

Design, Develop, Optimize and Characterize Sustained Release Transdermal Patch of Baclofen by Using Permeation Enhancer

Ganesh Suresh Tule¹, Saurabh Tukaram Ghule², Kiran Sudhakar Ghugare³, Rohit Ramdas Khairnar⁴
^{1,2,3}*Ratnadeep College of Pharmacy, Ratnapur, Tal – Jamkhed, Ahilyanagar, Maharashtra*
⁴*Siddhis Institute of Pharmacy Nandgaon Murbad 421401*

Abstract—Aim: The current study aims to design, develop, optimize and characterize sustained release transdermal patches of baclofen using permeation enhancer. **Methodology:** A 32full factorial design was used to prepare transdermal patches of baclofen using ethyl cellulose as the polymer and span 80 as the penetration enhancer. The prepared patches were evaluated for various physicochemical parameters, such as water vapor transmission rate, moisture content, thickness, folding endurance, and drug content. **In vitro** drug release studies were conducted using the Franz Diffusion cell. **Results:** The compatibility study using FTIR spectroscopy confirmed the compatibility of baclofen with the polymers. The prepared patches showed good physical appearance, flexibility, and uniformity. The water vapor transmission rate ranged from 0.0178 to 0.0380 g/cm²/day, and the moisture content varied from 1.980 to 3.435%. The thickness of the patches was between 0.28 and 0.38 mm, and the folding endurance ranged from 201 to 221. The drug content was found to be in the range of 96 to 99%. The **in vitro** drug release studies showed that the patches released up to 88.89% of the drug over 24 hours. **Conclusion:** The results of this study demonstrate that transdermal patches of baclofen can be successfully prepared using ethyl cellulose and span 80. The prepared patches exhibited desirable physicochemical properties and **in vitro** drug release characteristics, suggesting their potential as a novel drug delivery system for baclofen.

I. INTRODUCTION

Drug delivery systems have undergone significant development in recent years, with increasing emphasis on improving therapeutic efficacy, reducing adverse effects, enhancing patient compliance, and maintaining drug concentrations within the desired therapeutic range. Conventional routes of drug

administration, particularly oral administration, are widely used because of their convenience and patient acceptability. However, oral drug delivery may be associated with several limitations, including gastrointestinal degradation, variable absorption, hepatic first-pass metabolism, fluctuations in plasma drug concentration, and the requirement for repeated dosing. These limitations have encouraged the development of alternative drug delivery approaches capable of providing controlled and sustained drug release. Among these approaches, transdermal drug delivery systems (TDDS) have attracted considerable attention as a promising non-invasive method for systemic drug administration. [1, 4]

Transdermal drug delivery involves the administration of a therapeutic agent through the skin into the systemic circulation at a predetermined or controlled rate. The skin provides a large and readily accessible surface area for drug administration and can potentially provide prolonged drug delivery. Transdermal systems may offer several advantages over conventional routes, including avoidance of gastrointestinal degradation and hepatic first-pass metabolism, maintenance of relatively consistent plasma drug concentrations, reduction in dosing frequency, improved patient compliance, and the possibility of terminating therapy by removing the dosage form. However, the major limitation of transdermal delivery is the highly efficient barrier function of the outermost layer of the skin, particularly the stratum corneum. This barrier restricts the penetration of many therapeutic molecules and therefore limits the number of drugs that can be effectively administered through the skin. [7, 8]

The stratum corneum is composed primarily of keratinized corneocytes embedded within an organized lipid matrix. It acts as the principal barrier against the penetration of foreign substances and prevents excessive loss of water from the body. Consequently, a drug intended for transdermal delivery must possess suitable physicochemical characteristics, including appropriate molecular size, lipophilicity, melting point, and potency. Drugs with inadequate skin permeability may require specialized formulation approaches to enhance their transport across the skin. One of the commonly investigated approaches is the incorporation of chemical permeation enhancers into the transdermal formulation. [7, 8]

Permeation enhancers are substances capable of temporarily modifying the barrier properties of the stratum corneum and increasing the rate or extent of drug permeation through the skin.

Different classes of permeation enhancers include alcohols, glycols, fatty acids, fatty acid esters, terpenes, surfactants, pyrrolidones, sulfoxides, and other chemical agents. Their mechanisms may involve disruption or fluidization of intercellular lipids, interaction with keratin within corneocytes, improvement of drug partitioning into the skin, or enhancement of drug diffusion through the skin. The selection of an appropriate enhancer is important because an effective enhancer should improve drug permeation without causing significant skin irritation or permanent damage to the skin barrier. [7, 8]

Baclofen is a centrally acting skeletal muscle relaxant and a selective γ -aminobutyric acid type B (GABA-B) receptor agonist. It is primarily used for the management of spasticity associated with conditions such as multiple sclerosis, spinal cord disorders, and other neurological conditions. Baclofen acts mainly at the spinal level by reducing excitatory neurotransmission and thereby decreasing muscle spasticity and associated muscle spasms. Although baclofen is therapeutically useful, conventional oral administration may require repeated dosing and may be associated with adverse effects such as drowsiness, dizziness, weakness, fatigue, nausea, and other dose-related effects. Rapid changes in systemic drug concentrations can also contribute to variations in therapeutic response and adverse effects. [1, 4]

The development of a sustained-release transdermal patch of baclofen represents an approach intended to provide prolonged drug delivery and potentially reduce fluctuations in systemic drug exposure. A transdermal patch can be designed using suitable polymers that form a drug-containing matrix or reservoir from which baclofen is released gradually. The drug then partitions into the skin, diffuses through the stratum corneum and underlying skin layers, and enters the systemic circulation. The incorporation of a suitable permeation enhancer may further facilitate this process by reducing the resistance offered by the stratum corneum. [1, 4]

The performance of a transdermal patch depends on several formulation and process variables. The selection and concentration of polymers, plasticizers, permeation enhancers, drug loading, solvent system, patch thickness, drying conditions, and other formulation parameters can significantly influence mechanical properties, drug release, skin permeation, adhesion, and stability. Therefore, systematic formulation development is necessary to obtain a patch with desirable characteristics. Modern formulation development increasingly utilizes Quality by Design (QbD) principles and Design of Experiments (DoE) to identify critical material attributes and critical process parameters and to understand their effects on critical quality attributes of the final dosage form. [7, 8]

Characterization of a developed transdermal patch is also essential for establishing its quality and performance. Physical evaluation may include appearance, thickness, weight variation, folding endurance, flatness, moisture content, moisture uptake, drug content, tensile strength, percentage elongation, and adhesive properties. Drug-release characteristics can be investigated using appropriate in-vitro methods, while ex-vivo permeation studies using suitable animal or human skin models can provide information about the ability of baclofen to cross the skin barrier. Mathematical models such as zero-order, first-order, Higuchi, and Korsmeyer–Peppas models may be applied to understand the mechanism and kinetics of drug release. [1, 4]

Thus, the development of a baclofen transdermal patch requires an integrated understanding of drug properties, polymer science, skin physiology, permeation enhancement, formulation optimization,

drug-release mechanisms, and skin permeation. The use of appropriate permeation enhancers combined with a suitable polymeric matrix may provide a rational approach for achieving sustained baclofen delivery. This review therefore discusses the design, development, optimization, and characterization of sustained-release transdermal patches of baclofen using permeation enhancers, with particular emphasis on formulation strategies, mechanisms of skin permeation, optimization approaches, evaluation parameters, challenges, and future prospects. [1, 4]

Baclofen: Drug Profile

Chemical Name

Baclofen is a centrally acting skeletal muscle relaxant belonging to the class of GABA-B receptor agonists. Chemically, it is known as 4-amino-3-(4-chlorophenyl) butanoic acid. It is structurally related to γ -aminobutyric acid (GABA), but the presence of a para-chlorophenyl group allows it to act selectively on GABA-B receptors. [1, 4]

Molecular Formula and Molecular Weight

The molecular formula of baclofen is $C_{10}H_{12}ClNO_2$, and its molecular weight is approximately 213.66 g/mol. Baclofen is generally described as a white or off-white crystalline powder and is soluble in water to a limited extent. Its physicochemical properties are important when considering its suitability for transdermal delivery because successful passive transdermal transport depends on factors such as molecular size, aqueous solubility, lipid solubility, ionization, and partitioning between the formulation and skin. [1, 4]

II. MECHANISM OF ACTION

Baclofen primarily acts as an agonist at GABA-B receptors, which are metabotropic receptors associated with inhibitory neurotransmission. These receptors are present in the central nervous system, particularly within the spinal cord. [1, 4]

After reaching the central nervous system, baclofen stimulates GABA-B receptors located on presynaptic and postsynaptic neuronal membranes. Activation of these receptors decreases excitatory neurotransmitter release and reduces neuronal excitability. This action results in suppression of excessive excitatory signaling responsible for muscle spasticity. [1, 4].

A simplified mechanism can be represented as:

Baclofen administration $\rightarrow$ GABA-B receptor activation $\rightarrow$ inhibition of excitatory neurotransmission $\rightarrow$ reduced spinal neuronal activity $\rightarrow$ decreased muscle spasticity and muscle spasms [1, 4]

The muscle-relaxant activity of baclofen is therefore primarily related to its inhibitory effects on spinal reflexes rather than direct relaxation of skeletal muscle. [1, 4]

Pharmacokinetics

Baclofen is absorbed following oral administration, although its absorption and systemic exposure can vary among individuals. It is distributed throughout the body and can cross the blood-brain barrier to reach its central nervous system sites of action. [1, 4]

Baclofen is eliminated predominantly through the kidneys, with a substantial proportion being excreted as unchanged drug. Therefore, renal function is an important consideration during baclofen therapy. [1, 4]

From a transdermal formulation-development perspective, the pharmacokinetic profile of baclofen is particularly relevant. A controlled transdermal system is intended to provide gradual drug input rather than the relatively rapid drug input associated with conventional immediate-release administration. The desired outcome is a more sustained exposure while avoiding excessive fluctuations in systemic drug concentration. [1, 4]

Therapeutic Applications

Baclofen is primarily used for the treatment of spasticity, particularly spasticity associated with neurological disorders. It may be used in conditions such as: [1, 4]

- Multiple sclerosis
- Spinal cord injuries
- Cerebral or neurological disorders associated with spasticity
- Other conditions involving pathological muscle spasm or increased muscle tone

The therapeutic objective is to reduce abnormal muscle tone and involuntary muscle spasms, thereby improving mobility, comfort, and functional ability in appropriately selected patients.

III. LIMITATIONS OF CONVENTIONAL ORAL THERAPY

Although oral baclofen is clinically useful, conventional therapy has several limitations that provide a rationale for investigating alternative drug-delivery approaches. [1, 4]

Frequent administration

Depending on the therapeutic requirement, baclofen may require multiple doses during the day. Frequent administration can affect patient convenience and adherence. [1, 4]

Fluctuation in drug concentration

Conventional immediate-release administration can result in changes in plasma drug concentration over time. Such fluctuations may contribute to variations in therapeutic response and adverse effects.

Adverse effects

Common adverse effects associated with baclofen include drowsiness, dizziness, weakness, fatigue, nausea, and sedation. The intensity of adverse effects may be influenced by dose and individual patient characteristics. [1, 4]

Gastrointestinal route

Oral administration exposes the drug to the gastrointestinal environment and involves gastrointestinal absorption and hepatic handling before systemic distribution. [1, 4]

Dose-related limitations

Increasing the dose to obtain a stronger therapeutic response may also increase the likelihood of adverse effects. Consequently, controlled drug delivery is an attractive formulation objective. [5, 15]

A transdermal system could potentially provide a more continuous input of baclofen and reduce the need for repeated administration. However, this potential must be demonstrated through appropriate formulation, permeation, pharmacokinetic, and clinical studies. [1, 4]

3.1. Transdermal Drug Delivery System

Definition

A transdermal drug delivery system (TDDS) is a dosage form designed to deliver a drug through the

skin into the systemic circulation at a controlled or predetermined rate. [7, 8]

Unlike topical preparations, which are primarily intended to produce a local effect on the skin, transdermal systems are generally designed for systemic drug delivery. [7, 8]

The basic pathway can be represented as:

Transdermal patch → drug release → partitioning into skin → diffusion through skin → systemic circulation → therapeutic effect [7, 8]

Transdermal patches may be designed to provide drug delivery over several hours or days depending on the drug, formulation, patch design, and intended therapeutic application. [7, 8]

3.2. Components of a Transdermal Patch

A typical transdermal patch may contain several functional components.

Drug

The active pharmaceutical ingredient provides the desired therapeutic effect. In the present formulation concept, baclofen is the active drug. [1, 4]

Polymer

The polymer forms the structural matrix or controls drug release. Examples include: [5, 15]

- Hydroxypropyl methylcellulose (HPMC)
- Polyvinyl alcohol (PVA)
- Polyvinylpyrrolidone (PVP)
- Ethyl cellulose
- Eudragit polymers
- Polyethylene oxide
- Various synthetic and natural polymers

Permeation enhancer

A permeation enhancer is incorporated to improve the movement of baclofen across the stratum corneum. [1, 4]

Plasticizer

Plasticizers improve flexibility and reduce brittleness of the polymeric film.

Examples include polyethylene glycol, propylene glycol and glycerol, depending on formulation requirements. [6, 14]

Backing membrane

The backing membrane provides mechanical protection and helps prevent drug loss from the outer surface of the patch.

Adhesive

The adhesive allows the patch to remain attached to the skin during the intended application period. [5, 15]

Release liner

The release liner protects the drug-containing surface before application and is removed immediately before the patch is applied to the skin. [5, 15]

3.3. Advantages

Important advantages of transdermal drug delivery include:

- Avoidance of gastrointestinal degradation
- Potential avoidance of hepatic first-pass metabolism
- Controlled and sustained drug release
- Reduction in dosing frequency
- Improved patient convenience
- Better compliance in suitable patients
- Ability to terminate delivery by removing the patch
- Potential reduction in plasma concentration fluctuations
- Non-invasive administration
- Relatively easy application

For drugs that are appropriate candidates, these properties make transdermal delivery an attractive alternative to conventional routes. [7, 8]

3.4 Limitations

Despite its advantages, TDDS has important limitations:

- The stratum corneum provides a strong barrier to drug transport.
- Only drugs with suitable physicochemical properties are readily suitable for passive transdermal delivery. [7, 8]
- Large doses are generally difficult to deliver.
- Skin irritation or sensitization may occur.
- Adhesion can be affected by sweating, movement, hair, or environmental conditions.
- Formulation components may influence drug stability.

3.5 Types of Transdermal Patches

A. Drug-in-Adhesive System

In this system, the drug is incorporated directly into the adhesive layer. [5, 15]

Backing layer → drug-containing adhesive → release liner

This design is relatively simple and can provide a thin patch.

B. Matrix System

The drug is uniformly dispersed or dissolved within a polymeric matrix.

Backing membrane → drug-polymer matrix → adhesive/release liner

Drug release occurs primarily through diffusion from the polymeric matrix.

C. Reservoir System

The drug is contained within a separate reservoir.

Backing membrane → drug reservoir → rate-controlling membrane → adhesive → skin [5, 15]

The membrane controls drug release from the reservoir.

D. Multilayer System

Multilayer systems contain multiple drug-containing or rate-controlling layers. They can be designed to modify drug-release characteristics but are more complex to manufacture.

IV. RATIONALE FOR DEVELOPING A BACLOFEN TRANSDERMAL PATCH

The development of a sustained-release transdermal patch of baclofen is based on the possibility of providing prolonged and controlled drug input while improving administration convenience. [1, 4]

Oral baclofen administration can require repeated dosing and may produce variations in systemic drug exposure. A transdermal system could theoretically provide a more continuous drug input and reduce the frequency of administration. [1, 4]

The major scientific challenge is that the skin, particularly the stratum corneum, is an efficient barrier to drug penetration. Therefore, the formulation must be designed to achieve adequate drug release and skin permeation. [7, 8]

The incorporation of a suitable permeation enhancer can potentially increase baclofen transport by

temporarily modifying the barrier properties of the stratum corneum. However, the enhancer must be selected carefully because excessive disruption of the skin barrier can cause irritation or toxicity. [1, 4]

The overall rationale can therefore be represented as:
Baclofen → polymeric matrix → sustained drug release → permeation enhancement → improved skin transport → prolonged systemic drug delivery [1, 4]
The proposed system should ultimately be evaluated for:

- Drug release
- Skin permeation
- Skin retention
- Adhesion
- Mechanical properties
- Skin compatibility
- Stability

Importantly, successful in-vitro or ex-vivo permeation does not by itself establish clinical effectiveness. Pharmacokinetic and clinical studies would be required to confirm therapeutic performance. [23, 24]

Skin as a Barrier to Drug Permeation

Skin is the largest organ of the human body and serves as a protective barrier against environmental agents and excessive water loss. For transdermal drug delivery, however, this protective function represents the primary obstacle to drug absorption. [7, 8]

The skin can broadly be divided into:

1. Epidermis
2. Dermis
3. Subcutaneous tissue

Stratum Corneum

The stratum corneum is the outermost layer of the epidermis and represents the principal barrier to transdermal drug delivery. [7, 8]

It consists of flattened, dead corneocytes embedded in a lipid-rich intercellular matrix. The structure is commonly described using the “brick-and-mortar” model, in which corneocytes act as bricks and intercellular lipids act as mortar.

The major lipids include:

- Ceramides
- Cholesterol

- Free fatty acids

The highly organized lipid structure restricts the movement of many molecules through the skin.

Permeation enhancers are therefore frequently investigated to temporarily modify this barrier.

Viable Epidermis

The viable epidermis lies beneath the stratum corneum. It consists of metabolically active cells and contains much more water than the stratum corneum. [7, 8]

Although it is less resistant to drug diffusion than the stratum corneum, it still contributes to the overall diffusional resistance of the skin. [7, 8]

Once a drug crosses the stratum corneum, it must diffuse through the viable epidermis before reaching the dermis. [7, 8]

Dermis

The dermis lies beneath the epidermis and contains:

- Blood vessels
- Nerve endings
- Hair follicles
- Sweat glands
- Connective tissue

Once a drug reaches the dermal microcirculation, it can enter systemic circulation.

Therefore:

Stratum corneum → viable epidermis → dermis → dermal blood vessels → systemic circulation [7, 8]

Routes of Permeation

Drugs can cross the skin through three principal pathways.

A. Intercellular Route

The drug travels between corneocytes through the lipid domains.

Drug → intercellular lipid pathway → viable epidermis → dermis

This pathway is particularly important for many small molecules.

B. Transcellular Route

The drug passes directly through corneocytes and the intercellular lipid regions.

This route requires repeated partitioning between hydrophilic and lipophilic environments.

C. Appendageal Route

The drug may enter through skin appendages such as:

- Hair follicles
- Sweat glands

Although these pathways occupy a relatively small fraction of the skin surface, they may contribute to the permeation of certain molecules.

V. PERMEATION ENHANCERS

Definition

Permeation enhancers are substances incorporated into a formulation to increase the rate and/or extent of drug transport across the skin. [6, 14]

An ideal permeation enhancer should:

- Increase drug permeation
- Act rapidly
- Be reversible
- Produce minimal skin irritation
- Be chemically stable
- Be compatible with the drug and excipients
- Not interfere excessively with drug stability
- Not produce permanent damage to the skin

Mechanism of Action

Permeation enhancers can improve drug transport through several mechanisms:

Lipid disruption

Some enhancers disturb the highly organized lipid structure of the stratum corneum. [7, 8]

Lipid fluidization

Enhancers may increase the mobility of skin lipids and thereby reduce resistance to diffusion. [6, 14]

Protein interaction

Some enhancers interact with keratin within corneocytes and modify the structure of the protein matrix. [6, 14]

Increased drug partitioning

Some compounds improve the partitioning of the drug from the formulation into the skin. [5, 15]

Increased drug solubility

Certain enhancers may improve drug solubilization within the formulation and influence the thermodynamic activity of the drug. [6, 14]

Hydration

Increased hydration of the stratum corneum can alter its barrier properties and facilitate diffusion. [7, 8]

Chemical Enhancers

Common chemical permeation-enhancer classes include:

- Alcohols
- Glycols
- Fatty acids
- Fatty acid esters
- Terpenes
- Surfactants
- Pyrrolidones
- Sulfoxides

The choice depends on drug properties, concentration, polymer compatibility, skin tolerability, and desired permeation enhancement. [5, 15]

Alcohols and Glycols

Examples include:

- Ethanol
- Propylene glycol
- Polyethylene glycol
- Transcutol-type solvents

Alcohols can improve drug solubility and may interact with stratum-corneum lipids. Some alcohols can also increase skin hydration. [17, 18]

Propylene glycol is particularly useful as a multifunctional excipient because it can act as a solvent, plasticizer, and permeation-enhancing agent depending on the formulation. [6, 14]

However, excessive concentrations may affect film properties or cause skin irritation.

Fatty Acids

Examples include:

- Oleic acid
- Lauric acid
- Linoleic acid
- Capric acid

Fatty acids can interact with intercellular lipids and alter their organization. Unsaturated fatty acids such as

oleic acid have frequently been investigated for enhancing transdermal drug permeation. [7, 8]
The concentration must be optimized because excessive lipid disruption may produce irritation.

Terpenes

Terpenes are naturally occurring compounds found in essential oils.

Examples include:

- Menthol
- Limonene
- Eucalyptol
- Terpineol

They can interact with skin lipids and may increase drug partitioning and diffusion. Terpenes are particularly interesting because some can provide substantial permeation enhancement at relatively low concentrations. Nevertheless, their safety and compatibility with the drug and polymer must be evaluated. [6, 14]

Surfactants

Surfactants contain both hydrophilic and lipophilic regions.

Examples include:

- Sodium lauryl sulfate
- Polysorbates
- Nonionic surfactants
- Various ionic surfactants

They can alter lipid organization and improve drug wetting and partitioning. However, ionic surfactants may cause greater irritation than some nonionic surfactants, so their selection requires careful evaluation. [6, 14]

Pyrrolidones

Examples include:

- N-methyl-2-pyrrolidone (NMP)
- 2-pyrrolidone

Pyrrolidones can enhance drug partitioning into the skin and interact with skin components. They have been studied extensively as chemical penetration enhancers, although concentration and safety considerations are important during formulation development. [6, 14]

Sulfoxides

Dimethyl sulfoxide (DMSO) is a well-known penetration enhancer. It can substantially alter skin

permeability by interacting with components of the stratum corneum. Because strong enhancement can be associated with irritation and changes in skin barrier function, DMSO must be evaluated carefully for the intended formulation. [7, 8]

VI. DESIGN AND DEVELOPMENT OF BACLOFEN TRANSDERMAL PATCH

The development of a baclofen transdermal patch requires systematic selection of formulation components. [1, 4]

Drug Selection

Baclofen is selected as the active pharmaceutical ingredient because of its established therapeutic role as a centrally acting muscle relaxant. [1, 4]

Before formulation development, the following drug properties should be assessed:

- Solubility
- Melting point
- Partition coefficient
- pKa
- Molecular weight
- Drug-polymer compatibility
- Drug-enhancer compatibility
- Stability

These properties help determine whether passive transdermal delivery is feasible and what formulation strategy may be required. [7, 8]

Polymer Selection

Polymers provide the structural framework of matrix-type patches and influence drug release. [5, 15]

Potential polymers include:

- HPMC
- PVA
- PVP
- Ethyl cellulose
- Eudragit grades
- Polyethylene oxide
- Natural polymers

Polymer selection should consider:

- Drug compatibility
- Film-forming ability
- Mechanical strength

- Flexibility
- Drug-release characteristics
- Stability
- Skin compatibility

Polymer concentration can strongly influence drug diffusion. Increasing polymer concentration may increase matrix density and reduce drug diffusion, although the effect depends on the specific polymer and formulation. [5, 15]

Permeation Enhancer Selection

The enhancer should be selected according to:

- Enhancement efficiency
- Skin compatibility
- Drug compatibility
- Polymer compatibility
- Concentration requirement
- Stability
- Regulatory acceptability

A screening study can compare several enhancers before selecting the most suitable candidate. [6, 14]

Plasticizer

Plasticizers improve flexibility and reduce brittleness of the polymeric film.

Examples include:

- Propylene glycol
- Polyethylene glycol
- Glycerol
- Dibutyl phthalate alternatives where appropriate

The concentration should be optimized because excessive plasticizer can make the film soft or sticky, whereas insufficient plasticizer can produce brittle films. [5, 15]

Backing Membrane

The backing membrane protects the formulation from the external environment and minimizes drug loss away from the skin. [5, 15]

An ideal backing material should be:

- Impermeable or minimally permeable to the drug
- Flexible
- Non-irritating
- Chemically stable
- Compatible with the formulation

Examples of backing materials include polyethylene and other suitable polymeric films.

Release Liner

The release liner protects the adhesive or drug-containing surface before application.

It should:

- Protect the patch from contamination
- Prevent premature drug loss
- Be chemically compatible
- Be easily removable before application

Siliconized films and fluoropolymer-coated materials are commonly used for this purpose.

Adhesive

The adhesive maintains intimate contact between the patch and skin.

Important adhesive properties include:

- Tack
- Peel adhesion
- Shear adhesion
- Skin compatibility
- Stability
- Compatibility with drug and enhancer

Poor adhesion may result in incomplete drug delivery, whereas excessive adhesion may cause discomfort or skin damage during removal.

VII. FORMULATION APPROACHES

Solvent Evaporation

In the solvent-evaporation method, drug, polymer, plasticizer, and permeation enhancer are dissolved or dispersed in an appropriate solvent system. The mixture is then cast into a suitable mold or substrate and the solvent is evaporated under controlled conditions. [6, 14]

General process:

Drug + polymer + enhancer + plasticizer → homogeneous mixture → casting → controlled solvent evaporation → film formation → cutting → packaging [6, 14]

Important parameters include:

- Solvent composition
- Polymer concentration
- Drying temperature
- Drying time
- Film thickness

Excessively rapid drying may cause uneven films, whereas incomplete solvent removal may affect stability and safety. [22, 25]

Solvent Casting

Solvent casting is a widely used technique for preparing polymeric transdermal films. The drug and excipients are dissolved or dispersed in a suitable solvent.

The resulting solution is poured onto a flat surface and dried to form a uniform film. [7, 8]

The process can be described as:

Polymer solution preparation → drug incorporation → enhancer addition → mixing → casting → drying → film removal → cutting → evaluation [6, 14]

Uniform mixing is essential to prevent variation in drug content.

Matrix System

In a matrix system, baclofen is incorporated into a polymeric matrix.

Backing membrane → baclofen-polymer matrix → adhesive/release liner

Drug release occurs primarily through diffusion from the matrix.

The release rate can be modified by:

- Polymer type
- Polymer concentration
- Drug concentration
- Plasticizer
- Permeation enhancer
- Matrix thickness

Matrix systems are attractive because their design is comparatively simple and they can provide sustained release.

Reservoir System

In a reservoir system, the drug is maintained in a separate reservoir and released through a rate-controlling membrane. [5, 15]

Backing layer → drug reservoir → rate-controlling membrane → adhesive → skin [5, 15]

Reservoir systems can provide controlled drug release but may involve greater manufacturing complexity than matrix systems. [5, 15]

VIII. OPTIMIZATION OF FORMULATION

Optimization is an essential part of developing a transdermal patch because several formulation variables can simultaneously affect drug release, permeation, mechanical properties, and stability. [7, 8]

8.1. Critical Formulation Variables

Potential critical variables include:

- Polymer concentration
- Polymer ratio
- Baclofen concentration
- Permeation-enhancer concentration
- Plasticizer concentration
- Solvent composition
- Film thickness
- Drying temperature
- Drying time

Potential responses include:

- Drug release
- Cumulative drug permeation
- Flux
- Folding endurance
- Tensile strength
- Adhesion
- Drug content

Design of Experiments

Design of Experiments (DoE) is a systematic statistical approach used to study the effect of multiple formulation variables. Instead of changing one factor at a time, DoE allows simultaneous investigation of several factors and their interactions. [5, 15]

For example:

Independent variables:

X_1 = Polymer concentration

X_2 = Permeation-enhancer concentration

X_3 = Plasticizer concentration [6, 14]

Dependent variables:

Y_1 = Percentage drug release

Y_2 = Cumulative drug permeation

Y_3 = Folding endurance [19, 20]

The resulting mathematical model can help identify an optimized formulation region.

Factorial Design

Factorial designs investigate multiple factors at different levels.

For example, a 2^3 factorial design involves three independent variables, each studied at two levels.

It can provide information about:

- Main effects
- Interaction effects
- Formulation-variable relationships

Factorial designs are useful during preliminary formulation optimization.

Response Surface Methodology

Response Surface Methodology (RSM) is used to develop mathematical models describing the relationship between formulation variables and responses. [5, 15]

Common designs include:

- Central Composite Design (CCD)
- Box–Behnken Design (BBD)

For example:

Polymer concentration + enhancer concentration + plasticizer concentration $\rightarrow$ response surface $\rightarrow$ optimized formulation region [6, 14]

RSM is particularly useful when formulation variables interact with each other.

IX. CHARACTERIZATION AND EVALUATION

Appearance

The prepared patch should be visually inspected for:

- Color
- Transparency
- Smoothness
- Uniformity
- Air bubbles
- Cracks
- Drug crystallization
- Surface defects

A good film should have a uniform appearance and should not show visible imperfections.

Thickness

Thickness is generally measured at several points using a digital micrometer or vernier caliper. The

mean thickness and standard deviation are calculated. Uniform thickness is important because differences in thickness can result in variation in drug content and release. [5, 16]

Weight Variation

Individual patches of identical dimensions are weighed separately. The average weight is calculated and individual variation is determined. Low variation indicates uniformity of the prepared films.

Folding Endurance

Folding endurance indicates the flexibility of the film. A strip of the patch is repeatedly folded at the same position until it breaks.

The number of folds required to produce breakage is recorded. [5, 16]

Higher folding endurance generally indicates better flexibility.

Moisture Content

The patch is weighed initially and then maintained under controlled drying conditions until a constant weight is obtained.

Moisture content can be calculated as:

$$\% \text{ Moisture content} = \frac{[(\text{Initial weight} - \text{Final weight}) / \text{Initial weight}] \times 100}{[5, 16]}$$

Moisture content can influence film flexibility, stability, and drug release.

Moisture Uptake

The ability of the patch to absorb moisture from the environment is determined by exposing the film to controlled humidity conditions. [5, 16]

Excessive moisture uptake may affect:

- Mechanical strength
- Adhesion
- Drug stability
- Drug release

Drug Content

A known area or weight of the patch is dissolved or extracted using a suitable solvent, followed by quantitative analysis using a validated analytical method.

The result is expressed as the percentage of the labeled or theoretical drug content.

Uniform drug content indicates good formulation homogeneity.

Surface pH

Surface pH can be determined by allowing the patch surface to equilibrate with a small amount of distilled water and measuring the pH. A skin-compatible pH is desirable to minimize the possibility of irritation.

Tensile Strength

Tensile strength measures the force required to break the film. It provides information regarding mechanical resistance. [5, 16]

A patch should possess sufficient strength to withstand handling and application but should also remain flexible.

Percentage Elongation

Percentage elongation indicates the extent to which a film can stretch before breaking.

It can be calculated as:

$$\% \text{ Elongation} = \frac{(\text{Final length} - \text{Initial length})}{\text{Initial length}} \times 100$$

The parameter provides information about film flexibility.

Flatness

Flatness determines whether the film maintains its original shape without significant contraction or curling. A uniformly flat patch is desirable because curling can reduce contact with the skin and adversely affect drug delivery.

Adhesive Properties

Adhesive performance is critical for a transdermal patch.

Important parameters include:

Tack

Tack represents the ability of the adhesive to establish immediate contact with the skin. [5, 15]

Peel adhesion

Peel adhesion measures the force required to remove the patch from the skin or a standardized substrate.

Shear adhesion

Shear adhesion evaluates the ability of the patch to remain attached under prolonged stress.

An appropriate balance between adhesion and removability is required.

In-Vitro Drug Release

In-vitro drug release studies determine the rate at which baclofen is released from the patch. [1, 4]

Appropriate diffusion or dissolution apparatus may be selected based on the formulation and validated methodology. [5, 15]

The cumulative percentage of drug released is plotted against time.

Typical release profiles can be evaluated using:

- Zero-order model
- First-order model
- Higuchi model
- Korsmeyer–Peppas model

The objective of sustained-release formulation development is generally to obtain controlled drug release over the intended period. [5, 15]

Ex-Vivo Permeation

Ex-vivo permeation studies evaluate the movement of baclofen across excised skin.

Common experimental arrangements use a Franz diffusion cell.

Basic arrangement:

Donor compartment

↓

Transdermal patch + skin

↓

Receptor compartment

Samples are withdrawn from the receptor compartment at predetermined intervals and analyzed for baclofen concentration. [1, 4]

Important parameters include:

Cumulative amount permeated

The cumulative amount of drug crossing the skin is plotted against time.

Flux

Flux represents the amount of drug crossing a unit area of skin per unit time.

It can be expressed as:

$$J = dQ / (A \times dt)$$

where:

- J = steady-state flux
- dQ/dt = rate of drug permeation

- A = diffusion area

Permeability coefficient

The permeability coefficient provides information about the ability of the drug to cross the skin under the experimental conditions.

Enhancement ratio

When a permeation enhancer is evaluated, its effect can be compared with the control formulation. [6, 14]

Enhancement ratio = Flux of enhanced formulation / Flux of control formulation [5, 15]

Skin Retention

Skin-retention studies determine the amount of baclofen remaining within different skin layers after the permeation experiment. The skin may be carefully washed, separated if required, extracted with a suitable solvent, and analyzed for drug content. Skin retention can provide information about whether the formulation predominantly promotes systemic permeation or produces substantial drug accumulation within the skin. [1, 4]

Kinetic Modelling

Mathematical kinetic models help identify the mechanism of drug release.

Zero-order model

$$Q = Q_0 + K_0t$$

This model describes a constant drug-release rate.

First-order model

The release rate depends on the amount of drug remaining in the dosage form. [5, 15]

Higuchi model

$$Q = K_H \sqrt{t}$$

The Higuchi model is commonly associated with diffusion-controlled drug release from matrix systems. [19, 20]

Korsmeyer–Peppas model

$$M_t/M_\infty = Kt^n$$

The release exponent n can provide information regarding the mechanism of drug transport, although interpretation depends on the geometry and experimental conditions of the dosage form. A comparison of the coefficient of determination and other appropriate statistical parameters can be used to

determine which model best describes the experimental release data. However, model fitting should be interpreted mechanistically and not solely on the basis of the highest correlation coefficient. [5, 15]

X. Mechanism of Baclofen Permeation

The transdermal permeation of baclofen is a multistep process involving drug release from the patch, partitioning into the stratum corneum, diffusion through the skin, and subsequent uptake into the systemic circulation. Since the stratum corneum is the principal barrier to transdermal delivery, the formulation must facilitate sufficient drug transport across this layer while maintaining controlled drug release. [1, 4]

Drug Release from the Patch

Following application of the transdermal patch to the skin, baclofen is released from the polymeric matrix or reservoir. In a matrix-type system, drug molecules diffuse through the polymer network toward the surface of the patch. [1, 4]

The rate of release is influenced by:

- Polymer type
- Polymer concentration
- Drug loading
- Polymer–drug interaction
- Plasticizer concentration
- Patch thickness
- Permeation enhancer
- Drug solubility within the matrix

The released drug must then partition from the formulation into the outer layer of the skin. [5, 15]

Partitioning into the Stratum Corneum

After release from the patch, baclofen must partition between the formulation and the stratum corneum. The extent of partitioning is influenced by the physicochemical characteristics of baclofen and the composition of the formulation.

The presence of a suitable permeation enhancer may increase the thermodynamic activity of the drug or modify the skin environment, thereby facilitating drug partitioning. [1, 4]

Diffusion through the Stratum Corneum

Once baclofen enters the stratum corneum, it moves down a concentration gradient toward the viable epidermis. The diffusion process can be conceptually described by Fick's first law of diffusion: [1, 4]

$$J = -D(dC/dx)$$

where:

- J = flux of drug
- D = diffusion coefficient
- dC/dx = concentration gradient

In a practical transdermal system, the overall permeation process is influenced by both the diffusion coefficient and partitioning of the drug into the skin. [7, 8]

Role of Permeation Enhancers

A permeation enhancer can facilitate baclofen transport by temporarily modifying the barrier properties of the stratum corneum. Depending on the enhancer, mechanisms may include: [1, 4]

Permeation enhancer → interaction with stratum-corneum lipids → lipid fluidization/disorganization → reduced diffusional resistance → increased drug permeation [6, 14]

Alternatively:

Enhancer → improved drug partitioning → increased concentration of drug within skin → increased concentration gradient → enhanced diffusion [6, 14]

The actual mechanism depends on the chemical nature and concentration of the enhancer. [6, 14]

Movement Through the Viable Epidermis

After crossing the stratum corneum, baclofen enters the viable epidermis. The viable epidermis generally offers less resistance to drug transport than the stratum corneum. The drug subsequently reaches the dermis. [1, 4]

Uptake into Systemic Circulation

The dermis contains an extensive network of blood vessels. Once baclofen reaches the dermal microcirculation, it can enter systemic circulation. [1, 4]

The overall pathway can therefore be represented as:
Baclofen patch

↓

Drug release from polymer matrix

↓

Partitioning into stratum corneum

↓

Diffusion through stratum corneum

↓

Viable epidermis

↓

Dermis

↓

Dermal blood vessels

↓

Systemic circulation

↓

GABA-B receptor-mediated pharmacological effect [1, 4]

The objective of formulation optimization is to achieve an appropriate balance between drug release, skin permeation, and sustained systemic delivery. [7, 8]

Factors Affecting Transdermal Permeation

Transdermal drug permeation is influenced by several drug-related, formulation-related, skin-related, and environmental factors. [7, 8]

Drug-Related Factors

Molecular Weight

Generally, smaller molecules diffuse through the skin more readily than larger molecules. Increasing molecular size can decrease the rate of passive skin permeation. [7, 8]

Lipophilicity

The ability of a drug to partition into the lipid-rich stratum corneum is an important determinant of transdermal delivery. However, excessive lipophilicity can reduce movement from the stratum corneum into the more aqueous viable tissues. Therefore, an appropriate balance between hydrophilic and lipophilic properties is desirable. [7, 8]

Solubility

Drug solubility influences the amount of drug available for diffusion. The formulation should maintain an appropriate drug concentration and thermodynamic activity. [5, 15]

Ionization

The degree of ionization influences skin permeation because the unionized form of many compounds generally partitions into the lipid-rich stratum corneum more readily than the ionized form. [7, 8]

Melting Point

Drugs with a lower melting point may sometimes exhibit greater transdermal permeation because of increased thermodynamic activity. However, melting point should be considered together with other physicochemical properties. [7, 8]

Formulation-Related Factors

Polymer Type

Different polymers produce different matrix structures and consequently influence drug diffusion.

Polymer Concentration

Increasing polymer concentration can increase matrix density and may reduce drug mobility. However, the relationship is formulation-specific. [5, 15]

Permeation Enhancer

The type and concentration of enhancer can have a major effect on skin permeability. [6, 14]

Plasticizer

Plasticizers modify polymer flexibility and may also influence drug diffusion and partitioning. [5, 15]

Drug Loading

Increasing drug concentration can increase the concentration gradient and potentially increase permeation, but excessive loading may lead to crystallization or instability. [22, 25]

Patch Thickness

Thicker films may increase the diffusion path length and can alter drug-release kinetics. [19, 20]

Adhesive

The adhesive influences the contact between the patch and skin and can also affect drug diffusion. [5, 15]

Skin-Related Factors

Skin Thickness

Different anatomical sites have different skin thicknesses, resulting in different permeability characteristics. [5, 16]

Hydration

Hydration can increase the permeability of the stratum corneum.

Age

Skin structure and barrier properties can change with age and may influence transdermal absorption. [7, 8]

Skin Condition

Damaged or diseased skin may have altered barrier properties. A formulation intended for normal intact skin should not automatically be assumed to have the same behavior on damaged skin. [5, 15]

Skin Temperature

Temperature can influence diffusion and blood flow and therefore potentially alter transdermal drug absorption. [7, 8]

Environmental Factors

Environmental conditions such as:

- Temperature
- Humidity
- Sweating
- Occlusion
- Physical activity can influence patch adhesion and skin permeability.

XI. OPTIMIZATION AND STATISTICAL ANALYSIS

Optimization is an important step in developing a sustained-release baclofen transdermal patch because several formulation variables can simultaneously influence drug release, permeation, mechanical properties, and stability. [1, 4]

Objectives of Optimization

The main objectives may include:

- Achieving controlled drug release
- Maximizing or appropriately controlling skin permeation
- Obtaining suitable mechanical strength
- Maintaining adequate flexibility
- Achieving acceptable adhesion
- Minimizing skin irritation
- Maintaining drug stability
- Obtaining reproducible formulation characteristics

Critical Formulation Variables

Potential critical variables include:

Variable	Possible influence
Polymer concentration	Drug release, thickness, mechanical strength
Permeation enhancer concentration	Skin permeation, irritation
Plasticizer concentration	Flexibility, tensile properties
Drug concentration	Drug loading and concentration gradient
Solvent composition	Film formation and drug distribution
Drying conditions	Film structure and residual solvent
Patch thickness	Drug release and diffusion path

Critical Quality Attributes

Potential CQAs include:

- Appearance
- Thickness
- Drug content
- Folding endurance
- Tensile strength
- Percentage elongation
- Adhesion
- In-vitro drug release
- Ex-vivo permeation
- Flux
- Skin retention
- Stability

Design of Experiments

DoE allows several factors to be evaluated simultaneously rather than changing one factor at a time. [23, 24]

For example:

X_1 = Polymer concentration

X_2 = Permeation enhancer concentration

X_3 = Plasticizer concentration [6, 14]

Possible responses:

Y_1 = Percentage drug released

Y_2 = Cumulative amount permeated

Y_3 = Flux

Y_4 = Folding endurance [19, 20]

A suitable experimental design can identify significant main effects and interactions.

Factorial Design

Factorial designs are useful during screening and optimization. A 2^3 factorial design, for example, evaluates three factors at two levels each and provides information regarding: [23, 24]

- Main effects
- Interaction effects
- Response behavior

Response Surface Methodology

Response Surface Methodology can be used to establish mathematical relationships between formulation factors and responses. [5, 15]

Common designs include:

- Central Composite Design
- Box–Behnken Design

A polynomial model may be generated to describe the experimental response. The optimized formulation should subsequently be prepared independently and compared with the predicted responses. [5, 15]

Statistical Analysis

Experimental data may be expressed as:

Mean $\pm$ Standard Deviation (SD)

where appropriate.

Statistical tests may include:

- Analysis of variance (ANOVA)
- Student's t -test
- Regression analysis
- Multiple regression
- Model adequacy testing

The selected statistical method should correspond to the experimental design and data distribution. Statistical significance is commonly assessed using a predefined significance level, such as $p < 0.05$, but statistical significance should be interpreted together with effect size and practical relevance. [23, 24]

Stability Studies

Stability studies are required to determine whether the baclofen transdermal patch maintains its physical, chemical, and performance characteristics during storage. The formulation should be evaluated under

appropriate temperature and humidity conditions according to applicable stability-study principles. [1, 4]

Objectives

Stability studies determine changes in:

- Physical appearance
- Drug content
- Drug-release characteristics
- Permeation behavior
- Adhesive properties
- Mechanical properties
- Moisture content
- Chemical stability

Parameters for Stability Testing

At predetermined intervals, the following parameters may be examined:

1. Appearance
2. Thickness
3. Weight
4. Folding endurance
5. Drug content
6. Tensile strength
7. Adhesion
8. In-vitro drug release
9. Ex-vivo permeation, where justified
10. Chemical degradation

Packaging

Proper packaging is important because transdermal films can be affected by:

- Moisture
- Oxygen
- Light
- Temperature

The patch may therefore require protective packaging with suitable moisture and oxygen barrier characteristics. [5, 16]

Stability-Indicating Analysis

A validated stability-indicating analytical method should be capable of distinguishing baclofen from its degradation products. Chromatographic techniques such as HPLC may be used where appropriate. A formulation can be considered physically and chemically stable only when it maintains acceptable specifications throughout the defined storage period. [1, 4]

XII. CONCLUSION

Baclofen is an established GABA-B receptor agonist used primarily for the management of spasticity. Conventional oral administration is effective but can involve repeated dosing and systemic adverse effects, creating interest in alternative controlled drug-delivery approaches. A sustained-release transdermal patch represents a potential strategy for providing prolonged drug delivery and improving administration convenience. The principal challenge in developing a baclofen transdermal system is the barrier function of the stratum corneum. Appropriate selection of polymers, plasticizers, adhesives, backing materials, and particularly permeation enhancers is therefore essential.

Permeation enhancers may increase baclofen transport by modifying the lipid structure of the stratum corneum, improving drug partitioning, or altering the diffusional resistance of the skin. Nevertheless, enhancement must be balanced against the possibility of skin irritation and barrier damage. Matrix-type systems prepared by solvent casting or related film-forming approaches provide a practical platform for investigating sustained baclofen delivery. Systematic optimization using Design of Experiments and Quality by Design principles can help establish relationships between formulation variables and critical quality attributes. Comprehensive characterization, including physical properties, mechanical properties, drug content, in-vitro drug release, ex-vivo skin permeation, skin retention, and release-kinetic analysis, is necessary to establish formulation performance.

Future research may combine permeation enhancers with advanced approaches such as nanocarriers, microneedles, iontophoresis, and smart delivery systems. However, successful laboratory formulation and ex-vivo permeation alone cannot establish clinical effectiveness. Further pharmacokinetic, safety, stability, scale-up, and clinical investigations are required. Overall, the systematic design, development, optimization, and characterization of a baclofen sustained-release transdermal patch using an appropriate permeation-enhancement strategy represents a scientifically relevant area of pharmaceutical research. Such a system has the potential to provide controlled drug delivery, but its

suitability must ultimately be established through rigorous formulation, pharmacokinetic, safety, and clinical evaluation. [1, 4]

REFERENCES

- [1] L. S. Goodman, L. L. Brunton, R. Hilal-Dandan, and B. C. Knollmann, eds., *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 13th ed. New York, NY, USA: McGraw-Hill Education, 2018.
- [2] L. L. Brunton, R. Hilal-Dandan, and B. C. Knollmann, eds., *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 14th ed. New York, NY, USA: McGraw-Hill, 2022.
- [3] S. C. Sweetman, ed., *Martindale: The Complete Drug Reference*. London, U.K.: Pharmaceutical Press.
- [4] H. P. Rang, M. M. Dale, J. M. Ritter, R. J. Flower, and G. Henderson, *Rang & Dale's Pharmacology*, 9th ed. Elsevier, 2019.
- [5] M. E. Aulton and K. M. G. Taylor, eds., *Aulton's Pharmaceutics: The Design and Manufacture of Medicines*, 6th ed. Elsevier, 2022.
- [6] A. C. Williams and B. W. Barry, "Penetration enhancers," *Advanced Drug Delivery Reviews*, vol. 56, no. 5, pp. 603–618, 2004.
- [7] M. R. Prausnitz and R. Langer, "Transdermal drug delivery," *Nature Biotechnology*, vol. 26, no. 11, pp. 1261–1268, 2008.
- [8] M. R. Prausnitz, S. Mitragotri, and R. Langer, "Current status and future potential of transdermal drug delivery," *Nature Reviews Drug Discovery*, vol. 3, no. 2, pp. 115–124, 2004.
- [9] B. W. Barry, *Dermatological Formulations: Percutaneous Absorption*. New York, NY, USA: Marcel Dekker, 1983.
- [10] J. Hadgraft and M. E. Lane, "Passive transdermal drug delivery systems," *American Journal of Drug Delivery*, vol. 4, no. 3, pp. 153–160, 2006.
- [11] H. A. E. Benson, "Transdermal drug delivery: Penetration enhancement techniques," *Current Drug Delivery*, vol. 2, no. 1, pp. 23–33, 2005.
- [12] R. H. Guy and J. Hadgraft, eds., *Transdermal Drug Delivery*, 2nd ed. New York, NY, USA: Marcel Dekker.
- [13] B. W. Barry, "Novel mechanisms and devices to enable successful transdermal drug delivery," *European Journal of Pharmaceutical Sciences*, vol. 14, no. 2, pp. 101–114, 2001.
- [14] B. C. Finnin and T. M. Morgan, "Transdermal penetration enhancers: Applications, limitations, and potential," *Journal of Pharmaceutical Sciences*, vol. 88, no. 10, pp. 955–958, 1999.
- [15] H. A. E. Benson and A. C. Watkinson, eds., *Transdermal and Topical Drug Delivery: Principles and Practice*. Wiley, 2012.
- [16] L. V. Allen, Jr., and H. C. Ansel, *Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems*, 10th ed. Wolters Kluwer, 2014.
- [17] P. J. Sinko, ed., *Martin's Physical Pharmacy and Pharmaceutical Sciences*, 6th ed. Lippincott Williams & Wilkins, 2011.
- [18] L. Lachman, H. A. Lieberman, and J. L. Kanig, *The Theory and Practice of Industrial Pharmacy*, 3rd ed. Lea & Febiger.
- [19] T. Higuchi, "Mechanism of sustained-action medication. Theoretical analysis of rate of release of solid drugs dispersed in solid matrices," *Journal of Pharmaceutical Sciences*, vol. 52, pp. 1145–1149, 1963.
- [20] R. W. Korsmeyer, R. Gurny, E. Doelker, P. Buri, and N. A. Peppas, "Mechanisms of solute release from porous hydrophilic polymers," *International Journal of Pharmaceutics*, vol. 15, no. 1, pp. 25–35, 1983.
- [21] Y. Qiu, Y. Chen, G. G. Z. Zhang, L. Yu, and R. V. Mantri, eds., *Developing Solid Oral Dosage Forms: Pharmaceutical Theory and Practice*, 2nd ed. Academic Press, 2017.
- [22] International Council for Harmonisation (ICH), *Q1A(R2): Stability Testing of New Drug Substances and Products*.
- [23] International Council for Harmonisation (ICH), *Q8(R2): Pharmaceutical Development*.
- [24] International Council for Harmonisation (ICH), *Q9: Quality Risk Management*.
- [25] International Council for Harmonisation (ICH), *Q10: Pharmaceutical Quality System*.