Design, Optimization, and Evaluation of an Ethosomal Gel System for Topical Delivery of Acyclovir

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***Abstract*—The objective of the present investigation was to design and evaluate an ethosomal gel-based delivery system of acyclovir (ACV) intended for the topical management of herpes zoster infections. Conventional topical and oral acyclovir formulations are associated with limited skin permeation and low bioavailability, resulting in suboptimal therapeutic outcomes. Ethosomes, which are phospholipid vesicular carriers enriched with a high concentration of ethanol, have demonstrated significant potential in enhancing dermal and transdermal drug delivery.**

In this study, acyclovir-loaded ethosomes were prepared using the cold method with varying concentrations of phospholipid and ethanol. The prepared vesicles were characterized for vesicle size, morphology, zeta potential, entrapment efficiency, and in-vitro drug release. Among the developed formulations, AEF5 showed optimal vesicle size and the highest drug entrapment efficiency. The optimized ethosomal dispersion was further incorporated into carbopol-based gels at different polymer concentrations (0.5%, 1.0%, and 1.5% w/w). The resultant ethosomal gels were evaluated for physicochemical properties, spreadability, viscosity, drug content, in-vitro release behavior, and stability.

FT-IR studies confirmed the compatibility of acyclovir with formulation excipients. The formulation containing 1% w/w carbopol (AEG2) exhibited superior gel characteristics and sustained drug release, achieving 82.23% cumulative drug release over 8 hours, following zero-order kinetics. The findings suggest that the developed ethosomal gel represents a promising and patient-friendly topical delivery system for acyclovir.

***Index Terms*—Acyclovir, Ethosomes, Topical gel, Vesicular drug delivery, Herpes zoster, Controlled release**

I. INTRODUCTION

Topical drug delivery remains an attractive route for the treatment of dermatological and localized viral infections due to its ability to deliver therapeutic agents directly to the site of action while minimizing systemic adverse effects. However, the outermost layer of the skin, the stratum corneum, poses a significant barrier to drug permeation, particularly for hydrophilic and high molecular weight drugs.

Traditional liposomal systems have been extensively investigated for topical drug delivery, yet their effectiveness is limited due to insufficient penetration beyond the superficial layers of the skin. To address these limitations, advanced vesicular systems such as ethosomes have been developed. Ethosomes are soft, flexible lipid vesicles composed of phospholipids, ethanol, and water. The presence of ethanol enhances vesicle flexibility and disrupts the lipid arrangement of the stratum corneum, thereby facilitating deeper skin penetration. Acyclovir is a well-established antiviral agent used in the treatment of herpes simplex, herpes zoster, and varicella infections. Despite its effectiveness, topical acyclovir formulations often fail to achieve adequate drug concentrations in deeper skin layers, while oral administration is associated with low bioavailability and frequent dosing requirements. Incorporation of acyclovir into an ethosomal gel system may significantly enhance its skin permeation, prolong residence time, and improve therapeutic efficacy. The present study was therefore undertaken to formulate, optimize, and evaluate an ethosomal gel of acyclovir for enhanced topical delivery and controlled drug release.

II. MATERIALS AND METHODS

Materials

Acyclovir was kindly supplied by Macleods Pharmaceuticals (Mumbai, India). Phospholipids were procured from HiMedia Laboratories (Mumbai,

India). Ethanol, propylene glycol, and carbopol were obtained from CDH Chemicals (New Delhi, India). All other reagents used were of analytical grade. Determination of Maximum Absorption Wavelength Acyclovir solutions (5–25 µg/mL) were prepared in phosphate buffer pH 7.4, and the absorbance was measured using a UV–Visible spectrophotometer in the range of 200–400 nm to determine the λmax.

Preparation of Acyclovir Ethosomes Ethosomal formulations were prepared by the cold method. Acyclovir, phospholipid, and polyethylene glycol were dissolved in ethanol under continuous stirring. Distilled water was slowly added to the mixture while maintaining constant stirring at controlled temperature. The dispersion was sonicated to reduce vesicle size and improve homogeneity.

Characterization of Ethosomes

Prepared ethosomes were evaluated for:

Vesicle morphology using optical microscopy

Vesicle size and zeta potential by dynamic light scattering

Entrapment efficiency by centrifugation followed by UV analysis of free drug

Formulation of Ethosomal Gel

The optimized ethosomal formulation was incorporated into carbopol gel bases at varying concentrations (0.5%, 1%, and 1.5% w/w) by gentle mechanical mixing to obtain uniform gels.

Evaluation of Ethosomal Gel

The prepared gels were assessed for homogeneity, pH, viscosity, spreadability, extrudability, drug content, washability, and in-vitro drug release using a Franz diffusion cell.

In-vitro Drug Release and Kinetic Analysis

Release data were analyzed using zero-order, first-order, and Higuchi models to determine the mechanism of drug release.

Stability Studies

The optimized formulation was stored at different temperature conditions for 45 days and evaluated for physical stability and vesicle size.

III. RESULTS AND DISCUSSION

All ethosomal formulations produced spherical vesicles with acceptable size distribution. Among them, formulation AEF5 exhibited the smallest vesicle size (331.6 nm), highest entrapment efficiency (79.98%), and suitable zeta potential, indicating good stability and enhanced drug loading capacity.

The ethosomal gels demonstrated acceptable pH values compatible with skin application. Among the tested gels, AEG2 (1% carbopol) exhibited optimal viscosity, superior spreadability, and maximum drug release. In-vitro release studies revealed sustained drug release up to 8 hours, with cumulative drug release of 82.23%. Kinetic analysis confirmed that drug release followed a zero-order pattern, indicating controlled release behavior.

IV. CONCLUSION

The present investigation successfully developed an ethosomal gel formulation of acyclovir with enhanced skin permeation and controlled drug release characteristics. The optimized formulation demonstrated favorable physicochemical properties and sustained zero-order drug release, making it a promising topical therapeutic option for the management of herpes zoster infections. This delivery system may improve patient compliance, reduce dosing frequency, and enhance clinical effectiveness.

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