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Review Article

Conforming to Cure: Advances in Film-Forming Sprays for Targeted Wound Care

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Abstract

Wound care is still a critical clinical issue, mainly in the handling of chronic as well as drug-resistant injuries that need extended and targeted treatment. Traditional topical treatments often do suffer from limitations, like bad retention, irregular drug distribution, and less patient compliance. Film-forming sprays (FFS) have generally emerged as an alternative, offering several advantages such as uniform application, non-intrusive use, sustained drug release, and protective barrier formation. This review presents the definition and mechanism of film-forming sprays, their characterization, and several of the recent advancements within FFS technology, including the integration of a certain number of smart polymers, pH-responsive systems, and of many nanoparticle-based carriers for improved wound healing and antimicrobial efficacy. Despite their advantages, the translation of FFS into overall clinical practice is obstructed via formulation complexity, scalability issues, regulatory barriers, and a need for standardized evaluation protocols. Furthermore, effective wound care demands many solutions tailored for nearly all diverse wound environments. These FFS are at a higher rate being designed to address them. Research hereafter must focus on how to meet all these needs via interdisciplinary advances, by focusing on incorporating biodegradable substances, tailored treatments of, and multifunctional compounds. Sprays that form films are poised now to become a keystone in advanced systems for next-generation wound care.

Keywords: Film-forming sprays (FFS), wound healing, sustained drug release, pH-responsive systems, nanoparticle carriers, smart polymers, biodegradable polymers, topical drug delivery, chronic wounds, antimicrobial efficacy.

Abbreviations: FFS – Film-Forming Spray, MDS – Metered Dose Spray, ES – Electrostatic Spray, TEM – Transmission Electron Microscopy, SEM – Scanning Electron Microscopy. Other abbreviations include PVA – Polyvinyl Alcohol, PVP – Polyvinylpyrrolidone, PEG – Polyethylene Glycol, CS – Chitosan, ECM – Extracellular Matrix, and hEGF – Human Epidermal Growth Factor.

Introduction

The largest sense organ in human is the skin, which act as the principal defence system of human body, provide a barrier, protect internal organs from external environment. Many external and internal factors such as physical injury cause loss of skin integrity and damage, known as wounds¹. Wounds are primarily classified as acute or chronic based on their cause and healing pattern. Acute wounds result from external injuries such as surgical incisions, burns, cuts, or trauma, and generally heal within a predictable timeframe, provided appropriate care is given. On the contrary, underlying problems like poor circulation, diabetes, or prolonged pressure are usually the cause of chronic wounds, such as diabetic foot ulcers, pressure sores, and venous or arterial ulcers. These wounds heal slowly and often unpredictably due to impaired tissue repair mechanisms and contributing factors such as age, obesity, poor nutrition, or immunosuppression. Wound healing can occur through primary, secondary, or tertiary intention, depending on the extent of tissue damage and the presence of infection, with primary involving direct closure, secondary relying on natural tissue growth, and tertiary combining both after infection control².

Haemostasis, inflammation, proliferation, and remodelling are the four physiological stages that normal wound healing comprises³. Haemostasis starts with vasoconstriction and clotting to cease blood loss and create an intermittent matrix for cell migration following an injury. Growth factors and cytokines released by platelets draw in fibroblasts, immunological cells, and endothelial cells to initiate the healing process. Neutrophils and macrophages prevail during the seven-day inflammatory phase. While monocytes evolve into macrophages that carry out further removing and attract cells for tissue healing, neutrophils emit ROS and enzymes to combat infection and remove debris. As inflammation resolves, the proliferation phase begins with granulation tissue formation, angiogenesis, and epithelialization. Finally, the remodelling phase can last up to 1–2 years, during which collagen is reorganized. Impaired healing can lead to chronic wounds like diabetic foot ulcers and pressure sores, increasing complications, treatment costs, and amputation risk⁴. Figure 1 depicts the four unique yet interconnected stages of wound healing: haemostasis, inflammation, proliferation, and remodelling, with each phase playing an essential role in the repair of tissue integrity.

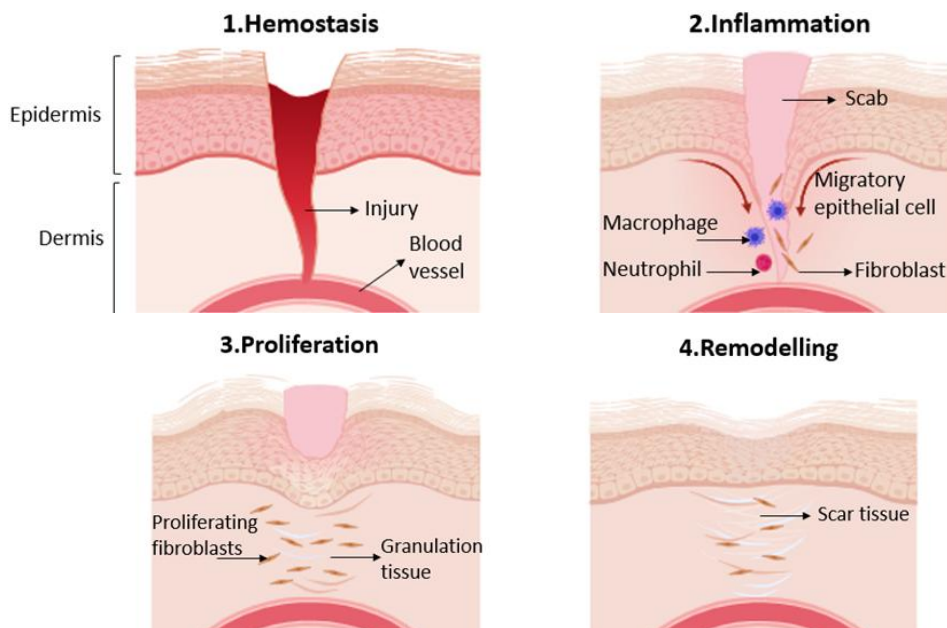


Figure 1: The four stages of wound healing: (1) Hemostasis – immediate vasoconstriction and clot formation to stop bleeding; (2) Inflammation – immune cell infiltration to clear debris and prevent infection; (3) Proliferation – tissue regeneration marked by fibroblast activation, collagen deposition, and angiogenesis; (4) Remodelling – maturation and reorganization of collagen fibers leading to restored tissue strength and function.

An effective wound dressing must strike a balance between its advantages, safety of the patient, and economic efficiency. The perfect wound dressing should be compatible with biological tissues, biodegradable, and possess the right water vapor permeability to create and sustain an optimum environment throughout the healing process⁵. From the invention of clay tablets and cotton gauze to the creation of modern dressings, wound dressings have undergone substantial changes over time. Today, there are over 2000 pharmaceutical products available for wound care, ranging from topical creams, gels, and ointments to advanced medical technologies such as bacteria-eradicating lasers and 3D stem cell printers⁴.

Existing dosage forms such as patches, ointments, and creams present several challenges, including skin

irritation, application difficulties, and low patient adherence. In contrast to creams and ointments, which generally do not keep extended contact with the skin, are easily removed, and leave a greasy residue that requires frequent reapplication for chronic illnesses, patches may cause irritation owing to occlusion and discomfort when removed. Therefore, there is a need for a dosage form that offers extended skin contact with less frequent dosing to improve patient compliance⁶. Emergence of novel dosage forms, such as film-forming spray systems (FFS), which offer an exciting substitute for conventional topical and transdermal formulations, is gaining popularity⁷. A comparison between various traditional topical dosage forms and film-forming spray (FFS) based on key parameters is illustrated in Figure 2.

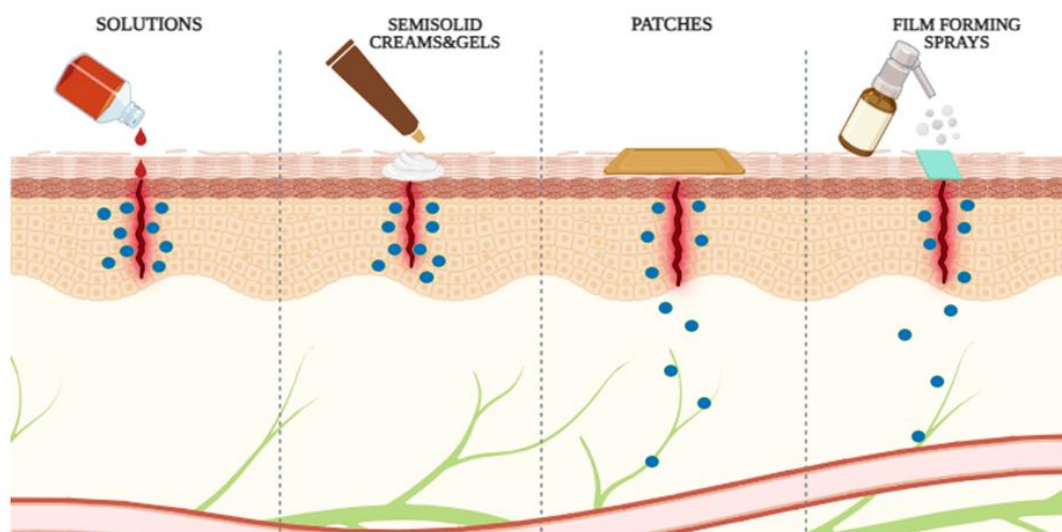


Figure 2: Comparison of topical wound care forms: solutions, creams/gels, patches, and film-forming sprays. FFS offer superior adhesion, flexibility, and drug delivery compared to traditional formulations.

Film forming spray: An overview

An innovative substitute for traditional topical and transdermal formulations is a film-forming system (FFS). It is a non-solid dosage form that, when applied, immediately forms a film on the skin or another body surface. For topical or transdermal application, film-forming systems are usually made as solutions or sprays with a medicinal product, volatile solvents, and film-forming excipients. When the solvent is applied to the skin, it quickly evaporates, leaving behind a thin, consistent layer of the drugs and excipients on the skin's surface.

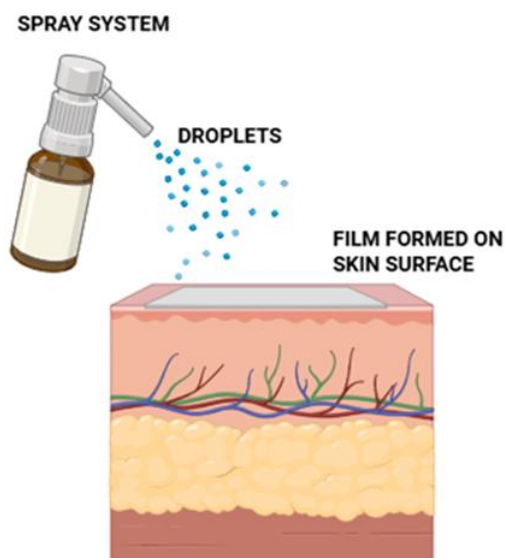


Figure 3. Mechanism of a film-forming spray system: the spray delivers uniform droplets onto the skin, which rapidly dry to form a protective and adhesive film over the application site.

This in-situ film serves as a reservoir for long-term administration of medication^{6,8}. Because the resultant film is thin, non-sticky, and adheres to the skin well, it increases the drug's permeability and contact time. This prolonged interaction with the skin allows for sustained and controlled drug release. Additionally, the film helps prevent drug crystallization, ensuring a greater amount of the drug remains in a soluble and bioavailable form. As a result, film-forming systems can offer improved therapeutic efficacy compared to conventional topical formulations, which may suffer from shorter contact time and reduced drug absorption⁹. The working mechanism of the film-forming spray (FFS) system is illustrated in Figure 3.

Mechanism of action of film-forming sprays

To prepare film-forming systems (FFSs), the medication and film-forming excipients are typically dissolved or dispersed in one or more volatile solvents. The solubility of the drug and excipients, or the dispersion of drug-loaded micro or nanoparticles within the solvent, determines the formulation's liquid state. The solvent evaporates rapidly when applied to the skin, leaving behind a film made up of the excipients. After the film is produced, the drug is released gradually over time through the polymer matrix, similar to the way transdermal patches work. By varying the amount of solution sprayed, dosages of drugs in film-forming formulations can be customized, allowing the user to control either the local or systemic effects of the medicine. Additionally, these technologies facilitate consistent and effective drug distribution at the application area. Additionally, their ease of application contributes to improved patient compliance¹⁰. Figure 4 illustrates the film-forming spray (FFS) system's stepwise mechanism.

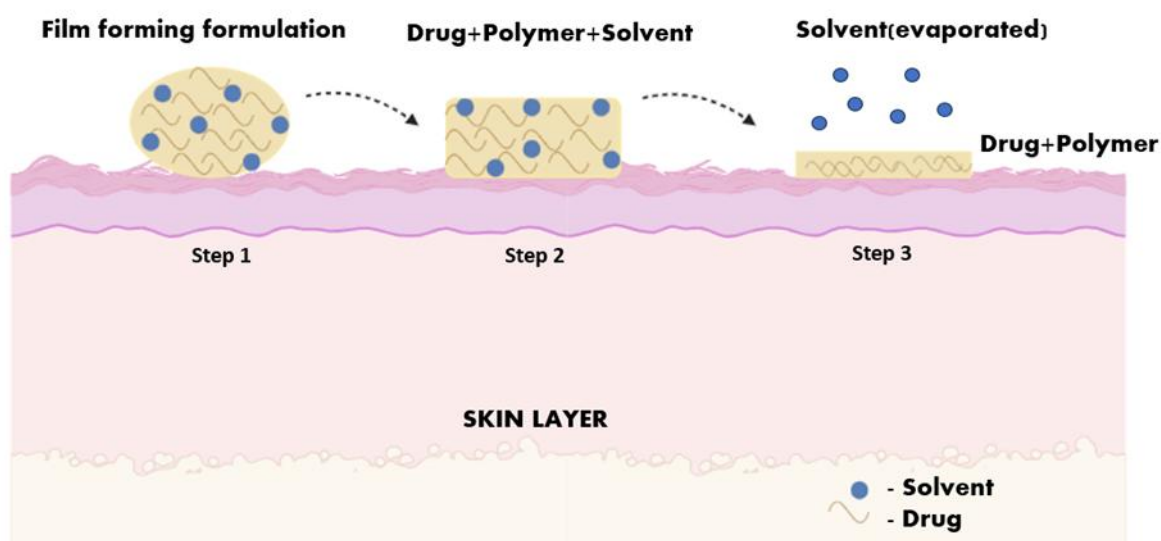


Figure 4. Mechanism of film-forming spray: Step 1 – application of a drug-polymer-solvent formulation on the skin; Step 2 – distribution and initial adhesion; Step 3 – solvent evaporation leads to the formation of a drug-loaded polymeric film over the skin surface.

Film-forming sprays (FFS) actively engage with the wound microenvironment and support healing through various mechanisms. After application, film-forming sprays create a thin, protective coating over the wound that plays a crucial role in maintaining a moist environment. This moisture retention is vital for the wound healing process, as it supports the movement of cells such as keratinocytes across the wound bed, which is necessary for tissue regeneration. Additionally, by encouraging the development and migration of new skin cells to more effectively cover the wound surface, a moist environment speeds up re-epithelialization, lessens discomfort, and aids in the breakdown of dead tissue¹¹. This film acts as a selective barrier, preventing microbial contamination while allowing oxygen exchange, essential for fibroblast proliferation and angiogenesis. The interaction with wound exudate plays a vital role, as some FFS are designed to regulate moisture levels and enable controlled drug release, thereby modulating inflammation and infection^{12,13}. Overall, the interaction of FFS with the wound microenvironment provides a multifaceted approach to wound healing, enhancing both antimicrobial efficacy and tissue regeneration.

Types of sprayers

A. Ordinal Spray

Ordinal sprays are a type of spray that usually come in an aluminium or plastic container with a dip tube and a dispensing orifice. This kind of spray operates without the need for any special technology during application. It produces a fine mist at a moderate spray angle and can release a small amount of film-forming solution. The containers are generally well-sealed, with minimal leakage. Both vertical and horizontal distributions are possible for ordinal sprays, and specific nozzle designs aid in preserving the film-forming fluid's sterility throughout usage and storage¹⁴.

B. Metered Dose Spray

A metered dose spray (MDS) is a device designed to deliver a controlled amount of spray, commonly used for administering medications through the skin or mucous membranes into the systemic circulation. Since the dosage is linked to the amount of spray released, the spray volume is an important consideration in film-forming spray formulations. The volume of spray released can vary depending on a number of parameters, such as the bottle's capacity, the uniformity of particle dispersion, and the container's orientation when in use. MDS devices are appropriate for accurate and effective drug administration because they usually have a low leakage rate and an even spray pattern^{14,15}.

C. Electrostatic Spray

Electrostatic spray (ES) is a technique that can be adapted for pharmaceutical applications, particularly for enhancing the delivery and coverage of formulations. This method offers benefits such as reduced spray drift, improved droplet formation, uniform coverage, and efficient deposition of the sprayed solution. Properties of the formulation, such as electrical resistance, surface tension, and viscosity, affect the manner in which

electrostatic spraying works in pharmaceuticals. To ensure effective spraying, the solution must possess suitable conductivity characteristics. The droplets generated through this method are typically fine, allowing for precise and consistent application¹³

D. Ultrasonic Spray

Ultrasonic spray technology holds significant promise for delivering film-forming solutions in pharmaceutical applications. It produces fine droplets that can form thin films, often approaching the nanoscale. This method operates effectively across a range of pressures and is known for generating consistently uniform droplets. When it involves producing layer-by-layer coating films, ultrasonic spraying is very helpful since it provides improved particle size uniformity, which is advantageous in medical formulations. The type of polymer used can affect how well ultrasonic spray systems work; both natural and synthetic polymers are used in film-forming spray formulations¹⁶.

Composition and formulation of film-forming sprays

Polymeric base materials:

Polymers are essential to the effectiveness of film forming spray (FFS) formulations. In addition to controlling drug release, they serve as the primary component responsible for forming the film. Polymers also help maintain the stability of the formulation by preventing issues like unwanted crystal formation. Key factors to consider when selecting polymers include their water washability, stability, biodegradability, and potential to be non-irritating to the skin. In FFS, polymers can be synthetic or natural as long as they behave viscoelastically or gel in situ. Thermo-sensitive polymers remain liquid at room temperature and gel upon contact with body heat, while pH-sensitive polymers transition to a gel when triggered by pH changes. Viscoelastic polymers temporarily become elastic under pressure during spraying and revert to a thicker consistency once the pressure is released¹⁶. The various polymers used in film-forming systems are summarized in Table 1.

Natural Polymers

Natural polymers, derived from sources like microbes, animals, or plants, can mimic the cellular environment and extracellular matrix (ECM). However, they often show variability in quality between batches and are prone to biochemical degradation, which may alter their properties and drug release behaviour in the body. Risks of disease transmission due to their animal or human origin, along with poor mechanical strength and limited stability, further restrict their use in wound care. To overcome these limitations, various chemical modifications have been explored¹⁷.

Chitosan and Derivatives

A linear copolymer made from chitin, which is present in the shells of crustaceans such as crab and shrimp, chitosan (CS) is well-known for its antibacterial, biodegradable, and non-toxic qualities. It is useful in medical applications since it has haemostatic and

wound-healing properties. Because of its great versatility, CS can be chemically altered at the amino and hydroxyl groups to create a variety of useful derivatives, including chitosan that is N-carboxymethyl and O-carboxymethyl. Drug delivery systems have made considerable use of these compounds. CS interacts with negatively charged molecules such as proteins and polysaccharides in the skin and dissolves in weak organic acids. Additionally, it binds effectively to wound surfaces, promotes blood clotting and tissue repair, and exhibits slight gelation and film-forming properties. Interestingly, CS films with minimal deacetylation have shown promise in the treatment of superficial wounds¹⁸.

Cellulose and Derivatives

The most prevalent natural polymer, cellulose serves as the primary structural element of plant cell walls and is both economical and environmentally friendly. It is made up of repetitive cellobiose structures made of β -1,4 connected D-glucose units, and because of its mild inflammatory reaction, it is very biocompatible. Cellulose is not resorbed in tissues because human cells do not contain cellulase enzymes. According to studies, cellulose aids in the release and management of growth factors such as PDGF, bFGF, and EGF, which restrict bacterial development and increase fibroblast activity, hence promoting wound healing. These growth factors regulate key healing processes such as cell proliferation, angiogenesis, inflammation control, and tissue remodelling. Chronic wounds often exhibit reduced levels of growth factors, so external delivery becomes beneficial. As a result, cellulose-based wound dressings have been enhanced with antimicrobial agents like PHMB and silver to improve healing outcomes¹⁹.

Alginate

β -D-mannuronate and α -L-guluronate residues are arranged in different sequences to form alginate, a naturally occurring polymer that is extensively researched in tissue engineering and drug delivery. Alginate is well-known for its potent mucoadhesive qualities, low toxicity, and outstanding biocompatibility, making it a good choice for wound healing applications. It is pH-sensitive, with reduced drug release under acidic conditions ideal for delivery systems targeting neutral pH environments. To improve stability, alginate is often combined with other polymers like gelatin, heparin, PVA, or chitosan via ionic or covalent cross-linking. Despite its benefits, alginate's poor enzymatic degradability in mammals and its high hydrophilicity limiting interaction with skin proteins are notable drawbacks²⁰.

Dextran

Dextran is a naturally occurring polymer that is extremely reactive because of its hydroxyl groups but also has good hydrophilicity, water solubility, biocompatibility, and biological inertness. It is widely utilized in medical and biological fields, particularly in dermal and subcutaneous tissue repair and as a carrier for drug delivery. Dextran promotes wound healing by inducing inflammatory cells to infiltrate the site of injury and angiogenic cells to migrate there²¹.

Gellan Gum

Gellan gum (GG) is a viscoelastic, thermosensitive, and pH-responsive polymer suitable for spray systems. Its viscoelasticity allows it to thin out when sprayed and regain its original consistency upon skin contact. GG forms gels at body temperature (30–40 °C), making it ideal for in situ applications, including cell encapsulation and delivery. Additionally, it has potent mucoadhesive qualities. Its yield stress is increased when NaCl is used as a crosslinker. In NaCl mixtures, high-acyl GG thickens at higher temperatures (~78°C), whereas low-acyl GG reacts at lower temperatures (~35°C) with better drug release¹⁶.

Xanthan Gum

A heteropolysaccharide composed of D-glucose, D-mannose, and D-glucuronic acid units, xanthan gum is usually generated by aerobic fermentation using *Xanthomonas campestris*. It exhibits pseudo-plastic behaviour in water and disperses easily in hot or cold conditions, with minimal impact from temperature or pH. When combined with gelatin, it forms transparent films with strong UV resistance, low moisture and solubility, reduced water vapor permeability, and improved mechanical and thermal properties²².

Synthetic Polymers

Carbopol

Carbopol works well on open wounds because of its thixotropic flow and viscoelastic qualities, which create an amorphous hydrogel that aids in wound moisture management. These characteristics also raise the drug's diffusion coefficient. Carbopol performs better when combined with Poloxamer than when used alone, resulting in a film that is more sprayable, has an ideal drying time, has a uniform amount per spray, and releases the medication effectively at a concentration of 0.05%. Furthermore, gels based on carbopol exhibit improved heat resistance²³.

Eudragit

Eudragit is a synthetic polymer that comes in a variety of forms and is frequently used to improve skin penetration in topical preparations and alter the release of drugs in tablets. While Eudragit S100 creates a film that dissolves in water at pH values higher than 7 and is mild on the skin, other variations, such as Eudragit EPO, E 100, S 100, RL 100, and RS 100, create glossy, non-translucent, water-resistant coatings. Though greater concentrations (15%) decrease washability, Eudragit RS provides good flexibility, adhesion, and sprayability while forming a thicker film layer. Better film quality is produced by combining Eudragit RLPO and ethyl cellulose at the right amounts²⁴.

Poly vinyl alcohol (PVA)

Through hydrolysis, alcoholysis, or aminolysis, vinyl acetate is transformed into polyvinyl alcohol (PVA), a biocompatible, biodegradable, hydrophilic, non-toxic, and non-carcinogenic polymer. It is widely used in tissue engineering and delivery of drugs due to its high hydrophilicity and remarkable capacity for water

absorption. PVA is very adaptable for biomedical applications since it can be readily processed into a variety of forms, including particles, fibres, fabrics, sponges, and films²⁵.

Poly (vinyl pyrrolidone) (PVP)

PVP (polyvinylpyrrolidone), a water-soluble, non-toxic, biocompatible, and non-carcinogenic polymer, is produced from the monomer N-vinylpyrrolidone. For pharmaceutical and biological applications, its strong film-forming capabilities, excellent adhesive properties, and moisture retention make it a popular option.

Polyethylene glycol (PEG)

PEG (polyethylene glycol), also known as PEO or POE, is a non-immunogenic, hydrophilic, and biocompatible polyether. Because of its capacity to increase the stability and solubility of active ingredients, it is of great importance in biomedical formulations and drug delivery systems. PEG is also more adaptable in formulation design since it may be mixed with other polymers, such as chitosan or PLGA, to improve its mechanical strength, thermal behaviour, viscosity, and crystallinity²¹.

Table 1: Polymers used in film forming systems.

| SN. | Polymer | Nature | Characteristics | Ref |
|-----|----------------------------|-----------|--|-----|
| 1 | Chitosan (CS) | Natural | Biodegradable, biocompatible, antimicrobial, non-toxic; supports haemostasis and wound healing; dissolves in weak acids; forms gels and films; effective for superficial wounds. | 18 |
| 2 | Cellulose | Natural | Abundant, low inflammatory response, non-resorbable; supports growth factor release (EGF, bFGF, PDGF); angiogenesis, and tissue remodelling. | 19 |
| 3 | Alginate | Natural | Biocompatible, low toxicity, mucoadhesive, pH-sensitive; poor enzymatic degradability; often crosslinked with gelatin, chitosan, etc., for stability. | 20 |
| 4 | Dextran | Natural | Water-soluble, hydrophilic, biocompatible, biologically inert; supports inflammatory and angiogenic cell migration. | 21 |
| 5 | Gellan Gum (GG) | Natural | Thermosensitive, pH-responsive, viscoelastic; thins during spraying, thickens on skin; forms gels; mucoadhesive; improved by NaCl crosslinking. | 16 |
| 6 | Xanthan Gum | Natural | Pseudoplastic, stable in hot/cold and varying pH; combines well with gelatin; UV resistant, low solubility, good mechanical properties. | 22 |
| 7 | Carbopol | Synthetic | Thixotropic, viscoelastic, forms hydrogel; helps manage wound moisture; enhanced with Poloxamer for better sprayability, drying, uniformity, and drug release; heat-resistant. | 23 |
| 8 | Eudragit | Synthetic | Enhances skin penetration; forms shiny, water-resistant films; S100 dissolves at pH >7; RS gives flexible, adhesive films; blends improve film quality. | 24 |
| 9 | Polyvinyl Alcohol (PVA) | Synthetic | Biodegradable, biocompatible, hydrophilic, non-toxic; good water absorption; can be processed into films, fibres, sponges, etc. | 25 |
| 10 | Polyvinylpyrrolidone (PVP) | Synthetic | Water-soluble, biocompatible, non-toxic; strong film-former, adhesive, retains moisture. | 21 |
| 11 | Polyethylene Glycol (PEG) | Synthetic | Hydrophilic, biocompatible, non-immunogenic; improves solubility and stability of actives. | 21 |

Active ingredients:

A medication must first penetrate the stratum corneum, the skin's outermost layer and the main lipophilic barrier, in order to be applied to the skin. As a result, medications with high lipophilicity (log P > 2) can more easily pass through this layer and frequently don't need penetration enhancers²⁶. Skin permeability is influenced not just by lipophilicity but also by molecule weight and size. In

general, transdermal administration works better for medications whose molecular weight is less than 500 Daltons. To avoid crystallization when the volatile solvent evaporates, the medication should also continue to dissolve in the formulation's non-volatile component. In order to minimize irritation and promote skin compatibility, the formulation's pH should ideally be between 5 and 10, which is in close proximity to the skin's natural pH of about 5²⁷.

Solvent systems:

Both volatile and non-volatile solvents are employed in film-forming spray (FFS) systems to balance the drying rate of the film. If the film forms and dries too soon, it may impede skin penetration and drug release. In order to attain the required drying time, film integrity, and drug delivery profile, a mixture of solvents is frequently used. Even if the skin barrier is somewhat weakened during solvent evaporation, the chosen solvent must be gentle on the skin and shouldn't irritate it. It's important that the film-forming polymer either dissolves or disperses well in the solvent, and that the film forms within an appropriate timeframe not too fast to affect quality, nor too slow to delay application. Commonly used volatile solvents in such formulations include ethanol and isopropanol, while non-volatile solvents like isopropyl myristate and propylene glycol also provide penetration-enhancing benefits¹⁰. Table 2 provides a summary of the solvents frequently utilized in film-forming systems²⁸.

Table 2: Solvents used in the film forming system²⁸

| S.N. | Solvents | Nature |
|------|---------------------|--------------|
| 1 | Water | Non volatile |
| 2 | Isopropyl myristate | Non volatile |
| 3 | Propylene glycol | Non volatile |
| 4 | Ethanol | Volatile |
| 5 | Isopropyl alcohol | Volatile |
| 6 | Isopropanol | Volatile |
| 7 | Butanol | Volatile |
| 8 | Acetone | Volatile |

Additives:

Plasticizers

Plasticizers aid in preserving the flexibility of films while they are being formed and guard against cracking. Additionally, they can maintain the stability of such molecules and improve the penetration of active

substances. It is well known that certain plasticizers, such as Poly Ethylene Glycol (PEG) and Propylene Glycol (PG), enhance how chemicals are delivered through the skin. PG serves as both a plasticizer and a solubilizer, which facilitates transdermal administration. However, because PG concentration significantly affects the viscosity of the film-forming solution, it must be carefully controlled. In most cases, a little amount of PG is enough to improve penetration. Conversely, PEG 400 has the ability to affect the amount of spray that is dispensed; higher concentrations result in a broader application area and a bigger spray volume. The non-volatile characteristic of PEG is associated with a decrease in vapor pressure¹⁴.

Penetration enhancers

To increase the absorption of substances, penetration enhancers also known as sorption promoters or accelerants are chemical agents that momentarily weaken the skin's barrier function. There are several classes of these enhancers, such as fatty acids, urea, pyrrolidones, sulphoxides, azone, terpenes and terpenoids, oxazolidinones, and essential oils. The field of improving skin penetration is developing quickly and has a lot of promise for increasing the number of medications that can be administered transdermally²⁹.

Crosslinkers

Crosslinkers affect polymers' flexibility, viscosity, solubility, glass transition temperature, and film stiffness. The use of NaCl as a crosslinking agent in gellan gum influences the gel's temperature sensitivity in addition to enhancing and accelerating film formation. Additionally, NaCl enhances gellan gum's encapsulating ability¹⁶.

Marketed film-forming sprays for topical applications⁷

Marketed film-forming sprays (FFS) have gained significant attention for their convenience, ease of application, and controlled drug release. These products are commonly used in wound care and dermatological treatments. Table 3 provides a summary of various marketed film-forming sprays, outlining their composition and therapeutic applications.

Table 3: Marketed film forming sprays.

| S.N. | Brand Name | Manufacturer | Indication/Use | Ingredients |
|------|-----------------------------------|----------------------|---|--|
| 1 | BENEV-Silicone-Spray | BENEV, USA | Aerosol film dressing for surgical/superficial wounds; waterproof, permeable, and elastic. | Water, Dimethicone, Parabens |
| 2 | 3M Cavilon™ No Sting Barrier Film | 3M, USA | Barrier film for minor abrasions and wounds; prevents impurities and provides waterproof coverage with flexible film formation. | Not specified |
| 3 | Afaplast® | Argofarm LLC, Russia | Spray film for protecting skin; alcohol-free, terpolymer-based; promotes adhesion and air permeability. | Polymers, Isopropanol, Panthenol, Colloidal Silver |

| | | | | |
|----|--|------------------------------|---|---|
| 4 | Nexcare™ No-Sting Liquid Bandage | 3M, USA | Used for disinfecting and accelerating wound regeneration; waterproof with long-lasting elasticity. | Dexpanthenol, Colloidal Silver, Siloxanes, Acrylates |
| 5 | LUXPLAST® | FARMAC – ZABBAN S.p.A, Italy | For minor injuries (from cuts to large abrasions); dries quickly, waterproof, and alcohol-free. | Diethyl ether, Acetone, PVM/MA butyl ether copolymer, Alcohol |
| 6 | Pharm-X® Second Skin / Vtoraya kozha Super Farm-KH Sprey | Green Life, Russia | Forms a protective, water-repellent film with antibacterial and anti-inflammatory effects. | Methylene Chloride, Propane, Butane, Ethyl Acetate |
| 7 | Hansaplast Spray Plaster | Hansaplast, Germany | Used in wound healing (especially for cuts); forms a dense, elastic film to prevent dirt entry and cross-contamination. | Acrylic Copolymer, Polyurethane, Ethanol, Water |
| 8 | Pentazol | Valeo Club, Russia | Covers wounds with a transparent and elastic antiseptic film; waterproof. | Ethyl alcohol (active), others unspecified |
| 9 | Elastoplast Spray Plaster | Beiersdorf, Germany | Forms a breathable, flexible film that protects wounds from water, dirt, and microorganisms. | Acrylic Copolymer, Polyurethane, Ethanol, Water |
| 10 | Medspray® the Patch-in-a-Can® | MedPharm Ltd, UK | Novel patch-in-a-can system for extended-release drug delivery; applied as a spray-on film onto the skin or mucosal surfaces. | Not specified |
| 11 | Liqui-Patch Technology | Epinamics GmbH, Germany | Uses film-forming technology to create a stable, flexible film that supports enhanced drug delivery with comfortable dosing. | Not specified |
| 12 | Opsite® | Smith & Nephew | Polyurethane-based film-forming spray used in wound and burn care; provides effective protection and favorable healing times. | Polyurethane |
| 13 | Nobecutan® | INIBSA S.A., Spain | (Now suspended) Initially developed as a polymethacrylate-based aerosol for traumatic wounds, mild burns, and suture resorption; delivered antiseptics. | Acrylic copolymer, Ethyl acetate, Tetramethylthiuram disulfide, Dimethyl ether (propellant) |

Characterisation of film forming sprays

pH

To increase the stability of the active ingredient or make it appropriate for the application site, the pH value is measured and adjusted. The preparation's pH modification attempts to stop inflammation and alterations in the physiological condition of the wound during the healing phase. Furthermore, the amount of medication that reaches the skin may vary depending on the drug's level of ionization. The pH of the spray formulations is measured with a pH meter³⁰.

Viscosity

The viscosity will vary depending on the polymer's nature and concentration. It is an important property since the viscosity of the film-forming solution affects its sprayability. When the concentration of the film-forming solution is raised, the coverage area of the spray will be reduced. With a spindle rotating at 1 rpm, the Brookfield viscometer measures the viscosity of the solutions at 25±1°C³⁰.

Bioadhesive strength of the film

The bioadhesive strength of a film can be tested by applying it to mouse skin (2 x 5 cm). After that, 0.5 mL of distilled water is used to moisturise the skin. Five minutes are provided for interaction between the tissue surface and the film. It is noted how much force (F) is required to remove the film off the skin's surface¹⁰.

Tensile strength of the film

A texture analyser or tests for breaking under the force of the load's weight are used to measure the strength of the separated film. Several methods can be used to measure the film's elongation and elasticity in addition to its strength¹⁴.

Swelling index

The purpose of this test is to determine how well the resulting layer can either provide or absorb moisture from the wound. An injury will heal more quickly if it receives enough moisture, but too much moisture could harm the tissue surrounding the wound. The initial

weight (W_i) was recorded after the film was cut into 2 cm \times 2 cm pieces. While immersed in phosphate buffer (pH 7.4) at 37°C, the weight of the swollen film (W_s) was recorded hourly. The swelling index of the film was calculated³¹.

Occlusive potential of the film

Since the film's permeability to wound fluid influences the wound's moisture content, it is crucial to identify this property. Excessive moisture will promote bacterial growth and cause infection. The film-forming spray was activated by placing a Whatman filter paper over a beaker filled with 50 mL of water. The control consisted of beaker with 50 mL of water and no sample. These were kept for no more than 48 hours at room temperature and humidity. Weighing each sample after 48 hours allows us to determine how much water evaporates through a barrier. The occlusion factor was determined¹⁵.

Surface morphology of the film

The test uses either transmission electron microscopy (TEM) or scanning electron microscopy (SEM) to assess the film's homogeneity, surface roughness, and microscopic form¹⁴.

Film formation/drying/evaporation time

The drying time of the film determines how quickly the film forms when the solution is sprayed. The rate of film formation is determined by the drying time. The produced formulations are sprayed onto filter paper, and the drying time of the film is measured (the amount of time needed for films to dry)³². In certain instances, the drying time was ascertained by spraying on a petri dish with the optimum film-forming solution. After a predetermined amount of time, a glass slide was placed stress-free on the film. If there is no more moisture visible on the glass slide, the film is considered dry³³.

Volume of solution delivered upon each actuation

It was determined how much solution was delivered for each actuation utilizing following equation,

$$A_L = \frac{[w_0 - w_t]}{D_n}$$

Where A_L was the volume of solution delivered with each actuation, W_0 was the initial weight of the formulation before actuation, W_t was weight of formulation after actuation, , and D_n was the density of the formulation.

Spray angle

The sprays were directed horizontally onto white paper that was positioned 10 cm away from the nozzle. Three separate measurements of the circle's radius were made on the paper from various angles. The spray angle (θ) was computed using following equation,

$$\theta = \tan^{-1} \frac{L}{r}$$

where L was the distance of paper from the nozzle, and r was the average radius of the circle³⁴.

Spray pattern

Whatman filter paper that was placed at a specific distance was sprayed with the formulation. To provide a sturdy base for the experiment, this paper was firmly attached to a board. At a distance of 15 cm from the paper surface, the spray formulations were released from the container. The resultant spray pattern on paper may be observed and evaluated. By this test, the homogeneity and distribution of the spray may be visually inspected and evaluated for efficacy and consistency³⁵.

in vitro drug penetration/release study

Usually, nylon membranes (pore size 0.22 mm), cellulose membranes (pore size 0.45 m), or silicone membranes are used in conjunction with Franz diffusion cells as compartment barriers in this test. The medium is a 7.4 pH phosphate buffer. The donor compartment is filled with the film-forming solution. Measurements are made after samples of the solution that permeates the cells is taken at predetermined intervals. The same volume of fluid is refilled once the samples are collected³⁶.

in vivo skin irritation test

Nine healthy male Wistar rats weighing 200–250 g should be used for a skin irritation study. They should be split into three groups: test (film-forming formulation), standard (drug in solvent), and control (placebo). After removing the dorsal hair 24 hours before application, an antiseptic treatment should be administered. The depilated areas should be treated with the appropriate formulations, and skin reactions should be assessed at regular intervals over the course of 24 hours and a seven-day observation period in accordance with OECD recommendations. Formulations should be classified as non-irritating, irritant, or extremely irritant based on their scores. Exclude any animals that exhibit extreme irritability or disease³⁵.

Stability Study

Characteristics that are regularly studied include changes in the levels, chemical and three-dimensional structures, particle size, and therapeutic activity of active substances following storage in different environments. Sometimes, the recrystallization of meta-stable active substances is assessed by thermal analysis. The usage of the antinucleon polymer allows the medication to remain in its original crystalline form¹³.

Applications in wound care

Film-forming sprays (FFS) are a new and adaptable topical medication delivery method that is becoming increasingly popular in dermatological and wound care applications. As the solvent evaporates after spraying, these systems cover the application site with a thin, transparent, and sticky layer. This film permits targeted and prolonged medication release in addition to acting as a barrier against outside pollutants. FFS formulations are especially helpful in treating burns, wounds, and skin infections because they minimize pain during application and removal by reducing direct contact with the wound bed, which is a significant drawback of conventional wound dressings³⁶.

FFS loaded with antibiotics, like mupirocin, has demonstrated encouraging outcomes in the treatment of infected wounds. An FFS with pH-responsive hybrid nanoparticles loaded with mupirocin that selectively release the medication in the acidic pH of infected wounds, increasing antibacterial efficacy and lowering systemic exposure. This method guarantees effective bacterial removal and quicker wound healing, particularly when dealing with common pathogens like *Staphylococcus aureus*¹². Chlorhexidine gluconate sprays and other antiseptic-based FFS have also been developed to provide long-lasting antibacterial activity, ease of application, and quick drying without leaving a sticky residue. Because of its clarity, flexibility, and quick drying characteristics, the chlorhexidine gluconate FFS demonstrated strong antibacterial properties and improved patient acceptance. Because of these qualities, these sprays are perfect for addressing superficial wounds where barrier protection and hygiene are crucial, or for disinfecting the skin prior to surgery³⁷

Furthermore, using natural biopolymers such as silk fibroin into FFS improves wound healing by adding a bioactive component. A silk-based film-forming spray that produced a permeable, biodegradable film that promotes tissue regeneration in addition to efficiently delivering medicinal ingredients. The silk matrix was very helpful for diabetic and chronic wounds because it promoted cell proliferation and accelerated healing rates³⁸. Altogether, FFS provide a highly customizable platform for wound treatment, combining protective, antimicrobial, and healing-promoting functions. Their advantages in terms of ease of use, sustained drug release, targeted action, and patient comfort make them a compelling alternative to conventional topical formulations and wound dressings.

Advantages over traditional dressings^{14,16,39}

Enhanced patient compliance

When it comes to application, film forming sprays are more practical than conventional dressings. A thin, even layer that sticks to the application site is created when they are simply sprayed onto the skin. Patients may find it easier to use than changing traditional dressings on a regular basis, which can greatly increase patient compliance.

Reduced skin irritation

Film forming sprays limit direct skin contact by creating a protective barrier, in contrast to standard dressings that can cause friction and irritation when applied or removed. They are therefore a better choice for those with sensitive skin since they may result in less discomfort and skin irritation.

Controlled and sustained drug release

Film-forming sprays serve as a reservoir for drug release, delivering the medication gradually while maintaining control. Compared to conventional dressings, which could not offer the same degree of drug release control, this is a major benefit. The spray's polymeric film improves therapeutic results by enabling a continuous release of the active component.

Improved bioavailability

When compared to conventional dressings, the formulation of film-forming sprays can improve the drug's bioavailability. By improving skin penetration, the spray's thin layer can enhance the active chemical substances' absorption into the bloodstream.

Versatility in drug incorporation

A variety of medicinal substances, including as proteins, peptides, and tiny compounds, can be included into film-forming sprays. This versatility is an important benefit over conventional dressings, which could only be able to provide a small number of drugs.

Non-invasive and pain-free application

Film forming sprays are a painless solution for patients because they don't require needles or intrusive procedures. For people who need to take their medications frequently, this is especially helpful because it eliminates the discomfort that comes with using more conventional techniques.

Uniform drug distribution

The active therapeutic ingredient is uniformly and consistently distributed throughout the wound site using film-forming sprays. This consistency guarantees that the medication is administered uniformly, perhaps increasing its therapeutic effectiveness. On the other hand, conventional dressings might not provide as uniform coverage, which could result in undertreated areas.

Quicker wound healing

The FFS-formed film's ability to regulate moisture is essential for accelerating wound healing. FFS can promote healing by preserving the ideal moisture balance, which lowers the possibility of infection and irritation that conventional dressings may cause. FFS is a more efficient choice for wound care because of its ability to retain moisture, which speeds up the healing process.

Patient comfort

The FFS-created thin, non-sticky layer enhances patient comfort during regular activities. Traditional dressings can be rough and sticky, whereas FFS offers a smooth surface that is less prone to irritate or create discomfort. Better adherence to treatment plans may result from this comfort since patients are more inclined to stick with a product that feels nice on their skin.

Ease of removal

FFS is readily removed with water, making the treatment easier for both patients and medical professionals. Traditional dressings, on the other hand, may stick to the skin tightly and be painful or uncomfortable to remove. One major benefit in wound care is the ability to remove the film without causing damage to the skin.

Adaptability to skin contours

FFS's formulation enables them to tightly conform to the wound's or skin's natural contours. This flexibility guarantees that the medication may efficiently target an

infected location, improving the effectiveness of treatment. Conventional dressings might not adhere to uneven surfaces as effectively, which could result in coverage gaps and decreased efficacy.

Challenges and limitations^{7,14,16,27}

Selection of polymers and excipients

The selection of polymers and excipients in the formulation has a significant impact on their efficacy. Different combinations may result in different film properties, including drug release profiles, flexibility, and adherence. Finding the best combinations to improve therapeutic efficacy while maintaining patient comfort is the difficult part.

Stability issues

The stability of the drugs in film-forming sprays is an important hurdle. Stability of the active ingredients and the film itself can be impacted by variables like temperature, humidity, and light exposure. To make sure the formulation stays effective for the duration of its shelf life, this requires thorough stability testing.

Mucoadhesion challenges

The performance of FFS depends on achieving the proper degree of mucoadhesion. Strong adhesion is required for efficient medication delivery, but too much mucoadhesion might make it difficult to remove the film and may result in discomfort or skin injury.

Application technique variability

The method employed during application can affect how effective film-forming sprays are. Drug delivery may be impacted by uneven film formation caused by variations in spray angle, distance from the skin, and pressure.

Regulatory hurdles

To prove the quality, safety, and effectiveness of their products, manufacturers have to comply with a number of intricate regulatory standards. This procedure can take a long time and could delay the release of novel formulations.

Recent advances and emerging technologies

Recent advancements in film-forming sprays for wound care have focused on enhancing wound healing efficacy through innovative formulations and delivery systems. Notable developments include:

Water-soluble chitosan with hEGF-liposomes: Researchers used water-soluble chitosan that contained human epidermal growth factor (hEGF) encapsulated in liposomes to create a film-forming spray. In mice, this formulation showed faster wound closure, with full healing occurring by day six. While the chitosan-based spray guaranteed consistent administration and long-lasting release, the liposomal coating enhanced the stability of hEGF⁴⁰

Silk protein and *Centella Asiatica* extract: To promote wound healing, a silk-based film-forming spray containing *Centella Asiatica* extract was created. Asiaticosides from the extract encouraged the

manufacture of collagen, whereas silk protein served as a framework for fibroblast activity. The formulation showed promise as a successful wound dressing with favorable pH, viscosity, and drying time³⁸.

Polymer complex with mesenchymal stem cell secretome: A complexed polymer film-forming spray including collagen tripeptides, hyaluronic acid, and carboxymethyl chitosan was suggested as a mesenchymal stem cell secretome delivery method. Using the polymer complex's bioadhesive and biocompatible qualities, this strategy sought to maximize secretome potency and retention in order to improve diabetic wound healing⁴¹

pH-responsive mupirocin-loaded hybrid nanoparticles in film-forming spray: To treat resistant bacterial wound infections, a pH-responsive film-forming spray (FFS) containing mupirocin-loaded lipid-polymeric hybrid nanoparticles (MUP-LPHNs) was created recently. With improved activity at pH 7.4, which is important to wounds, the optimized nanoparticles (~271 nm, 88% entrapment efficiency) allowed for prolonged, pH-dependent drug release. The antibacterial activity of MUP-LPHNs-FFS against *S. aureus*, MRSA, and *P. aeruginosa* was greatly improved (4–6 times), and it also showed superior in vivo wound healing, as seen by decreased inflammation, increased collagen deposition, and decreased bacterial load. The promise of FFS based on nanoparticles for advanced wound care is demonstrated by this formulation¹².

Future prospects and research directions

With their simplicity of use, consistent coverage, and enhanced patient compliance, film-forming sprays (FFS) are a potential new development in topical medication delivery. In order to promote the best possible wound healing, future research is probably going to concentrate on creating sophisticated polymers with improved mechanical and physicochemical qualities, like flexibility, adhesion, and moisture permeability. Another new approach to FFS is the use of nanotechnology, since formulations laden with nanoparticles can increase drug solubility, offer sustained release, and boost antibacterial or regenerative activity at the wound site. Furthermore, biodegradable and biocompatible film materials are being investigated to guarantee low residue and do away with the necessity of manual film removal, hence improving patient compliance and comfort.

Customizing FFS formulations according to patient-specific factors such as wound kind, pH, microbial profile, and skin sensitivity is another important approach. Addressing multifactorial problems in chronic wound care can also be accomplished by combining several therapeutic agents such as growth factors, antimicrobials, and anti-inflammatories within a single FFS. Furthermore, studies on technology such as microneedle-assisted administration and skin penetration enhancers could expand the application of FFS to systemic treatments. For FFS breakthroughs to be translated into clinically approved treatments, regulatory standardization and the development of consistent evaluation methodologies are essential. FFS has the

potential to revolutionize topical medication distribution and wound care with sustained interdisciplinary cooperation.

Conclusion

With a number of benefits over conventional topical formulations, such as enhanced patient compliance, consistent medication distribution, and adjustable drug release profiles, film-forming sprays (FFS) have developed into a cutting-edge and adaptable method in contemporary wound care. The therapeutic potential of FFS has been greatly increased by recent developments in pH-responsive systems, polymer science, and nanotechnology integration, especially in the treatment of chronic and infected wounds. These developments have shown increased absorption of active drugs, faster wound healing kinetics, and improved antibacterial activity. A number of obstacles still need to be overcome in spite of these encouraging advancements, such as formulation stability, regulatory uniformity, and clinical application scalability. Future studies should look into areas including combination medicines, biodegradable polymers, and personalized medicine in an effort to overcome these constraints. The future generation of improved wound care techniques is expected to rely heavily on FFS, provided that interdisciplinary collaboration and innovation continue.

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