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REVIEW

Film-Forming Gels for Topical Drug Delivery: A Systematic Review of the Effects of Formulation on Film Performance, Drug Release, and Skin Permeation

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Abstract: Film-forming gels (FFGs) are increasingly recognized as a medium for topical drug delivery. However, existing evidence correlating specific formulation characteristics with drug delivery efficacy remains fragmented across many studies and is only partially organized. This systematic review aimed to consolidate these findings into a single framework and examine how important formulation variables affect three main outcome domains: film characteristics, drug release behavior, and skin permeation. A systematic search of PubMed and Scopus was conducted until October 2025, adhering to the PRISMA criteria. Studies were included if they examined topical FFG formulations and reported at least one of the predetermined outcomes. A total of 27 studies fulfilled the inclusion criteria, with solvent evaporation identified as the predominant method for FFG preparation. Across this body of research, the selection and relative ratio of polymers and plasticizers have consistently emerged as critical determinants influencing drying time (<15 min), mechanical strength, flexibility, and bioadhesive properties of the film on the skin. Most formulations released the drug slowly over approximately 8–48 hours. In studies that measured permeation, FFGs usually exhibited a higher flux and/or better drug retention in the skin than regular topical formulations. The film's ability to block the skin and the use of penetration enhancers in the matrix are thought to cause these effects. In summary, these results show that FFGs are a flexible and customizable formulation platform, where the film's characteristics, release rate, and skin penetration are all strongly linked to the composition's design. To obtain this technology with clearer therapeutic benefits, we need to employ Quality by Design principles more widely and have more consistent evaluation methodologies across studies.

Keywords: film-forming gels, topical drug delivery, film properties, drug release, skin permeation

Introduction

In recent decades, topical and transdermal medication delivery has evolved from conventional dose forms to more sophisticated platforms designed for both local and systemic treatments, reflecting an enhanced understanding of percutaneous absorption and modern dermal product design.[1,2] These routes leverage the vast surface area of the skin to avoid first-pass metabolism and gastrointestinal side effects, offering a viable option for long-term therapy of chronic disorders.[3–5] Nevertheless, commonly utilized formulations such as patches, creams, and gels possess inherent

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limitations; their clinical efficacy may be hindered by skin irritation, residual drug accumulation on the surface, physical instability, including recrystallization during storage and scale-up, and a relatively short duration of adherence to the skin.[6] Furthermore, the stratum corneum serves as a significant barrier that inherently limits passive diffusion, particularly for compounds whose lipophilicity, molecular size, and ionization state fall outside acceptable ranges. This difficulty is particularly evident in lipophilic medicines and poorly water-soluble natural compounds, which often provide a low concentration gradient that serves as the driving force for penetration.[7–10] An established example is α-mangostin, which typically requires solubility-enhancing techniques, such as amorphous solid dispersions (ASDs), nanocrystals, or hydrogel matrices, to augment solubility, maintain a supersaturated state, and consequently enhance the diffusion driving force across the skin.[11–16]

Traditional semi-solid formulations have recognized limitations, leading to the development of film-forming gels (FFGs) as hybrid delivery systems that maintain the ease of application characteristics of creams or gels while offering prolonged on-skin retention typical of solid dosage forms.[3,17] Within the extensive category of film-forming systems, FFGs are distinguished by their initial application as a liquid or gel, which subsequently transforms in situ into a continuous film when the volatile solvent is evaporated. The drying phase results in a thin, often translucent film that adheres tightly to the skin, functioning as a localized drug reservoir that facilitates controlled release of the active ingredient over time.[18–20] Experimental research involving various active compounds substantiates this notion: polymer-based ketoprofen and acyclovir FFGs have demonstrated the ability to create films exhibiting adequate tensile strength and elasticity, while enhancing cutaneous drug accumulation and optimizing pharmacodynamic responses in animal models relative to conventional bases.[21,22] An identical platform has been modified for additional applications, including chlorhexidine sprays that create uniform, aesthetically pleasing films and formulations based on natural polymers such as nitrocellulose, sericin, and bee-derived substances that can safeguard wounds, enhance tissue regeneration, and inhibit the proliferation of acne-associated bacteria.[23–26] These observations collectively reflect recent reviews on film-forming systems, highlighting their potential as topical delivery platforms that can provide sustained topical delivery while maintaining favorable aesthetic acceptability by adjusting the composition of polymers, plasticizers, and solvents to regulate the formation of an on-skin reservoir and influence the subsequent drug-release profile.[18,27,28]

The mechanism by which FFGs work becomes easier to appreciate when set alongside conventional creams or gels and classical transdermal patches, as conceptually depicted in Figure 1. In conventional semi-solid formulations, the

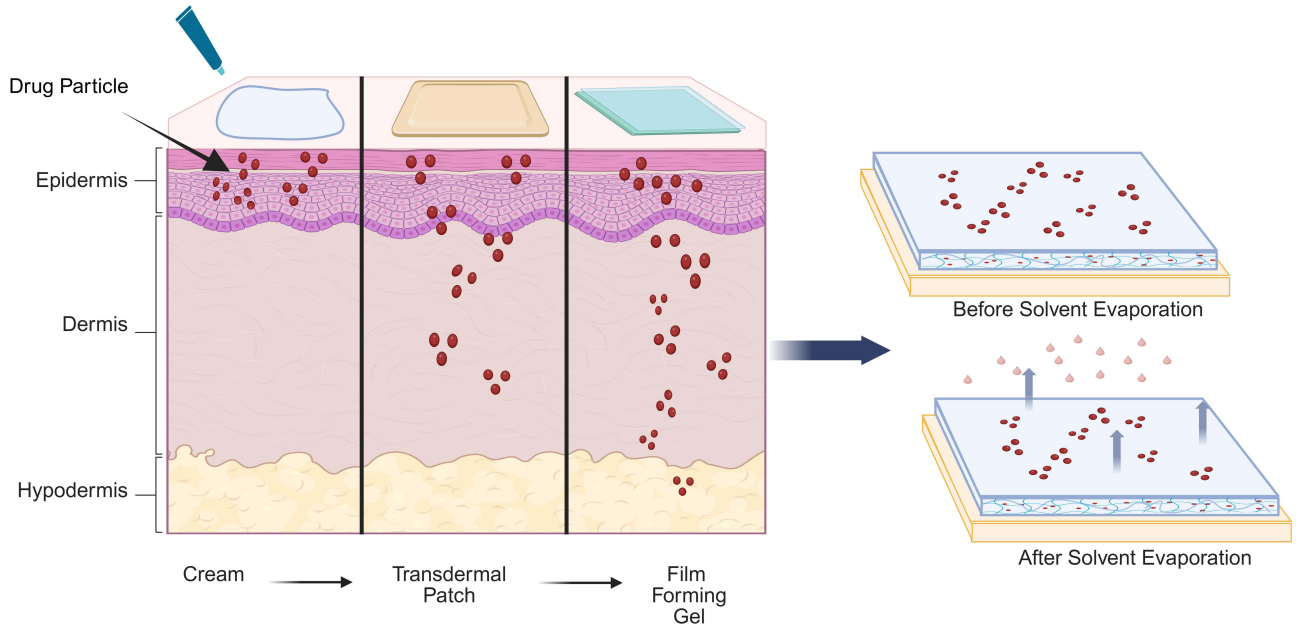

Figure 1 Schematic Comparison of Conventional Topical Dosage Forms (Creams and Patches) versus The Film Forming Gel Mechanism (Created in BioRender. Sriwidodo, (S) (2026) https://BioRender.com/9jws8sg).

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applied cream or gel creates a dense heterogeneous layer on the skin. The properties of the vehicle, the solubility of the active ingredient in the continuous phase, and the ability of the active ingredient to partition into the stratum corneum are the main factors that affect drug release. This layer can be removed by sweating and bathing, which means it will not last long on the skin and needs to be reapplied often.[29,30] Transdermal patches have numerous layers. The backing is occlusive, the drug-containing reservoirs or adhesive matrices are in the middle, and the adhesive layers touch the skin directly. These designs make it easier to manage the release and hydration of the stratum corneum, but they are rather inflexible, have a specific application area, give a set dose per patch, and may be uncomfortable or unpleasant because of the backing.[31–33] FFGs depend on an alternative form of dermal metamorphosis. The formulation is initially applied as a gel or viscous solution in a thin layer. The polymer concentration rises as the volatile solvent evaporates, which makes the chains rearrange into a thin, continuous coating that sticks closely to the skin's microrelief.[18,27] At this stage, the medicine that was first dissolved in the liquid phase is now concentrated in the residual polymer layer. The concentrations at the skin contact could be close to or even higher than the medicine's thermodynamic solubility. This temporary supersaturation increases the thermodynamic driving force for diffusion and makes the concentration gradient stronger. At the same time, the semi-occlusive nature of the film reduces transepidermal water loss, improves stratum corneum hydration, and together they make penetration easier.[19,27] Comparative studies indicate that film-forming techniques exhibit superior resistance to water and mechanical abrasion compared to creams or gels. This means that the applied dose stays on the skin for longer, which allows for longer dosing intervals because the dose is released from the established on-skin reservoir.[34,35] The film is formed directly on the skin and conforms to its contours, allowing FFGs to be applied over extensive or irregular surfaces, resulting in an exceedingly thin layer that is frequently imperceptible to the naked eye. In reality, they function as "patch-no-patch" systems, integrating the retention and release mechanisms characteristic of patches with the adaptable coverage and aesthetic appeal of semi-solids, including sprayable formats that ensure uniform dose distribution.[6,36] From a formulation perspective, film-forming devices serve as a connection between conventional semi-solid formulations and standard patches. Depending on the parameters of the reservoir, polymer backbone, and therapeutic target, their formulation can be changed to focus on surface or upper-epidermal effects or to make transdermal absorption into the systemic circulation more effective.[35,37] This conceptual framework is illustrated in Figure 1, which shows the formation of a supersaturated film and a drug reservoir within the stratum corneum while contrasting drug delivery characteristics for creams/gels, patches, and FFGs.[6,27,35,37]

Current knowledge regarding film-forming gels is fragmented, comprising individual experimental reports and narrative summaries that primarily address polymer types and therapeutic applications, yet fail to systematically correlate specific formulation choices with quantifiable performance outcomes.[36–38] A critical appraisal of the available literature also reveals substantial methodological heterogeneity across primary studies, including differences in in vitro and ex vivo models, evaluation methods, and reported endpoints for drying behavior, mechanical performance, release, and skin permeation.[6,35,37] As a result, it remains difficult to compare studies directly or to define consistent structure–performance relationships for FFGs. In particular, there is still limited synthesis of how specific formulation variables, such as polymer composition, plasticizer level, solvent system, and enhancer use, influence key outcome domains, including film properties, drug-release behavior, and skin permeation. This lack of consolidated evidence hinders rational formulation design and encourages continued trial-and-error excipient selection, particularly for products intended for prolonged skin contact.[13] Accordingly, the present systematic review was undertaken to collect, organize, and critically analyze the available evidence on how the compositional elements of FFG formulations influence these three core outcome domains. Unlike earlier descriptive summaries, this work provides a structured, evidence-based synthesis that clarifies the interplay between formulation design and targeted performance, while also highlighting the relevance of Quality by Design (QbD) principles for future FFG development.

Materials and Methods

Eligibility Criteria

We defined the inclusion criteria using the Population, Intervention, Comparator, Outcome (PICO) framework but applied it in a way that could accommodate both experimental and clinical studies (Table 1). Eligible populations (P)

Table 1 Eligibility Criteria for Study Selection

Parameter	Inclusion Criteria	Exclusion Criteria
Population/Model (P)	In vitro and ex vivo models (eg, Franz diffusion cells, excised skin/synthetic membranes) and preclinical in vivo animal models	Non-dermal applications, mucosal delivery routes (eg, buccal, nasal, vaginal), studies focusing solely on systemic outcomes without local dermal metrics
Intervention (I)	Topical or transdermal Film-Forming Gels (FFGs)	Formulations lacking an in situ film-forming phase transition (eg, conventional gels, creams, or patches)
Comparator (C)	Conventional topical dosage forms or internal comparisons among varying FFG compositions	N/A (Single-arm formulation studies were eligible)
Outcomes (O)	Primary: (i) Film properties, (ii) drug release kinetics, (iii) skin permeation Secondary: Safety profiles (toxicity or skin irritation)	Studies not reporting at least one of the primary functional outcomes of interest

were used to evaluate topical or transdermal drug delivery, encompassing in vitro and ex vivo systems (such as Franz diffusion cells with synthetic membranes, excised animal skin, or human cadaver skin), preclinical in vivo animal studies, and clinical trials involving healthy volunteers or patients. The intervention of interest was film-forming gels (FFGs) designed for the dermal or transdermal delivery of an active pharmaceutical agent. Formulations specifically designed for mucosal administration (eg, buccal, nasal, ocular, vaginal, or rectal) were excluded from the definitions of topical or transdermal administration. For the comparator (C), we accepted both external and internal comparisons, which encompassed conventional topical products (creams, ointments, transdermal patches, or non-film-forming gels) as well as direct comparisons between various FFG formulations differing in polymer type, plasticizer content, or permeation enhancer. Single-arm studies lacking a definitive external comparator were also admissible, contingent on the provision of detailed formulation characteristics and performance metrics. Outcomes (O) were determined as three fundamental domains indicative of drug delivery efficacy: (i) characteristics of the resultant film, (ii) drug release kinetics, and (iii) assessment of skin penetration/permeation including steady-state transdermal flux. Additionally, safety parameters, such as toxicity and skin irritation, were considered as secondary outcomes.

A study was deemed eligible if it examined an FFG as a medium for topical or transdermal drug delivery to the skin, employed a suitable experimental framework (in vitro, preclinical in vivo in animals, ex vivo, or a clinical trial in humans), and reported at least one of the following predetermined outcome domains: physical attributes of the formed film, drug release dynamics, or metrics related to skin penetration or permeation. Records were excluded if they lacked an assessed FFG formulation, did not report outcomes pertinent to film properties, drug release, skin permeation, or publication type that did not present complete original data, including narrative reviews, editorials, letters to the editor, or conference abstracts. No limitations were imposed on the indications, therapeutic domains, or active ingredients.

Information Sources and Search Strategy

We systematically searched PubMed and Scopus, covering all records indexed in each database from inception to October 2025. To complement the electronic search, we examined the reference lists of all the included papers and relevant review articles to identify additional studies that met our eligibility criteria. The search strategy combined Medical Subject Headings (MeSH) with free-text terms related to film-forming gels and topical drug delivery, including "film-forming gel", "topical drug delivery", "transdermal drug delivery", "skin permeation", and "drug release", linked with the appropriate Boolean operators. We did not restrict the search by publication year; only studies available as full-text articles in English were considered.

Study Selection

At the initial stage of study selection, one reviewer (FF) screened the titles and abstracts of all retrieved records using the Rayyan Web platform to support a structured and consistent screening workflow.[39] Records judged to be irrelevant were

excluded at this stage, whereas those considered potentially eligible were retained for full-text assessment. In the subsequent stage, full-text versions of all potentially eligible articles were obtained and examined in detail against the predefined inclusion and exclusion criteria by the same reviewer. Whenever uncertainties or borderline cases arose during the full-text assessment, they were discussed among the review team until a shared judgement was reached. If consensus could not be achieved, a third reviewer (AB or LC) made the final decision. Data extraction was performed by FF and FSN, and any issues or inconsistencies identified at this point were jointly reviewed and resolved with M and NW. All of the graphics and figures in this publication were developed by FA and conceptualized by FF to support the visual presentation of the technique and data synthesis. The complete process of study discovery, screening, inclusion, and exclusion is outlined in the PRISMA 2020 flow diagram (Figure 2) presented in the Results section.[40]

Data Extraction Process

Data extraction was performed by FF and FSN, who worked independently and then cross-checked each other's entries using a piloted data extraction form to ensure consistency and reproducibility in data collection. Each eligible study documented key bibliographic details (first author, year of publication, and country) along with formulation variables, including the type and concentration of the film-forming polymer, plasticizer, permeation enhancer, solvent system, and active ingredients.

Three main domains comprised the performance metrics: (i) Film Characteristics (such as drying time, tensile strength, and flexibility); (ii) Release Dynamics (such as cumulative release and kinetic modeling); and (iii)

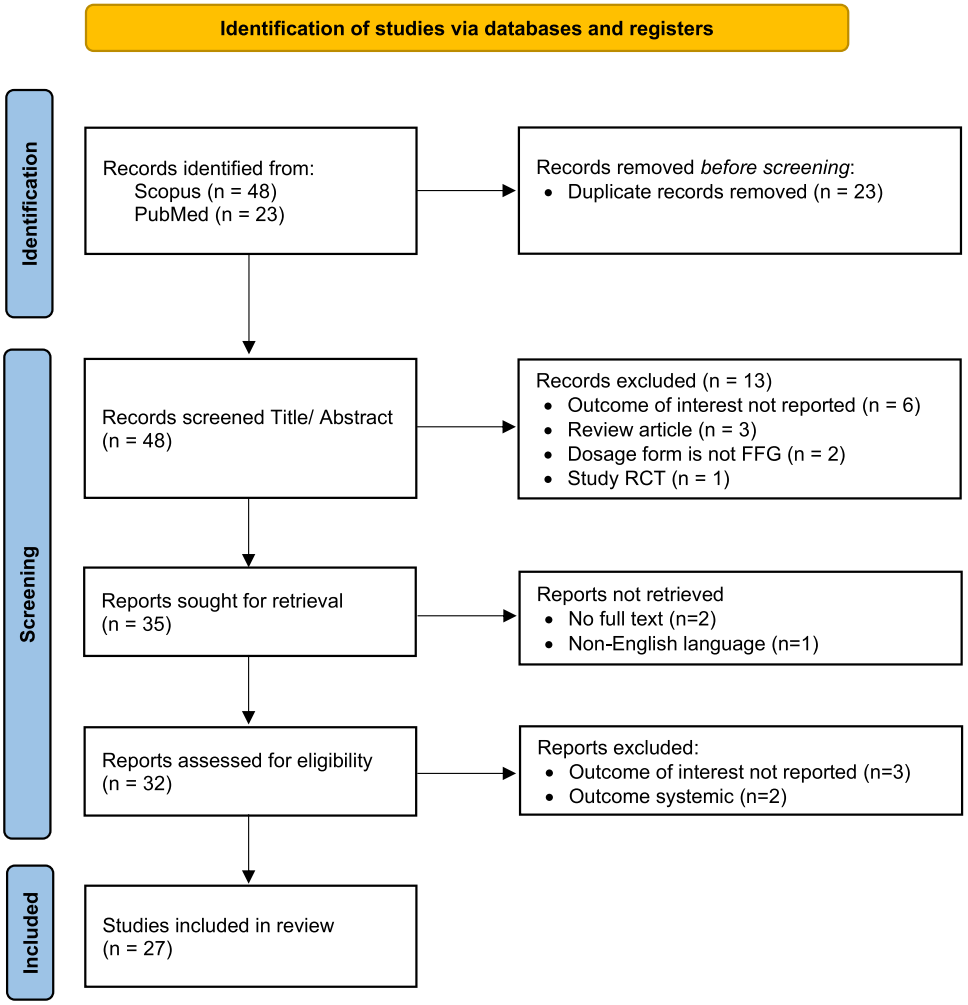

Figure 2 PRISMA Flow Diagram of Study Selection.

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Permeation Parameters (such as steady-state flux, lag time, and skin deposition). Additionally, to supplement the formulation features, secondary safety data about toxicity and skin irritation were extracted where reported. In cases where numerical data were only presented graphically, values were estimated using digital image analysis tools. Discrepancies between the two extractors were addressed through discussion and, when necessary, consultation with senior team members (M and NW).

Results

Study Selection

The study selection process is summarized in the PRISMA flowchart (Figure 2). The database search yielded 71 records: 48 from Scopus and 23 from PubMed. After removing 23 duplicates, 48 unique records were screened for titles and abstracts. At this stage, 13 records were excluded, most often because they did not report the outcomes of interest, were review articles, did not involve a film-forming gel dosage form, or were randomized controlled trials that did not meet the predefined eligibility criteria. Full-text articles were obtained from 35 records. Three articles could not be retrieved: two lacked full-text access and one was not in English. The remaining 32 full-text articles were examined in detail. Five were eliminated at this point, either because their main focus was on systemic rather than local delivery (n = 2) or because they did not publish results pertinent to topical performance or skin penetration (n = 3). Ultimately, the final systematic review included 27 studies that met the inclusion criteria.

Characteristics of Included Studies

A review of the 27 eligible studies, summarized in Table 2, showed that research on Film-Forming Gels (FFGs) is still concentrated in the preclinical domain, with many investigations combining in vitro characterization with animal or ex vivo models (n = 12). Rodent skin and synthetic membranes were the predominant tools used for permeation testing (21 studies), whereas human models, ex vivo or in vivo, were used in only six formulations. Evidence from true clinical settings is therefore sparse; only one report provided patient-level data describing FFG applied as an adjunct to laser therapy in vitiligo.[41] Other human studies have generally been confined to early irritation or tolerability assessments.[42] From a manufacturing perspective, solvent evaporation was the main fabrication route and was adopted in 23 of the 27 studies, with in situ sol–gel systems described only for tramadol, a combined 5-FU/ibuprofen product, and cubebin formulation.[43–45] Single wound-dressing FFG containing CHE was produced by solvent casting.[46]

The therapeutic spectrum represented in these studies is dominated by pain management, particularly formulations containing analgesics or NSAIDs, followed by products for superficial infections (antifungal or antiviral agents), with a smaller number addressing other dermatological conditions. Interest in phytopharmaceutical FFGs appears to be growing, with examples based on alpha-mangostin, sericin, and various essential oils, although in vivo confirmation of these natural activities remains less developed than that of synthetic drugs. Where in vivo endpoints were reported, FFGs generally outperformed their reference formulations, including longer anesthetic duration with ropivacaine FFGs[47] and greater reductions in fungal infection scores for terbinafine and tavaborole-based systems.[50,53] Regarding secondary safety outcomes, a specific subset of the included literature incorporated local biocompatibility evaluations. Three of these studies used in vitro toxicity tests using pertinent cell lines, whereas nine used in vivo primary cutaneous irritation models (such as the Draize test on animal models). Overall, the safety results across these studies were very positive. Excellent biocompatibility was repeatedly shown by formulations that were applied continuously over lengthy periods of time, with minimal to no erythema and edema. These combined results verify that FFGs' improved penetration and extended skin retention do not impair epidermal biocompatibility or cause toxicity that is clinically meaningful.

Formulations Composition

As crudely illustrated in Figure 3, the research reveals that the majority of FFGs have a structural logic based on three fundamental components: a film-forming polymer network, one or more plasticizers, and at least one permeation enhancer. Table 2 provides unique formulation variables for each of the included studies. The film matrix is drawn from a broad palette of materials that can be divided into three groups. The first group includes natural polymers such

Table 2 Characteristics of Included Studies on Topical Film-Forming Gels

Study Design	Model Design	Drug Used | Activity	FFG Method	Results	Ref
In vitro; ex vivo; in vivo	Synthetic; Animal	Ropivacaine | Local anaesthetic	Solvent evaporation	• FFG Ropivacaine > marketed > placebo (6.5 s/ 4 h; p≤0.05); • Effect lasts ≤ 7 hours	[47]
	Animal; Human	Tramadol HCl | Analgesic	In situ sol-gel	• FFG vs Control showed a significant analgesic effect (p<0.05) up to 90 min • Non-irritant (Score 0.000)	[43]
	Synthetic; Animal; Human	Clotrimazole | Antifungal	Solvent evaporation	• Drying time 4.19–13.73 min; • Skin simulation maintained ≥10 µg/mL	[42]
	Synthetic; Animal	Domperidon | Antiemetic	Solvent evaporation	No irritation/ erythema at 24 & 48 h	[48]
	Synthetic; Animal	MTX | Rheumatoid arthritis	Solvent evaporation	No erythema at 24 h	[49]
In vitro; in vivo	Synthetic; Human	5-FU; IBU | Antimetabolite; NSAID	In situ sol-gel	No irritation after 120 h (TMIS < 0.5)	[44]
	Animal	Ketoprofen | NSAID	Solvent evaporation	• SI CbFG–OA 0.5% (76%) vs Marketed (26%) p<0.05; • WB CbFG–OA 0.5% (44%) vs Marketed (38%)	[21]
	Animal	Terbinafine | Antifungal	Solvent evaporation	DA5505 ↓culture-positive feet & infection score vs Marketed (p<0.001)	[50]
	Synthetic; Animal; Human	Tranexamic acid | Antifibrinolitic	Solvent evaporation	• Drying 8–12 min; • No erythema until 72 h (Draize=0).	[51]
	Animal	MCCA | Analgesic and antiinflammation	Solvent evaporation	Pain inhibition FFG (54.37%) vs marketed (48.2%)	[52]
	Synthetic; Animal	Tavaborole | Antifungal	Solvent evaporation	• Antifungal Efficacy FFG (95.83%) > Drug suspension (87.62%) > Marketed gel (76.79%) > Control (8.37%) • Non-irritant (Score 0.000)	[53]
	Animal; Human	Acyclovir | Antiviral	Solvent evaporation	Macroscopic - No erythema, not irritating	[54]

(*Continued*)

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Table 2 (Continued).

Study Design	Model Design	Drug Used | Activity	FFG Method	Results	Ref
In vitro; ex vivo	Animal	Aceclofenac | NSAID	Solvent evaporation	NR	[47]
	Synthetic; Animal	5-Fluorouracil | Antimetabolit	Solvent evaporation	NR	[55]
	Synthetic; Animal	Curcumin | Antiiflammation	Solvent evaporation	NR	[56]
	Synthetic; Animal	Curcumin; Terbinafine | Antiiflammation; Antifungal	Solvent evaporation	NR	[57]
	Synthetic; Animal	Curcumin | Antiiflammation	Solvent evaporation	NR	[58]
In vitro	Animal	α-Mangostin | Antibacterial, Antiinflammatory, Antioxidant	Solvent evaporation	NR	[59]
	Synthetic	Aceclofenac | NSAID	Solvent evaporation	NR	[60]
	Animal	Acyclovir | Antiviral	Solvent evaporation	NR	[22]
	Synthetic	Cinnamon leaf essential oil | Antibacterial	Solvent evaporation	NR	[25]
	Animal	Royal jelly; Honey water | Antioxidant	Solvent evaporation	NR	[61]
	Animal	Sericin | Wound healing	Solvent evaporation	Non-cytotoxic; cell viability >80%	[24]
	Synthetic	CHE | Wound healing	Solvent casting	Non-cytotoxic	[46]
	Synthetic	Cubebin | Antioxidant	In situ sol-gel	Low Cytotoxicity	[45]
Ex vivo; in vivo	Animal	Etoricoxib | NSAID	Solvent evaporation	• Edema inhibition at 0.5 at 8 hours oral (10.89/ 96,72%) vs FFG (4.00/ 82.88%) • Highly tolerable (Score = 0.555)	[62]
In vitro; Clinical	Synthetic; Human	5-Fluorouracil | Antimetabolit	Solvent evaporation	• 5-FU FFG + CO_2 laser → ↑Repigmentation (Excellent 40% vs 0% Control) • Safe and well-tolerated	[41]

Notes: ↑: increase; ↓: decrease; →: leads to.

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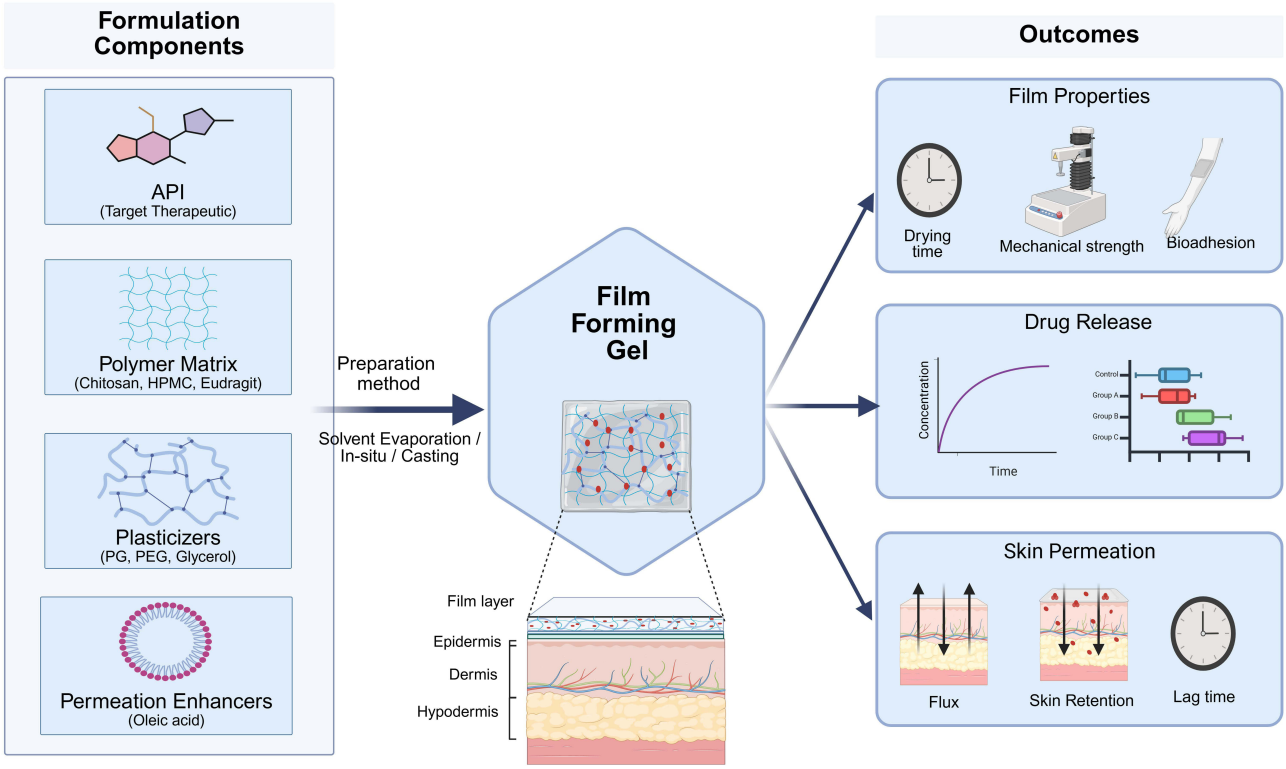

Figure 3 Schematic Overview of Film Forming Gel Formulation Components and Outcomes Performance. (Created in BioRender. Sriwidodo, (S) (2026) https://BioRender.com/j8pzf02).

xanthan gum, zein, chitosan, and sericin. The second category comprises semisynthetic cellulose derivatives, most frequently HPMC, HPC, sodium CMC, and HEC. The third group includes fully synthetic polymers, such as PVA, PVP K30, various grades of Eudragit®, Carbopol, and several organic–inorganic hybrids based on GPTMS or TEOS. Rather than relying on a single polymer, many formulations use composite matrices that intentionally combine two polymer types (eg, natural with synthetic or semisynthetic with synthetic) to balance the film strength, flexibility, swelling behavior, and surface characteristics.

The plasticizer part is the main way to change how the material works. This research utilized low-molecular-weight PEGs (400/600) and polyols such as glycerol and propylene glycol. Some examples of these systems are triethyl citrate, xylitol, and sorbitol. Chemical enhancers are often used to change how much of a chemical the skin takes in. N-methyl-2-pyrrolidone, a polar aprotic co-solvent, non-ionic surfactants such as Tween 80 or Cremophor RH40, and fatty acids such as oleic acid are among the examples. In order to facilitate the solvent's rapid evaporation following application, the vehicle phase is typically a hydroalcoholic mixture, such as ethanol and water. However, only aqueous or single organic vehicles are used when solubility limits are required. In combination, these formulation choices and their interactions underpin the behavior of FFGs in three critical performance domains: the physical properties of the resulting film, the pattern of drug release, and the extent and profile of skin permeation, as shown in the conceptual framework in Figure 3.

Film Properties Outcomes

For all of the formulations that were looked at, the resulting films were most often described as transparent and visually consistent, with their pH adjusted to a level that is appropriate for long-term skin contact (around 4.0–8.0). Antifungal medications are a distinct category, as they are often formulated for a more acidic environment, around pH 4–6, which aligns with cutaneous physiology and antifungal efficacy.[50,62] The drying time is one useful characteristic that exhibits significant variance. While water-rich systems or those with high concentrations of polymers like chitosan typically take 30 to 60 minutes to generate a dry film, formulations based on volatile solvents can do so in around 1 to 2 minutes.[57,59]

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Viscosity measurements show good agreement with reported spreadability, indicating that most systems continue to be simple to use and adhere to the skin's surface satisfactorily.[63]

The excipients employed to change the matrix have a big effect on how these films react to mechanical stress. When polyol plasticizers are added, the hardness and tensile strength, which are usually between 0.2 and 0.7 MPa, tend to go down, but the elongation at break often goes up to 200%[21,44,46] When you mix these two things together, the films become less brittle and can move with the skin without breaking. Complementary solid-state work using XRD and DSC frequently shows a reduction or disappearance of sharp crystalline peaks and the appearance of amorphous patterns for the drug, which is consistent with the active presence of stable molecular dispersion within the polymer network.[41,43]

Drug Release Outcomes

The in vitro release data indicate widespread behavior across the different FFG formulations. Only a portion of the 27 studies provided numerical release profiles, most of them over test periods of 8–24 hours, with a few extending the measurements to 48 hours.[48,51] Drug release is usually described as a cumulative percentage, though a small number of authors went further to fit the data to kinetic models such as zero- or first-order equations.[49,55]

The proportion of drug release ranged from modest to nearly complete, depending on the system design. At the lower end of the spectrum, a clotrimazole FFG built on a CP–PU–TC matrix released approximately 22.94% of its load over 24 hours, with a profile comparable to that of a marketed cream.[42] Conversely, several other formulations delivered a much higher cumulative release (>90%), including specific FFGs designed for tranexamic acid, tavaborole, and cubebin.[51,53] These variations highlight that drug release is highly tunable. For instance, increasing the sericin content or tuning the chitosan–lactic acid ratio was directly associated with higher amounts of drug liberated during testing.[24,49] Burst-then-sustained patterns were also frequently observed, allowing an initial loading dose followed by prolonged delivery.[46]

Skin Permeation Outcomes

Out of the 27 papers included, 14 provided quantitative data on ex vivo skin permeability. Table 3 shows all of the quantitative permeation outcomes, such as steady-state transdermal flux (Jss), cumulative amount penetrated (eg, Q24), and skin retention. This makes it easy to compare them. When you look at these datasets next to each other, FFGs always work better than regular topical products (such creams or gels that are sold on the market) in terms of flux and overall delivery through the skin. For example, specific formulations of ketoprofen,[21] terbinafine,[50] and acyclovir[22] demonstrated substantial multi-fold increases in permeability and steady-state flux relative to their commercial counterparts (Table 3).

The design of the formulation has a big effect on how well the medicine is absorbed and kept in the skin. For example, a clotrimazole FFG showed better flux and better drug retention in the skin than the reference cream.[42] Altering the polymer network, such as utilizing thiolated polymers,[49] or employing distinct enhancer combinations[48,62] provides an additional level of control over the transport behavior. Table 4 gives a full summary of how these different formulation variables affect the characteristics of films, drug release, and skin permeation.

Discussion

Overview of Research Landscape

According to the body of evidence, film-forming gel (FFG) technology is presently in the process of transitioning from preclinical validation to clinical application. Most research still only use in vitro, ex vivo, and animal models, and human trials are mostly limited to small case series or initial irritation assessments.[41,42,49] Stringent bioequivalence requirements, high trial costs, and a lack of reliable pharmacokinetic surrogates are the driving forces behind the delayed clinical translation that is typical of complex topical formulations.[64–67] In addition, the stratum corneum's natural biological characteristics, like variances in hydration, age, and disease condition, make it hard to apply in vitro results to a wide range of patient groups.[68–71]

Table 2 shows a clear maturity gap between FFGs made using synthetic medications and those made with natural products when looked at from a therapeutic point of view. Synthetics, such as analgesics and anti-infectives, typically have significant in vivo efficacy, often surpassing traditional gels or creams.[47,50] On the other hand, phytopharmaceutical

Table 3 Formulation Components and Performance Outcomes of Film-Forming Gels (FFG)

Drug	Comparator	FFG Composition (Polymer; Plasticizer; Enhancer; Solvent)	Outcomes			Reff
			Film Properties	Drug Release	Skin Penetration/Permeation	
5-FU	Control	• HPMC; Zein; • PG; • NR; • Ethanol; Water	• pH 5.02–5.34; • Drying 4.1–8.5 min; • Drug content 97.4–99.3%; • DSC: endotermic peak 283°C	• ↑HPMC → ↑Release; • ↑Zein → ↓Release; • Optimal 85.1% at 12 h (HPMC 4%, Zein 1%)	NR	[41]
	Control; Marketed: FU Cream	• Chitosan; • PG; • Oleic acid; Tween-80; • Ethanol; Water	• Drying 10–15 min; • pH 6.20–6.70; • Viscosity 0.95–0.99 Pa.s	• Release FFG9 (2.5:1) 83%; • Kinetics: first-order (R^2 = 0.996); • Enhancer vs %release → p>0.05	FFG9 (81.45%) vs marketed (48.99%) → ~1.66× higher	[55]
	Control	• PVA–GPTMS–PVP; • Glycerol; • NR; • Water	• ↑GPTMS → ↑Tensile stress, ↓Elongation • ↑Mechanical strength → ↑Adhesion	↑GPTMS (10–34%) → ↑Release	NR	[44]
α-Mangostin	Control	• PVA; Eudragit NE 30D; Kollidon 90F; Carbopol 934; • Sorbitol; • NR; • Ethanol; Water	• Drying 30 min; • Thickness 0.01 mm; • Elongation 211%; • Tensile 1.33 MPa	NR	• Bifasic; plateau ≤30 min–480 min; • Epidermis: FFG1 35–38% > FFG2 25–28%; • ↑Amorph AM → ↑Difusi	[59]
Aceclofenac	Control	• HPMC; Chitosan; • PEG-400; • Tween 80; • Ethanol	• ↑HPMC → ↑Drying, ↓Spreadability • Spreadability 5.47–25.81 g·cm/s; • Drying 7.27–12.52 min;	NR	NR	[63]
	Control	• HPMC; Eudragit RL100; • PEG-400; • Tween 80; • Ethanol	• ↑Polimer→ ↑Viscosity, ↑Drying, ↑Film thickness and weight, ↓Spreadability; • pH 5.4–6.3; • ↑Drug content 99.83%	NR	• ↑Polimer → ↓Permeation (sustained); • F1 release 97.54% at 12h; permeation 80% at 12h	[60]
Acyclovir	Marketed: Acyclovir cream	• Chitosan; PVP K30; • PEG 600; • NR; • Ethanol; Water	• Film time 5 min; • ↓PEG600 → ↓Break elongation, ↑Young's modulus, ↓Flexibility; • ↓Crystalinity	NR	Flux FFG ACV (50.2) vs Marketed (8.70) μg/cm^2; ↑PEG → ↑Permeability	[22]
	Placebo; Marketed: Zovirax®	• Polycarbophil; PVP; • Glycerin; PG; • NR; • Water	• Transparant and flexibility; • Drying 60 min; • Viscosity 156.6–175.6 Pa.s; • pH 6.7–7.0	NR	Acyclovir FFG (11.9%) vs Zovirax® (0.5%) → ↑23.8× (p≤0.05)	[54]
CHE	Control	• PVA; XG; AG; CMC-Na; • Glycerol, 1.3.-P; Xylitol; • NR; • Ethanol; Water	↑Glycerol → ↓Hardness, ↓Tensile, ↓Young's modulus, ↑Elongation	• ↑Xantan→ ↑Swelling, ↑Release; • Burst 60.33% at 1h → Sustained to 88.00% at 8h	NR	[46]

(*Continued*)

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Table 3 (Continued).

Drug	Comparator	FFG Composition (Polymer; Plasticizer; Enhancer; Solvent)	Outcomes			Reff
			Film Properties	Drug Release	Skin Penetration/Permeation	
CLEO	Control	• Nitrocellulose; • Castor oil; • NR; • Ethanol; Ethyl acetate	• F6 > F5 Tensile strength → 0.1948 > 0.0728 MPa, pH → 4.45 > 4.28; • F5 > F6 Drying → 3.10 > 2.30 min	NR	NR	[25]
Clotrimazole	Clotrimazole | Control and Marketed: Canesten® cream	• CP; PU; TC; • NR; • Oleic Acid; • Water	• Spreadability 35.71 g.s; • Bioadhesion (81.9 g) → TC>CP>PU; ↑CP→ ↑WOS, ↓Spreadability	FFG CTZ (22.94%) vs Marketed (23.78%) at 24 h	• Flux FFG vs Marketed (μg/cm^2/h) 32.28 vs 6.44; • Tlag (h) 4.37 vs 2.09; • Retention (μg/cm^2) 111.22 vs 86.77	[42]
Cubebin	Control	• Tri-ureasil; • NR; • NR; • Ethanol; Water	• ↑HCl/Si→ ↓Film forming time; • Wettability 81–88°→ ↓Water uptake	• ↑Cubebin→ ↑Release; • 1>5>10% → 90% at 24h	NR	[45]
Curcumin	Control	• Zein, HPMC 4000; • Glycerol; Oleic acid; • NR; • Ethanol; Water	• ↑HPMC → ↑Viscosity; • Film forming time → OA > Glycerol ($p<0.05$); • Drying 4.5 min	F5–N7 (FFH + CUR-GNPs) → >60% at 12h; 85% at 24h	NR	[56]
	Control	• Zein; PVP; HPMC 4000; • Oleic acid; • NR; • Ethanol; Water	• Drying < 1 min in skin; • FTIR/PXRD (amorph) → D1 >D2; D4>D3	• Curcumin: D1 (5.0 μg) > D2 (4.0 μg); • TBH: D4 (176.7 μg) > D3 (134.5 μg) in 24h; • PVP (TBH) > Zein based (Cur)	NR	[57]
	Control	• Zein; PVP; HPMC 4000; • Oleic acid; • NR; • Ethanol; Water	• Drying FFN < D; • SEM/PXRD: FFN3 uniform → highest 24h, no recrystallization	24h (μg) → FFN3 ≈ 30 » FFN2 ≈ 13 > FFN1 ≈ 7 > FFN4 ≈ 5	NR	[58]
Domperidon	Control; Conventional gel (CG)	• Chitosan; • PG; • Tween 80; • Ethanol; Water	• CG vs TG viscosity 0.441 vs 0.538 Pa.s; • Spreadability 17.904 vs 15.61 g/cm^2	• PS vs TS: 96.109% vs 76.396% at 8h; • CG vs TG: 49.67% vs 36.079% at 8h	• PS vs TS: 24,67% vs 58,47% at 8h; • CG vs TG: 19.70% vs 48.20% at 8h	[48]
Etoricoxib	Control (-); Oral etoricoxib suspension	• Eudragit RL100; HPMC K100M; • PG; • NR; • Ethanol; Water	• ↑HPMC → ↑Viscosity; • pH 6.81–8.18; • Drying 3.24–6.43 min; • Drug content 91.0–99.5%	NR	• ↑Polimer → ↓Permeation; • Q24: 4639 μg/cm^2	[62]
Ketoprefen	Marketed: Ketotop®/ Kenofen®	• Chitosan; • PG; • Oleic acid; Tween 80; NMP; Cremophor RH40; • Ethanol; Water	• ↑OA → ↑Tensile strength, ↑Elongation; • Viscosity 5.0 Pa.S; • Drying 10 min	NR	• CbFG–OA (0.5) showed a flux of 308.6 μg/cm^2/h vs Marketed 95.5 μg/cm^2/h ($p<0.05$); • OA (0.5%) → ↑Permeation	[21]

MCCA	Control; Marketed: Diclofenac diethylamine emulgel	• CMC-Na; PVP; • Glycerol; • Mint; NMP; • Water	The thick chocolate gel forms a homogeneous film in 2.40 min	NR	• Enhancer → ↑Permeation (μg/cm^2); • Mint 2% → Q24 h 32.57 ± 0.92; • Mint 1% + NMP 1% → Q24 h 31.12 ± 1.21;	[52]
MTX	Conventional FFG; Marketed gel	• Chitosan; • PG; • NR; • Lactic acid; Water	• CL-FFG > TE-FFG: Spreadability, viscosity, drug content • 19.59 g/cm^2 vs 17.84 g/cm^2; • 728.58 vs 881.80; 80.38% vs 74.45%	• CL-FFG 97.90% (first order); • TE-FFG 62.559% (zero order) → TE-FFG < CL-FFG (sustained)	• TE-FFG vs CL-FFG → Permeation (μg/cm^2) → 2,147.71 vs 1,280.49; • Flux (μg/cm^2/h) → 186.97 vs 120.36	[49]
Ropivacaine	Placebo; Marketed lidocaine gel	• HPMC; HPC; • Methyl Gluceth-10/-20; • NR; • Ethanol	• ↑Polymer → ↑Viscosity, ↑Drying time; • Transparant; Drying ≤1 min	• ↑Polymer (reduced diffusion) → ↓Release; • >90% diffusion for low molecular weight polymers	• ↓Polymer → ↑Diffusion, ↑Permeation; • Flux 211 μg/cm^2/h	[47]
Royal Jelly; Honey water	Control	• PVA 117; CMC; HEC; • PEG 400; • NR; • Water	↑RJ → ↑Viscosity, ↑Mechanical strength (Young/ Adhesion), ↓Drying (glass slide)	NR	NR	[61]
Sericin	Control; Dexamethasone	• PVA; Sericin; • Glycerol; • NR; • Ethanol; Water	• Drying 3.54–4.54 min; • Spreadibility 1.48–2.39; • pH 5.22–5.37; • ↑Sericin→ ↑Swelling, ↓Spreadability	• ↑Sericin→ ↑Release (μg/mL); • F4 (800) > F5 (260) > F6 (140) at 24h ($p<0.05$)	NR	[24]
Tavaborole	Control; Drug suspension; Marketed gel	• Eudragit L-100; HPC; • TEC; • NR; • Ethanol	• pH 5.24–5.83; • Drying 1.40–2.40 min; • ↑Polimer→ ↑Viscosity	• ↑Polimer→ ↑Release; • F1-F9 → 91.10–98.76% / 24h	NR	[53]
Terbinafine	Marketed: Terbinew® gel, Lamisil® Cream, Lamisil Once®	• Chitosan; • NR; • NR; • Ethanol; Water	• Forming a bioadhesive film; • pH 4.0±0.1; • Drug content 99.8±0.1%	NR	DA5505 ↑100× vs cream, 30× vs gel, 4.5× vs solution ($p<0.05$).	[50]
Tramadol HCl	Control	• PVA; TEOS; • Glycerine; • NR; • Water	• pH 6.6–7.1; • Drying ≤ 2 min; • Film thickness 0.458 mm; • Swelling index: 89.45; • XRD: ↓PVA crystalinity → ↑Amorph	NR	• ↑PVA → ↓Permeability; • ↑Excess TEOS → Compaction → ↓Permeability; • Hybrid gel 92.36% vs PVA film 69.55%	[43]
Tranexamic acid	Control	• PVA; HPMC; Carbopol; NaCMC; • PG; • NR; • Ethanol; Water	• F8< F7< F9 Drying → 8.30< 11.23< 12.14 min, • Spreadability → 24.2< 25< 25.43 mm	• TXA-FFG sustained release up to 48 h; • >95% cumulative at 48 h	NR	[51]

Notes: ↑: increase; ↓: decrease; →: leads to.

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Table 4 Summary of the Effects of Formulation Variables on Film Performance, Drug Release, and Skin Permeation

Formulation Factor	Category (Examples)	Effect on Film Properties	Effect on Drug Release	Effect on Permeation
Polymers	Semi-synthetic (HPMC, HPC, NaCMC)	• ↑Conc. → ↑Viscosity and Drying time • Forms clear, transparent films	↑Conc. → Denser matrix → ↓Drug release rate	↑Conc. → ↓Diffusion and Transdermal flux
	Synthetic (PVA, PVP, Eudragit)	• Robust and water-resistant films • Semi-occlusive effect	Stable and prolonged sustained release profiles	Stable occlusive effect supports sustained permeation
	Natural (Chitosan)	• Highly bioadhesive films • Slower drying time (30–60 min)	Swelling-dependent release	• Mild permeation enhancer • Quicker onset
Plasticizers	Polyols/Hydrophilic (Glycerol, PG, PEG-400)	• ↑Flexibility and Elongation at break • ↓Brittleness	• Alters matrix pathways • ↑Release rate	Ensures continuous contact area for partitioning
Enhancers	Lipid disruptors (Oleic Acid, Tween 80, NMP)	• Modulate mechanical properties • ↑Conc.→ ↑Tensile strength and Elongation	Minimal direct effect on matrix	• Disrupts stratum corneum lipids • ↑Transdermal flux
Solvents	Volatile (Ethanol, Water)	Rapid drying (1–2 min)	Leaves highly concentrated drug reservoir	• Drugs supersaturated • ↑Skin permeation

Notes: ↑: increase; ↓: decrease; →: leads to.

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FFGs are still mostly in the early stages of formulation. Well-known problems with herbal standardization, like batch-to-batch variability, extraction inconsistencies, and active constituent instability, are making it harder for them to move forward.[72–75] Metabolomics and Quality by Design (QbD) are new methods that could help with these problems, but they are not being used much in the production of herbal FFGs right now.

The predominance of solvent evaporation methods (Table 2) as a manufacturing approach suggests a preference for scalable, regulator-friendly processes. This method makes films that are all the same and does not have the problems that come with pH-triggered or high-surfactant in situ gelling systems.[37,76] The safety profiles of the trials that were looked at are very good. Excellent biocompatibility (>80% cell viability) is confirmed by in vitro assays.[24,45,46] While in vivo models report Draize irritation scores of zero or near-zero, even after 48 to 120 hours of continuous application.[43,44,48,49,62] This preclinical safety is particularly applicable to clinical environments, evidenced by the significant dermatological tolerance observed in patients administered a 5-FU FFG.[41] These results show that FFGs can improve transdermal distribution without using harsh chemicals that can hurt the skin.

Research in wound care indicates a gradual transition toward more advanced hybrid systems in the future. You can get very precise adhesion and moisture control by combining solvent-based FFGs with hydrogel scaffolds or polymers that respond to stimuli.[25,46,77,78] In the end, the research in Table 2 show a practical formulation technique based on safe, well-known technologies. FFGs effectively address two fundamental issues associated with conventional topicals: the brief duration of skin residence and the dose variability that results from rubbing off. This is accomplished by ensuring that the medication is released gradually and has favorable safety profiles.

Film Properties Outcome

The parameters that directly influence clinical performance and user comfort, such as drying time, mechanical strength, elasticity, spreadability, and bioadhesion, were the primary focus of the characterization of film properties in the included studies. This is consistent with the critical quality attribute (CQA) framework for dermal film-forming systems, which stipulates that films must form promptly, adhere effectively, and maintain flexibility during skin movement.[35,36,76] These formulation-dependent variables are systemically summarized in Table 4 to facilitate a more rapid comprehension of their generalized trends.

The majority of FFGs in the dataset formed films in less than 15 minutes. Although a 5–10 minutes drying window is generally regarded as a pragmatic goal for routine dermal applications, the acceptable limits are determined by specific therapeutic requirements. For example, clinical studies on psoriasis mists indicate that patients are highly satisfied with drying times of 1.5–5 minutes.[79] In contrast, highly bioadhesive systems or wound-covering hydrogels, which are frequently composed of natural polymers such as chitosan, necessitate extended drying times. This trade-off is intentionally accepted in order to enhance local protection and barrier formation.

Film-forming polymers in this context are consistently identified as the primary determinants of film mechanics and adhesion.[19,20,27] Table 4 summarizes the fact that the viscosity, film thickness, and curing time are all predicted to increase as the polymer concentration increases.[47,51,53,62,80] Nevertheless, the boundaries of this mechanical reinforcement are frequently the subject of debate. Although some studies indicate that tensile strength increases linearly as polymer loads increase, new evidence indicates a paradoxical effect: excessive polymer packaging can cause micro-phase separation, which abruptly compromises both strength and flexibility, rather than reinforcing the matrix.

The structural stability and barrier function of polymer films are largely dictated by the organization and interaction of polymer chains, as schematically depicted in Figure 4A.[81] The reviewed literature (Table 4) groups these polymers into three functional classes. Starch and chitosan are examples of natural polymers that exhibit extensive hydrogen bonding. In the presence of water, these polymers create hydrophilic structures that stick to living things very well and can swell up significantly.[82,83] Contrastingly, synthetic polymers, including PLA and methacrylate derivatives, generate hydrophobic networks that are densely packed and produce films that are resistant to water. The ideal choice for prolonged transdermal delivery is that they substantially reduce transepidermal water loss (TEWL).[36,84,85] In an intermediate niche, semi-synthetic polymers, including HPMC, are able to form flexible, semi-occlusive films that are readily adjustable due to the expansion of free volume by substituent groups on the cellulose backbone.[86,87] A number of formulations have effectively implemented hybrid networks to counteract these inherent class limitations. Hydrophobic acrylates or proteins

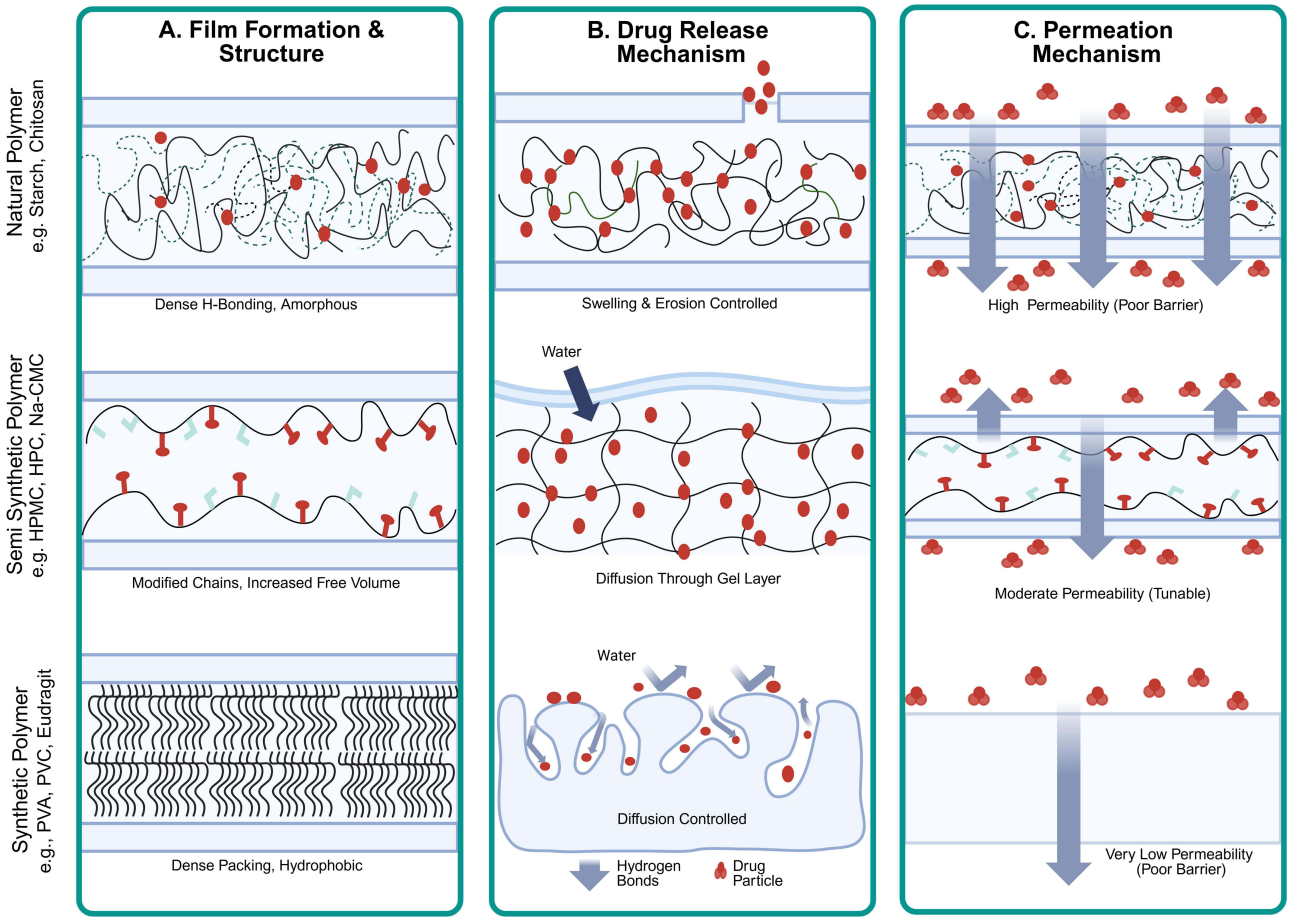

Figure 4 Impact of Polymer Class on (**A**) Film Formation and Structure, (**B**) Drug Release Mechanisms, and (**C**) Skin Permeation (Created in BioRender. Sriwidodo, (S) (2026) https://BioRender.com/qpc8dvd).

(eg, PVA/Eudragit or HPMC/zein) are combined with hydrophilic cellulose derivatives to produce ultrathin, continuous films that optimize the trade-off between structural integrity, swelling capacity, and elasticity.

Plasticizers, like polyols, PEG 400, and citrate esters, are the second main way to change how films behave. They are in addition to the polymer backbone.[88,89] At the right amounts, they lower the glass transition temperature (Tg) and make the chains move more freely, which lowers tensile strength and raises elongation at break.[22,46] Quality by Design (QbD) studies often advise against over-plasticization, which can make films stiffer and cause rapid surface crystallization, which entirely ruins film homogeneity.[89–91]

Penetration enhancers and solvents have a big effect on the film's physical mechanics because they are important secondary modifiers. Oleic acid is a well-known molecule that helps other chemicals get through the skin by breaking down lipids in the stratum corneum. But there are still conflicting results about how it affects film mechanics in a secondary way. In some chitosan-based FFGs, oleic acid unexpectedly made both tensile strength and elongation go up. This suggests that it worked together to strengthen hydrophobic domains.[21] In contrast, new research on other polysaccharide-based composite films shows the opposite: instead of strengthening the matrix, increased levels of oleic acid created micropores and microcracks that weakened the film and made it less stretchy.[92,93] These different results support the idea that enhancers should be seen as important material properties that change both drug flux and film mechanics, rather than just as things that make things more permeable.[18,94]

At the same time, choosing the right solvent gives you more control over how the material dries and how it responds to stress (Table 4). When the ethanol fraction is large, hydroalcoholic formulations usually dry faster and make films that are thinner and stiffer. Water-based or water-glycol systems, on the other hand, tend to take longer to dry but make films

that are more flexible and have a higher elongation at break.[95,96] The ratio of volatile to non-volatile solvents is an important quality parameter that connects the solution state to the qualities of the dried film, especially drying time, tack, and mechanical resistance.[97]

The formulations in Table 2 were specifically designed to have strong bioadhesion, with the purpose of keeping the medicine at the application site for a longer time. When you mix carbopol or polycarbophil with PVP and polyols, you usually get clear, flexible films that are quite thick, take a long time to cure, and stick well to wet surfaces.[54,98] These traits make them good for wound dressings or mucosal applications, but not so good for normal skin use, when quick drying and easy spreading are important. The film's elastic modulus should be lower than that of the stratum corneum from a mechanical design point of view. This will make sure that the film is flexible enough to stay on even after the skin changes shape many times.[35,36,79]

Most films were made with a pH range of about 4 to 7, which is in line with modern dermal guideline that says the skin's acidic mantle should stay between 4 and 6. This is important for safety and patient comfort.[99] Recent studies demonstrate that products in this pH range are better at maintaining the balance of the stratum corneum, the barrier, and the microbiota, which is important for long-term use.[99,100] The PVA-TEOS and HPMC–zein systems made clear, uniform films that did not show any signs of drug crystallization.[41,43] These qualities are in line with current advice that dermal FFS should not separate into phases, not cause too much occlusion (maceration), and look good.[6,37,101] Despite being comforting, these short-term results do not provide conclusive proof of long-term tolerability because there is still a lack of information on repeated, long-term administration on sick skin.

Collectively and as synthesized in Table 4, these studies indicate that the efficacy of FFGs is influenced by complex interactions among the polymer backbone, plasticizer, enhancer, and solvent system, which are further adjusted by safety-related factors, such as pH and physical stability. Despite this complex interplay, most studies still optimize only one or two variables at a time and report mechanical properties using heterogeneous methods, which complicates cross-study comparisons and limits quantitative modelling of composition–film property relationships and their connection to drug release and permeation. Only a limited subset of formulations has begun to employ design of experiments (DoE) strategies, such as factorial designs or response surface methodology, to simultaneously investigate the effects of polymers, plasticizers, and enhancer levels on tensile strength, elongation, drying time, and bioadhesion, in line with quality-by-design (QbD) approaches already applied to film-forming sprays and mucoadhesive systems[36,102,103] Going forward, more systematic use of DoE and more harmonized reporting of key parameters – for example, on-skin drying time, tensile strength, Young's modulus, and tack, consistently paired with release, permeation, and in vivo data – will be essential to define a genuine "optimal window" of formulation. Overall, the most defensible conclusion from the current evidence is not that one excipient class is uniformly superior, but that polymer architecture and plasticizer level are the most reproducible drivers of film behavior, whereas the contributions of enhancers and solvents remain more context dependent.

Drug-Release Outcomes

In the 27 trials described in Table 3, film-forming gels (FFGs) regularly moved traditional topical dose forms toward drug-release profiles that lasted longer, usually between 8 and 48 hours. For small-molecule APIs (eg, NSAIDs, antifungals, antivirals), cumulative release often surpassed 80% within 12–24 hours. On the other hand, formulations made for wound care usually had a biphasic profile, with a strong initial burst followed by a longer maintenance phase that lasted 8–24 hours.[24,46] This burst-maintenance pattern is very helpful in wound care because the quick initial release gives immediate local effect and the sustained phase keeps the wound bed moist and delivers a steady supply of medicine.[24,104]

A consistently replicable finding in the examined literature is the role of FFGs as "on-skin reservoirs". After the volatile solvent evaporates, the polymeric matrix that was produced takes over as the main way to control how drugs move.[18,28,35] However, the quantity and therapeutic significance of this sustained release exhibited considerable variation among formulations, suggesting that extended release is a customisable, formulation-dependent characteristic rather than a universal indicator of FFG superiority. In this context, polymer composition is the main factor that affects release kinetics. Table 4 shows that adding more hydrophilic polymers (like HPMC or PVA) makes the network thicker, lowers

the diffusion coefficient, and slows down drug release. Figure 4B shows how this works in theory.[28] Highly hydrophilic biopolymers (like chitosan or alginate) release drugs by quickly hydrating, swelling up, and eroding the matrix, which often leads to the burst-maintenance profile mentioned above.[105–107] On the other hand, synthetic hydrophobic matrices (such PLA/PLGA and acrylates) make it very hard for water to get in, which leads to diffusion-controlled, near-zero-order release patterns that are great for long-term delivery.[108–110]

Combining hydrophilic and hydrophobic polymers is a popular way to change release, but the research shows that this does not always work. Some investigations indicate that augmenting the hydrophobic fraction consistently retards diffusion.[45,55] On the other hand, several labs discovered that adding a second polymer phase actually generated new watery micro-pathways, which sped up release even if the overall matrix was denser.[35] So, polymer concentration cannot just be thought of as a way to make things thicker; its effects must be understood in the context of polymer chemistry, the ability of water to bind to polymers, and the unique drug-polymer affinities. The drug's physical condition and the presence of certain excipients also affect how it is released. For highly lipophilic substances (eg, curcumin, essential oils), formulations that effectively preserve the medication in an amorphous state, using solid dispersions or nanocarriers, exhibit a steeper concentration gradient and enhanced diffusion efficiency.[58,111,112] But this benefit only works if you can stop drugs from recrystallizing after they evaporate.

Plasticizers and solvents are important secondary modulators (Table 4). Plasticizers like glycerol or PEG make diffusion easier by increasing free volume and chain mobility.[113,114] However, using too much of these can cause a bigger initial burst because the matrix gets too soft and water is absorbed too quickly.[25,42] At the same time, hydroalcoholic solvents usually speed up early release by causing rapid thermodynamic supersaturation during evaporation.[94,115] But if the volatile portion is too large, it could cause the API to precipitate on the skin too soon, which would stop transdermal flow.

A significant differentiation underscored in recent research is the recurrent disjunction of in vitro release from in vivo or ex vivo transdermal distribution, especially with nanocarrier-integrated FFGs. Transethosomes or nanogels in systems often show slower in vitro donor-phase release than regular gels, but they have much higher transdermal flux and deep skin deposition.[48,56,116] This supports a basic idea: for successful skin penetration, the donor matrix does not need to release quickly. The therapeutic efficacy is determined by the integrated profile of release, partitioning into the stratum corneum, and subsequent tissue permeation.[38,112]

More and more research are employing Quality by Design (QbD) and Design of Experiments (DoE) frameworks to look at medication release because they know how complicated it is. Using factorial and response surface designs, researchers have been able to figure out how polymers, plasticizers, and solvents affect the release kinetics of different APIs, from antifungals to local anesthetics.[42,53,62,91,103] These methods make sure that formulation variables are set in a clear design space, such that the release profiles match the Target Product Profile (QTPP), whether the purpose is to quickly relieve pain or care for a persistent wound.[35,117–119] This is still a new strategy, not a common one, because only a small number of the FFG studies that were included used formal DoE procedures to improve release.

Critically, the synthesis of these 27 studies indicates that FFGs offer high flexibility in generating diverse release patterns. However, the design of in vitro release testing (IVRT) remains highly heterogeneous. Variations in membrane selection, receptor media, and sampling schedules severely complicate cross-study comparisons and quantitative modeling.[28,35,55] Therefore, the current literature more strongly supports the broad conclusion that FFG release can be modulated by formulation design, rather than providing a precise quantitative benchmark for an "optimal" release profile. Ultimately, the key challenge is no longer simply to "obtain prolonged release", but to connect a target release pattern with a specific clinical context.[28,35,38,118] Harmonizing IVRT methodologies and integrating kinetic modeling will be crucial to establish FFGs as predictable delivery platforms. The most defensible interpretation of the current evidence is that sustained or biphasic release in FFGs must be judged solely by its fit to the therapeutic objective, rather than operating under the assumption that slower or faster release is inherently superior.

Skin Permeation Outcomes

The examined corpus of work reveals that only about half of the FFG formulations were assessed utilizing quantitative skin permeation endpoints, including steady-state transdermal flux (Jss), cumulative penetrated quantity, or drug

concentrations within specified skin layers. The other research focused on in vitro release profiles or in vivo pharmacodynamic effects without a full permeation dataset. When penetration was measured, a pattern emerged: FFGs always increased flow and/or drug deposition in the skin compared to standard creams, gels, or other reference products. This superiority encompassed lipophilic small molecules, including NSAIDs, antifungals, analgesics, as well as antiviral and antimetabolite agents.

As extracted in Table 3, the quantitative flux values (μg/cm^2/h) consistently highlight the superiority of FFGs. In one chitosan-based ketoprofen FFG containing oleic acid, the transdermal flux was almost threefold higher than that of a marketed comparator, while a terbinafine FFG (DA5505) achieved skin drug concentrations tens to hundreds of times greater than those obtained with benchmark creams and gels.[21,50] These observations support the concept of FFGs as "on-skin reservoirs" that prolong contact time and sustain a high concentration gradient at the skin surface, thereby driving active passage across the stratum corneum.[35,94,120] But because only certain research measured permeation and testing methods (membranes, receptor media, comparators) were not standardized, the evidence right now points more toward better delivery than a specific number.

As systematically summarized in Table 4, polymer content and matrix packing fundamentally shape these permeation profiles. Reducing the level of the film-forming polymer generally increases the diffusion coefficient and transdermal flux, provided the film's structural integrity remains intact.[43,47] In contrast, increasing the polymer content in etoricoxib or aceclofenac FFGs tended to lower the amount of drug that crossed the membrane over 8–24 h, although the overall release remained sustained.[43,47,60,62] This trade-off seems to be one of the more common trends in the present literature: tighter matrices often keep film integrity and extend residence, but they may also make diffusional transport harder. Even said, the relationship is not exactly linear. A minor increase in matrix density could still improve total delivery if longer skin contact makes up for the decrease in instantaneous flux.

From a conceptual standpoint, Figure 4C shows how various polymer classes modify occlusion and water content to create a continuum of skin permeability. Following the class-level trends shown in Table 4, natural polymers that expand a lot make open networks that help the skin stay hydrated and permeable, but they do not block water vapor as well.[121] At the hydrophobic end of the scale, synthetic films (eg, methacrylates, polyurethanes) significantly reduce transepidermal water loss (TEWL) and create a strongly occlusive microenvironment.[36,122] While beneficial for moisture retention, excessive occlusion may sequester the drug in the uppermost skin layers, limiting deeper penetration.[123–125] Thus, skin permeation is shaped by how the polymer backbone negotiates the interplay between hydration, occlusion, and diffusion pathways.

Chemical penetration enhancers also exert direct and reproducible effects on transdermal flux (Table 4). Moderate levels of enhancers like oleic acid or polar aprotic solvents (eg, NMP) effectively increase flux by fluidizing the stratum corneum lipids.[21,52] Higher concentrations of hydrophilic plasticizers, like PEG, have also been linked to higher flow in acyclovir FFGs because more of the medication is dissolved and free to diffuse. Importantly, these considerable improvements in transdermal flux are often accomplished without concurrent increases in cellular toxicity or clinically noticeable skin irritation, as corroborated by secondary safety results, suggesting a very favorable risk-to-benefit ratio for FFGs.[8,126] On the other hand, film integrity may be jeopardized by high enhancer concentrations. Therefore, even though enhancers are effective permeability modifiers, the extent of their enhancement is still formulation-specific.

The solvent composition introduces an additional layer of influence. Extensive evidence confirms that hydroalcoholic systems (eg, ethanol–water) produce higher flux and dermal deposition than pure aqueous vehicles. The rapid evaporation of volatile solvents temporarily leaves the drug in a supersaturated state, drastically spiking the thermodynamic driving force for permeation before crystallization occurs.[21,94,127] Nevertheless, if the volatile solvent concentration is excessively high, it causes rapid drug crystallization on the skin surface immediately after application, halting the diffusion gradient and paradoxically reducing flux. Conversely, more hydrophilic water–glycol systems often favor substantial retention in superficial skin layers with controlled systemic permeation, which is advantageous for localized surface targets.[120] Therefore, when interpreting flux data, the solvent ratio must be viewed as a critical, context-dependent variable. Importantly, these observations also indicate that a higher initial flux is not always the sole objective. In some cases, notably those that aim to treat superficial infections or have a longer local effect, it may be better to have more retention in the upper layers of skin than to have the most transdermal route. This distinction elucidates why

seemingly contradictory solvent effects may yet constitute logical design decisions aimed at diverse therapeutic objectives.

A striking theme in the literature is how nanocarriers shift the balance between donor-phase release and actual tissue permeation. As detailed in Table 3, methotrexate (MTX) FFGs based on transethosomes (TE-FFG) exhibited slower in vitro release than a conventional MTX FFG. Yet, the ex vivo transdermal flux (Jss) increased significantly from 120.36 μg/cm^2/h in the conventional gel to 186.97 μg/cm^2/h in the TE-FFG, resulting in a massively superior cumulative permeation (2,147.71 μg/cm^2/h versus 1,280.49 μg/cm^2/h).[49] This phenomenon, echoed in other vesicular systems,[128,129] reinforces a key concept: slower donor-phase release does not necessarily indicate poorer delivery; it may reflect more efficient partitioning and vesicle-mediated colloidal transport into the skin. When examined across indications, the clinical target dictates the permeation strategy. For acute pain (eg, ropivacaine, etoricoxib), FFGs are engineered for high systemic flux (1.5 to 3.0-fold gains) to rapidly reach subcutaneous tissues.[43,62] On the other hand, for topical antifungals like terbinafine or wound treatment, the design puts more emphasis on high stratum corneum deposition and local retention than on systemic exposure.[53,55] Consequently, a formulation that prioritizes local retention over systemic flux is not underperforming; it is merely in accordance with its specific therapeutic target.[130,131]

Figure 5 shows how penetration enhancers and plasticizers work together to control drug release and skin permeability. The left panel shows (Figure 5A) how enhancers including fatty acids, terpenes, and hydroalcoholic carriers change the way stratum corneum lipids are arranged so that drugs can move more easily, with less lag time, and with higher fluxes. The right panel (Figure 5B) focuses on hydrophilic plasticizers (glycerol, PEG 400), which lower the polymer's glass transition temperature (Tg). This makes the intermolecular packing less tight, allowing for flexible, long-lasting skin contact without a big burst.

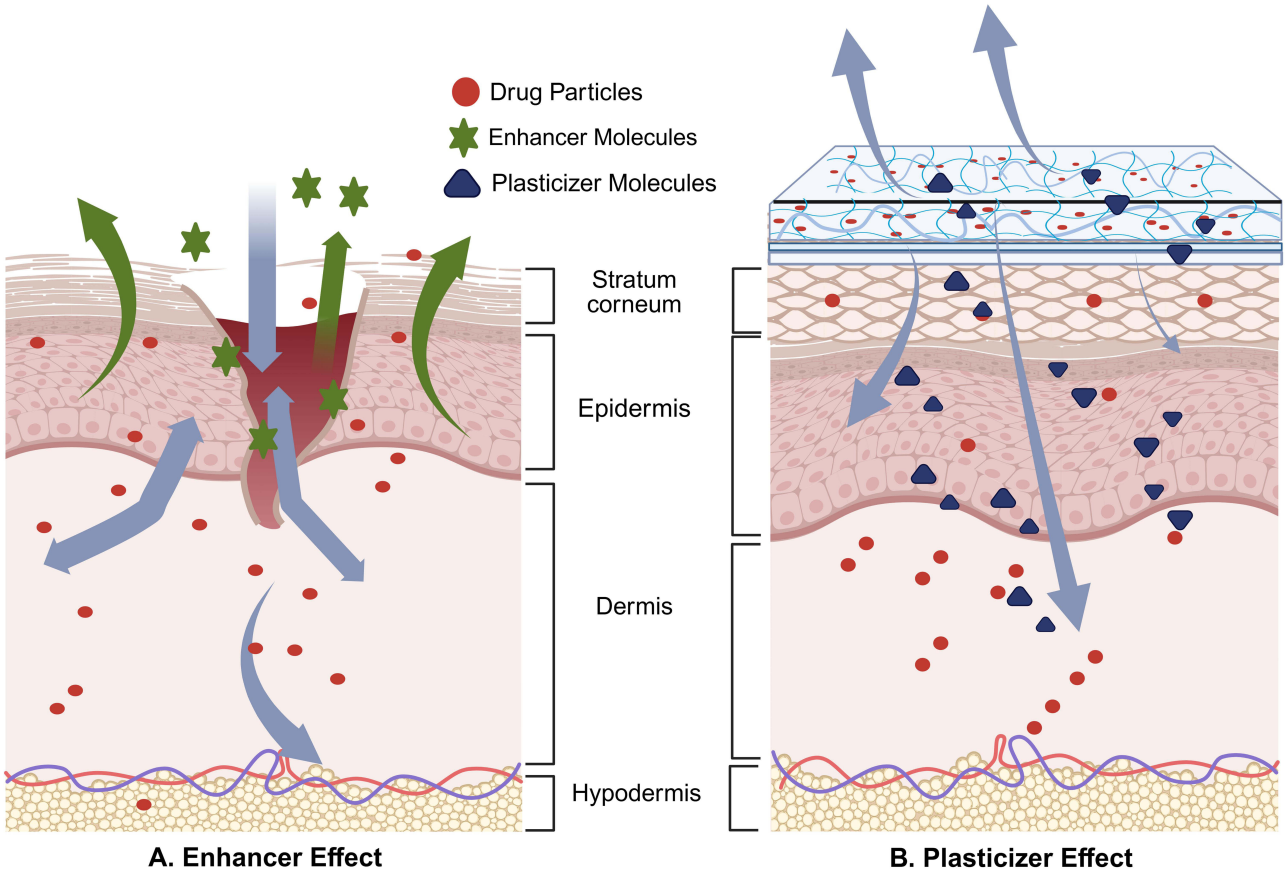

Figure 5 Mechanistic Illustration of (**A**) Enhancer and (**B**) Plasticizer on Drug Release and Skin Permeation (Created in BioRender. Sriwidodo, (S) (2026) https://BioRender.com/ozwr18c).

In the end, FFGs provide us a lot of room to change how skin barrier interactions work, but it's still hard to connect the dots between in vitro formulation design and in vivo therapeutic effect. To make quantifiable, translational links for FFG performance, it will be important to standardize permeation testing methodologies and use minimally invasive dermatopharmacokinetic techniques, like sequential tape stripping and skin open-flow microperfusion.[132,133] The existing evidence robustly endorses overarching permeation-design principles, underscoring that the ideal arrangement of polymers, enhancers, and nanocarriers must invariably be determined by the particular clinical need.

Future Perspective

The development of film-forming gels (FFGs) must shift from reliance on volatile organic solvents to safer, more sustainable systems, in which both the solvent phase and polymeric matrix are inherently biodegradable and biocompatible. Natural deep eutectic solvents (NaDESs) are becoming more and more popular as strategic alternatives because they can make lipophilic chemicals more soluble and easier to transport through the skin. They also have a better toxicological and environmental profile than traditional organic solvents.[134–137] As cosolvents or parts of the film matrix, they help make water-based or water-lean formulations with a tiny organic solvent footprint while yet allowing for appropriate supersaturation and occlusive properties. The simultaneous development of stimulus-responsive polymers and hydrogel networks, especially those that respond to changes in pH, temperature, or other physical stimuli, is likely to make it easier to make the "next generation" of FFGs that can change the rate of film formation and drug release based on the microenvironment of the skin.[138,139] This strategy is consistent with findings from film-forming sprays, where careful selection of the polymer backbone and viscoelastic modifiers is necessary to maximize drug delivery effectiveness, drying time, and user comfort.[6]

At the same time, FFG research would benefit from a clearer shift to a Quality by Design (QBD) approach. QbD studies of topical dosage forms have shown that defining a formulation design space that links polymer type and concentration, plasticizer, and enhancer levels to important quality attributes like film properties, release behavior, and permeation can reduce the need for trial-and-error methods and make products more durable.[6,140] To connect formulation insights with clinical benefits, future FFG evaluations must consistently incorporate dermatopharmacokinetic assessments in human skin, including stepwise tape stripping, quantitative skin imaging, and techniques like microdialysis and open-flow microperfusion that enable real-time monitoring of unbound drug concentrations in the dermis.[132,141,142] These methods help us understand how drugs are distributed in the skin and how long they stay there, giving us a quantitative basis for regulatory guidance and FFG-specific bioequivalence criteria. The future of FFG development will be determined by the integration of green solvent technologies, intelligent polymer systems, established Quality by Design (QbD) frameworks, and standardized dermatopharmacokinetic methodologies, facilitating a logical transition from formulation design to clinical topical therapy.

Limitation of the Review

A major methodological shortcoming of this analysis is the lack of a standardized risk of bias (RoB) tool that has been specially created and tested for in vitro drug release and ex vivo skin permeation studies. A formal, tool-based evaluation was not possible due to the absence of a globally recognized RoB tool for this particular topic in the literature. As a result, the quality of the study was carefully evaluated based on how clear the described experimental protocols were, whether there were technical or biological replicates, and whether the authors had control over the main experimental variables that affect permeation outcomes. The synthesis was further limited by the significant variability in experimental designs and reporting methods among the papers considered. Researchers utilized several membrane types, receptor and donor media, diffusion zones, and sampling intervals. Outcomes were expressed by various criteria, including transdermal flux, cumulative penetrated quantity, and differing measures of skin deposition. Due to this methodological variance, a stringent quantitative meta-analysis could not be convincingly substantiated. Data harmonization was necessary for comparison; for example, different skin deposition parameters were combined into a larger category linked to penetration, and missing quantitative data were labeled as "Not Reported" (NR).

Moreover, the existing evidence is primarily preclinical, consisting mainly of in vitro and ex vivo models, and there is a notable absence of controlled clinical trials or in vivo dermatopharmacokinetic studies involving human subjects.

Consequently, any direct association between certain formulation characteristics and conclusive clinical results should be regarded with circumspection. In this case, the results of this review should not be used to get exact estimations of effect size. Instead, they should be seen as a qualitative synthesis of the patterns and connections between FFG formulation parameters and three main result areas: drug release, skin permeability, and film characteristics. This work establishes a standard and underscores the necessity for future research to employ uniform experimental designs, explicit reporting requirements, and enhanced connections between laboratory findings and clinically significant outcomes.

Conclusion

The results of this large investigation show that film-forming gels (FFGs) can be used to deliver both topical and transdermal drugs. By transitioning from a liquid or semi-solid state to a solid on-skin reservoir, FFGs can alleviate some of the challenges associated with traditional moisturizers and patches on the skin. Four key points emerge from the critical summary of the presented research. The polymer architecture consistently influences mechanical strength and drying behavior in terms of film qualities. Plasticizers, on the other hand, are key parts that make the film stronger and easier to wear. Secondly, the release of drugs from FFGs is highly flexible but significantly influenced by the formulation, as it is influenced by the interplay of polymer characteristics, matrix organization, and solvent composition, rather than a simple uniform effect of polymer concentration. Third, with respect to skin permeation, many FFGs improve steady-state transdermal flux and/or local dermal deposition relative to comparator formulations, although the optimal permeation strategy depends on the intended clinical target and should distinguish between superficial retention and systemic delivery. Available safety data were generally reassuring, with several studies reporting minimal in vivo skin irritation and low in vitro cytotoxicity; however, these findings should be interpreted cautiously because safety assessment was not performed uniformly across all included studies. Finally, greater methodological standardization and wider adoption of Quality by Design (QbD) principles are needed. The current literature remains limited by substantial heterogeneity in release and permeation testing; therefore, more harmonized methods and stronger translational links will be important for converting promising laboratory FFG systems into more predictable clinical performance. Overall, the available evidence suggests that rational balancing of polymers, plasticizers, enhancers, solvents, and carrier systems will be central to the future development of FFGs as a promising platform for dermatological and transdermal therapy.

Abbreviations

5-FU, 5- Fluorouracil; ACV, Acyclovir; AG, Accacia gum; AM, Alpha mangostin; CbFG, Chitosan-based film forming gel; CHE, Chinese herbal extract; CL, Conventional; CO_2, Carbon dioxide; CP, Carbopol ®971P; cP, centipoise; CLEO, Cinnamon leaf essential oil; CMC, Carboxymethyl cellulose; CMC-Na, Carboxymethyl cellulose-Natrium; Conc, Concentration; CTZ, Clotrimazole; CQA, Critical Quality Attribute; DA5505, Terbinafine film forming gel; DoE, Design of Experiment; DSC, Differential scanning calorimetry; FF, Ferdy Firmansyah; FA, Fauzan Afandi; FFG, Film forming gel; FFH, Film forming hydrogel; FNS, Fauzia Ningrum Syaputri; FTIR, Fourier transform infrared spectroscopy; GPTMS, Glycidyloxypropyl trimethoxysilane; HPC, Hydroxypropyl cellulose; HEC, Hydroxyethyl cellulose; HPMC, Hydroxypropyl methylcellulose; Ibu, Ibuprofen; MCCA, Mixture of corydalis yanhusuo, cynanchum paniculatum and armadillidium vulgare; MPa, Megapascal; MTX, Methotrexate; NMP, N-methyl-2-pyrrolidone; NSAID, Non steroid anti-inflammatory disease; NR, Not reported; NW, Nasrul Wathoni; OA, Oleic acid; PEG, Polyethylene glycol; PG, Propylene glycol; PLA, Poly Lactic Acid; PU, Pullulan; PS, Pure drug solution; PVA, Polyvinyl alcohol; PVP, Polyvinyl pyrrolidone; PXRD, Powder X-ray diffraction; QbD, Quality by Design; QTPP, Quality Target Product Profile; RJ, Royal jelly; SEM, Scanning electron microscopy; SI, Swelling inhibition; TBH, Terbinafine hydrochloride; TC, Terminalia catappa; TE, Transethosomes; TEC, Triethyl citrate; TEOS, Tetraethylorthosilicate; TEWL, Transepidermal Water Loss; Tg, Glass transition temperature; TS, Transethosomal suspension; WB, Weight bearing; WOS, Work of shear; XG, Xanthan gum.

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Disclosure

The author(s) declare (s) no conflict of interest.

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