Advances and Perspectives Chitosan-Sodium Tripolyphosphate as an Effective Drug Delivery System for Skin Applications

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Abstract. Effective topical drug delivery systems pose a significant chal-lenge in dermatological therapy, particularly in overcoming physiological barriers such as stratum corneum penetration, ensuring drug stability, and preventing uncontrolled release. Chitosan–sodium tripolyphosphate (TPP)-based nanoparticles offer an innovative solution, providing advantages in bioadhesion, biocompatibility, encapsulation efficiency, and controlled drug release capabilities. This article reviews recent advances in the formulation, physicochemical characteristics, and mechanism of action of chitosan–TPP nanoparticles in enhancing permeability and therapeutic efficacy. Additionally, this article reviews the potential of this system in delivering various types of active compounds, including those from natural extracts and synthetic drugs. It compares it with other polymer-based nano-particle systems. Advanced formulation approaches, such as ultrasonication after ionic gelation, are also discussed as a strategy to improve particle size and stability of the preparations. Applications include wound healing, skin cancer therapy, treatment of chronic inflammation, and delivery of cosmetic active ingredients. With a multidisciplinary approach and adequate clinical validation, chitosan–TPP nanoparticles have the potential to become a new standard in adaptive, efficient, and personalized dermal drug delivery systems.

Keywords: Chitosan, Sodium Tripolyphosphate, Nanoparticles, Topical Drug Delivery.

1 Introduction

The topical drug delivery system is an application of a therapeutic approach that functions to treat dermatological and systemic complaints. The advantage of this system is that it can provide a targeted therapy system, reducing the risk of systemic side effects and allowing the topical drug delivery system to offer a higher level of comfort to the

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patient during therapy skin [1]. In addition, the use of an effective topical drug delivery system will help reduce the level of toxicity by limiting drug exposure to a specific location without affecting other tissues, making it an important component of drugs that exhibit toxicity at high doses [2]. However, problems related to the complex skin structure in the outermost layer of the stratum corneum, which functions as a strong defence system, can limit penetration and reduce the bioavailability of active drug substances [3]. Topical preparation formulations available on the market, such as creams, ointments, and gels, remain conventional and less effective in addressing issues like drug degradation, poor drug stability, and permeability, as well as the failure to achieve therapeutic effects [4]. This problem requires an innovative solution in advanced drug delivery system technology to overcome it and ensure the level of comfort and safety of topical drug preparations. The solution offered to address these challenges is a nanotechnology system called nanoparticles. Nanoparticles in various innovations, especially those based on chitosan polymers and sodium tripolyphosphate cross-linkers, have garnered significant attention due to their potential to overcome the limitations of conventional topical formulations [5]. Chitosan, a natural polysaccharide derived from chitin, exhibits excellent bioadhesive and biocompatible properties, thereby enhancing the permeability of drugs to the deepest layers of the skin [6]. Meanwhile, the use of sodium tripolyphosphate as a cross-linking agent can form ionic bonds with chitosan, resulting in good preparation stability and increased biocompatibility of topical preparations [7]. Chitosan polymers, when combined with ionic sodium tripolyphosphate cross-linkers through the ionic gelation method, form stable nanoparticles with characteristics including particle size, polydispersity index, zeta potential, optimal encapsulation efficiency, and a controlled drug release profile [8]. Thus, these characteristics make chitosan-sodium tripolyphosphate nanoparticles a promising candidate for overcoming problems related to effective topical drug delivery systems. Several studies have also shown that the effectiveness of this system can vary depending on the type of active substance delivered, be it compounds from natural extracts or synthetic drugs. Therefore, the evaluation of the suitability of chitosan-TPP in various contexts of active ingredients is essential to be studied systematically. In addition, advanced formulation approaches, such as ultrasonication treatment after particle formation through ionic gelation, are also gaining increasing attention because they can enhance homogeneity and reduce particle size, which directly impacts the efficiency of skin penetration and the stability of the preparation. No less critical, chitosan-TPP also needs to be compared with other polymers that have been used as topical nanoparticle matrices to gain a more comprehensive understanding of the advantages and limitations of this system in dermatological applications. This study aims to provide a more comprehensive review covering the progress and potential of chitosan–sodium tripolyphosphate nanoparticles in dermatological applications. This study can directly address issues related to drug penetration through the stratum corneum, stability of the preparation in storage, and controlled drug release. This review also offers new perspectives through a critical analysis of the effectiveness of this system in delivering various types of active ingredients, comparing it with other nanoparticle polymers, and reviewing additional formulation strategies such as post-gelation ultrasonication as an approach to improve system performance. Thus, this

article is expected to contribute to the development of a more targeted, effective, and applicable topical drug delivery system.

2 Methodology

This review was compiled by searching and selecting literature from various indexed scientific databases, including Scopus, PubMed, Web of Science, ScienceDirect, and Google Scholar, using relevant keywords to obtain a broad and up-to-date study coverage. The articles obtained were then filtered based on inclusion and exclusion criteria, where the inclusion criteria in this review included articles that specifically discussed the formulation and characterization of chitosan-sodium tripolyphosphate nanoparticles in dermatological drug delivery systems, including studies evaluating the effectiveness of skin penetration, as well as publications highlighting aspects of bioadhesion, stability, and controlled drug release. The exclusion criteria were established to filter articles that discussed the application of chitosan-TPP, excluding those unrelated to topical drug delivery. Furthermore, it was analyzed systematically by prioritizing scientific novelty, identifying advantages compared to conventional methods, and proposing innovation prospects and future challenges, resulting in an in-depth, structured study that contributes to the development of research in the fields of pharmacy, dermatology, and nanotechnology.

3 Results and Discussion

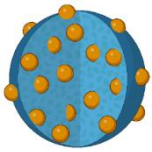
3.1 Characteristics of Chitosan-Sodium Tripoliphosphate Nanoparticles (NPs)

Chitosan is a natural polymer widely used in various biomedical applications, particularly in the development of drug delivery systems. Chitosan comes from the deacetylation of chitin, which is widely obtained from the exoskeletons of marine animals such as crustaceans, fungi, yeast, and microalgae [9]. Chitosan is an excipient used in pharmaceutical formulations, both orally and in other dosage forms, such as cosmetic preparations. Chitosan polymers are commonly used in formulations due to their non-toxic nature, making them safe for various applications, particularly as topical preparations on the skin [10]. Due to its anti-inflammatory and antimicrobial properties, its biocompatibility properties have been proven on both healthy and infected skin [11]. Chitosan reduces the production of inflammatory cytokines and chemokines, including TNF-α, IL-1β, IL-6, and monocyte chemoattractant protein-1 (MCP-1). Additionally, it interacts with toll-like receptors (TLRs) on immune cells, which play a role in detecting microbial components and mediating inflammatory responses. In addition, chitosan also affects the NF-κβ transcription factor pathway, which regulates the production of pro-inflammatory cytokines and has the activity of counteracting reactive oxygen species, thereby strengthening the inflammatory response. [12–14]. Another advantage of chitosan is its ability to be biodegraded biologically, making it a safe choice for cosmetic applications. Chitosan is easily broken down into harmless products (amino sugar) that the body can fully absorb. In addition, chitosan is also hemostatic,

fungistatic, bacteriostatic, spermicidal, anticholesteric, and anticancerogenic [15]. Sodium tripolyphosphate (TPP) is the most widely used and developed cross-linking agent in nanoparticle preparations, especially as an anionic cross-linking agent that interacts with chitosan through the ionic gelation method [16]. Sodium tripolyphosphate is a sodium salt derived from polyphosphoric acid with the chemical formula Na5P3O10 and a molecular weight of 367.864 g · mol^{-1}, consisting of three phosphate units connected by oxygen atoms that form a long chain structure. Sodium tripolyphosphate is an organic compound in the form of white crystals, easily soluble in water, odourless, and stable under good storage conditions. Sodium tripolyphosphate will interact with the protonated amine group (NH3+) in chitosan, forming a stable electrostatic bond and creating a nanoparticle structure used in drug delivery applications [17]. Sodium tripolyphosphate is the most widely used crosslinking compound due to its non-toxic nature [18]. Additionally, the use of sodium tripolyphosphate in the formation of chitosan nanoparticles can help strengthen the matrix of the resulting nanoparticles. The more cross-links that will be formed between the chitosan compound and sodium tripolyphosphate, the stronger the nanoparticle matrix will be and difficult to break into smaller parts [19]. According to research by Sang et al. (2020), the rate of drug release from myricetin chitosan nanoparticles with phytic acid and sodium hexametaphosphate crosslinkers resulted in a release of 43.7 % and 44 % respectively, significantly slower than the sodium tripolyphosphate crosslinker, which resulted in a release of 103.4 % [20]. Nanoparticles are defined as particulate dispersions or solid particles with sizes in the range of 10 nm – 1000 nm [21]. Some literature states that nanoparticles show typical characteristics in the size range of 20 nm – 100 nm [22]. The characteristics of the nanoparticle preparation type in the drug delivery system are presented in Table 1. The dissolved active drug compounds will be trapped, encapsulated, or attached to the matrix of nanoparticles according to the type of preparation, namely nanospheres, nanocapsules, and nanofibers [23]. Nanospheres are solid particles consisting of a polymer matrix that is evenly dispersed throughout the particle. The drug compound in the nanosphere is not trapped in the cavity but is distributed uniformly throughout the particle. The nanosphere type is usually used for drug delivery systems where rapid release is desired. Examples of matrices are PLGA (poly-lactic-co-glycolic acid), chitosan, and PBCA (poly-butyl cyanoacrylate). The nanocapsule type is a system that contains drugs in the core surrounded by a membrane or polymeric shell. In this nanocapsule system, the drug is typically trapped in the cavity or central core, coated by a polymer. This structure allows for more controlled drug release because the drug is released through core diffusion or shell degradation. Examples of matrices are polycaprolactone (PCL), PLA (poly-lactic-acid), and ethyl cellulose[21, 24]. In comparison, nanofiber-based systems have great potential in drug delivery applications. Several studies have been conducted to evaluate the potential for chemical drugs, proteins, peptides, and macromolecular drug delivery, such as siRNA, miRNA, and DNA [25–27]. The overall characteristics of the various nanoparticle preparations and their applications are presented in Table 1. The primary advantage of nanoparticles is their ability to control and regulate the release of drugs during distribution in the body or at the target site of therapy. This can be interpreted that nanoparticles can release drugs in a controlled and gradual manner

so that the active compound of the drug will be retained longer in the body's circulation or the target location of therapy so that it can increase the effectiveness of treatment and reduce the risk of side effects caused by drug accumulation in unwanted areas [21].

Table 1. Characteristics of nanoparticle preparation types in drug delivery systems (Created in BioRender.com; accessed on 14 March 2025).

Preparation Type	Characteristics	Figure	Application
Nanospheres	Solid spherical particles, composition of polymer, lipid, silver, silica, slow release control of the entire matrix.		Drug delivery, cosmetics, bioimaging [28], [29]
Nanocapsules	Particles are formed from a liquid/solid core and a polymer shell, and controlled drug release from the core.		Vaccines, cosmetics, nutritional delivery systems [30], [31]
Nanofibers	Long, nano-sized fibre-shaped particles, made of natural or synthetic polymers, gradually released from the fibre surface.		Gene therapy, Patch wound dressing, tissue engineering, cosmetic sheet mask [32], [33]

Nanoparticles based on the chitosan-sodium tripolyphosphate polymer have been widely used in topical therapy as a delivery system for drugs, as shown in Table 2. In addition, nanoparticles can be administered through several routes, including orally, nasally, parenterally, and even through the intraocular route, where their application covers various clinical conditions, allowing for more targeted and specific use according to the therapeutic objectives required [28].

Table 2. Summary of selected recent research studies exploring nanoparticle-based chitosan-sodium tripolyphosphate for topical, dermal and transdermal drug delivery systems (publication years 2020-2024).

Delivery System	Excipients	Active Ingredient (Category)	Route	Purpose	Ref.
Hybrid Chitosan-Lipid NPs	Chitosan, sodium tripolyphosphate, lecithin	Caffeine, catechin, epicatechin, epigallocatechin gallate (Anti-cellulite agent)	Topical	Developing a hybrid-lipid nanoparticle-based drug delivery system containing green tea leaf extract to effectively and safely	[29]

Delivery System	Excipients	Active Ingredient (Category)	Route	Purpose	Ref.
				reduce cellulite through topical application.	
Polymeric NPs	Chitosan, sodium tripolyphosphate	Diphenhydramine hydrochloride (Antihistamine, antiallergic)	Topical	Developing a chitosan-based nanoparticle system containing diphenhydramine hydrochloride that enhances the effectiveness of antihistamines for topical application.	[30]
Polymeric NPs	Chitosan, sodium tripolyphosphate, Triton X-100, Poloxamer 188	Cefdinir (antibiotic)	Topical	Developing and optimizing chitosan-based nanoparticle formulations modified with surfactants and cefdinir to treat burn wound infections, increase skin penetration and accelerate healing.	[31]
Polymeric NPs	Chitosan, sodium tripolyphosphate, gelatin type B (bovine skin with bloom 225), hyaluronic acid	Metformin hydrochloride (Antiproliferative)	Topical	Developing a chitosan-gelatin-based nanoparticle formulation coated with hyaluronic acid as a topical delivery system for the active substance metformin hydrochloride in the treatment of melanoma with controlled drug release.	[32]
Polymeric NPs	Chitosan, sodium tripolyphosphate, mannitol	Tedizolide Phosphate (Antibiotic)	Ocular topical	Developing a chitosan nanoparticle-based drug delivery system for topical ocular application that enhances the efficiency of the antibiotic tedizolid phosphate by	[33]

Delivery System	Excipients	Active Ingredient (Category)	Route	Purpose	Ref.
Pickering Emulsions Stabilized by Polymeric NPs	Chitosan, sodium tripolyphosphate, hyaluronic acid, flaxseed gum, flaxseed oil	Ferulic acid (Antioxidant, Anti-inflammatory)	Topical	prolonging drug retention. Developing a pickering emulsion-based delivery system stabilized by chitosan nanoparticles that is effective for topical application of ferulic acid to produce a potential formulation for cosmetics.	[34]
Polymeric NPs	Chitosan, sodium tripolyphosphate, hyaluronic acid	Argireline (acetyl hexapeptide-8) (Cosmeceuticals, Antiaging)	Transdermal	Developing a chitosan-based nanoparticle gel formulation for the delivery of the active substance Argireline (acetyl hexapeptide-8) in cosmetic applications for antiaging care.	[35]
Polymeric NPs	Chitosan, sodium tripolyphosphate, dextran sulphate	Amphotericin B (Antifungal, Antileishmanial agent, Antiparasitic)	Topical	Developing a chitosan-based nanoparticle formulation as a topical drug delivery system for Amphotericin B for the treatment of Cutaneous Leishmaniasis by helping to reduce the systemic toxicity of the active substance and increasing the penetration of the active substance.	[36]
Polymeric NPs	Chitosan, sodium tripolyphosphate, gum arabic	Ciprofloxacin (Antibiotic)	Topical	Developing a chitosan-based nanoparticle formulation as a topical delivery system for ciprofloxacin to treat bacterial skin infections by increasing the	[37]

Delivery System	Excipients	Active Ingredient (Category)	Route	Purpose	Ref.
				effectiveness and stability of the preparation.	

Nanoparticles in this study can be made using the ionic gelation method. This method was first introduced by Calvo et al. (1997). This method involves electrostatic interactions between positively charged amine groups and negatively charged polyanion groups that undergo a process of cross-linking polymer chains to produce a continuous three-dimensional network, where water can be trapped in it, forming a solid and rigid structure[38]. This ionic gelation method utilizes the ability of macromolecules to form cross-links with oppositely charged ions, leading to the formation of hydrogels. This technique has been widely applied in polysaccharide encapsulation using a combination of chitosan polymers with sodium tripolyphosphate cross-linkers [39]. The ionic gelation method is widely used in the process of forming nanoparticles because the process is simple, efficient, and can produce nanoparticles at room temperature without requiring complicated treatment or extreme conditions [40]. In the process of making nanoparticles through ionic gelation, chitosan polymer, which is a natural polysaccharide, is dissolved in a previously diluted glacial acetic acid solution [41].

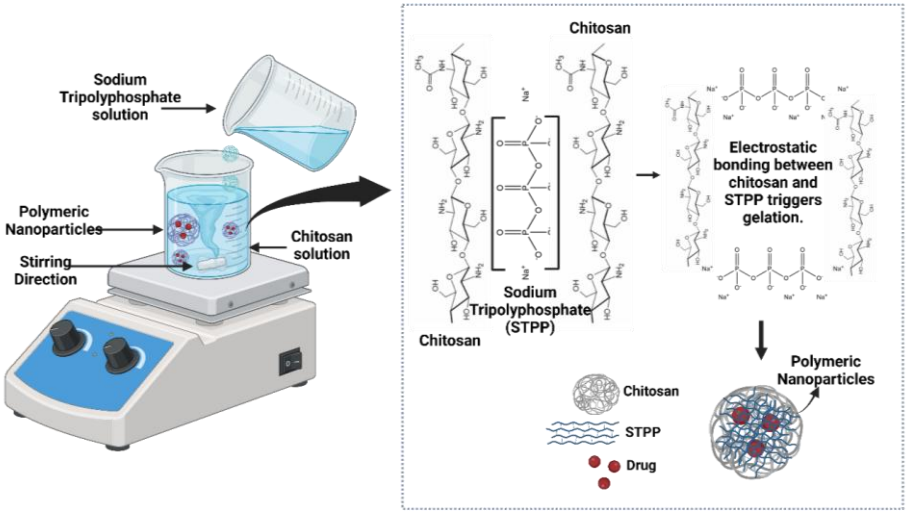


Fig. 1. Scheme of chitosan nanoparticle preparation using sodium tripolyphosphate as a cross-linker through the ionic gelation method (Created in BioRender.com; accessed on 14 March 2025).

This dissolution process will cause chitosan to experience protonation of the amine group to -NH3+. After that, surfactant in the form of Tween 80 is added as a stabilizing

agent. The addition of Tween 80 will cause the particles to form micelles. These micelles are formed when surfactant molecules gather and interact with each other so that the surface of the particles is covered by a layer of surfactant [42]. Then, the sodium tripolyphosphate solution acts as a cross-linking agent, added dropwise to the chitosan solution, and is then stirred using a high-speed stirrer, such as a magnetic stirrer. When sodium tripolyphosphate reacts with chitosan, an ionic bond forms between the positively charged amino groups of chitosan and the negatively charged phosphate groups of sodium tripolyphosphate, producing nanoparticles characterized by the appearance of a suspension. This process is illustrated in Fig. 1. After the suspension is formed, ultrasonication is performed to achieve a smaller particle size [6, 37]. Research by Leonida et al. (2019) showed that the use of ultrasonication in the formulation of chitosan-TPP nanoparticles plays an important role in producing particles with small sizes of 194 nm – 366 nm, PDI of 0.30 – 0.54, and positive zeta potential of 9.2 mV – 17.1 mV. The ultrasonication process not only helps homogenize the solution and form particles but also enhances the encapsulation efficiency and loading capacity of enzymes, particularly catalase (CAT) and histaminase (DAO), while maintaining their enzymatic activity during storage. In addition, the in vitro enzyme release profile showed a significant initial burst release pattern, followed by a gradual release that continued for up to seven days, reflecting the potential for high initial permeability and controlled release from the nanoparticle matrix. These findings suggest that ultrasonicated nanoparticles have significant potential as a stable and effective topical delivery system for enhancing the bioavailability of therapeutic enzymes [43]. In the discussion of Table 2. The use of post-ionotropic gelation ultrasonication in the formulation of chitosan-sodium tripolyphosphate nanoparticles plays a crucial role in controlling particle size and enhancing the performance of the active substance delivery system. Several studies, such as those conducted by Abosabaa et al. (2021), Badie et al. (2024), Ebrahimnejad et al. (2023), Li et al. (2024), and Riezk et al. (2020), applied the ultrasonication process after the formation of nanoparticles [29, 31, 32, 36]. This approach has been shown to produce smaller particle sizes and more uniform size distributions, as well as preventing particle aggregation that is common in natural polymeric systems such as chitosan. For example, Abosabaa et al. (2021) reported a particle size of 292.6 ± 8.98 nm with a PDI of 0.253 ± 0.02, while Ebrahimnejad et al. (2023) recorded a particle size of 329 ± 6.3 nm with a significant increase in skin penetration. Li et al. (2024) also demonstrated successful penetration of ferulic acid into the dermis with particles measuring 262 nm. In contrast, studies that did not apply ultrasonication, such as those by Aziz et al. (2020), showed very different results. In this study, the size of the formed nanoparticles ranged from 656.10 ± 5.1 % nm to 1168.33 ± 28.4 % nm, with the polydispersity index (PDI) varying from 0.16 ± 0.26 to 0.67 ± 0.28. The relatively large particle size and wide PDI range indicate the irregularity of particle distribution and the potential for aggregate formation during or after the nanoparticle formation process. This condition has the potential to reduce the efficiency of topical penetration because particles measuring above 500 nm have limitations in crossing the stratum corneum layer effectively. This fact indicates that, without mechanical intervention, such as ultrasonication, the ionotropic gelation process tends to produce particles with larger and heterogeneous sizes, which in turn

can hinder the topical bioavailability of the delivered active substances. On the other hand, the application of ultrasonication has been proven to support the formation of a more stable, uniform, and permeable nanoparticle system. Therefore, the ultrasonication process is a critical step in optimizing the formulation of Chitosan-TPP nanoparticles to enhance the effectiveness of transdermal and topical delivery of various types of active substances, including both synthetic and natural materials [8]. In vitro evaluation of the active substance profile in this study involved testing the release of active drug substances from nanoparticles under conditions that mimic the physiological environment. Adapted from the research of Abdallah et al. (2020) and Jung et al. (2019), who conducted drug release tests using mouse skin membranes using the Franz Diffusion Cell method [41, 42]. This process is carried out to understand the rapid and controlled release of drugs within a certain time. The controlled release plays a crucial role in the application of long-term drug delivery preparations, as it provides a gradual and consistent release of drugs into the therapeutic target [44]. Some factors that can affect the nature and characteristics of nanoparticles produced through the ionic gelation method include the ratio of chitosan to sodium tripolyphosphate used as crosslinkers. The use of the right concentration of chitosan and sodium tripolyphosphate produces characteristics of small particle size, homogeneous polydispersity index, high encapsulation efficiency and zeta potential that meets the standardization of more than ±30 mV [35, 37, 41].This method is widely studied for drug delivery applications because nanoparticles formed through this method can be adjusted in terms of size, charge and stability, making them very suitable for use as carriers for various therapeutic agents.

3.2 Mechanism of Action for Drug Delivery Through the Skin

The drug delivery system based on chitosan polymer nanoparticles and sodium tripolyphosphate has garnered wide attention as an innovative technology in dermatological therapy, owing to its advantages of being effectively utilized in non-invasive treatment, protection of the gastrointestinal tract, and avoidance of first-pass metabolism in the liver [45]. The mechanism of drug delivery to the skin can be evaluated through a release testing process, such as in vitro testing, which aims to understand the drug release pattern, how the drug penetrates skin tissue, and its effectiveness in reaching the therapeutic target [46]. The formulation of chitosan polymer nanoparticles and sodium tripolyphosphate is generally well accepted by patients because the nano-form preparation can increase the permeability of the active drug substance, thereby providing good delivery of the active substance into various layers of the skin to produce the desired therapeutic effect [47]. The resulting therapeutic effect depends on three factors: the release of the active substance from the carrier system (matrix), the penetration or permeability of the active substance into the outer skin layer (stratum corneum) or other skin layers, and the effect on the target site. All these processes determine the safety and effectiveness profile of a product [48].

Skin is an essential indicator in dermal drug delivery [49]. The skin consists of three main layers, namely: epidermis, dermis, and subcutaneous tissue. The epidermis is the outermost layer of skin and does not have blood vessels; therefore, nutrients diffuse

through the dermo-epidermal tissue to maintain the survival of its cells. The epidermis consists of 5 layers, namely: stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale [50]. As the body's outermost defense system, the skin protects the body from dehydration (maintaining moisture), the entry of microorganisms, and harmful substances. The outermost layer of the skin is the stratum corneum, which serves as the primary barrier to the penetration of drugs through the skin. The stratum corneum consists of corneocytes and an intercellular lipid matrix [51]. Corneocytes are solid cells, with a number ranging from 15 layers to 20 layers, and a thickness of 10 µm – 15 µm. When hydrated, corneocytes will have a thickness of up to 40 µm, indicating an increase in permeability. In addition, the intercellular lipid matrix consists of a mixture of fat, ceramide, cholesterol, cholesterol esters, and a small portion of cholesterol sulfate, which functions to limit the permeability of drugs through the skin [52]. Three different routes allow the active drug to pass through the skin barrier (stratum corneum). The three main routes of passive diffusion penetration are illustrated in Fig. 2. The first route is the intercellular pathway, which shows the active drug passing through the intercellular space between corneocytes. This route is generally used for fat-soluble (lipophilic) molecules because they can easily pass through the lipid layer between cells. The polycationic nature of chitosan makes it more soluble in water. It has a high bioadhesion ability, which can open tight junctions between skin epithelial cells, allowing chitosan to interact electrostatically and bind easily to negatively charged surfaces, such as skin cells [53]. Therefore, nanoparticles based on the chitosan polymer and sodium tripolyphosphate will directly pass through the gaps between stratum corneum cells by disrupting the lipid structure, thereby increasing the permeability of the drug into the skin [54].

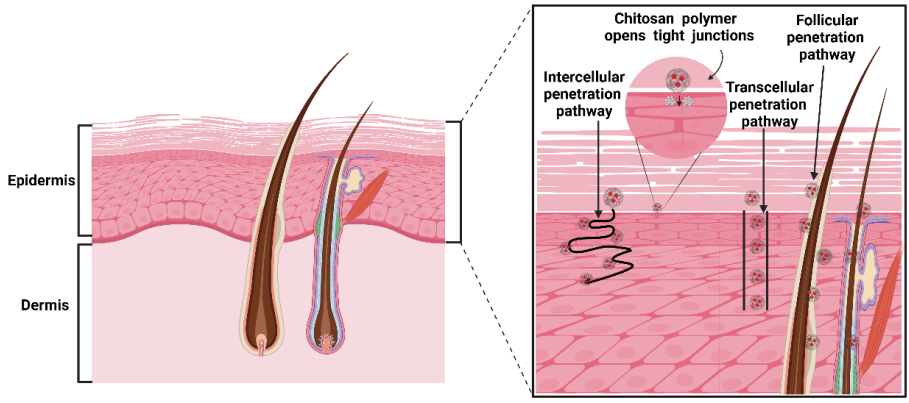


Fig. 2. Three main routes of passive diffusion for the penetration of polymeric chitosan-sodium tripolyphosphate nanoparticles (Created in BioRender.com; accessed on 14 March 2025).

The second route is the follicular penetration pathway, which shows that the active substance of the drug penetrates the hair follicles and sebaceous glands in the skin. This alternative route will provide deeper penetration through the natural openings in the skin, specifically in the hair follicles. This route allows large molecules or other active

substances that have difficulty penetrating the stratum corneum to bypass it through the hair follicles, thereby facilitating penetration into the skin. Research presented by Ta et al. (2021) utilizes the ionic gelation method to produce chitosan and sodium tripolyphosphate polymer nanoparticles with uniform particle sizes of 200-300 nm, which are positively charged to enhance adhesion properties, allowing them to enter and penetrate the skin through the follicular route. These nanoparticles can maintain up to 98 % water content for 48 hours, making them an ideal matrix for active pharmaceutical ingredients in cosmetic product formulations such as moisturizers [37].

The third route is the transcellular penetration pathway, which shows that the active drug substance can penetrate directly through corneocyte cells. The active drug substance must penetrate the cell membrane continuously when passing through the cell, so this route is more difficult because the active drug molecule must penetrate the lipid membrane repeatedly. This route is used by active drugs that can penetrate the lipid membrane (lipophilic) well through the water component of corneocyte cells. Some nanoparticles with small particle sizes can penetrate directly through the cell membrane, allowing active pharmaceutical ingredients to penetrate the skin [50, 51]. Alam et al. (2023) reported that using a chitosan polymer with a concentration of 0.2 % w/v resulted in a relatively small particle size of 60-88 nm, with an encapsulation efficiency of 79 % – 84.54 %, thereby providing good stability in storage and optimal drug delivery effectiveness [55]. According to the European Food Safety Authority (EFSA), the distinction between skin penetration and permeation refers to the distinct mechanisms by which an active substance enters and moves through the skin layers. Research conducted by Buist et al. (2017) defines skin penetration as the entry of an active drug substance into the skin's layers. Still, the active substance has not reached a deeper layer, namely, fully penetrating the systemic circulation. Permeation is the ability of an active substance to penetrate all layers of the skin and enter the systemic circulation to reach the therapeutic target. Drug penetration through the skin is influenced by various modifying factors involving interactions between the drug, skin, and carrier medium (vehicle). These interactions include: drug release from the formulation, penetration through the stratum corneum, and penetration through deeper layers of the skin [56]. The process of releasing active pharmaceutical ingredients from a formulation applied to the skin until it reaches systemic circulation involves several stages including: release of API (Active Pharmaceutical Ingredients) from the preparation formulation, partition of the drug into the stratum corneum, diffusion of the drug through the stratum corneum, partition of the drug from the stratum corneum to the epidermis layer, diffusion through the epidermis layer to the dermis layer [57].

Nanoparticles serve as a carrier medium, significantly affecting the physical condition and permeability of the skin. Due to their small size and surface properties in the form of nanoparticles, nanoparticles enable more effective drug penetration into the skin layer. The mechanism that occurs when a nanoparticle preparation formulation is carried out is that the matrix in the nanoparticles will help the active substance to be in a stable condition in passing through the stratum corneum barrier through the intercellular and follicle pathways and allows it to pass through the transcellular pathway by programming the particle size to be smaller <100 nm so that it is easy to penetrate the transcellular route [46, 55]. To achieve optimal particle size, several

studies have reported that the application of ultrasonication after the ionic gelation process is effective in producing smaller and more uniform particles. Although this method is not a new approach, its application has not been a universal practice across studies, so this strategy is considered important in improving the quality of the final formulation, especially in the context of more controlled drug release and increased topical and transdermal penetration capabilities [55].

3.3 Dermatological Applications

Nanoparticles based on the chitosan polymer and sodium tripolyphosphate have received extensive attention in the pharmaceutical field, particularly in dermatology, as an innovative approach to overcoming challenges in skin-related disease therapy. Nanoparticle technology, which combines chitosan and sodium tripolyphosphate, has successfully produced a sophisticated drug delivery system that overcomes the limitations of conventional topical formulations. The advantages of this system are seen in the bioadhesion properties, biocompatibility and have the ability to release drugs in a controlled manner but its flexibility is adjusted to the therapy needed [58]. These nanoparticles exhibit bioadhesion properties that enable strong adhesion to the skin surface, particularly in the stratum corneum. Research by Abd-Allah et al. (2020) analyzed the bioadhesive strength of chitosan-sodium tripolyphosphate nanoparticles produced at 1.93 ± 0.29 N with an adhesion strength of 18.19 ± 1.02 mJ. This study has a controlled release that is deposited in high concentrations in various layers of the skin with a distribution of around 20.99 % in the stratum corneum, 33.22 % in the epidermis and 14 % in the dermis and 3.65 % penetrates into the receptor compartment by using the Franz-type diffusion cell approach [59]. Chitosan-sodium tripolyphosphate nanoparticles offer an innovative solution to address the challenges of limited drug penetration through the skin, low drug stability, and uneven drug release commonly encountered in conventional topical formulations. This system overcomes this by creating nanoscale particles that can penetrate deep into the skin microstructure to reach the dermis layer [60]. The use of sodium tripolyphosphate cross-linker provides high stability to the nanoparticles and ensures that the active drug substance is protected during the drug delivery process until it reaches its therapeutic target [61]. With these characteristics, chitosan and sodium tripolyphosphate nanoparticles become advanced candidates for use in topical drug delivery applications on the skin. The following is an exploration of the application of chitosan-sodium tripolyphosphate in wound healing, skin cancer therapy, psoriasis and dermatitis treatment and cosmetic formulations.

Wound Healing. In the nanoparticle system, the chitosan polymer plays a crucial role in the wound healing process. This natural polymer derived from "chitin" has the main ability to stimulate the proliferation of fibroblasts, which is very important in the regeneration of skin tissue [62]. Additionally, chitosan aids in the formation of collagen deposits, which are crucial for repairing and strengthening damaged skin tissue. This process is accompanied by the formation of granulation tissue, which is a basic stage in the regeneration of complex skin tissue [63]. Another advantage of chitosan is its antimicrobial properties [64]. This ability will significantly reduce the risk of infection in the wound area, thus providing a safe environment for healing skin wounds. Li et al.

(2023) examined chitosan-sodium tripolyphosphate nanoparticles, which demonstrated significant antibacterial activity against both gram-positive and gram-negative bacteria, including Staphylococcus aureus and Escherichia coli. The cationic properties of chitosan have a damaging effect on the bacterial membrane, thereby reducing the likelihood of infection in the injured area. The addition of p-coumaric acid to the active substance of nanoparticles can increase antioxidant activity. In vitro testing demonstrates the ability of nanoparticles to neutralize free radicals, which helps reduce oxidative stress in the wound area, thereby accelerating tissue regeneration. These nanoparticles show high cell viability, reaching (>80 %) against human skin fibroblasts, indicating that the combination of chitosan-sodium tripolyphosphate nanoparticles is safe to use for topical application, and shows that these nanoparticles are not toxic and help in the process of cell growth, which is important in skin tissue regeneration. In vivo studies yielded significant results, showing that wounds treated with chitosan-TPP nanoparticles exhibited a faster re-epithelialization rate compared to the control group. Mice treated with chitosan-TPP nanoparticles showed more rapid wound closure on day 7, with almost complete closure compared to the control group, which still showed open wounds. Histological analysis revealed thicker granulation tissue formation, accompanied by increased collagen deposition and more optimal epidermal regeneration in the nanoparticle-treated group [65]. Additionally, treatment with chitosan-TPP nanoparticles helps reduce inflammation in the wound area, as indicated by a decrease in neutrophil infiltration. This suggests that these nanoparticles can not only accelerate healing but also reduce pain and swelling during the healing process [66]. Research by Sriwidodo et al. (2020) showed that chitosan-TPP nanoparticles have a homogeneous particle distribution with a polydispersity index of 0.259. High stability is indicated by a zeta potential value of +41.29 mV, which means that the nanoparticles do not easily clump. The encapsulation efficiency obtained was 99 %, suggesting that these nanoparticles can effectively encapsulate human epidermal growth factor (hEGF), thereby providing a high level of protection for delivering active drug substances to the wound area. In NIH3T3 fibroblast cells, it was shown that nanoparticles with a concentration of hEGF 50 ng · mL^{-1} provided the highest cell viability of 192 % which indicates that the cell proliferation rate doubled within 4 hours [67]. In addition, SEM and TEM results show that the active substances are perfectly trapped in the nanoparticle matrix, so that they can ensure controlled release of the active drug substances [7]. Research by Hajji et al. (2022) demonstrated that chitosan-TPP nanocomposites exhibited strong antibacterial activity against both gram-positive and gram-negative bacteria. The inhibition zone for Escherichia coli was 9.02 ± 0.55 mm, and the inhibition zone for Staphylococcus aureus was 9.11 ± 0.29 mm. This activity stems from the positive charge of chitosan, which disrupts the negatively charged bacterial membrane, leading to cell leakage and ultimately bacterial death. The antioxidant activity of the nanocomposite film yielded a significant value, with an inhibition percentage of 82.45 % ± 0.83, thereby helping to reduce oxidative stress in the wound area. In vivo tests demonstrated that wounds in mice treated with chitosan-TPP nanocomposites healed faster, closing completely by the 14th day, compared to the control group. The growth of new epidermal tissue in the treated wounds, as shown by histological analysis, demonstrated significant development in thicker granulation

tissue with increased collagen deposition compared to the control group [68]. Research by Piran et al. (2018) indicated that chitosan-TPP nanoparticles provide a gradual release of 83 % of the active substance PDGF-BB over one week, suggesting the potential for long-term therapeutic activity in wound treatment. The MTT test showed that the PDGF-BB nanoparticle scaffold significantly enhanced fibroblast proliferation up to day 5 compared to the control. In addition, the expression of the actin-related protein 2 (Arp2) gene and platelet-derived growth factor receptor beta provided a two-fold increase in fibroblast cells stimulated by nanoparticles, so that it has high potential to increase collagen production and form granulation tissue, which is an important process in wound healing [69]. Badie et al. (2024) reported that the chitosan-TPP nanoparticle formulation exhibited a sustained release profile of 75.5 % ± 3.8 over 48 hours. Permeation studies using mouse skin showed that nanoparticles increased drug penetration into the stratum corneum compared to controls, with a total active substance deposited in the skin layer of 83.38 % which provided the ability to deliver drugs effectively to the target wound area. Cytotoxicity tests using fibroblasts showed cell viability of more than 80 %, indicating that chitosan-TPP nanoparticles are safe for topical application. The antibacterial activity of nanoparticles significantly inhibited S. aureus and P. aeruginosa at concentrations of 25 $\mu g \cdot mL^{-1}$ and 50 $\mu g \cdot mL^{-1}$. Wounds treated with nanoparticles will effectively inhibit the formation of S. aureus bacterial biofilms by up to 67.2 %, thereby helping to prevent secondary infections in burns and promoting the healing of chronic wounds. The antioxidant activity of CFD chitosan-TPP nanoparticles inhibited free radicals by 83.3 %, demonstrating a significant increase in antioxidant activity compared to free CFD and Void-CSNP, with an IC50 value of 125.29 ± 5.41 $\mu g \cdot mL^{-1}$ ($p < 0.05$). Ascorbic acid demonstrated potent antioxidant activity, serving as a reference standard with an IC50 value of 10.23 ± 0.75 $\mu g \cdot mL^{-1}$. This increase in antioxidant capacity can be attributed to the formulation of chitosan-TPP nanoparticles, which enhances the accessibility of reactive groups, thereby facilitating accelerated wound regeneration. Histological results showed a thicker epidermis layer, the formation of granulation tissue, new blood vessels (angiogenesis), which were better than the control treatment, and decreased inflammatory cell infiltration in the wound area [31]. The biocompatibility properties of chitosan provide safe, non-irritating, and non-allergic characteristics for use on injured skin. The bioadhesion ability of chitosan will give a film or protective layer over the wound, helping to protect the wound area from contamination and maintaining optimal skin moisture conditions. A moist environment supports the cellular and enzymatic processes used in the optimal wound healing process. Overall, the combination of active substance, antimicrobial, and bioadhesive properties makes chitosan a candidate for wound healing therapy [62]. When compared with other natural polymers, such as sodium alginate, it gives different results as studied by Gaudio et al. (2020). The alginate-pectin polymer offers advantages in in situ hydrogel formation and the ability to quickly absorb wound exudate, while maintaining the stability of the Ac2-26 peptide and accelerating keratinocyte migration. However, this system exhibits a high initial burst release (>50 %) and a significant loss of gel fluid within 12 hours, which can disrupt the local stability of the wound [70]. In contrast, the development of a topical drug delivery system by Aslan et al. (2016) revealed that chitosan-TPP-based

nanoparticles exhibited superior performance compared to the alginate-pectin system, particularly in wound healing. Based on the characterization results, chitosan-TPP nanoparticles have a particle size of around 317 nm – 1007 nm with a spherical morphology and homogeneous dispersion, a low polydispersity index (PDI) value indicating a uniform size distribution, and a positive zeta potential that supports system stability and effective interaction with wound tissue. This system also showed 100% encapsulation efficiency of Interleukin-2 (IL-2) and controlled release after the initial burst, creating a healing environment that supports regeneration and immune response. In vivo results showed that chitosan-TPP significantly decreased MDA levels and increased GSH levels in wound tissue, indicating stronger antioxidant and regenerative activities. Thus, chitosan-TPP nanoparticles are superior in terms of physical characteristics, therapeutic efficiency, and biological impact, making them a more promising candidate for effective and controlled topical wound therapy [71].

Delivery of Anti-Cancer Agents for Skin Cancer. Skin cancer is a disease that is often caused/triggered by excessive exposure to UV rays, making it one of the biggest challenges in the world of health [72]. Skin cancer therapy presents an interesting challenge because it requires consistent delivery of cytotoxic agents to ensure effectiveness in target tissues while minimizing systemic side effects. In nanotechnology systems, especially chitosan-TPP polymer-based nanoparticles are a promising technology to overcome the problems of conventional therapy to help improve drug stability and minimize drug degradation, with good bioadhesion properties that increase drug penetration and controlled release into the target tissues of therapy [73]. To find a more effective solution, several studies have succeeded in developing polymer-based nanoparticles encapsulated with the active substance 5-Fluorouracil (5-FU), which is a chemotherapy agent known for its strong systemic side effects [74]. Nanoparticle systems are designed to overcome the limitations of conventional therapies by providing more targeted delivery of active agents and reducing systemic side effects. Samy et al. research (2020) evaluated the formulation, characterization and in vitro release test of chitosan-TPP nanoparticles containing 5-FU. The results of the encapsulation efficiency formulation at a concentration of 5 mg/mL and a ratio of 5:1 yielded the highest percentage of encapsulation efficiency (EE) of 21.82 %. The particle size obtained was 319.1 nm – 631.7 nm. A lower molecular weight of 150,000 $g \cdot mol^{-1}$ resulted in a smaller particle size, which in turn led to lower viscosity and improved drug penetration into the target tissue for therapy. According to TEM analysis, the nanoparticles appear to be spherical and do not exhibit aggregation. Based on this formula, the release of the 5-FU drug exhibits a biphasic release pattern, characterized by a rapid initial rate in the first hour, followed by a gradual increase to a cumulative release of up to 34.17 %, which persists for up to 48 hours. The drug release model follows the Higuchi kinetic model, which shows a diffusion-based release mechanism pattern. The obtained nanoparticles are capable of protecting the active substance 5-FU from initial degradation, thereby enhancing drug stability during use and storage [75]. The bioadhesive properties of chitosan will provide longer contact on the skin surface, thereby helping to increase drug penetration through the stratum corneum and towards the therapeutic target in the skin [76]. In conventional formulations, for example, a free solution of the active substance 5-FU

will cause the drug to spread through the bloodstream (systemic distribution), increasing the risk of side effects, such as poisoning in non-target organs or other skin reactions. By being made in nanoparticle preparations, drug release will occur specifically in the application area so that only a small amount of the drug enters the systemic circulation and causes relatively minimal side effects [75]. Yadav et al. (2024) conducted a study on the development of chitosan polymer-based nanoparticles for encapsulating the active substance 5-FU in skin cancer therapy, focusing on the cell lines A375 (human skin melanoma) and A431 (human skin epidermoid carcinoma). The cytotoxicity results explained that 5-FU nanoparticles could significantly reduce the viability of cancer cells within 72 hours. In A375 cell lines, the viability decreased to 16.47 %, while in A431 cells, the viability reached 20.20 %. These results demonstrate that chitosan polymer-based nanoparticles for encapsulating the active substance 5-FU exhibit a strong cytotoxic effect, which is even higher than that of doxorubicin solution, achieving a viability of 5.512 % for A375 cell lines and 6.0468 % for A431. The advantages of nanoparticles are not only seen in the viability of cells but also the mechanism of nuclear damage observed by DAPI staining. The yellow fluorescence microscopy image reveals significant morphological changes and DNA damage resulting from the apoptosis mechanism [77]. By targeting drugs specifically to cancer cells, nanoparticles will reduce the risk of harm to healthy cell tissues, thereby increasing the effectiveness and safety of therapy. Overall, the nanoparticle system using chitosan-TPP polymer is effective in encapsulating sensitive active ingredients such as 5-Fluorouracil (5-FU), and providing stability and controlled release, making it a suitable platform for local delivery of skin cancer therapy, considering its bioadhesive, biocompatible, and penetration characteristics into the epidermis and dermis tissues which are the primary targets of the treatment.

Treatment of Psoriasis and Dermatitis. Psoriasis (PSO) is a chronic autoimmune disease characterized by excessive and rapid skin cell growth, resulting in thickened, scaly patches on the skin's surface. The symptoms experienced are itching accompanied by pain that interferes with the patient's comfort and quality of life [78]. Treatment of psoriasis aims to relieve symptoms, reduce inflammation, and slow the rate of excessive skin cell growth. However, the use of conventional topical therapy has limited effectiveness and can potentially cause unwanted side effects. A new approach in topical drug delivery systems using nanoparticle systems will provide great potential in improving psoriasis treatment [79]. In recent decades, polymer nanoparticles have emerged as a promising innovation in psoriasis therapy, offering more effective and controlled drug delivery. The ability to encapsulate various types of drugs provides advantages in releasing medications for a long period and provides more efficient treatment because it can reduce the side effects that often occur in conventional psoriasis therapy [80]. One of the main advantages of nanoparticle polymers is the control of drug release. In the case of plaque psoriasis, the condition is characterized by skin thickening due to keratinocyte hyperproliferation and abnormal inflammatory response, so nanoparticle polymers play a vital role in ensuring that the drug can work for a longer duration [81]. Compared to conventional delivery systems, polymer nanoparticles can reduce the frequency of drug use, thereby increasing patient compliance and minimizing side effects that often occur due to the excessive use of

corticosteroids or immunomodulatory agents. Research by Nair et al. (2019) on chitosan-sodium tripolyphosphate polymer nanoparticles demonstrates controlled drug release with encapsulation efficiency exceeding 80 % in the transdermal penetration of curcumin. Small particle size of 161-251 nm with a positive charge that supports skin interaction and increases permeability, so that it is categorized as an ideal candidate for topical therapy, good biocompatibility and low cytotoxic effects on human skin cells strengthen its potential as a topical drug delivery system for dermatological applications [82]. Additionally, the ability of the chitosan-TPP nanoparticle polymer to enhance skin penetration makes it an ideal choice for topical psoriasis therapy. With a modifiable particle structure, these nanoparticles will be able to cross the thickened stratum corneum layer in psoriasis patients, allowing the drug to reach deeper layers of the skin with high efficiency. This is very important in overcoming skin resistance to conventional topical therapies that often find limitations in drug penetration [83]. Research by Wang et al. (2022) indicated that chitosan-TPP nanoparticles containing methotrexate (MTX) and 5-aminolevulinic acid (ALA) can significantly enhance the penetration and retention of active substances in the skin compared to conventional suspension formulations. This can be seen from the fluorescence results of protoporphyrin IX from ALA, showing a deeper distribution of up to 70 μm in the skin layer; this distribution is higher than the control group, which is only 20 μm. In addition, chitosan-TPP nanoparticles enhance the absorption of MTX and ALA, assisted by keratinocyte cells (HaCaT), resulting in a higher conversion of protoporphyrin IX and the generation of reactive oxygen species (3.93-fold), thereby contributing to the inhibition of proliferation and apoptosis in irritated cells. In a psoriasis model induced in mice, chitosan-TPP nanoparticles reduced clinical symptoms, including peeling, erythema, and skin thickening. In addition, the nanoparticle formulation significantly reduced the levels of the pro-inflammatory cytokines TNF-α and IL-17A, both in the skin and in the serum. The reduction of the mechanism is better compared to other therapeutic methods, such as oral MTX or ALA-PDT. The formulation of chitosan-TPP nanoparticles demonstrated a significant ability to induce apoptosis and inhibit the proliferation of hyperproliferative keratinocytes, with a 78.6 % increase compared to the MTX suspension, 5-ALA solution, and MTX-ALA suspension groups, which produced 30.9 %, 23.6 %, 50.2 %, and 78.6 % reductions, respectively. Chitosan-TPP nanoparticles are also capable of reducing systemic toxicity, which is commonly observed with oral MTX administration. This will also provide significant benefits in minimizing side effects on the liver and kidneys, so that it provides the potential as a safer and more effective therapeutic option in all types of drug delivery systems [84]. With all its advantages, chitosan-TPP polymer in nanoparticles continues to be developed as the main strategy in more effective, sustainable, and comfortable psoriasis therapy. Along with technological advances in polymer formulation design, it is hoped that this innovation can provide better and more specific therapeutic solutions for each type of psoriasis in the future.

Table 3. Formulation, Characterization, and cosmetic applications of chitosan-sodium tripolyphosphate nanoparticles.

Bioactive	Excipients	Method	PS (nm), PDI, ZP (mV)	Application	Ref.
Ferulic Acid (FA)	Chitosan, Flaxseed gum, Hyaluronic acid, Sodium tripolyphosphate, Diacylglycerol	Ionic gelation	262.4 ± 2.2 0.25 ± 0.020 36.62 ± 0.2	Enhances skin protection, anti-aging, and brightening effect in cosmetic formulations	[34]
Extract Ilex paraguariensis (Yerba Mate)	Chitosan, Sodium tripolyphosphate, Deionized water	Ionic gelation	N/A N/A +29.4 ± 4.69	Provides antioxidant, anti-aging, and skin shoothing benefit in cosmetic formulations	[88]
Extract rosehip (Rosa canina L.) and blackthorn (Prunus spinosa L.)	Chitosan, Pentasodium Tripolyphosphate, Phytic acid, Sodium alginate	Ionic gelation	185.33 ±12.01 0.190 ± 0.045 +27.49 ± 0.56	Deliver antioxidant, skin-rejuvenating effect in cosmetic formulations	[89]
Hydroxytyrosol	Chitosan, Sodium Tripolyphosphate	Ionic gelation	~300 N/A N/A	Provides powerful antioxidant, anti-aging, and skin protective benefits in cosmetic formulations	[90]
Extract green tea	Chitosan, Sodium Tripolyphosphate	Ionic gelation	292.6 ± 8.98 0.253 ± 0.02 41.03± 0.503	Offers antioxidant, anti-inflammatory, anti-aging benefits for skin protection and rejuvenation	[29]
L-ascorbic acid	Chitosan, Sodium Tripolyphosphate	Ionic gelation	428 ± 6 0.05 -30	Boosts collagen production, brightens skin, and provides antioxidant protection in cosmetic formulations	[87]
Nicotinamide	Chitosan, Sodium	Ionic gelation	116.4 ± 2.1 0.28 ± 0.00 +29.5 ± 1.1	Improves skin barrier, reduces inflammation, and	[59]

Bioactive	Excipients	Method	PS (nm), PDI, ZP (mV)	Application	Ref.
	Tripolyphosphate			brightens complexion in cosmetic formulations	

Cosmetic Application. Nanoparticles with chitosan polymer have become a popular ingredient in skin care cosmetic formulations. Chitosan is a natural biopolymer derived from chitin [85]. Its biocompatible, biodegradable, and film-forming properties provide benefits in cosmetic products. Through the ionic gelation process, this polymer nanoparticle system will be able to encapsulate active ingredients with a higher level of efficiency and provide protection against environmental degradation [6]. Summary Table 3 presents various combinations of suitable bioactive substances formulated using chitosan-sodium tripolyphosphate polymer-based excipients, which exhibit optimal physicochemical characteristics for topical cosmetic applications. The formulations are designed to produce stable and effective nanoparticle delivery systems that enhance the penetration of active ingredients into the skin. The right combination of excipients not only supports the stability of the active ingredients during storage but also ensures their therapeutic efficacy when applied to cosmetic products [86]. As a reinforcement of the performance of this formulation, recent studies in Table 3 demonstrate that the application of the ultrasonication process after ionic gelation can further enhance the quality of the nanoparticle system, particularly in terms of reducing particle size and increasing distribution homogeneity. Research by Baek et al. 2021 describes the use of the ultrasonication method during the formation of chitosan-based vitamin C nanocapsules, resulting in particle sizes of 428 ± 6 nm and 450 ± 8 nm, but still smaller than other non-sonication systems that reach >600 nm. This process works by providing high mechanical energy that breaks particle aggregates and accelerates colloidal dispersion more evenly. With a smaller and more uniform particle size, the delivery system becomes more efficient in penetrating the stratum corneum layer, thereby increasing the bioavailability of active ingredients in topical applications. Therefore, the integration of ultrasonication in the post-gelation stage can be a very useful additional strategy to optimize the effectiveness of chitosan-TPP-based nanoparticle formulations [87].

One of the latest innovations is the combination of chitosan with sodium tripolyphosphate, which forms nanoparticles with high stability and increases the penetration of active ingredients into the skin. In cosmetics, chitosan-sodium tripolyphosphate polymer nanoparticles serve as an effective delivery system, as they can control the release of active substances, enhance skin hydration, and aid in repairing the skin barrier. The combination of polymers also provides antibacterial and anti-inflammatory effects, making it an ideal choice for sensitive and acne-prone skin care [84, 85]. Cosmetic products such as moisturizers and serums, which are formulated with chitosan-sodium tripolyphosphate polymers, can help extend the duration of the hydration effect and accelerate skin cell regeneration [38]. In addition, chitosan's ability to bind water provides a higher level of effectiveness in reducing trans-epidermal water

loss (TEWL) so that the skin remains hydrated for longer [91]. With the addition of sodium tripolyphosphate as a cross-linker, the nanoparticle structure encapsulating active ingredients, such as antioxidant compounds, vitamins, and herbal extracts, becomes more dispersed and functions optimally in the skin layer. Trans-epidermal water loss (TEWL) combined with environmental stress factors such as ultraviolet radiation causes skin aging (photoaging) because it triggers the formation of reactive oxygen species, which result in faster damage to skin cells [92]. However, to counteract these adverse effects, the human body has a robust natural antioxidant mechanism, often referred to as coenzyme Q10 (CoQ10). Research by Madronal et al. (2023) suggests that CoQ10 can enhance cellular energy production, thereby reducing skin cell damage caused by UV radiation in human fibroblast cells. The characteristics of CoQ10, which are unstable to light, inhibit its effectiveness in therapeutic applications. Therefore, a nanoparticle formulation based on a chitosan-rosmarinic acid polymer with a sodium tripolyphosphate cross-linker was developed. The results obtained for the nanoparticles were 382±3 nm in hydrodynamic diameter, 0.04±0.02 in polydispersity, and -18±3 mV in surface charge, with a release kinetics of 82 % within 40 minutes. Meanwhile, this study confirmed the presence of radical scavenger activity assay activity and confirmed the antioxidant properties of these polymeric nanoparticles [93]. The mechanism that occurs in CoQ10 nanoparticles in anti-aging activity is by inhibiting the production of reactive oxygen species (ROS), IL-6, and metalloproteinase-1, preventing the activation of caspase-9, which helps maintain the viability of dermal fibroblasts that are exposed to UV radiation [94]. Chitosan and sodium tripolyphosphate-based nanoparticles have been successfully formulated using the ionic gelation method, incorporating hyaluronic acid and ferulic acid as active ingredients. The results obtained showed a particle size characterization of 400.8 nm under optimal ratio conditions of the chitosan: TPP formulation (5:1 w/w), a hyaluronic acid concentration of 0.25 mg · mL^{-1}, and a ferulic acid dose of 25 μM. These nanoparticles form a stable Pickering emulsion with an internal diacylglycerol phase of 50 % – 80 % (v/v) and a contact angle surface activity approaching 90 °C, which provides a dense arrangement of particles on the surface of the emulsion droplet. The resulting emulsion nanoparticles exhibit high stability at various temperatures, ionic conditions, and oxidation conditions, and provide controlled release of ferulic acid in the dermal layer. The combination of hyaluronic acid and diacylglycerol provides a quality delivery system for active ingredients that are not only effective in therapy but also environmentally friendly [34]. Thus, the results of this study indicate that chitosan-sodium tripolyphosphate nanoparticles have great potential as an innovative drug delivery system in anti-aging skin care.

4 Recent Advances

The development of drug delivery system technology through the skin has increased rapidly due to advances in nanotechnology and biomimetic materials. In this context, chitosan-based nanoparticles with sodium tripolyphosphate (TPP) cross-linker have proven to be one of the promising systems, both in terms of delivery effectiveness, drug

release efficiency, and biocompatibility and bioadhesion properties. Although this technology has shown many advantages, various recent innovations continue to be developed to further optimize the performance of this system in more complex clinical and therapeutic scenarios, particularly in dermatological applications. Pure chitosan has limitations, including its limited solubility in acidic environments, limited cationic charges, and a lack of specific targeting capabilities. Therefore, chemical modification of chitosan has become an important strategy to enhance the efficiency of drug delivery systems, both in terms of solubility, skin affinity, and drug loading capacity. Modification of chitosan is changed into N,N,N-Trimethyl chitosan (TMC) form which is soluble in water and has permanent positive charge proven to significantly increase the permeability of epithelial membrane through opening tight junction and increasing the pH spectrum of the solution so that it affects the effectiveness of absorption of macromolecular drugs such as peptides and proteins efficiently. In addition, the antibacterial activity given is proven to be better than pure chitosan [95]. Other studies have shown that TMC has high antibacterial activity against Staphylococcus aureus >99 % and Eschericia coli up to 92 % and a non-toxic profile in vitro against fibroblast cells. In vivo tests on injured rat models also demonstrated a significant increase in re-epithelialization and wound contraction, indicating that TMC is a superior candidate for wound dressing applications [96]. Meanwhile, the potential of TMC as an antigen carrier (nano carrier) and immune adjuvant is very promising, especially in mucosal vaccination applications. The mechanism of mucoadhesion and opening of tight junctions in the mucosa will extend the contact time of nanoparticles in facilitating a stronger immune response [97]. This study emphasizes the importance of the degree of quaternization in influencing the activity and efficiency of drug delivery systems. Recent studies have shown that carboxymethyl chitosan (CMCS) modification can improve the efficiency of drug delivery systems, especially in chronic wound therapy. Yue et al. (2024) developed a hydrogel based on CMCS and oxidized hyaluronic acid (OHA) containing stem cell exosomes. Exosomes from human umbilical cord mesenchymal stem cells (HUCMSC-Exo) were chosen because of their high bioactivity. The characterization results showed that the hydrogel was able to release exosomes gradually for 6 days as well as good hemocompatibility properties (hemolysis <5 %) and induce the transition of M1 to M2 macrophages. Thus accelerating the healing of chronic inflammatory wounds significantly [98]. On the other hand, the development of CMCS-CEBT composite hydrogel with the addition of chitosan nanoparticles, bioactive glass and TIO2 showed the results of increasing cell proliferation and migration, angiogenesis, and anti-inflammatory and antibacterial activities. This combination hydrogel has high effectiveness in healing diabetic wounds and burns [99]. Modification of chitosan through conjugation with specific ligands has become an important approach in drug delivery systems, in the study of Escareno et al. (2021) a polymeric nanoparticle system based on PLGA-chitosan loaded with doxorubicin conjugated with trastuzumab antibody (anti-HER2) using microfluidics-assisted bioconjugation technique produced homogeneous particle sizes, measuring 97.1 nm and having controlled ligand density compared to conventional mixing methods. In vitro results showed a significant increase in drug release efficiency, cell uptake and cytotoxic activity against HER2+ breast cancer cells compared to non-

conjugated chitosan nanoparticles [100]. Meanwhile, the strategy of various chitosan conjugations, such as galactose, mannose, folate, and antibodies, is to obtain active targeting. The conjugation mechanism will increase the specificity of drug delivery and reduce toxicity to healthy tissues. Chitosan conjugated with folate effectively targets cancer cells with high expression of folate receptors, while mannose conjugation is intended for delivery to dendritic cells and macrophages [101]. The results of the latest study on the combination of nanoparticles and iontophoresis indicate that the distribution of hen egg-white lysozyme (HEL) antigen on the skin will significantly increase IgG1 and IgG2a titers and reduce total IgE and plasma histamine levels. This shows that PLGA nanoparticles coated with chitosan hydroxypropyltrimonium chloride can increase the effectiveness of antigen delivery through the skin efficiently [102]. Another study utilizing chitosan/hyaluronic acid/miRNA-21 based nanoparticles for smooth titanium coating showed that the coating increased adhesion, proliferation and extracellular matrix gene expression (COL1A1, COL3A1, α-SMA) of human gingival fibroblasts without increasing cytotoxicity which has the potential to create stable percutaneous implants and prevent infection or decreased tissue integrity [103]. The study described by Nawaz et al. (2022) developed a chitosan-gelatin based thermosensitive hydrogel loaded with 5FU-alginate nanoparticles for skin delivery system. This system showed a delayed drug release profile that could avoid the initial burst release effect and enhance drug retention in skin tissue. Ex-vivo and in vivo studies showed that this formulation provided higher therapeutic accumulation in the skin compared to the control thus having potential for local skin cancer therapy such as melanoma and actinic keratosis [104]. The integration of advanced technology with chitosan-based drug delivery systems has helped in improving therapy. Lin et al. (2025) study developed a chitosan-hyaluronic acid-based microneedle loaded with biomineralized insulin nanoparticles and glucose oxidase. This system is responsive to blood glucose which will result in controlled insulin release and significantly lower blood glucose levels with a high level of safety [105]. The same study also described the use of chitosan nanoparticles loaded with rasagiline mesylate in a dissolving microneedle formulation for transdermal delivery. This formulation significantly increased skin permeability by 160 % compared to conventional patches and provided a relatively stable systemic effect [106]. In addition to microneedles, Saleem et al. (2025) designed a chitosan-hyaluronic acid-based nano-hydrogel containing minoxidil for alopecia therapy, this formulation will increase permeability two-fold compared to conventional gels and prolong drug release up to 24 hours as well as a minimal irritation topical use safety profile [107]. The study showed that the integration of microneedles, biomineralization and nanoparticle hydrogel with chitosan-sodium tripolyphosphate polymer significantly improved the efficiency, stability and convenience in the drug delivery system.

5 Future Perspective

Sustainable local resources, especially chitosan derived from shrimp shell waste. This approach not only supports cost-effective production, especially in developing coun-

tries, but also aligns with the principles of circular bioeconomy by promoting waste valorization. Optimization of the extraction and purification processes of chitosan from marine biomass will be essential to ensure consistent quality and performance for high-end pharmaceutical applications. In addition to the source of the material, clinical validation remains a crucial step to bridge the gap between preclinical research and real-world therapeutic implementation. Although extensive in vitro and in vivo studies have demonstrated the bioadhesive properties, controlled release capabilities, and enhanced skin penetration of chitosan-TPP nanoparticles, large-scale clinical trials are needed to evaluate the safety, efficacy, pharmacokinetics, and patient acceptability. Clinical trials, particularly in the areas of chronic wound care, psoriasis, atopic dermatitis, and skin cancer treatment, will provide critical evidence for regulatory approval and clinical translation. In parallel, future innovations are expected to focus on the integration of intelligent technologies, such as wearable biosensors and artificial intelligence (AI), into topical drug delivery platforms. Drug delivery based on physiological characteristics such as skin pH, moisture levels, or inflammatory markers can significantly improve therapeutic accuracy and patient compliance. Integrating AI-based algorithms to analyze patient-specific data and control drug release kinetics offers a pathway to intelligent and responsive drug delivery systems.

6 Conclusion

An effective topical drug delivery system plays a vital role in improving the success of dermatological therapy, especially in overcoming biological barriers such as stratum corneum penetration, drug stability, and the need for controlled release. Nanoparticles based on chitosan–sodium tripolyphosphate (TPP) polymer are a good solution because they have bioadhesive, biocompatible properties, and are able to form a stable delivery system with high encapsulation efficiency. Supporting physicochemical characteristics, such as small particle size, positive surface charge, and the ability to interact directly with the skin, allow effective penetration to the epidermis layer. The application of these nanoparticles has been successfully developed for various needs, ranging from wound healing, skin cancer therapy, and inflammatory disease treatment, to cosmetic formulations. Evaluation of the effectiveness of the delivery of active compounds shows that this system has high flexibility in encapsulating compounds such as natural compounds and synthetic drugs, each with its own formulation challenges. Compared with other polymer-based nanoparticle systems, chitosan–TPP offers advantages in terms of biological safety, simpler formulation process, and potential for further modification. One of the innovative approaches highlighted is the use of post-ionic gelation ultrasonication, which has been shown to enhance particle quality through size reduction, improved distribution uniformity, and enhanced dosage form stability. This strategy enhances the system's performance in the context of modern topical applications that demand local efficacy, ease of use, and long-term stability. With the advancement of formulation technology, integration with intelligent delivery systems, and support from sustainable raw materials, chitosan–TPP nanoparticles have broad prospects for translation into clinical and cosmetic practice. Further research should

focus on in vivo validation or clinical trials, optimization for each type of active ingredient, and formulation approaches that support large-scale production. Thus, this system has the potential to become a future topical delivery platform that is safe, effective, and adaptive to patient needs.

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