomatitis; Nanostructured Lipid Carriers; Mucoadhesive Gel; Lycopene; Coenzyme Q10; Box–Behnken Design; Buccal Delivery; In Vivo Study.*

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I. INTRODUCTION

Aphthous stomatitis, also referred to as recurrent oral ulcers or canker sores, is a frequently occurring inflammatory disorder of the oral mucosal tissue. It is characterized by painful ulcerative lesions that cause discomfort during eating, speaking, and swallowing. The exact cause of aphthous stomatitis is not fully understood, but factors such as stress, nutritional deficiencies, microbial infection, hormonal imbalance, and immune dysfunction are considered responsible for its development. Conventional treatments including corticosteroids, antiseptics, and analgesics provide only temporary relief because of poor retention time in the oral cavity due to saliva and tongue movement.(Benahmed, 2021)

Mucoadhesive drug delivery systems have gained attention for the treatment of oral ulcers because they can adhere to the oral mucosa and prolong the residence time of the drug at the site of action. Mucoadhesive gels enhance drug retention at the site of application, increase local drug availability, improve therapeutic effectiveness, and minimize the need for frequent administration. (Sharma & Yadav, 2022) Recently, Nanostructured Lipid Carriers (NLCs) have attracted significant interest as advanced drug delivery systems because of their biocompatibility, high drug incorporation efficiency, controlled release behavior, and improved stability. These carriers consist of a blend of solid and liquid lipids stabilized with surfactants, which contribute to enhanced drug permeation and bioavailability.(Suharyani et al., 2021)

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The incorporation of NLCs into mucoadhesive gels combines the advantages of nanotechnology and mucoadhesion, resulting in prolonged drug retention, sustained release, improved permeation, and better management of aphthous stomatitis. Therefore, NLC-based mucoadhesive gels represent a promising approach for effective localized treatment of oral ulcers with enhanced patient compliance and therapeutic outcomes. (Müller, 2007)

II. MATERIALS AND METHODS

The materials used in this study included Sorbitan monooleate (Span 80), polyoxyethylene (20) sorbitan monooleate (Tween 80), oleic acid, methylcobalamin (a biologically active form of Vitamin B12), and double-distilled water.

Furthermore, lycopene and coenzyme Q10 were selected as active pharmaceutical ingredients due to their potent antioxidant activity and potential therapeutic benefits in the management of oral aphthous stomatitis. Chloroform was utilized as the organic solvent to improve the solubility of the lipophilic drugs. Oleic acid served as the liquid lipid, whereas glycerol monostearate (GMS) was selected as the solid lipid component for the preparation of nanostructured lipid carriers (NLCs). Tween 80 and Span 80 acted as surfactants to enhance the stability and uniformity of the formulation. All chemicals and reagents used throughout the study were of analytical grade and were applied without any additional purification.

A. Nanostructured Lipid Carrier (NLC):

Nanostructured lipid carriers (NLCs) have gained considerable interest over the past few decades as an advanced drug delivery system because of their excellent biocompatibility, biodegradability, enhanced bioavailability, and improved storage stability. In addition, these carriers are capable of protecting chemically unstable drugs from degradation while also enabling sustained and controlled drug release. (Okonogi & Riangjanapatee, 2015)

NLCs are nanosized lipid-based delivery systems prepared using a combination of solid lipids and liquid lipids. This unique lipid matrix is particularly suitable for incorporating hydrophobic or poorly water-soluble drugs, thereby improving their solubility, stability, and therapeutic performance. Generally, solid lipids are combined with liquid lipids or oils to create an imperfect lipid matrix, which enhances drug incorporation and improves formulation stability when compared with conventional lipid-based carriers such as liposomes. Owing to their nanoscale particle size, NLCs can enhance drug absorption, improve therapeutic efficacy, and minimize adverse effects through site-specific drug delivery.

Furthermore, nanoparticulate carriers have emerged as highly promising systems for drug delivery due to their unique physicochemical characteristics and nanoscale dimensions. These systems offer several advantages, including protection of active pharmaceutical ingredients from environmental factors such as moisture, enzymatic degradation, and physiological pH conditions. They also contribute to enhanced bioavailability, reduced drug dosage requirements, controlled and prolonged drug release, extended circulation time, improved cellular uptake, and targeted delivery to specific tissues or organs through surface modification techniques. (Khosa et. Al., 2018)

➢ *Component of NLC*

Nanostructured lipid carriers (NLCs) are composed of solid lipids, liquid lipids, surfactants, co-surfactants, and an aqueous phase. These components produce a stable nanoscale drug delivery system capable of enhancing drug entrapment and providing controlled release characteristics.(Salvi & Pawar, 2019)

- *Solid Lipids:*

Solid lipids form the core matrix of NLCs and remain solid at room and body temperature. They provide stability and control drug release. Common examples include glyceryl monostearate, stearic acid, cetyl palmitate, and Compritol® 888 ATO.

- *Liquid Lipids:*

Liquid lipids or oils are mixed with solid lipids to create imperfections in the lipid matrix, which increases drug loading capacity and reduces drug expulsion. Oleic acid, Miglyol®, castor oil, and olive oil are commonly used liquid lipids.

- *Surfactants:*

Surfactants stabilize the NLC dispersion by reducing interfacial tension and preventing aggregation of nanoparticles. Tween 80, Poloxamer 188, lecithin, and Tween 60 are widely used surfactants.

- *Co-surfactants:*

Co-surfactants further improve stability and help in the formation of uniform nanoparticles. Span 80, ethanol, and propylene glycol are commonly used co-surfactants.

- *Aqueous Phase:*

The aqueous phase acts as the dispersion medium and generally consists of purified or double-distilled water containing dissolved surfactants.

➢ *Advantage of NLC*

- High drug loading capacity.
- Improved stability of encapsulated drugs.
- Controlled and sustained drug release.
- Enhanced bioavailability of poorly soluble drugs.
- Biodegradable and biocompatible nature.
- Better penetration and retention at the target site.
- Reduced drug leakage during storage.
- Suitable for multiple routes of administration.

B. Mucoadhesive Gel

Mucoadhesive gels are widely used in buccal drug delivery because they increase the residence time of the formulation at the site of application and improve local therapeutic action within the oral cavity. Conventional oral

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formulations are easily removed by saliva, swallowing, and tongue movement, which reduces their effectiveness. In comparison, mucoadhesive gels can firmly adhere to the buccal mucosa, providing prolonged drug retention and improved drug availability.

Buccal gels also offer advantages such as simple formulation, good patient acceptability, flexibility, and biocompatibility. They spread easily over the mucosal surface and promote rapid drug release while maintaining strong adhesion to the application site. Furthermore, these gels are generally safe and are removed naturally from the body with minimal irritation or adverse effects.

C. NLC-Loaded Mucoadhesive Gel Preparation Method

➢ *Step 1: Nanostructured Lipid Carrier Preparation:*

Nanostructured lipid carriers (NLCs) were prepared by the solvent injection method. The solid lipid, liquid lipid, and drug were dissolved in an organic solvent and heated above the melting point of the lipid phase. Separately, the aqueous phase containing surfactant was heated to the same temperature.

The organic phase was slowly injected into the aqueous phase under continuous stirring, resulting in the formation of lipid nanoparticles due to rapid solvent diffusion. The dispersion was further stirred to remove the organic solvent and cooled to room temperature to obtain stable NLCs.(Gomaa et al., 2023)

➢ *Step 2: Gel Base Preparation:*

The mucoadhesive gel base was prepared by dispersing the required quantity of polymer such as Carbopol 934 or HPMC in purified water with continuous stirring. The dispersion was allowed to hydrate completely for several hours to obtain a clear gel base. Additional excipients such as glycerine, preservatives, and pH-adjusting agents were incorporated into the formulation. The pH was adjusted to an appropriate range suitable for buccal application.

➢ *Step 3: Encapsulation of NLC into GEL:*

The prepared NLC dispersion was gradually incorporated into the gel base under gentle stirring to obtain a uniform NLC-loaded mucoadhesive gel. Mixing was continued until a homogeneous gel was formed without air entrapment. The final formulation was stored in a closed container for further evaluation studies.(Selvamuthukumar & Velmurugan, 2012)

D. Formulation Optimization Using DoE:

A three-factor, three-level Box–Behnken Design (BBD) was utilized to optimize the formulation of Lycopene and Coenzyme Q10 (CoQ10)-loaded Nanostructured Lipid Carrier (NLC) gel and to evaluate the influence of formulation variables on its physicochemical characteristics and performance. The Box–Behnken experimental design is an efficient statistical approach for the development of quadratic models and response surface analysis. The experimental design and data analysis were carried out using Design-Expert® software version 13 (Stat-Ease Inc., USA). (Kim et al., 2019)

Based on preliminary trials and literature findings, three independent formulation variables were selected for optimization:

➢ Independent Variables (Factors)

- Amount of Glyceryl Monostearate (GMS) (mg) – solid lipid
- Amount of Oleic Acid (µl) – liquid lipid
- Amount of Span 80 (µl) – surfactant

These formulation factors were investigated at three different levels to determine their effect on the characteristics of the prepared NLC gel formulation.

E. Characterization of NLC-Loaded Mucoadhesive GEL:

- Particle size analysis
- Polydispersity index (PDI) determination
- Zeta potential measurement
- pH determination
- Viscosity measurement
- Spreadability study
- In vitro drug release study
- Stability study

III. IN-VIVO STUDY

➢ *Animal Model*

The experimental study was conducted after receiving approval from the Institutional Animal Ethics Committee (IAEC). Healthy Wistar Rat were procured from the animal House. All experimental procedures were performed in accordance with the guidelines of the Committee for the Control and Supervision of Experiments on Animals (CPCSEA), India.

The animals were maintained under standard laboratory conditions at a temperature of 23–25°C with relative humidity ranging between 50–60%, along with a 12-hour light and dark cycle. Standard pellet feed and water were provided ad libitum throughout the study period.(Ali & Rasool, 2011)

➢ *Experimental Design*

The animals were randomly divided into four experimental groups, with six animals in each group.

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Table 1 Experimental Design

Species	Strain	Age	Body Weight	Sex
Rats	Wistar Rats	8–10 Weeks	200–250 g	Either sex

Group (n = 6)	Treatment Schedule
Group 1 – Control Group	No ulcer induction
Group 2 – Negative Control Group	Ulcer induced without treatment
Group 3 – Standard Treatment Group	Administration of Orasore Gel twice daily
Group 4 – Test Formulation Group	Administration of Lycopene & CoQ10 NLC Gel twice daily

IV. CONCLUSION

The present study successfully developed a Lycopene and Coenzyme Q10-loaded Nanostructured Lipid Carrier (NLC)-based mucoadhesive gel for the treatment of aphthous stomatitis. The formulation combined the advantages of NLCs and mucoadhesive gels, resulting in prolonged retention, improved drug stability, and sustained drug release at the site of application.

Optimization using the Box–Behnken Design helped in obtaining a stable formulation with suitable physicochemical properties. Characterization studies confirmed acceptable particle size, pH, viscosity, spreadability, and stability of the prepared gel.

In vivo studies demonstrated improved ulcer healing and better therapeutic performance of the developed formulation. Therefore, the NLC-loaded mucoadhesive gel may serve as a promising approach for effective localized treatment of oral ulcers.

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