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REVIEW

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Advanced drug delivery systems for the management of local conditions

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ABSTRACT

Localized disorders, even though originally confined to a specific body part, can progress into potentially life-threatening systemic disorders if treated inappropriately. Local treatment is often highly challenging due to poor penetration of therapeutic agents from their vehicles into the affected body site. Systemic treatment on the other hand often comes with unspecific side effects. The skin is the largest organ of the body, and conditions such as wounds and bacterial or fungal infections disrupt its natural barrier properties, important for the homeostasis of the human body. Advanced drug delivery systems for treating these conditions could greatly improve the treatment outcome and patient compliance. Other parts of the body that are of interest regarding localized treatment are, for example, the eyes along with mucosal tissues which are present in the vagina and lungs. Rather than focusing on specific diseases or parts of the body, this review provides an overview of the different drug delivery platforms that have been employed for enhanced local treatment. The following systems will be discussed: nanoparticle-based systems, such as nanocrystals, polymeric, lipidic, and inorganic nanoparticles, and nanogels; cyclodextrin inclusion complexes; and several devices like microarray patches, wound dressings, and films.

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1. Introduction

Localized disorders originate in, and are confined to, a certain area of the body or an organ system. When treated inappropriately, many of these conditions can progress to a systemic state, affecting the entire body. Most of the research focused on local delivery based this approach by the idea that the systemic treatment using model drugs leads to inevitable side effects, and local delivery instead appears to be a more effective and safer route with regard to the minimal invasiveness. Nonetheless, the development of effective local treatment options is highly challenging. One of the main reasons is poor penetration of therapeutic agents from the drug delivery system to the affected side, and advanced delivery platforms are highly desirable.

The commonly researched local treatment systems in alignment with the abundance of conditions associated with them include skin, eyes, mucosal epithelium-lined organs like the vagina, and lungs, which have been a focus of this review. Clearly, these are not easily accessed by most therapeutic agents given the protective nature of our bodies aiding in survival.

The skin is the largest organ of the human body which forms a barrier between the body and its surroundings and plays a vital role in maintaining homeostasis [1]. Whilst a treatment of skin conditions offers a noninvasive administration to patients, the skin barrier effect interferes with active agents' delivery [2]. The biggest challenge for any therapeutic materials is to overcome the function of the *stratum corneum* which is blocking external agents regarded as hazards and permeate into deeper skin layers (Figure 1(a)). Moreover, considering the complex structure of the skin, the ideal molecule for delivery should be extremely small and amphiphilic, which are often unmet criteria by current medicines [3].

The administration of drugs to the eye is also challenging and is associated with poor levels of bioavailability (<5%) and patient discomfort. This stems off from the multiple evolutionary protective mechanisms that occur in the eye including tear production, tear flow, and blinking [7,8] (Figure 1(b)). Over 90% of marketed ocular formulations are either solutions or suspensions which, although the promoters of drug absorption, are easily washed away, explaining the low residence time of these formulations and therefore frequent dosing [9]. Considering the effective barriers for topical delivery, this includes cornea and efflux pumps which limit the passage of exogenous substances and in a such way protect ocular tissues [10].

When considering local delivery to organs like the eyes, vagina, and lungs, the primary challenge that is common among these is the mucus barrier's complexity and function

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Article highlights

- **Nanoparticle-based drug delivery systems**

Enhancing local drug delivery, different nanoparticle-based systems offer noninvasive, effective formulations by leveraging nanoscale size for improved adhesion, penetration across biological barriers, and targeted therapeutic delivery.

- **Cyclodextrin inclusion complexes**

Optimizing local drug delivery, cyclodextrins and their derivatives enhance drug solubility, dissolution rates, and permeability across biological membranes, thereby improving therapeutic efficacy while minimizing local adverse effects.

- **Devices loaded with actives for local conditions**

Microarray patches, advanced wound dressings, and mucoadhesive films are innovative drug delivery systems that improve treatment effectiveness and patient outcomes across various medical conditions by enhancing precision, absorption, and therapeutic efficacy while minimizing side effects.

(Figure 1(c,d)). This hydrogel biopolymer has a clever mechanism which simultaneously inhibits the passage of pathogens and external materials, like actives, whilst ensuring an exchange of gases and nutrients [11]. Furthermore, the fate of drug delivery to these organs is dependent on the physiochemical properties of this barrier including pH, size of pores, viscoelasticity, ionic strength, and charge [12]. For the vaginal route, the success of drug delivery is also interfered by individual patient differences, for example, the thickness of vaginal epithelium and veins causing different absorption profiles, the prominent enzyme activity or the pH alteration of the medium by cervical mucus and vaginal transudate (Figure 1(c)). On the contrary, in the modern era, the lungs are primarily considered as an ideal target for the pulmonary drug delivery as they display a low extracellular enzyme activity, a large absorption surface due to the presence of many blood vessels and air-blood exchange pathways. Yet, this process is relatively complex given the defense mechanisms of respiratory tract omitting any inhaled material from reaching the lungs or removing any material after their deposition (Figure 1(d)) [13]. Other than mechanical barriers, this may also be impacted by the behavioral influences, for instance, the correct usage of inhaler devices [14].

Overall, scientists and manufacturers must produce more clever mechanisms in drug delivery to overcome evolutionary defense mechanisms, which despite the local pathologies occurring leading to their weakening or disruption, remain the primary obstacles to a successful therapy. Advanced drug delivery systems set the promise to resolve the occurrence of major side effects and improve therapeutic outcomes through increasing the drug concentration at the affected body site. They can further enhance patient acceptance and compliance by being less invasive and more efficient. In the past, many techniques have been developed for an enhanced local treatment of a wide range of diseases. Rather than focusing on specific diseases or parts of the body, this review gives an overview of the different drug delivery platforms that

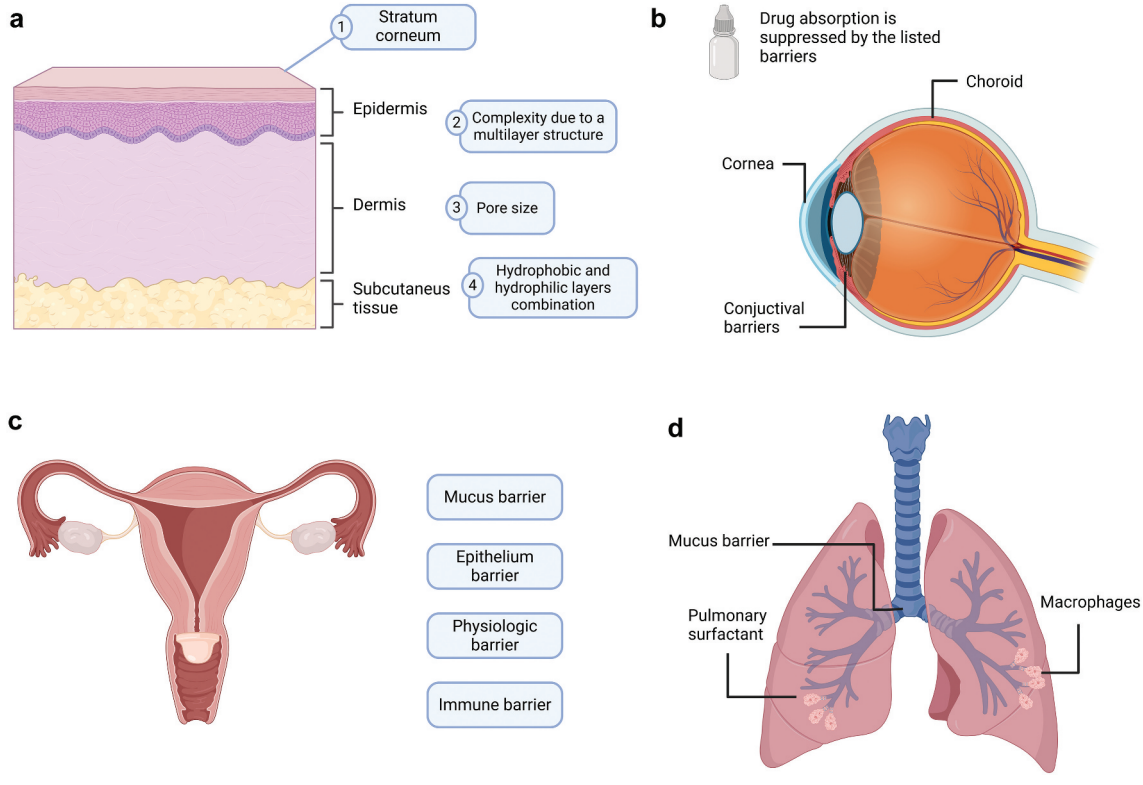

Figure 1. The summary of mechanical barriers that interfere with drug delivery. (a) Represents transdermal delivery physical barriers inspired by ref [3]. and created with BioRoender.com. (b) Displays the physical barriers for the topical delivery to the eye inspired by ref [4]. and adapted with BioRender.com. Panel (c) Reveals the biological barrier for vaginal delivery inspired by ref [5]. In the (d) Panel, the image reveals the main biological barriers for pulmonary delivery inspired by ref [6]. The images have been modified to meet the scope of this review.

have been employed by researchers and manufacturers for a local therapy. The following systems will discuss the use of nanoparticle-based systems: nanocrystals, polymeric, lipidic, and inorganic nanoparticles, and nanogels, cyclodextrin inclusion complexes and some existing devices' examples including microarray patches, wound dressings for mucosal tissues, and films. Further, for each system, the current research and its' struggles will be highlighted with the most recent application examples for a localized treatment.

2. Nanoparticle-based drug delivery systems

Since liposomes were discovered in the 1960s, they were adopted for diverse therapies which also opened the doors to other nanomaterials' discoveries [15], and from there now, the nanotechnologies play a key role in drugs' delivery.

Drug nanocarriers are excellent candidates for overcoming physiological barriers and reaching both local and systemic targets. Their nanometric size enhances therapeutic effectiveness through active or passive targeting mechanisms, such as enhanced permeability and retention [16,17]. It is important to consider the physicochemical properties of nanomaterials, including factors like shape, charge, size, surface modifications, and loading methods, as these attributes determine the efficacy of nanocarriers [18]. Nano systems can be classified in various ways, and in this discussion, they will be described based on their composition or key features. Figure 2 illustrates the different nanoparticle-based drug delivery systems that will be discussed below.

2.1. Drug nanocrystals

Drug nanocrystals (NCs), as their name suggests, are nanometer-sized crystalline drug particles [19,20]. In contrast to other nanoparticle types, NCs have a relatively simple structure which consists of the nanonised drug crystals coated with

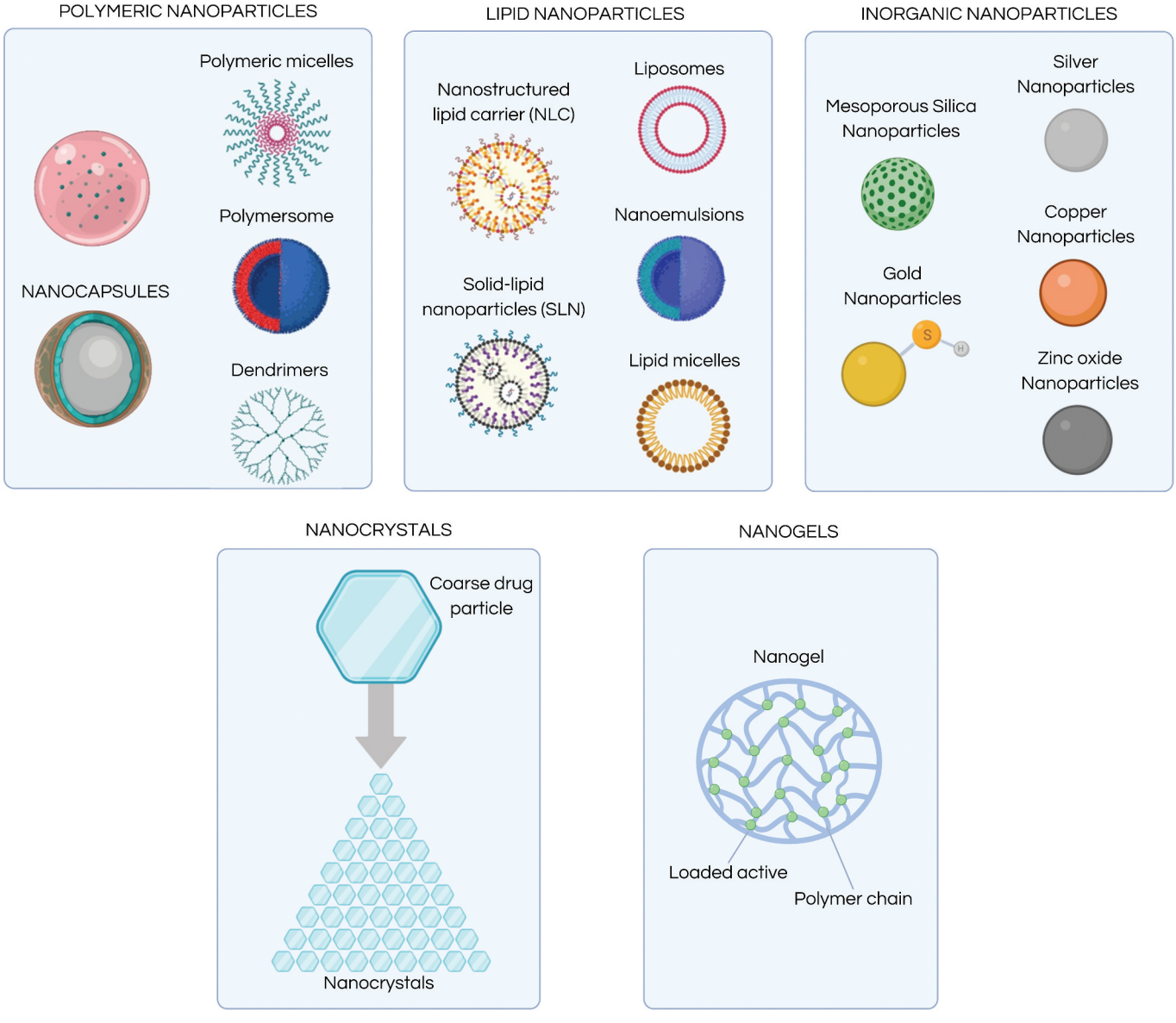

Figure 2. Graphical summary of the various Nanoparticle-based drug delivery systems discussed in the article. The image was obtained with BioRender.com.

a thin layer of polymer or surfactant to promote particle stability and prevent aggregation [21]. The key purpose of NCs formation is to enhance the solubility and dissolution rate of a poorly soluble drug. This is achieved through particle size reduction, which increases the overall surface area of a compound, and serves to improve the bioavailability observed following drug administration [22]. Owing to their composition, which is theoretically 100% drugs, NCs are associated with a high drug loading and avoid issues related to encapsulation efficiency, a common criticism of other nanomaterials [23]. Moreover, the rate at which the drug is released from a NC formulation can be finely tuned by altering the particle size. Additional benefits include prolonged retention time of NCs in systemic circulation, passive and site-specific tissue targeting, and enhanced stability due to the use of stabilizers [24]. It is possible to deliver NCs in powdered form; however, more commonly they are formulated into a liquid dispersion known as a nanosuspension [25]. A further advantage of NCs is the simplicity of their formulation, which lends itself to industrial scale-up.

Whilst not extensively, studies also focus on medium-soluble actives' (e.g., acyclovir and caffeine) enhancement with this technology as these face poor permeability and bioavailability issues despite displaying a degree of solubility. This is particularly useful for topical delivery, whereby NCs can achieve a higher saturation solubility leading to no recrystallization of the crystalline formulation and thus exhibit a continuous treatment through a passive diffusion gradient establishment between the applied formulation and the skin membrane as well as *via* hair follicular route. The improved adhesiveness to the skin from both the increased surface area of NCs as well as the stabilizers' properties which were coating NCs can also advocate for improved residence time and less wastage of formulation, which is an inevitable downside for commercial creams and ointments for instance [26,27]. Also, the encapsulation of NCs using a highly scalable technique, spray-drying, has been recently studied [27]. This methodology could be relevant for topical delivery, as it could be used to coat NCs with polymers that enable greater interaction with surfaces of interest. Another way to achieve an impactful disease management is through high particle specificity which is attained through particle surface functionalisation using different chemical reactions. This is a newly hot topic for NCs field; nonetheless, the present research has barely scratched the surface to realize the potential held by this approach for different drugs. Cellulose nanocrystal (CNC) functionalisation knowledge, work, and successful examples can serve as a guide for those wanting to apply this method for problematic drugs [28].

Currently, over 20 NC-based formulations have received market authorization with a similar number of formulations embarking clinical trials [22]. Majority of the marketed medications based on NCs are indicated for systemic conditions such as auto-immune diseases, cancer, and hypercholesterolemia etc.; however, the numerous reports in the literature support NCs' potential alone and in combination with different vehicles in being effective for local treatment as summarized in Table 1 and some of them are discussed further.

Table 1. Recent applications of drug NCs' in local areas.

Drug NCs	Problems with the drug	Application area	Drug delivery vehicle	Main improvements	Ref.
Acyclovir	Poor permeability, high lipophilicity, and bioavailability	Skin	NS formulation	Saturation solubility, drug penetration	[26]
Hesperetin and/or rutin	Poor aqueous solubility	Skin	Formulations, hydrogel, oleogel, and cream	Small particle size, dermal penetration	[29]
			Gel	Permeation, prevention of skin photaging and tissue damage	[30]
Curcumin	Poor aqueous solubility high lipophilicity and low bioavailability	Skin and hair follicles	Formulations, hydrogel, oleogel, cream	Enhanced follicular penetration, an establishment of passive dermal penetration.	[31]
			Eutectogels	Mechanical strength of the gel, long-acting drug delivery at high drug concentrations	[32]
Nile Red	Water insoluble photostable molecule	Hair follicles	NS formulation	Effective penetration and accumulation in hair follicles	[33]
Luliconazole	Low solubility and poor dermal bioavailability	Skin	Hydrogel	Solubility, dissolution, skin retention, and antifungal activity	[34]
Triamcinolone acetonide	Poor aqueous solubility	Eyes	*In situ* gelling system	Higher plasma concentration for longer duration	[35]
Itraconazole	Low solubility, limited bioavailability	Eyes	Thermosensitive and mucoadhesive ocular gel	*In vitro* and *ex vivo* action against a fungal strain	[36]
Genistein	Low solubility and high lipophilicity	Lungs	Lipid coated NC formulation	Slow release, residence of drug, reduced systemic absorption and macrophage clearance	[37]
C109 inhibitor	Low solubility	Lungs	Cyclodextrin	Reduction of infectious strains, inhibition of biofilms	[38]
Glibenclamide	Poor solubility	Skin	Patch	Reduction in blood sugars and counteracted hyperglycemia, and high drug content maintenance	[39]
Dexamethasone	Poor solubility	Skin	NC formulation	Drug penetration and fast delivery	[40]
Montelukast	Poor solubility and chemical instability	Skin	NS formulation and hydrogel	Drug stability and transdermal delivery	[41]
Apremilast	Modest lipophilicity and low solubility	Skin	Formulation, gel and cream	Saturation solubility and drug penetration	[42]
Acetazolamide	Poor solubility and permeability	Eyes	NC formulation with the choice of polypeptides	Safety, tolerability, and efficient ocular hypotensive activity	[43]
Indomethacin	Practically insoluble, very lipohillic	Eyes	*In situ* gelling system	Retention time, corneal permeation, faster diffusion	[44]
Curcumin	As above	Lungs	NC formulation	Faster dissolution, diffusion, plasma concentration and systemic absorption	[45]

2.1.1. Skin formulations

Due to effective barrier properties of the skin, a majority of drug molecules are unsuited for transdermal drug delivery in a passive manner, and due abundance of the research using NCs for skin conditions this is considered as a very bright approach for transdermal drug delivery [46]. The effect of NCs formation on the transdermal delivery of one such drug, hesperetin, was investigated by Pelikh *et al*. (2018), where it was found that both particle size and excipient/vehicle type directly influenced the permeation of this poorly soluble molecule across the pig ear skin [29]. A reduction in particle size resulted in enhanced transdermal permeation both in terms of total drug delivered and the depth to which it was delivered in the used skin [29]. Furthermore, the use of common hydrophilic permeation enhancers such as urea, glycerol, ethanol, or propylene glycol led to reduced transdermal permeation of hesperetin, whereas lipophilic oils, creams, and oleogels enhanced drug delivery across the skin.

Building on this work, the same group investigated the influence of vehicle properties on the delivery of curcumin NCs into hair follicles. This research revealed that the skin hydration was the most important characteristic that a vehicle must possess in order to facilitate NCs delivery into hair follicles and highlighted the flexibility in terms of formulation for such formulations [31]. In a similar manner, Corrias *et al*. (2017), formulated NCs of the poorly soluble model drug Nile Red *via* media milling and investigated the potential of these NCs for targeted delivery to hair follicles [33]. Following topical administration, scanning electron microscopy, confocal microscopy, and *in vitro* skin permeation studies confirmed the accumulation of Nile Red NCs inside hair follicles and surrounding layers of skin and suggested the formation of a drug depot and therefore an extended drug release profile.

NCs incorporated within a gel formulation containing a topical anti-septic therapeutic, nitrofurazone, that is effective against a wide range of gram-positive and gram-negative bacteria has enhanced dissolution and permeation of this drug compared to the commercial medicine as observed in an *in vivo* rat model [47]. Moreover, the formulation of a hydrogel containing luliconazole NCs for the treatment of topical fungal infections was reported by Kumar *et al*. (2019). This NC-containing polymer system demonstrated an improved *in vitro* skin permeation, and importantly, was significantly more effective against *Candida albicans* when compared to the control containing coarse drug particles [34].

2.1.2. Ocular formulations

Following the approved safety and efficacy of nanotechnology-based ocular drug delivery, triamcinolone acetonide, a cost-efficient treatment for many ocular diseases, has been combined with more complex carriers like liposomes, lipid nanocapsules, nanoemulsions, etc., [48]. However, none of these options would maintain the low total cost of the potential medicine, except for NCs which offer a more straightforward optimization method resulting in a simple and scalable formulation. In situ gels in combination with this drug's NCs were thought to be a great alternative to an intravitreal administration as they achieved significantly sustained and higher concentrations of the NCs, which was crucial for an effective combating of posterior uveitis in an *in vivo* model. Thus, the intimate contact leading to higher exposure of this topical formulation with the precorneal membrane was important for the formulation to permeate into deeper ocular tissues [35]. Another thermosensitive *in situ* gel was formulated with a wide spectrum antifungal agent, itraconazole NCs, by Permana *et al*. (2021). As predicted by the usage of NCs for ocular indications, the formulation achieved increased solubility of this agent as well as residence time causing a 93% antifungal activity in an *ex vivo* infected model expressing the possibilities that are present to effectively alleviate fungal keratitis [36].

2.1.3. Pulmonary formulations

Building on the past examples whereby the pulmonary drug NCs would result in a rapid solubilization and a systemic absorption, He et al., (2023) have developed the combination of genistein NCs with a phospholipid coating to achieve a sustained-release profile with a prolonged retention avoiding intercellular and transcellular distributions [37]. This was a promising development to ensure that effective drug concentration was not lost before the therapeutic effect was exhibited. Another pegylated NS of C109 blocker combined with a cyclodextrin inhabitable system led to a higher exposure, saturation solubility and thus diffusion into lung fluids [38]. This was essential for a pronounced *Burkholderia cenocepacia's* biofilm inhibitory effect, which is notorious for worsening Cystic Fibrosis in patients, but only in a case of combined therapy with a conventional antibiotic.

2.2. Polymeric nanoparticles

Polymeric nanoparticles comprise a subset of nano systems that can be divided into two groups: nanocapsules and nanospheres. The former presents cavities surrounded by a polymeric shell and the latter a polymeric matrix system. According to shape or specific structures, these two categories can be further subclassified into polymersomes, dendrimers, and polymeric micelles. Other polymer-based nanocarriers, such as nano-cubosomes and polymeric nanofibers, can also be found in the literature [49].

Active pharmaceutical ingredients (APIs) can be encapsulated within the core, entrapped in the polymer matrix, chemically conjugated to a polymer or bound to the surface. This enables the delivery of hydrophobic and hydrophilic compounds, as well as of cargos with different molecular weights, including small molecules, biological macromolecules, and proteins, making polymeric nanoparticles highly useful for co-delivery applications. Furthermore, loading efficacy and drug release can be precisely controlled by modulating composition, stability, and surface charge. Thus, the main advantage of polymeric nanoparticles is their versatility. A drawback of polymeric nanoparticles is that they present an increased risk of particle aggregation and toxicity, and these are the reasons accounting for the limited number of products present on the market compared to the approved medicine of lipid-based nanoparticles. However, the risk of toxicity of polymeric

nanoparticles for topical applications is considerably lower than for the systemic administration [50].

2.2.1. Skin formulations

One study showed that the pre-treatment of skin with polyamidoamine dendrimers promoted an increase in the depths of permeation and the amount delivered of the topically applied antimicrobial drug chlorhexidine digluconate [51]. Nano-cubosomes loaded with norfloxacin for the management of otitis externa, were formulated with glyceryl monooleate, Cremophor EL, and either Pluronic F108 or Pluronic F127 as polymeric stabilizers. Good permeation capability of nano-cubosomes and enhanced deposition of norfloxacin were observed in rabbit ear skin without signs of skin irritation or inflammation compared to the drug suspensions [52].

2.2.2. Ocular formulations

Polymeric nanoparticles have also demonstrated their utility for ophthalmological local applications. Stability and ocular biodistribution of topically administered polylactic-co-glycolic acid, PLGA, nanoparticles loaded with lutein, a carotenoid antioxidant associated with ocular health, were studied to address eye diseases [53]. The stability of formulation was only achieved at refrigeration conditions without any decay of the drug; however, it did not favor the elevated temperatures. When nanoparticles were administered topically, an increased uptake into exterior eye tissues and an interior tissue, corticoid, was recorded. Nonetheless, these particles have not escaped the rapid elimination from the eye, inferring the need for further development.

Another promising study has employed an alteration of the surface charge of polymeric nanoparticles of tacrolimus, which is known as immunosuppressant, with a potential use in ophthalmology to aid in inflamed corneal penetration and slower particle clearance. The obtained results suggested an extended-release profile with an increased ocular delivery and bioavailability and no signs of ocular irritation supporting this developmental direction's feasibility [54].

To prompt nanoparticles specifically to a target and avoid rapid clearance, Xu *et al*. (2018) developed functional intercalated nanocomposites with chitosan-glutathione-glycylsarcosine and layered double hydroxides. Glycylsarcosine is an active target ligand of the peptide transporter-1 (PepT-1) that can interact specifically with the PepT-1 on the cornea and guide the nanoparticles to the site of action. The developed nanoparticles showed internalization through active transport by PepT-1 and clathrin-mediated endocytosis. In addition, nanocomposites have demonstrated longer precorneal retention and higher drug distribution without ocular irritations, and exhibited an enhanced cellular uptake compared to the pure drug solution [55].

2.2.3. Vaginal formulations

Bioadhesion, easy penetration of the mucosa, controlled release, as well as less adverse side effects are the main advantages for the development of new pharmaceutical formulations based on nanoparticles for vaginal administration compared to conventional pharmaceutical forms [56]. Lucena *et al*. (2018) demonstrated an improvement of the treatment of vulvovaginal candidiasis of itraconazole-loaded polycaprolactone nanocapsules after topical administration. These nanocapsules were tested on female Balb/C mice infected with *Candida albicans* and showed superior performance compared to nanospheres [57]. In another study, two natural polymers were explored to retain imiquimod in the vaginal tissue for human papillomavirus (HPV) treatment and prevention of cervical cancer: chitosan-coated poly(ε-caprolactone)-nanocapsules were incorporated into hydroxyethyl cellulose gel and into chitosan hydrogel. Considering permeation, mucoadhesion, and retention, the combination of drug-loaded polymeric nanocapsules with chitosan gel showed the best performance for HPV treatment [58].

2.2.4. Pulmonary formulations

Non-invasive aerosol inhalation is a recognized method of drug delivery to the lung and remains a desirable route for nucleic-acid-based therapy. Hyperbranched poly(beta amino esters) were synthesized with diacrylate and amine monomers to enable suitable for inhalation nano formulation containing stable and concentrated mRNA polyplexes. Repeat dosing of inhaled hyperbranched mRNA polyplexes led to protein production in the lungs, without local or systemic toxicity, and resulted in a promising treatment option for respiratory diseases [59].

Considering the site-specific nature of periodontal disease and also the poor bioavailability of curcumin, Zambrano *et al*. (2018) conducted a proof-of-concept study to evaluate the biological effect of curcumin nanoparticles locally administered on experimental periodontal disease. Curcumin-loaded nanoparticles were prepared with PLA and PGA by emulsification and solvent evaporation. It was found that curcumin encapsulated in the polymeric nanoparticles effectively and inhibited inflammation and bone resorption associated with periodontal disease in an experimental model [60].

2.3. Lipidic nanoparticles

Lipid-based nanoparticles are mostly spherical platforms. Depending on the type, they often contain at least one bilayer of lipids surrounding at least one internal aqueous core [50,61]. Based on the composition of excipients, lipid nanocarriers include solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC) (also known as lipid nanocarriers (LNC)), liposomes, nanoemulsions, and lipid micelles [62].

Lipid nanoparticles are highly versatile for different administration routes, and they can deliver both lipophilic APIs, such as small organic molecules, and hydrophilic APIs, including proteins and peptides. Extended pharmacokinetics or controlled drug release can be achieved, especially with SLN. Lipid nanoparticles for topical applications show good patient compliance, improved therapeutic efficacy due to API accumulation at the site of action and, consequently, reduced side effects caused by systemic circulation. Physicochemical properties can be controlled to modulate their biological characteristics. For topical applications, certain excipients may provide enhanced occlusion and API penetration into the skin, ensuring local drug retention [50,63,64]. These

advantages have turned lipid nanoparticles into the most approved nanomedicine type from a regulatory perspective.

2.3.1. Skin formulations

SLN and NLC have been studied as potential carriers for both dermal and transdermal drug delivery of resveratrol, vitamin E, and epigallocatechin gallate. Lipid nanoformulations showed high uniformity, stability, and sustained release. Lipid nanoparticles improved the penetration of resveratrol through the *stratum corneum*, and they held promise for the delivery of resveratrol and vitamin E to provide long-lasting antioxidant benefits to the skin [65].

A clinical study for the treatment of pityriasis versicolor was carried out to investigate the effect of a topical gel containing fluconazole loaded SLN. High shear homogenization and ultrasonication methods using different concentrations of solid lipids (Compritol 888 ATO, Precirol ATO5) and surfactants (Cremophor RH40, Poloxamer 407) were used to prepare the SLN. The optimized formulation was incorporated into a gel using Carbopol 934. A significant improvement in therapeutic response compared to a marketed cream was observed [66].

Topical curcumin, although effective in hyperpigmentation and irritant contact dermatitis, is a challenging molecule due to poor solubility. Encapsulation of curcumin into SLN and subsequent loading into a gel makes it amenable to topical formulations. *In vitro* and *in vivo* studies demonstrated that this approach is a safe and effective alternative to conventional vehicles for the treatment of skin disorders [67].

2.3.2. Vaginal formulations

Most vaginal progesterone formulations have immediate drug release and require repeated administrations. For improved patient compliance, Correia *et al*. (2020) proposed the development of pessaries containing nanolipid capsules for prolonged vaginal delivery of progesterone, an innovative therapeutic strategy and a promising alternative for the vaginal application of progesterone [68]. Further, Badawi *et al*. (2021) performed clinical studies on metronidazole-loaded SLN, incorporated into Carbopol® emulgel, for bacterial vaginosis. They recorded significant enhancement in the therapeutic response of the optimized formulation regarding clinical treatment and low recurrence rate when compared to a marketed vaginal gel [69].

2.4. Inorganic nanoparticles

With the rise of organic chemistry and small-molecule drugs, the interest in inorganic materials was lost [70]. However, the advent of nano engineering has provided us with a toolbox for developing inorganic materials at a length scale that is relevant to wound healing processes and other topical treatments. Currently, inorganic nanoparticles can be manufactured with many compositions (silver, gold, iron oxide, silica, etc.) and shapes (spheres, cubes, stars, prisms, core-shell, etc.), making them an excellent alternative for designing advanced drug delivery systems for local delivery. This is mainly due to the high chemical reactivity that allows for them to be functionalized with biological materials or chemical species that add new advantages. Moreover, their plasmonic or magnetic properties enable them to react to external stimuli. The synthesis' robustness, versatility, and stability of inorganic nanoparticles give them potential advantages over small-molecule drugs. The following subsections highlight the most relevant inorganic nanomaterials for applications in local therapies.

2.4.1. Silver nanoparticles (AgNPs)

AgNPs possess antibacterial activity and have been used throughout the world for wound dressings, coatings, and impregnation of medical devices that provide a continuous release of silver ions [71,72]. Several studies have evaluated the possible interactions between AgNPs, keratinocytes, and fibroblasts during wound healing. The studies demonstrate that AgNPs increase the wound closure process in two ways: through the more significant proliferation and migration of keratinocytes and through promoting the differentiation of fibroblasts into myofibroblasts [73]. Additionally, Arora *et al*. (2015) have clarified the potential use of AgNPs against UVB radiation aimed at preventing skin carcinogenesis, obtaining greater efficacy than titanium dioxide nanoparticles (TiO_2NPs) and zinc oxide nanoparticles (ZnONPs) [74].

2.4.2. Gold nanoparticles (AuNPs)

Several recent works address the possibilities offered by gold nanoparticles (AuNPs) to combat skin diseases and transdermal drug delivery. Mahmoud *et al*. (2017) have described the preferred accumulation of AuNPs in hair follicles and their different behaviors according to the surface charge of the nanoparticles [75]. The AuNPs made the film resistant to microbial growth for long-term skin applications [76]. Additionally, AuNPs have also been found to be helpful for the treatment of psoriasis. In particular, methotrexate loaded AuNPs were tested in mice, demonstrating that they can penetrate through the epidermis with a slight arrival to the dermis, where psoriasis inflammation occurs. The results suggest that this new system would be of great value as a topical therapy in psoriasis patients [77].

2.4.3. Copper nanoparticles (CuNPs)

CuNPs have received increasing attention due to their antibacterial activity against inherent bacterial strains such as *Staphylococcus aureus* and *Escherichia coli* in diabetic foot ulcer infections. Tiwari *et al*. (2014) studied the biosynthesis of CuNPs and their use in wound healing activity in a rat and observed an increase in the wound healing rate [78]. Xiao *et al*. (2018) hypothesized that copper-based nanoparticles with metal organic frameworks (Cu-MOF NPs), when degraded in protein solutions and by modifying them, give Cu^{2+} ions that minimize toxicity and increase the effectiveness of curing the ulcer of the diabetic foot [79]. Furthermore, the addition of folic acid with CuNPs promisingly controls the release of Cu^{2+} ions from MOFs, improving biocompatibility. However, the rapid oxidation and aggregation of CuNPs are critical issues during their use. It is necessary to control the stability of CuNPs through the use of biocompatible stabilizers such as chitosan [80].

2.4.4. Zinc oxide nanoparticles (ZnONPs)

ZnONPs are used primarily in skin creams due to their antiseptic and anti-inflammatory properties [81]. Furthermore, the

effective use of ZnONPs enhances the wound healing process by remaining at the wound site for an extended period. In addition, the extensive use of ZnONPs in the medical field based on their effective antimicrobial action, low-cost and environmentally friendly synthesis has been highlighted [82].

2.4.5. Mesoporous silica nanoparticles (MSNPs)

Currently, MSNPs play a leading role as a carrier of drugs based on properties such as the absence of cytotoxicity, pore size, thermal stability, high surface area, and a well-organized mesoporous structure. Additionally, this structure can be modified to be sensitive to either response residues or to different stimuli [83]. In terms of skin-directed therapies, numerous scientific papers have been published on MSNP-based nanotechnologies. Ugazio *et al*. (2016) have designed a heat-resistant MSNPs-quercetin system that provides a controlled release of this antioxidant, depending on the temperature conditions of the skin and a protective effect of the antioxidant molecules [84]. Furthermore, it was shown that MSNPs act as efficient topical nanocarriers and show interesting properties to increase the stability of delicate antioxidant molecules such as flavonoid derivatives including vitamin E and quercetin [85,86].

2.5. Nanogels

Nanogels, or hydrogel nanoparticles, have gained tremendous attention in recent years since they combine the features of hydrogel systems and nanoparticles. Among the available typologies of nanoparticles and colloidal systems, nanogels are upcoming structures with specific and interesting properties [87]. Hydrogels are composed of hydrophilic polymers, displaying three-dimensional viscoelastic networks that retain water many times their dry weight and exhibit swelling under physiological conditions. In hydrogel nanoparticles, APIs can be conjugated to the surface or encapsulated inside the core [88,89]. On the contrary, nanogels are associated with issues in encapsulation efficiency of hydrophobic drugs (e.g., anticancer drugs) which simultaneously restrain drug loading and in entrapment of drug molecules due to loss of hydrophilicity caused by drug–polymer interactions [90]. However, as it is reflected in the abundance of research, these problems do not overshadow the enormous promises held by this platform in biomedical field and formulations' developments.

2.5.1. Skin formulations

Recently, a Carbopol® 980-based nano emulgel was developed for topical delivery of desonide to improve skin disorders [91]. Compared with a commercially available gel, the nano emulgel prolonged the drug release allowing for reduced administration frequency and dosing. Another type of nanogel, a micellar one, containing lidocaine and prilocaine indicated to provide a local anesthesia, with a thermoresponsive mixture composed of Pluronic® F127 and Tween 80, was developed by Sharma *et al*. (2016). The system altered its phase state (sol-to-gel) in response to temperature changes, making it suitable for topical application. These developed nanogels have improved the anesthetic effect in animal models and did not show histological changes as opposed to those observed with conventional systems [92]. Further, Giulbudagian *et al*. (2017) demonstrated an enhanced topical delivery of dexamethasone using β-cyclodextrin decorated thermoresponsive nanogels, which were based on dendritic polyglycerol as a crosslinker and linear thermoresponsive polyglycerol. Compared to commercial dexamethasone cream, this nanogel resulted in an efficient drug delivery to human skin's epidermis and dermis in an *ex vivo* study [93].

A biodegradable nanogel was composed of PLGA, chitosan, and 5-fluorouracil for the targeted treatment of skin cancer [94]. First, 5-fluorouracil was entrapped in a PLGA core followed by coating with chitosan for ionic interaction with anionic skin cancer cell membranes. Interestingly, an eucalyptus oil was employed by authors to coat the surface and aid in penetration of this nanogel into the *stratum corneum* for an enhanced antitumor activity. Nonetheless, in this system being cleverly designed to offer little invasiveness for skin cancer, only ~ 40% of an entrapped bioactive was available to penetrate the tumor tissue, which is likely to be further reduced until it reaches the target area indicating the need for further improvements.

Topical delivery approach has been further exploited for the case of inflammatory therapy. The gellan-cholesterol nanohydrogels loaded with baicalin showed a wound healing activity suggested by ~20% of baicalin deposition in the epidermis and dermis and the reestablished normal skin conditions [95]. Whilst this *in vitro* study might not be considered triumphant, the authors of this study were positive about the potential of this technology given the enhanced polyphenol accumulation which was deemed to aid in a complete skin recovery as suggested by inhibition of specific inflammatory markers present in the mice skin.

2.5.2. Ocular formulations

Another attempt to boost the topical bioavailability of acetazolamide in an ocular setting was the development of ocular surfactant-based nanovesicles in combination with a mucoadhesive nanogel [96]. The nanovesicles based on Span 60 and sodium deoxycholate were embedded in different concentrations of chitosan-sodium tripolyphosphate nanogels. Intraocular pressure lowering was significantly prolonged when comparing the nanogels to oral tablets. Minimal irritation after application of the nanogel formulation was observed compared to topical suspensions.

Furthermore, a nanocomposite platform composed of nanogels was designed for efficient delivery of ferulic acid to the cornea for wound healing after a trauma or a chemical injury [97]. This addressed the reports that corneal healing aligns with the detected levels of antioxidants, like ferulic acid, at the surface of the eye. In this case, the nanogel formulation was restrained from the release for a few days but was found to facilitate accumulation of this antioxidant in both control and unhealthy corneas as per reported values of >100 μg/cm^2.

2.6. Challenges of nano systems for local treatments

Despite the numerous benefits that nanoparticles offer for local treatments, there are several challenges that hinder

their clinical translation. For NCs, the production machinery consumes a significant amount of energy and faces wear issues, and if the drug is temperature-sensitive, this can pose further complications. Regarding lipid nanoparticles, their composition, the use of multi-lipid excipients, unique core-bilayer structures, and nanoscale size complicate critical quality attributes [98]. Limitations such as insufficient drug loading, drug expulsion (particularly due to phase transitions during storage), and relatively high-water content are noteworthy concerns [63]. The thermosensitivity of small molecules may also limit the selection of formulations based on lipid nanoparticles. Additionally, denaturation and degradation events can be problematic when considering biomacromolecules [99]. Despite the promising effects of inorganic nanoparticles, there are concerns about their toxicity. Regulatory agencies, including the Food and Drug Administration (FDA) and the scientific community, have recently intensified discussions about the safety concerns of inorganic nanomaterials and their application to intact skin in cosmetic products [70]. Moreover, applying these particles in wound care products is limited due to long-term tissue deposition (argyrosis), the formation of granulomas, and poor stability leading to limited clinical applications [100,101]. Thus, this becomes a challenge for formulation scientists to balance the good and bad aspects of inorganic nanoparticles. In the case of nanogels, a major challenge is controlling the size distribution in conjunction with process scalability. Conventional fabrication methods often result in high polydispersity of nanogels and present practical difficulties in modulating the physicochemical properties of the nanocarriers unless the polymeric material is altered. In this context, microfluidics offer highly controllable large-scale production yields, thereby creating new opportunities for advanced nanogel design. Furthermore, the integration with 3D printing technologies may provide additional benefits for the production of three-dimensional structured nanogels for biomedical and pharmaceutical applications [87].

3. Cyclodextrin (CD) inclusion complexes

One of the most promising and versatile tools for constructing new drug delivery systems are natural CDs and their derivatives. They have a typical truncated cone shape composed of D-glucopyranose units linked to α-1–4 glycosidic bonds. The three most common CDs are α-, β- and γ-CDs with 6, 7, or 8 units, respectively [102]. They differ in properties like melting point, solubility, and their dimensions. From a structural point of view, the hydrogen and glycosidic oxygen bonds simultaneously are directed toward the cone's interior, thus giving it a hydrophilic outer surface and an internal cavity with hydrophobic character. These macromolecules act as hosts, interacting through weak bonds with molecules within a hydrophobic region and suitable dimensions, while remaining soluble in an aqueous medium, a phenomenon known as inclusion complex formation. Despite the many factors involved, the CD-drug complexation is simple, even when the CD is part of more sophisticated molecular architectures, such as polymers, nanosponges, or nanoparticles.

In particular, in the pharmaceutical field, CDs are widely and successfully used as an important tool to modulate several properties affecting the performances and therapeutic profiles of drugs. CDs enhance the apparent aqueous solubility and rate of dissolution of poorly water-soluble drugs, reducing adverse reactions such as gastrointestinal or ocular irritation and other side effects, increasing permeability through biological membranes, reducing evaporation, and stabilizing flavors, improving palatability and handling and chemical stability in formulations [103–106].

However, different factors have stalled their use as drug carriers, including the limited solubility of native CDs, restrictions on the pool of possible molecules to be included, the short half-life in blood following *in vivo* administration and the non-control of drug release during its transport, which depends on the host–guest interactions, the pH and species present in the surrounding biological environment [107]. Consequently, studies into CD derivatives have advanced significantly since chemical modifications improve their properties and even grant new ones. In this new stage, attention is focused on CDs modified with functional groups, among which hydroxypropyl-β-CDs (HPβCDs), used for their greater solubility and improved entrapment properties, stood out, or amino-CDs and sulfo-CDs, which allow for expanding their functions through the binding of species by simple reactions or being grafted onto other materials.

Undoubtedly, the combination of CDs and their derivatives with nanomaterials substantially improves the properties and applications of both, especially in the field of drug delivery [108,109]. References to nanomaterials include all types of particles, polymeric, lipidic structures, or other types of systems that have dimensions on the nanometric scale and, therefore, acquire new properties and characteristics. Nanomaterials have been employed to improve the biopharmaceutical properties of several drugs through strategies such as nanoencapsulation, bioaccumulation, and passive and active targeting to the site of interest [105,110]. Therefore, to develop a successful drug delivery system, it is necessary to incorporate different materials that show synergistic results in combination. In this sense, biocompatible polymers have contributed significantly [105]. These are frequently used together with nanomaterials for pharmaceutical applications because they can improve drug loading, increase stability and bioavailability of nano systems, and add new functions such as controlled release through stimuli. These advantages translate into a decrease in the frequency of dosing, reducing costs and side effects. CD-based formulations are especially useful in noninvasive drug administration routes, such as ocular, nasal, pulmonary, and topical. The following subsections summarize some applications of these drug delivery systems. An overview is given in Figure 3 and the up-to-date research is summarized in Table 2.

3.1. Skin formulations

CDs can also be incorporated into creams and gels for topical drug delivery [103]. Although less explored, nanosponges may show great promise for treating skin disorders in this way.

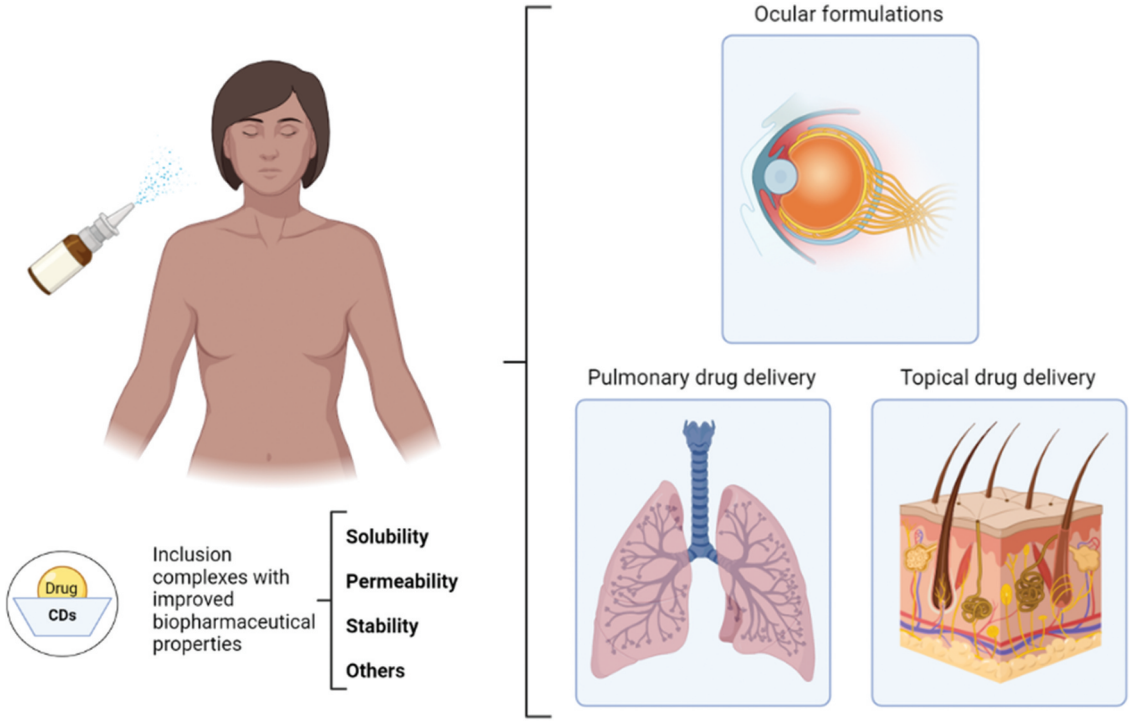

Figure 3. Graphic summary of different cyclodextrins-based advanced drug delivery systems applied to local therapies. The image was obtained with BioRender.com.

Table 2. Recent applications of cyclodextrins in drug delivery to local areas.

Drug NCs	Problems with the drug	Application area	Drug delivery vehicle	Main improvements	Ref.
Imiquimod	Poor aqueous solubility and skin penetration ability	Skin	Nanosponge hydrogel	Enhanced permeation and retention	[111]
Clobetasol propionate	Adverse drug reactions like skin atrophy, acne etc	Skin	Nanosponges	Improved anti-psoriatic activity due to better solubility, (photo)stability, and establishment of controlled release	[112]
Econazole nitrate	Poorly absorbed and accumulates	Skin	Nanosponge	Slow release and antimicrobial management	[113]
Curcumin and caffeine	Curcumin is poorly soluble, photoreactive, derived absorption and bioavailability.	Skin	Nanosponge	Anti-psoriatic activity and shorter treatment time, sustained drug release	[114]
Benzoyl peroxide	Skin irritation caused with drug	Skin	Nanosponges gel	Zero order release	[115]
Prednisolone	Lipophillic, poor solubility	Eye	Mucoadhesive CD-modified thiolated poly (aspartic acid)	In situ gellable, mucoadhesive formulation. Prolonged drug release	[116]
Cyclosporin	Rapid drainage from eye, poor solubility and lipohillic	Eye	Porous inserts	Cytocompatibility, prolonged release	[117]
Levofloxacin	Low ocular bioavailability	Eye	Chitosan NPs based on sulfobutyl-ether-β-cyclodextrin	Positive charge interaction with ocular tissue, two-times higher antimicrobial activity	[118]
Budesonide	Hydrophobic and of low bioavailability	Lungs	Nanosponge	Sustained drug release	[119]
Rolfumilast and farmoterol fumarate	Rolfumilast has narrow therapeutic window, dose associated with side effects	Lungs	Hydroxypropyl-β-cyclodextrin (HPβCD)	Reduced airway hyperresposivenes, high permeability, effective reduction in inflammation	[120]
Fisetin	Low solubility	Lungs	Sulfobutylether-β-cyclodextrin (SBE-β-CD)	Improved solubility	[121]

Nanosponges for topical drug delivery for resveratrol, γ-oryzanol, diclofenac sodium, and babchi oil have been mentioned in the literature [122–125]. Additionally, this nanoformulation helps to alleviate the local irritation problems associated with topical drugs. A more recent study has attempted to formulate econazole nitrate nanosponges using the quality by design (QbD) approach to handle a fungal infection on the selected animal model's skin [126]. The drug release in the favorable formulation was controlled by a diffusion mechanism and within 24 h only 77% of drug

content was achieved compared to the coarse drug release of 99% at the 4th hour. This was useful for this study as it confirmed the effective absorption of this drug to nanosponges, and the detected content was impactful for antimicrobial management compared to the conventional product.

3.2. Ocular formulations

Several studies have revealed that CDs and their derivatives are valid for the administration of ophthalmic drugs as eye drops as a preferred administration route despite low-administered dose [127]. One study formulated dexamethasone-γCD microparticles soluble in aqueous eye drops to deliver dexamethasone to the retina non-invasively. In experiments with rabbits, this formulation allowed 86% dexamethasone to reach the vitreous, it was chemically stable for 7 months and showed no side effects [103]. A formulation containing CDs and prednisolone on a thiolated poly(aspartic acid) gel showed excellent mucoadhesiveness and sustained release [128]. A study was also conducted to develop a cyclosporin A ocular implant that combined hyaluronate (HA) with HP-βCD. Drug release patterns were evaluated to determine the appropriate ratio of HA to HP-βCD, and this formulation was shown to be appropriate for ocular surface peptide drug release. Formulations combining HA and HP-βCD showed a controlled release of cyclosporin and promoted accumulation in the sclera, resulting in a suitable platform [117]. The development of formulations using CDs is expected to be effective for eye diseases such as glaucoma and conjunctivitis. The development of formulations using CDs is expected to be effective for eye diseases such as glaucoma and conjunctivitis.

3.3. Pulmonary formulations

The administration of drugs to the lungs has shown great potential as a local route of administration of protein drugs because this route of administration is appropriate for rapid absorption and efficacy [129]. As with other ways of administration, the use of CDs as drug carriers has been shown to increase drug solubility and membrane permeability, thus enhancing drug absorption from the lungs [130]. A study was conducted evaluating the suitability of the roflumilast and formoterol fumarate combinations of dry powder inhaler for pulmonary administration using HP-βCD [131]. This new formulation showed potential as a pulmonary delivery agent through *in vitro* stability and permeability tests and *in vivo* studies in animal models with asthma. In addition, a testing was conducted to evaluate the use of natural materials. CDs were used to improve the solubility of the natural flavonoid fisetin. The fisetin-SBE-βCD complex produced a dry powder with better aerosol properties and water solubility [121].

4. Devices loaded with actives ingredients

As noted previously, drugs or their nano derivates interchangeably are used in either different formulations and/or devices for selected indications. Herein, we briefly focused on several devices holding promise for topical applications.

4.1. Microarray patches (MAPs)

MAPs are minimally invasive devices used for local, transdermal, or intradermal drug delivery and diagnostic purposes, with a primary focus on skin conditions. These systems consist of arrays of microneedles (MNs) [132]. Although the primary research surrounding MAPs has concentrated on systemic drug delivery, they can also be effectively employed to enhance the treatment of local skin conditions. The early MAP systems developed for this purpose include hollow, coated, and dissolvable variants, which are illustrated in Figure 4.

MAPs can also be designed to be dissolvable or biodegradable, with the therapeutic agent incorporated into their matrix. These types of MAPs operate using a 'poke and release' strategy. The matrix, typically composed of biocompatible

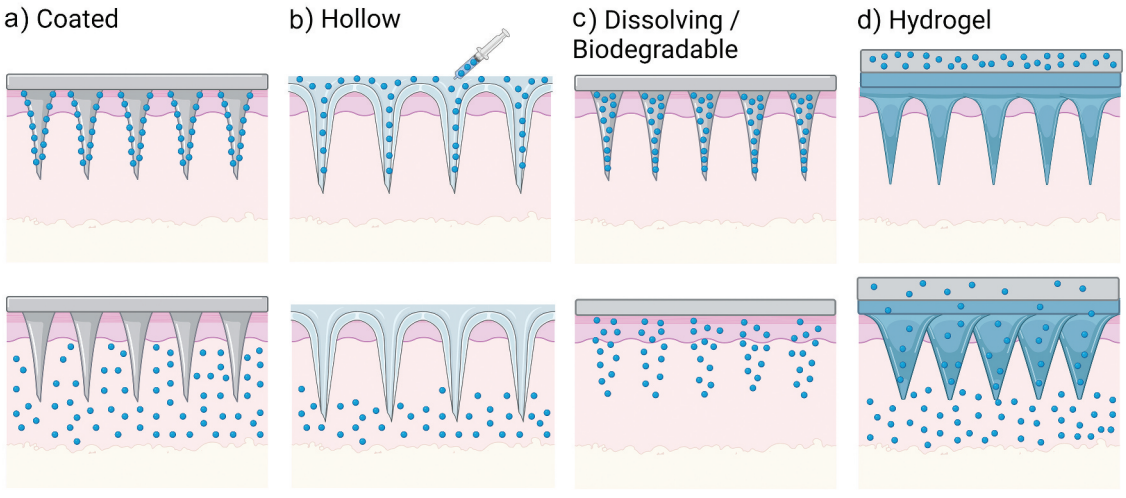

Figure 4. Schematic representation of the four different microarray patch (MAP) delivery strategies for local conditions including (a) coated, (b) hollow, (c) dissolving/biodegradable and (d) hydrogel. The image was obtained with BioRender.com.

sugars or polymers, dissolves, or biodegrades upon insertion into the skin when in contact with interstitial fluid. The matrix composition controls the release kinetics of the drug. In addition to enabling controlled drug delivery, dissolvable and biodegradable MAPs offer advantages such as the use of low-cost polymeric materials and straightforward, scalable micromoulding fabrication processes. The most recently invented system is hydrogel-forming MAPs. These follow a 'poke and swell' approach. The idea was first described in 2007 [133] and first utilized in 2012 [134]. Hydrogel-forming or swellable MAPs are made from cross-linked polymers and carry no drugs themselves. Upon skin insertion, they rapidly take up skin interstitial fluid and form aqueous hydrogel conduits that allow for drug permeation from a drug containing reservoir placed on top of the MAP through the unblockable conduits into the viable epidermis. They can be removed completely intact from the skin, thus, overcoming the issue of polymer deposition. Further, they cannot be reinserted due to the loss of sharpness upon swelling. As the therapeutic agent is located in a separate reservoir, the dose is not limited to the volume or surface of the MNs. Hydrogel-forming MAPs facilitate the delivery of molecules of various molecular weights, including proteins, but delivery is mainly limited to hydrophilic compounds due to the aqueous nature of the created conduits.

These have been employed in investigation stages for the delivery of a range of drugs showing considerable improvement in treatment outcomes compared to conventional systems for acne vulgaris, fungal infections, or chronic wounds, but this has not yet been elaborated into the market. In these cases, a sufficient piercing equals to therapeutically relevant levels of the active agent; however, this should avoid a systemic effect due to potential side effects.

For the acne indication, Zhang *et al*. (2018) developed MAPs with a crosslinked, reactive oxygen species (ROS) responsive polyvinyl alcohol (PVA) matrix for controlled release of clindamycin and to enhance skin healing by absorption of purulent exudates and debris, the base of MAPs was formulated from hyaluronic acid and diatomaceous earth. An *in vivo* mouse model confirmed these MAPs' considerable superiority in the reduction of skin swelling and inhibition of bacterial growth using the sustained-release profiling compared to clindamycin cream [135].

Considering topical treatment is often insufficient for deep cutaneous fungal infections, caused by the penetration of pathogens such as *Candida albicans* into deeper skin layers, the feasibility of MAPs for deep intradermal delivery of antifungals such as itraconazole [136,137]; and amphotericin B [138,139]. As an example, the intradermal delivery of micronized amphotericin B particles *via* dissolving MAPs with a matrix of PVA and Polyvinylpyrrolidone (PVP) increased the dermal bioavailability of amphotericin B 264-fold compared to intravenous application. Furthermore, the biodistribution into plasma and various organs was significantly lower, thus avoiding possible systemic toxicity [139].

Chronic wounds are often associated with bacterial biofilms, and their eradication is highly challenging. Multiple studies have investigated MAPs, combined with antibacterial agents, for enhanced penetration and, thus, eradication of biofilms and improved wound healing. To give an example, one study developed bacterial sensitive nanoparticles of poly (lactic-co-glycolic acid) and poly(-caprolactone) decorated with chitosan and loaded with doxycycline. The incorporation into dissolving MAPs significantly improved the dermatokinetic profiles compared to needle-free patches [140]. To overcome antibacterial resistances, the same authors explored the delivery of bacteria-responsive silver microparticles *via* dissolving MAPs, resulting in an eradication of 100% of bacterial bioburdens in an *ex vivo* model [141]. Dissolving MAPs can further be coupled with advanced systems such as electro spun nanofibers to deliver antimicrobial peptides [142] or other agents [143]. These examples give an idea of the various possibilities of improved local treatment using MAP products.

4.2. Wound dressings

A wound is characterized as a disruption in the epithelial lining of the skin or mucosa caused by physical, thermal, or chemical damage. Wound healing is a dynamic process and is based on the duration and nature of the healing process. The promotion of healing can be hindered by concurrent conditions that a patient may have, such as diabetes, cancer, coronary artery disease, or peripheral vascular disease, however, effective use of appropriate wound dressings could overcome these. These wound dressings are associated with the maintenance of a moist environment, facilitation of gaseous exchange, protection from bacterial infection, and promotion of wound debridement [144].

Wound dressings can be loaded with therapeutic agents establishing a dual role, as promoters of wound healing and as drug delivery platforms. Types of medicated wound dressing include those that are based on alginate, hydrocolloid, polyurethane foam, polymer hydrogels, and nanofiber scaffolds [145]. The active agents contained in medicated wound dressings can range from cleaning or debriding agents for necrotic tissue removal, to growth factors, antimicrobials, and anti-inflammatories. In the case of antibacterial agent loading, Zhang *et al*. (2018), loaded minocycline agent into a hydrogel wound dressing composed of PVA and chitosan, and reported reduced inflammation, increased collagen proliferation and more extensive microvasculature remodeling compared to a marketed product or sterile gauze, using an *in vivo* rat model [146].

4.3. Films for localised drug delivery to mucosal tissues

Mucoadhesion describes the adhesion between two materials, at least one of which is a mucosal surface (the lining of the respiratory, gastrointestinal, and urogenital tracts) and is a particularly important phenomenon in the field of drug delivery to mucosal surfaces [147]. Many different types of mucoadhesive dosage forms have been developed for the purpose of mucosal drug delivery including powders, compacts, sprays, semisolids, or films. Mucoadhesive films are of particular interest as they demonstrate flexibility in terms of their physical properties, design, drug-loading, and manufacture. Furthermore, sustained drug release can be achieved easily through modification of film composition, which directly

influences both mucoadhesion and rate of drug release. Films are most commonly made from either natural or synthetic polymers that are biocompatible, biodegradable, nontoxic, and nonirritant in nature and their design should lend itself to rapid disintegration yet ensuring adequate mechanical strength. They are applied easily and in a noninvasive manner, which is clinically advantageous and is characteristic for those with swallowing difficulties, dexterity issues, or needle phobia [148]. Whilst the technology is promising and is introducing a vast flexibility in the development area, the constraints arising from polymers used to build these systems impede their developmental progress.

In this instance, the vaginal drug delivery via polymeric films has garnered a substantial degree of attention due to the multiple conditions that can affect the female reproductive system, as well as the suitability of the vaginal mucosa for drug absorption [149]. Following a heavy focus on HIV-treatment developments in research, the antibiotics ciprofloxacin and metronidazole have been formulated into biocompatible polymeric films, which resulted in an enhanced drug delivery [150,151]. Significantly improved drug release was also observed for ciprofloxacin films, with adequate stability confirmed for metronidazole films [150,151]. Apart from vaginal applications, new films are also applied to the eyes allowing simultaneous delivery of lipophilic and hydrophilic drugs [152]. Or skin conditions including a film built from exopolysaccharides extracted from the thermophile and loaded with an antibiotic, amikacin, which resulted in 12-h steady release and a significant bactericidal effect experienced only in 48 h with negligible signs of cytotoxicity to skin components [153].

5. Other systems

The landscape of drug delivery systems for treating local conditions is broad, with an important number of emerging technologies in constant development. For instance, 3D printing (also known as additive manufacturing) presents competitive advantages for developing complex, personalized, and on-demand products, creating opportunities to improve the safety and efficacy of treatments for local conditions. Although there are nine different types of 3D printing techniques, only three have shown promising results in the pharmaceutical field: laser-based writing systems, inkjet-based printing systems, and nozzle-based deposition systems.

Table 3. Compilation of the different drug delivery systems (DDS) discussed in the review along with their advantages and disadvantages.

DDS	Advantages	Disadvantages	Efficacy data
NCs	Enhance solubility, dissolution rate and permeation of poorly soluble drugs. Easily scalable to industry.	Risk of instability and particle aggregation	NCs have demonstrated improved ocular retention time and prolonged drug action in ocular delivery [172]. Drug nanocrystals show great potential for pulmonary delivery, achieving higher lung tissue concentrations [173].
Polymeric NPs	High versatility, loading efficacy and controlled drug release.	Risk of particle aggregation and toxicity, Polymeric degradation can lead to loss of stability	Polymeric NPs have shown efficacy in skin diseases like psoriasis and atopic dermatitis [174], as well as in pulmonary infections [175], and ocular conditions [54].
Lipid NPs	Enhance drug delivery, controlled drug release, versatility, capability to encapsulate a wide range of drugs.	Low drug loading capacity, batch-to-batch variability, instability	Solid lipid NPs of budesonide have shown 80% pulmonary deposition in rats and a high in vitro emission rate [176]. In ocular delivery, anti-inflammatory lipid NPs demonstrated increased bioavailability compared to commercial drugs or free drug suspensions [172].
Inorganic NPs	High chemical reactivity, Diverse compositions and shapes, Robust synthesis.	Potential toxicity, Long-term tissue deposition, Poor stability.	Inorganic NPs have shown efficacy in combating skin diseases [72]. An increase in the wound healing rate has also been observed [75,79].
Nanogels	Stimuli-responsive properties, biocompatibility and biodegradability,	Complex synthesis process. Poor stability	In dermal applications, nanogels have enhanced the absorption of high molecular weight drugs, such as tacrolimus, thereby improving their anti-proliferative effects in skin conditions. In ocular drug delivery, they contribute to increased retention, controlled release, improved penetration, and sustained biocompatibility [177].
CD inclusion complexes	Enhanced solubility, stability, nontoxic and biocompatible	Complex synthesis process, Limited inclusion capacity	For ophthalmic and dermal treatments, complexes with ciprofloxacin, dexamethasone, hydrocortisone, and piroxicam demonstrated enhanced drug release and pharmacological activity [178].
MAPs	Minimally invasive, enhanced drug delivery, wide range of drug types	Limited drug loading capacity, complex manufacturing	MAPs has demonstrated efficacy on skin diseases and chronic wounds [134,135].
Wound dressings	Occlusive properties, protection from infections, variety of material options	Can cause skin irritation or allergic reactions	Wound dressings loaded with therapeutic agents as antibacterial agents has demonstrated reduced inflammation, increased collagen proliferation and more extensive microvasculature remodeling [142].
Mucoadhesive films	Flexibility in physical properties, design, drug-loading, and manufacture. Biocompatibility and biodegradability.	Limited surface area, mechanical stress, limited in drug loading capacity.	Mucoadhesive films has shown efficacy in vaginal drug delivery [150,151].
3D printed devices	Personalization and customization, on-demand, enhanced drug delivery.	High cost, limited material options, post-processing may be required.	3D printed devices have shown promising results in local cancer treatments [156,157], wound healing and skin applications [179].
Electrospun nanofibers	High surface area (enhanced drug absorption), high porosity, versatile composition, biocompatibility.	Production costs, complex process, scalability issues, stability concerns, limited drug loading capacity.	Electrospun nanofibers efficacy has been proved in localized cancer treatments [161] and wound healing [163].

CD: Cyclodextrin. MAPs: Microarray Patches. NCs: Nanocrystals. NPs: Nanoparticles.

Numerous articles can be found regarding their use in the treatment of local conditions, such as ocular therapies [154], gastric devices [155], local cancer treatments [156,157], vaginal rings, and intrauterine devices [158,159], among others. Another innovative approach that has gained considerable interest in recent years is the use of electrospun nanofibers. Electrospinning is a simple and versatile technique that relies on the electrostatic repulsion between surface charges to continuously draw nanofibers from a viscoelastic fluid [160,180]. In the field of local drug delivery, electrospun nanofibers have been explored for a range of applications, including local cancer therapies [161], controlled delivery of growth factors in tissue regeneration [162], and antimicrobial wound dressings [163]. The nanofiber scaffolds for the purpose of wound healing have garnered much attention recently due to their high surface-to-volume ratio and ability to mimic the fibrillar organization of the extracellular matrix and an achievement of uniform adherence and sufficient moisture occlusion [164,165]. Although nanofiber scaffolds promote wound healing without the addition of therapeutic agents, the combination of loading of these structures with drugs can function as a synergistic approach to achieve enhanced wound reparation. For example, antibiotics, such as ampicillin and ciprofloxacin, have been successfully loaded into various types of nanofiber scaffolds, with each demonstrating a rate-controlled drug release in an *in vitro* setting [166,167]. Electrosprayed nanoparticles also represent a promising technology in the field of treating local conditions. Electrospraying is a technique closely related to electrospinning; however, instead of forming continuous fibers, it generates nanoparticles by applying electrical forces to atomize liquids [168]. One interesting application of electrosprayed nanoparticles is in the local therapy of cancer [169,170,182]; however, studies can also be found exploring their potential in the field of ocular drug administration [171]. In Table 3, a summary of the advantages and disadvantages of the drug delivery systems discussed throughout the review can be observed, alongside data collected regarding their efficacy in local treatments.

6. Conclusion and future perspective

Current advancements, such as NCs, various nanoparticles, CDs, and nanogels, still face inherent biological barriers that limit their clinical application. These nanosystems and devices share certain challenges: limited or absent translation to the market, the need to manage the limitations of existing marketed drugs and a lack of in vivo trials. Nevertheless, the significant body of research focused on localized conditions of the skin, eyes, vagina, and lungs underscores the demand for innovative solutions, the untapped potential of these technologies, and the advantages of this route of administration. Despite the high scalability of certain innovations, such as NCs and lipid-based NPs, limitations persist, including encapsulation efficiency, drug loss, and toxicity issues. However, the landscape of advanced drug delivery systems for treating local conditions is evolving rapidly, with increasing focus on novel systems, such as core-shell nanostructures and Janus nanoparticles [183,184]. These systems offer unique advantages, including controlled release, the capacity to combine multiple functionalities, and the potential for multimodal therapies. While certain obstacles still need to be overcome, these technologies are expected to progress from research to clinical applications, providing new solutions for localized treatments.

Disclosure statement

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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