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Polymeric Matrix-Based Transdermal Drug Delivery Systems for Brexpiprazole: A Review of Formulation Strategies, Release Kinetics, Skin Permeation, and Stability

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Abstract- ***Brexpiprazole is a second-generation atypical antipsychotic and serotonin–dopamine activity modulator approved for schizophrenia and as adjunctive therapy in major depressive disorder. Although the molecule is well absorbed after oral dosing, its clinical use in chronic psychiatric disease is constrained by the well-documented problem of poor long-term medication adherence, by fluctuations in plasma concentration associated with once-daily oral regimens, and by the practical difficulties of sustained tablet-taking in this patient population. Its very long elimination half-life makes it an attractive candidate for a delivery system that maintains steady systemic exposure with minimal user intervention. The present review critically examines the rationale, scientific principles, formulation strategies, and evaluation framework for a polymeric matrix-based transdermal drug delivery system (TDDS) of brexpiprazole. The structure and barrier properties of the skin, the principal pathways of percutaneous transport, and the quantitative descriptors of permeation are discussed in relation to the physicochemical profile of the drug. Matrix-type patch architecture, film-forming polymers, plasticizers, and chemical permeation enhancers are reviewed alongside solubility-enhancement strategies appropriate to a lipophilic, poorly water-soluble molecule. The role of the solvent-casting technique and its critical process parameters, the in-vitro release and ex-vivo permeation testing framework, mathematical modelling of release kinetics, and the application of Design of Experiments (DoE) and Quality-by-Design (QbD) principles for systematic optimization are described. Stability considerations under International Council for Harmonisation (ICH) conditions and local skin tolerability are also addressed. The review concludes that a rationally engineered polymeric matrix patch, optimized through DoE and supported by mechanistic release–permeation correlation and ICH-compliant stability data, represents a scientifically sound route toward improving adherence and therapeutic consistency in long-term brexpiprazole therapy.***

Keywords: Brexpiprazole, Transdermal Drug Delivery System, Polymeric Matrix Patch, Controlled Release, Skin Permeation, Solvent Casting, Design of Experiments, Quality-By-Design, Release Kinetics, Stability Evaluation, Antipsychotic Adherence.

I. INTRODUCTION

A. Clinical role of brexpiprazole

Brexpiprazole is a second-generation (atypical) antipsychotic that acts as a serotonin–dopamine activity modulator. It is approved for the treatment of schizophrenia and as an adjunctive agent in major depressive disorder, and its pharmacological signature is defined by partial agonism at dopamine D^2 and serotonin 5-HT^{1A} receptors together with antagonism at 5-HT^{2A} receptors and at several adrenergic subtypes [1–4]. This balanced receptor activity is thought to underlie the favourable efficacy-to-tolerability ratio of the drug relative to some older agents, with a comparatively low propensity for akathisia and metabolic disturbance. Because schizophrenia and recurrent depressive illness are chronic conditions that demand months to years of uninterrupted pharmacotherapy, the way in which brexpiprazole is

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delivered to the systemic circulation is as clinically important as its intrinsic receptor pharmacology.

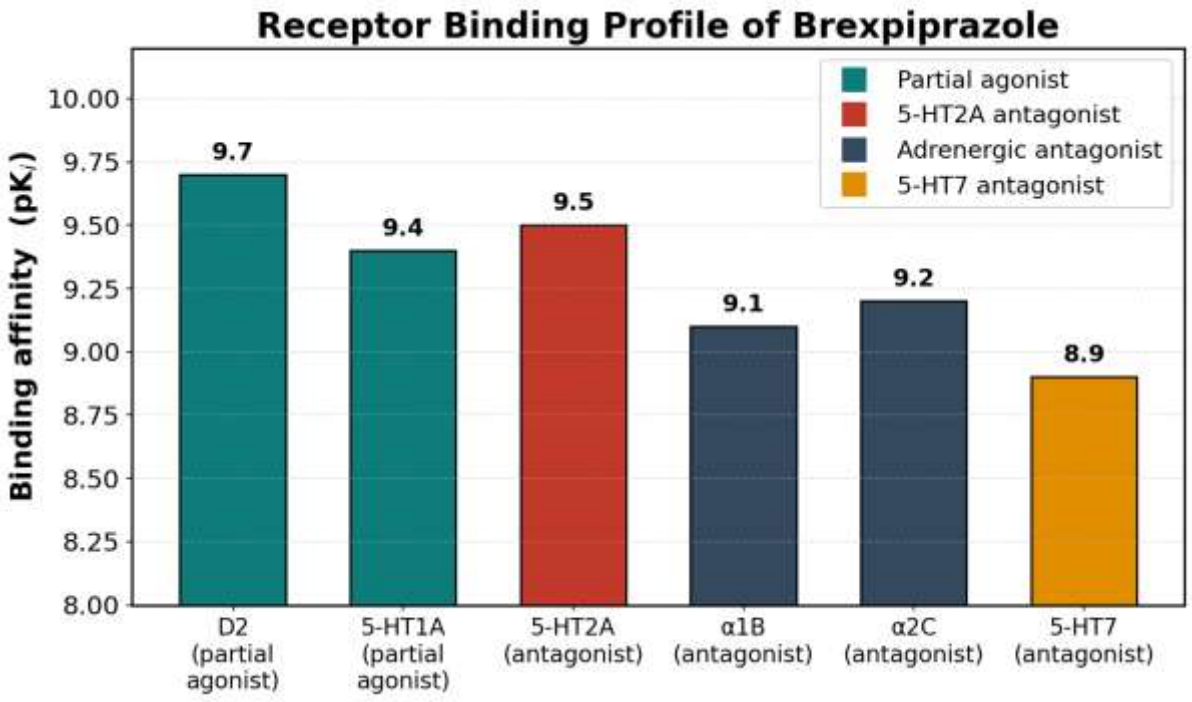

Figure 1. Representative receptor binding profile of brexpiprazole, illustrating partial agonism at D2 and 5-HT1A receptors and antagonism at 5-HT2A and adrenergic receptors (illustrative pKi values).

B. Key physicochemical and pharmaceutical attributes

Brexpiprazole has the molecular formula $C^{25}H^{27}N^{3}O^{2}S$ and a molecular weight of approximately 433.6 g·mol⁻¹ [1]. It is a white to off-white crystalline solid with limited aqueous solubility but appreciable lipophilicity, a combination that classifies it within Biopharmaceutics Classification System (BCS) class II in several reports and that strongly conditions any formulation strategy [1,2]. A molecular weight near the upper region of what is practical for passive percutaneous transport, coupled with low water solubility, means that delivery across the skin cannot be assumed to be straightforward; it must instead be engineered through deliberate selection of matrix polymers, solubilizing excipients, and permeation enhancers. At the same time, the lipophilic character that complicates aqueous handling is favourable for partitioning into the lipid-rich stratum corneum, so the same property that creates a solubility challenge also offers an opportunity for skin transport when the formulation is correctly designed.

Table 1. Representative physicochemical and pharmaceutical profile of brexpiprazole relevant to transdermal formulation.

Parameter	Value / comment	Relevance to TDDS
Molecular formula	C25H27N3O2S	Defines molecular identity
Molecular weight	≈ 433.6 g·mol⁻¹	Near upper limit for passive permeation
Aqueous solubility	Low (poorly water-soluble)	Requires solubility-enhancement strategy
Lipophilicity	Appreciable (lipophilic)	Favours stratum-corneum partitioning

Parameter	Value / comment	Relevance to TDDS
BCS class (reported)	Class II (low solubility, high permeability)	Guides amorphous / solid-dispersion design
Oral bioavailability	High (≈ 95%)	First-pass metabolism is NOT the limitation
Elimination half-life	Long (≈ 91 h)	Well-suited to sustained, infrequent dosing
Pharmacology	D2 & 5-HT1A partial agonist; 5-HT2A antagonist	Defines therapeutic indication

C. Limitations of conventional oral therapy

It is important to frame the limitations of oral brexpiprazole accurately, because the correct rationale shapes the entire formulation programme. Brexpiprazole is, in fact, well absorbed after oral administration and exhibits high oral bioavailability (on the order of ninety-five percent), so extensive hepatic first-pass metabolism is not the principal barrier to effective oral therapy [2]. The genuine and clinically decisive limitations lie elsewhere. First, adherence to daily oral antipsychotic regimens in schizophrenia and chronic depression is notoriously poor; a substantial proportion of patients take their medication irregularly or discontinue it, and non-adherence is one of the strongest predictors of relapse, re-hospitalization, and deteriorating long-term outcome. Second, once-daily oral dosing produces peak-to-trough fluctuations in plasma concentration; although brexpiprazole's long half-life buffers this to some extent, smoother and more constant exposure is generally desirable for tolerability in psychotropic therapy. Third, oral administration depends on reliable swallowing and gastrointestinal function, which cannot always be assumed in acutely unwell, cognitively impaired, or non-cooperative psychiatric patients. These adherence- and exposure-related considerations—rather than first-pass metabolism—constitute the true motivation for exploring an alternative, sustained, and minimally intrusive delivery route [5,6].

Brexpiprazole's pharmacokinetic profile is particularly compatible with a sustained, controlled-input delivery system. Its very long elimination half-life (reported to be on the order of ninety-one hours) indicates slow systemic turnover, which means that a delivery system providing a steady, low-level transdermal input could maintain therapeutic plasma concentrations over an extended dosing interval with infrequent application. A transdermal patch that a patient or carer applies once every few days, rather than a tablet that must be swallowed every single day, directly addresses the adherence problem while exploiting the drug's intrinsically long residence in the body [5,6].

II. RATIONALE FOR TRANSDERMAL DELIVERY OF PSYCHOTROPIC AGENTS

A. Advantages of transdermal drug delivery

Transdermal drug delivery systems (TDDS) deliver a drug across intact skin into the systemic circulation at a controlled rate, bypassing the gastrointestinal tract entirely [5,7]. For chronic therapy this carries several advantages. By providing a continuous, programmed input, a patch can produce sustained and relatively constant plasma concentrations, smoothing the peaks and troughs associated with intermittent oral dosing and thereby reducing the likelihood of concentration-related adverse effects. The most decisive advantage in psychiatry, however, is the impact on adherence: a once-every-few-days patch is far simpler to integrate into a treatment plan than a strict daily oral schedule, and its application can be observed and documented by caregivers or community health workers, providing a visible, verifiable record of treatment [6,8]. The route is non-invasive and painless, can be discontinued rapidly by simply removing the patch should an adverse reaction occur, and avoids the swallowing and palatability issues that complicate oral and even orodispersible dosage forms. Contemporary reviews emphasize that the applicability of TDDS now extends to molecules of moderate molecular weight and adequate lipophilicity, provided the formulation

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incorporates appropriate strategies to enhance skin permeation [7,8].

B. Particular suitability of brexpiprazole

Brexpiprazole sits at an interesting intersection of properties for transdermal development. Its molecular weight of roughly 433.6 daltons places it near the upper practical limit for passive transdermal transport, and its low aqueous solubility means that simple incorporation into a hydrophilic film would not be expected to liberate the drug efficiently. Yet its lipophilicity favours partitioning into and through the stratum corneum, and its long half-life relaxes the flux requirement: because the body clears the drug slowly, a therapeutically meaningful steady-state plasma level can in principle be sustained with a comparatively modest transdermal flux. A rationally designed polymeric matrix patch that combines an optimized polymer blend with one or more chemical permeation enhancers, and that keeps the drug in a high-energy amorphous or molecularly dispersed state to maximize thermodynamic activity, therefore offers a credible route to clinically relevant delivery. The formulation must, above all, solve two coupled problems: maintaining the drug in a soluble, high-activity state within the matrix, and overcoming the diffusional resistance of the stratum corneum [9,10].

III. SKIN AS A DRUG DELIVERY BARRIER: STRUCTURE AND TRANSPORT PATHWAYS

A. Skin architecture relevant to percutaneous absorption

The skin is a stratified, multilayered organ whose outermost layer is the principal obstacle to drug entry. From the surface inward, the relevant layers are the stratum corneum, the viable epidermis, the dermis with its microvasculature, and the underlying subcutaneous tissue [9]. The stratum corneum, typically only ten to twenty micrometres thick, is the rate-limiting barrier to passive diffusion. It is organized as a "brick-and-mortar" structure in which flattened, keratin-filled corneocytes (the bricks) are embedded in a highly ordered, multilamellar matrix of intercellular lipids (the mortar) composed chiefly of ceramides, cholesterol, and free fatty acids. The integrity and lamellar organization of this lipid matrix, together with the hydration state and protein composition of the tissue, govern how readily a molecule can traverse the barrier. Once a drug crosses the stratum corneum and the viable epidermis, it reaches the dermal capillary network and is swept into the systemic circulation [9,10].

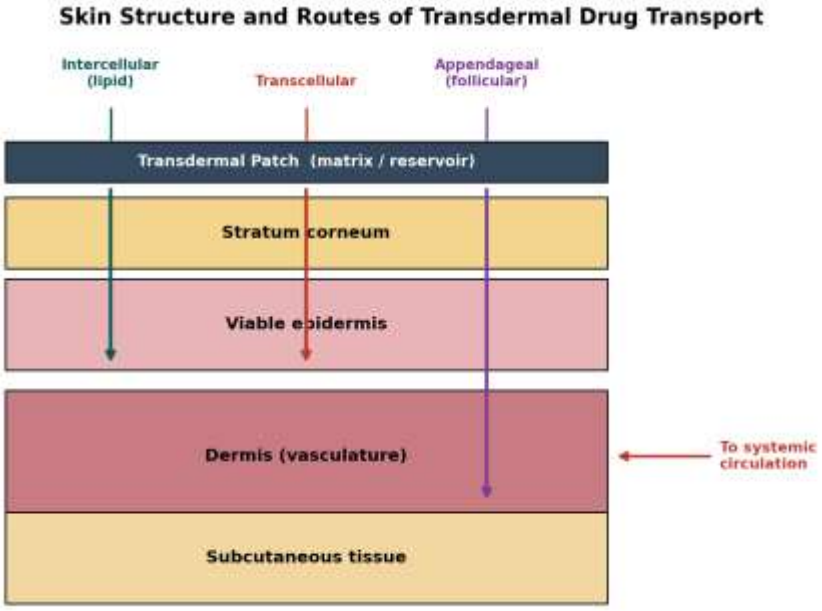

Figure 2. Schematic of skin architecture and the three principal routes of percutaneous transport—intercellular (lipid), transcellular, and appendageal (follicular)—from a transdermal patch to the systemic circulation.

B. Pathways of transdermal transport

Three principal routes of percutaneous penetration are recognized, as illustrated in Figure 2. The intercellular (lipid) pathway, in which the permeant diffuses through the tortuous lipid matrix surrounding the corneocytes, is the dominant route for most small to moderately sized drugs and is especially relevant for lipophilic molecules. The transcellular route passes directly through the corneocytes and the intervening lipids and demands repeated partitioning between hydrophilic and lipophilic domains. The appendageal route exploits hair follicles and sweat glands as shunt pathways; although these occupy only a small fraction of the skin surface area, they can be important for larger molecules and for follicular targeting. Which pathway predominates for a given compound is determined by its molecular size, its lipophilicity, and its relative affinity for lipid versus aqueous domains [10,11]. Brexpiprazole's lipophilic character makes the intercellular lipid route its most plausible principal pathway, which in turn justifies the use of lipid-perturbing chemical enhancers in the formulation [12–14].

C. Quantitative parameters: flux, permeability, and lag time

The performance of a transdermal system is described quantitatively by parameters derived from Fick's laws of diffusion. The steady-state flux (J^{ss}, expressed in $\mu g \cdot cm^{-2} \cdot h^{-1}$) is the rate at which the drug crosses unit area of skin once a constant gradient is established. The permeability coefficient (K^{p}) normalizes flux to the donor concentration, the cumulative permeated amount captures total delivery over time, and the lag time (t^{lag}) reflects the delay before steady state is reached as the skin's diffusional reservoir fills. These quantities depend on the concentration and thermodynamic activity of the drug in the donor matrix, the partition coefficient between the patch and the skin, and the diffusion coefficient within the stratum corneum [9,11]. They are measured experimentally in vitro and ex vivo using Franz diffusion cells or flow-through cells, and the resulting data feed directly into formulation optimization and into the mechanistic modelling described later in this review.

IV. POLYMERIC MATRIX TRANSDERMAL PATCHES: PRINCIPLES AND COMPONENTS

A. Matrix versus reservoir design

Transdermal patches fall into two broad architectural classes, shown side by side in Figure 3. In a reservoir system, a liquid or gel drug compartment is separated from the skin by a rate-controlling membrane that meters drug release. In a matrix (monolithic) system, the drug is dispersed homogeneously throughout a solid polymer network, and release is governed primarily by diffusion out of that network. Matrix patches are generally preferred for development programmes of this kind because they are simpler and more robust to manufacture, carry a lower risk of dose-dumping or leakage if the patch is damaged, and scale more readily from laboratory to production. In a matrix system the choice of polymer and the homogeneity of drug dispersion are the dominant determinants of release kinetics, which places polymer selection at the centre of the formulation effort [15,16].

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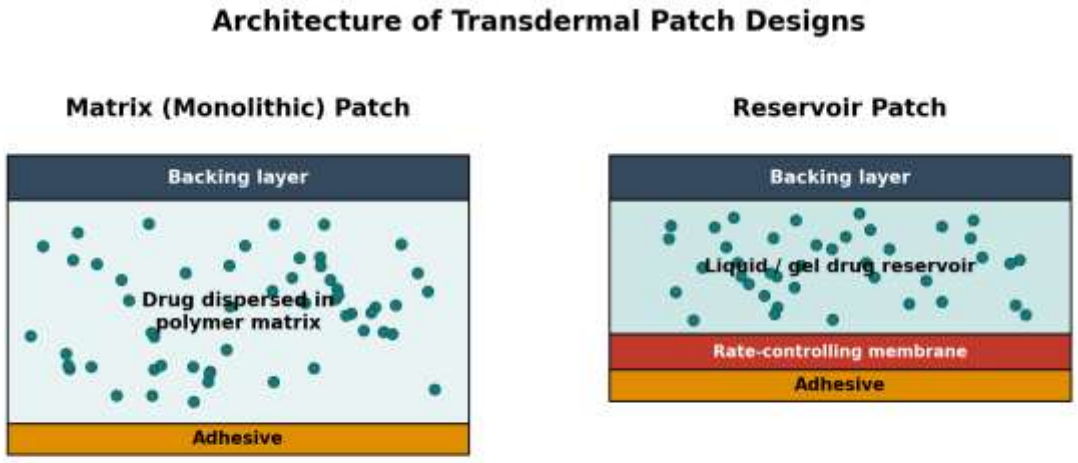

Figure 3. Comparative architecture of matrix (monolithic) and reservoir transdermal patches, showing backing layer, drug-containing layer, rate-controlling membrane (reservoir only), and adhesive.

B. Film-forming polymers: types and functional roles

Polymers form the continuous phase that houses the drug and dictates the mechanical character, drug diffusivity, and adhesion of the finished patch. Several classes are commonly employed in matrix systems, and they are most powerful when blended. Hydrophilic cellulose derivatives such as hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) promote water uptake and increase drug mobility within the matrix, favouring release where a degree of hydrophilicity is desirable. Ethyl cellulose, a hydrophobic film former, slows water ingress and drug diffusion and is therefore valuable for sustaining the release of lipophilic drugs. Methacrylate copolymers of the Eudragit family are available in neutral, cationic, and anionic grades, allowing release rate and pH-dependent behaviour to be tailored and contributing to mechanical strength. Polyvinylpyrrolidone (PVP) acts chiefly as a solubilizer and dispersant that can raise drug release, although on its own it may compromise mechanical integrity [16,17]. The art of matrix design lies in combining a hydrophilic and a hydrophobic polymer in a ratio that simultaneously delivers the target flux and acceptable film strength, as summarized in Table 2.

Table 2. Common film-forming polymer classes used in matrix patches and their functional impact.

Polymer class	Examples	Functional impact on the patch
Hydrophilic cellulose derivatives	HPMC, HPC	Increase water uptake and drug mobility; accelerate release; good film formation
Hydrophobic film-formers	Ethyl cellulose	Slow water ingress and diffusion; sustain release of lipophilic drugs
Methacrylate copolymers	Eudragit grades	Tailorable release and pH response; modulate mechanical strength
Solubilizing polymers	PVP	Enhance drug dispersion; may weaken film if used alone

C. Plasticizers, backing membranes, and adhesives

Plasticizers such as polyethylene glycol, triethyl citrate, propylene glycol, and dibutyl phthalate are incorporated to increase film flexibility and reduce brittleness. They act by increasing the free volume within the polymer network, which also raises the diffusion coefficient of the drug and therefore influences release; plasticizer level is thus a genuine formulation variable rather than a passive additive [18,19]. The backing layer must be impermeable to the drug and to moisture and must provide mechanical protection and occlusion, while the pressure-sensitive adhesive must maintain intimate, continuous skin contact for the wear period without causing irritation on application or trauma on removal. Optimizing the adhesive involves balancing tack, peel strength, and removability against skin health, and the release liner protects the adhesive until the moment of use [20].

V. FORMULATION STRATEGIES FOR A LIPOPHILIC DRUG SUCH AS BREXPIPRAZOLE

A. Solubility-enhancement approaches

Because brexpiprazole is poorly water-soluble, the formulation must deliberately raise the apparent solubility and the available chemical potential of the drug within the matrix. Established tactics include preparing a solid dispersion in which the drug is dispersed at the molecular level within a hydrophilic carrier so that it remains amorphous rather than crystalline; using cosolvents and solubilizers such as ethanol or propylene glycol; forming inclusion complexes with cyclodextrins; or incorporating nanocarriers such as lipid nanoparticles or nanoemulsions into the matrix [21,22]. The solid-dispersion-within-a-matrix approach has been used successfully in recent transdermal work to raise apparent solubility and to sustain flux, and it is particularly attractive here because keeping the drug amorphous both increases its thermodynamic activity and, if the carrier is well chosen, helps to stabilize it against recrystallization during storage [23,24].

B. Drug loading and thermodynamic activity

The driving force for transdermal permeation is the thermodynamic activity—the effective chemical potential—of the drug in the donor matrix rather than its absolute concentration. Strategies that raise this activity, such as bringing the matrix close to saturation, generating transient supersaturation, or using cosolvent systems, can substantially increase flux. The difficulty is that high-activity, supersaturated states are thermodynamically metastable and tend to relax by crystallization of the drug within the matrix during storage, which both reduces flux and threatens content uniformity. The formulation therefore aims to hold the drug in an amorphous or molecularly dispersed state using polymers that inhibit nucleation and crystal growth, accepting a controlled compromise between maximal instantaneous flux and long-term physical stability [22,23]. This tension between activity and stability is one of the central design problems of the entire programme and is monitored throughout development by thermal and diffraction techniques.

C. Use of permeation enhancers

Chemical penetration enhancers (CPEs) increase skin permeability by reversibly perturbing the ordered lipid lamellae of the stratum corneum or by altering corneocyte protein conformation, thereby lowering the diffusional resistance of the barrier. Common enhancers include oleic acid, isopropyl myristate, dimethyl sulfoxide, short-chain alcohols, and various fatty acids and esters. For a lipophilic drug such as brexpiprazole, lipid-fluidizing enhancers like oleic acid and partitioning promoters like isopropyl myristate are especially relevant and are widely used in matrix patches [12–14]. The selection and, critically, the concentration of enhancer must be optimized to maximize flux while keeping local irritation within acceptable limits, since the same lipid-disrupting action that improves permeation can compromise skin tolerability if pushed too far. Enhancer level is therefore one of the key independent variables carried forward into the formal Design of Experiments described in Section 8, and representative enhancers and their mechanisms are collated in Table 3.

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Table 3. Representative chemical permeation enhancers, their mechanisms, and practical considerations.

Enhancer	Mechanism of action	Practical use notes
Oleic acid	Disrupts stratum-corneum lipid packing; increases fluidity	Effective for lipophilic drugs; may irritate at high concentration
Isopropyl myristate (IPM)	Solubilizes lipids; promotes partitioning into skin	Commonly used in matrix patches; raises steady-state flux
Dimethyl sulfoxide (DMSO)	Strong lipid and protein perturbant	Highly effective but irritant; use cautiously at low levels
Short-chain alcohols (ethanol)	Enhance drug solubility; transiently extract lipids	Often used as co-solvent during solvent casting

VI. MANUFACTURING: SOLVENT CASTING AND PROCESS CONSIDERATIONS

A. The solvent-casting technique

Solvent casting is the most widely used and reproducible laboratory method for preparing matrix patches. In outline, the film-forming polymer or polymers, the drug, the plasticizer, and the permeation enhancer are dissolved or uniformly dispersed in a suitable volatile solvent system; the resulting homogeneous solution is degassed, cast onto a level, non-adhering substrate, and the solvent is allowed to evaporate under controlled temperature and humidity to leave a uniform film, which is then cut into patches of defined area [15,18]. The choice of solvent strongly influences the tendency of the drug to crystallize, the drying rate, the level of residual solvent, and the final mechanical properties of the film, so the casting solvent is itself a formulation decision and not merely a processing convenience. Ethanol-based and mixed-solvent systems with controlled drying are representative of recent matrix-patch work and are well suited to a lipophilic drug that must be kept amorphous.

B. Critical process parameters

Several process variables must be controlled to ensure a reproducible product. These critical process parameters include the composition of the solvent system, the cast thickness, the drying temperature, and the drying rate, which together determine residual solvent content, film porosity, and the physical state of the dispersed drug; a post-drying conditioning step may also be required. Slow, controlled drying generally favours a uniform, low-porosity film and discourages drug crystallization, whereas overly rapid solvent loss can trap solvent, introduce voids, and trigger phase separation. Process control is essential not only for predictable release kinetics and content uniformity but also for regulatory compliance with limits on residual solvents under ICH Q3C [31]. In the proposed programme, drying is conducted at a controlled temperature of approximately 40 ± 2 °C, and the relationship between these process settings and the measured critical quality attributes is examined systematically rather than left to trial and error.

VII. EVALUATION: IN-VITRO, EX-VIVO, AND ANALYTICAL CONSIDERATIONS

A. Physicomechanical testing

A battery of standard physicomechanical tests establishes that a patch is robust, uniform, and comfortable to wear. Thickness is measured at several points with a digital micrometre to confirm uniformity; weight variation is assessed across individual patches; and folding endurance, determined by repeatedly folding a film at the same point until it breaks, gauges flexibility and resistance to cracking during wear. Tensile strength and percent elongation, measured with a texture analyser, quantify mechanical strength and ductility, while surface pH—measured by applying a pH electrode to a hydrated patch on an agar surface—confirms compatibility with skin and minimizes irritation potential. Drug content uniformity, moisture content, and moisture uptake complete the picture, informing both dose consistency and storage behaviour under varying humidity [25,26]. Figure 9 illustrates how such attributes can be compared across candidate batches to guide selection.

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B. In-vitro release testing and kinetics

In-vitro release testing measures the liberation of drug from the patch into a receptor medium, usually using a Franz diffusion cell or a paddle-over-disk arrangement, with phosphate buffer at physiological pH maintained at 37 ± 0.5 °C and regular sampling with replacement of fresh medium [25]. The resulting release profiles are then fitted to mathematical models to infer the underlying mechanism, as discussed in detail in Section 8 and shown in Figure 4. For matrix patches of lipophilic drugs the early phase of release is frequently described well by the Higuchi or Korsmeyer–Peppas models, indicating diffusion-controlled transport, but reliable interpretation requires careful attention to the time window over which each model is applied and to the goodness of fit across the whole profile.

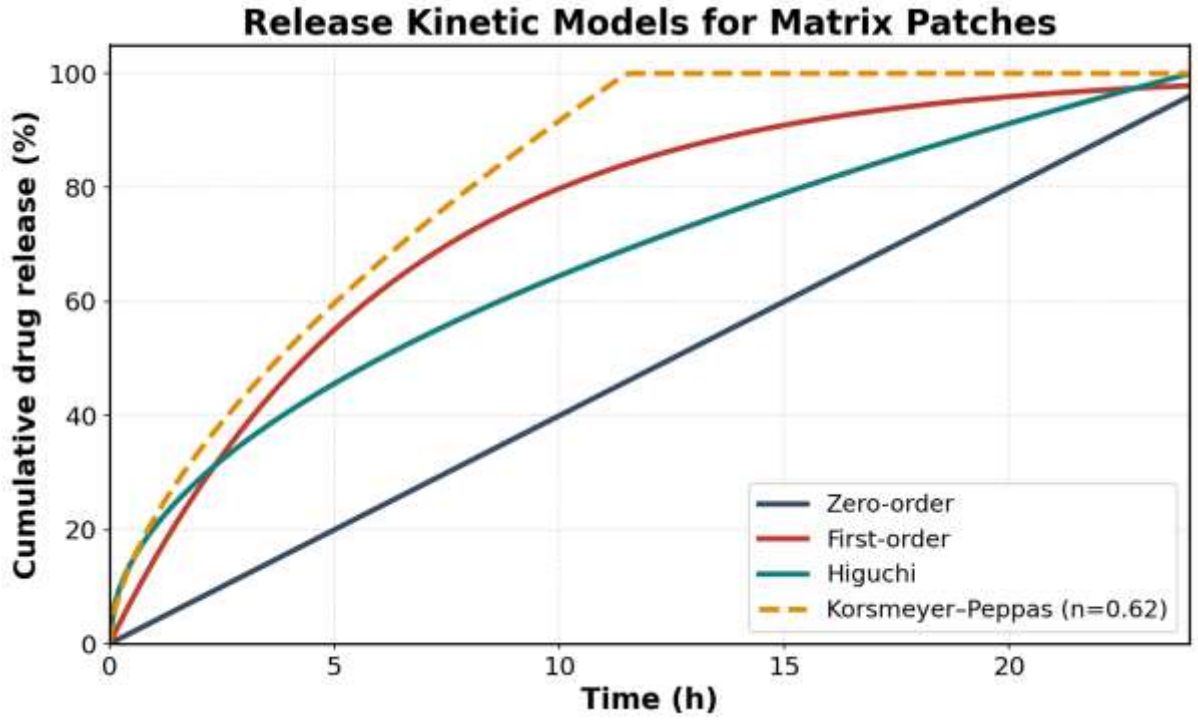

Figure 4. Cumulative in-vitro drug release fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas kinetic models for a representative matrix patch (illustrative data).

C. Ex-vivo permeation and skin retention

Ex-vivo permeation studies use excised skin—commonly rat, porcine, or human cadaver skin—mounted on a Franz diffusion cell with the stratum corneum facing the donor compartment, to quantify the cumulative amount permeated, the steady-state flux, the permeability coefficient, and the lag time under conditions that approximate real skin transport [9,11]. These studies can also reveal drug retention within the skin and any local cutaneous metabolism, both of which are relevant to performance and safety. Skin integrity must be verified before use, for example by transepidermal water loss or electrical-resistance measurements, and tissue must be ethically sourced. Figures 5 and 6 show how cumulative permeation and steady-state flux can be compared across formulation batches to identify the most promising candidates; in the illustrative data shown, increasing the proportion of hydrophobic polymer and the enhancer level progressively raises flux, consistent with the formulation logic developed above.

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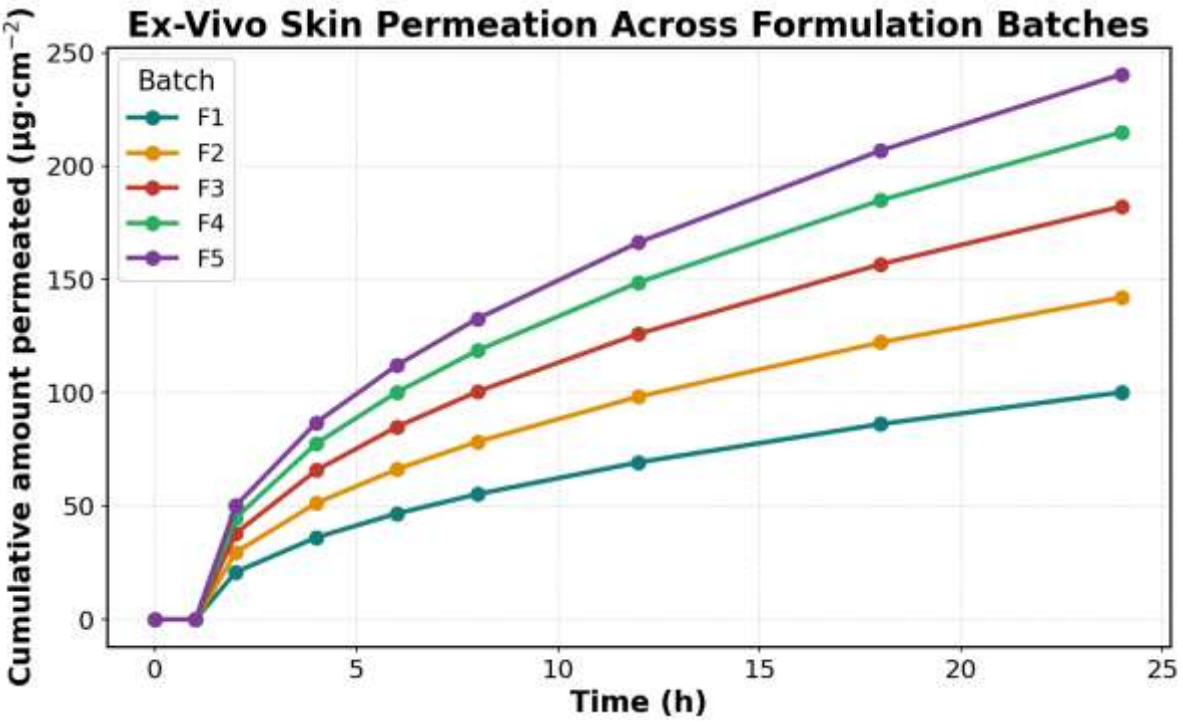

Figure 5. Cumulative amount of brexpiprazole permeated across excised skin over 24 hours for screening batches F1–F5 (illustrative data).

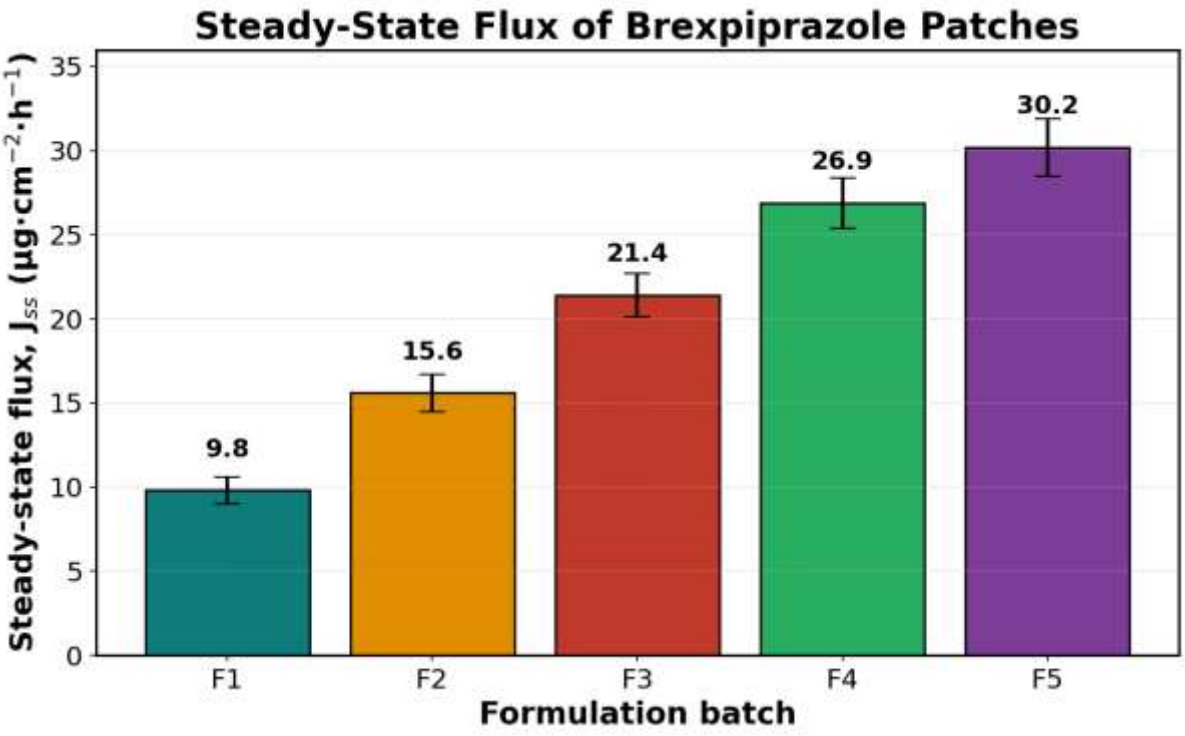

Figure 6. Steady-state flux (Jss) of brexpiprazole across formulation batches F1–F5; error bars denote standard deviation (illustrative data).

D. Analytical method development and stability-indicating assays

Accurate quantification of the drug in the donor matrix, the receptor medium, and patch extracts depends on robust, validated analytical methods. A UV–visible spectrophotometric method, based on a calibration curve constructed at the wavelength of maximum absorption in phosphate buffer, provides a convenient routine assay, while a reversed-phase high-performance liquid chromatography (HPLC) method using a C^{18} column, an acetonitrile–buffer mobile phase, and ultraviolet detection offers the selectivity and sensitivity required for precise quantification and for resolving any degradation products. Both methods are validated in accordance with ICH Q2 guidance for linearity, accuracy, intra- and inter-day precision, limits of detection and quantification, and robustness [32]. Stability is assessed by storing patches under ICH long-term and accelerated conditions and monitoring appearance, drug content, the release profile, and mechanical properties over time, supported by thermal analysis, infrared spectroscopy, and X-ray diffraction to confirm that the drug remains in its intended physical state [31,33].

VIII. DESIGN OF EXPERIMENTS AND QUALITY-BY-DESIGN APPROACHES

A. Rationale for DoE and QbD

Design of Experiments (DoE) and the broader Quality-by-Design (QbD) framework provide a statistically efficient and scientifically rigorous means of identifying which critical material attributes and critical process parameters most strongly influence the critical quality attributes of the patch—chiefly flux, drug content uniformity, and mechanical strength. Rather than varying one factor at a time, DoE varies several factors simultaneously according to a structured design, enabling main effects and interactions to be estimated from a modest number of experiments and supporting the construction of response-surface models. Factorial, central composite, and Box–Behnken designs are widely used, and the resulting models define a design space within which the formulation is robust to small variations [27,28]. The increasing adoption of these methods in transdermal research reflects both a reduction in experimental burden and an improvement in reproducibility and regulatory acceptability [29].

B. Typical factors and responses in matrix-patch DoE

In a matrix-patch DoE for brexpiprazole, the natural independent variables are the polymer ratio (the proportion of hydrophilic to hydrophobic polymer), the plasticizer content expressed as a percentage by weight, and the permeation-enhancer concentration; drug loading may be added as a further factor. The dependent responses typically include cumulative percentage release at 24 hours (Y^1), steady-state flux (Y^2), tensile strength (Y^3), and drug content (Y^4). Multivariate analysis and desirability functions are then used to locate the combination of factor levels that best satisfies all targets simultaneously. Figure 7 illustrates the kind of response surface generated by such an analysis, mapping predicted release as a joint function of polymer composition and enhancer level and revealing the region of the design space that delivers the desired performance.

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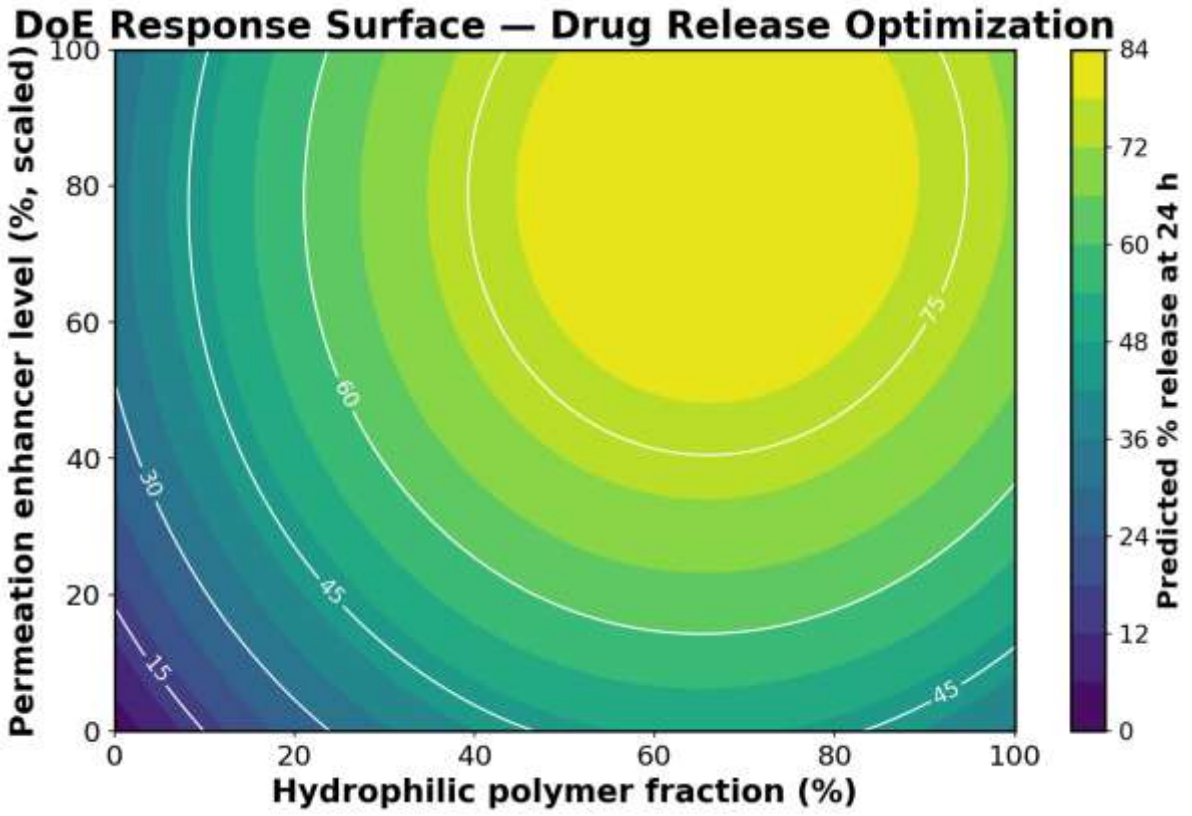

Figure 7. Representative Design-of-Experiments response surface showing predicted 24-hour drug release as a function of hydrophilic polymer fraction and permeation-enhancer level (illustrative model).

In practice, a development programme begins with a set of screening batches that span a wide range of polymer ratios, plasticizer levels, and enhancer concentrations, as illustrated in Table 4. These preliminary trials map the boundaries of the formulation space, expose batches that fail outright on film quality or release, and identify the promising region within which a formal optimization design is then deployed. The screening data also provide initial estimates of the magnitude of each factor's effect, which improves the efficiency of the subsequent response-surface design and helps to set sensible high and low levels for each variable.

Table 4. Representative composition of preliminary screening batches (all percentages expressed as w/w of total polymer weight).

Batch	HPMC (%)	Ethyl cellulose (%)	Plasticizer (%)	Enhancer (%)
F1	100	0	15	0
F2	70	30	15	5
F3	50	50	20	5
F4	30	70	20	7
F5	40	60	25	7

C. Statistical analysis and model validation

All experiments are conducted in triplicate and the results expressed as mean ± standard deviation. Inferential statistics—one-way and two-way analysis of variance with a Tukey post-hoc test—are used to establish whether differences between formulations

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are significant at a threshold of $p < 0.05$, while the response-surface models are validated by comparing predicted with observed values and computing the percentage prediction error. Dedicated software for experimental design, statistical analysis, charting, and chromatographic data handling supports this workflow and ensures that conclusions rest on a reproducible, auditable analytical basis. This statistical rigour is what allows the optimized formulation to be defended as genuinely optimal within a defined design space rather than merely the best of an arbitrary set of trials.

IX. STABILITY, SAFETY, TOLERABILITY, AND REGULATORY CONSIDERATIONS

A. Physical and chemical stability

Stability testing under ICH Q1A conditions—typically accelerated storage at 40 °C and 75% relative humidity and long-term storage at 25 °C and 60% relative humidity over six months—monitors drug content, physical appearance, release profile, and mechanical properties to confirm that the formulation remains within specification throughout its intended shelf life [31]. For an amorphous or supersaturated system the principal physical risk is recrystallization of the drug within the matrix, which would reduce both flux and content uniformity; this is tracked by differential scanning calorimetry and X-ray diffraction in addition to assay. Figure 8 shows the kind of drug-content stability profile expected from a well-designed patch, in which content remains comfortably above the acceptance limit under both storage conditions over the study period [33].

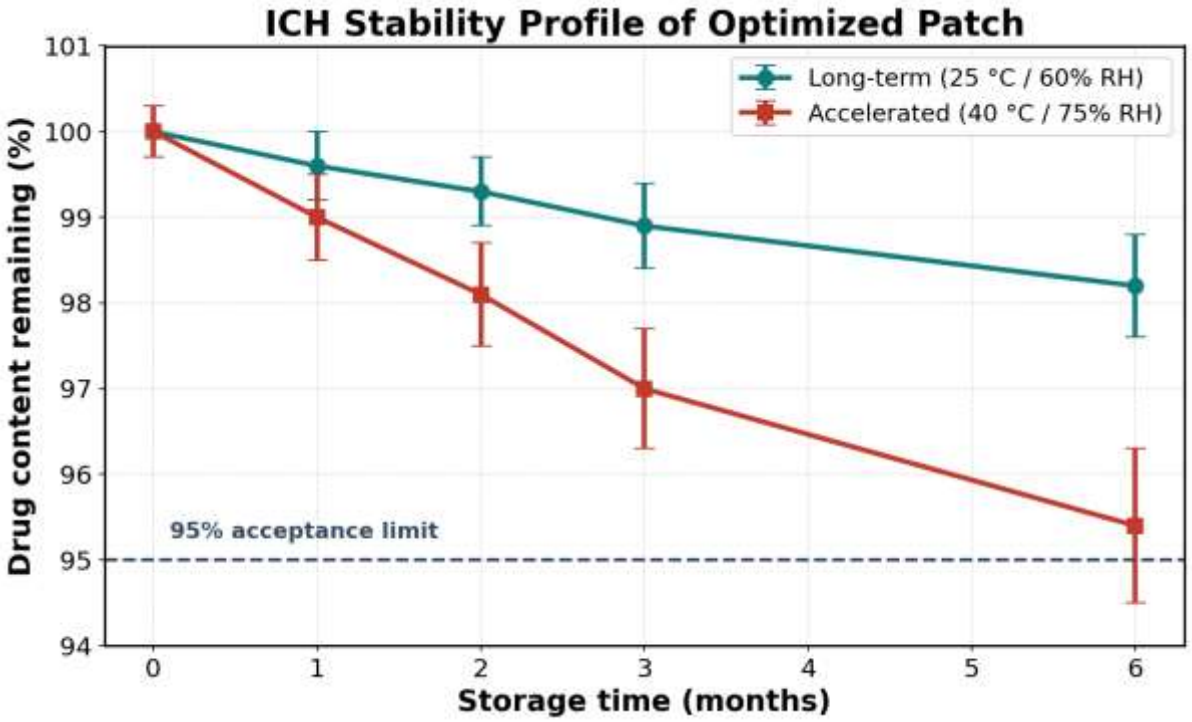

Figure 8. ICH stability profile of an optimized patch under long-term and accelerated conditions, showing retained drug content relative to a 95% acceptance limit (illustrative data).

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B. Local skin tolerability

Because a transdermal patch is applied repeatedly to the same general body region over long-term therapy, local tolerability is a first-order safety consideration. The risk of irritation or sensitization is influenced by the adhesive, by residual casting solvent, and above all by the concentration of permeation enhancer, since lipid-disrupting enhancers can provoke erythema and oedema if used at excessive levels. Tolerability is assessed preclinically by standardized irritation scoring on a suitable animal model and, where appropriate, by in-vitro assays using reconstructed human epidermis, with enhancer concentration titrated to the minimum level that achieves the target flux [12,14]. The comparative performance profiling shown in Figure 9 helps to select a candidate that balances flux against the mechanical and tolerability attributes that determine real-world wearability.

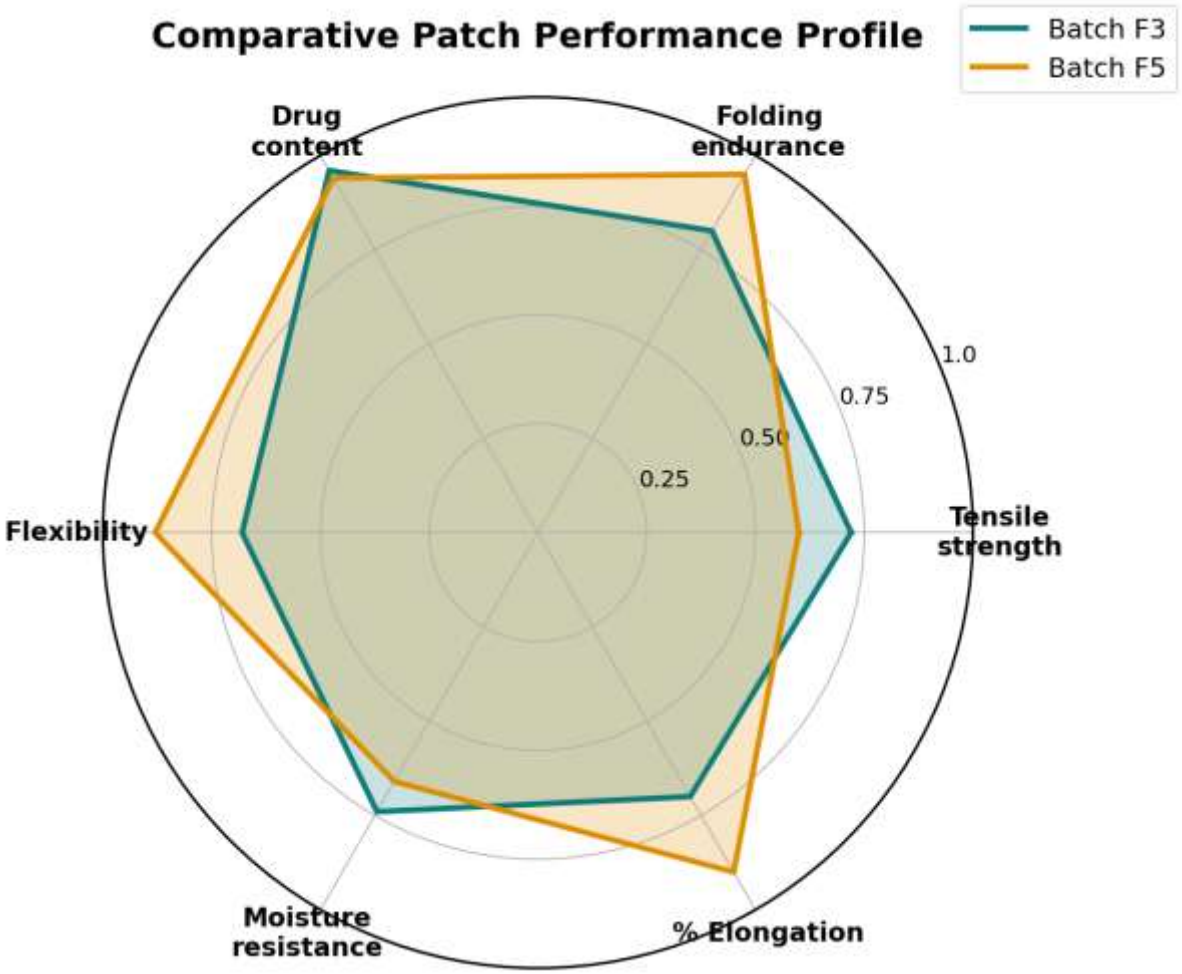

Figure 9. Comparative performance profile of two candidate batches across mechanical, content, and wearability attributes, used to guide formulation selection (illustrative data).

C. Regulatory and CMC considerations

Chemistry, manufacturing, and controls documentation for a transdermal product must address polymer and adhesive specifications, residual solvents under ICH Q3C, extractables and leachables from the backing and adhesive, stability, and in-use safety [31,34]. Because a transdermal patch represents a new route of administration for an already approved drug, regulators will require bridging pharmacokinetic studies to relate transdermal exposure to the established oral data and to support dose selection. Standard pharmaceutical references and compendia provide the specifications and methods that underpin this documentation [35–37]. Engaging with these

requirements from the outset, rather than retrofitting them, is part of the QbD philosophy that frames the entire development effort.

X. REVIEW OF PRIOR WORK AND THE CURRENT EVIDENCE LANDSCAPE

A body of work spanning more than two decades supports the feasibility of matrix-type transdermal delivery and informs the design choices made here. Foundational studies established the standard evaluation protocols for matrix patches: Arora and Mukherjee demonstrated controlled transdermal delivery of a model drug and codified methods for assessing thickness, tensile strength, drug content, and in-vitro release that remain in routine use [25]. The mechanistic understanding of the skin barrier was advanced by Barry and by Hadgraft, who clarified the structure and lipid organization of the stratum corneum, the physicochemical requirements for transdermal candidates, and the interaction of enhancers with skin lipids and proteins, providing the theoretical foundation on which modern formulation rests [9–12].

Subsequent investigators refined the component choices. Studies on sustained-release patches using ethyl cellulose and HPMC blends established the direct relationship between the proportion of hydrophobic polymer and the rate of release, showing that higher hydrophobic content slows release and improves stability [19]. Work on plasticizers demonstrated that agents such as polyethylene glycol and triethyl citrate markedly improve flexibility and folding endurance, but that excessive plasticizer increases drug diffusion and weakens the film, so that plasticizer level must be optimized rather than maximized [20]. Preformulation-focused studies using infrared spectroscopy, thermal analysis, and X-ray diffraction underscored that compatible excipients keep the drug amorphous and prevent crystallization during storage, whereas incompatible combinations reduce release and undermine physical stability [22]. The solid-dispersion strategy for poorly soluble and antipsychotic drugs was shown to raise apparent solubility and permeation flux, directly motivating its use for brexpiprazole [23,24].

More recent work has emphasized systematic optimization and composite design. Investigations applying factorial and Box–Behnken designs confirmed that statistically structured experimentation captures the influence of polymer concentration, plasticizer, and casting thickness on release and mechanical properties, with release frequently conforming to the Higuchi model, and that such designs shorten development time while improving reproducibility [26,27]. QbD-based studies on polymeric transdermal patches used response-surface methodology to reveal strong correlations between formulation variables and performance and highlighted QbD as a valuable route to regulatory-oriented development [28,29]. Composite polymer systems incorporating chemical enhancers have been shown to improve flux and sustain release by modifying polymer microstructure and skin partitioning, reinforcing the importance of polymer–drug–enhancer interactions in determining long-term performance [30]. Comprehensive reviews of penetration enhancers have classified these agents by mechanism—lipid disruption, protein denaturation, and solvent effects—and have stressed the need to balance efficacy against irritation, particularly for fatty acids and esters used with lipophilic drugs [13,14]. Collectively, this literature establishes both the feasibility of the approach and the specific levers—polymer blend, plasticizer, enhancer, and drug physical state—that an optimization programme must control.

XI. GAPS IN KNOWLEDGE AND FUTURE DIRECTIONS

Despite this substantial foundation, several gaps justify a focused, integrated programme for brexpiprazole. First, integrated optimization specific to brexpiprazole matrix patches is limited: while isolated reports describe solid dispersions or nanocarrier approaches for the drug, a comprehensive matrix-patch programme that links polymer-blend selection, drug physical state, permeation enhancement, DoE-based optimization, and ICH-level stability within a single coherent design space remains underdeveloped. Second, much of the existing work reports either release or permeation data in isolation and lacks the mechanistic correlation—release kinetics through to skin partitioning and flux—that is

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needed for predictive design and regulatory confidence. Third, few studies combine an optimized flux with extended stability data and formal skin-tolerability assessment, which are precisely the attributes that determine viability for chronic psychiatric indications. Addressing these gaps requires a study that develops the patch through systematic DoE and QbD, characterizes both release and permeation mechanistically and relates them to one another, and pairs that characterization with comprehensive ICH stability and tolerability evaluation.

The conceptual framework that follows from this analysis is summarized in Figure 10. Preformulation and compatibility work first identifies a polymer, plasticizer, and enhancer combination that maintains brexpiprazole in an amorphous, solubilized state. Solvent casting under controlled drying then produces uniform films, and DoE optimization targets the critical quality attributes of flux, controlled release, and mechanical integrity. Mechanistic evaluation combines in-vitro release with ex-vivo permeation and kinetic modelling to expose the relationship between release and permeation, and the optimized formulation is finally subjected to ICH stability testing and skin-irritation assessment. Looking further ahead, the same matrix platform could be combined with mild physical enhancement, such as microneedle-assisted application, to lift flux for proof-of-concept work, and supersaturation or complexation strategies could be deployed under careful stability monitoring where additional flux is required.

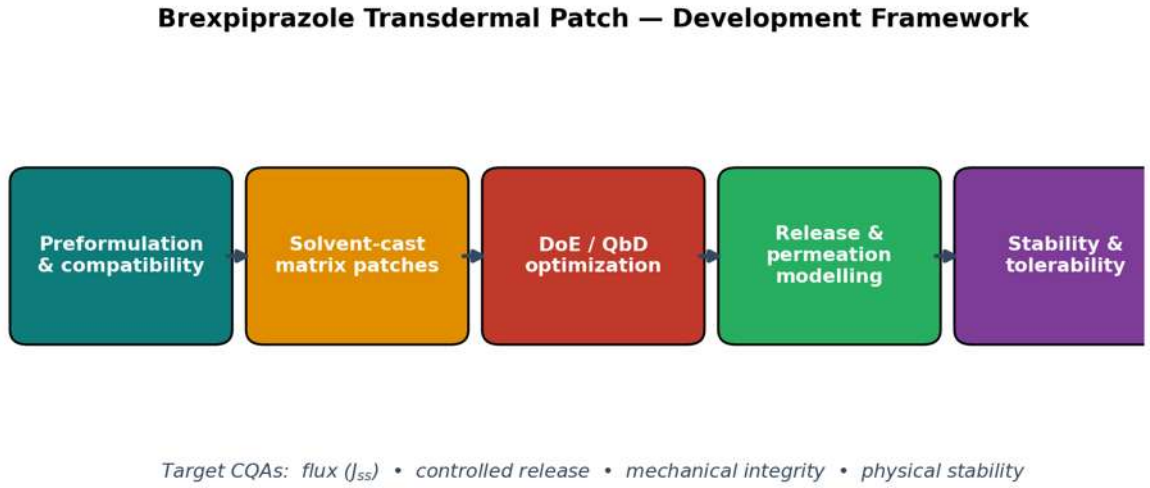

Figure 10. Conceptual development framework for the brexpiprazole transdermal patch, from preformulation through DoE optimization, mechanistic evaluation, and stability and tolerability assessment.

XII. CONCLUSION

Brexpiprazole is a clinically valuable atypical antipsychotic whose long-term effectiveness is limited less by its absorption than by the practical realities of chronic oral therapy—poor adherence, plasma-concentration fluctuation, and dependence on reliable daily dosing in a patient population for whom that cannot be assumed. Its high oral bioavailability means that first-pass metabolism is not the problem to be solved; rather, its very long elimination half-life makes it an unusually well-suited candidate for a sustained, low-maintenance delivery system that improves adherence and smooths systemic exposure. A polymeric matrix-based transdermal patch addresses these needs directly. The scientific path to such a product is well defined: a rationally chosen blend of hydrophilic and hydrophobic film-forming

polymers, an optimized plasticizer level, and carefully titrated chemical permeation enhancers, with the drug held in a high-activity amorphous state, manufactured by controlled solvent casting and refined through DoE and QbD. Coupled with mechanistic release–permeation characterization and ICH-compliant stability and tolerability evaluation, this approach offers a credible route to an optimized transdermal delivery system for brexpiprazole with controlled release, therapeutically relevant flux, acceptable physical stability, and the potential to improve real-world outcomes in long-term psychiatric care. Realizing that potential will require the integrated, systematically optimized programme outlined in this review.

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