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REVIEW

Nanodelivery of Gentiopicroside for Inflammatory Skin Lesions: Insights from Psoriasis and Diabetic Foot Ulcers

Wenjie Wang[1], Libo Du[2], Huanfeng Ye[2], Wenjing Liu[3], Liyun Sun[1,*], Huahao Wang[2,*]

[1]Department of Dermatology, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, 100000, People's Republic of China; [2]Stable Key Laboratory for Structural Chemistry of Unstable and Stable Species, Institute of Chemistry Chinese Academy of Sciences, Beijing, 100190, People's Republic of China; [3]School of Pharmacy, Shenyang Pharmaceutical University, Shenyang, Liaoning, 110016, People's Republic of China

*These authors contributed equally to this work

Correspondence: Liyun Sun, Department of Dermatology, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, 23 Museum of Fine Arts Backstreet, Dongcheng District, Beijing, 100010, People's Republic of China, Email doctorsunny18@126.com; Huahao Wang, Stable Key Laboratory for Structural Chemistry of Unstable and Stable Species, Institute of Chemistry Chinese Academy of Sciences, Beijing, 100190, People's Republic of China, Email whh9885@gmail.com

Abstract: Inflammation-associated skin lesions, including psoriasis (PsO) and diabetic foot ulcers (DFU), greatly impair patients' quality of life. Gentiopicroside (GPS), a key iridoid glycoside from Gentiana species, exhibits anti-inflammatory, antioxidant, and wound-healing properties, but its clinical application is limited by low oral bioavailability and poor skin permeability. Nanodelivery strategies have been actively explored to overcome these limitations. The objective of this review was to critically analyze recent breakthroughs in GPS-loaded nanodelivery approaches for the treatment of inflammation-associated skin lesions, especially PsO and DFU, including the impact of these approaches on GPS bioavailability, efficacy, and safety profile. Oral bioavailability of GPS can be improved by poly (lactic-co-glycolic acid) (PLGA) nanospheres and phospholipid-complex self-nanoemulsifying drug delivery systems (PC-SNEDDS), while skin-targeted delivery and sustained release can be enhanced by chitosan (CHI) nanoparticles, electrospun nanofibers, ZIF-8 metal-organic frameworks, and nanoscale hydrogels. These nanodelivery technologies improve the translational potential of GPS for chronic inflammatory skin diseases. Although GPS-loaded systems have not yet entered clinical trials, analogous nanotechnologies have demonstrated enhanced drug stability, bioavailability, safety, and patient tolerability in treatments of other skin diseases, highlighting their strong potential for clinical translation. Future efforts toward clinical translation may focus on establishing common evaluation criteria, conducting full-scale toxicological and biodistribution tests, and implementing Good Manufacturing Practice (GMP)-scale-up projects with multicenter preclinical trials.

Keywords: gentiopicroside, nanodelivery, psoriasis, diabetic foot ulcers, chitosan, skin lesions

Introduction

A variety of inflammation-associated skin lesions pose great challenges to global public health. Representative conditions include psoriasis (PsO) and diabetic foot ulcer (DFU), both characterized by skin barrier disruption and persistent activation of inflammation.[1,2] PsO is a chronic proliferative and inflammatory skin disease characterized by well-demarcated red plaques covered with silvery-white scales, affecting approximately 3% of the global population.[3–5] DFU is a common and serious skin complication of diabetes, often manifested as chronic, poorly healing and recurrent skin ulcers of the distal lower limbs,[6,7] affecting approximately 2.6% of the global population and carrying a 19–34% risk among diabetic patients.[8] Together, PsO and DFU represent a substantial public health and economic burden worldwide, reflecting their high prevalence, chronic progression, and impact on patients' quality of life.

PsO is commonly treated with oral retinoids and topical corticosteroids.[9] Standard management of DFU focuses on proper wound care, infection control, and tight glycemic regulation.[10] Although these conventional therapies can achieve

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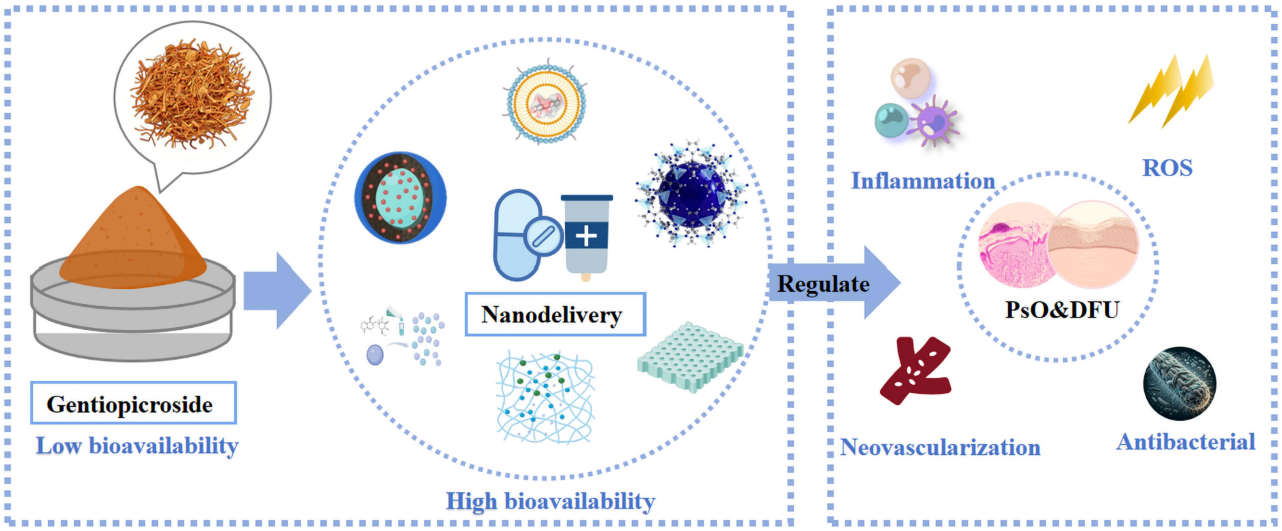
Graphical Abstract



therapeutic benefit, they are frequently accompanied by adverse effects, slow healing, or recurrent lesions.[9,11] These limitations underscore the importance and urgency of developing more effective and targeted therapeutic strategies. Although PsO and DFU manifest dramatically differently, both diseases have closely intertwined pathogenic mechanisms involving dysregulation of the immune response, impaired vascular regeneration, and skin microbiome dysregulation.[9,12,13] These shared pathogenic mechanisms establish PsO and DFU as pivotal models for research on inflammation-associated skin lesions.[14,15] The earliest recognition of GPS in modern research dates back to the 19th century (1862).[16] In China, gentiopicroside (GPS), as a principal anti-inflammatory constituent from traditional Chinese medicine, has been used for centuries in the treatment of both PsO and DFU, with documented clinical efficacy.[17,18]

GPS is an iridoid glycoside derived from Gentianaceae plants such as those belonging to the genus Gentiana (eg, Gentiana macrophylla). Its molecular formula is $C_{16}H_{20}O_9$ (Figure 1), with an exact molecular weight of 356.3 g/mol.[19] There is increasing pharmacological evidence suggesting that GPS may act through several mechanisms and targets that contribute to the management of PsO and DFU. For example, GPS could alleviate lesion inflammation by suppressing proinflammatory cytokines, including interleukin-6 (IL-6), interleukin-23 (IL-23), and interleukin-17A (IL-17A), thereby modulating the local immune microenvironment.[20] GPS also modulates the aberrant proliferation and differentiation of epidermal keratinocytes and dermal fibroblasts, counteracting pathological hyperplasia and promoting epidermal repair.[20,21] Moreover, GPS was reported to bidirectionally modulate vascular endothelial growth factor (VEGF)-mediated angiogenesis, which may recover aberrant blood vessels in psoriatic plaques and improve blood supply in DFU.[20,22] In addition, multiple studies have revealed that GPS supports cellular metabolic homeostasis and protects dermal fibroblasts from glycation-related injury via pathways involving Fibroblast Growth Factor Receptor 1 (FGFR1), Progestin and AdipoQ Receptor Family Member 3 (PAQR3), and the Receptor for Advanced Glycation End Products (RAGE).[21,23,24] GPS further exhibits antimicrobial activity, inhibiting the growth of Gram-positive and Gram-negative bacteria, which may help restore the cutaneous microbial balance in inflammation-associated skin lesions.[25] The action mechanism of GPS nanodelivery in inflammation-associated skin lesions is briefly illustrated in Figure 1.

However, GPS shows highly hydrophilic and poorly lipophilic properties, presenting low oral availability of 10.3% and skin permeability of 5.41%.[26,27] Such pharmacokinetic (PK) properties make this compound less effective as a drug when administered either orally or topically. Due to the PK problems associated with GPS, globally increasing effort has been placed on the development of new and effective drug delivery systems. Its potential, combined with the limitations of current therapies, has driven research toward innovative delivery strategies. The development of advanced drug

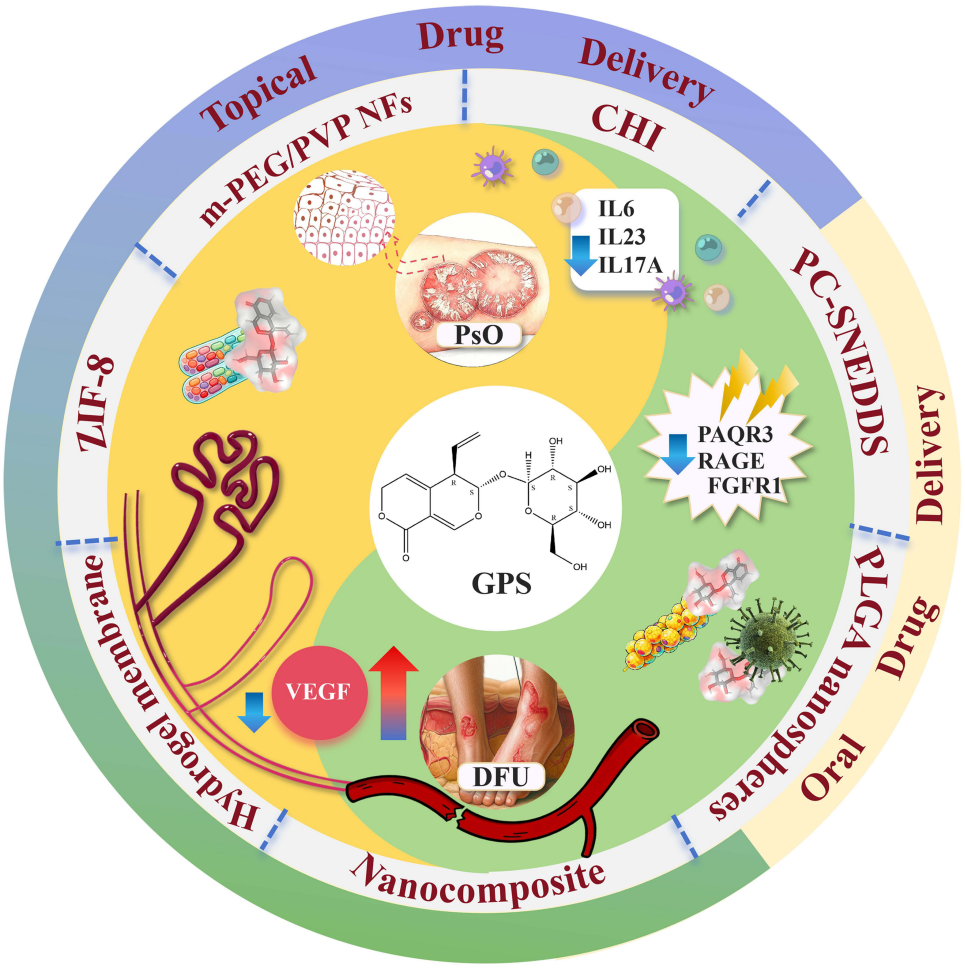


Figure 1 Schematic overview of the mechanism of action for GPS nanodelivery in inflammation-associated skin lesions (using PsO and DFU as examples).

delivery systems, such as chitosan-based nanoparticles and nanoemulsions, has become a major focus, aiming to enhance efficacy, improve safety, and address the challenges of managing these inflammation-associated skin lesions.[28,29]

Over the past twenty years, scientists have tested various strategies for delivering GPS, some of which appeared quite promising. In particular, nanocarrier-based formulations such as chitosan (CHI)-based nanoparticles, nanospheres, hydrogel membranes, phospholipid complexes, and so on, have shown great potential in overcoming GPS delivery challenges. These techniques aim to increase the stability, skin permeability, and oral bioavailability of GPS, leading to great improvements in treatment efficiency against inflammation-associated skin lesions like PsO or DFU. Some of these nanodelivery strategies have also demonstrated advantages in clinical studies of other drugs for inflammatory skin conditions, providing supporting evidence for their potential translational applications. In this review, we provide a comprehensive overview of recent advances in GPS-loaded nanodelivery systems, with a focus on PsO and DFU. We further discuss remaining challenges and consider how these strategies might be applied in future clinical translation, with the goal of providing useful information to support future research.

Method

This review aimed to summarize the research progress of nanodelivery systems for GPS to treat inflammation-associated skin lesions, represented by PsO and DFU. In order to collect relevant literature systematically, the PubMed, Web of Science, Scopus and Cochrane Library databases were retrieved respectively. The retrieval time range was until November 2025, and the retrieval language was limited to English. The search strategy combined the following keywords: (i) “gentiopicroside” or “gentiopicrin”; (ii) “psoriasis” or “diabetic foot ulcer” or “inflammation-associated

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skin lesions" or "chronic wound"; (iii) "nanodelivery system". After preliminary screening, by reading the title, abstract and full text of the article, literature unrelated to the topic, repeated reports and non-experimental research were excluded. In addition, relevant research was further retrieved through the list of references included in the article to ensure the comprehensiveness of the literature. Finally, a total of seven studies were included, focusing on the application of GPS nanodelivery systems in PsO and DFU models, including in vitro, in vivo and preparation research. This review summarized the types, preparation methods, drug release characteristics and therapeutic effects of different nanodelivery systems, and discussed their advantages, limitations and clinical transformation potential in combination with existing data.

Extraction and Purification of GPS

GPS is widely distributed in the rhizomes of Gentiana species, eg, Gentiana macrophylla.[30,31] Industrially, it is produced mainly by extraction from plant material, supplemented in some cases by semisynthesis in limited quantity.[31] Academic interest in this bitter iridoid glycoside dates from the 19th century. In 1862, Kromayer reviewed the early attempts by Henry, Caventou, Trommsdorff, and Leconte to isolate the bitter constituents of Gentiana lutea roots, and he described a relatively purified bitter fraction obtained through water extraction, fermentation-assisted deglycosylation, and precipitation with metal salts.[16] Over the next decades, progress in phytochemistry replaced single-step crystallization with multistep purification procedures offering finer control. Modern schemes of extraction usually start with reflux extraction either in water or 50–70% (v/v) aqueous ethanol, followed by concentration under reduced pressure, then chromatographic purification on macroporous adsorption resins, silica gel, or reversed-phase systems.[32,33]

In recent years, researchers have begun testing natural deep eutectic solvents (NaDES) together with ultrasound-assisted extraction as a way to obtain GPS from *Gentiana asclepiadea*.[34] Although the conditions are relatively mild, the yields reported so far have been quite promising, and the approach is now regarded as a realistic alternative to the usual ethanol-based procedures.[34,35] Using NaDES formulated from lactic acid and choline chloride has also been shown to stabilize GPS throughout the extraction process.[34,35] This added stability tends to make the compound easier to purify and to work with later on, particularly during structural identification.[36] Research on how to extract and prepare GPS has gradually encouraged more work on the compound itself, including studies on its structure and biological activities. These advances also provide the practical groundwork needed to improve its solubility and stability in nanocarrier systems and to maintain consistent formulation quality.

Detailed Mechanisms of the Effects of GPS on PsO and DFU

GPS is increasingly viewed as a promising option for managing inflammation-associated skin lesions, including PsO and DFU. It seems to work through multiple biological processes. It can temper inflammatory responses, lessen oxidative injury, help regulate dysregulated angiogenesis, and reduce susceptibility to infection. Several recent studies have indicated that GPS could inhibit the overexpression of IL-6, IL-23, and IL-17A, while also reducing the levels of keratin 17 (K17) and antigen Kiel 67 (Ki-67), a combination of effects that helps curb excessive keratinocyte proliferation.[20,37] Subsequent studies have revealed that GPS activates the Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid 2–related factor 2 (Nrf2) anti-oxidative signaling pathway.[38] Through the enhancement of the antioxidant effect of the skin and the rehabilitation of the immune balance, PsO-like inflammatory lesions can be relieved effectively.[38] In the environment of DFU, which is compromised by metabolic dysfunction and inflammation, GPS may effectively inhibit the RAGE signaling pathway, thereby potentially reducing oxidative and inflammatory damage in fibroblasts.[21] Multiple studies have suggested that GPS would appear to regulate FGFR1 and PAQR3 and to activate the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) and AMP-activated protein kinase (AMPK) signaling pathways, which may help improve glucose and lipid metabolism and support fibroblast migration and granulation tissue formation.[23,24]

GPS appears to modulate angiogenic abnormalities under diverse pathological conditions. In the PsO model, GPS is shown to inhibit the overexpression of VEGFA exacerbated by Tumor Necrosis Factor alpha (TNF-α) in the human keratinocytes (HaCaT) cell line, suggesting that it may help limit abnormal neovascularization.[20] With the decreased efficiency of angiogenesis in the high glucose-high fat environment, GPS could upregulate the expression of the AKT1 gene while stimulating the Hypoxia-Inducible Factor 1 alpha (HIF-1α)/VEGF pathway in the L929 cell line.[22] These

processes may be relevant to the reconstitution of the altered locoregional perfusion in support of regenerative processes.[22,39] By adapting to the pathological condition, GPS can restore normal vascular function, consequently enhancing the vascular repair process in inflammation-associated skin lesions.[22] More importantly, GPS has been demonstrated to have the capability to inhibit gram-positive and gram-negative bacteria.[25,40,41] This activity could reduce the risk of secondary infection in the inflamed surface of the skin, presenting possible advantageous effects.

Research Advances of GPS Nanodelivery Techniques

The therapeutic potential of GPS in these applications is impeded by systemic and topical routes of administration due to low oral bioavailability and skin permeability. Recently, advances in nanodelivery techniques have provided useful means of stabilizing the drug, accumulating it in inflamed lesional skin sites, and controlling drug release. For optimal GPS nanodelivery design, there is an urgent need to factor in the pathological microenvironment associated with inflammation in skin lesions. Variations in pH exhibited in PsO and DFU skin lesions, for example, play important roles in determining the optimal drug-delivery route to be applied.[42,43] Thus, optimal drug-delivery systems need to target the skin lesion, react to environmental stimuli in the skin, and deliver GPS in controlled dosages dependent on the target skin microenvironment to fully exploit its multi-target drug property. Optimal GPS nanodelivery exploiting changes in skin pH in both PsO and DFU skin lesions can greatly increase the drug efficacy in inflammation-associated skin lesions. We have directly compared representative nanocarriers for GPS delivery in Table 1, examining aspects such as their characteristics and current application.

Nanocarriers for Oral Delivery

Poly (Lactic-Co-Glycolic Acid) Nanospheres

Nanospheres belong to a class of nanodelivery systems through the use of polymers or composite materials.[52] These nanostructures incorporate therapeutic agents within an amphiphilic polymer network, a design that enhances colloidal stability and enables a more predictable, sustained release profile, ultimately improving oral bioavailability.[44,53] Among the polymers used for this purpose, poly (lactic-co-glycolic acid) (PLGA) has become one of the most common choices, and the US Food and Drug Administration (FDA) has already cleared it for a range of drug-delivery applications.[53,54] After administration, PLGA could gradually break down through hydrolysis, producing lactic and glycolic acid monomers. These breakdown products subsequently enter the tricarboxylic acid (TCA) cycle, where they can be converted to carbon dioxide and water.[52,55] By modifying the proportion of lactic to glycolic acid and by adjusting polymer features

Table 1 Representative Nanocarriers for GPS Delivery and Their Characteristics

Carrier Type	Size (nm)	EE (%)	DL (%)	Release Features	Model/Application	Reference
Oral administration						
PLGA Nanospheres	~250	>80	–	Biphasic; sustained to 72 h	DFU model (in vivo)	[44]
PC-SNEDDS	20–100	~99.5	–	Self-emulsifying; absorption-enhanced	Oral PK	[45]
Topical administration						
CS-CHI	~50	96.2	6.3	pH-responsive; faster in acidic pH	PsO model (in vitro and in vivo)	[20,37]
m-PEG/PVP NFs	Adjustable	81.74–89.30	–	Sustained; ~60% in 2 h	DFU model (in vivo)	[46]
ZIF-8	131.9–149.9	~84	10.77	pH-responsive; in vitro drug release	Antibacterial activity; in vitro release	[47]
Hydrogel Membrane	Adjustable	Controllable	–	Sustained in weak alkaline; temp/humidity-dependent	In vitro release and PK	[48]
Other delivery systems						
Hybrid nano-systems	Adjustable	High	–	Multi-stimuli responsive	PsO and DFU model	[49–51]

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such as molecular weight or particle size, researchers tuned how quickly the matrix degraded and, correspondingly, how the drug was released, while still keeping the system biocompatible.[56] In another study, researchers prepared GPS-loaded PLGA nanospheres using a single emulsion solvent evaporation method. The particles obtained were approximately 250 nm in diameter, showed encapsulation efficiency (EE) greater than 80%, and displayed two recognizable modes of drug release.[44]

In the case of the DFU model, the oral administration of GPS-loaded PLGA nanospheres provides a stable drug release system. By enabling a steadier systemic delivery of GPS, the nanospheres could assist with creating a more favorable microenvironment for chronic wound repair. In vivo studies using diabetic rats made clear that the GPS nanodelivery system increases systemic exposure to GPS, with stable plasma concentrations sustained after the peak exposure. Further postulates related to mechanistic aspects hint that the sustained release of GPS from PLGA nanospheres constantly inhibits the exaggerated production of inflammatory factors such as TNF-α and IL-6, thereby suppressing chronic inflammation. At the same time, PLGA nanospheres could effectively stimulate collagen synthesis and angiogenesis in the target lesion area, contributing to rapid skin repair and closure. Besides, the inherent antimicrobial property further lessens the potential risk of infection in chronic skin lesions.[44] Construction and release mechanism GPS-PLGA Nanospheres are shown in Figure 2. In summary, PLGA nanospheres offer superior biocompatibility, are easily controllable in size, and have long-lasting drug release, signifying PLGA as a suitable drug carrier in inflammation-associated skin lesions.

Although there are few studies evaluating GPS-PLGA nanospheres in PsO, the immune-modulating and anti-inflammatory properties, angiogenic potential, and antimicrobial activity of these nanoparticles imply that they could potentially ameliorate symptoms of PsO through similar mechanisms. Future studies could target combined deliveries of GPS-PLGA nanospheres along with antimicrobial peptides, or factors that stimulate angiogenesis, or small-molecule

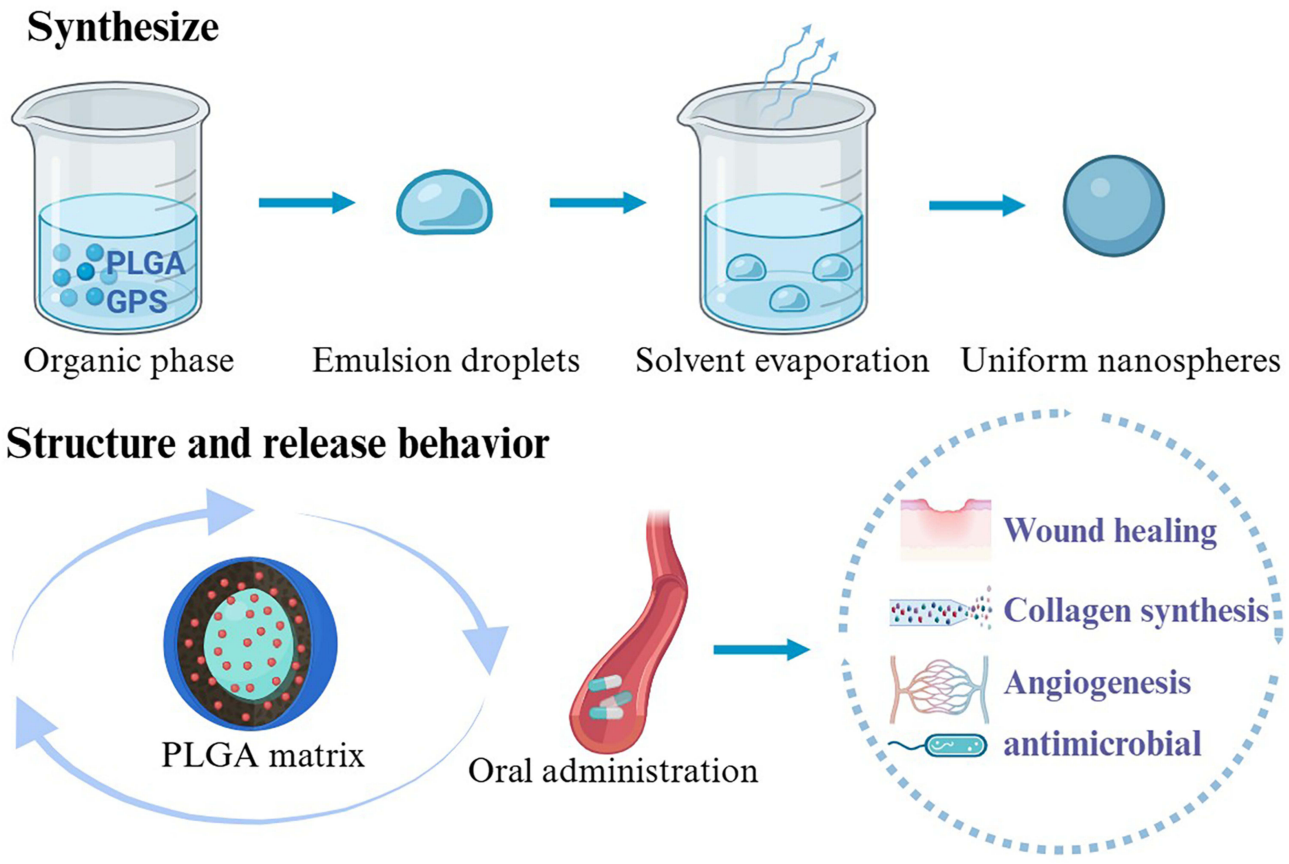

Figure 2 Schematic of GPS-PLGA Nanospheres Construction and Release Mechanism.

immune modulators. These are predicted to help in personalizing treatment in complex cases of inflammation-associated skin lesions, such as PsO.

Phospholipid Complex-Self-Nanoemulsifying Delivery System

Phospholipid complexes were developed by Indena in the twentieth century, formed between highly water-soluble drugs and phospholipids, enhancing drug lipid solubility and binding to biomembranes.[57,58] Subsequent studies have shown that the addition of oils, surfactants, and cosurfactants, such as Lauroglycol caprylocaproyl macrogol-8 glycerides (FCC), Cremophor polyoxyl castor oil derivative (EL), or Labrafil oleoyl macrogol-6 glycerides (M1944CS), to drug-phospholipid complexes produces self-nanoemulsifying drug delivery systems (SNEDDS) with a mean particle size of less than 100 nm.[59,60]

Oral administration of GPS in the form of a phospholipid complex combined with SNEDDS significantly enhances its gastrointestinal absorption compared with conventional formulations.[45] By applying combined strategies, researchers have found that the process of transporting GPS through the lymphatic system easily bypasses first-pass metabolism, hence promoting intestinal permeability and overall oral uptake.[45,61] In addition, when the nano-sized SNEDDS dispersive composition is exposed to gastrointestinal fluids, a nanoemulsion would readily form, in which the synergistic activity of solubilization by bile salts combines with stabilizing-hepatoprotective phosphatidylcholine activity to increase GPS in vivo accessibility.[45,61,62] Formation mechanism and absorption pathway of GPS-PC-SNEDD are shown in Figure 3. A study reported a high efficiency in complexation (99.50%) and a dissociation constant of 1.60 hr^{-1} of the GPS-phospholipid complex (PC) from soybean lecithin in pH 6.8 phosphate-buffered saline (PBS). The GPS-PC could form stable nanoemulsions in an SNEDDS composition comprising Maisin 35–1 or Miglyol as oil phase components, Labrasol and Cremophor EL as surfactants, and Transcutol P as cosurfactant, having mean sizes of around 20 nm.[45] The GPS-PC-SNEDDS retains stable GPS-PC, leading to enhanced solubility and uptake by the intestines. The PK analysis indicated around ten times increased bioavailability compared to the free GPS with a Cmax value of 4.369 ± 1.503 μg mL^{-1}, suggesting increased systemic exposure.[45]

As the author confirmed, no direct study has explored the application of GPS-PC-SNEDDS in PsO or DFU yet. Nonetheless, the model appears promising in terms of boosting the oral uptake of poorly absorbed drugs. In a research of the diabetic rat model, the lecithin-SNEDDS showed an increase in proteolysis protection of exenatide up to 77.6 ± 2.8%, and the peak plasma concentration (Cmax) was attained at 5.8 ng/mL, showing nine times the area under the curve (AUC) value when compared to that of the oral monomer solution.[63] Another study of the osteoporosis rat model reported the relative bioavailability of 295.79 ± 83.21% when compared to commercial tablets in the case of pamidronate disodium in osteoporosis.[64] These observationally compiled data reveal that PC-SNEDDS not only improves the oral uptake and PK aspects of GPS but also has widespread applications in several biologic compounds as well. The drug-delivery model has the potential to act as an effective and systemic tool in combating inflammation-associated skin lesions like PsO and DFU with high possibility.

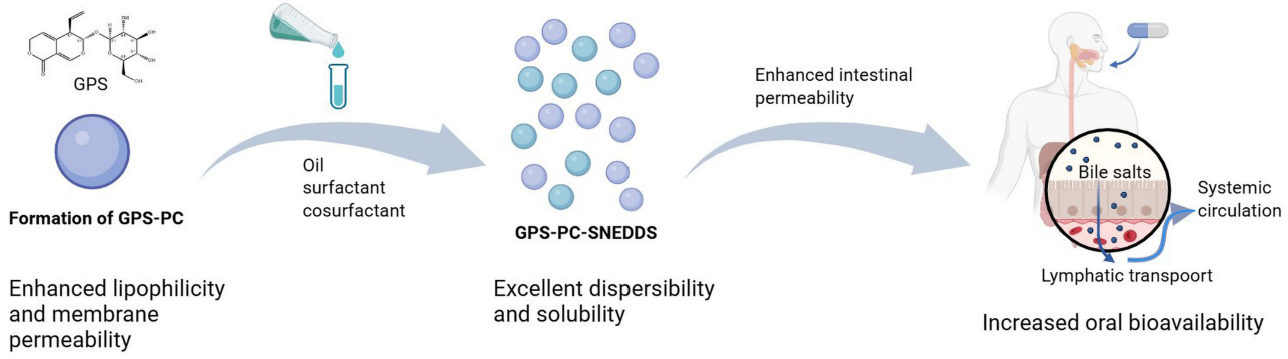

Figure 3 Schematic of GPS-PC-SNEDD Formation Mechanism and Absorption Pathway.

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Nanocarriers for Topical Delivery

Chitosan Nanoparticles

CHI is an example of cationic polysaccharides obtained from chitin through deacetylation, which consists of glucosamine as the main structural element.[65,66] In physiological environments, the main amino groups from CHI get protonated, leading to the gain of positive charge and hence increasing electrostatic interactions with negatively charged cellular membranes, thereby contributing to enhanced cellular uptake mechanisms like clathrin-mediated endocytosis and macropinocytosis.[20,67,68] CHI can go through degradation in part using nonspecific glycosidases such as lysozyme in the human body, showing good biodegradability and biocompatibility. These characteristics make CHI an important ingredient in drug delivery systems.[69,70]

In recent studies, the self-assembling property of CHI derivatives has been utilized to develop carrier systems for plant-originated active compounds, such as GPS. Hydroxyethyl chitosan (HECS) nanoparticles have been developed as carrier systems for GPS. GPS should be dissolved in PBS solution and slowly dripped into an anhydrous ethanol solution of HECS. By taking advantage of electrostatic interactions and hydrogen bonding, self-assembly would be realized, and the resultant solution would be evaporated to remove ethanol, resulting in GPS-loaded HECS nanoparticles (GPS@HECS).[20,71] For further stabilization of the drug carrier system and increasing GPS EE, lipid-assisted coating methodology should be used to coat GPS-loaded lipid nanoparticles with CS, resulting in CHI-coated lipid GPS nanoparticles (CS@GPS). Co-self-assembly of HECS components and lipid components has been demonstrated to help to retain biocompatibility and sustained-release features of drug-loaded HECS components while exhibiting enhanced GPS EE and preventing degradation. A research reported CS@GPS with the EE of 96.2%, the drug loading (DL) capacity of 6.3%, and an average size of about 50 nm, proving the efficiency of GPS encapsulation and construction of drug-loaded carrier nanostructures.[37] The structure and drug release mechanism of CS@GPS are shown in Figure 4.

CHI nanoparticles are known to possess a pronounced pH-responsive profile: under conditions of a slightly acidic pH (pH≈5.5, mimicking psoriatic skin lesions), the amino groups of chitosan are increasingly protonated. Enhanced electrostatic repulsion between the polymer chains ensues, causing network swelling, which is conducive to GPS release. Using a model cell line of HaCaT, researchers reported that cellular internalization of CHI-based GPS nanoparticles proceeds via macropinocytosis. Further intracellular delivery of GPS was observed to occur within acidic subcellular compartments, such as lysosomes.[20,37] All these processes collaborate to enhance the local bioavailability of GPS and improve its anti-inflammatory action, leading to the alleviation of symptoms of PsO.

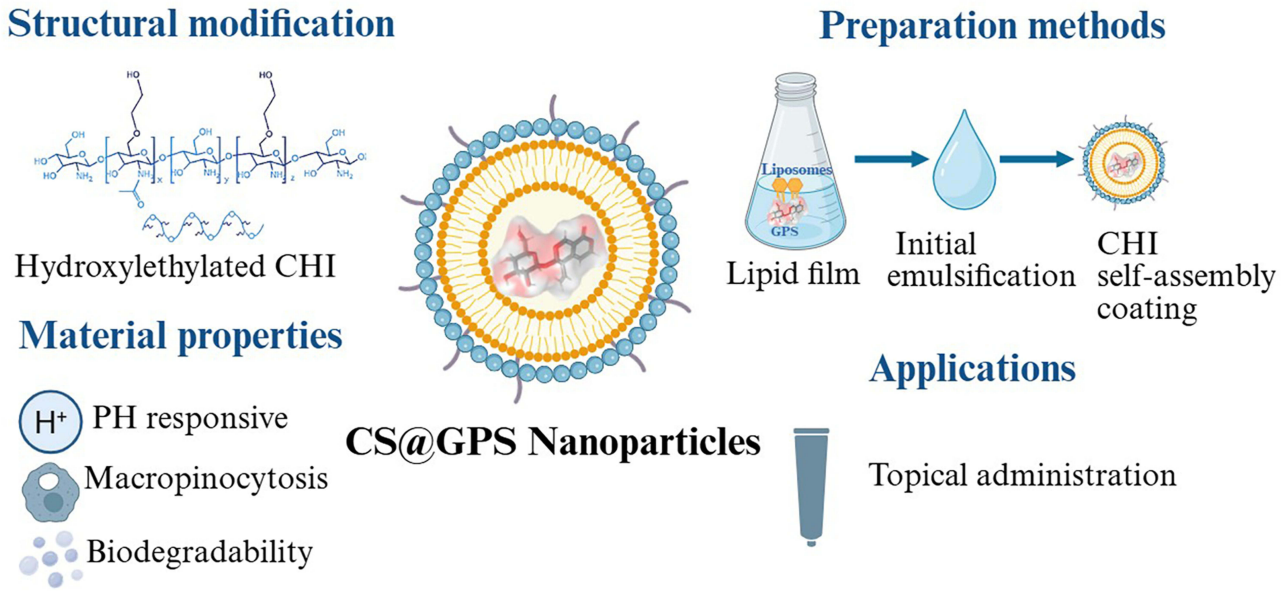

Figure 4 Schematic of CS@GPS Structure and Drug Release Mechanism.

However, CHI is not stable in some pathological microenvironments. Chronic wounds, such as DFU, exhibit a neutral to mildly alkaline pH (pH >7) microenvironment, where the amino groups in CHI would be deprotonated, reducing the solubility of CHI and, therefore, precipitating or aggregating it.[66,72,73] This situation has been proven to impair the stability of CHI-based carriers and their performance in drug release.[74,75] To dissolve the limitations, several such approaches have been assessed in the models of DFU by modifying the chemical composition and composite formulations of CHI. For instance, 5-methyl-2-pyrrolidone-modified CHI (NMP-CHI, MPC) was prepared by a research group in Portugal, which conferred sustained anti-inflammatory delivery and thereby accelerated wound healing in diabetic mice.[76] A different study published by researchers in the United States combined CHI nanoparticles with a sodium alginate hydrogel to create a layered delivery system. This composite appears to maintain structural integrity and allow for pH-responsive, controlled release under mildly alkaline conditions, which may help prevent the precipitation of unmodified CHI, potentially facilitating better inflammation resolution and tissue regeneration in DFU models.[77]

Based on these approaches, future studies will be able to focus their efforts on intelligent CHI-based delivery systems responsive to the presence of GPS, hopefully. Further improvement in the stability of the GPS-loaded nanocarriers in skin lesions can be achieved by chemical modification of CHI through quaternization, hydroxyethylation, or NMP derivatization, which, together with a smart composite encapsulation structure design, may allow for more sustained and targeted local delivery.

Electrospun Nanofibers

Electrospun nanofibers (NFs) represent a class of drug-delivery systems at the nanoscale, and their preparation is made by techniques of polymer electrospinning.[46,78] Due to their large surface area, striking flexibility, and high porosity, NFs have gained huge interest in recent times while studying aspects related to drug delivery and lesion repair.[46,79] A high-voltage electrostatic field should be utilized in fabrication in order to stretch a polymer solution or melt into nanoscale, continuous fibers, closely resembling the three-dimensional structure of the extracellular matrix (ECM) on a microscale, creating a supportive environment for cell adhesion, proliferation, and migration.[46,80] In comparison with other traditional carriers, such fibers obviously possess superiority in DL and release, where the therapeutic molecules would homogeneously disperse at the molecular or amorphous states, increasing both the solubility and stability, and allowing sustained and site-specific delivery.[81,82]

Among the range of polymers, polyvinylpyrrolidone (PVP) is widely applicable owing to its biocompatibility and excellent water solubility.[83,84] Further, its fiber-forming and spinnable properties are reliably useful in the fabrication of drug-loaded NFs. Its physicochemical characteristics are supposed to be further improved by blending with other hydrophilic polymers.[85] Methoxypolyethylene glycol (m-PEG) is one of the most used hydrophilic polymers, enabling to form a homogenous solution with PVP, thereby making the blend suitable for electrospinning.[46] (Figure 5)

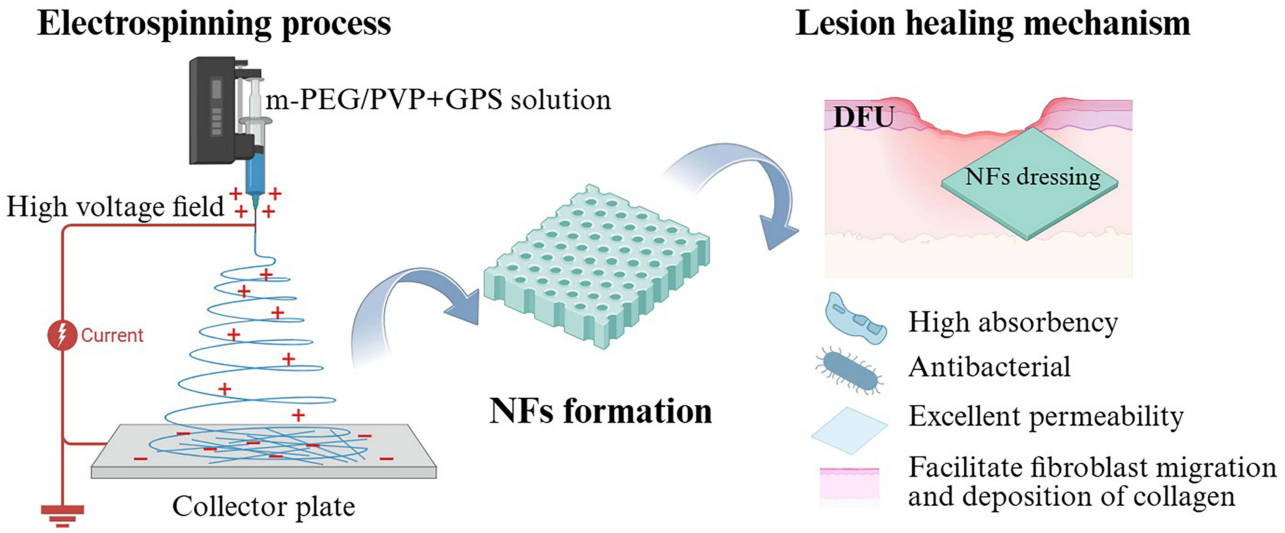

Figure 5 Schematic of m-PEG/PVP NFs Structure and GPS Sustained Release.

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Meanwhile, m-PEG could enhance the hydrophilicity of fibers, while its flexible chain segments improve plasticity and increase skin adhesion to promote drug release.[86] Furthermore, it has been proven that PVP confers robust fiber-forming capability and enhances solid-phase drug solubility through the means of amorphous solid dispersion.[46,87] As a result, the combination of m-PEG and PVP is expected to form a system that can balance hydrophilicity, biocompatibility, and fiber-forming performance to encapsulate hydrophobic compounds such as GPS with improved solubility and physicochemical stability.

Indeed, m-PEG/PVP NFs generated through electrospinning have been successfully employed for the encapsulation of GPS, reporting a mean EE of 85.52 ± 3.78% (n = 3). Upon local application of GPS, a cumulative release of 60.75 ± 6.74% within two hours was recorded by researchers, greatly improving the local bioavailability of the medicament.[46] In diabetic mouse models of wound infection, the nanofiber dressings have been observed to form a uniform film releasing GPS continuously into the exudate and attenuate the local inflammatory response. The NFs could further exert an antibacterial effect against pathogens such as Pseudomonas aeruginosa, promoting the elimination of bacteria and reducing the risk of infection.[46] In addition, the high absorbency and excellent permeability of NFs contribute to maintaining a moist environment, facilitating fibroblast migration and deposition of collagen, and accelerating wound closure and tissue regeneration.[46,88] Generally speaking, m-PEG/PVP NFs show stable performance, controlled release, and favorable biocompatibility that distinctly improves the localized therapeutic effect of GPS with potential for clinical treatment of diabetic wounds complicated by infection.[46]

Recently, NFs are increasingly used in the topical management of various inflammation-associated skin lesions.[88–90] However, related research into m-PEG/PVP NFs for GPS delivery in these diseases is still rare. There is a big space for wider applications for the NFs because of their contribution not only to the improvement of GPS stability and skin permeability but also to the alleviation of the stickiness and the problematic contamination of clothes common in traditional Chinese medicine ointments, resulting in a significant improvement in the subjective comfort of patients.[46]

Zeolitic Imidazolate Frameworks

Metal-organic frameworks (MOFs) are porous nanostructured materials synthesized by coordination interactions of metal ions or ion clusters like zinc (Zn), iron, magnesium, calcium, and copper with organic compounds like 2-methylimidazole and terephthalic acid.[91,92] These materials have high surface area, adjustable pore size, good biocompatibility, and high sensitivity, which make them superior candidates as drug-delivery materials.[91,92]

Zinc-based Zeolitic Imidazolate Framework 8 (ZIF-8) is one of the widely studied MOFs that can be prepared from reagents including zinc nitrate hexahydrate and 2-methylimidazole.[93,94] These materials have huge potential for efficient delivery of GPS drugs because of their high surface area, antibacterial properties, and drug release channels depending on pH.[93,95] Researchers have reported that ZIF-8 exhibits pH-dependent dissolution under an acidic environment, where the protonation of imidazolate linkers weakens the coordination of Zn-N, resulting in the collapse of the framework and thus accelerating the drug release process. Conversely, under neutrality or a slightly basic pH, ZIF-8 retains a stable framework structure that enables the facilitation of sustained drug release.[93,96] Moreover, ZIF-8 itself shows inherent antimicrobial activities because of its positive charge on the surface, allowing it to interact with negatively charged bacterial membranes through electrostatic interactions.[47,97] The released ions could inactivate respiratory enzymes inside bacteria and further stimulate the generation of reactive oxygen species to form lipid peroxides within the cell membrane. Simultaneously, the 2-methylimidazole moiety would impair the bacterial cell wall integrity, thereby potentiating the antibacterial activity.[47,98]

A recent research has demonstrated that ZIF-8 is an effective carrier for GPS, and that the motivation of their association includes van der Waals forces, π–π interactions, and electrostatic attraction.[47,99] The obtained GPS@ZIF-8 nanoparticles were reported as a phase-pure crystalline pattern by researchers, with an average diameter of 140.9 ± 9 nm, an EE of 84%, and a loading capacity of approximately 10.77%. Moreover, both Fourier transform infrared (FTIR) spectroscopy and X-ray diffraction (XRD) could provide evidence for the successful incorporation of GPS into the ZIF-8 framework. Additionally, antibacterial assays have revealed that GPS-loaded nanoformulation exhibits a greatly stronger inhibitive effect than that of GPS alone.[47] The structure and action mechanism of GPS@ZIF-8 are presented in Figure 6.

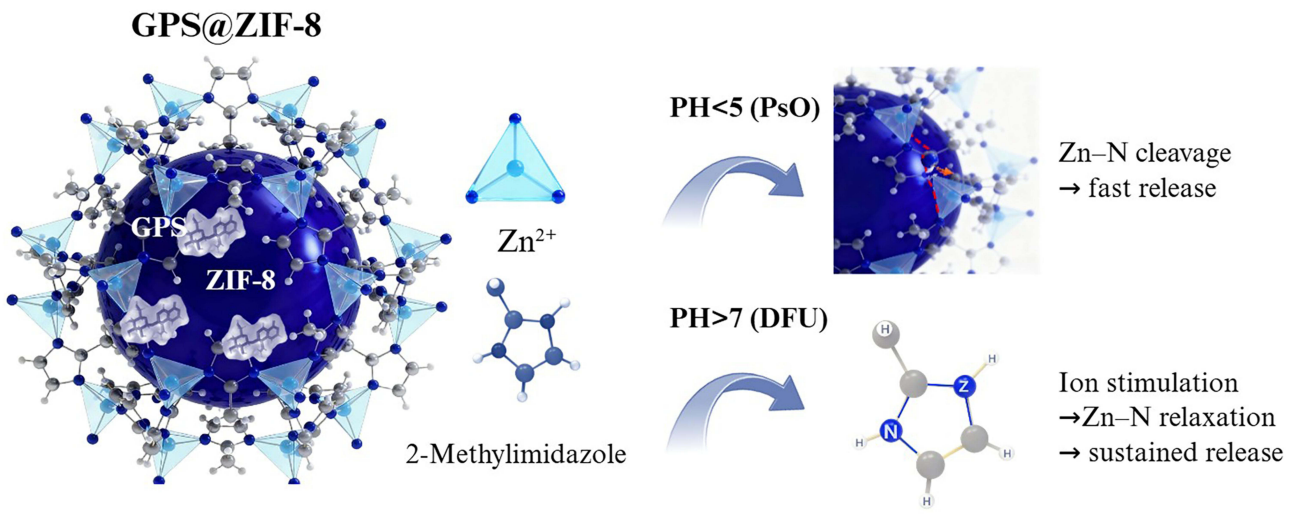

Figure 6 Schematic of the structure and mechanism of action for GPS@ZIF-8.

In vitro release experiments showed that GPS@ZIF-8 effectively released GPS at pH 5, with an accumulative release of 81.31% within 50 hours, reflecting pronounced pH responsiveness.[47] This provides a rationale for using it as a topical agent in inflammatory acidic skin lesions, including PsO. In the weakly alkaline microenvironment of DFU and similar conditions, this framework is expected to have strong stability, effectively extending the duration of drug action and inhibiting undue drug leakage. In addition, a variation in ion concentration at the site of a DFU lesion by wound exudate leads to the slow relaxation of the Zn-N bonds of the ligand, resulting in a controlled and sustained release of the drug in response to ionic fluctuations. Notably, the application of ZIF-8 with Dihydroquercetin has been demonstrated to enhance diabetic wound healing, including DFU.[100] Together with the potent broad-spectrum antibacterial properties of GPS@ZIF-8, there is great potential for application in treating other inflammation-associated skin lesions via infection control and facilitation of skin lesion repair.

Hydrogel Membrane

Hydrogels, referred to as hydrogel membranes, represent three-dimensional networks of hydrophilic polymers capable of absorbing and sustaining a high amount of water (50%) while still maintaining excellent softness, biocompatibility, and biodegradability.[101,102] Swelling of hydrogels results in their gel-like state as one hydrogel film that acts as either a wound dressing or a local drug delivery platform.[103,104] With the addition of a support layer, a backing film, or an adhesive layer, it is possible to prepare adhesive hydrogel patches for the treatment of inflammatory skin lesions.[48,105] Notably, hydrogel membranes are able to be designed to respond to external or internal specific stimuli, such as pH, temperature, or enzymatic activity, allowing on-demand drug release.[106–108]

A recent research reported that sodium polyacrylate (NP-700) could be used as the main polymer in the hydrogel patch, where adding glycerin as a humectant, aluminum glycinate as a cross-linking agent, and carbomer 980 as a thickener, with the inclusion of GPS as the principal active ingredient.[48] (Figure 7) This hydrogel formulation makes the cumulative skin penetration of GPS threefold in a rat dorsal skin model compared to controls, and the in vitro release profile is greatly enhanced as well. PK studies in rats exhibited that the half-life of GPS administered via the hydrogel patch was 0.74 ± 0.88 hours, while the time to reach peak plasma concentration was prolonged to 2 hours, greatly improving the in vivo bioavailability of iridoid components.[48]

As the author confirmed, though, no systematic investigation of GPS hydrogels has been conducted in PsO or DFU models yet. Plenty of research regarding the controlled-release and adhesive properties of hydrogels and their derivatives in skin lesions related to inflammation exists. For example, one study reported that, in a diabetic rat skin ulcer model, hydrogels containing borate ester dynamic bonds exhibited strong tissue adhesion and hemostatic activity, with the tissue viscosity approximately 1.2–1.5 times that of honey, reducing bleeding by about 2.5-fold and improving dressing

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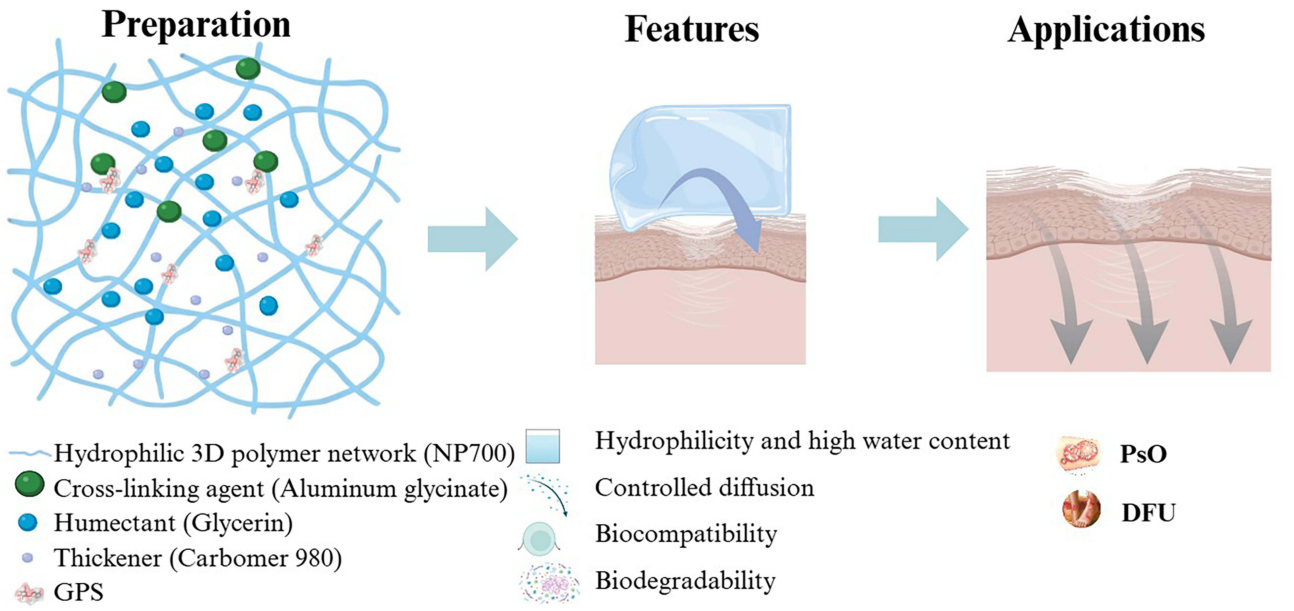

Figure 7 Schematic of the structure and controlled release mechanism for localized delivery of GPS via hydrogel membranes.

stability.[109] Another research demonstrated that curcumin-loaded hydrogels maintained a sustained release for up to 21 days in diabetic wounds with significant improvement in local drug bioavailability.[110] In the mouse model of PsO, the binary glycoside-carbomer hydrogel was used for the local delivery of the anti-PsO agent upadacitinib (UPA). The formulation had an average particle size of 114.42 ± 2.88 nm, with the EE of 73.75 ± 2.24% and DL of 21.16 ± 0.49%. Skin penetration reached 7.04 μg/cm^2·h, approximately 2.3 times higher compared to the cream formulation, 3.12 μg/cm^2·h, which greatly improved the local bioavailability and therapeutic efficacy of the drug.[111] Therefore, the development of hydrogel delivery techniques for GPS treating PsO or DFU patients holds great research potential and value in the future, especially combined with other nanodelivery techniques.

Other Delivery Strategies

Until now, research into GPS delivery systems has mainly focused on oral and topical routes of administration. However, recent advances in the field of materials science and transdermal drug delivery indicate that exploring alternative modes of administration may further improve the therapeutic outcomes of GPS in inflammation-associated skin lesions. The deployment of nanocarriers is inherently flexible since the way of their application depends on factors such as biocompatibility, degradability, drug release kinetics, and processability.

Injectable Nanocarrier Strategies

For instance, although MOFs, such as ZIF-8 and hydrogel films, have been conventionally employed for topical delivery, their structural stability and controlled degradability enable their use in injectable, locally sustained-release formulations. In previous work, ZIF-8 was incorporated into injectable hydrogels for the subcutaneous delivery of small molecules, for example, cinnamyl alcohol. The resultant strategy achieved prolonged local drug retention and sustained anti-inflammatory effects in diabetic wound models and thus significantly accelerated the healing process.[112] Such a strategy implies that with good tissue compatibility, a drug carrier can be used to address the limitations in skin penetration of traditional topical formulations and thus enable drug distribution in deeper tissues while maintaining high therapeutic concentrations. As a Biopharmaceutics Classification System (BCS) Class III compound, GPS is characterized by low membrane permeability. Injectable nanocarriers, therefore, represent an attractive strategy through which local retention may be enhanced, anti-inflammatory effects prolonged, and more precise targeting within the chronic inflammatory skin microenvironment achieved.

Nanocomposite Delivery Systems

Apart from extending the administration routes, nanocomposite delivery systems provide more integrated and multi-functional approaches to GPS delivery. Nanocomposites represent solid hybrid systems consisting of two or more different materials, with at least one component in the nanoscale range.[113,114] Combining materials of complementary properties allows functions that a single carrier seldom may provide, such as higher drug-loading capacity, stronger adhesion to biological barriers, improved mechanical strength, and release responsive to local pH or enzymatic activity.[113,115] Based on their matrix composition, nanocomposites are divided into polymer-based multi-material nanocomposite (PMMC), metal-based multi-material nanocomposite (MMNC), or ceramic-based multi-material nano-composite (CMNC) systems.[113]

Such systems have already been used in models of inflammatory skin lesions. For example, in the PsO model, flexibility, adhesion, and mechanical stability were conferred by a dual-network hydrogel containing CHI and polyacrylic acid. This also controlled the release of CeNPs and betamethasone, hence enhancing the local availability of the drug and inducing a synergistic anti-inflammatory and antibacterial response.[49] In another recent study, shikonin was incorporated into PLGA nanoparticles for topical delivery via a hydrogel, and the nanoparticles stabilized the compound and provided controlled release, whereas the hydrogel maintained an appropriate moist wound environment and enhanced local drug accumulation.[50] These combined effects ensure a more long-lasting and mild anti-inflammatory repair response. A similar research was performed in the treatment of DFU with liposome (PPD-Lipo) and Bletilla striata polysaccharide (BSP) hydrogel microspheres loaded with 20(S)-protopanaxadiol. Here, the liposomal core was proven to play a role in protecting the drug, enhancing tissue penetration, and enabling prolonged release.[51] This system modulates the local immune microenvironment, reduces inflammation, allows the controlled release of drugs and lesion repair, and thus accelerates refractory ulcer closure.[51]

A shift in the routes of administration, along with the addition of composite multifunctional structures, is expected to significantly improve GPS delivery. Composite nanosystems like hydrogel microspheres, liposome-hydrogel hybrids, PLGA nanospheres, CHI-based nanonetworks, NFs, or MOFs would permit targeted accumulation, stimuli-responsive release, and enhanced local retention of GPS. Systems designed with such features not only overcome the limitations observed with conventional formulations of GPS but also represent novel approaches and viable technical strategies for precise and sustained treatment of inflammation-associated skin lesions.

Clinical Studies of Nanodelivery Technologies

Although GPS-loaded nanodelivery strategies have not been used in clinical trials, the above mentioned technologies have exhibited some advantages in clinical trials of other drugs for skin diseases. For example, a clinical trial of 21 patients suffering from chronic pain or itching used PLGA nanospheres encapsulating capsaicin to reduce the discomfort caused by capsaicin patches applied on the skin. The treatment exhibited positive outcomes, improving the tolerance of the patients' skin to the treatment. The sustained release of the nanospheres maintained the skin irritation at low levels for over two weeks. This example indicates that PLGA nanospheres may be used as an effective delivery system for the management of chronic skin irritation.[116] In several oral clinical trials, drugs delivered using PC-SNEDDS demonstrated good oral absorption, stable PK, and a favorable safety profile. For example, the coefficients of variation of the pharmacokinetic parameters of a cyclosporine microemulsion formulation (Sandimmune Neoral) used in a clinical trial were 2–6 times lower than those of other formulations. This reduction may indicate that the delivery system can reduce the changes in the blood levels of the tested drug, improving the stability of the drug.[117] In another randomized controlled trial, ultra-small phospholipid nanoparticles were used to deliver high-density lipoprotein (HDL) phospholipids, which effectively regulated non-HDL cholesterol and triglyceride levels. Adverse events were noted in 14 patients (28%) in the treatment group compared to 17 patients (34%) in the placebo group. No serious adverse events were noted in either group. This shows that this method is safe and well tolerated.[118]

The other delivery systems have also started to attract growing attention in the management of inflammation-associated skin lesions, which hold significant clinical potential. A multicenter randomized controlled trial in China (n=96) is currently evaluating CHI nanocrystals as carriers for a combination of Chinese herbal medicines in the

treatment of PsO, with the study expected to conclude in December 2026.[29] In a separate randomized controlled trial conducted in 2025 (n=36), polycaprolactone (PCL)/polyethylene oxide (PEO) nanofiber patches were used to deliver Indigo Naturalis (IN) for PsO, addressing the limitations of traditional IN formulations such as poor absorption and skin staining. After four weeks of treatment, patients' psoriasis area and severity index (PASI) scores decreased by more than threefold. Compared with calcipotriol ointment, the nanofiber patch did not cause skin irritation ($p < 0.001$), and no abnormalities were observed in blood counts or liver and kidney function tests, reflecting favorable safety and tolerability.[119] For DFU treatment, a trial (n=28) using mesenchymal stem cells demonstrated that gelatin nanofiber scaffolds prepared by electrospinning provided an environment conducive to cell growth and proliferation, promoting wound healing at ulcer sites.[120] In another study (n=56), the wound healing time with topical sodium hyaluronate was 25 ± 4 days, whereas the use of nanoscale hydrogels delivering quercetin and oleic acid significantly shortened healing time ($P < 0.01$).[121]

The nano-delivery technologies discussed in this review have enhanced the bioavailability, delivery efficiency, stability, and safety of the relevant drugs across multiple clinical trials. As a result, patients experienced improved treatment tolerance and adherence. These approaches also show strong potential for clinical translation. Such technologies could open new avenues for clinical exploration and application of GPS in the treatment of inflammation-associated skin lesions.

Limitations and Future Perspectives

Biosafety and PK Considerations

Evidence so far indicates that, in general, GPS nanosystems are well-tolerated and display favorable short-term safety. However, long-term toxicity, immune responses, and in vivo metabolic pathways have been rarely investigated in a systematic manner up to now. With differences in degradation behavior and resultant metabolites among different carriers, such as PLGA, ZIF-8, and CHI, skin microenvironments may be uniquely influenced. That indicates future studies should be performed in combination with PK analysis and long-term toxicological investigations to establish a more precise definition of safety margins and translation into clinical practice.

Standardization of Formulation Techniques and Quality Control for GPS

The pronounced hydrophilicity and complex molecular structure of GPS render formulation development particularly challenging. The comparison of results and reproduction of findings has not been easy to date, due to the variation in the methods of preparation and process parameters in different research groups. Standardization of quality control, refinement in formulation procedures, and stability testing are some of the areas that need to be focused on in future efforts. These steps will be vitally necessary for Good Manufacturing Practice (GMP)-compliant manufacturing and industrial translation of GPS-based formulations.

Further Research on Multi-Model Disease Systems and Mechanisms of Effects

Most of the current studies on PsO and DFU have focused on wound or inflammation models, while there is only limited research on other inflammation-associated skin lesions, which include atopic dermatitis and contact dermatitis. Specific disease models, when combined with multi-omics approaches, may allow the investigation of how different GPS nanodelivery systems work against inflammatory conditions while identifying further applications for these systems in the treatment of a wide range of inflammatory skin lesions.

Clinical Translation Challenges of Nanodelivery Technologies

Nanodelivery technologies have demonstrated therapeutic benefits in clinical trials, but several challenges remain for their translation into routine clinical practice. Nanomaterials can aggregate or degrade because of their high surface area, and stabilizing them often requires freeze-drying and cryoprotectants. These additional steps increase production costs and tend to concentrate treatments in well-resourced medical centers, limiting accessibility in primary care settings.[122] Clinical translation is also complicated by evolving regulatory frameworks and lengthy approval procedures, which can

slow market entry. Maintaining consistent quality across production batches is another critical concern for clinical applications. Long-term safety and the influence of individual patient variability on therapeutic outcomes have not yet been fully characterized.[123] In brief, although nanotechnology shows considerable promise, successful implementation will require solutions to challenges related to cost, regulation, and quality control.

Conclusion

PsO and DFU have always received great attention in clinical practice and research due to their high prevalence rate and complicated pathological mechanisms. They seriously decrease the quality of life of patients and put a huge economic burden on society. The methods of diagnosis and treatment remain limited in the present circumstances, which calls for urgent development of safe and effective therapies. GPS is a natural iridoid glycoside with multifunctional anti-inflammatory, antioxidant, angiogenesis-regulating, and antibacterial properties, demonstrating considerable pharmacological potential in the treatment of these diseases. However, the drawback of poor oral bioavailability and the limitation of permeability through skin have greatly restricted its clinical application until now. In recent years, the development of nanodelivery systems has greatly improved the solubility and stability of GPS, increased retention of drugs within target tissues, and enhanced local bioavailability, providing a novel strategy for the therapeutic application of GPS in the treatment of inflammatory skin lesions.

Nanocarriers with various material properties and structural features provide different advantages for local drug delivery. To tackle the rapid clearance of GPS, PLGA nanospheres perform biphasic release, ensuring their systemic exposure for an extended period. More importantly, PC-SNEDDS formulations improve oral bioavailability by enhancing the lipid solubility of drugs, promoting lymphatic transport, and reducing first-pass metabolism. Excellent biocompatibility, pH responsiveness, and mucoadhesive property of CHI-based nanocarriers may provide additional improvements in GPS retention and cellular uptake in the affected skin area. NFs are characterized by high surface area and feature tunable drug release, thus becoming particularly suitable for wound dressings with enhanced drug dissolution and lesion repair. ZIF-8 metal-organic frameworks are expected to provide microenvironment-targeting delivery through pH-responsive release and synergistic antibacterial effects of zinc ions. Hydrogels and their derived nanomaterials can enhance local therapy by maintaining a moist environment and accomplishing sustained drug release. Most importantly, an integrated design of composite nanosystems expands the functions of materials, hence allowing more precise control of GPS release kinetics and responsiveness to the local microenvironment.

Although these methods have been proven to be highly effective in preclinical studies, the successful translation of GPS nanodelivery systems into the clinic is still hampered by several challenges related to long-term safety, process control, and quality standardization. Future studies should focus on material modification, process optimization, and establishment of a complete evaluation system for nanopreparations in line with the essential parameters, including particle size distribution, EE, DL and release, and stability. In parallel, GMP-grade formulations should be scaled up and strict quality control implemented to ensure reproducibility and consistency of formulation. Dose-ranging studies and long-term toxicological evaluation should be performed in relevant animal models of PsO and DFU, respectively, in which complete PK tests should be conducted to provide practical suggestions for clinical translation of GPS in the treatment of inflammation-associated skin lesions. In addition, efforts should be made to evaluate these nanodelivery strategies in clinical settings, considering factors such as treatment accessibility, patient tolerability, and regulatory compliance. Addressing these aspects will be crucial for successfully bridging the gap between preclinical findings and real-world clinical applications.

This review aims to highlight the connection between nanomaterial design and clinical translation, offering a perspective on how GPS-loaded nanodelivery strategies could potentially be applied to the treatment of inflammation-associated skin lesions. The GPS-loaded nanodelivery system opens new practical avenues toward the therapy of inflammation-associated skin lesions. Interdisciplinary collaboration, in addition to standardized validation, enables findings to be effectively translated from the laboratory to clinical therapies and thus opens new horizons for the application of natural products in treating inflammation-associated skin lesions.

Abbreviations

AUC, area under the plasma concentration–time curve; AKT, protein kinase B; AMPK, AMP-activated protein kinase; BSP, Bletilla striata polysaccharide; CHI, chitosan; Cmax, peak plasma concentration; CMNC, ceramic-based multi-material nanocomposite; CS@GPS, chitosan-coated lipid GPS nanoparticles; DFU, diabetic foot ulcer; DL, drug loading; ECM, extracellular matrix; EE, encapsulation efficiency; EL, Cremophor polyoxyl castor oil derivative; FDA, US Food and Drug Administration; FCC, lauroglycol caprylocaproyl macrogol-8 glycerides; FGFR1, fibroblast growth factor receptor 1; FTIR, Fourier transform infrared; GMP, Good Manufacturing Practice; GPS, gentiopicroside; GPS@HECS, GPS-loaded HECS nanoparticles; HDL, high-density lipoprotein; HIF-1α, hypoxia-inducible factor 1 alpha; HECS, hydroxyethyl chitosan; IL-6, interleukin-6; IL-17A, interleukin-17A; IL-23, interleukin-23; IN, Indigo Naturalis; K17, keratin 17; Keap1, Kelch-like ECH-associated protein 1; Ki-67, antigen Kiel 67; M1944CS, Labrafil oleoyl macrogol-6 glycerides; MMNC, metal-based multi-material nanocomposite; MOFs, metal-organic frameworks; m-PEG, methoxy-polyethylene glycol; MPC, 5-methyl-2-pyrrolidone-modified chitosan; NaDES, natural deep eutectic solvents; NFs, electrospun nanofibers; NMP, 5-methyl-2-pyrrolidone; NP-700, sodium polyacrylate; Nrf2, nuclear factor erythroid 2–related factor 2; PAQR3, progestin and AdipoQ receptor family member 3; PASI, psoriasis area and severity index; PBS, phosphate-buffered saline; PC, phospholipid complex; PCL, polycaprolactone; PEO, polyethylene oxide; PI3K, phosphoinositide 3-kinase; PK, pharmacokinetic; PLGA, poly (lactic-co-glycolic acid); PMMC, polymer-based multi-material nanocomposite; PsO, psoriasis; PVP, polyvinylpyrrolidone; RAGE, receptor for advanced glycation end products; SNEDDS, self-nanoemulsifying drug delivery system; TCA, tricarboxylic acid cycle; TNF-α, tumor necrosis factor alpha; UPA, upadacitinib; VEGF, vascular endothelial growth factor; XRD, X-ray diffraction; ZIF-8, zinc-based zeolitic imidazolate framework-8; Zn, zinc.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The author(s) report no conflicts of interest in this work.

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