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Cyclodextrin-based dermatological formulations: Dermopharmaceutical and cosmetic applications

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ABSTRACT

The progress in new delivery systems for active ingredients has boosted the dermopharmaceutical and cosmetic fields by allowing formulations to display enhanced skin permeation capabilities. Cyclodextrins (CDs) are cyclic oligosaccharides able to form host-guest inclusion complexes with guest active molecules, resulting in improved physicochemical properties of such molecules. The incorporation of CDs in dermopharmaceutical and cosmetics formulations has received much attention since the late 1970 s by enhancing modulation of the passage through the skin and vectorization into the target site while simultaneously offering a biocompatible delivery system. This paper features the advantages of CDs in dermopharmaceutical and cosmetic applications, such as the improvement of the apparent solubility and the stability of the active ingredients, the possibility of masking unpleasant odors, among others that are be described, emphasizing that these versatile skin active ingredient carriers are strongly promising both in the treatment of skin diseases and in the improvement of cosmetic formulations.

1. Introduction

The delivery of several active ingredients in the skin is challenging owing to its intrinsic characteristics but also because of the powerful barrier function of the *stratum corneum* (SC). Most topical products appear in the market in conventional semisolid dosage forms, including gels, creams, and lotions [1]. However, more recently, consumer expectations led to the investment of pharmaceutical along with cosmetic research toward the development of novel formulations based on nanodelivery systems capable of offering superior technological performances. Such nanodelivery systems have the purpose of controlling the skin delivery of active ingredients by controlled and targeted release

Abbreviations: **Akt-mTOR**, Serine/threonine kinase; **BO,**, Babchi oil; **CD**, Cyclodextrin; **Cur,**, Curcumin; **Ce,**, Ceria; **CGTase**, Cyclodextrin glycosyltransferase; **DIT,**, Dithranol; **DM-β-CD**, Dimethyl-β-cyclodextrin; **DPS,**, Dapsone; **EE**, Encapsulation efficiency; **EMA**, European Medicines Agency; **EU**, European Union; **FDA**, Food and Drug Administration; **GMP**, Good Manufacturing Practice; **HP-β-CD**, 2-hydroxypropyl-β-cyclodextrin; **HP-γ-CD**, Hydroxypropyl-γ-cyclodextrin; **HSC-1 cells**, Human cutaneous squamous carcinoma cells; **MAPK**, Mitogen-Activated Protein Kinase; **M-β-CD**, Methyl-β-cyclodextrin; **NP,**, Nanoparticle; **ROS,**, Reactive Oxygen Species; **SBE-β-CD**, Sulfobutylether-β-cyclodextrin; **SC,**, *Stratum Corneum*; **SPF**, Sun Protection Factor; **US,**, United States; **UV**, Ultraviolet; **VC-IP**, Vitamin C Ascorbic Tetraisopalmitate; **α-CD**, α-cyclodextrin; **β-CD**, β-cyclodextrin; **β-CD-MA**, β-cyclodextrin-methacrylate; **γ-CD**, γ-cyclodextrin.

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profiles, improving their duration of action and their penetration into the target skin layer while contributing to a concomitant enhancement of the formulation stability. All these mechanisms bring a desired enhancement of the pharmacological and/or cosmetic effect. An example of topical formulations with such evident requirements is sunscreens, which are intended to be retained at the skin surface for the longest possible period, as well as antiperspirants and deodorants, which are intended to be applied to reduce body odors caused by bacteria and fungi without skin absorption [2]. In this context, cyclodextrins (CDs), a group of safe and biocompatible cyclic oligosaccharide molecules derived from starch, have shown great promise as active ingredient carriers for topical formulation development. CDs have relevant applications in several distinct industries, with a particular highlight in the pharmaceutical and cosmetic industries [3]. Currently, active ingredients with drawbacks such as low solubility, low stability, and high sensitivity can be improved through the development of host-guest inclusion complexes with CDs. The formation of host-guest ICs allows the retainment of guest molecules of different shapes and sizes in the cavities of CDs, protecting them against harmful conditions, and may reduce the systemic absorption of the guest molecules, leading to a decrease in undesired side effects [2]. Overall, the use of CDs holds recognized advantages for skin applications related to the improvement of stability, tolerance, apparent solubility, and organoleptic characteristics of the active ingredients, as well as their controlled-release of ingredients in the skin [4]. With such recognized and versatile functions, CDs are suitable ingredients to be included in topical products by the European Commission [5] and are responsible for the use of more than 30 types of CDs in cosmetic and pharmaceutical formulations already marketed [6].

Topical and transdermal applications of CDs include not only the use of host-guest inclusion complexes arising from their complexation with active ingredients such as dexamethasone and silymarin [7] but also the use of free CDs to retain sebum or odor molecules, as occurs in shampoos and deodorants formulations [8].

For the last two decades, the use of CDs as an encapsulation strategy for dermopharmaceutical, cosmetic, and even cosmeceutical products has been notorious [4]. CDs present a great margin of safety in all skin applications, meaning that they can be employed to optimize transdermal active ingredient delivery for the treatment of local and systemic disorders, as well as to upgrade cosmetic formulations [9,10], like masking unpleasant odors. For example, in sun lotions, CDs can shield and stabilize active ingredients against degradation from light, and in fragranced goods, CDs can be used to stabilize aroma compounds and stimulate long-lasting fragrance effects [11,12].

In addition to dermopharmaceutical and cosmetic applications, CDs are an advantageous way of carrying and delivering active ingredients endowed with both cosmetic and therapeutic effects, impacting skin health and beauty, known as “cosmeceuticals” [13].

The current evidence clearly emphasizes the skillfulness and potential of CDs as active ingredient carriers in the optimization of dermatological formulations, including dermopharmaceutical and cosmetic formulations. Thereby, in this review, the formulations based on CDs in dermatological research and industry areas are described. First, the description of the applications of CDs in dermopharmaceutical formulations, targeting the most prevalent skin diseases, including psoriasis, acne, wound healing, dermatitis, microbial skin diseases, onychomycosis, and skin cancer, are discussed. Second, the contribution of CDs as excipients and ingredients in cosmetic formulations, including anti-aging skin care, sunscreens, deodorants and antiperspirants, shampoos, and fragrances formulations, is addressed. This review is intended to cover the advances in the various and beneficial features of CDs toward skin delivery of active ingredients, detailing information about its structure, properties, the resulting host-guest inclusion complexes, their advantages; gathering the most relevant reports and data related to their application in dermopharmaceutical and cosmetic formulations; referring also cosmetics presently available on the market, and last, the toxicological aspects and the current regulatory framework associated with these products will be discussed.

2. Cyclodextrins: structure, properties, and host-guest inclusion complexes

CDs are cyclic oligosaccharides characterized by a hydrophobic cavity capable of accommodating hydrophobic molecules *via* host-guest inclusion complexes [14]. These complexes are formed through hydrogen bonds, Van der Waals interactions, or hydrophobic interactions between the guest molecule and the host, which increases the chemical stability of the molecule, particularly by protecting against hydrolysis, oxidation, dehydration, and photodecomposition [15]. The structure of CDs consists of a hydrophobic interior cavity, due to the presence of a cone truncated-like structure composed of glycosidic oxygen atoms and carbon-hydrogen groups, and an exterior hydrophilic surface, owing to the presence of primary and secondary functional hydroxyl groups [16] oriented to the exterior, with the primary hydroxyl groups at the narrow side and the secondary groups at the wider side (see Fig. 1). This structure allows the protection of hydrophobic active ingredients as well as their transport to the target site [17,18].

CDs are classified according to the number of glucopyranose units present in their structure. The most frequently applied natural CDs are α-cyclodextrin (α-CD), β-cyclodextrin (β-CD), and γ-cyclodextrin (γ-CD), depending on the number (six, seven, or eight, respectively) of glucopyranose units. Regardless of being cyclic oligosaccharides, the bonds between glucopyranose units of CDs show free rotation, and the units are not cylindrical [6]. Additionally, the number of glucose units present in the structure influences the solubility of CDs. The extremely low water solubility of β-CD, when compared to α-CD or γ-CD, is due to the high energy hydrogen-bond network between the C2 and C3 hydroxyl groups [19]. γ-CD depicts more favorable properties in terms of the size of its internal cavity, water solubility, and bioavailability in comparison to α-CD and β-CD, making γ-CD more desirable for applications in the pharmaceutical field. Nevertheless, γ-CD shows a low yield and high price, making β-CD the most commonly used natural CD, followed by α-CD [20], in the pharmaceutical industry. Nonetheless, β-CD and α-CD still demonstrate difficulties, namely, the enhancement of the apparent molecule solubility, reduction of toxicity, and the capability to include guest molecules into their cavity [14]. Thus, research has led to the development of chemically modified CDs produced by amination, etherification, and esterification to improve these mapped features. To do so, methyl, ethyl, hydroxyethyl, carboxymethyl, hydroxypropyl, and functional groups are added to the natural CDs to manufacture chemically modified CDs with different solubilities [21]. Among the three natural CDs, β-CD inclusion complex provides the most stabilizing effect

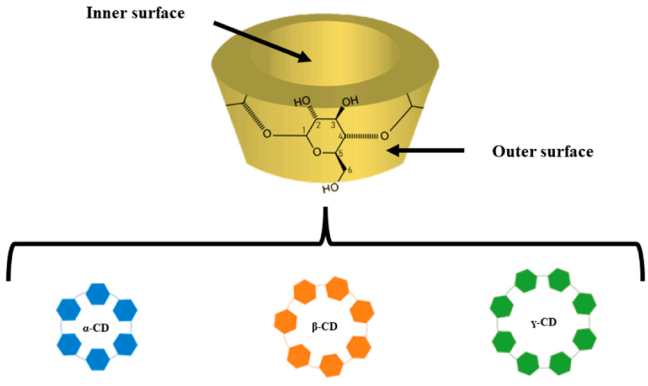


Fig. 1. Illustration of the chemical structure of CDs, with an hydrophilic exterior and hydrophobic interior. According to their number of glucopyranose units (six, seven or eight) can be α-CD, β-CD, and γ-CD respectively, **Abbreviations: α-CD -** α-cyclodextrin; **β-CD -** β-cyclodextrin; **ɣ-CD -** ɣ-cyclodextrin.

[15,19]. Furthermore, many studies have shown that CDs have the capability of stabilizing liquid formulations containing proteins due to the binding between hydrophobic residues of proteins with the surface of CDs, resulting in the inhibition of protein aggregation and providing significant physical stability [22].

Currently, several dermopharmaceutical and cosmetic products contain CDs in their composition to improve their formulation and performance, considering the noteworthy assets that their application provides, which will be detailed further ahead.

3. Dermatological applications of cyclodextrins

The delivery of active compounds through the skin presents advantages as an outstanding route of administration, not only for local treatment of skin diseases but also for the systemic delivery of active ingredients [23], owing to its large surface area and accessibility [24].

Considering its normal state of function, the skin constitutes a very efficient barrier that challenges the topical and transdermal administration of active ingredients [25,26]. Additionally to its protective function against chemical agents, pathogens, and external damage, the skin possesses a thermoregulatory function as a barrier to the loss of fluids and supports the regulation of body temperature, an endocrine function by the secretion of hormones, cytokines, and other molecules, and an excretory function by the release of substances throughout its pores and glands [27,28]. Moreover, this organ can be segmented into three main layers: The epidermis – containing the most superficial layer of the skin, the *stratum corneum* (SC), which comprises dead keratinocytes with high keratin content, corneocytes enveloped by a lipid-enriched matrix and is above the viable keratinocyte strata of the epidermis; dermis – composed of fibroblasts and connective tissue, and hypodermis – where sweat and sebaceous glands, hair follicles, vessels, and nerve fibers are located [29]. Regarding skin structure, there are three diffusion pathways for the permeation of active compounds: the intracellular route across the SC, the intercellular route through the gaps of the SC, and the transfollicular route through hair follicles and connected sweat and sebaceous glands. However, the intercellular route is considered the major route for the permeation of molecules through the skin [30].

SC is the layer that mostly contributes to avoiding the passage of most molecules into the intact skin [31]. SC serves as a rate limit for the entry of lipophilic molecules and acts as a barrier to hydrophilic and large molecules. Thus, characteristics such as polarity, molecular weight, type and composition of the formulation, and apparent solubility of the molecules in oil and water significantly affect the permeation of molecules. In general, for skin delivery, the considered molecular weight is 500 Da; nevertheless, for topical administration, molecules with a higher molecular weight (800 Da) were applied [32,33]. Another interesting challenge to consider is finding the right balance between enhancing the passage of active ingredients through the skin and, at the same time, certifying sufficient retention to maintain therapeutic concentrations [23].

Furthermore, concerning skin delivery, it is important to note that there is a difference between topical and transdermal delivery: topical delivery is primarily intended for a local effect, whereas transdermal delivery is aimed for a systemic effect with the skin merely being the entry gateway into the body for active ingredients [24,31].

Nanodelivery systems are a smart and multifunctional approach to the skin delivery of active ingredients [29]. Several nanoparticles (NPs) have been engineered and evaluated for applications in dermatology, such as permeation improvement of conventional molecules, delivery of novel active ingredients, or targeted delivery to specific cell populations. These systems include lipid NPs [34], polymeric NPs [35], nanoemulsions [36], metallic NPs [37], and vesicular systems [38], among others [32]. Nevertheless, various parameters, such as size or shape, should be considered for the application of these structures. It should also be noted that the penetration of free nanocarriers does not guarantee the same effect for matching loaded systems, as relevant particle properties such as hydrophilicity/hydrophobicity, size, and others can be altered [23].

From the vast research involving NPs in the past two decades, there is no doubt that nanodelivery systems have the potential to efficiently deliver active ingredients across the skin barrier [30]. Thus, in skin care, it has gained relevance, especially for the innovation of treatments for immunomodulatory skin diseases and modernization in the cosmetics industry. As nanomaterials represent a large group of variable physical and chemical substances, specific toxicological studies are needed for each product before commercialization. Thus, as nanotechnology develops, there will be a tendency toward the development of more nanomaterials, with the probability of a deeper *in vitro* and *in vivo* understanding and the emergence of new treatments for different skin diseases [24,39].

CDs play a substantial role in the optimization of topical and transdermal delivery. Although CDs are generally considered too large to penetrate the SC, they can be used as skin permeation enhancers, as they are capable of enhancing the apparent solubility of active ingredients and creating an *in situ* reservoir effect [40].

The application of CDs as skin carriers improves the stability of the active ingredients in the formulation and at the target site, alleviates active ingredient-induced local irritation, and enables a controlled release pattern [41]. Besides, methylated CDs may modify the skin barrier by interacting with skin phospholipids or cholesterol, leading to increased active ingredient permeation. Although methylated CDs may have good performance in topical and transdermal delivery, it should be noted that skin irritancy and damage are often related [4].

3.1. Dermopharmaceutical formulations with cyclodextrins

The ability of CDs to form host-guest inclusion complexes allows the improvement of several properties of the complexed active ingredients (drugs, cosmetics, or cosmeceutical-related molecules).

Low water solubility and a low dissolution rate of active ingredients are crucial factors that restrict their applications, affecting the development of dermopharmaceutical and cosmetic formulations. Although several techniques, like iontophoresis and electroporation [42], can be used to increase the apparent solubility of active ingredients and improve their bioavailability, these techniques show several drawbacks, such as low loading capacity and the need for high doses of active ingredients, calling for the development of new alternatives. In this context, CDs have emerged as an exceptional alternative for skin delivery of active ingredients. This is accomplished by the alteration of the partition coefficient, contributing to the respective increment of the apparent solubility and, consequently, to the improved permeation of the active ingredients. In fact, instead of disturbance and direct interaction with the components of the SC, CDs impact solubilization and create a barrier between the active ingredient and the skin, decreasing skin irritation [43] and thus leading to an increase in the active ingredient concentration in the skin layers. One example is the flavonoid silymarin, which is extracted from the seeds of milk thistle (*Silybum marianum*) [44]. Due to its lower solubility and bioavailability, complexation with CDs improves these silymarin properties, which enhances its therapeutic application. The silymarin-sulfobutylether-β-CDs (SBE-β-CDs) inclusion complexes are especially useful in decreasing facial redness in rosacea-prone skin, preventing skin aging, increasing collagen production, and reducing oxidative stress in skin cells [7,45]. Similarly, we have the example of ultraviolet (UV) filters (*e.g.*, ethylhexylmethoxycinnamate). These, for enhanced efficiency, must remain stable on the surface of the skin over the UV exposure time. The complexation of UV filters with CDs is mainly used to surpass the photostability issue and to avoid their penetration into the skin [46].

The stability and shelf life of several active ingredients may be improved by CD use, making these very convenient and versatile carriers for skin formulation development [15,47]. Numerous investigations

support the protective effect that CDs exhibit over several natural compounds, with terpenes, once again, being among the most reported compounds. These compounds are highly sensitive to light and oxidation, and when not protected, the formation of p-cymene is likely to occur, which can cause skin irritation. β-CDs have been used for the complexation of these molecules, conserving the properties of the essential oil [48]. Another reported oil is the seed oil from *Celastrus paniculatus*, which is composed of oleic acid, palmitic acid, linoleic acid, and stearic acid. These compounds together are commonly applied in massages with attributed benefits for muscle pain, paralysis, and joint stiffness from arthritis. Although it is used topically frequently, the oil suffers oxidation during storage and processing, affecting its quality, stability, and safety. 2-Hydroxypropyl-β-CD (HP-β-CD) is used for oil complexation, increasing its stability by the protection conferred against oxidation [49]. Tretinoin, an active ingredient utilized for the treatment of psoriasis, acne vulgaris, and cutaneous neoplasms, along with signs of skin aging, namely, small wrinkles and dark spots, shows low photostability and is prone to degradation when exposed to UV and visible radiation. In fact, after being topically applied to the skin and exposed to light, tretinoin degrades approximately 40.0% after 4 h. The instability of tretinoin can be significantly reduced by its inclusion in the cavity of β-CD, which offers protection against UV and fluorescent light, decreasing its photodegradation [15].

Inclusion complexes of volatile organic compounds have shown increased stability and decreased rate of evaporation, thus leading to the improvement of their organoleptic characteristics. Aroma compounds are usually added to products such as perfumes and deodorants, among other products of personal care; however, some of these compounds can be toxic and not biodegradable [50]. Additionally, most aroma compounds are poorly water-soluble, requiring the presence of surfactants to enhance their physicochemical characteristics. However, surfactants can limit their fragrance effect and lead to formulation problems, such as turbidity (not desirable for transparent formulations), sensitization to light, and skin irritation. Thereby, the host-guest inclusion complexes formed between aroma compounds and CDs can reduce their evaporation to produce a long-lasting fragrance effect without toxicological concerns [51].

Interestingly, in addition to the use of host-guest inclusion complexes for the improvement of organoleptic characteristics, free CDs are also frequently applied for the removal of unpleasant aromas by retaining the volatile malodors molecules in their cavity and preventing their volatilization through the formation of nonvolatile host-guest inclusion complexes. CDs are thus used in numerous formulations to eliminate mouth, body, and hair malodors [52].

The formation of host-guest inclusion complexes also contributes to the increase in the bioavailability of active ingredients through the modulation of their cutaneous permeation [22]. The differences between CDs and other permeation enhancers reside in the method of interaction with the skin. Contrary to CDs, chemical permeation enhancers increase the permeation of the active ingredients by decreasing the barrier properties of the skin through the alteration of their intracellular lipid matrix [40].

The improvement of active ingredient apparent solubility and stability in dermatological formulations conferred by CDs, in addition to the contribution to the modulation of the permeability of active ingredients through the skin, may also decrease the possible topical irritation at the administration site [47]. These biocompatible carriers may be responsible for a reduction of the inherent toxicity, modification of metabolism, and increase of active ingredient bioavailability, which, together, may result in the tolerance improvement of active ingredients [53]. Several active ingredients, when applied to the skin, promote local irritancy characterized by a burning sensation, erythema, or desquamation, leading to the discontinuation of treatment by the patients. Host-guest inclusion complex formation by using CDs offers a protective environment to the active ingredient, leading to a decrease in topical irritation reactions and an increase in efficiency, resulting in a superior active ingredient concentration that is available at the administration site. The incorporation of CDs into dermatological formulations may constitute, thereby, a valuable alternative to reduce side effects and increase therapy clinical compliance [54].

Many active ingredients used to treat skin diseases show problems related to low permeation through the skin, and several approaches have been undertaken to overcome this obstacle. These methods can be mainly divided into either passive or active, where the former includes strategies that try to improve skin delivery by adjusting the formulation properties, and the latter tries to augment cutaneous permeation by altering the barrier nature of SC [55]. Several studies have shown that active delivery methods, such as iontophoresis, electroporation, and ultrasound, can increase cutaneous permeation and penetration, which consequently improves the delivery of certain active ingredients [42]. According to other studies, permeation enhancers, *e.g.*, alcohols and fatty acids are an alternative to decrease SC barrier properties; however, 99.5% of permeation enhancers must be excluded because of their irritancy to the skin or their low potency. The use of fatty acids and alcohols to decrease SC barrier properties shows some disadvantages when compared to CDs. CDs can form biocompatible host-guest inclusion complexes, reducing toxic side effects, instead of interacting with the components of SC and modifying their organization [43]. The advantages granted by CDs allow their application in the resolution of many formulation problems in dermopharmaceutical products. Host-guest inclusion complexes with notable active ingredients have been added to formulations to treat or attenuate skin-related diseases, including psoriasis, acne, dermatitis, microbial skin diseases, wound healing, onychomycosis, and skin cancer, which will be discussed separately below. Therefore, at the end of this section, Table 1 gives examples of active ingredient delivery systems and their main characteristics produced for these purposes.

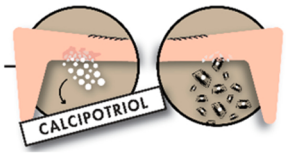
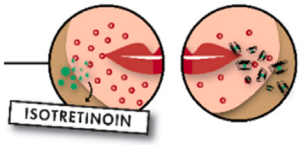
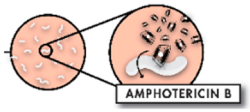
3.1.1. Psoriasis

Psoriasis is a frequent genetic chronic disease that affects the normal function of the skin, joints, and scalp [56]. It is characterized by excessive growth and abnormal differentiation of keratinocytes and amplified dermal vascularity [57]. Psoriasis affects approximately 3.0% of the population worldwide and can cause a high level of morbidity due to pain, itching, cosmetic impairments, and depression that can lead to suicidal thoughts, which current treatment is based on controlling the inflammatory process [58,59].

Vitamin D analogs are one of the most commonly used agents for psoriasis treatment. These include calcipotriol, a synthetic analog that reduces the proliferation and differentiation of keratinocytes. Although calcipotriol is generally used for the treatment of psoriasis, it is a water-insoluble active ingredient and can induce skin irritation. To overcome these constraints, calcipotriol-SBE-β-CD inclusion complexes were developed and incorporated into an emulgel base. This formulation base was chosen since emulgels are more spreadable for psoriatic lesions than other creams or ointment formulations. The results demonstrated that this inclusion complex was able to reduce skin irritation and showed increased apparent solubility (approximately 35.2-fold) and dissolution in comparison to free calcipotriol [60].

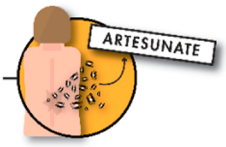
It is believed that the augmented production of reactive oxygen species (ROS) can stimulate the pathogenesis of psoriasis. Thus, antioxidative strategies may act as useful options for the treatment of psoriasis through the decrease in ROS levels in cells. Investigators decided to test Ceria NPs (CeNPs), as they are known to have enormous antioxidant potential regarding natural antioxidant enzymes. In their study, Wu, 2020 [59] introduced β-CDs on the surface of CeNPs to increase their biocompatibility, apparent water solubility, and antioxidant capacity and then investigated the encapsulation efficiency (EE) and antipsoriasis effect of the NPs. The lipophilic active ingredient dithranol (DIT), which is used in conventional psoriasis treatment, was loaded in the β-CDs *via* host-guest interactions (Fig. 1 (A)). A carbopol gel was chosen to incorporate the DIT-β-CDs-CeO_2 NPs, and these NPs showed a

Table 1
Characteristics of host-guest inclusion complexes regarding dermopharmaceutical applications of cyclodextrins (CDs) in the treatment of skin diseases.

Skin disease	Active ingredient	CD (s)	Relevant outcomes	Reference
Psoriasis 	Calcipotriol	SBE-β-CD (Captisol®)	EE: 96.6 ± 2.12% (1:1 ratio) ↑ Apparent active ingredient solubility (approximately 35.2-fold)[1] ↓ Skin irritation[1]	[60]
	DIT	β-CD	EE: 94.7% ↓ Erythema[2] ↓ Skin thickness[2] ↑ ROS scavenging Viability of keratinocytes: no changes	[59]
	BO	β-CD	EE: 93.05 ± 0.28% ↑ Orthokeratosis[3] ↑ Controlled active ingredient release[4]	[61]
Acne 	Retinoic acid	β-CD	↑ Active ingredient stability[1] ↑ Apparent active ingredient solubility[1] ↑ Controlled active ingredient release[5] ↑ Skin tolerance[5] (↓ erythema and irritation)	[2,65]
	Isotretinoin	HP-β-CD	EE: 90.1 ± 8.3% ↑ Active ingredient permeability (approximately 21.0-fold)[1] ↓ Photodegradation: (approximately 1.5- fold)[1]	[66]
	DPS	M-β-CD (Kleptose®)	↑ Apparent active ingredient solubility (approximately 94.1-fold)[1] Antimicrobial activity: no significant differences[6] ↓ Inflammation (approximately 4.5-fold)[6]	[69]
 Dermatitis	Fluocinolone acetonide	β-CD	EE (β-cycloethosomes): 82.49 ± 1.21% ↑ Physical stability[7] ↑ Active ingredient permeability[7]	[74,75]
 Microbial skin diseases	Chlorhexidine	α-CD, β-CD, and HP-β-CD	↑ Antimicrobial activity[1]: Microbial growth (For β-CD): 0.0% for *S.aureus*, 99.7 ± 0.4% for *P.aeruginosa* and 63.5 ± 2.6% for *C. albicans* ↓ Cytotoxicity in eukaryotic cells[1] ↑ Biocompatibility	[80,82]
	Iodine	β-CD	↑ Antimicrobial activity[1]: Microbial growth: 49.6 ± 9.4% for *S.aureus*, 74.3 ± 31.2% for *P.aeruginosa* and 96.7 ± 1.6% for *C. albicans* ↑ Biocompatibility	[82]
	Polihexanide	β-CD	↑ Antimicrobial activity[1]: Microbial growth: 0.0% for *S.aureus*, 18.8 ± 13.6% for *P. aeruginosa* and 0.0% for *C. albicans* ↑ Biocompatibility	[82]
	Amphotericin B	γ-CD	↑ Apparent active ingredient solubility (more than 200.0-fold)[1] ↑ Antifungal activity[1] ↓ Active ingredient self-association[1] ↓ Toxicity[1]	[84,85]
Wound healing 	Insulin	HP-β-CD	↑ Active ingredient stability[1] ↑ Controlled active ingredient release[1] ↓ Active ingredient self-association[1] ↓ Toxicity[1] ↑ Bioavailability[1] ↑ Reepithelization[1] ↑ Angiogenesis[1]	[88]
	Curcumin	HP-γ-CD	↑ Apparent active ingredient solubility[1] ↓ Photodegradation (> to 14 days)[8] ↑ Active ingredient release rate (approximately 5.0-fold)[1] ↑ Bioavailability[1] ↑ Reepithelization[8]	[91]
	Imiquimod	HP-β-CD, carboxymethyl-β-CD, and β-CD	↑ Apparent active ingredient solubility (Carboxymethyl-β-CD, approximately 125.0-fold)[9] ↑ Physical stability (> for β-CD-based nanosponges)[10] ↑ Active ingredient release (> for HP-β-CD, approximately 85.0%)[11] ↑ Active ingredient permeability (> for carboxymethyl-β-CD, approximately 19.0%)[12] ↑ Total skin retention (> for β-CD-based nanosponges)[10]	[93]

(*continued on next page*)

Table 1 (*continued*)

Skin disease	Active ingredient	CD (s)	Relevant outcomes	Reference
Skin cancer	Saikosaponin	HP-β-CD	↑ Apparent active ingredient solubility (for inclusion complex of 1:1 ratio, approximately 350.0-fold; 1:5 ratio, approximately 1074.0-fold; and 1:10 ratio, approximately 906.0-fold)[1] ↑ Apoptosis in HSC-1 cells (inclusion complex of 1:5 ratio)[1]	[103]
	Artesunate	Randomly methylated-β-CD, heptakis (2,6-di-O-methyl)-β-CD, and heptakis (2,3,6-tri-O-methyl)-β-CD	↑ Thermal stability[1] ↑ Anticancer activity[1] ↓ Viability of keratinocytes[1]	[106]

Abbreviations: BO - Babchi oil; **CD -** Cyclodextrin; **DIT -** Dithranol; **DPS -** Dapsone; **EE -** Encapsulation efficiency; **HGF -** Hydrogel film; **HP-β-CD -** 2-Hydroxypropyl-β-cyclodextrin; **HSC-1 cells** - Human cutaneous squamous carcinoma cells; **HP-γ-CD -** Hydroxypropyl-γ-cyclodextrin; **M-β-CD** - Methyl- β-cyclodextrin; **Sac -** Sacran; **SBE-β-CD -** Sulfobutylether-β-cyclodextrin.

[1] Concerning free active ingredient formulation
[2] Concerning the nontreatment control group
[3] BO nanogel concerning blank gel, clobetasol propionate gel, and standard free BO gel
[4] BO nanogel concerning standard free BO gel
[5] Concerning commercial product (without β-CDs)
[6] Concerning commercial product (Aknemycin® 2.0%)
[7] Concerning reference ethosome gel (without β-CDs)
[8] Cur-HP-γ-CDs inclusion complexes in Sac-HGF concerning all other formulations
[9] Concerning imiquimod-HP-β-CD inclusion complexes
[10] Concerning imiquimod-HP-β-CD and imiquimod-carboxymethyl-β-CD inclusion complex
[11] Concerning imiquimod-carboxymethyl-β-CD inclusion complex and β-CD-based nanosponge
[12] Concerning imiquimod-HP-β-CD imiquimod-carboxymethyl-β-CD inclusion complex and β-CD-based nanosponge and β-CD-based nanosponge

DIT EE of 94.7%. Through the MTT assay, no significant alterations in the viability of the tested keratinocyte cell line were observed (Fig. 1 (B)). Using the same method, it was noticed that the β-CDs-CeO_2 NPs are capable of preventing cellular damage triggered by H_2O_2 (Fig. 1 (C)). Utilizing 2',7'-dichlorofluorescein diacetate as a fluorescence probe, the results corroborated the MTT study, as a great reduction in the fluorescent intensity of the H_2O_2-treated cells was observed when previously treated with DIT-β-CDs-CeO_2 NPs, which indicates active intracellular ROS scavenging (Fig. 2 (E)). The DIT-β-CD-CeO_2 NP potential was also assessed *in vivo* in BALB/c mice. The group treated with DIT-β-CDs-CeO_2 NPs presented fewer symptoms of psoriasis (reduced erythema and skin thickness). The histopathology study of the skin samples confirmed this observation (Fig. 2 (F)). Additionally, the spleen/body weight ratio of the DIT-β-CDs-CeO_2 NPs of the treated group was inferior in comparison to the nontreated group (Fig. 2 (D)), which indicates reduced persistent activation of adaptive immunity. This study demonstrates that DIT-β-CDs-CeO_2 NPs have great potential in controlling symptoms and the inflammatory process of psoriasis.

Other investigators [61] incorporated babchi oil (BO), a complex mixture of phytotherapeutic molecules with antipsoriasis effects, in a β-CD-based nanostructured carbopol 934 gel (BO nanogel, with 5.0% w/v of BO) and investigated its potential in a mouse tail psoriasis model. Two weeks of treatment with the BO nanogel resulted in marked *in vivo* histological variations in the tail skin sections. Additionally, with an EE of 93.05 ± 0.28%, antipsoriasis effects were assessed as % orthokeratosis (percentage of the normal pattern of keratinization), and the BO nanogel demonstrated a higher percentage (73.66 ± 2.20%) than the blank gel (47.28 ± 1.32%), clobetasol propionate gel (0.05% w/v; 58.11 ± 1.01%), and standard free BO gel (5.0% w/v; 60.59 ± 1.58%). Likewise, the BO nanogel showed identical antipsoriasis effects to standard free BO gel (10.0% w/v), indicating that the inclusion of BO in β-CDs would lead to a dose cut by 50.0% compared to standard free BO gel (5.0% w/v). *In vitro* studies demonstrated the enhanced performance of inclusion complexes of β-CDs to provide controlled release over an extended time, as 99.91 ± 0.52% BO was released from the standard free BO gel within 4 h, and 34.21 ± 0.62% BO was released from the BO nanogel in 24 h. The enhanced activity of the BO nanogel (5.0% w/v) can be explained by the increased penetration of BO loaded in CDs and by the optimized controlled release pattern. There was no sign of skin rash or redness after the application of the BO nanogel.

3.1.2. Acne

Acne vulgaris is a skin condition that can produce severe inflammatory lesions on the face, back, and chest due to numerous sebaceous follicles producing an elevated rate of sebum, leading to sebum accumulation and *Propionibacterium acnes* colonization on the skin surface [62]. Most of the population, at some point in their lifetime, suffers from this condition, usually due to hormonal changes that could scar the skin and cause emotional distress in individuals [63]. Hence, the first line of therapy for acne patients is oral antibiotic therapy along with diet management [64].

Retinoic acid is being used in the treatment of acne vulgaris due to its noteworthy keratolytic activity; however, it can leave the skin with erythema and xerosis. The efficacy of retinoic acid-β-CD inclusion complex was investigated in subjects with acne, and the results showed that the overall percentage of retinoic acid topical side effects was approximately 92.9% in subjects who used the commercial product (without CDs) compared to 27.3% in subjects using the hydrogel containing the retinoic acid-β-CD inclusion complex, and no topical side effects were observed in the moisturizing cream formulation with the retinoic acid-β-CD inclusion complex; thus, both formulations presented higher skin tolerance. These results were associated with high solubility and stability and a controlled release of the active ingredient of the β-CDs. Furthermore, the moisturizer cream containing the retinoic acid-β-CD inclusion complex offered the greatest hydration and lower excessive sebum [65].

Isotretinoin (13-cis-retinoic acid) is included in the retinoid group and presents several drawbacks, such as skin irritation, very low water solubility, and susceptibility to photodegradation. To overcome these limitations, host-guest inclusion complexes with HP-β-CDs have been applied to raise the stability and apparent water solubility of isotretinoin and to decrease its photodegradation. Kaur, 2010 [66] conducted a study to investigate the potential of a liposomal formulation containing isotretinoin-HP-β-CD inclusion complexes, with an EE of approximately 90.1 ± 8.3%. To evaluate the penetration capacity of this formulation and deposit in the deeper layer of the skin, a skin retention study was conducted, and the quantity of isotretinoin deposited was 21.0-fold superior to the liposomes of isotretinoin-HP-β-CD inclusion complexes

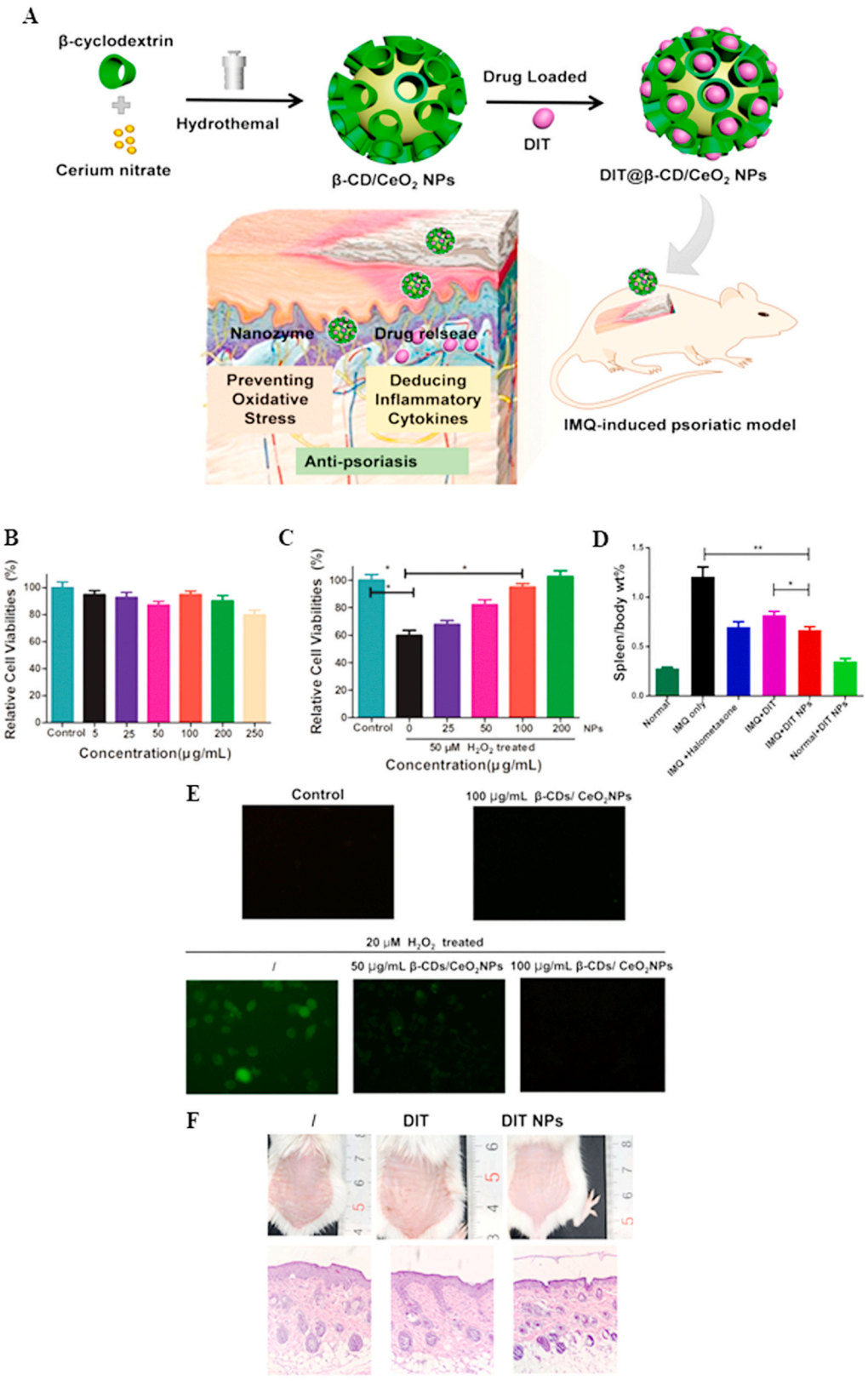


Fig. 2. (A) Schematic representation of the study global strategy, from the construction of the β-CDs-CeO_2 NPs, loaded with DIT until their application, *in vivo*, for the observation of the antipsoriatic effect on IMQ-induced psoriatic models. Note: DIT-β-CDs-CeO_2 NPs represent DIT@ β-CDs/CeO_2 NPs. (B) Viabilities of HaCaT cells treated with several doses of DIT-β-CDs/CeO_2 NPs. (C) Viabilities of HaCaT cells to test the protective effect of DIT-β-CDs/CeO_2 NPs at various concentrations incubated with 50 μM H_2O_2. (D) The ratio of the spleen to the body (weight %) of IMQ and remaining treatments in distinct groups. **(E)** Fluorescence images of HaCaT cells after several treatments with only H_2O_2 (20 μM), only β-CDs/CeO_2 NPs (100 μg/mL), H_2O_2 and β-CDs/CeO_2 NPs marked with dichloro-dihydro-fluorescein diacetate. **(F)** IMQ-induced psoriatic models on the dorsal skin of mice. Pictures from the mice and histological images were obtained to spot the

differences in the treatments. **Abbreviations: β-CD -** β-cyclodextrin; **Ce -** ceria; **DIT -** dithranol; **IMQ -** imiquimod; **NP -** nanoparticle. Adapted from [59].

concerning free isotretinoin. Regarding photodegradation, after 1 h under UV light exposure, free isotretinoin exhibited 52.2% degradation; however, the isotretinoin liposomal formulation and isotretinoin-CD inclusion complex formulation demonstrated only 11.4% and 7.8% degradation, respectively. As expected, isotretinoin-HP-β-CD inclusion complexes showed a superior photoprotective effect [67,68] (approximately 1.5-fold) than the free isotretinoin liposomal formulation. These results can be explained by the higher EE of isotretinoin-HP-β-CD inclusion complexes in comparison to the free isotretinoin liposomal formulation (81.2 ± 7.3%) and the barrier effect provided by the CD cavity. Thus, this study demonstrates the potential of CDs with isotretinoin, which is very useful for its topical delivery [66].

Owing to its antimicrobial and anti-inflammatory activities, dapsone (DPS) has demonstrated various potential applications in various dermatological diseases. However, its clinical use is restricted due to its poor water solubility, which hampers the design of DPS formulations with suitable bioavailability. In this investigation, Shamma, 2019 [69] prepared DPS-CD inclusion complexes with methyl-β-CD (M-β-CD, Kleptose®) and incorporated them into a thermosensitive Pluronic F127 gel according to Fig. 3 (B). Phase solubility studies led to the conclusion that the apparent water solubility of DPS was greatly improved (approximately 94.13-fold) in the presence of M-β-CD (Fig. 3 (A)). Additionally, the *in vivo* efficacy of the prepared gel was addressed and compared to Erythromycin 2.0% (Aknemycin® 2.0%), which is the standard acne treatment (Fig. 3 (E) (F) and (G)). The DPS-M-β-CD inclusion complex gel formulation was directly applied to the skin on *Propionibacterium acnes* mice infected ears, and the results were compared to those of the Aknemycin®-treated group. Antimicrobial activity was assessed, and no significant differences in the reduction in bacterial load were found for the DPS gel- and Aknemycin®-treated groups; however, their antibacterial effect was higher (100.0-fold) than that of the untreated control group (Fig. 3 (C)). In addition, the *in vivo* studies confirmed superior anti-inflammatory activity in the DPS gel-treated group, which demonstrated more than a 66.0% reduction of inflammation in comparison to the Aknemycin®-treated group (14.7%) (Fig. 3 (D)). Such evidence asserts the importance of developing appropriate skin active ingredient carriers with CDs to optimize DPS physicochemical and biological properties and hence its topical application in the gel.

3.1.3. Dermatitis

The word “dermatitis” is a compound word that combines the root word “derma”, which means skin, with the suffix “itis”, which means inflammation. Although there are different types of dermatitis, almost all types are characterized by the same symptoms that occur in several areas of the body. These symptoms arise from skin inflammation, which can produce pruritus and vesicles, endorsing an itchy and uncomfortable feel [70,71]. Atopic dermatitis is one of the most common multiple forms of dermatitis. It is described as hyperexpression of proinflammatory cytokines such as interleukin-4, interleukin-13, and interleukin-25 [72]. This skin illness is characterized by loss of water from the SC ending in dry skin and numerous dysfunctions at the epidermal level, which results in a greater vulnerability to environmental alterations in the skin. Although children under five years old are the most vulnerable group to suffering from dermatitis, the majority of patients experience remission before adolescence that occurs spontaneously, particularly in industrialized countries [73]. Depending on the severity of the disease, the treatment of atopic dermatitis is still challenging, with a major focus on attenuating the symptoms and preventing acute exacerbations, as well as improving the appearance of the skin to increase the quality of life of patients. Although the choice of therapy mainly includes topical corticosteroids, their chronic use is not a desirable option, particularly in young children, due to serious adverse effects, like atrophy and skin infections. Research has been performed to improve some side effects and the solubility of several active ingredients used in formulations to treat atopic dermatitis [71].

The topical corticosteroid fluocinolone acetonide is used for the treatment of atopic dermatitis and is commercially available as a cream and ointment. Nevertheless, local side effects, low permeability in the epidermis of atopic skin, unwanted stickiness, and uncomfortable feelings after application of these formulations are problems that affect the success of these formulations. Ethosomes are lipid nanodelivery systems with great potential for topical skin delivery since they exhibit higher SC compatibility and permeability (see Fig. 4) and elevated EE [74]. β-cycloethosomes, a nanodelivery system comprising β-CDs and ethosomes, were loaded in carbomer gel and then studied for EE, vesicle dimensions and *in vitro* permeability to deliver fluocinolone acetonide to the skin [75]. In a preliminary investigation, 20 formulations were considered, and for topical skin delivery, the best formulation for further studies comprised 40.0% (w/v) ethanol and 1.2% (w/v) β-CD. β-cycloethosomes showed elevated EE (82.49 ± 1.21%) regarding reference ethosomes without β-CD (74.09 ± 1.04%), a suitable vesicle size (228 ± 1.23 nm), a maximum superior *in vitro* permeability (83.22 ± 0.72%) compared to reference ethosomes without β-CD (66.55 ± 1.02%), and higher physical stability, which depicts β-CD as an excellent skin active ingredient carrier.

Moreover, other authors have been working with further poorly soluble active molecules to improve their apparent solubility and biological activity with CDs for the treatment of dermatitis [76–78].

3.1.4. Microbial skin diseases

Ubiquitous, pathogenic, and multiresistant bacteria are widely present in the human body. Microbial skin diseases can be either constrained at a region or to all the body surface and can vary in severity similarly, from nondangerous to lethal. An important application of antimicrobial agents, both in pharmaceutical and cosmetic areas, is to hamper the formation of biofilms. Therefore, the development of biofilms by inhibition of bacterial adhesion and proliferation and modifications of surfaces with an antimicrobial agent combined with a surface coating is being designed. These modifications include antibiotics, antiseptics, and enzymes that are used to prevent the formation of biofilms. The elimination of biofilms requires high concentrations of antimicrobial agents, although, with the high level of antibiotic resistance and nosocomial infections found worldwide, alternatives should be sought [79].

For example, chlorhexidine, an antiseptic that is effective against Gram-positive and Gram-negative bacterial strains, functions as a bactericidal and bacteriostatic agent causing bacterial membrane interruption [79] but has the disadvantage that it can be toxic to mammalian cells, with serious cytotoxic effects in osteoblasts, chondrocytes, and fibroblasts. Teixeira, 2015 [80] investigated the antimicrobial activity - through the determination of the minimal inhibitory concentration (MIC) against representative microorganisms and by the sterol quantification method - and the cellular cytotoxicity of free chlorhexidine and chlorhexidine complexed with α-CDs, β-CDs, and HP-β-CDs - through the neutral red assay. For antimicrobial activity, the results showed that chlorhexidine-CD inclusion complexes of HP-β-CD were more potent against Gram-positive bacteria, α-CD toward *C. albicans*, and β-CD against Gram-negative bacteria. In addition, in the sterol quantification method, HP-β-CD and β-CD inclusion complexes exhibited a lower ability to extract ergosterol than α-CD inclusion complexes; therefore, α-CD inclusion complexes are likely to induce toxic effects. Additionally, in the cell viability assay and among the CDs evaluated, chlorhexidine-HP-β-CD inclusion complexes exhibited higher

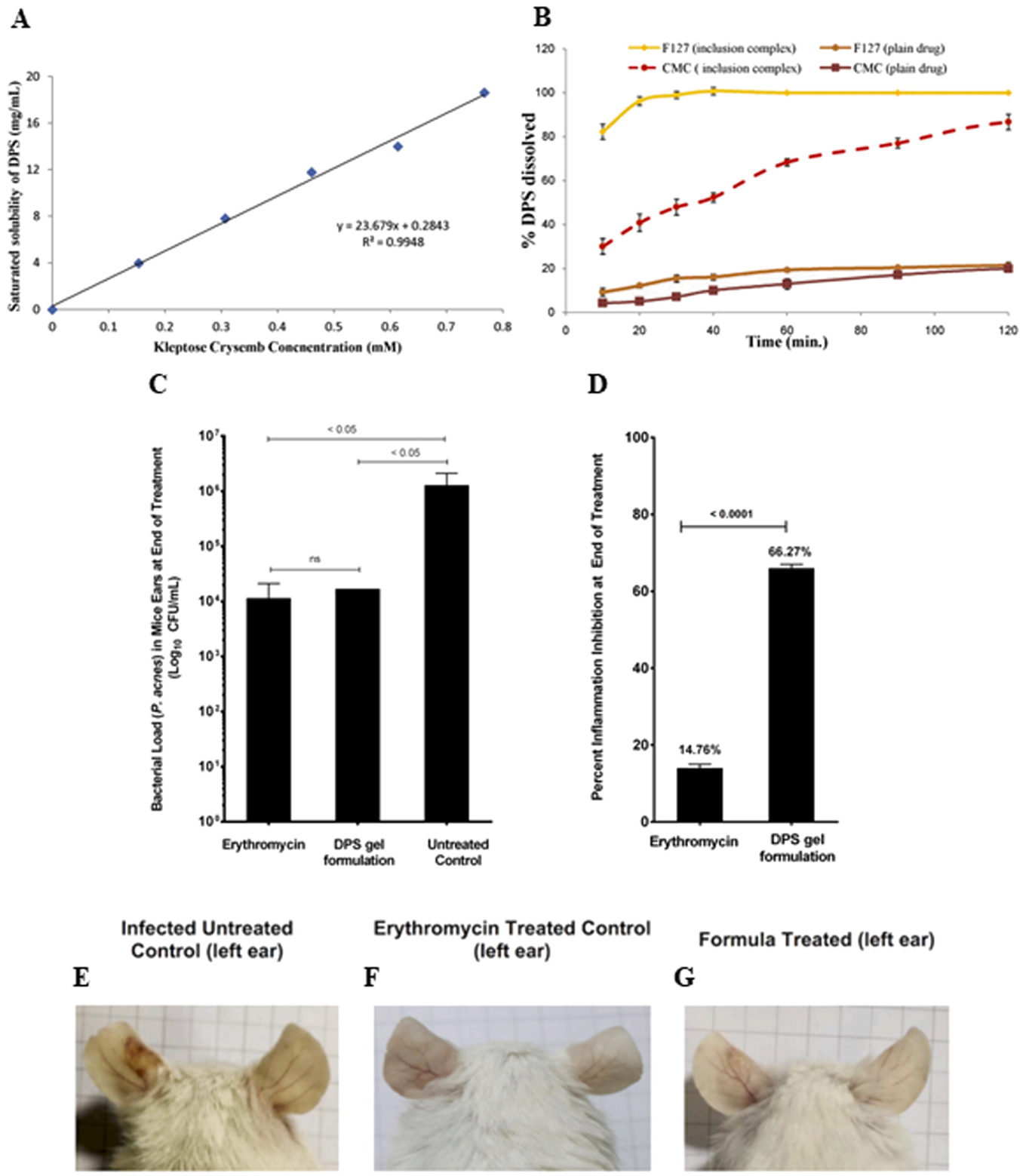


Fig. 3. (A) Effect of Kleptose® Crysemb on DPS solubility. (B) The DPS - loaded gels release profiles. (C) *P. acnes* mice infected ears were evaluated, and the DPS gel and Aknemycin®-treated group showed a great reduction in the bacterial load considering the untreated control. (D) The anti-inflammatory effect of the DPS-M-β-CD inclusion complex gel corresponds to 66.27% percent inflammation inhibition compared to erythromycin with 14.76%. *In vivo* evaluation of anti-inflammatory and antimicrobial effects of DPS-M-β-CD inclusion complex gel in comparison to the effects caused by erythromycin (Aknemycin®): (E) Infected untreated control ears, where the left ear displays contact dermatitis features. (F) Erythromycin-treated mice ear exhibited enhancement compared with the untreated control group, with reduced inflammation and a nearly normal appearance of ear tissue. (G) DPS gel-treated mice ears showed regular ear aspect as in **(F)**. Adapted from [69], ***Abbreviations: CFU*** *- colony forming unit;* ***CMC*** *- carboxymethyl cellulose sodium;* ***DPS*** *- dapsone;* ***M-β-CD*** *- methyl-β-cyclodextrin.*

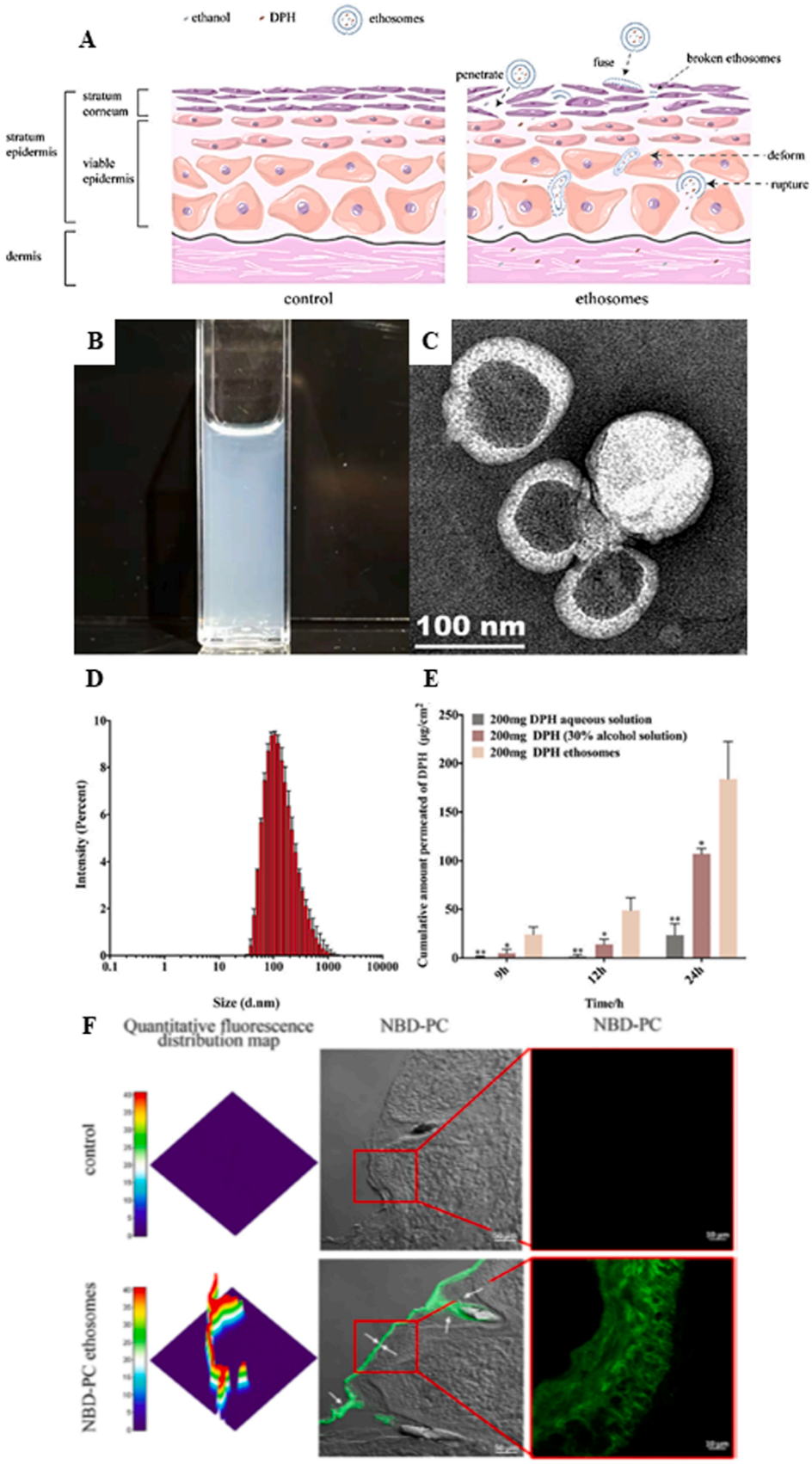


Fig. 4. (A) Scheme of ethosomes transdermal performance. (B and C) Aspect and transmission electron microscope images of ethosomes. (D) Diagram regarding size distribution of ethosomes. (E) Graphic concerning the transdermal effect of several donepezil hydrochloride preparations. (F) Confocal laser scanning microscopy pictures of pig skin samples from the skin penetration assay: distribution of NBD-PC labeled ethosomes in the skin after treatment for 24 h. Adapted from [74], ***Abbreviations:*** ***DPH*** *- donepezil hydrochloride;* ***NBD-PC*** *- 1-palmitoyl-2-{12-[(7-nitro-2–1,3-benzoxadiazol-4-yl)amino] dodecanoyl}-sn-glycero-3-phosphocholine.*

cytotoxicity against Caco-2 cells, which supports anticancer activity and good biocompatibility. However, in general, the chlorhexidine-CD inclusion complexes induced inferior cytotoxicity against fibroblasts, osteoblasts, and Caco-2 cells, regarding free chlorhexidine. Together, these data imply that CDs can be a promising tool to improve the activity of chlorhexidine, *i.e.*, low cytotoxicity and high efficacy at lower concentrations.

Inside the various applications of textile materials, which can be made from a natural or synthetic source, their use in the medical field stands out. Several applications include wound dressing, hygienic and personal care products, hospital clothes, sutures, and others. Over the years, developments in tissue engineering and nanotechnology have produced functionalized textiles with better biocompatibility [81]. To reduce or prevent open wound microbial contamination, functionalized medical textiles constitute an interesting option; then, antiseptic agents such as chlorhexidine diacetate, iodine, and polyhexanide β-CD inclusion complexes were evaluated for their antimicrobial activity and cytocompatibility in medical textiles. The results proved notable efficacy against Gram-negative and Gram-positive bacteria for all antiseptic-CD inclusion complexes, except for the inclusion complex of chlorhexidine, which showed no activity against *Pseudomonas aeruginosa*. Likewise, chlorhexidine diacetate and polyhexanide β-CD inclusion complexes were the most efficient for the fungus *Candida albicans*. Cytocompatibility was verified by the ApoTox-Glo™ triplex assay (exam cytotoxicity, viability, and apoptosis events), and the LC_{50} values considered from the viability curve of the test were 6.70 mg/mL for iodine-β-CD inclusion complexes and 3.85 and 0.32 mg/mL for chlorhexidine diacetate and polyhexanide-β-CD inclusion complexes, respectively, which indicates that the latter possess a higher cytotoxic effect on keratinocytes. Nevertheless, apoptotic keratinocyte death was also observed for iodine-β-CD inclusion complexes, and for chlorhexidine diacetate and polyhexanide β-CD inclusion complexes, no apoptotic events were detected. In conclusion, it can be assumed that the polyhexanide β-CD inclusion complex is an alternative to applying only at low concentrations on medical materials, combining superior antimicrobial activity and reduced cytotoxic effects. Therefore, when incorporated in textiles, these active ingredient carriers may be used in biomedical applications, improving wound healing and inhibiting the proliferation of possible pathogens [82].

Amphotericin B is an antifungal agent that exhibits low solubility and low membrane permeability. Its low solubility results from self-association and the formation of aggregates when above a critical micellar concentration, which increases amphotericin B toxicity [83]. This fact is one of the major limitations in the development of new formulations of amphotericin B. To avoid these drawbacks, γ-CDs (or derivatives) were used due to their ability to form host-guest inclusion complexes with amphotericin B as an approach to prevent its self-association, avoiding toxicity regarding aggregate forms and increasing its apparent solubility (approximately 200.0-fold), which augments its skin accumulation and thereafter its bioavailability [84]. Moreover, investigators assessed the antifungal *in vitro* activity of two amphotericin B topical formulations against several *Candida* species and *Saccharomyces cerevisiae*, and all the fungal isolates tested were susceptible (halo inhibition greater than 15 mm) to the formulation containing amphotericin B-γ-CD inclusion complexes, in comparison to the reference formulation (without γ-CD), where most of the isolates were classified as intermediate due to a halo inhibition between 10 and 14 mm [85]. Thus, the application of γ-CDs with amphotericin B can be an excellent approach for topical antifungals, since their inclusion complex enhanced their apparent solubility, bioavailability, and antifungal *in vitro* activity.

3.1.5. Wound healing

Wound healing is a physiological process that involves a combination of angiogenesis, inflammation, cell proliferation, and the synthesis of extracellular matrix [86]. Skin lesions can become chronic if the wounds fail to heal properly, with persistent inflammation, insufficient extracellular matrix synthesis, and neovascularization [87], generally connected to medical conditions, such as vascular disease, diabetes, or aging [88]. New products containing active ingredients, such as foams, gauzes, and hydrogels, can be used to maintain favorable environmental conditions, helping the wound heal properly.

The conjugation between CDs and hydrogels is advantageous due to the moist environment provided by the high water content of hydrogels and the capacity of CDs to act as skin carriers and release active ingredients [89]. Although the most well-known biological activity of insulin is the transport of glucose into cells, this macromolecule is a peptide hormone synthesized in the pancreas that has various biological activities, *e.g.*, the healing of skin lesions through the stimulation of the proliferation and migration of keratinocytes. Therefore, the insulin molecular structure must be in the form of a monomer to be able to bind and activate the insulin receptor. However, in dermopharmaceutical formulations, this peptide is found in hexameric form due to the self-aggregation of monomers into dimers and hexamers. To overcome this issue, Besson, 2017 [88] complexed insulin with HP-β-CD to reduce its capacity for self-aggregation, enhance insulin stability and increase its absorption rate. Then, the wound healing activity of the insulin-HP-β-CD inclusion complexes incorporated in the gel was assessed *in vitro* and *in vivo*. The studies showed that insulin-HP-β-CD inclusion complexes extended and controlled the proliferation and migration of keratinocytes in comparison to free insulin gel and modulated the inflammatory activity and angiogenesis, which can be associated with the raised concentration of insulin and corroborates its higher bioavailability. Additionally, there was no cytotoxicity or irritation related to the assessed formulations. Thus, the application of insulin-HP-β-CD inclusion complexes in gels can be an excellent option for wound healing, mainly for ulcers.

Curcumin (Cur) present in the rhizome of *Curcuma longa L.* shows many biological activities, such as anti-inflammatory, anticoagulant, and antioxidant activities. However, due to its poor water solubility, photodegradation, and poor bioavailability, its therapeutic efficacy is limited [90], and an effective skin carrier is needed to apply curcumin to wound regions. Since hydrogel films have the potential to produce and maintain a humid environment around lesions, Wathoni, 2017 [91] applied them as vehicles to accelerate wound healing, along with HP-γ-CD. Hydroxypropyl-γ-CD (HP-γ-CD) has an elevated affinity for curcumin, and its inclusion complex exhibited high solubility (this was presumed to be due to the uniformity and thickness of the sacran-based hydrogel film with HP-γ-CD inclusion complex, in contrast with all other formulations) (Fig. 5 (A) and (D)), reduced photodegradation in more than 14 days, increased the Cur release rate (approximately 5.0-fold) (Fig. 5 (B)), and consequently enhanced its bioavailability. Fig. 5 (E) illustrates the outcomes of the *in vivo* wound healing studies. On the dorsal side of the mice, two full-thickness excisions were performed. At 3 and 7 days, the wound healing effect in the mice treated with Cur-HP-γ-CD inclusion complex in sacran-based hydrogel film inclusion complex was remarkable in comparison to the control. The contraction of the wound was also higher in comparison with the other treatment groups (Fig. 5 (C)), which suggests that Cur-HP-γ-CD inclusion complex in sacran-based hydrogels is a novel skin active ingredient carrier since it enhances Cur wound healing properties.

Microorganisms delay the wound healing process due to the induction of tissue necrosis, which can damage the skin. Hence, the use of antiseptic dressings with antimicrobial agents, namely, chlorhexidine, is desirable to inhibit the formation of biofilms and prevent wound infections. An example of these antiseptic dressings consists of the formation of a multilayer system with the first layer of chitosan, a polymer with biocompatible, biodegradable, and mucoadhesive properties crosslinked with genipin, which is a natural and low-toxic crosslinking agent used to stabilize the structure, building a polyelectrolyte multilayer based on self-assembled layers of chitosan and M-β-CD polymer. Later, this multilayer system was loaded with chlorhexidine, providing a

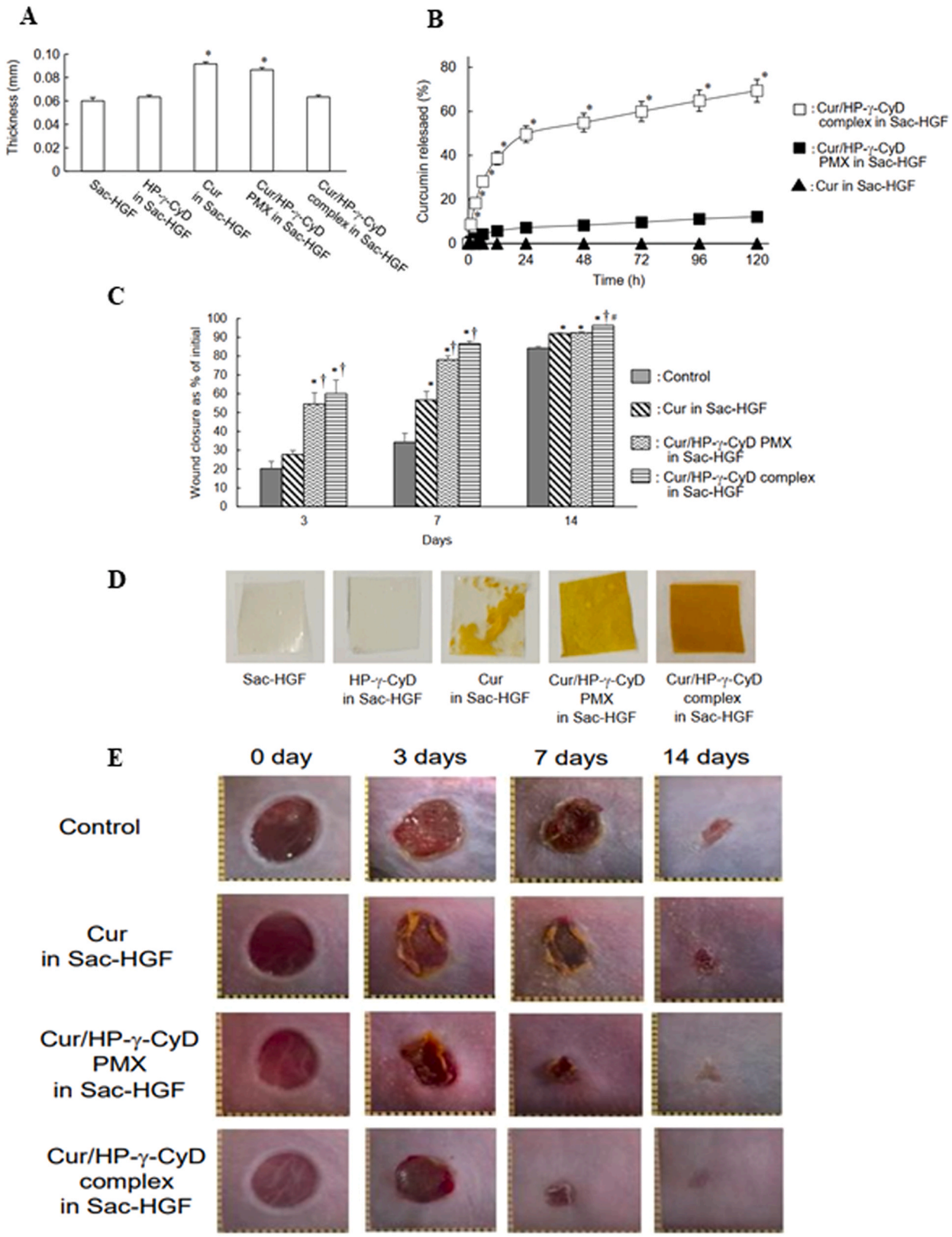


Fig. 5. (A) The thickness of the Cur/HP-γ-CD complex in sac-HGF. (B) *In vitro* release rates of Cur from the Cur/HP-γ-CD complex in sac-HGF. (C) Wound closure of the Cur/HP-γ-CD complex in sac-HGF compared to the initial aperture (%). (D) Macroscopic observation of the Cur/HP-γ-CD complex in Sac-HGF. **(E)** *In vivo* wound healing study illustration: The four groups were treated in the wound region with the following interventions: Control, which stands for no treatment; free Cur in the Sac-HGF; a physical mixture of Cur-HP-γ-CDs in Sac-HGF; and Cur-HP-γ-CD inclusion complexes in Sac-HGF. Adapted from [91], ***Abbreviations: Cur*** *- curcumin;* ***CyD*** *- cyclodextrin;* ***HGF -*** *hydrogel film;* ***HP-γ-CyD -*** *hydroxypropyl-γ-cyclodextrin;* ***PMX -*** *physical mixture;* ***Sac*** *- sacran.*

controlled release of the active ingredient [92].

Contrary to the delay of the healing process, hypertrophic scars are the result of uncontrolled and abnormal wound healing where extreme fibrosis and extracellular matrix deposition occur. Invasive and noninvasive methods to treat damaged skin have been studied to improve patient quality of life, and some novel nanodelivery system-based formulations have been developed for scar healing [87]. Imiquimod is an immune response modifier able to stimulate the production of proinflammatory cytokines, including interferon-α, which is used in the treatment of multiple dermatological diseases and, particularly, in hypertrophic scars. Nevertheless, imiquimod exhibits low water solubility and permeability, which can surpass its loading in β-CD-based nanosponges, resulting in a nanodelivery system with enhanced solubility, higher permeability, and efficient treatment against hypertrophic scars. β-CD-based nanosponges have building blocks that are obtained through a reaction between cross-linking agents and β-CD to assemble a polymeric frame. An investigation compared imiquimod-CD inclusion complexes of β-CD derivatives (HP-β-CD and carboxymethyl-β-CD) against β-CD-based nanosponges, each dispersed in a suitable hydrogel for the treatment of hypertrophic scars. The imiquimod-CD inclusion complexes showed an enhancement of imiquimod apparent solubility, although, with carboxymethyl-β-CD, the improvement was superior (approximately 125.0-fold), which confirms carboxymethyl-β-CD as the best solubilizer. Likewise, the zeta potential of the β-CD-based nanosponges was raised enough to prevent aggregation of the hydrogel formulation, and consequently, the nanosponges presented superior physical stability. Regarding the *in vitro* release results, the imiquimod-CD inclusion complexes with HP-β-CD exhibited 85.0% release after 6 h, carboxymethyl-β-CD exhibited 56.0% release, and the β-CD-based nanosponges exhibited less than 30.0% release under the same conditions. *In vitro* permeation studies also corroborated these outcomes, owing to the higher amount of imiquimod accumulated in the skin after 24 h with the CD inclusion complexes (approximately 7.7% for HP-β-CD and approximately 19.0% for carboxymethyl-β-CD), in comparison to the β-CD-based nanosponges (approximately 4.0%); however, the total accumulated quantity of imiquimod with the β-CD-based nanosponges was higher, showing better skin retention. Thus, HP-β-CD and carboxymethyl-β-CD can interact with imiquimod to enhance the apparent solubility and permeability. β-CD-based nanosponges maintain a slow controlled release of imiquimod, which can reduce the number of applications of the hydrogel, acting as a reservoir for this active ingredient [93].

3.1.6. Onychomycosis

Onychomycosis is a fungal infection of the nail provoked by dermatophytes that can cause thickening, detachment, discoloration, and distortion of the nail in the patient. The prevalence of this infection is almost 5.5% worldwide [94]. Various factors affect the prognosis of onychomycosis, with age being a crucial factor. Lifestyle and personal hygiene also appear to have a key role in the resolution and development of fungal infections. Made of higher quantities of keratin and containing disulfide bonds, nail plates act as the roughest barrier to the permeation of active ingredients. Despite the present low cost, oral therapy is related to adverse effects, which explains why topical treatment is best recommended. However, the low permeability of the rigid structure of the nails is a major shortcoming of this application [95].

Currently, conventional onychomycosis treatments include the application of nail polishes containing the approved and authorized antifungal active ingredients ciclopirox, terbinafine, or tioconazole. Despite the therapeutic properties, these active ingredients demonstrate low permeability in the nails, impairing them from reaching their deepest areas and compromising their antifungal action. Therefore, it is necessary to apply vehicles that facilitate their passage through the skin barrier to achieve therapeutic concentrations in the nail. CDs, such as HP-β-CD and M-β-CD formulated in aqueous solutions, in the presence of poloxamer interact to form a macromolecular complex called polypseudorotaxane that can establish nanotube-like structures. These structures can be placed on the surface of the nail, creating a hydrated film, which facilitates the solubilization and permeation of antifungal agents, such as ciclopirox olamine with limited water solubility (see Fig. 6) [96].

3.1.7. Skin cancer

Skin cancer is a large public health problem worldwide. The most prevalent types are basal skin cancer, squamous skin cancer, and melanoma skin cancer, with the last being less common than the first; however, it has a higher rate of growth and dissemination [97]. Nephrotoxicity, bone marrow suppression, neurotoxicity, and several toxic side effects are, for example, attributed to chemotherapy, which can be combined with surgical resection and/or radiotherapy for anticancer treatment [98,99]. Considering that prolonged UV radiation exposure is the principal risk factor related to skin cancer development [97], research toward the design of novel anticancer agents or technological strategies for the enhancement of conventional anticancer drugs or their formulation is needed. Moreover, many active ingredients with proven anticancer activity are not effective because of their instability, poor water solubility, and low biocompatibility [18]. Thus, the construction of smart active ingredient carriers capable of increasing the efficacy and safety of skin anticancer therapies is of the utmost relevance.

CDs can overcome cellular and noncellular mechanisms of resistance and exert targeted active ingredient delivery to cancer cells with decreased toxicity. The possibility of targeted delivery makes it possible to directly target the tumor region, reducing the risk of undesirable effects on other tissues. Once the host-guest inclusion complexes reach the tumor (target), CDs dissociate, and active ingredients are released to exert their anticancer activity [100, 101]. CD-based nanodelivery systems can also passively achieve tumors through the enhanced permeation and retention effect. This is believed to contribute to the selectivity of tumor cells due to the increased vascular permeability, which allows the accumulation of host-guest inclusion complexes on the tumor site [102].

Saikosaponins are triterpene saponins isolated from Bupleurum species that are used in traditional Japanese and Chinese medicine with remarkable effects against skin cancer, as well as antioxidant and anti-inflammatory activity. However, their applications in anticancer therapy are limited owing to their low water solubility, which results in low bioavailability. In a study by Hu, 2019 [103], host-guest inclusion complexes were developed between saikosaponin and HP-β-CD with superior features. In addition, its effects in HSC-1 cells (human cutaneous squamous cell carcinoma) were studied, as well as the involved signal transduction pathways, including MAPK (mitogen-activated protein kinase) and Akt-mTOR (serine/threonine kinases involved in the apoptosis of cancer cells). The results showed an improvement of approximately 350.0-fold, 1074.0-fold, and 906.0-fold in apparent water solubility with saikosaponin-HP-β-CD inclusion complexes of 1:1, 1:5, and 1:10 ratios, respectively, which highlights the 1:5 ratio as the top inclusion complex to conduct further studies (see Fig. 7). Additionally, *in vivo* studies revealed that saikosaponin-HP-β-CD inclusion complexes caused apoptosis in HSC-1 cells *via* MAPK activation and elimination of Akt-mTOR pathways, in contrast to free saikosaponin in phosphate-buffered saline, which did not demonstrate apoptotic activity, possibly associated with its low water solubility. These results indicate that saikosaponin-HP-β-CD inclusion complexes can be an efficient active ingredient carrier for skin cancer therapy.

Artesunate - a semisynthetic derivative of the antimalarial drug artemisinin - in addition to its antimalarial activity, holds huge potential as an anticancer agent [104]. This anticancer activity is related to the production of ROS, inhibition of tumor angiogenesis, DNA damage, and induction of apoptosis but also have a lower risk of recurrence and metastasis and fewer adverse effects than conventional anticancer drugs [105]. Nonetheless, its low water solubility impairs its efficacy and bioavailability. To overcome these problems, investigators used three

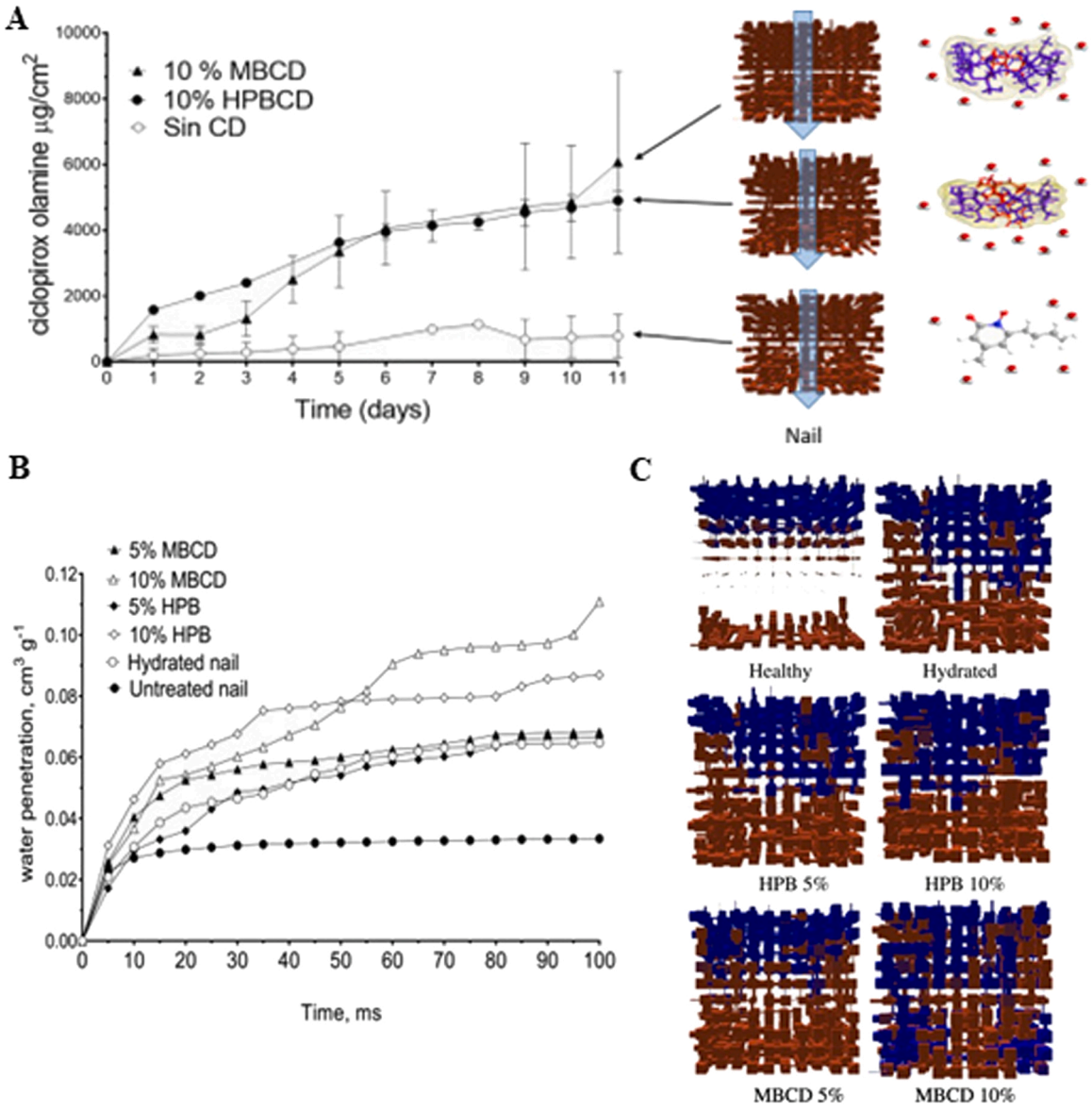


Fig. 6. (A) Distribution of ciclopirox olamine through bovine hoof with M-β-CD or HP-β-CD. (B) Nail water diffusion kinetics exposed to several treatments. (C) Nail model structure of the water diffusion exposed to several treatments. Adapted from [96], ***Abbreviations: CD*** *- cyclodextrin;* ***HPB -*** *2-hydroxypropyl-β-cyclodextrin;* ***MBCD -*** *methyl-β-cyclodextrin.*

types of CDs, randomly methylated-β-CD, heptakis (2,6-di-*O*--methyl)-β-CD, and heptakis (2,3,6-tri-*O*-methyl)-β-CD, to produce artesunate-CD inclusion complexes and carry out physicochemical and biological assessments. Molecular modeling, FTIR, and thermal analysis corroborated the spontaneous formation of the three artesunate-CD inclusion complexes and partial insertion of artesunate into CD cavities, with enhanced thermal stability compared to free artesunate. However, regarding *in vitro* biological assessment, the anticancer activity of the artesunate-CD inclusion complexes was verified in a human melanoma cell line (A375) and a HaCaT human keratinocyte line. Artesunate-CD inclusion complexes showed relevant toxic effects on healthy and cancer cells, which disables the application of free artesunate and its inclusion complexes against skin cancer. Although the inclusion complexes exhibited toxicity in healthy cell lines, the associated toxic effects were lower in comparison to free artesunate (mostly for artesunate-heptakis (2,6-di-*O*-methyl)-β-CD inclusion complexes), and these results should be considered in other studies of artesunate-CD inclusion complexes used in different cancer cell lines [106].

In summary, there is an urgent unmet need for more investigations on this topic to expand the scale-up of more active ingredient-CD carriers and CD-based delivery systems for the treatment of skin diseases.

3.2. Cosmetic formulations and cosmetic ingredients containing cyclodextrins

Many cosmetics already contain NPs for UV protection, greater skin penetration, anti-aging, controlled release, whitening, coloring, and many others. Among these, the cosmetic industry has shown particular interest in CDs as nanomaterials to improve some qualities of their products [107].

Most studies have focused on the use of free CDs and active ingredient-CD inclusion complexes. In cosmetics, the key functions of CDs are the following: [1] increase the apparent water solubility of hydrophobic molecules, [2] protect labile molecules against degradation, [3] preserve the stability of emulsions and suspensions, [4] convert fluids into dry powders, [5] decrease skin sensitivity, [6] avoid unwanted interactions between the components of the formulations, [7] mask unpleasant odors, and [8] modulate skin permeability and control

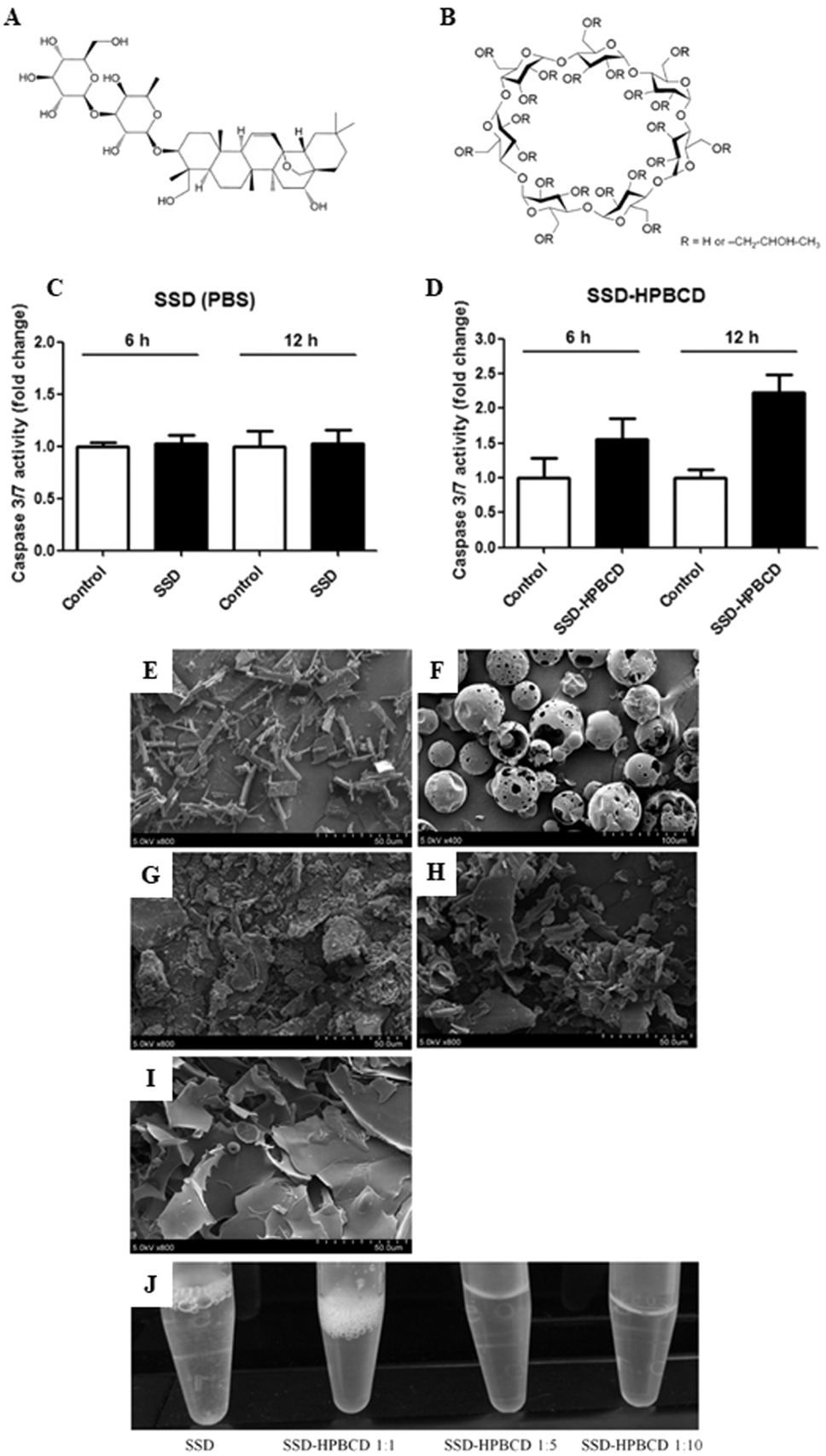


Fig. 7. (A) Molecular structure of saikosaponin. (B) Assessment of pure saikosaponin and (C) saikosaponin-HP-β-CD inclusion complex (1:5) on HSC-1 cell apoptosis, as determined by caspase 3/7 activity at 6 and 12 h. (D) Molecular structure of HP-β-CD. Surface morphology of pure saikosaponin, HP-β-CD, and different ratio formulations of saikosaponin-HP-β-CD inclusion complexes under scanning electron microscopy. (E) Scanning electron microscope image of pure saikosaponin. (F) Scanning electron microscope image of pure HP-β-CD. (G, H, and I) Scanning electron microscope image of saikosaponin-HP-β-CD inclusion complexes (1:1, 1:5, and 1:10 ratios, respectively). (J) The aspect of different aqueous preparations. Adapted from [103], ***Abbreviations: CD** - cyclodextrin; **HPBCD** - 2-hydroxypropyl-β-cyclodextrin; **PBS** - phosphate-buffered saline; **SSD** - saikosaponin.*

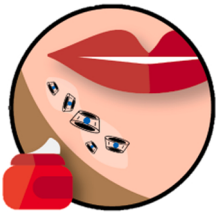
the release of active ingredients [51].

Recent data revealed the use of CDs in cosmetic formulations, mostly in perfumes, by forming host-guest inclusion complexes for controlled release of fragrances [47]. In addition to the controlled release of active ingredients, CDs offer other advantages in the field of cosmetics, such as applications in anti-aging skin care, sunscreens, deodorants, antiperspirants, and shampoos. Examples of cosmetics and cosmeceuticals commercialized containing free CDs or active ingredient-CD inclusion complexes are summarized in Table 2.

3.2.1. *Anti-aging skin care*

Aging is a natural process that occurs in all living organisms. Extrinsic and intrinsic factors are responsible for the aging of the skin. Intrinsic factors include genetic factors, metabolic process slowdown, and hormonal changes. Extrinsic factors include environmental exposures to pollutants and UV rays (photoaging), as well as harmful lifestyle elements [108, 109]. UV radiation produces free radicals that can lead to oxidative stress and damage to proteins and enzymes [110], which impact the repair capacity of the body, diminishing the differentiation of

Table 2
Examples of cosmetic products and ingredients containing β-CD or HP-β-CD available on the market [120, 129].

Cosmetic use	Active ingredient	Commercial name	Cosmetic function
Sunscreen	Avobenzone	Vichy Laboratories liftactiv peptide C sunscreen lotion, SPF 30	β-CD retains the active ingredient in the upper layers of the skin, blocking their entrance into the blood circulation
	Zinc oxide; Titanium dioxide	Dr. Dennis Gross dark spot sun defense sunscreen broad spectrum SPF 50	HP-β-CD enhances apparent water solubility of ingredients and increases the stability of the product
Anti-aging	Retinyl palmitate (Vitamin A palmitate) Tocopheryl acetate (Vitamin E acetate)	L'Oreal Paris Men expert vita lift anti-wrinkle & firming daily moisturizer	β-CD promotes cutaneous permeation of the active ingredients
		Artnaturals® hyaluronic acid serum	HP-β-CD promotes cutaneous permeation of the active ingredients
Deodorants and antiperspirant	–	Secret® aluminum free deodorant; Old Spice clinical sweat defense anti-perspirant deodorant	β-CD entraps body odors
	–	Shiseido deodorant natural spray	HP-β-CD entraps body odors
Shampoo	–	Klorane dry shampoo with oat milk, ultra-gentle	HP-β-CD retains oil and dirt into its cavity, increasing the time between hair washings
			
Fragrance	ND	Amorepacific, Fradore *This is how you feel inside* Eau de toilette for the body	HP-β-CD acts as aroma compound solubilizer, providing a long-lasting fragrance effect, and absorbing body malodors (dual-effect)
			

Abbreviations: CD - Cyclodextrin; **HP-β-CD -** 2-hydroxypropyl-beta-cyclodextrin; **ND -** Not discriminated; **SPF -** Sun protection factor.

the cells and, consequently, stimulating the progression of skin aging [111]. With age, the cell renewal process of the skin slows, and the skin becomes drier, fragile, and less elastic. After menopause, the production of female hormones decreases, and women experience hormone skin aging modulation, which results in lower production of endogenous estrogen that ultimately affects skin rejuvenation [112].

Anti-aging formulations have active ingredients that help reduce inflammation, scavenge free radicals, prevent extracellular matrix damage, and repair the elasticity and consistency of the skin. Retinoids and antioxidants, such as vitamins, have been used in a variety of anti-aging products [113]. Furthermore, these products can include isoflavones as active ingredients that, because of their structure (such as 17-β-estradiol), can connect to estrogen receptors. Estrogen receptors are situated in the dermis, so transporters are needed to help these molecules permeate through the outer skin layer, also known as vectorization. Active ingredient-CD inclusion complexes have been described as promoters of skin permeation of active ingredients and could improve anti-aging formulations, with the advantage of having unique biocompatibility characteristics [114].

Polyphenol mangiferin is an antioxidant and antimicrobial agent with maximum efficacy when formulated at pH values lower than 5 and higher than 7. It presents poor water solubility and bioavailability, limiting its use in cosmetic formulations. α-CDs, β-CDs, γ-CDs, HP-β-CDs, and HP-γ-CDs are patented by L'Oréal as carriers of mangiferin since several CDs can improve mangiferin apparent solubility and stability, regardless of pH values [115].

Ascorbic acid, also known as vitamin C, is applied to the skin to eliminate free radicals, decrease melanogenesis, and stimulate collagen synthesis [116]. Vitamin C is commonly used as an anti-aging agent in the cosmetic and dermopharmaceutical fields. However, because of its low stability, its use in skin delivery involves limitations, and novel formulations have been designed to overcome these limitations. Vitamin C ascorbyl tetraisopalmitate (VC-IP) is a form of vitamin C that is stable at elevated temperatures and has favorable solubility in nonaqueous solvents. It shows remarkable cutaneous permeation and, in contact with skin, is converted to free ascorbic acid. Bastianini, 2017 [117] studied the possible conversion of VC-IP present in an oil phase to VC-IP in a powder form, using γ-CD as a skin carrier to produce a nanomaterial capable of being dispersible both in water and oil phases, appropriate for cosmetic applications. Thus, γ-CD was used to form inclusion complexes with VC-IP due to its cavity with suitable dimensions and protection from water, oxygen, and other compounds included in the formulation, acting as a reservoir for the controlled release of vitamin C in the skin.

A high level of particulate matter, the primary air pollutant, promotes skin aging toward the development of wrinkles and pigmentation. Presently, many skin care products have antioxidants and plant extracts in their compositions to protect the skin from environmental pollutants. Polyphenol 7,3',4'-trihydroxyisoflavone has shown benefits including anticancer activity and antioxidant and photodegradation protection. However, 7,3',4'-trihydroxyisoflavone efficacy is decreased by its low water solubility, which restricts its cutaneous permeation and impairs its biological activity. To optimize 7,3',4'-trihydroxyisoflavone properties, investigators have explored its use with HP-β-CD. They concluded that the host-guest inclusion complex formed between the active ingredient and HP-β-CD displayed increased apparent water solubility and cutaneous permeation. In addition, this active ingredient limits particulate matter-induced skin damage and is considered an anti-pollutant agent in cosmetic products [118].

The incorporation of retinol in anti-aging formulations helps to decrease wrinkles and cell renovation of UV radiation-damaged tissue. Host-guest inclusion complexes between retinol and β-CDs or HP-β-CDs are used in many available cosmetics on the market [119], such as L'Oreal Paris Men expert vita lift anti-wrinkle & firming daily moisturizer [120], which includes a retinol-HP-β-CD inclusion complex with increased solubility, stability, and active ingredient permeability.

3.2.2. Sunscreens

UV radiation is essential for important processes in human skin. Vitamin D synthesis requires a low exposure to UV radiation, usually from the sun, but long-term exposure can trigger negative effects, *e.g.*, erythema, skin aging, and cancer, due to mutations and induction of immunosuppression. With the increasing data about the effects of UV radiation on the skin, an increased interest in sunscreen formulations has been raised, being currently the most important product used to protect the skin from UV radiation. Sunscreens contain UV filters where UV radiation can be reflected, absorbed, or dispersed by chromophores instead of being retained in the SC. Nonetheless, UV filters could permeate into the bloodstream and cause adverse systemic effects. In this context, CDs can be used as skin active ingredient carriers in sunscreens, reducing phototoxicity, improving photostability, and restraining incompatibilities between the ingredients of the formulation [46,121].

Eusolex® 4360 (Avobenzone), Eusolex® 232 (Ensulizole) and Eusolex® 9020 (Oxybenzone) are the most common chemical filters approved by the FDA to block UVA and UVB radiation. Complexation with β-CD or its derivatives can improve the characteristics of these active ingredients, enhancing their concentration in the upper layers of the skin, creating a barrier against UV rays, and decreasing the direct contact between the skin and the active ingredient [122]. Among them, avobenzone possesses a chemical structure configuration that in contact with UV radiation leads to the production of free radicals, resulting in the loss of UVA protection, which provokes skin injuries. Yuan, 2019 [123] evaluated the photodegradation of avobenzone-HP-β-CD inclusion complex, and with 3.3 h of irradiation exposure, the inclusion complex showed 8.0% degradation, in contrast to free avobenzone with 49.0%, which indicates that the insertion of avobenzone in the cavity of HP-β-CD prevents its degradation. Additionally, UV–Vis spectrophotometry, thermal analysis, and other methods confirmed the formation of avobenzone-HP-β-CD inclusion complex in the liquid and solid states. Further *in vivo* and *in vitro* studies are necessary to aid these observations; nonetheless, CDs are an amazing encapsulation strategy for the formulation of marketed UV filters to augment skin photoprotection and avoid side effects.

trans-Ferulic acid is one of the most common cinnamic acid derivatives and possesses anti-inflammatory and anticancer effects but mainly has great antioxidant activity against the damaging effects of exposure to UV radiation and a high UV absorption ability; therefore, it has been described as a candidate for natural UV filters [124]. However, *trans*-ferulic acid presents low water solubility, which limits its potential for cosmetic applications. For that reason, investigators assessed the behavior of *trans*-ferulic acid with various CDs to verify which ones are prone to form host-guest inclusion complex and to evaluate its characteristics. The apparent water solubility of *trans*-ferulic acid was increased with α-CD (~5.0-fold), Me-β-CD (~4.8-fold), HP-β-CD (~4.5-fold), and HP-γ-CD (~8.3-fold) in comparison to free trans-ferulic acid solution. Additionally, the *trans*-ferulic acid-HP-γ-CD inclusion complexes were evaluated and compared to commonly used UV filters for sun protection factor (SPF) and UVA protection factor. *trans*-Ferulic acid-HP-γ-CD inclusion complex exhibited the maximum SPF and UVA protection factor measurements between the sample sunscreens, with an increase of 1.4- and 1.6-fold, respectively, regarding free trans-ferulic acid solution. This result indicated that the UVA-SPF value of the sunscreen sample was more strongly affected than the SPF value of an inclusion complex. Additionally, due to the bathochromic shift detected in UV–Vis spectrophotometry of the *trans*-ferulic acid-CD inclusion complexes, its UV absorption skills were significantly enhanced between 320 and 370 nm, which can be an advantage for the development of outstanding sunscreens since UVA radiation (320–400 nm) can provoke the early development of wrinkles and aged skin [125]. Last, these skin carriers retain the active ingredient in the upper skin layers and block their entrance into the bloodstream, making them suitable for sunscreen formulations [126].

3.2.3. Deodorants and antiperspirants

Deodorants and antiperspirants are cosmetics used against unpleasant odors associated with perspiration. Sebaceous glands secrete fatty acids that, when metabolized by bacteria, cause the production of body malodor molecules [127]. Deodorants contain antimicrobial agents and/or fragrances to mask the odors produced by the secretion of sweat glands. They are typically applied topically on the underarm or other skin areas [52]. Although deodorant sticks are very popular, the occurrence of skin irritation after their application is not uncommon.

Free CDs can be used in this type of product to entrap perspirant malodors. Deodorants and antiperspirants are formulated as roll-ons, aqueous lotions, and gels, with the advantage of being safe and gentle to the skin, providing exceptional malodor-controlling properties without skin irritation [128]. Examples of these formulations containing CDs are the products Secret® Aluminum Free Deodorant and Old Spice Clinical Sweat Defense Anti-Perspirant Deodorant by Procter & Gamble [120, 129], where CDs act as an absorbing agent to capture malodors. Another example is CAVASOL® W7 HP TL by Wacker, which is a 40.0% aqueous solution of free HP-β-CD used in deodorant/antiperspirant formulations as a solubilizer cosmetic ingredient to form host-guest inclusion complexes with the molecules that originate malodor [130].

3.2.4. Shampoos

Hair provides sensory and protective purposes to living creatures. Good-looking and clean hair is an important part of personal care. Cosmetic products for hair and scalp cleaning, *e.g.*, shampoos, are conceived to remove dust, dirt, and excess oil, helping the hair have a good appearance [131].

Shampoos containing CDs can prolong the contact time of the active ingredients with the hair and scalp. To combat oily hair, various cosmetic companies market dry shampoo that contains free β-CDs to retain the oil and dirt in their cavity, increasing the time between hair washings [2]. An example is Klorane Dry Shampoo with oat milk [120, 129], which contains CDs to absorb the lipids present in the hair and scalp, providing clean hair without soaking.

3.2.5. Fragrances

It is undeniable that the odor of cosmetic products has to fulfill the needs of consumers. Able to offer a pleasurable odor, aroma compounds are useful to cover the smell of the bases of cosmetic products and to provide them with a unique identity [132, 133]. One of the initial uses of CDs in the cosmetic field was to prepare host-guest inclusion complexes with aroma compounds [134], preventing their evaporation to obtain a long-lasting fragrance effect. Similarly, since aroma compounds have low water solubility and stability, the use of CDs to overcome these drawbacks is naturally justified [51]. The particular characteristics of aroma compounds, such as their small size and geometry, make them exceptional guests for CDs. For instance, when body lotion with aroma-CD inclusion complexes is applied on the skin, contact with the air results in vaporization of the free fractions, and due to an existing disequilibrium between the free fractions and the aroma-CD inclusion complexes, the aroma compound is released from the CD cavity, facilitating their controlled release [135, 136].

In a study by Kfoury, 2014 [137], HP-β-CD was complexed with eight different monoterpenes (aroma compounds), and the properties of the corresponding host-guest inclusion complexes were analyzed. The results revealed that oxygenated monoterpenes (linalool, eucalyptol, thymol, pulegone, and geraniol) presented a higher EE (above 82.1%) than monoterpene hydrocarbons (α-pinene, β-pinene, and limonene; inferior to 24.9%). This outcome can be due to the extremely low water solubility of monoterpene hydrocarbons; however, further investigation is needed to develop innovative fragrance products. In another study, formulations containing linalool and benzyl acetate with or without CDs were compared. The inclusion complexes with HP-β-CD exhibited greatly improved apparent water solubility and stability regarding free aroma compounds. Moreover, the inclusion complex formation allowed the conversion of the liquid aroma compounds into powder, upgrading the handling characteristics of the cosmetic formulations. Additionally, in another study, it was shown that formulations containing aroma-CD inclusion complexes with HP-β-CD and linalool or benzyl acetate retained the fragrance for 4 months more than formulations with both free linalool and benzyl acetate [51].

Beauté by Roquette® CD 110 is a cosmetic ingredient, accepted by the European, United States (US), Japanese, and China regulations, containing HP-β-CD that acts as a fragrance solubilizer, which provides a long-lasting fragrance effect (Wang and Chen 2005). Another example is 'This is how you feel inside', Body eau de toilette by Fradore [120, 129], which is commercialized as a perfume for body odor care with HP-β-CDs, assuring a long-lasting fragrance aroma effect due to the HP-β-CDs' capacity to release the fragrance at a slow rate.

4. Safety of cyclodextrins for skin application: regulatory and toxicological aspects

The products developed to be topically applied to the skin can be classified as drugs, cosmetics, or, in some cases, medical devices. Although the term 'cosmeceutical' is commonly used to refer to products that satisfy both drug and cosmetic features, the authorities do not officially recognize this term, and according to their characteristics, the marketed region can be framed as drug or cosmetic, *e.g.*, sunscreens in the European Union (EU) are classified as cosmetics, although in the US, they are considered over-the-counter drugs. In the US, topical medicines follow the normal course of overall drugs regarding regulatory authorization and safety assessment, and cosmetics are regulated by the FDA, but unlike drugs, cosmetics do not need premarket approval for their commercialization. However, the safety of cosmetics and cosmetic ingredients, such as CDs, must be assured by manufacturers or their distributors, either through the execution of toxicological tests or the assessment of toxicological tests performed on similar products [138]. Regarding the EU, topical medicines follow the same paths as the remaining drug, yet cosmetics are governed by the EU Cosmetic Products Regulation (EC) No. 1223/2009. All the Member States of the EU have their national competent authority to enforce the regulation compliance, and its safety is warranted by manufacturers and distributors by a complete technical dossier on the cosmetic product with a safety assessment report that ensures the safety of ingredients and formulation [139]. CDs in the EU are managed as excipients, and their usage is authorized by the European Medicines Agency (EMA) depending on the delivery route. For topical products, native CDs are considered safe at concentrations up to 0.1%, and HP-β-CDs are accepted as harmless [140].

Regarding the selection of any compound for topical formulations, and despite the relatively high safety margin presented by CDs, as with any substance applied on the skin, CDs can provoke irritation at high concentrations [1,4]. Free CDs are poorly absorbed through the skin, but in formulations where they are combined with other permeation enhancers or with occlusive ingredients (such as Vaseline), CDs are capable of penetrating the skin; however, this depends also on the nature of the CD applied [140]. Methylated CDs are more lipophilic than natural CDs, possessing deeper permeation capacity into the skin. Heptakis-2, 6-di-O-methyl-β-CD, a methylated CD, can interfere with the SC and increase the permeability of active ingredients. The same happens with randomly methylated-β-CD, which can interact with fatty acids and ceramides from SC and reduce the barrier function of the skin [4].

Nevertheless, CDs have a notable safety margin for topical application. Tests conducted on healthy volunteers have demonstrated that natural CDs and HP-β-CD do not cause irritation following application for 24 h of CD dispersed in Vaseline or stirred in water [141]. In addition, inclusion in the CD cavity of these active ingredients protects biological membranes from their direct contact, reducing their local irritation and side effects but, most importantly, without reducing the

efficacy of the active ingredient [47].

Considering that the regulatory status of various CDs is still in progress, various monographs of natural CDs are available in well-known pharmacopeias such as the US Pharmacopeia, European Pharmacopoeia, and National Formulary. Monographs for modified CDs, such as HP-β-CD and SBE-β-CD, are included in The Handbook of Pharmaceutical Excipients, as well as in the US and European Pharmacopoeia [101, 142]. Furthermore, most of these compounds have approved toxicological profiles for human use [143].

5. Future perspectives

Topical and transdermal delivery of active ingredients offers several advantages, such as an extended duration of action, a decrease in systemic adverse effects, and a reduction in the active ingredient dose due to the avoidance of first-pass metabolism. Nonetheless, it remains limited to a few molecules due to the strong barrier exerted by the skin, which acts as a natural and protective barrier against harmful external agents [144]. Therefore, the preparation of host-guest inclusion complexes and/or the development of CD-based delivery systems to surpass these active ingredients' drawbacks are crucial for skin application. CDs can improve the bioavailability of challenging active ingredients, increasing their solubility, stability, penetration, and retention, and present good biocompatibility that restricts toxicity related to the active ingredients. Moreover, CDs are also used and useful by themselves, without the presence of active ingredients, *e.g.*, to retain sebum or odor molecules, as occurs in shampoos and deodorants, which makes CDs an extremely valuable nanomaterial for dermopharmaceutical and cosmetics formulations.

Despite being a well-characterized excipient in medicinal products, knowledge of CDs is very limited for regular consumers. Additionally, it remains difficult to accurately predict their behavior due to the lack of evidence from clinical studies of their dermopharmaceutical and cosmetics applications and compatibility with other components included in the formulations. With more clinical evidence, it would be possible to increase the harmonization and validation of regulatory guidelines for several modified CDs and CD-based delivery systems that are emerging for skin delivery. Interdisciplinary cooperation between regulatory agencies, academic institutions, and the pharmaceutical and cosmetic industry is crucial to boost preclinical (*in vivo* and *in vitro* studies) and clinical outcomes for the assessment and development of optimized, safer, and well-tolerated topical products suitable for each purpose, whether cosmetic or dermopharmaceutical.

As demonstrated throughout the present review, the application of CDs in the cosmetic and dermopharmaceutical fields represents a promising tool in the resolution and/or treatment of many diseases and contributes to the health and well-being of consumers.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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