

The Next Generation of Advanced Wound Therapy: In-Situ Film Forming Drug Delivery System

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ABSTRACT

Therapeutic management of chronic and acute wounds still remains a challenging aspect in clinical settings, primarily due to the ineffective use of wound dressings as therapy. In situ forming (ISF) film systems: The ISF system recently unveils an innovative wound care concept that presents a conformal drug delivery platform, a less painful application, and sustained release of the drugs. Such systems undergo a sol-gel transition at the site of injury, locally transforming from liquid to solid through solvent evaporation, phase change, and/or cross-linking. In this article, we systematically reviewed the fundamentals, polymeric compositions, formulation technologies, and clinical applications of ISF in wound treatments. Opportunistic evaluation is strengthened by the therapeutic potential and film-forming property of natural polymers, like chitosan and gellan gum; synthetic polymers, such as polycaprolactone (PCL) or poly (lactic-co-glycolic acid) (PLGA); and thermosensitive systems from the poloxamer family. This review reports the characterization methods and drug-release mechanisms, as well as the application in acute wounds (burns, surgical incisions) and chronic ones (diabetic ulcers, pressure sores). New technologies, including smart responsive and combination therapies, are covered along with clinical translation, regulatory, and scaling-up issues. This review aims to help readers understand the different strategies of ISF-based wound healing systems and offers a view on recent advancements and emerging topics in the field, including how those technologies may fundamentally change topical drug administration as well as dressings for wound healing.

Keywords: In-situ forming films; Spray wound dressings; Biodegradable polymers; Topical drug delivery; Wound healing; Film-forming systems

How to cite this article: Sunita Nirban 1 Manisha Pandey 1 Sumit Kumar. The Next Generation of Advanced Wound Therapy: In-Situ Film Forming Drug Delivery System. *Int J Drug Deliv Technol.* 2026;16(85s):1814-1826. DOI: 10.25258/ijddt.16.85s.183.

Source of support: Nil.

Conflict of interest: None

1. Introduction

1.1 Wound Healing: Clinical Needs and Current Limitations

Wound management is a formidable health challenge worldwide, and at least 2% of the population in developed countries suffer from chronic wounds, which cost an estimated \$25B per year in the US alone [1]. The wound healing process is a highly organized and closely regulated evolution of overlapping phases consisting of haemostasis, inflammation, proliferation, and remodelling that requires some microenvironmental conditions to best accomplish it [2]. Disruption of this intricate process, which leads to chronic non-healing wounds, has an enormous impact on a patient's quality of life and health care.

Gauze, hydrocolloids, and preformed film forms are all traditional dressings that have their limitations [3]. Gauze dressings are not able to properly conform to the shape of non-planar wounds, can adhere to granulating tissue and cause pain/damage upon removal, and may not sufficiently manage moisture [4]. A further improved barrier performance is achieved by preformed films and membranes, which, however, may not fully adapt to complex 3D wound surfaces, leading possibly to air trapping and incomplete contact with the entire wound area [5]. Additionally, many conventional dressings are multi-step applications and require experienced medical personnel for application of these products with frequent stripping of healing tissue during dressing changes [6].

Growing understanding of moist wound healing has driven the development of more advanced delivery systems, which offer maximum moisture while preventing colonization by

bacteria but still permit gaseous exchange and release therapeutic agents in a controlled manner [7]. To fulfil this demand, there is a growing interest in the development of sprayable and mouldable technologies that can overcome the geometric shortcomings of classical dressings while retaining enhanced therapeutic properties.

1.2 Rationale and Concept of In-Situ Forming Films

The mural wound care approach of ISF film technology is unique compared to all standard topical wound treatments because it is applied in liquid form, and the phase transition application generates seamless adhesive films directly on the wound bed [8,9]. This approach eliminates the need for prefabricated dressing and achieves total conformal dressing coverage irrespective of wound size, shape, or location on the body [10]. The general process is to apply the liquid polymer-containing formulation by spray, brush, or direct pour, followed by rapid conversion yielding a solid or semi-solid film through physical-chemical means [11].

This change can occur through evaporation of solvent, phase inversion following contact with wound exudates, temperature-triggered gelation, and chemical/photo-cross-linking reactions [12, 13].

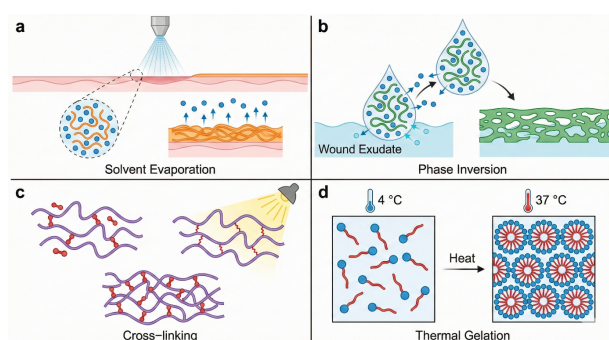


Figure 1 shows the four main processes of ISF film formation. The formed film can act as a protective coating against foreign substances, keep a wound site moist, offer mechanical support, or serve as a reservoir for local controlled drug delivery [14].

Some of the main merits of ISF systems include perfect adaptation to the non-planar shape of wounds, painless and non-invasive application, even distribution of drugs over tissue, as well as visualization through transparent matrices for monitoring the process of wound healing [15,16].

The ISF concept was introduced in the 1960s when Artz published for the first time the use of a plastic-film covering over surgical incisions [18]. Movement developed slowly across the decades, and pieces like Opposite were created in the 1970s and 1980s, but they were performed films [19]. One reason why the ISF idea has only taken off to its real potential in the 1990s-2000s is because of advances made with polymer science, and this development has accelerated exponentially with nanotechnology, including smart materials [20, 21].

2. Fundamental Principles of ISF Technology

2.1 Formation Mechanisms

Conversion of liquid to solid films at the wound site is accomplished by different physicochemical mechanisms that render each capable of providing distinct advantages and limitations for use in wounds [22]. Figure 1 provides a schematic overview of these four mechanisms: solvent evaporation, phase inversion, cross-linking, and thermal gelation.

Solvent Evaporation-Based Systems

Solvent evaporation is the simplest process of ISF formation, in which volatile organic solvents evaporate quickly at ambient or body temperature conditions and form a polymer film matrix [23]. The rate of film formation is also affected by solvent vapour pressure, polymer concentration, ambient temperature and humidity, and the surface area available to air [24]. Typical solvents used are ethanol, isopropanol, acetone, ethyl acetate, and dichloromethane, chosen on the basis of their evaporation rate and polymer solubility [25].

TABLE 1: Critical Quality Attributes and Characterization Methods for ISF Systems

Quality Attribute	Clinical Relevance	Test Method/Standard	Acceptance Criteria	Key Parameters	Reference
Spray Pattern	Ensures even	Spray pattern	CoV <15%	Drop let size,	[27]

The formation of the film occurs in different steps, beginning with the initial wetting of the wound surface by the liquid formulation (1-5s), followed by solvent evaporation, which endows an increased viscosity and polymer chain entanglement (5-60 s), and finally ends with a final solidification event where a coherent film is obtained with residual solvent content typically below 5% (1-5 min) [26]. Spray dressings that are based on polyurethane polymers are a good example of this, being prepared as commercial formulations that can lead to touch-dry films in 30-60 seconds [27].

Phase Inversion/Precipitation Systems

PI mechanisms take advantage of the different solubility of a polymer in an organic as compared to an aqueous medium [30]. Water-soluble organic solvents such as N-methyl-2-pyrrolidone (NMP), DMSO, or PEG with a C₃₀ substituent dissolve the formulation polymer [31]. Once an organically soluble preparation comes into contact with wound exudates or tissue fluids, organic solvent partitions into the aqueous phase, and water enters into the polymer solution, leading to precipitation of the polymer and formation of a film [32]. This approach provides benefits for unstable biomolecules and thermolabile drugs [33].

Cross-Linking Systems

Cross-linkage can be provided by covalent or physical bonding between polymer chains, resulting in the creation of a three-dimensional structure [36]. Chemical cross-linking can be induced photochemically by UV or visible light (when using appropriate photoinitiators), thermally when the catalyst is heat-activated, or chemically by applied activators shortly prior to application [37–38]. Photo-cross-linking allows for spatial and temporal control, where the resulting gelation time is in the range of 30–300 s when exposed to proper light [39].

As far as physical gelation is concerned, ion-mediated cross-linking (e.g., calcium-mediated cross-linking of alginate or gellan gum), thermal gelation with LCST/UCST (lower critical solution temperature or upper critical solution temperature) character, and pH-induced gelation are central in this context [40,41]. Poloxamer-containing systems reverse thermogel, being liquid at a temperature of 50% [53]. 24–72h dosing would be indispensable to attain therapeutic levels [56]. Cytotoxicity of the system needs to be tested to show biocompatibility (cell viability over 80%) [59] and biodegradation with healing time [60]. An MVTR of 2000–2500 g/m²/24 hours provide an ideal environment for moist wound healing and also controls pooling of exudates [61].

Uniformity	coverage of the wound bed	analysis (ASTM E1620)		spray cone angle	
Film Formation Time	Patient compliance,	Drying time measurement (<i>in vitro</i>)	30–120 s	Temp., humidity	[26]

	prevents runoff				
Film Thickness	Affects flexibility, drug loading, MVT R	Micrometre/optical profilometry	50–500 µm	Uniformity across the wound surface	[19]
Tensile Strength	Durability under movement	Universal testing machine (ASTM D882)	0.5–5.0 MPa	Crosshead speed, sample dimensions	[20]
Elongation at Break	Flexibility on joints/mobile areas	Tensile testing (ASTM D882)	50–300%	Strain rate, grip separation	[21]
Bioadhesion Strength	Retention on the moist wound surface	Texture analyzer/peel test (ASTM F2258)	0.1–0.5 N/cm ²	Substrate moisture, contact time	[22]
MVT R	Moisture balance, prevents maceration	Gravimetric method (ASTM E96)	500–2500 g/m ² /24h	Temp., RH gradient	[61]

3. Polymeric Materials for ISF Formulations

3.1 Natural Polymers

Chitosan

Chitosan, a linear glucosamine polysaccharide derived from deacetylated chitin, is one of the most relevant natural polymers employed for ISF wound dressing material due to its inherent antimicrobial and haemostatic activities as well as biocompatible features [63, 64]. The polymeric chain is made up of β-(1→4)-linked D-glucosamine and N-acetyl-D-glucosamine randomly linked units, and the DD ranges from 70 to 95%, affecting the dissolved state and biological activity [65].

The film-forming properties of CS are significantly affected by its molecular weight (50–2000 kDa), DD, pH, solvent, and concentration [66]. In the presence of dilute acidic solutions (acetic or lactic acid), pH < 6, chitosan is dissolved,

Drug Content Uniformity	Consistent therapeutic delivery	HPLC/UV (USP <905>)	90–110% label claim	Sampling across the film area	[24]
Residual Solvent	Safety, tissue irritation	GC-MS (ICH Q3C)	< Class 2 limits	Extraction method, detection limits	[25]
Drug Release Profile	Therapeutic efficacy, dosing frequency	Franz diffusion cell (USP <724>)	Sustained 24–72 h	Receptor medium, sampling intervals	[56]
Antimicrobial Activity	Infection prevention	Zone of inhibition (CLSI M02)	>5 mm zone	Test organisms, incubation	[62]
Cytotoxicity	Biocompatibility, wound healing support	MTT assay (ISO 10993-5)	Cell viability >70%	Cell line, exposure duration	[59]

forming viscous solutions that could be used as sprays [67]. On the wound surface, the chitosan is precipitated and absorbed as adherent films (50–200 µm thick) after being dissolved in an aqueous or organic solvent, then evaporating or neutralizing its pH [68].

The antimicrobial activity of chitosan against gram-positive and gram-negative bacteria, fungi, and some viruses is explained by electrostatic interactions between the positively charged -NH₂ groups and negatively charged microbial cell membranes, resulting in a loss of membrane integrity and interference with microorganism growth [69, 70]. MIC values vary between 0.01% and 0.1% according to species of microorganism, molecular weight, and DD [71]. In comparison to conventional gauze, chitosan-dressed wounds are shown in clinical studies to have a lower incidence of infection [72].

For instance, chitosan acetate solutions in ethanol-water systems result in transparent films when put through a spray application [73]. Silver sulfadiazine addition increases the antimicrobial effectiveness against resistant organisms [74]. Drawbacks are pH sensitivity, low solubility in the physiological pH range, and the risk of allergic reaction to patients with intolerance to shellfish [75].

Gellan Gum

Gellan gum is also an anionic exopolysaccharide synthesized by *Sphingomonas elodea*, composed of tetra saccharide repeating units that exhibit ion-triggered gelation, good for ISF treatment [76]. In solution, the polymer appears as random coils, but upon cooling or addition of cations (Ca^{2+} , Mg^{2+}), double helices are formed, resulting in a three-dimensional network. [77].

Ion-activated gelation allows for the spraying of gellan gum solutions, which rapidly form a gel upon contacting calcium-rich wound exudates [78]. The gelation temperature of the nanoparticle dispersion can be tailored by both ion concentration and polymer molecular weight, which provides desirability for a range of different topical applications [79]. In wound healing research, it has been reported that gellan gum films accelerated re-epithelialization and attenuated inflammation when compared with conventional dressings [80].

The mechanical properties and drug loading capacity of the combination systems based on chitosan or alginate were improved [81]. Gellan as a matrix for growth factor delivery. The high morphological and mechanical stability of gels obtained from gellan gum was found to be particularly useful for entrapment of growth factors, with studies reporting sustained release of EGF concentration in diabetic wound healing over no less than 7 days [82].

3.2 Synthetic Polymers

Polycaprolactone (PCL)

For example, polycaprolactone (PCL) has a good film-forming ability and is highly biodegradable with FDA approval for biomedical uses, so it can be simply prepared using the ring-opening polymerization of ϵ -caprolactone [85, 86]. PCL has a slow degradation time (2–4 years for complete degradation) due to ester bond hydrolytic cleavage and is suitable as a material for long-term drug delivery [87].

As the polymer is permeable to many drugs and compatible with numerous actives, they present an ease in formulation development [88]. These PCL-based ISF systems, organic solvents including dichloromethane, chloroform, or ethyl acetate, are used to dissolve the polymer and then cast with spray deposition followed by evaporation of HV [89]. 1–2 min is required for film formation, and the films formed have flexibility and transparency with tensile strength in the range of 10–30 MPa, depending on molecular weight [90]. Other drug delivery applications range from long-term antibiotic (e.g., gentamicin, ciprofloxacin) release for wound prophylaxis [91], anti-inflammatory (ibuprofen, diclofenac) inclusion to relieve pain [92], and growth factor delivery towards chronic wound healing [93]. Clinically, translation efforts are now directed at achieving commercially acceptable spray formulations with tolerable solvent safety profiles [94].

Drawbacks are hydrophobicity, which reduces cell adhesion; slow degradation (about 2–3 weeks), which may not be compatible with skin regeneration rates; and use of organic solvents that pose safety concerns [95]. Approaches to bypass these shortcomings include copolymerization with hydrophilic polymers, surface functionalization with bioactive molecules, and fabrication of electrospun nanofiber-mediated delivery platforms [96].

Poly (lactic-co-glycolic acid) (PLGA)

PLGA, which is a copolymer of glycogen and lactic acids, is considered to be the gold standard for polymer drug delivery due to FDA approval, adjustable degradability kinetics, and a wide clinical history [97, 98]. The ratio of lactide to glycolide can be varied (50:50, 65:35, 75:25, 85:15) to tune degradation from weeks to months [99]. The fastest degradation (1–2 months) is seen in the 50:50 composition, as it has more hydrophilicity owing to the presence of glycolic acid; however, 85:15 PLGA degrades over 5–6 months [100].

For ISF systems using PLGA, water-miscible organic solvents (NMP, DMSO) or volatile solvents (ethyl acetate, acetone) are used for the dissolution of the polymer [101]. The process of phase inversion upon exposure to wound exudate leads to porous films that are beneficial for both drug release and exudate absorbency [102]. The molecular weight selection (10–150 kDa) directly affects both the mechanical property and the degradation rate of films [103].

In the field of wound healing, the technique has been utilized in the delivery of antimicrobial drugs for infection prevention after surgeries [104], sustained release of growth factors (VEGF, bFGF) to promote angiogenesis in chronic wounds [105], and inclusion of anti-inflammatory cytokines playing a modulating role with immune system responses [106]. Spray-on films containing PLGA microspheres allow pulsatile drug release profiles [107].

Degradation products (i.e., lactic and glycolic acid) are metabolized through the tricarboxylic acid cycle and excreted by breathing, generating biocompatibility [108]. Nevertheless, bulk degradation might lead to a local pH lowering and inflammatory reactions [109]. Several methods of acidification reduction are based on the use of pH buffering agents and low-MW PLGA [110].

3.3 Thermosensitive Polymers

Poloxamers (Pluronics)

The most well-known poloxamer example is Pluronic F127 (poloxamer 407), which is a triblock copolymer containing hydrophobic polypropylene oxide (PPO) in the middle and both sides covered by hydrophilic polyethylene oxides (PEO) [111]. These amphiphilic polymers demonstrate reverse thermal gelation, existing as viscous liquids at cold (4–10°C) temperatures and then transitioning to semi-solid gels above a critical gelation temperature (15–25°C, depending on concentration) [112].

The mechanism of gelation proceeds to micelle formation and packing at high temperature [113]. At low temperatures, isolated polymer chains are still distributed in the aqueous phase. PPO blocks self-associate with increasing temperature to form micelles with PEO coronas. Micelle-packing and -entangling at higher temperatures results in the gel state [114]. A common set of concentrations (15–30% w/v)

gives rise to gelation temperatures of 20–35°C, ideal for room temperature storage and body temperature administration [115].

FIGURE 2: Chemical Structure of Poloxamer 407

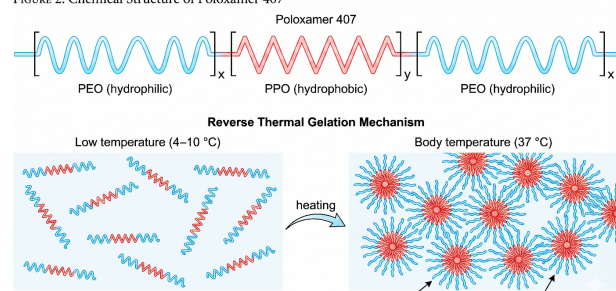


Figure 2:The chemical structure of poloxamer 407 as well as its mechanism of thermal gelation.

Pluronic F127 has also been shown as a wound healing agent in animal models; mechanisms suggested include

TABLE 2: Summary of Polymeric Materials Used in ISF Wound Dressings

Pol- y- mer	Type	Fil m For mat ion Mec han ism	Key Prop erties	Ad- vant ages	Lim- ita- tions	Ref.
Chi- to- san	Natu- ral (pol- ysac- chari- de)	Sol- vent eva- po- ra- tion, pH neu- tral- iza- tion	Cati- onic, anti- micro- bial, hemo- static	Bio- com- patibl e, anti- microbi- al, mu- coad- hesive	pH- sen- sitive, poor sol- ubility at neu- tral pH	[63 – 75]
Gel- lan Gu- m	Natu- ral (pol- ysac- chari- de)	Ion- trig- gere d ge- la- tion (Ca ²⁺ , Mg ²⁺)	Ani- onic, ion- re- spon- sive gela- tion	Rapi- d ge- la- tion, sup- ports grow- th fac- tors	Mechani- cal weak- ness, re- quire s cat- ions	[76 – 82]
Al- gi- nat- e	Natu- ral (pol- ysac- chari- de)	Ion- cros- slink- ing (Ca ²⁺)	Ani- onic, high- water absorp- tion	Hemo- static, gel- form- ing,	Slow dis- solution, lim- ited cell	[40, 83]

improved epithelial growth factor activity [116]. The polymer's low toxicity, biocompatibility, and FDA approval make it suitable for clinical translation [117]. Applications are the delivery of the antimicrobial peptides with controlled release over 4–7 days [118], a controlled release of growth factors that retain their activity during formulation and storage [119], or a thermosensitive gel-to-film transition for irregular wound geometries.

Combination primarily conjugates improve the performance by loading with PLGA microparticles in polysaccharide-based gels for biphasic drug release [121], mixing with chitosan to enhance antimicrobial efficacy [122], and supplementing with nanoparticles for stimuli-responsive delivery [123].

Table 2 provides a comprehensive comparison of the polymeric materials discussed, including their film formation mechanisms, key properties, advantages, and limitations.

				bio- com- patibl e	ad- he- sion	
PC L	Syn- thetic (pol- yes- ter)	Sol- vent eva- po- ra- tion	Semi- crys- tal- line, hydro- pho- bic, slow degra- dation	FDA -ap- prove d, flexi- ble, long- term deliv- ery	Hy- dro- phob ic, or- ganic sol- vents re- quire d	[85 – 96]
PL GA	Syn- thetic (pol- yes- ter)	Pha- se in- ver- sion , sol- vent eva- po- ra- tion	Tuna- ble degra- dation (week s– month s)	FDA -ap- prove d, ad- justa- ble re- lease kin- etics	Acid deg- rada- tion prod- ucts, sol- vent resid- ues	[97 – 110]
Pol- ox- am- er 407	Syn- thetic (tribl- ock)	The- rmal ge- la- tion (re- vers- e)	Ther- morev- ersible (sol- gel at ~25°C)	Aque- ous for- mu- lation , bio- com- patibl e, FDA -ap- prove d	Wea- k me- chani- cal stren- gth, rapid ero- sion	[11 1– 123]

4. Formulation Strategies and Optimization

4.1 Choice of Solvent and Formulation Principle

The selection of solvents is one important formulation parameter affecting polymer dissolution, spray properties, film-formation kinetics, and safety profile [124]. Organic solvents used in ISF: These are ethanol, isopropanol, acetone, ethyl acetate, and dichloromethane with different vapor pressures [125], polarity (all from Sigma Aldrich), and polymer-dissolving properties. These are the preferred ones for commercial formulations due to low toxicity, regulatory acceptance, and fast evaporation (ethanol: 44 mmHg-20°C) [126].

Water-miscible solvents, such as NMP and DMSO, allow phase inversion processes to occur with the choice of solvent depending on the polymer's miscibility properties, biocompatibility, and residual limits [127]. Solvent mixtures help in minimizing several performance properties at once; for instance, ethanol is mixed with ethyl acetate to compromise evaporation rate with polymer solubility [128]. Regulatory issues demand compliance with ICH Q3C guidelines on acceptable levels of residual solvents in final preparations (Class 2 solvents <50 ppm, Class 3 solvents <5000 ppm) [129].

4.2 Plasticizers and Film Modifiers

Plasticizers are responsible for improving the film flexibility, lessening the brittleness, and improving mechanical properties due to an increase in molecular mobility and a decrease in polymer crystallinity [130]. Various plasticizers such as polyethylene glycols (PEG 200–600), propylene glycol, glycerol, triethyl citrate, and diethyl phthalate are usually used at a percentage level of 5–30% w/w polymer concentration [131]. Biocompatible, regulatory-approved PEG-based plasticizers are known in which the molecular weight can be used to modulate plasticization efficiency [132].

Film-forming agents like hydroxypropyl cellulose, polyvinylpyrrolidone, or carbomers improve film cohesiveness and suppress tackiness [133]. Concentration optimization allows a balance between mechanical properties and drug release profile since high amounts of plasticizer could lead to decreasing film integrity and increasing degradation [134].

4.3 Drug Incorporation and Stability

Active pharmaceutical ingredient selection takes into account form (i.e., solubility) in the formulation solvent, as well as chemical stability during processing and storage, therapeutic dose requirements, and compatibility with the polymer matrix [135]. Antimicrobials are the most utilized drug class in ISFs for wound dressings such as silver sulfadiazine, ciprofloxacin, gentamicin, and mupirocin [136]. Anti-inflammatory drugs (ibuprofen, diclofenac) have pain-killing properties and modify inflammation [137].

Growth factors and peptides, which are sensitive to organic solvents and temperature, need special focus [138]. The strategies are by encapsulation in protective carriers (liposomes, nanoparticles), integration with the aqueous phase of a biphasic system, or addition just prior to application [139]. Antimicrobial peptides have also exhibited potential and retained activity in ISF formulations [140].

Strategies to solubilize poorly water-soluble drugs consist of complexation with cyclodextrins, inclusion in mixed micelles, and employment of co-solvents [141]. Stability

testing comprises chemical stability (HPLC assay at room temperature), physical stability, such as phase separation and precipitation, and retention of antimicrobial activity [142].

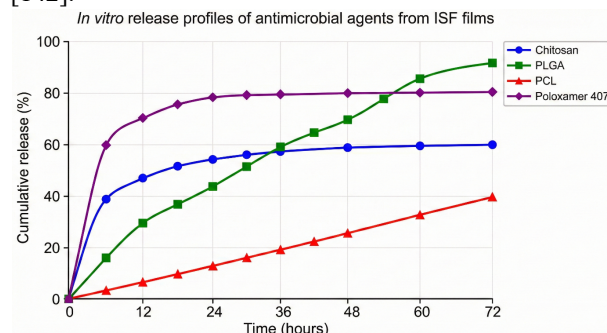


Figure 3 illustrates typical drug release profiles from different ISF formulations, demonstrating sustained release over 24–72 hours.

5. Applications in Wound Healing

5.1 Acute Wounds

Burns and Thermal Injuries

ISF systems show specific advantages ranging from wound management and conformable coverage of irregular surfaces to moisture retention and antimicrobial protection in the management of burn injuries [143]. Silver-containing preparations have a wide range of antimicrobial activity against the commonly found burn pathogens, including *Pseudomonas aeruginosa* and *Staphylococcus aureus* [144]. There are lower rates of time to healing and infection when using spray-on silver-containing films in clinical studies vs. silver sulfadiazine cream [145].

Polyurethane-based spray dressings provide a transparent film that allows visual wound assessment without removal of dressing [146]. Steen et al. [147] found little difference in healing compared to conventional dressings but increased patient comfort and less frequent dressing changes in patients with partial-thickness burns. Formulations combining local anaesthetics (lidocaine) achieve instantaneous pain relief at the time of use [148].

Surgical Wounds

Post-surgical wound care is an emerging application for ISF systems that offers the benefits of sterile application, moisture management, and infection prevention [149]. Cyanoacrylate-based tissue adhesives have been used as a surgical site protection product, and polymer-based ISF systems expand the functionality to drug delivery [150]. Studies have demonstrated non-inferiority to standard sutures with better cosmetic results in clean surgical wounds [151].

5.2 Chronic Wounds

Diabetic Ulcers

Diabetic foot ulcers affect 15–25% of diabetics within their lifetime and are the most common cause for non-traumatic amputation of a lower extremity [152]. ISF not only enables infection prevention but also the delivery of growth factors and moisture regulation, which are the possible pathophysiological features of a diabetic wound [153]. Chitosan-based formulations also show improved wound healing in diabetic animal models by antimicrobial properties and fibroblast proliferation-like activity [154].

Delivery of growth factors using ISF systems eliminates the limitation of stability & short half-life coupled with susceptibility to degradation in the harsh wound bed [155]. PLGA-based formulations that offer sustained release of epidermal growth factor (EGF) or platelet-derived growth factor (PDGF) have increased wound healing rates in clinical settings [156]. Antimicrobial agents are combined with growth factors in combination therapy that can target both infection and dysfunctional healing cascades [157].

Ulcers of Pressure; Ulcer, Venous Leg

Pressure ulcers are a problem that affects immobile patients, and ISF systems provide benefits to dressing hard-to-treat anatomical sites [158]. Flexible film allows for total coverage of sacral and heel ulcers devoid of the bulk that may interfere with patient positioning [159]. Comparable rates

TABLE 3: Preclinical and Clinical Studies of ISF Systems for Wound Healing

Polymer(s)	Drug/Active Agent	Wound Model	Key Outcomes	Ref.
Chitosan acetate	Silver sulfadiazine	Rat full-thickness wound	Reduced bacterial count, accelerated re-epithelialization	[74]
Gellan gum	EGF	Diabetic mouse (db/db)	Sustained EGF release over 7 days, enhanced closure rate	[82]
PCL	Gentamicin	Rat-infected wound	Prolonged antibiotic release, infection control	[91]
PLGA	VEGF	Mouse ischemic wound	Improved angiogenesis,	[105]

of healing to hydrocolloid compounds are reported with better patient acceptance [160].

ISF systems compatible with compression therapy are also beneficial for venous leg ulcers, which are the most common form of these wounds [161]. Thin, flexible films do not affect the application of a compression bandage and retain effectiveness under pressure [162]. Formulations comprising anti-inflammatory moieties and proteolytic enzyme inhibitors have been designed to target chronic inflammatory conditions associated with venous ulcers [163].

Table 3 summarizes key preclinical and clinical studies of ISF systems applied to various wound types, highlighting the diversity of formulations and therapeutic outcomes.

			granulation tissue formation	
Poloxamer 407	Antimicrobial peptide	Rat full-thickness wound	Sustained peptide release, reduced bio-film formation	[118]
Chitosan/PLGA	Ciprofloxacin	Rabbit infected wound	Synergistic antimicrobial effect, complete healing by day 14	[121]
Polyurethane	(none, barrier only)	Human second-degree burns	Transparent film, comparable healing, less pain	[147]
PLGA	PDGF	Human diabetic ulcer	Accelerated wound closure in	[156]

			phase II trial	
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6. Clinical Translation and Regulatory Considerations

6.1 Scalability and Manufacturing

Transfer from a laboratory/feasibility phase to commercial manufacturing is associated with formulation stability, packaging needs, and spray device compatibility [164]. Aerosol propellants are required to be optimized in terms of atomization efficiency and their implications for users' health and the environment [165]. Commercial products use hydrofluoroalkane (HFA) propellants instead of chlorofluorocarbons [166]. Non-aerosol pump sprays, mechanical, non-aerosol pump sprays have the advantage of not requiring a propellant at all, but can lead to reduced spray uniformity [167].

Quality-by-design approaches have been used to determine critical process parameters, which include spray pressure, nozzle-to-substrate distance, application temperature, and humidity [168]. Process analytical tools (PAT) can monitor the process of film formation as well as drug content uniformity in real time [169].

6.2 Regulatory Framework

ISF-based devices could be a drug, device, or combination product depending on the predominant mechanism of action [170]. The FDA designates medical devices as Class II or III, which are subject to premarket notification or approval based on substantial equivalence with a predicate device, unless clinical trials for efficacy and safety are conducted [171]. Similar requirements are also stated in the European MDR for CE marking [172].

For drug release ISF systems ('combination products'), a more stringent regulatory pathway would be followed, with the requirements for current good manufacturing practices, pharmaceutical-grade manufacture, and long-term stability studies, as well as the requirement of pharmacokinetic data [173]. Guidelines are regulatory frameworks for development and approval [174].

Challenges and Future Perspectives

7.1 Current Limitations

Some of these constraints are that, despite great technical strides, several obstacles inhibit widespread clinical application [175]. Advancing aqueous or low-solvent formulations should be worked on due to safety concerns with solvents [176]. Films are still challenged in the optimization of mechanical properties, including flexibility versus strength [177]. Another major problem is the stability of a drug during storage and application [178]. Reimbursement needs a cost-effective profile versus standard dressings [179].

7.2 Emerging Technologies

Smart-responsive ISF devices are also fabricated by incorporating stimuli-responsive polymers, which can trigger drug release in response to infection (pH-responsiveness), inflammation (ROS-responsiveness), or temperature change [180]. Nanoparticles enhance drug loading, and antimicrobial features and multifunctional performance are also available [181]. ISF, a 3D bioprinting tissue-engineering technology, can achieve ISF preparations in the form of individual wound shapes [182].

Gene therapy-based studies explore ISF as a medium for nucleic acid (siRNA, plasmid DNA) delivery to silence wound-healing pathways [183]. In addition to the above-discussed stimulatory factors, stem cells in ISF matrices represent a new frontier where the rationale of cell therapy merges with that of biomaterial scaffolds [184]. Obstacles to realizing necessary therapeutic action and cell survival have, however, not been addressed for these advanced applications [185].

Conclusions

In-situ forming film systems aspects (Cs): Concepts in-situ formed films are a very promising breakthrough in wound healing and dermal drug delivery due to the benefits of intimate contact, pain-free application, prolonged drug release, and patient compliance. The technology has progressed from a basic polymeric film platform to sophisticated 'smart' systems and combinatory therapy modalities. Natural polymers, such as chitosan that present intrinsic antimicrobial activity; synthetic polymers, such as PCL or PLGA, that allow controlled degradation and subsequent release of drugs; and thermosensitive systems, which gel when the temperature rises, are examples.

An overview of the critical quality attributes, polymer selection process, formulation strategy, drug release profiles, and preclinical/clinical data supporting ISF technology has been elaborated in Tables 1–3 and Figures 1–4. A clinical translation characterization requires the optimization of kinetic film formation, mechanical properties, drug loading and release profiles, and biocompatibility with consideration to regulatory requirements and manufacturability. Applications include acute wounds (burns and surgical sites) and chronic wounds (diabetic ulcers and pressure sores). Recent advances in smart response polymers, nanoparticles, and biologics may further allow for broadening of the capabilities themselves.

Future research areas consist of the development of aqueous-based formulations to eliminate solvent-related safety concerns, the tuning of film properties according to wound type, the performance of well-designed clinical trials demonstrating superiority over standard care, and the investigation of combination therapies associating different therapeutic modalities. Their potential is such that when the ISF paradigm is more fully developed, it may form a significant component of wound therapy and, still more so, serve as a vehicle for second-generation therapeutics.

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