A comprehensive review on acyclovir self-emulsifying buccal nano-film (SEBNF): a novel hybrid drug delivery approach for enhancing bioavailability of BCS class IV drugs

Mr. Yogesh Kailas Palhal[1], Mrs. Amanpreet Kaur Dumda Palaya[2]
[1]*Student, Yashodeep Institute of Pharmacy, Chh. Sambhajinagar*
[2]*Principal, Yashodeep Institute of Pharmacy, Chh. Sambhajinagar*

***Abstract*—Acyclovir is a widely prescribed antiviral drug used in the treatment of infections caused by herpes simplex virus and varicella-zoster virus. Although acyclovir exhibits strong antiviral activity and a well-established safety profile, its clinical performance is significantly compromised by poor aqueous solubility, low epithelial permeability, and variable gastrointestinal absorption. These limitations categorize acyclovir as a Biopharmaceutics Classification System (BCS) Class IV drug. Conventional oral dosage forms often result in low and inconsistent bioavailability, requiring frequent administration and leading to reduced patient compliance. Over the past few decades, numerous formulation strategies have been explored to overcome these drawbacks; however, most approaches focus on either solubility enhancement or permeability improvement alone. Self-emulsifying buccal nano-film (SEBNF) systems represent a novel hybrid drug delivery strategy that integrates the solubilization advantages of self-emulsifying drug delivery systems with the benefits of buccal transmucosal delivery, including avoidance of first-pass metabolism and rapid systemic absorption. This review provides a comprehensive and critical evaluation of the biopharmaceutical challenges associated with acyclovir, summarizes relevant literature on buccal and self- emulsifying delivery systems, and highlights the scientific rationale for SEBNF as a promising platform for improving the bioavailability of BCS Class IV drugs.**

***Index Terms*—Acyclovir, Self-emulsifying drug delivery system, Buccal nano-film, BCS Class IV drugs, Bioavailability enhancement.**

I. INTRODUCTION

The development of effective drug delivery systems for poorly bioavailable drugs remains a major challenge in pharmaceutical research. A significant proportion of newly discovered and existing drug molecules exhibit low solubility, poor permeability, or both, leading to suboptimal therapeutic performance. The Biopharmaceutics Classification System categorizes drugs based on solubility and permeability, and drugs belonging to BCS Class IV represent the most challenging category due to the presence of both limitations simultaneously.[28]

Acyclovir is a synthetic purine nucleoside analogue that has been extensively used for the treatment of viral infections such as herpes simplex and herpes zoster. Despite its potent antiviral efficacy, the clinical usefulness of acyclovir is limited by poor oral bioavailability, which typically ranges between 10 and 20%. Early pharmacokinetic studies by De Miranda and Good (1983) demonstrated that acyclovir shows incomplete and variable gastrointestinal absorption.

These findings were further confirmed by Weller et al. (1983), who reported that increasing the oral dose of acyclovir does not proportionally increase plasma concentration due to saturable absorption processes. [1,2]

The requirement for frequent dosing associated with conventional oral formulations often results in poor patient adherence, particularly during long-term antiviral therapy. Although prodrug approaches such as valacyclovir have been introduced to improve absorption, they involve higher cost and dependence on metabolic activation, which may vary among individuals. Consequently, formulation-based approaches that improve bioavailability without chemical modification of the drug molecule have gained increasing attention. Among these

approaches, buccal drug delivery and lipid-based self-emulsifying systems have emerged as promising strategies.[6]

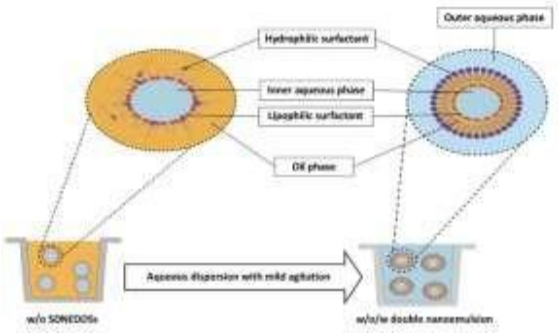

Fig. 1. Schematic representation of self-emulsifying buccal nano-film drug delivery system

II. LITERATURE REVIEW

Early investigations into the absorption characteristics of acyclovir clearly identified significant pharmacokinetic limitations. De Miranda and Good (1983) reported that acyclovir exhibits poor and inconsistent gastrointestinal absorption, leading to low systemic exposure following oral administration. Their work indicated that absorption is not only incomplete but also subject to considerable inter- individual variability. [1]

Subsequently, Weller et al. (1983) conducted detailed clinical studies and confirmed that acyclovir absorption is dose-dependent and saturable in nature.

Their findings demonstrated that increasing the oral dose beyond a certain limit does not produce proportional increases in plasma drug concentration, highlighting the presence of intrinsic permeability barriers. These observations contributed to the classification of acyclovir as a poorly bioavailable drug. [2]

Further mechanistic insights were provided by Sinko et al. (1995), who identified epithelial permeability as the primary factor limiting acyclovir absorption. Their research demonstrated that even when solubility constraints are minimized, restricted membrane transport significantly reduces systemic availability. Based on such evidence, acyclovir was categorized under BCS Class IV, indicating the need for advanced delivery strategies. [3,28]

Buccal drug delivery systems were explored as an alternative route to overcome gastrointestinal and hepatic barriers. Shojaei (1998) reviewed transmucosal drug delivery and emphasized that the buccal route bypasses first-pass metabolism and enzymatic degradation, making it particularly suitable for drugs with poor oral bioavailability. [4]

Later, Sudhakar et al. (2006) compared various mucoadhesive systems and concluded that buccal films provide better flexibility, patient comfort, and prolonged residence time than buccal tablets and gels. [5]

Parallel research focused on lipid-based systems to enhance solubility of poorly water-soluble drugs. Pouton (2000) introduced the concept of self-emulsifying drug delivery systems and described their ability to form fine oil-in-water emulsions upon aqueous dilution. Gursoy and Benita (2004) emphasized the importance of surfactant composition and hydrophilic–lipophilic balance in determining nano-emulsion formation and stability. Later, Porter et al. (2008) demonstrated that nano-sized droplets significantly improve absorption by increasing interfacial surface area and reducing diffusional resistance. [7,8,9]

The integration of self-emulsifying systems into solid dosage forms was proposed by Madhav and Yadav (2009) to improve stability and patient convenience.
Extending this concept, Borges et al. (2013) reported that self-emulsifying films provide rapid hydration, uniform drug distribution, and enhanced mucosal permeation. Studies by Perioli et al. (2008) further confirmed improved mucosal residence time and enhanced delivery of acyclovir from buccal films. Collectively, these studies support the development of hybrid self-emulsifying buccal systems. [11,13,14,15]

III. BIOPHARMACEUTICAL CHALLENGES OF BCS CLASS IV DRUGS

BCS Class IV drugs pose significant formulation challenges due to their poor solubility and limited permeability. For acyclovir, poor membrane transport, short gastrointestinal residence time, and potential efflux mechanisms collectively restrict absorption. Unlike BCS Class II drugs, where solubility enhancement alone may lead to significant improvement, Class IV drugs require strategies that simultaneously address both solubility and permeability barriers.

In addition, variability in gastrointestinal conditions such as pH, motility, and food intake further contributes to inconsistent absorption. These challenges highlight the limitations of conventional formulation approaches and underscore the need for multifunctional drug delivery systems capable of overcoming multiple barriers to absorption. [3,28]

IV. LIMITATIONS OF CONVENTIONAL DELIVERY ROUTES

Oral administration of acyclovir remains the most common route but is associated with low and variable bioavailability. Transdermal delivery has been investigated; however, the hydrophilic nature of acyclovir limits its ability to permeate the stratum corneum. Nasal delivery systems face challenges related to mucociliary clearance, limited dosing volume, and irritation of nasal tissues.

These limitations indicate that while alternative routes have been explored, none adequately address both solubility and permeability constraints. Buccal delivery emerges as a promising non-invasive route capable of bypassing gastrointestinal and hepatic barriers while maintaining patient convenience. [2,27]

V. BUCCAL MUCOSA AS A DRUG DELIVERY ROUTE

The buccal mucosa is non-keratinized, well vascularized, and relatively permeable, making it suitable for systemic drug delivery. Drug absorption through the buccal mucosa occurs primarily via passive diffusion, and direct access to systemic circulation allows avoidance of first-pass metabolism. [4,31]

However, challenges such as salivary wash-out and limited residence time may reduce drug absorption. Buccal films address these issues by providing prolonged contact with the mucosa, controlled drug release, and improved patient comfort. Their thin and flexible nature enhances acceptability, particularly for pediatric and geriatric patients. [5,20]

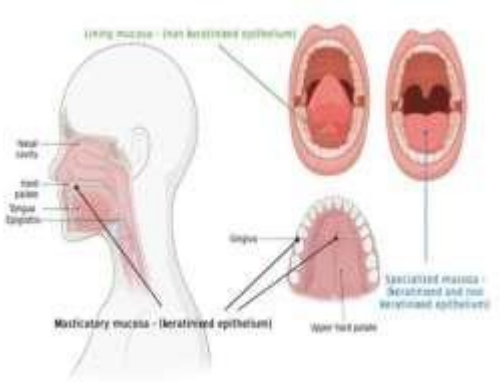

Fig. 2. Structure of buccal mucosa highlighting drug absorption pathway

VI. SELF-EMULSIFYING DRUG DELIVERY SYSTEMS

Self-emulsifying systems enhance drug solubilization by forming nano-emulsions upon contact with aqueous fluids. The increased surface area facilitates rapid dissolution and absorption. Surfactants used in these systems may also transiently modify membrane fluidity, thereby enhancing permeability.[7,8]

For poorly soluble and poorly permeable drugs such as acyclovir, self-emulsifying systems help maintain the drug in a solubilized state at the site of absorption, minimizing precipitation and improving absorption efficiency. [9,29]

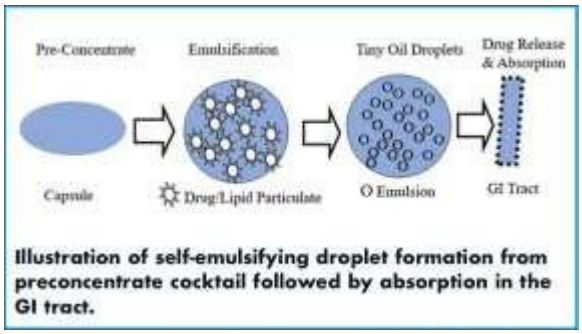

Fig. 3. Formation of nano-emulsion droplets from self- emulsifying system upon hydration

VII. RATIONALE FOR SELF-EMULSIFYING BUCCAL NANO-FILMS

SEBNF systems combine the advantages of buccal delivery and self-emulsifying formulations into a single dosage form. While buccal delivery improves permeability and bypasses first-pass metabolism, self- emulsifying systems enhance solubility. Their integration results in a synergistic platform capable

of overcoming the dual limitations of BCS Class IV drugs.

Nano-emulsion formation directly at the buccal mucosa, coupled with prolonged residence time provided by the film matrix, enhances drug absorption and consistency of therapeutic response. [11,13,30]

VIII. TRANSLATIONAL AND REGULATORY CONSIDERATIONS

SEBNF systems offer several clinical advantages, including reduced dosing frequency, improved patient compliance, and potential dose reduction. However, regulatory challenges related to nano-enabled systems include stability, reproducibility, and scale-up. Dokania and Joshi (2015) emphasized the need for robust manufacturing processes and quality control strategies to ensure consistent performance.[12,19]

IX. CONCLUSION

Self-emulsifying buccal nano-films represent a promising hybrid drug delivery approach for enhancing the bioavailability of acyclovir. By simultaneously addressing solubility and permeability limitations, SEBNF systems offer improved therapeutic performance and patient compliance. Literature evidence supports their potential application for acyclovir and other BCS Class IV drugs, making them a valuable platform in advanced drug delivery research.

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