


## Review

# Recent Development of Nanomaterials for Transdermal Drug Delivery

Moong Yan Leong<sup>1,†</sup>, Yeo Lee Kong<sup>2,†</sup>, Kevin Burgess<sup>3</sup>, Won Fen Wong<sup>4,\*</sup> , Gautam Sethi<sup>5,\*</sup> and Chung Yeng Looi<sup>1,\*</sup>

<sup>1</sup> School of Biosciences, Faculty of Health and Medical Sciences, Taylor's University Lakeside Campus, Subang Jaya, Selangor Darul Ehsan 47500, Malaysia

<sup>2</sup> Department of Engineering and Applied Science, America Degree Program, Taylor's University Lakeside Campus, Subang Jaya, Selangor Darul Ehsan 47500, Malaysia

<sup>3</sup> Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, TX 77842, USA

<sup>4</sup> Department of Medical Microbiology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur 50603, Malaysia

<sup>5</sup> Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117600, Singapore

\* Correspondence: wonfen@um.edu.my (W.F.W.); phcgs@nus.edu.sg (G.S.); chungyeng.looi@taylors.edu.my (C.Y.L.)

† These authors contributed equally to this work.

**Abstract:** Nano-engineered medical products first appeared in the last decade. The current research in this area focuses on developing safe drugs with minimal adverse effects associated with the pharmacologically active cargo. Transdermal drug delivery, an alternative to oral administration, offers patient convenience, avoids first-pass hepatic metabolism, provides local targeting, and reduces effective drug toxicities. Nanomaterials provide alternatives to conventional transdermal drug delivery including patches, gels, sprays, and lotions, but it is crucial to understand the transport mechanisms involved. This article reviews the recent research trends in transdermal drug delivery and emphasizes the mechanisms and nano-formulations currently in vogue.

**Keywords:** nanomaterials; transdermal drug delivery; transdermal mechanisms



**Citation:** Leong, M.Y.; Kong, Y.L.; Burgess, K.; Wong, W.F.; Sethi, G.; Looi, C.Y. Recent Development of Nanomaterials for Transdermal Drug Delivery. *Biomedicines* **2023**, *11*, 1124. <https://doi.org/10.3390/biomedicines11041124>

Academic Editor: Ali Nokhodchi

Received: 22 February 2023

Revised: 21 March 2023

Accepted: 24 March 2023

Published: 7 April 2023



**Copyright:** © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Targeted medication comprises selective deployment of pharmaceutically active components at predetermined sites to reduce adverse effects and enhance treatment efficacy [1–3]; essentially, these methods increase therapeutic indices. Targeted approaches have been significantly advanced by colloidal carrier forms centered on biocompatible and biodegradable polymerics, including nanoparticles (NPs) [4]. According to one definition [5,6], nanoparticles are small solid colloidal substances of 1–1000 nm diameter, made from polymers, lipids, or metals. Active particles in NP may be dissolved, encapsulated, entrapped, or absorbed [7]. Preferred NPs for nanomedicine are loosely regarded as less than 200 nm [8]. Particle size plays a crucial role on drug distribution, release rates, targeting abilities, and toxicities [9]. NPs can be classified according to their properties, shapes, sizes [10], or into nanospheres (matrix structure for dispersing functional biological materials) and nanocapsules (membrane structure using an oil or aqueous core to contain drugs) [11].

NPs modify permeability [12], half-life [13], cytotoxicity [14,15], pharmacokinetics of medications, and diagnostic agents [16]. They can be nanosensors [17,18], drug carriers [19,20], and diagnostic agents [21,22]. Research has emphasized improving absorption through the skin to maintain homeostasis [23–25] using micelles [26], liposomes [27], or polymers [28]. NPs can infiltrate the skin via intracellular, intercellular, or transcellular pathways [29–31] where penetration depths are determined by particle size [32,33] initiated by hair movement within the follicle; 600 nm particle size may be optimal for some NPs [34];

however, permeation will depend on NP composition. Permeability images for 30 nm cadmium selenide/zinc sulfide (CS/ZnSO<sub>4</sub>) NPs through mouse skin after ultraviolet light (UV)-B radiation-induced epidermal disturbance [35] revealed that these NPs in sebaceous glands and in the skin are aggregated. NPs in this study tended to be localized in the epidermis interstitium [35–37].

## 2. Important NP Physical Compositions

### 2.1. Micellular

Micelles are amphiphilic spherical structures with hydrophobic and hydrophilic regions [38] varying from 5 to 100 nm [39]. The hydrophilic region of micelle allows intravenous administration, whereas hydrophobic regions tend to be for cargo storage [40]. These micellar NPs can deliver macromolecules as they offer a sustained and controlled release of biomolecules, physicochemical stability of the embedded molecules, enhanced drug pharmacokinetics, and drug bioavailability [41]. Micellar NPs promote small NPs, good entrapment efficiency, and are inexpensive relative to other nanocarriers (liposomes and niosomes) [42].

Micellar NP formulations have revolutionized transdermal therapeutics [43], enabling high concentrations of drugs to permeate the skin, forming a drug depot in the epidermis [44]. This route of administration minimizes gastrointestinal contact and hepatocyte's first-pass effects, and it is more cosmetically tolerable to patients [42]. Physicochemical characteristics of micellar NPs formulations can be modified for various routes of administration [45], e.g., by changing miscibilities to optimize transdermal penetration, combining a mucoadhesive for vaginal administration, changing the particulate size, or adjusting the zeta potential versus in suspension [42,46]. The following are illustrative examples of micellular formulations.

Polymeric micelles from hyaluronic acid (HA) of 200 nm did not stay on the epidermis but permeates it. Optical microscopy images revealed HA was in keratinocytes and fibroblasts and micelle disruption begins at approximately 10 mm deep in the skin [47].

Vinpocetine (VPC)-loaded D- $\alpha$ -tocopherol polyethylene glycol 1000 succinate (TPGS) and alpha lipoic acid (ALA) (VPC-TPGS-ALA) film was used for transdermal drug delivery [48]. This film enhanced VNP penetrability in the epidermis compared to raw VNP-loaded transdermal film; optimized TPGS-ALA gave improved penetration in the epidermis after 0.5, 2.0, and 4.0 h compared to the raw VNP-loaded transdermal film [48].

Azole antifungal agents-loaded micellar NPs increased in skin which led to deposition in hair follicles as revealed by confocal microscopy. Skin absorption using methoxy-poly(ethylene glycol)-di-hexyl-substituted lactide (MPEG-dihexPLA) micelles can enhance epidermal drug bioavailability, which might result in increased efficacy of in vivo treatment [49].

### 2.2. Magnetic NPs

Super paramagnet magnets (Fe<sub>3</sub>O<sub>4</sub>) and magnetite (Fe<sub>2</sub>O<sub>3</sub>), commonly used in medical applications [50], have particle sizes of 3–30 nm and size distributions of ~10–20% and they dissolve in water [51,52]. Iron oxide (Fe<sub>3</sub>O<sub>4</sub>) magnetic NPs of a small size are favored for biomedical and biological applications [53].

Magnetic NPs used in pharmaceutical applications have small sizes [54], good biocompatibilities [55,56], are easy to process [57], and can be endowed with unusual characteristics [58]. The number of research papers on magnetic NPs has dramatically increased over the last two decades [59–64]. Their magnetostrictive responses enable biomolecules to be magnetically detected, allowing new exciting perspectives on bio-separation [65,66], bio-detection [67,68], and targeted drug administration [69]. Furthermore, external magnetic fields can heat them, providing treatment options via magnetic fluid hyperthermia [70].

In one illustrative study [71], Fe<sub>3</sub>O<sub>4</sub> NPs were used as a core coating, followed by creating laser-sensitized magnetic nanoparticles (LMNs) loaded bacteria cellulose membrane (LMN/BC). Furthermore, the results reveal that laser-activatable and magnetostrictive

LMNs synergistically impact breast cancer inhibition, making it an alternative treatment option for superficial cancer [71].

A recent report described how cobalt ferrite magnetic ( $\text{CoFe}_2\text{O}_4$ ) NP could be used to remove azithromycin, an antibiotic for treating infectious diseases such as COVID-19, from hospital effluents via UV illumination [72].  $\text{CoFe}_2\text{O}_4$  NPs are attracted to magnetic fields and generate heat when they move; this magnetic fluid hyperthermia is central to these noninvasive cancer treatments [73]. Similarly, nickel (Ni) NP have a high surface area relative to their size, allowing for a large capacity of drugs to be carried in the drug delivery system, imaging, and cancer treatment [74].

### 2.3. Hollow NPs

Hollow NPs with penetrable and porous shells have unique properties relative to solid ones: a high surface area, high loading capacity [75], less expensive [76], and low density [77]. Research shows that hollow NPs with a high surface area could effectively accommodate strain throughout a chemical reaction while promoting complete electrolyte penetration [78]. The following are illustrative studies featuring hollow NPs.

Semiconductor hollow copper sulfide nanoparticles (HCuSNPs) are synthetic photo-absorbers [79] with a diameter ranging from 3 to 11 nm [80]. Furthermore, the photo-thermal [76,81] features of the HCuSNPs enable them to capture near-infrared light and reach temperatures of around 40 °C before partially damaging the stratum corneum and allowing the drug to deliver safely [76]. Thus, HCuSNPs have been used to deliver chlorin e6 (Ce6, a photosensitizer) and doxorubicin (DOX) to the 4T1 mouse mammary cells [82]. The thermo-responsive degradation of HCuSNPs can trap drugs for controlled release via light-induced thermal stimuli. This resulted in the minimal clearance of drugs non-specifically in the circulation, thereby increasing drug bioavailability in tumor tissues by improving permeability and retention effects [82].

Recently, Zan et al., 2022, incorporated copper sulfide nanodots (CuSND) into the intravenous thermo-responsive hydrogel to elicit alleviating remodeling via transdermal mild photo-thermal therapy on the transdermal white adipose depot. Meanwhile, mirabegron was also co-administered with CuSND hydrogels, resulting in a substantial therapeutic synergistic effect. The result demonstrated that in vivo CuSND hydrogel treated with high-fat diet mice were found to have lower triglyceride serum levels, insulin, cholesterol, and glucose, and enhanced insulin sensitivity compared to the untreated group [83].

Another study shows reactive oxygen species (ROS)-responsive hollow mesoporous silica nanoparticles (HMSNs) loaded with Glabridin were investigated by [84] as a nanocomposite for transdermal drug delivery and anti-pigmentation. The results demonstrated that HMSN-CD/1-adamantanemethylamine tagged polyarginine peptides (Ada-R8) (HMSN-CD/Ada-R8) loaded with Glabridin improved the broadening of Glabridin usage and achieved a great photoprotection ability. The NPs were highly stable in aqueous solutions and demonstrated good biocompatibility while releasing Glabridin in a controlled ROS-responsive way [84].

In previous study, (Wang et al., 2021) has produced glucose-responsive polymer grafted hollow mesoporous silica (HMSNs-PAPBA) NPs for in vivo culture for diabetes Sprague Dawley (SD) rats. The results show that drug diffusion was effectively inhibited and fast released under typical hyperglycemia conditions in an average blood glucose level [85].

Likewise, Zhang et al., 2018, developed the polydopamine/lauric-acid-coated (PDA/LA-coated) hollow mesoporous  $\text{SiO}_2$  for transdermal delivery. The result showed that the PDA/LA-coated hollow mesoporous  $\text{SiO}_2$  exhibits a good photothermal-response, and is non-toxic in in vivo type II diabetes SD rats [86].

### 2.4. Hydrogel NPs

Hydrogels have a high water absorbing capacity [87,88] which can be integrated as drug carriers for transdermal drug delivery [88] due to their adhesion ability to the skin

surface [89]. The porosity of the semisolid morphology of a hydrogel matrix allows a higher rate of drug loading and release [90,91].

Hydrogels can be biocompatible and biodegradable, particularly if made from natural materials. They are often used as biopolymers in transdermal drug delivery due to their hydrophilic properties and sensitivity to external stimuli [90,92]. Transdermal drug delivery using hydrogels has unique features including prolonged release behavior [89,93,94], low toxicity [95], and liver damage prevention [89]. Table 1 summarizes the recent studies of hydrogel in transdermal drug delivery.

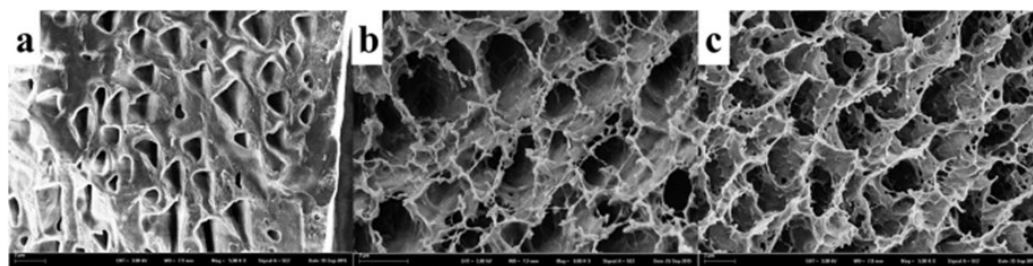
**Table 1.** The applications of hydrogel in transdermal drug delivery.

Hydrogel	Application	Results	References
Polyethylene glycol diacrylamide (PEG-DA) hybrid hydrogel	Mouse embryonic fibroblast cell lines (NIH 3T3)	Good mechanical property, excellent swelling capacity biocompatibility, and non-toxic to skin	[96]
Gelatin-polyacrylamide (Gel-PAAm) hydrogel	Human skin	Non-toxic to human cells, highly stretchable, and good swelling properties	[89]
Polyacrylamide-grafted-chondroitin sulfate (PAAm-g-CS) hydrogel	Rat abdominal skin	No inflammatory cell infiltration, small degradation of skin, and decreased pore size	[97]
Chitosan-azelaic acid (CS-AZ) hydrogel	L929 mouse fibroblast	Excellent swelling, water vapor permeability, high porosity, and low cytotoxicity	[98]
Carboxymethyl chitosan-silk fibroin peptide/oxidized pullulan (CMCS-SFP/OPL) hydrogel	Newborn porcine Tskin	Good swelling, water retention properties, skin permeability, water absorption ability, excellent mechanical properties, and biocompatibility	[99]
Carboxymethyl chitosan-grafted-2 hydroxyethyl acrylate (CmCHT-g-pHEA) hydrogel	Micropig dorsal skin	Good pH sensitivity, pores size decreased when ratio of grafting agent increased, improved skin penetration, and non-toxic to skin	[100]

### 2.5. Poloxamer Hydrogels

Poloxamers hydrogels are thermosensitive polymers commonly employed in situ [101]. Poloxamer 407 (P407) is widely used in transdermal applications due to its good absorbing ability [102], prolonged drug release [101], low toxicity [103], and high biocompatibility [104]. P407 hydrogels have been studied as potential nanocarriers in drug delivery systems owing to their non-irritating action on cellular membranes and sustained release of drugs with minimal side effects [105,106].

According to transdermal research, a P407 hydrogel matrix loaded with carboxymethyl cellulose sodium (CMCs) has been developed to investigate the transdermal permeability in porcine ear skin [107]. As observed in the study, CMCs improved the porosity of a P407 hydrogel structure, and the developed P407/CMCs hydrogel enhanced the overall drug penetrability into porcine ear skin without using chemical effectors [107]. P407/CMCs hydrogels have also been developed to treat atopic dermatitis (AD) and the results showed that the hydrogel exhibited favorable percutaneous [108]. The FESEM images showed that the porosity of the P407/CMCs hydrogel was increased due to the presence of CMCs, which consequently facilitated the drug release across the skin, as shown in Figure 1 [107].



**Figure 1.** FESEM images of P407/CMCs hydrogel across the skin (a) blank hydrogel (PC200), (b) 2% P407/CMC loaded hydrogel, (c) 4% P407/CMC loaded hydrogel (PC204) (Reprinted from [107] Wang, W. Wat, E. Hui, P.C.L. Chan, B. Ng, F.S.F. Kan, C.W. Wang, X. Hu, H. Wong, E.C.W. Lau, C.B.S. Leung, P.C. Dual-functional transdermal drug delivery system with controllable drug loading based on thermosensitive poloxamer hydrogel for atopic dermatitis treatment. Images reproduced with permission from Scientific Report (2016), <https://creativecommons.org/licenses/by/4.0/> (accessed on 16 February 2023)).

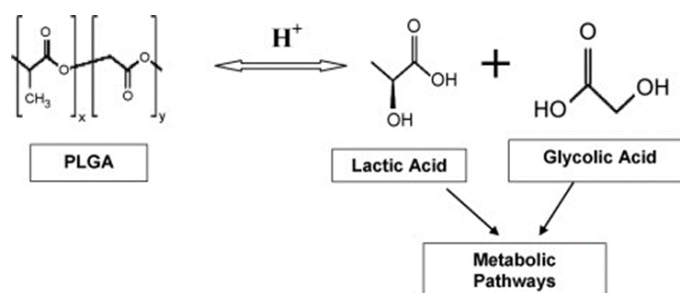
### 2.6. Acrylic Acid Copolymer Hydrogels

Furthermore, VACPH hydrogel was produced by copolymerizing acrylic acid (AA), vinyl benzyl trimethylammonium chloride (VBTMACl), polyvinylpyrrolidone (PVP), and choline ionic liquid (ChMACl) [109]. The strong polarization of ammonium cations in VBTMACl means microwaves enhance their thermal conversion capabilities, resulting in the heat killing of *S. aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) [109]. In another application, fluconazole and functionalized gold nanorods were conjugated and incorporated into a P407 hydrogel to produce a nano complex structure for non-toxic transdermal delivery to human dermal fibroblasts CCD-1064Sk cells [110].

Polyacrylamide (PAAm)-grafted-pectin (PCT) (PAAm-g-PCT) hydrogel was produced by free radical polymerization and alkaline hydrolysis techniques as rate-controlling membranes (RCMs) in an electro-sensitive transdermal drug delivery system [111]. The result reveal that drug permeability reduced with an increase in glutaraldehyde concentration and drugs in electro-sensitive transdermal drug delivery systems increased with an applied electric stimuli. The same group produced a polyacrylamide-graft-pullulan (PAAm-g-PLN) hydrogel and showed that drug permeation was minimal when no electric stimulus was applied but diffusion rates increased with electric stimulation [112].

### 3. Poly(lactide-co-glycolide) (PLGA) NPs

PLGA NPs [113,114] are particularly important due to their biodegradability [115], biocompatibility [116], lack of toxicity [117], and capacity to protect biomolecules from degradation [114]. PLGA NP sizes vary from 100 to 5000 nm [118] and the average intracellular delivery range is from 107.7 nm to 245.7 nm [119]. They hydrolyze in the body to produce innocuous smaller synthetic polymeric materials comprising lactic and glycolic acids [117,120], Figure 2.



**Figure 2.** Overview of hydrolysis of poly(lactic-co-glycolic acid) (Reprinted from [117]. Copyright (2010), with permission from Elsevier).



PLGA NPs are attractive for drug delivery and tissue engineering. Size of PLGA NPs can be tailored to suit particular drug delivery applications [121]. Smaller nanoparticles (<100 nm) deliver drugs to cells or tissues [122], while larger nanoparticles (>500 nm) deliver drugs to targeted organs or the entire body [123]. According to one reference [124], nanoprecipitation of PLGA NPs alters their sizes, causing increased intracellular delivery.

PLGA NPs can be functionalized using agents targeting moieties [125–127] or polyethylene glycol (PEG) [128–130] to improve stabilities. According to [131], PEGylated PLGA NPs and folate-functionalized PLGA NPs have been used to deliver chemotherapy drugs to targeted cancer cells. Moreover, the PLGA NPs are biodegradable in the body [132]; this is useful for sustained release, eg to treat glaucoma [133,134] or osteoarthritis [135–137].

The skin permeability of rat abdomen skin via indomethacin (IM)-loaded PGLA NPs was studied using antisolvent diffusion. It revealed that skin penetration indomethacin of 50 nm and 100 nm PLGA NPs with iontophoresis was substantially higher after 2 h administration. The use of iontophoresis resulted in a greater penetration of 50 nm PLGA nanoparticles into rat skin as compared to 100 nm PLGA nanoparticles [138]. The same group of researchers developed 17  $\beta$ -estradiol (E2)-loaded PGLA NPs. The results show higher density skin permeability in E2-loaded PGLA NPs than polyvinyl alcohol (PVA)-coated NPs; it also enhanced bone mineral density of the cancellous bone in an osteoporosis animal model [139]. Both studies conclude that transdermal delivery of PLGA NPs combined with IP will deliver the drug deep into the rat hair follicles [140]. Table 2 summarizes the recent studies of PGLA in transdermal drug delivery.

### 3.1. Ethylene-Vinyl Acetate Films

Solvent casting has been used to incorporate selegiline hydrochloride (SGN)-loaded PLGA NPs in ethylene-vinyl acetate (EVA) transdermal film. Field emission scanning electron microscopy (FE-SEM) analyses showed these NPs were smooth spherical surfaces. In rat's brain tissues, a small dose of reserpine initiates symptoms of Parkinson's disease by increasing monoamine oxidase B (MAO-B) level, and decreasing dopamine [141].

### 3.2. Poly(lactic-co-glycolic acid) Coating

The same group of researchers created PLGA-coated rasagiline mesylate-nanoparticles (RM-NPs) and loaded gellan gum in the transdermal film via solvent evaporation and a solvent casting method. They reported that gellan gum with 1.127 g transdermal hydrogel aids in non-chronic drug self-administration for >72 h without skin inflammation [142].

**Table 2.** Recent study of PLGA in transdermal drug delivery.

Drug Delivery System	Method	Application	Result	References
PGLA/collagen scaffold	Electrospinning	Human dermal fibroblast and human keratinocyte	High mechanical strength, good surface adhesion on both cell lines	[143]
Poly(dl-lactide-co-glycolide)-poly(ethylene glycol)-poly(dl-lactide-co-glycolide) copolymers (PLGA-PEG-PLGA) NPs	Antisolvent diffusion method	Rat skin	High thermodynamic activity, skin permeability and low irritation in PLGA-PEG-PLGA NPs	[144]
Gentamicin loaded PLGA (GM-PLGA) NPs	Solvent evaporation method	Rabbit	No sign of inflammation and non-toxic to all groups of rabbit	[145]
Hyaluronate-PGLA (HA-PGLA) NPs	Solvent evaporation method	Rat skin	No cytotoxicity, biocompatibility in cell viability, and high efficiency of transdermal delivery	[146]
Dictamnine-PGLA-nanocarrier (Dic-PGLA-NC)	Ultrasonication	Mouse dermatitis model	Dic-PGLA-NC can penetrate the dermal layer effectively and achieve sustained drug release	[147]

#### 4. Chitosan NPs

Chitosan is a natural polymer that emerged as one of the useful nanocarriers for various therapeutic agents in transdermal drug delivery. Functional properties such as biocompatibility and biodegradability [148] have facilitated the development of chitosan-based nanocarriers for medicinal applications [149,150]. Slow polymer erosion in chitosan allows effective drug encapsulation [151] for sustained and controlled drug release with low toxicity. For example, the functional properties (amine and hydroxyl functional groups) of chitosan can be altered by adding synthetic materials to fabricate microneedles for transdermal applications as it does not create an unwanted immune response in the body. Therefore, chitosan is notable for its role as a nanocarrier of hydrophilic therapeutic drugs [152].

##### 4.1. Chitosan-Sodium Alginate

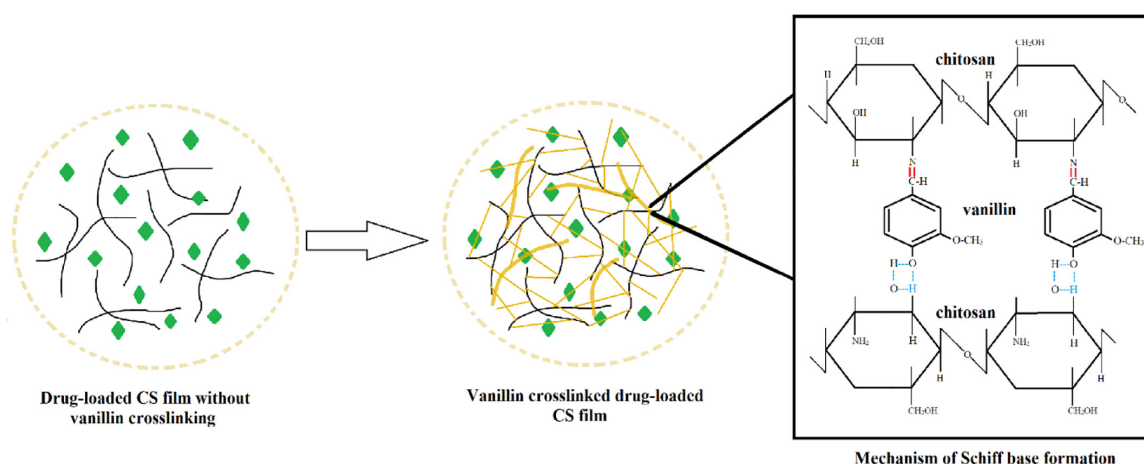
In research carried out by [153], chitosan-sodium alginate (CHI-SA) nanogel was synthesized to perform the transdermal delivery of the drug pirfenidone to treat pulmonary fibrosis. According to their observation, the loading capacity of the nanogel was  $\approx 50\%$  and the encapsulation efficiency was as high. The permeation of the drug pirfenidone across the skin has been remarkably enhanced using CHI-SA nanoparticles in an ex vivo study. In any case, the in vitro drug release profile has demonstrated the burst release of the drug pirfenidone in the first 5–7 h ( $\approx 12\%$ ) followed by sustained drug release behavior [153].

##### 4.2. Chitosan-Chondroitin

An antimalarial agent called artemether has been encapsulated into chitosan-chondroitin sulfate nanoparticles and subsequently loaded into transdermal patches to treat acute malaria, as reported by [154]. The positively charged chitosan were interacting with negatively charged chondroitin sulfate through the ionic gelation method to form nanoparticles that offer less toxicity, high stability, encapsulation efficiency, and loading capacity for transdermal delivery. The ex vivo study showed that using olive oil increased the drug permeability of the transdermal patch as a permeation enhancer. Moreover, a high cumulative drug release at a pH of 7.4 in contrast to a slow drug release rate at a pH of 5.5 was reported in their in vitro drug release study.

##### 4.3. Chitosan-Nanoemulsion Films

Nanoemulsions have proven to enhance the transport of drug molecules in transdermal analgesic patch systems. For instance, da Silva et al., 2020, have incorporated nanoemulsions into chitosan films to carry methyl salicylate, which displayed a homogeneous formulation with no phase separation. The chitosan-nanoemulsions films were reported to have a higher loading capacity of methyl salicylate and moisture levels as compared to physical mixture films [155]. In another study, chitosan (CS) and polyvinyl alcohol (PVA) was combined and crosslinked with vanillin (VA) to form a matrix transdermal system (Figure 3) to deliver the enrofloxacin drug, as reported by [156]. From their research findings, CS-PVA films can be produced by a simple solvent-casting method and the CS-PVA-VA nanocomposite has demonstrated sustained enrofloxacin release in the in vitro drug release profiles. The released kinetic study has confirmed that by altering the vanillin concentration, the diffusion mechanism and drug release rate can be controlled. As reported, the drug loading capacity was successfully increased by crosslinking 3% vanillin with the CS-PVA films. The controlled release of the enrofloxacin drug was achieved due to the lower swelling ratio of the 3% vanillin crosslinked films which also reduced the initial burst release [156].



**Figure 3.** The mechanism of Schiff base formation between chitosan and vanillin (reprinted from [156]. Copyright (2021), with permission of Elsevier).

#### 4.4. Chitosan-Coated Lipid Carriers

In previous research [157], chitosan-coated nano lipid carriers (Ch-NLC) were used in the transdermal delivery of tetrahydrocurcumin (THC) to treat triple-negative breast cancer (MD-MBA-231). THC-Ch-NLC is proven to demonstrate high skin permeation through an artificial membrane and enhanced cellular uptake with significant cytotoxicity to the MD-MBA-231 breast cancer cells. The THC-Ch-NLC also showed the sustained release of the drug through an in vitro release study which was confirmed by the Korsmeyer–Peppas model [157]. In another interesting study carried out by [158], nanoparticles made from chitosan whisker (CSWK) with oligo(lactic acid) (OLA) were used to transport lidocaine in the reticular dermis. They claimed that the CSWK-OLA nanocarriers offered high drug permeability into the skin without penetration enhancers and active strategies such as microwave technology and iontophoresis. It is due to the nano size of CSWL-OLA particles with amphiphilic properties, allowing the lidocaine-loaded nanocarriers to penetrate deep into the reticular dermis [158].

Table 3 below summarizes the incorporation of chitosan with different nanocomposites in various transdermal delivery systems.

**Table 3.** The development of various nanoconjugates from chitosan in the past decade.

Nanocomposite	Transdermal Drug	Findings/Results	References
Polyelectrolyte complexes (PEC) with carboxymethylagarose (CMA) and chitosan (CS) as pH-responsive carriers	Diclofenac sodium (DS)	Immortalized human keratinocyte (HaCat) cells showed approximately 100% survival with 67% cumulative drug release after 72 h at 37 °C and pH 6.0 through the Fickian diffusion mechanism.	[159]
Chitosan microneedle patches (85% deacetylated, molecular weight: 1526.464 g/mol)	Meloxicam	A higher concentration of acetic acid displayed greater resistance to compressive force as temperature increased and the penetration study indicated sustained insertion of microneedles in cow's ear cadaver skin.	[160]
Chitosan/hyaluronan transdermal film	Thiocolchicoside	Easy and reliable administration with high efficiency in drug release; flexible dosage, minimal drug dosage/frequency to reduce side effects.	[161]



Table 3. Cont.

Nanocomposite	Transdermal Drug	Findings/Results	References
Chitosan and phytigel (gellan gum) transdermal hydrogel	Ibuprofen	Chitosan improved the drug permeability to skin and increased the transdermal release rate of ibuprofen by a factor of 4.	[162]
Chitosan/phospholipids nanofibers	Curcumin, diclofenac, and vitamin B12	Cytotoxicity studies confirmed the good biocompatibility of the nanofibers, the drug release rate relied eminently on the drug solubility.	[163]
Carboxymethyl chitosan-grafted-2 hydroxyethyl acrylate (CmCHT-g-pHEA) hydrogel	Micropig dorsal skin	Good pH sensitivity, pores size decreased when ratio of grafting agent increased, improved skin penetration, and non-toxic to skin	[100]
Carboxymethyl chitosan/oxidized pullulan hydrogel-based microneedles	Salvia miltiorrhiza extract	Good mechanical strength, high water absorbing capacity, good skin permeability, and rapid drug release into the targeted porcine skin.	[99]
N-methacryloyl chitosan (N-MAC) microgels	Bovine serum albumin (BSA)	High cell viability in N- MAC hydrogel. Rapid transdermal curing hydrogels (in vivo) for localized and sustained protein delivery.	[164]
N,N,N-trimethyl chitosan (TMC), polyethylene glycolate hyaluronic acid (PEG-HA), and polysaccharide-based nano-conjugate of hyaluronic acid, chitosan oligosaccharide and alanine [HA-Ala-Chito(oligo)]	Chinese medicine CortexMoutan (CM)	The ex vivo transdermal release results showed significant drug permeability into the skin. The MTT assay results showed high cell viability of human HaCaT keratinocytes, suggesting no cytotoxicity on skin cells.	[165]
Chitosan-coated poly(dl-lactide-co-glycolide) (PLGA) nanoparticles	Donepezil hydrochloride (DP)	Chitosan-coated PLGA nanoparticles delivered drugs to the deep hair follicles more efficiently through iontophoretic transdermal delivery, as compared to the bare PLGA nanoparticles.	[166]
Polyvinyl alcohol-Chitosan (PVA/CS) bioconjugate	Colchicine	Significant colchicine deposition in the skin with remarkable cytotoxicity against a melanoma cell line.	[167]
Chitosan-coated nanoemulsion (NE2-CS), uncoated nanoemulsion (NE1), and quaternized chitosan (QCS)	Zingiber cassumunar Roxb (Plai extract)	QCS improved the stability and transdermal properties of the Plai extract, as compared to NE1 and NE2-CS. NE2-QCS showed higher cytotoxicity to the breast (BT474) and oral cavity (KB) cancer cell lines than the Plai extract alone and had 1.5-fold higher permeability and cumulative release of the Plai extract than NE1.	[168]
Chitosan sponges	Hormonal drug 17 $\beta$ -estradiol (E2) with a purity of 99%	High drug loading was reported. Uniform distribution of E2 crystallites in the chitosan sponge volume was observed, improving the bioavailability of the drug.	[169]
PLGA chitosan transdermal Pluronic nanogel	Temozolomide	The in vitro drug release showed 85% transdermal release at a mildly acidic pH mimicking the skin microenvironment. Ex vivo studies displayed a penetration rate with 80% Temozolomide uptake in porcine epidermal tissue.	[170]

Table 3. Cont.

Nanocomposite	Transdermal Drug	Findings/Results	References
Carboxymethyl chitosan/2-hydroxyethyl acrylate hydrogel	Nobiletin	Mechanism of the nobiletin from the hydrogel was confirmed to be Fickian diffusion. In vitro skin permeation experiments showed that the hydrogel improved the transdermal delivery of nobiletin.	[100]
ZnO nanorods with chitosan hydrogels crosslinked with azelaic acid	Acetylsalicylic acid	The controlled drug release behaviors of nanocomposites according to the first-order kinetic model and was confirmed to be non-toxic to L929 mouse fibroblasts by XTT assay.	[98]
Chitosan nanoparticles mucoadhesive gel	Propranolol hydrochloride	High encapsulation efficiency and drug loading improved systemic bioavailability and therapeutic efficacy of propranolol-HCl in a transdermal delivery system. Thixotropic behavior with prolonged drug release properties was observed.	[171]

## 5. Carbon Nanotubes CNTs

These have gained enormous research attention in the past decades for drug delivery applications, but there have been only applications in transdermal drug delivery. This may be due to poor skin penetration ability without the application of mechanical stress. Therefore, functionalized CNTs (f-CNTs) have been developed for greater biocompatibility and enhanced transdermal properties.

### 5.1. Functionalized Multi-Walled Carbon Nanotubes

The f-MWCNTs-KP-ES nanocomposite was reported high in drug loading rate, stability, and encapsulation efficiency as compared to CNTs or ES alone. Ex vivo results showed a fast skin penetration rate. Anyway, the f-MWCNTs-KP-ES nanocarriers had successfully prolonged the release of ketoprofen *in vivo* and caused no adverse effect on the observed rat skin [172].

### 5.2. Controllable CNT Membranes

A controllable CNT membrane device has been created for the transdermal delivery of nicotine in guinea pigs [173,174]. This CNT membrane device had successfully delivered nicotine fluxes when switched ON and OFF, respectively, according to an in vitro flow-cell test; meanwhile, nicotine flux has been detected through in vivo microdialysis with a membrane implanted in the guinea pig's skin. Nevertheless, the CNT membrane has low flexibility and tends to flatten the skin contact area which requires applying a small amount of hydroxyethyl cellulose gel on the skin surface underneath the membrane device [173,174].

### 5.3. “Bucky Paper”

Carbon nanotube film, also known as “buckypaper”, has been proposed for use in actuating, structural, and filtration systems, owing to their distinct and robust mechanical properties [175]. Bucky papers [176] assembled into functionalized single-walled CNTs (f-SWCNTs) and multi-walled CNTs (f-MWCNTs) in the transdermal delivery of four model drugs namely clonidine hydrochloride (CHC), selegiline hydrochloride (SHC), flurbiprofen (FB), and ketorolac tromethamine (KT). According to the in vitro transdermal test carried out in the study, using electrical bias can control the drug release rate and direction, where polarities rely on the charge of the drug. CNTs–bucky papers loaded with drugs demonstrated passive drug release behaviors which are highly dependent on the types of

drugs used and the electromodulation was successfully applied to accelerate and decelerate the drug release rate [176].

#### 5.4. CNT Gold NPs

Another similar study using electro-permeabilization was reported by [177], where CNT was incorporated with gold nanoparticles (GNP) into a transdermal patch matrix of polyvinyl alcohol/poly(dimethyl siloxane)-g-polyacrylate to deliver the drug diclofenac sodium (DS). The results showed a significant transdermal effect from the 1.5%-GNP-CNT patch at an applied bias of 10 V with no initial burst release. The 1.5%-GNP-CNT patch had the highest drug encapsulation efficiency, as compared to the other patches. Overloading of GNP-CNT will decrease the drug encapsulation efficiency remarkably due to the particle's agglomeration. The cell viability assay on HaCaT cell lines showed no cytotoxicity to the cells, suggesting good biocompatibility when applied to human skin [177].

#### 5.5. CNT Hydrogel Hybrid

Another group of researchers suggested embedding double-walled carbon nanotubes (DWCNTs) into hydrogel for potential transdermal drug delivery applications through electro-permeabilization [178]. In their study, hydrogel nanocomposites combining agarose (AG) and DWCNTs were prepared at different concentrations (DWCNTs-AG) and an agarose hydrogel without DWCNTs was used as the control (CTRL-AG). Due to the higher concentrations of DWCNTs in the hydrogels that shorten the electron jumping distance across the applied electric field, their results show the DWCNTs-AG nanocomposite had higher conductivity across the applied electric field as compared to the CTRL-AG nanocomposite, having the potential to increase skin permeability for transdermal delivery. Nevertheless, there was no show of in vitro and in vivo tests in the same study to verify skin permeability results [178].

### 6. Nanocellulose NPs

Nanocellulose (NC) is a cellulosic polysaccharide [179] widely used in antimicrobial applications in various industries. This material can be formulated into drug carriers [180] for transdermal drug delivery [181], and wound dressings. It has a large surface area [182], but remains light-weighted, biodegradable [183], biocompatible [182,184], and has a low production cost [185]. NC can combine with other biopolymers such as chitosan to enhance the structural properties of the composite structure due to its high tensile strength [186,187].

NC transdermal drug delivery is favored because it provides pain-free application [188–190], high water permeation [191], prolonged response [192,193], and therapeutic effectiveness in a low amount of dosages [194,195].

#### 6.1. Bacteria Nanocellulose

Bacterial nanocellulose (BNC) is a natural biomaterial [196] with unique characteristics, including low toxicity [197], biocompatibility [198], high purity [199], and a nano-porous structure. BNC-based products have been approved by the Food and Drug Administration (FDA) and Conformité Européenne (CE) for biomedical applications [200]. Numerous studies found that BNC membranes can be effectively loaded with diverse biological molecules with varying permeability and hydrophilicity [201]. Moreover, BNC membranes have previously been combined with drugs and bioactive compounds, including lidocaine [202], ibuprofen [203], and amoxicillin [204], or developed as ionic liquids [205,206] for transdermal drug delivery.

The recent work proposed by [207] was to develop patches using hyaluronic acid (HA), microneedles (MNs), and bacterial nanocellulose (BC) (HA-BC MNs). HA was utilized as a biomacromolecule with moisturizing, regenerative, and hydrating properties, while BC was used to protect the inclusion of another bioactive molecule such as rutin to illustrate the system's efficacy. The HA-BC MNs patches exhibit appropriate morphology, mechanical resistance, and biocompatibility. The in vivo patches applied on human volunteers

show tolerability as a dermo-cosmetic system and open up new opportunities for the incorporation of different active ingredients to broaden their application [207].

Another study (Abba et al., 2019) produced a crocin-BNC membrane for transdermal drug delivery. The swelling analyses and resonance peaks of FTIR analysis revealed that BNC had good crocin uptake. The crocin-BNC surface morphology indicated that the fibers were unchanged, with no fiber damage. The Franz diffusion tests showed that drug permeability was steady and long-lasting [208]. A nanocomposite film of bacterial cellulose (BC) modified with dopamine (DPM) and incorporating reduced graphene oxide (rGO)/silver (Ag) (BC-DOPA/rGO/Ag) NPs was successfully produced by [209] for antimicrobial patches. The result demonstrated that Ag NPs in the nanocomposite promote cell development and migration in NIH 3T3 fibroblast cells and A549 human lung epithelial cells, resulting in a faster wound-healing process. Another recent research study discovered that incorporating Fe<sub>3</sub>O<sub>4</sub> NPs coated with DOX on BC could be used in the treatment of breast cancer because they can permeate through the epidermis under magnetic flux and laser radioactivity [71].

Recent research investigated the depot stability of BNC membranes loaded with various APIs such as caffeine, lidocaine, ibuprofen, and diclofenac, and showed all systems were stable, with no morphological changes or differences in the drug release profile under optimal storage conditions. Moreover, the caffeine-loaded BNC membrane was selected for in vivo epidermal studies and the results revealed the APIs-loaded BNC membranes' good storage stability [201].

## 6.2. Cellulose Nanofibers

Cellulose nanofibers (CNFs) provide large areas for drug–CNF interaction and mechanical characteristics that improve the dosage from mechanical stability [210]. Moreover, CNF films have excellent water vapor permeability properties at low humidity [211], which improves the storage stability of oxygen-sensitive drugs during storage and allows them to be used effectively as excipients [193,212]. Recent CNF research focuses on producing environmentally sustainable nanocomposites which do not exhibit any adverse outcomes associated with the synthetic nanomaterials widely used for reinforcements [213,214].

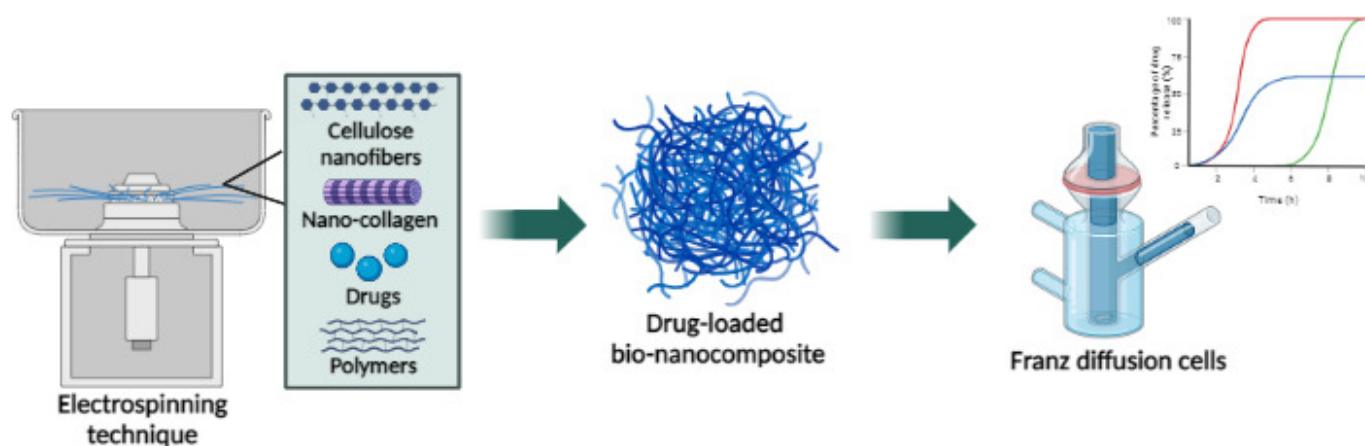
### 6.2.1. With Poly(N-isopropyl acrylamide)-Graft-Guar Gum (GG-g-PNIPAAm)

In another study [215], CNF produced from jute fiber was reinforced with a poly(N-isopropyl acrylamide)–graft–guar gum nanocomposite to test the controlled release of diltiazem hydrochloride in transdermal drug delivery. Compared to GG-g-PNIPAAm, the nanocomposite films demonstrated greater thermal resistance and barrier properties. The nanocomposite film containing 1wt% CNF performed better than other films. The toxicity test confirmed that the GG-g-PNIPAAm nanocomposite film is non-toxic to rat skin. Furthermore, the ideal nanocomposite's in-vitro release study revealed a controlled diltiazem hydrochloride release capability. As a result, GG-g-PNIPAAm contains 1wt% CNF nanocomposite that can be used as a transdermal patch due to its outstanding physico-mechanical, bio-interfacial, as well as permeability properties.

### 6.2.2. With CNF Transdermal Films

In a previous study, an electrospinning method was used to produce polyurethane/hydroxypropyl cellulose (PU/HPC) electrospun nanofibers [216]. In vitro studies across the skin imitating a polymeric membrane demonstrated model drug flux. The MTT assay showed the PU/HPC electrospun nanofiber non-toxic to mouse fibroblast cell line (BALB/3T3). These findings revealed that an PU/HPC electrospun nanofiber could be used as a transdermal drug delivery system [216]. Recent research isolated CNF from jute fibers and nano-collagen (NCG) from waste fish scales to form a CNF-NCG biocomposite by the electrospinning method to test the sustained release of ketorolac tromethamine (KT), as shown in Figure 4. In vitro drug release results revealed that the CNF-NCG (1wt%)-loaded polyvinyl alcohol/methylcellulose/polyethylene glycol

(PVA/MC/PEG) bio-nanocomposite demonstrated an excellent sustained drug release of ketorolac tromethamine, making it an ideal biocomposite for transdermal drug delivery systems [217]. Another study (Sarkar et al., 2017) proposed using a CNF/chitosan transdermal film to deliver ketorolac tromethamine. According to the release profile, researchers discovered that CNFs effectively resulted in prolonged drug release. The XRD analysis revealed the rise in crystallinity with the addition of CNFs in CNF/chitosan transdermal films [218].



**Figure 4.** Schematic represents the bio-nanocomposite produced via the electrospinning method and drug release of ketorolac tromethamine via Franz diffusion cells, (Figure generated with Biorender (<https://www.biorender.com/>), accessed on 13 March 2023).)

### 6.3. Cellulose Nanocrystal

Cellulose nanocrystals (CNCs) are promising due to their remarkable properties such as biocompatibility [219], non-toxicity [220], and high mechanical strength [221]. It is also utilized in transdermal preparations to improve clinical outcomes and the possibilities and potential benefits of developing various management strategies in interdisciplinary research [222].

#### 6.3.1. With Methylcellulose

In a recent study, CNCs derived from jute fibers were used to develop a non-toxic bio-nanocomposites transdermal patch formulated with methylcellulose (MC) and chitosan (CH) via the solvent evaporation method to analyze the sustained drug release of ketorolac tromethamine [223]. The results showed that adding CNC nanofillers in MC/CH improved the thermal properties of the bionanocomposite patches. Furthermore, incorporating CNCs into the MCCH blend improved the permeability, water absorption, mechanical properties, and sustained drug release ability than the pure matrix. The toxicity assay of the formulated bio-nanocomposite (MCCH1) revealed that it has a low cytotoxicity and performed good outcomes for transdermal drug delivery systems [223].

#### 6.3.2. CNC-Hydrogels

The most recent method proposed by [224] used inversion and tilting methods to produce a crosslinked CNC/donepezil hydrochloride (cCNC/DPZ) hydrogel to evaluate long-acting drug delivery through subcutaneous injection and reported that the addition of DPZ to the CNC dispersion caused gel aggregation, and pH control of the CNC/DPZ hydrogel increased elastic modulus. In any case, the cCNC/DPZ hydrogel showed a longer half-life, high mean residence time, and lower  $C_{max}$  values compared to the DPZ and CNC/DPZ hydrogel in a pharmacokinetic study [224].



### 6.3.3. Lanoconazole (LCZ)-Loaded CNC

LCZ-loaded CNC grafted with polyphosphoesters (LCZ-loaded CNC-PEs) were produced by [225] to improve the chronic inflammation efficiency of LCZ on mouse ear skin. The result revealed a high LCZ efficiency and small mean droplet size in CP-PEs. The long-lasting local action was assured by the sustained LCZ release and better transdermal delivery of the LCZ-loaded CP-PEs, probably due to the oil droplets' rigidity. Furthermore, a mouse ear model of 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation showed excellent anti-inflammatory efficacy of the LCZ-loaded CP-PEs [225].

## 7. Ionic Liquids (ILs)

Ionic Liquids (ILs) are organic salts comprised of an organic cation and an organic or inorganic anion that, when mixed in 1:1 molar ratio (true ionic liquid), give rise to a room-temperature ionic liquid (RTIL). Ionic liquids can solubilize amphipathic molecules and increase drug solubility and can favor topical drug delivery. The ionic liquid molecules are likely to slip through the fatty compounds that make up skin cells, creating small transient openings through which bioactive molecules (carried by ionic liquid) can permeate.

### 7.1. Choline Geranic Acid (CAGE)

In particular, choline and geranic acid (CAGE) has been used to enhance the transdermal delivery of several small and large molecules including proteins such as bovine serum albumin (BSA, molecular weight:  $\approx 66$  kDa), ovalbumin (OVA, molecular weight:  $\approx 45$  kDa) as well as insulin (INS, molecular weight: 5.8 kDa) [226].

Two major applications of CAGE are biofilm-disruption and enhanced antibiotic delivery across skin layers. Relatively few papers describe both these applications concomitantly, but the first was the use of neat ILs as antimicrobial agents and transdermal drug-delivery agents [227]. In another study, CAGE increased the delivery of cefadroxil, an antibiotic, by  $>16$ -fold into the deep tissue layers of the skin and is able to induce  $>95\%$  bacterial death after a 2 h treatment. Further research on CAGE revealed that it exhibits broad-spectrum antimicrobial activity against several drug-resistant bacteria, fungi, and viruses including clinical isolates of *Mycobacterium tuberculosis*, *Staphylococcus aureus*, and *Candida albicans* and laboratory strains of Herpes Simplex Virus. CAGE affords negligible local or systemic toxicity, and an approximately 180–14,000-fold improved efficacy/toxicity ratio over the currently used antiseptic agents in human keratinocytes and mice studies. CAGE penetrates deep into the dermis and treats pathogens located in deep skin layers. Thus, CAGE have been used in vivo to treat *Propionibacterium acne*. Overall, these studies demonstrate the promise of CAGE as transformative platforms for antiseptic agents used prophylactically as well as therapeutically [228].

Low percentage-loaded CAGE-IL (viz. 2.0%,  $w/w$ ) are effective for facilitating the passage of curcumin to transiently disrupt the skin barrier [229]. It emerged that the anion-cation ratio is fundamental in the design of suitable ionic liquids. This parameter can significantly alter their physical properties and interactions with biological tissues. Transport enhancement is also composition-dependent, since when different ratios of CAGE: 1:1, 1:2, 1:4, and 2:1 components exhibited variable dermal insulin delivery [230]. Similarly, choline oleate ionic liquid-based CAGE-promoted transdermal insulin permeation depends on the choline geranate ratios, with 1:2 being the best found (better efficacy with less cyto- and geno-toxicity [231]).

### 7.2. Surface Active Ionic Liquid (SAIL)

Besides that, IL has been used in formulations of nano-drug delivery system. Researchers from Japan developed ionic liquid (IL)-in-oil microemulsion formulations (MEFs) for transdermal insulin delivery using choline-fatty acids ([Chl][FAs])-comprising three different FAs (C18:0, C18:1, and C18:2) for biocompatibility. The MEFs were developed using [Chl][FAs] as surfactants, sorbitan monolaurate (Span-20) as a cosurfactant, choline propionate IL as an internal polar phase, and isopropyl myristate as a continuous oil phase.

MEFs significantly enhanced the transdermal permeation of insulin via the intercellular route by compromising the tight lamellar structure of SC lipids through a fluidity-enhancing mechanism. The *in vivo* transdermal administration of low insulin doses (50 IU/kg) to diabetic mice showed that MEFs reduced blood glucose levels (BGLs) significantly compared with a commercial surfactant-based formulation by increasing the bioavailability of insulin in systemic circulation and sustained the insulin level for a much longer period (half-life > 24 h) than subcutaneous injection (half-life 1.32 h) [232].

Another research study reported an advantageous carrier for the transdermal delivery of paclitaxel (PTX) comprising a new micelle formulation (MF) that consists of two biocompatible surfactants: cholinium oleate ([Cho][Ole]), which is a surface-active ionic liquid (SAIL), and sorbitan monolaurate (Span-20). A solubility assessment confirmed that PTX was readily solubilized in the SAIL-based micelles via multipoint hydrogen bonding and cation- $\pi$  and  $\pi$ - $\pi$  interactions between PTX and SAIL[Cho][Ole] [233]. A similar group of researchers developed a protein-containing nanocarrier (PCNC) comprising an antigenic protein (ovalbumin/OVA) stabilized by a combination of surfactants, i.e., a lipid-based surface-active ionic liquid (SAIL) and Tween-80. The PCNC was biocompatible both *in vitro* and *in vivo*, and is suitable for use in therapeutic transdermal drug delivery. The skin permeability of the PCNC was significantly ( $p < 0.0001$ ) enhanced, and the transdermal distribution and transdermal flux of the OVA delivery system were 25 and 28 times greater, respectively, than those of its aqueous formulation. The PCNC disrupted the order of lipid orientation in the skin's SC and increased intercellular protein delivery. It demonstrated effective antitumor activity, drastically ( $p < 0.001$ ) suppressed tumor growth, increased mouse survival rates, and significantly ( $p < 0.001$ ) stimulated the OVA-specific tumor immune response. The PCNC also increased the number of cytotoxic T cells expressing CD8 antibodies on their surfaces (CD8 + T-cells) in the tumor microenvironment. These findings suggest that PCNCs may be promising biocompatible carriers for transdermal antigenic protein delivery in tumor immunotherapy [234].

## 8. Natural Rubbers

Rubber can be natural from rubber trees [235], or synthetic from petroleum byproducts [236,237]. Natural rubbers are widely used in biomedical industries [238] and transdermal drug delivery systems [239] due to their biocompatibility [240], excellent mechanical properties [241], flexibility, and ability to form films easily [242]. It is a colloidal suspension composed of particles with poly(cis-1,4-isoprene) chains [238]. The most common natural rubber-based transdermal patches are nanocomposites, which serve as the polymer matrix, and the properties of transdermal patches depend on the type of penetration enhancers used [237].

### *Natural Rubber Layers*

A previous work by Marcelino et al., 2018, used the casting method to produce a fluconazole-loaded NRL to examine the *Candida albicans* (*C. albicans*) antifungal susceptibility. The release of fluconazole inhibited the growth of *C. albicans* for 48 h, indicating good properties for use as transdermal patches. Furthermore, adding fluconazole to NRL did not significantly alter the mechanical properties of the latex, resulting in a promising biomaterial for transdermal applications [243]. On the other hand, [244] used the casting method to produce a voriconazole-NRL (VCZ-NRL) membrane to evaluate the antifungal susceptibility of *Candida parapsilosis* (*C. parapsilosis*)-infected ulcers, and the results revealed no hemolytic effects or mechanical adaptability for dermal application. Anyway, the VCZ was released in two stages: a burst release of 13.2% of an initially incorporated VCZ in 1 h, followed by a slow release of 11% VCZ up to 48 h. The VCZ-NRL membrane performed well in mechanical, antifungal, and physiochemical tests, making it an intriguing alternative to treating *Candida*-infected wounds [244]. In addition, [245] discovered ketoprofen-NRL membranes for the treatment of tendinitis. The results showed that biocompatible NRL

membranes demonstrated a 60% sustained ketoprofen release in 50 h. Furthermore, adding ketoprofen into the NRL membrane was non-toxic to red blood cells [245].

Poly(p-phenylenevinylene) (PPV) was incorporated into a natural rubber latex (PPV-NRL) composite for electromechanical transdermal drug delivery [246]. Ibuprofen was used as doped for PPV, which acted as the drug polymeric carrier. The findings indicate that ibuprofen-NRL patches and ibuprofen-doped PPV/NRL matrices were successfully produced under ultraviolet (UV) radiation at various crosslinking metrics. In any case, using an electric flux will improve the penetration of drugs in the synergic effect by developing the PPV chain, changing the conductive polymer's oxidation condition, and the intravenous administration impact, as well as the continuation of pore size in keratinocytes. The NRL patches had a higher capacity modulus value and better physicochemical characteristics than transdermal drug delivery patches made from hydrogels.

## 9. Conclusions

NP-based carriers are a safe and efficient media for transdermal drug delivery. NP carriers can have high stabilities, reduced toxicities, biodegradability, high loading capacities, good storage stabilities, and can also be incorporated with hydrophilic and hydrophobic materials for controlled, time-dependent drug delivery [247]. They have provided viable treatment options for a variety of diseases, particularly to deliver drugs to cancer lesions. For example, NPs are extensively studied as potential carriers to transport drugs to the lining of blood vessels to treat arteriosclerosis and myocardial infarction [248,249]. At present, the most promising NP-based carriers are from polylactic acid (PLA-NP) or polyethylene glycol (PEG-NP). These have been used for controlled drug delivery to the liver and brain, and as multi stimuli-responsive entities to treat inflammation in rheumatoid arthritis or asthma. However, the slower biodegradation of polymeric NP carriers is a “double-edged sword” with regards to the chronic accumulation of toxic metabolites associated with causes of systemic toxicity.

## 10. Future Perspective

Optimal particle sizes for NP-based drug delivery systems could be further investigated as they are crucial in drug distribution, release rates, targeting efficacies, and toxicities; current understandings are probably overgeneralized as follows. Relationships between particle sizes and skin permeability are such that nanovesicles with 70 nm diameter or less are effective in delivering contents to epidermal and dermal layers, as compared to those with a diameter of 300 nm [250]. On the other hand, nanovesicles 600 nm diameter or more tend to remain on skin surfaces without penetrating deeper layers.

NPs have the potential to treat skin diseases such as alopecia, melanoma, and psoriasis [251]. Their penetration via intracellular, intercellular, or transcellular pathways are vastly affected by the particle size, composition [250], and skin conditions. Particles with a diameter smaller than 6–7 nm can be absorbed through the lipidic trans-epidermal routes, while those with a size below 36 nm can pass through aqueous pores. Particles of 10–210 nm tend to penetrate through trans-follicular routes. More research is required to fully understand inter-subject variability before they can be suitable for widespread medical use. Particle sizes are affected by encapsulation frequency, zeta potential, molecular weight, and degree of chitosan deacetylation [252]. These parameters can be further studied regarding their effects on the performance of transdermal drug delivery.

While NPs have shown great promise as drug carriers, it is important to thoroughly evaluate their long-term safety and efficacy. Future research could focus on preclinical and clinical studies to determine the optimal dosages, administration routes, and potential adverse effects of NP-based drugs.

Other research could focus on developing NP-based tools to increase sensitivity and specificity in detecting different types of biomarkers or diseases. Existing advances include NP-based lateral flow immunoassays to detect infectious agents and diseases [253], dextran NPs for diagnosing cardiovascular disorders, fumagillin and docetaxel loading to lipid-

based micelles for asthma management [254], NP-based platforms for magnetic resonance imaging (MRI) and photothermal therapy (PTT) tumor imaging [255], and NP-mediated combinatorial phototherapy to chemo-resistant ovarian cancerous tumors [256]. Even so, there is much more to be discovered about NP-assisted diagnostic tools [257].

**Author Contributions:** Conceptualization, M.Y.L., W.F.W., K.B., Y.L.K. and C.Y.L.; writing—review and editing, M.Y.L., K.B., Y.L.K., G.S. and C.Y.L.; supervision, Y.L.K., W.F.W. and C.Y.L. All authors have read and agreed to the published version of the manuscript.

**Funding:** The research was funded by the Malaysian Ministry of Higher Education (MOHE) through the Fundamental Research Grant Scheme (FRGS/1/2021/SKK06/TAYLOR/02/2). The work was also supported by the Singapore Ministry of Education Tier 1 grant to Gautam Sethi. The authors acknowledge a research grant from University Malaya (GPF004A-2020).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

**Acknowledgments:** All the authors of this manuscript are thankful to their respective departments for the successful completion of this review study.

**Conflicts of Interest:** The authors declare no conflict of interest.

## References

1. Raj, S.; Khurana, S.; Choudhari, R.; Kesari, K.K.; Kamal, M.A.; Garg, N.; Ruokolainen, J.; Das, B.C.; Kumar, D. Specific targeting cancer cells with nanoparticles and drug delivery in cancer therapy. *Semin. Cancer Biol.* **2019**, *69*, 166–177. [\[CrossRef\]](#)
2. Mishra, D.; Hubenak, J.R.; Mathur, A.B. Nanoparticle systems as tools to improve drug delivery and therapeutic efficacy. *J. Biomed. Mater. Res. Part A* **2013**, *101*, 3646–3660. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Hussein, H.A.; Abdullah, M.A. Novel drug delivery systems based on silver nanoparticles, hyaluronic acid, lipid nanoparticles and liposomes for cancer treatment. *Appl. Nanosci.* **2021**, *12*, 3071–3096. [\[CrossRef\]](#)
4. Gagliardi, A.; Giuliano, E.; Venkateswararao, E.; Fresta, M.; Bulotta, S.; Awasthi, V.; Cosco, D. Biodegradable Polymeric Nanoparticles for Drug Delivery to Solid Tumors. *Front. Pharmacol.* **2021**, *12*, 601626. [\[CrossRef\]](#) [\[PubMed\]](#)
5. Dubey, S.K.; Dey, A.; Singhvi, G.; Pandey, M.M.; Singh, V.; Kesharwani, P. Emerging trends of nanotechnology in advanced cosmetics. *Colloids Surf. B Biointerfaces* **2022**, *214*, 112440. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Manasa, R.; Shivananappa, M. Role of Nanotechnology-Based Materials in Drug Delivery. In *Advances in Novel Formulations for Drug Delivery*; Wiley: Hoboken, NJ, USA, 2023; pp. 279–307. [\[CrossRef\]](#)
7. Jeevanandam, J.; Barhoum, A.; Chan, Y.S.; Dufresne, A.; Danquah, M.K. Review on nanoparticles and nanostructured materials: History, sources, toxicity and regulations. *Beilstein J. Nanotechnol.* **2018**, *9*, 1050–1074. [\[CrossRef\]](#)
8. Biswas, A.K.; Islam, M.R.; Choudhury, Z.S.; Mostafa, A.; Kadir, M.F. Nanotechnology based approaches in cancer therapeutics. *Adv. Nat. Sci. Nanosci. Nanotechnol.* **2014**, *5*, 043001. [\[CrossRef\]](#)
9. Sabdoningrum, E.K.; Hidanah, S.; Chusniati, S. Characterization and Phytochemical Screening of Meniran (*Phyllanthus niruri* Linn) Extracts Nanoparticles Used Ball Mill Method. *Pharmacogn. J.* **2021**, *13*, 1568–1572. [\[CrossRef\]](#)
10. Khan, I.; Saeed, K.; Khan, I. Nanoparticles: Properties, applications and toxicities. *Arab. J. Chem.* **2019**, *12*, 908–931. [\[CrossRef\]](#)
11. Erdoğan, N.; Akkin, S.; Bilensoy, E. Nanocapsules for Drug Delivery: An Updated Review of the Last Decade. *Recent Pat. Drug Deliv. Formul.* **2018**, *12*, 252–266. [\[CrossRef\]](#)
12. Ravindran, S.; Suthar, J.; Rokade, R.; Deshpande, P.; Singh, P.; Pratinidhi, A.; Khambadkhar, R.; Utekar, S. Pharmacokinetics, Metabolism, Distribution and Permeability of Nanomedicine. *Curr. Drug Metab.* **2018**, *19*, 327–334. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Chu, Y.; Zhang, Z.; He, Q.; Chen, F.; Sheng, Z.; Zhang, D.; Jin, H.; Jiang, F.; Guo, L. Half-life determination of inorganic-organic hybrid nanomaterials in mice using laser-induced breakdown spectroscopy. *J. Adv. Res.* **2020**, *24*, 353–361. [\[CrossRef\]](#)
14. Makvandi, P.; Wang, C.Y.; Zare, E.N.; Borzacchiello, A.; Niu, L.N.; Tay, F.R. Metal-Based Nanomaterials in Biomedical Applications: Antimicrobial Activity and Cytotoxicity Aspects. *Adv. Funct. Mater.* **2020**, *30*, 1910021. [\[CrossRef\]](#)
15. Domanico, M.; Fukuto, A.; Tran, L.M.; Bustamante, J.-M.; Edwards, P.C.; Pinkerton, K.E.; Thomasy, S.M.; Van Winkle, L.S. Cytotoxicity of 2D engineered nanomaterials in pulmonary and corneal epithelium. *Nanoimpact* **2022**, *26*, 100404. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Carissimi, G.; Montalbán, M.G.; Fuster, M.G.; Villora, G. Nanoparticles as Drug Delivery Systems. In *21st Century Nanostructured Materials—Physics, Chemistry, Classification, and Emerging Applications in Industry, Biomedicine, and Agriculture*; IntechOpen: London, UK, 2021.
17. Dai, H.; Chi, Y.; Wu, X.; Wang, Y.; Wei, M.; Chen, G. Biocompatible electrochemiluminescent biosensor for choline based on enzyme/titanate nanotubes/chitosan composite modified electrode. *Biosens. Bioelectron.* **2010**, *25*, 1414–1419. [\[CrossRef\]](#)



18. John, S.A.; Chatterjee, A.; Ramteke, P.W.; Shanthi, P.; Nguyen, T.A.; Rajendran, S. Nanosensors for plant health monitoring. *Nanosens. Smart Agric.* **2022**, *18*, 449–461. [\[CrossRef\]](#)
19. Lammers, T.; Ferrari, M. The success of nanomedicine. *Nano Today* **2020**, *31*, 100853. [\[CrossRef\]](#)
20. Pham, D.T.; Tiyaaboonchai, W. Fibroin nanoparticles: A promising drug delivery system. *Taylor's Fr.* **2020**, *27*, 431–448. [\[CrossRef\]](#)
21. Kalyane, D.; Raval, N.; Maheshwari, R.; Tambe, V.; Kalia, K.; Tekade, R.K. Employment of enhanced permeability and retention effect (EPR): Nanoparticle-based precision tools for targeting of therapeutic and diagnostic agent in cancer. *Mater. Sci. Eng. C* **2019**, *98*, 1252–1276. [\[CrossRef\]](#)
22. Zhang, L.; Gu, F.; Chan, J.; Wang, A.; Langer, R.S.; Farokhzad, O.C. Nanoparticles in Medicine: Therapeutic Applications and Developments. *Educ. Policy Anal. Arch.* **2007**, *8*, 861–869. [\[CrossRef\]](#)
23. Tomoda, K.; Makino, K. Nanoparticles for transdermal drug delivery system (TDDS). In *Colloid and Interface Science in Pharmaceutical Research and Development*; Elsevier: Amsterdam, The Netherlands, 2014; pp. 131–147. [\[CrossRef\]](#)
24. Nqakala, Z.B.; Sibuyi, N.R.S.; Fadaka, A.O.; Meyer, M.; Onani, M.O.; Madihe, A.M. Advances in Nanotechnology towards Development of Silver Nanoparticle-Based Wound-Advances in Nanotechnology towards Development of Silver Nanoparticle-Based Wound-Healing Agents. *Int. J. Mol. Sci. Rev.* **2021**, *22*, 11272. [\[CrossRef\]](#)
25. Jamaledin, R.; Yiu, C.K.; Zare, E.N.; Niu, L.; Vecchione, R.; Chen, G.; Gu, Z.; Tay, F.R.; Makvandi, P. Advances in Antimicrobial Microneedle Patches for Combating Infections. *Adv. Mater.* **2020**, *32*, e2002129. [\[CrossRef\]](#)
26. Kandekar, S.G.; Singhal, M.; Sonaje, K.B.; Kalia, Y.N. Polymeric micelle nanocarriers for targeted epidermal delivery of the hedgehog pathway inhibitor vismodegib: Formulation development and cutaneous biodistribution in human skin. *Expert Opin. Drug Deliv.* **2019**, *16*, 667–674. [\[CrossRef\]](#)
27. Askarizadeh, A.; Butler, A.E.; Badiie, A.; Sahebkar, A. Liposomal nanocarriers for statins: A pharmacokinetic and pharmacodynamics appraisal. *J. Cell. Physiol.* **2018**, *234*, 1219–1229. [\[CrossRef\]](#)
28. Das, S.S.; Bharadwaj, P.; Bilal, M.; Barani, M.; Rahdar, A.; Taboada, P.; Bungau, S.; Kyzas, G.Z. Stimuli-Responsive Polymeric Nanocarriers for Drug Delivery, Imaging, and Theragnosis. *Polymers* **2020**, *12*, 1397. [\[CrossRef\]](#)
29. Cevc, G.; Vierl, U. Nanotechnology and the transdermal route: A state of the art review and critical appraisal. *J. Control. Release* **2010**, *141*, 277–299. [\[CrossRef\]](#)
30. Baroli, B.; Ennas, M.G.; Loffredo, F.; Isola, M.; Pinna, R.; López-Quintela, M.A. Penetration of Metallic Nanoparticles in Human Full-Thickness Skin. *J. Investig. Dermatol.* **2007**, *127*, 1701–1712. [\[CrossRef\]](#)
31. Yu, Y.-Q.; Yang, X.; Wu, X.-F.; Fan, Y.-B. Enhancing Permeation of Drug Molecules Across the Skin via Delivery in Nanocarriers: Novel Strategies for Effective Transdermal Applications. *Front. Bioeng. Biotechnol.* **2021**, *9*, 646554. [\[CrossRef\]](#)
32. Patzelt, A.; Richter, H.; Knorr, F.; Schäfer, U.; Lehr, C.M.; Dähne, L.; Sterry, W.; Lademann, J. Selective follicular targeting by modification of the particle sizes. *J. Control. Release Off. J. Control. Release Soc.* **2010**, *150*, 45–48. [\[CrossRef\]](#)
33. Lademann, J.M.; Patzelt, A.; Richter, H.; Antoniou, C.; Sterry, W.; Knorr, F. Determination of the cuticula thickness of human and porcine hairs and their potential influence on the penetration of nanoparticles into the hair follicles. *J. Biomed. Opt.* **2009**, *14*, 021014. [\[CrossRef\]](#)
34. Radtke, M.; Patzelt, A.; Knorr, F.; Lademann, J.; Netz, R.R. Ratchet effect for nanoparticle transport in hair follicles. *Eur. J. Pharm. Biopharm.* **2016**, *116*, 125–130. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Mortensen, L.J.; Oberdörster, G.; Pentland, A.P.; DeLouise, L.A. In vivo skin penetration of quantum dot nanoparticles in the murine model: The effect of UVR. *Nano Lett.* **2008**, *8*, 2779–2787. [\[CrossRef\]](#)
36. Zhu, Y.; Choe, C.S.; Ahlberg, S.; Meinke, M.C.; Alexiev, U.; Lademann, J.; Darvin, M.E. Penetration of silver nanoparticles into porcine skin ex vivo: fluorescence lifetime imaging microscopy, Raman microscopy, and surface-enhanced Raman scattering microscopy. *J. Biomed. Opt.* **2014**, *20*, 51006. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Lademann, J.; Knorr, F.; Richter, H.; Blume-Peytavi, U.; Vogt, A.; Antoniou, C.; Sterry, W.; Patzelt, A. Hair follicles—an efficient storage and penetration pathway for topically applied substances. Summary of recent results obtained at the Center of Experimental and Applied Cutaneous Physiology, Charité -Universitätsmedizin Berlin, Germany. *Ski. Pharm. Physiol.* **2008**, *21*, 150–155. [\[CrossRef\]](#)
38. Aguilar, Z.P. Types of Nanomaterials and Corresponding Methods of Synthesis. *Nanomater. Med. Appl.* **2013**, 33–82. [\[CrossRef\]](#)
39. Alexander-Bryant, A.A.; Berg-Foels, W.S.V.; Wen, X. Bioengineering Strategies for Designing Targeted Cancer Therapies. *Adv. Cancer Res.* **2013**, *118*, 1–59. [\[CrossRef\]](#)
40. Adams, M.L.; Lavasanifar, A.; Kwon, G.S. Amphiphilic block copolymers for drug delivery. *J. Pharm. Sci.* **2003**, *92*, 1343–1355. [\[CrossRef\]](#)
41. Joseph, M.; Trinh, H.M.; Mitra, A.K. Peptide and Protein-Based Therapeutic Agents. *Emerg. Nanotechnol. Diagn. Drug Deliv. Med. Devices* **2017**, 145–167. [\[CrossRef\]](#)
42. Lee, R.W.; Shenoy, D.W.; Sheel, R. Micellar Nanoparticles: Applications for Topical and Passive Transdermal Drug Delivery. *Non-Invasive Drug Deliv. Syst.* **2010**, 37–57.
43. Jijie, R.; Barras, A.; Boukherroub, R.; Szunerits, S. Nanomaterials for transdermal drug delivery: Beyond the state of the art of liposomal structures. *J. Mater. Chem. B* **2017**, *5*, 8653–8675. [\[CrossRef\]](#)
44. Chaudhari, Y. Nanoparticles—A paradigm for topical drug delivery. *Chron. Young- Sci.* **2012**, *3*, 82. [\[CrossRef\]](#)
45. Ghezzi, M.; Pescina, S.; Padula, C.; Santi, P.; Del Favero, E.; Cantù, L.; Nicoli, S. Polymeric micelles in drug delivery: An insight of the techniques for their characterization and assessment in biorelevant conditions. *J. Control. Release* **2021**, *332*, 312–336. [\[CrossRef\]](#)



46. Bashir, M.; Ahmad, J.; Asif, M.; Khan, S.-U.; Irfan, M.; Ibrahim, A.Y.; Asghar, S.; Khan, I.U.; Iqbal, M.S.; Haseeb, A.; et al. Nanoemulgel, an Innovative Carrier for Diflunisal Topical Delivery with Profound Anti-Inflammatory Effect: In vitro and in vivo Evaluation. *Int. J. Nanomed.* **2021**, *16*, 1457–1472. [\[CrossRef\]](#)
47. Šmejkalová, D.; Muthný, T.; Nešporová, K.; Hermannová, M.; Achbergerová, E.; Huerta-Angeles, G.; Svoboda, M.; Čepa, M.; Machalová, V.; Luptáková, D.; et al. Hyaluronan polymeric micelles for topical drug delivery. *Carbohydr. Polym.* **2017**, *156*, 86–96. [\[CrossRef\]](#)
48. Ahmed, O.A.A.; El-Say, K.; Aljaeid, B.M.; Badr-Eldin, S.M.; Ahmed, T.A. Optimized vinpocetine-loaded vitamin E D- $\alpha$ -tocopherol polyethylene glycol 1000 succinate- $\alpha$  lipoic acid micelles as a potential transdermal drug delivery system: In vitro and ex vivo studies. *Int. J. Nanomed.* **2018**, *14*, 33–43. [\[CrossRef\]](#)
49. Bachhav, Y.; Mondon, K.; Kalia, Y.; Gurny, R.; Möller, M. Novel micelle formulations to increase cutaneous bioavailability of azole antifungals. *J. Control. Release* **2011**, *153*, 126–132. [\[CrossRef\]](#) [\[PubMed\]](#)
50. Deng, L.; Que, F.; Wei, H.; Xu, G.; Dong, X.; Zhang, H. Solubilization of Tea Seed Oil in a Food-Grade Water-Dilutable Microemulsion. *PLoS ONE* **2015**, *10*, e0127291. [\[CrossRef\]](#) [\[PubMed\]](#)
51. Akhtar, S.; Rehman, S.; Almessiere, M.A.; Khan, F.A.; Slimani, Y.; Baykal, A. Synthesis of  $\text{Mn}_{0.5}\text{Zn}_{0.5}\text{SmxEuFe}_{1.8-2}\text{O}_4$  Nanoparticles via the Hydrothermal Approach Induced Anti-Cancer and Anti-Bacterial Activities. *Nanomaterials* **2019**, *9*, 1635. [\[CrossRef\]](#)
52. Koblishka, M.R.; Koblishka-Veneva, A.; Zeng, X.; Hannachi, E.; Slimani, Y. Microstructure and Fluctuation-Induced Conductivity Analysis of  $\text{Bi}_2\text{Sr}_2\text{CaCu}_2\text{O}_{8+\delta}$  (Bi-2212) Nanowire Fabrics. *Crystal* **2020**, *10*, 986. [\[CrossRef\]](#)
53. Lu, Y.; Xu, Y.-J.; Zhang, G.-B.; Ling, D.; Wang, M.-Q.; Zhou, Y.; Wu, Y.-D.; Wu, T.; Hackett, M.J.; Kim, B.H.; et al. Iron oxide nanoclusters for T1 magnetic resonance imaging of non-human primates. *Nat. Biomed. Eng.* **2017**, *1*, 637–643. [\[CrossRef\]](#)
54. Guo, X.; Wu, Z.; Li, W.; Wang, Z.; Li, Q.; Kong, F.; Zhang, H.; Zhu, X.; Du, Y.P.; Jin, Y.; et al. Appropriate Size of Magnetic Nanoparticles for Various Bioapplications in Cancer Diagnostics and Therapy. *ACS Appl. Mater. Interfaces* **2016**, *8*, 3092–3106. [\[CrossRef\]](#)
55. Almessiere, M.A.; Slimani, Y.; Korkmaz, A.D.; Taskhandi, N.; Sertkol, M.; Baykal, A.; Shirsath, S.E.; Ercan, İ.; Özçelik, B. Sonochemical synthesis of  $\text{Eu}^{3+}$  substituted  $\text{CoFe}_2\text{O}_4$  nanoparticles and their structural, optical and magnetic properties. *Ultrason. Sonochemistry* **2019**, *58*, 104621. [\[CrossRef\]](#) [\[PubMed\]](#)
56. Slimani, Y.; Almessiere, M.A.; Güner, S.; Tashkandi, N.A.; Baykal, A.; Sarac, M.F.; Nawaz, M.; Ercan, I. Calcination effect on the magneto-optical properties of vanadium substituted  $\text{NiFe}_2\text{O}_4$  nanoferrites. *J. Mater. Sci. Mater. Electron.* **2019**, *30*, 9143–9154. [\[CrossRef\]](#)
57. Tartaj, P.; Morales, M.P.; Veintemillas-Verdaguer, S.; Gonzalez-Carreno, T.; Serna, C.J. ChemInform Abstract: Synthesis, Properties and Biomedical Applications of Magnetic Nanoparticles. *Cheminform* **2008**, *39*, 403–482. [\[CrossRef\]](#)
58. Kudr, J.; Haddad, Y.; Richtera, L.; Heger, Z.; Cernak, M.; Adam, V.; Zitka, O. Magnetic Nanoparticles: From Design and Synthesis to Real World Applications. *Nanomaterials* **2017**, *7*, 243. [\[CrossRef\]](#) [\[PubMed\]](#)
59. Rao, Y.-F.; Chen, W.; Liang, X.-G.; Huang, Y.-Z.; Miao, J.; Liu, L.; Lou, Y.; Zhang, X.-G.; Wang, B.; Tang, R.-K.; et al. Epirubicin-Loaded Superparamagnetic Iron-Oxide Nanoparticles for Transdermal Delivery: Cancer Therapy by Circumventing the Skin Barrier. *Small* **2014**, *11*, 239–247. [\[CrossRef\]](#)
60. Dhal, S.; Mohanty, A.; Yadav, I.; Uvanesh, K.; Kulanthaivel, S.; Banerjee, I.; Pal, K.; Giri, S. Magnetic nanoparticle incorporated oleogel as iontophoretic drug delivery system. *Colloids Surf. B Biointerfaces* **2017**, *157*, 118–129. [\[CrossRef\]](#)
61. Berry, C.C.; Charles, S.; Wells, S.; Dalby, M.J.; Curtis, A.S. The influence of transferrin stabilised magnetic nanoparticles on human dermal fibroblasts in culture. *Int. J. Pharm.* **2003**, *269*, 211–225. [\[CrossRef\]](#)
62. Sundaresan, V.; Menon, J.U.; Rahimi, M.; Nguyen, K.T.; Wadaikar, A.S. Dual-responsive polymer-coated iron oxide nanoparticles for drug delivery and imaging applications. *Int. J. Pharm.* **2014**, *466*, 1–7. [\[CrossRef\]](#)
63. Ding, Y.; Shen, S.Z.; Sun, H.; Sun, K.; Liu, F.; Qi, Y.; Yan, J. Design and construction of polymerized-chitosan coated  $\text{Fe}_3\text{O}_4$  magnetic nanoparticles and its application for hydrophobic drug delivery. *Mater. Sci. Eng. C Mater. Biol. Appl.* **2015**, *48*, 487–498. [\[CrossRef\]](#)
64. Hao, R.; Xing, R.; Xu, Z.; Hou, Y.; Gao, S.; Sun, S. Synthesis, Functionalization, and Biomedical Applications of Multifunctional Magnetic Nanoparticles. *Adv. Mater.* **2010**, *22*, 2729–2742. [\[CrossRef\]](#)
65. Fatima, H.; Kim, K.-S. Magnetic nanoparticles for bioseparation. *Korean J. Chem. Eng.* **2017**, *34*, 589–599. [\[CrossRef\]](#)
66. Yang, Q.; Dong, Y.; Qiu, Y.; Yang, X.; Cao, H.; Wu, Y. Design of Functional Magnetic Nanocomposites for Bioseparation. *Colloids Surf. B Biointerfaces* **2020**, *191*, 111014. [\[CrossRef\]](#) [\[PubMed\]](#)
67. Huang, H.T.; Garu, P.; Li, C.H.; Chang, W.C.; Chen, B.W.; Sung, S.Y.; Lee, C.M.; Chen, J.Y.; Hsieh, T.F.; Sheu, W.J.; et al. Magnetoresistive Biosensors for Direct Detection of Magnetic Nanoparticle Conjugated Biomarkers on a Chip. *Spin* **2019**, *9*, 1940002. [\[CrossRef\]](#)
68. Piñeiro, Y.; Gómez, M.G.; Alves, L.D.C.; Prieto, A.A.; Acevedo, P.G.; Gudiña, R.S.; Puig, J.; Teijeiro, C.; Vilar, S.Y.; Rivas, J. Hybrid Nanostructured Magnetite Nanoparticles: From Bio-Detection and Theragnostics to Regenerative Medicine. *Magnetochemistry* **2020**, *6*, 4. [\[CrossRef\]](#)
69. Kianfar, E. Magnetic Nanoparticles in Targeted Drug Delivery: A Review. *J. Supercond. Nov. Magn.* **2021**, *34*, 1709–1735. [\[CrossRef\]](#)

70. Jeun, M.; Bae, S.; Tomitaka, A.; Takemura, Y.; Park, K.H.; Paek, S.H.; Chung, K.-W. Effects of particle dipole interaction on the ac magnetically induced heating characteristics of ferrite nanoparticles for hyperthermia. *Appl. Phys. Lett.* **2009**, *95*, 082501. [\[CrossRef\]](#)
71. Zhang, L.-K.; Du, S.; Wang, X.; Jiao, Y.; Yin, L.; Zhang, Y.; Guan, Y.-Q. Bacterial cellulose based composites enhanced transdermal drug targeting for breast cancer treatment. *Chem. Eng. J.* **2019**, *370*, 749–759. [\[CrossRef\]](#)
72. Modabberasl, A.; Pirhoushyaran, T.; Esmaeili-Faraj, S.H. Synthesis of  $\text{CoFe}_2\text{O}_4$  magnetic nanoparticles for application in photocatalytic removal of azithromycin from wastewater. *Sci. Rep.* **2022**, *12*, 19171. [\[CrossRef\]](#)
73. Kharat, P.B.; Somvanshi, S.B.; Khirade, P.P.; Jadhav, K.M. Induction Heating Analysis of Surface-Functionalized Nanoscale  $\text{CoFe}_2\text{O}_4$  for Magnetic Fluid Hyperthermia toward Noninvasive Cancer Treatment. *ACS Omega* **2020**, *5*, 23378–23384. [\[CrossRef\]](#)
74. Zhou, X.; Zhao, H.; Fu, Z.; Qu, J.; Zhong, M.; Yang, X.; Yi, Y.; Wang, C. Nanoporous Ni with High Surface Area for Potential Hydrogen Storage Application. *Nanomaterials* **2018**, *8*, 394. [\[CrossRef\]](#)
75. Lu, Y.; Yu, L.; Wu, M.; Wang, Y.; Lou, X.W.D. Construction of Complex  $\text{Co}_3\text{O}_4@\text{Co}_3\text{V}_2\text{O}_8$  Hollow Structures from Metal–Organic Frameworks with Enhanced Lithium Storage Properties. *Adv. Mater.* **2018**, *30*, 1702875. [\[CrossRef\]](#) [\[PubMed\]](#)
76. Hany, A. A review on nanoparticles in transdermal drug delivery: Polymers at variance with semiconductors and lipids. *Int. J. Eng. Appl. Sci. Technol.* **2020**, *5*, 27–36. [\[CrossRef\]](#)
77. Yu, L.; Yu, X.Y.; Lou, X.W. The Design and Synthesis of Hollow Micro-/Nanostructures: Present and Future Trends. *Adv. Mater.* **2018**, *30*, 1800939. [\[CrossRef\]](#)
78. Fang, Y.; Guan, B.Y.; Luan, D.; Lou, X.W. Synthesis of  $\text{CuS}@\text{CoS}_2$  Double-Shelled Nanoboxes with Enhanced Sodium Storage Properties. *Angew. Chem. Int. Ed.* **2019**, *58*, 7739–7743. [\[CrossRef\]](#)
79. Guo, L.; Panderi, I.; Yan, D.D.; Szulak, K.; Li, Y.; Chen, Y.-T.; Ma, H.; Niesen, D.B.; Seeram, N.; Ahmed, A.; et al. A Comparative Study of Hollow Copper Sulfide Nanoparticles and Hollow Gold Nanospheres on Degradability and Toxicity. *ACS Nano* **2013**, *7*, 8780–8793. [\[CrossRef\]](#) [\[PubMed\]](#)
80. Ku, G.; Zhou, M.; Song, S.; Huang, Q.; Hazle, J.; Li, C. Copper Sulfide Nanoparticles As a New Class of Photoacoustic Contrast Agent for Deep Tissue Imaging at 1064 nm. *ACS Nano* **2012**, *6*, 7489–7496. [\[CrossRef\]](#) [\[PubMed\]](#)
81. Ain, N.U.; Nasir, J.A.; Khan, Z.; Butler, I.S.; Rehman, Z. Copper sulfide nanostructures: Synthesis and biological applications. *RSC Adv.* **2022**, *12*, 7550–7567. [\[CrossRef\]](#)
82. Li, Q.; Sun, L.; Hou, M.; Chen, Q.; Yang, R.; Zhang, L.; Xu, Z.; Kang, Y.; Xue, P. Phase-Change Material Packaged within Hollow Copper Sulfide Nanoparticles Carrying Doxorubicin and Chlorin e6 for Fluorescence-Guided Trimodal Therapy of Cancer. *ACS Appl. Mater. Interfaces* **2018**, *11*, 417–429. [\[CrossRef\]](#)
83. Zan, P.; Than, A.; Zhang, W.; Cai, H.X.; Zhao, W.; Chen, P. Transdermal Photothermal-Pharmacotherapy to Remodel Adipose Tissue for Obesity and Metabolic Disorders. *ACS Nano* **2022**, *16*, 1813–1825. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Du, Q.; Liu, Q. ROS-responsive hollow mesoporous silica nanoparticles loaded with Glabridin for anti-pigmentation properties. *Microporous Mesoporous Mater.* **2021**, *327*, 111429. [\[CrossRef\]](#)
85. Wang, Y.; Cheng, S.; Hu, W.; Lin, X.; Cao, C.; Zou, S.; Tong, Z.; Jiang, G.; Kong, X. Polymer-grafted hollow mesoporous silica nanoparticles integrated with microneedle patches for glucose-responsive drug delivery. *Front. Mater. Sci.* **2021**, *15*, 98–112. [\[CrossRef\]](#)
86. Zhang, Y.; Jiang, G.; Hong, W.; Gao, M.; Xu, B.; Zhu, J.; Song, G.; Liu, T. Polymeric Microneedles Integrated with Metformin-Loaded and PDA/LA-Coated Hollow Mesoporous  $\text{SiO}_2$  for NIR-Triggered Transdermal Delivery on Diabetic Rats. *ACS Appl. Bio Mater.* **2018**, *1*, 1906–1917. [\[CrossRef\]](#)
87. Kwon, J.S.; Kim, D.Y.; Seo, H.W.; Jeong, S.H.; Kim, J.H.; Kim, M.S. Preparation of erythromycin-loaded poly(vinylalcohol) film and investigation of its feasibility as a transdermal delivery carrier. *Tissue Eng. Regen. Med.* **2014**, *11*, 211–216. [\[CrossRef\]](#)
88. An, Y.-H.; Lee, J.; Son, D.U.; Kang, D.H.; Park, M.J.; Cho, K.W.; Kim, S.; Kim, S.-H.; Ko, J.; Jang, M.-H.; et al. Facilitated Transdermal Drug Delivery Using Nanocarriers-Embedded Electroconductive Hydrogel Coupled with Reverse Electrodialysis-Driven Iontophoresis. *ACS Nano* **2020**, *14*, 4523–4535. [\[CrossRef\]](#) [\[PubMed\]](#)
89. Qiao, Z.; Tran, L.; Parks, J.; Zhao, Y.; Hai, N.; Zhong, Y.; Ji, H. Highly stretchable gelatin-polyacrylamide hydrogel for potential transdermal drug release. *Nano Sel.* **2020**, *2*, 107–115. [\[CrossRef\]](#)
90. Jung, H.; Kim, M.K.; Lee, J.Y.; Choi, S.W.; Kim, J. Adhesive Hydrogel Patch with Enhanced Strength and Adhesiveness to Skin for Transdermal Drug Delivery. *Adv. Funct. Mater.* **2020**, *30*, 2004407. [\[CrossRef\]](#)
91. Sun, J.-Y.; Zhao, X.; Illeperuma, W.R.K.; Chaudhuri, O.; Oh, K.H.; Mooney, D.J.; Vlassak, J.J.; Suo, Z. Highly stretchable and tough hydrogels. *Nature* **2012**, *489*, 133–136. [\[CrossRef\]](#)
92. Ahsan, A.; Tian, W.X.; Farooq, M.A.; Khan, D.H. An overview of hydrogels and their role in transdermal drug delivery. *Int. J. Polym. Mater. Polym. Biomater.* **2021**, *70*, 574–584. [\[CrossRef\]](#)
93. Ciolacu, D.E.; Nicu, R.; Ciolacu, F. Materials Cellulose-Based Hydrogels as Sustained Drug-Delivery Systems. *Materials* **2020**, *13*, 5270. [\[CrossRef\]](#)
94. Pal, K.; Banthia, A.K.; Majumdar, D.K. Polymeric hydrogels: Characterization and biomedical applications. *Designed Monomers and Polymers* **2009**, *12*, 197–220. [\[CrossRef\]](#)
95. Huang, D.; Sun, M.; Bu, Y.; Luo, F.; Lin, C.; Lin, Z.; Weng, Z.; Yang, F.; Wu, D. Microcapsule-embedded hydrogel patches for ultrasound responsive and enhanced transdermal delivery of diclofenac sodium. *J. Mater. Chem. B* **2019**, *7*, 2330–2337. [\[CrossRef\]](#) [\[PubMed\]](#)

96. Zhang, S.; Xin, P.; Ou, Q.; Hollett, G.; Gu, Z.; Wu, J. Poly(ester amide)-based hybrid hydrogels for efficient transdermal insulin delivery. *J. Mater. Chem. B* **2018**, *6*, 6723–6730. [\[CrossRef\]](#)
97. Birajdar, R.P.; Patil, S.B.; Alange, V.V.; Kulkarni, R.V. Synthesis and characterization of electrically responsive poly(acrylamide)-grafted-chondroitin sulfate hydrogel for transdermal drug delivery application. *Int. J. Polym. Mater. Polym. Biomater.* **2019**, *69*, 148–157. [\[CrossRef\]](#)
98. Radwan-Pragłowska, J.; Janus, L.; Piątkowski, M.; Sierakowska, A.; Matysek, D. ZnO nanorods functionalized with chitosan hydrogels crosslinked with azelaic acid for transdermal drug delivery. *Colloids Surf. B Biointerfaces* **2020**, *194*, 111170. [\[CrossRef\]](#)
99. Wei, H.; Liu, S.; Tong, Z.; Chen, T.; Yang, M.; Guo, Y.; Sun, H.; Wu, Y.; Chu, Y.; Fan, L. Hydrogel-based microneedles of chitosan derivatives for drug delivery. *React. Funct. Polym.* **2022**, *172*, 105200. [\[CrossRef\]](#)
100. Jeong, H.J.; Nam, S.J.; Song, J.Y.; Park, S.N. Synthesis and physicochemical properties of pH-sensitive hydrogel based on carboxymethyl chitosan/2-hydroxyethyl acrylate for transdermal delivery of nobiletin. *J. Drug Deliv. Sci. Technol.* **2019**, *51*, 194–203. [\[CrossRef\]](#)
101. Giuliano, E.; Paolino, D.; Fresta, M.; Cosco, D. Pharmaceuticals Mucosal Applications of Poloxamer 407-Based Hydrogels: An Overview. *Pharmaceutics* **2018**, *10*, 159. [\[CrossRef\]](#)
102. Laurano, R.; Abrami, M.; Grassi, M.; Ciardelli, G.; Boffito, M.; Chiono, V. Using Poloxamer®407 as Building Block of Amphiphilic Poly(ether urethane)s: Effect of its Molecular Weight Distribution on Thermo-Sensitive Hydrogel Performances in the Perspective of Their Biomedical Application. *Front. Mater.* **2020**, *7*, 594515. [\[CrossRef\]](#)
103. Shu, H.; Zhang, Y.; Zhang, M.; Wu, J.; Cui, M.; Liu, K.; Wang, J. Addition of free poloxamer 407 to a new gene vector P407-PEI-K12 solution forms a sustained-release in situ hydrogel that enhances cell transfection and extends gene expression. *Oncol. Lett.* **2019**, *17*, 3085–3096. [\[CrossRef\]](#) [\[PubMed\]](#)
104. Dumortier, G.; Grossiord, J.L.; Agnely, F.; Chaumeil, J.C. Expert Review A Review of Poloxamer 407 Pharmaceutical and Pharmacological Characteristics. *Pharm. Res.* **2006**, *23*, 2709–2728. [\[CrossRef\]](#) [\[PubMed\]](#)
105. Mansuri, S.; Kesharwani, P.; Jain, K.; Tekade, R.K.; Jain, N.K. Mucoadhesion: A promising approach in drug delivery system. *React. Funct. Polym.* **2016**, *100*, 151–172. [\[CrossRef\]](#)
106. Mayol, L.; Biondi, M.; Quaglia, F.; Fusco, S.; Borzacchiello, A.; Ambrosio, L.; La Rotonda, M.I. Injectable Thermally Responsive Mucoadhesive Gel for Sustained Protein Delivery. *Biomacromolecules* **2010**, *12*, 28–33. [\[CrossRef\]](#) [\[PubMed\]](#)
107. Wang, W.; Wat, E.; Hui, P.C.L.; Chan, B.; Ng, F.S.F.; Kan, C.-W.; Wang, X.; Hu, H.; Wong, E.C.W.; Lau, C.B.S.; et al. Dual-functional transdermal drug delivery system with controllable drug loading based on thermosensitive poloxamer hydrogel for atopic dermatitis treatment. *Sci. Rep.* **2016**, *6*, 24112. [\[CrossRef\]](#) [\[PubMed\]](#)
108. Wang, W.-Y.; Hui, P.C.L.; Wat, E.; Ng, F.S.F.; Kan, C.-W.; Lau, C.B.S.; Leung, P.-C. Enhanced Transdermal Permeability via Constructing the Porous Structure of Poloxamer-Based Hydrogel. *Polymers* **2016**, *8*, 406. [\[CrossRef\]](#) [\[PubMed\]](#)
109. Gao, Y.; Hao, Y.; Zhang, W.; Wei, Y.; Shu, Y.; Wang, J. Microwave-triggered ionic liquid-based hydrogel dressing with excellent hyperthermia and transdermal drug delivery performance. *Chem. Eng. J.* **2021**, *429*, 131590. [\[CrossRef\]](#)
110. Hamad, K.M.; Mahmoud, N.N.; Al-Dabash, S.; Al-Samad, L.A.; Abdallah, M.; Al-Bakri, A.G. Fluconazole conjugated-gold nanorods as an antifungal nanomedicine with low cytotoxicity against human dermal fibroblasts. *RSC Adv.* **2020**, *10*, 25889–25897. [\[CrossRef\]](#)
111. Patil, S.B.; Inamdar, S.Z.; Reddy, K.R.; Raghu, A.V.; Akamanchi, K.G.; Inamadar, A.C.; Das, K.K.; Kulkarni, R.V. Functionally Tailored Electro-Sensitive Poly(Acrylamide)-g-Pectin Copolymer Hydrogel for Transdermal Drug Delivery Application: Synthesis, Characterization, In-vitro and Ex-vivo Evaluation. *Drug Deliv. Lett.* **2020**, *10*, 185–196. [\[CrossRef\]](#)
112. Patil, S.B.; Inamdar, S.Z.; Das, K.K.; Akamanchi, K.G.; Patil, A.V.; Inamadar, A.C.; Reddy, K.R.; Raghu, A.V.; Kulkarni, R.V. Tailor-made electrically-responsive poly(acrylamide)-graft-pullulan copolymer based transdermal drug delivery systems: Synthesis, characterization, in-vitro and ex-vivo evaluation. *J. Drug Deliv. Sci. Technol.* **2020**, *56*, 101525. [\[CrossRef\]](#)
113. Pandita, D.; Kumar, S.; Lather, V. Hybrid poly(lactic-co-glycolic acid) nanoparticles: Design and delivery prospectives. *Drug Discov. Today* **2015**, *20*, 95–104. [\[CrossRef\]](#)
114. Hafez Mousa, A.; Agha Mohammad, S. Potential role of chitosan, PLGA and iron oxide nanoparticles in Parkinsons disease therapy. *J. Neurol. Psychiatry Neurosurg.* **2022**, *58*, 68.
115. Essa, D.; Kondiah, P.P.D.; Choonara, Y.E.; Pillay, V. The Design of Poly(lactide-co-glycolide) Nanocarriers for Medical Applications. *Front. Bioeng. Biotechnol.* **2020**, *8*, 48. [\[CrossRef\]](#)
116. Elmowafy, E.M.; Tiboni, M.; Soliman, M.E. Biocompatibility, biodegradation and biomedical applications of poly(lactic acid)/poly(lactic-co-glycolic acid) micro and nanoparticles. *J. Pharm. Investig.* **2019**, *49*, 347–380. [\[CrossRef\]](#)
117. Kumari, A.; Yadav, S.K.; Yadav, S.C. Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids Surf. B Biointerfaces* **2010**, *75*, 1–18. [\[CrossRef\]](#) [\[PubMed\]](#)
118. Huang, W.; Zhang, C. Tuning the size of poly(lactic-co-glycolic acid) (PLGA) nanoparticles fabricated by nanoprecipitation; Tuning the size of poly(lactic-co-glycolic acid) (PLGA) nanoparticles fabricated by nanoprecipitation. *Biotechnol. J.* **2018**, *13*, 1700203. [\[CrossRef\]](#) [\[PubMed\]](#)
119. Sahin, A.; Esendagli, G.; Yerlikaya, F.; Caban-Toktas, S.; Yoyen-Ermis, D.; Horzum, U.; Aktas, Y.; Khan, M.; Couvreur, P.; Capan, Y. A small variation in average particle size of PLGA nanoparticles prepared by nanoprecipitation leads to considerable change in nanoparticles characteristics and efficacy of intracellular delivery. *Artif. Cells Nanomed. Biotechnol.* **2017**, *45*, 1657–1664. [\[CrossRef\]](#)



120. Swetha, T.A.; Ananthi, V.; Bora, A.; Sengottuvelan, N.; Ponnuchamy, K.; Muthusamy, G.; Arun, A. A review on biodegradable polylactic acid (PLA) production from fermentative food waste - Its applications and degradation. *International Journal of Biological Macromolecules* **2023**, *234*, 123703. [\[CrossRef\]](#) [\[PubMed\]](#)
121. Barua, S.; Mitragotri, S. Challenges associated with penetration of nanoparticles across cell and tissue barriers: A review of current status and future prospects. *Nano Today* **2014**, *9*, 223–243. [\[CrossRef\]](#) [\[PubMed\]](#)
122. Trigueros, S. Nanoscale Metal Particles as Nanocarriers in Targeted Drug Delivery System. *J. Nanomed. Res.* **2016**, *4*, 1–6. [\[CrossRef\]](#)
123. Cataldi, M.; Vigliotti, C.; Mosca, T.; Cammarota, M.; Capone, D. Emerging Role of the Spleen in the Pharmacokinetics of Monoclonal Antibodies, Nanoparticles and Exosomes. *Int. J. Mol. Sci.* **2017**, *18*, 1249. [\[CrossRef\]](#) [\[PubMed\]](#)
124. Karasu, İ.; Akbaş, S.; Çapan, Y. Current progress in PLGA-based nanoparticles for treatment of cancer diseases. In *Poly(lactic-co-glycolic acid) Nanoparticles Drug Delivery*; Elsevier: Amsterdam, The Netherlands, 2023; pp. 153–177. [\[CrossRef\]](#)
125. Dobiasch, S.; Szanyi, S.; Kjaev, A.; Werner, J.; Strauss, A.; Weis, C.; Grenacher, L.; Kapilov-Buchman, K.; Israel, L.-L.; Lellouche, J.-P.; et al. Synthesis and functionalization of protease-activated nanoparticles with tissue plasminogen activator peptides as targeting moiety and diagnostic tool for pancreatic cancer. *J. Nanobiotechnology* **2016**, *14*, 1–18. [\[CrossRef\]](#)
126. Ambrogio, M.W.; Toro-González, M.; Keever, T.J.; McKnight, T.E.; Davern, S.M. Poly(lactic-co-glycolic acid) Nanoparticles as Delivery Systems for the Improved Administration of Radiotherapeutic Anticancer Agents. *ACS Appl. Nano Mater.* **2020**, *3*, 10565–10570. [\[CrossRef\]](#)
127. Salaheldin, T.A.; Bharali, D.J.; Mousa, S.A. Functionalized nano-targeted moieties in management of prostate cancer. *Futur. Oncol.* **2020**, *16*, 869–883. [\[CrossRef\]](#) [\[PubMed\]](#)
128. Galindo, R.; Sánchez-López, E.; Gómara, M.J.; Espina, M.; Ettcheto, M.; Cano, A.; Haro, I.; Camins, A.; García, M.L. Development of Peptide Targeted PLGA-PEGylated Nanoparticles Loading Licochalcone-A for Ocular Inflammation. *Pharmaceutics* **2022**, *14*, 285. [\[CrossRef\]](#)
129. Gonzalez-Pizarro, R.; Parrotta, G.; Vera, R.; Sánchez-López, E.; Galindo, R.; Kjeldsen, F.; Badia, J.; Baldoma, L.; Espina, M.; García, M.L. Ocular penetration of fluorometholone-loaded PEG-PLGA nanoparticles functionalized with cell-penetrating peptides. *Nanomedicine* **2019**, *14*, 3089–3104. [\[CrossRef\]](#)
130. Samani, S.E.; Naderimanesh, H.; Asghari, S.M.; Hoseinkhani, S. Optimization of Preparation of PEG-PLGA Nanoparticles by Solvent Evaporation Method. *J. Biotechnol.* **2018**, *9*, 201–205.
131. El-Hammadi, M.M.; Arias, J.L. Recent Advances in the Surface Functionalization of PLGA-Based Nanomedicines. *Nanomaterials* **2022**, *12*, 354. [\[CrossRef\]](#)
132. Makadia, H.K.; Siegel, S.J. Poly lactic-co-glycolic acid (PLGA) As biodegradable controlled drug delivery carrier. *Polymers* **2011**, *3*, 1377–1397. [\[CrossRef\]](#)
133. Patel, K.D.; Silva, L.B.; Park, Y.; Shakouri, T.; Keskin-Erdogan, Z.; Sawadkar, P.; Cho, K.J.; Knowles, J.C.; Chau, D.Y.; Kim, H.-W. Recent advances in drug delivery systems for glaucoma treatment. *Mater. Today Nano* **2022**, *18*, 100178. [\[CrossRef\]](#)
134. Yadav, K.S.; Rajpurohit, R.; Sharma, S. Glaucoma: Current treatment and impact of advanced drug delivery systems. *Life Sci.* **2019**, *221*, 362–376. [\[CrossRef\]](#) [\[PubMed\]](#)
135. Rahimi, M.; Charmi, G.; Matyjaszewski, K.; Banquy, X.; Pietrasik, J. Recent developments in natural and synthetic polymeric drug delivery systems used for the treatment of osteoarthritis. *Acta Biomater.* **2021**, *123*, 31–50. [\[CrossRef\]](#)
136. Jin, Z.; Zhan, Y.; Zheng, L.; Wei, Q.; Xu, S.; Qin, Z. Cannabidiol-loaded poly lactic-co-glycolic acid nanoparticles with improved bioavailability as a potential for osteoarthritis therapeutic. *Chembiochem* **2022**, *1–4*. [\[CrossRef\]](#) [\[PubMed\]](#)
137. Pontes, A.P.; Welting, T.J.M.; Rip, J.; Creemers, L.B. Polymeric Nanoparticles for Drug Delivery in Osteoarthritis. *Pharmaceutics* **2022**, *14*, 2639. [\[CrossRef\]](#)
138. Takeuchi, I.; Suzuki, T.; Makino, K. Skin permeability and transdermal delivery route of 50-nm indomethacin-loaded PLGA nanoparticles. *Colloids Surf. B Biointerfaces* **2017**, *159*, 312–317. [\[CrossRef\]](#) [\[PubMed\]](#)
139. Takeuchi, I.; Kobayashi, S.; Hida, Y.; Makino, K. Estradiol-loaded PLGA nanoparticles for improving low bone mineral density of cancellous bone caused by osteoporosis: Application of enhanced charged nanoparticles with iontophoresis. *Colloids Surf. B Biointerfaces* **2017**, *155*, 35–40. [\[CrossRef\]](#)
140. Takeuchi, I.; Suzuki, T.; Makino, K. Iontophoretic transdermal delivery using chitosan-coated PLGA nanoparticles for transcutaneous immunization. *Colloids Surf. A Physicochem. Eng. Asp.* **2020**, *608*, 125607. [\[CrossRef\]](#)
141. Bali, N.R.; Salve, P.S. Selegiline nanoparticle embedded transdermal film: An alternative approach for brain targeting in Parkinsons disease. *J. Drug Deliv. Sci. Technol.* **2019**, *54*, 101299. [\[CrossRef\]](#)
142. Bali, N.R.; Salve, P.S. Impact of rasagiline nanoparticles on brain targeting efficiency via gellan gum based transdermal patch: A nanotheranostic perspective for Parkinsonism. *Int. J. Biol. Macromol.* **2020**, *164*, 1006–1024. [\[CrossRef\]](#)
143. Sadeghi-Avalshahr, A.; Nokhasteh, S.; Molavi, A.M.; Khorsand-Ghayeni, M.; Mahdavi-Shahri, M. Synthesis and characterization of collagen/PLGA biodegradable skin scaffold fibers. *Regen. Biomater.* **2017**, *4*, 309–314. [\[CrossRef\]](#)
144. Takeuchi, I.; Kagawa, A.; Makino, K. Skin permeability and transdermal delivery route of 30-nm cyclosporin A-loaded nanoparticles using PLGA-PEG-PLGA triblock copolymer. *Colloids Surf. A Physicochem. Eng. Asp.* **2020**, *600*, 124866. [\[CrossRef\]](#)
145. Akhtar, N. Microneedles: An innovative approach to transdermal delivery—A review. *Innovare Acad. Sci.* **2014**, *6*, 18–25.
146. Jeong, W.Y.; Kim, S.; Lee, S.Y.; Lee, H.; Han, D.-W.; Yang, S.Y.; Kim, K.S. Transdermal delivery of Minoxidil using HA-PLGA nanoparticles for the treatment in alopecia. *Biomater. Res.* **2019**, *23*, 16. [\[CrossRef\]](#) [\[PubMed\]](#)

147. Lin, C.-Y.; Hsieh, Y.-T.; Chan, L.Y.; Yang, T.-Y.; Maeda, T.; Chang, T.-M.; Huang, H.-C. Dictamnine delivered by PLGA nanocarriers ameliorated inflammation in an oxazolone-induced dermatitis mouse model. *J. Control. Release* **2020**, *329*, 731–742. [\[CrossRef\]](#)
148. Marapureddy, S.G.; Thareja, P. Synergistic effect of chemical crosslinking and addition of graphene-oxide in Chitosan—Hydrogels, films, and drug delivery. *Mater. Today Commun.* **2021**, *31*, 103430. [\[CrossRef\]](#)
149. Pourseif, T.; Ghafelehbashi, R.; Abdihaji, M.; Radan, N.; Kaffash, E.; Heydari, M.; Naseroleslami, M.; Mousavi-Niri, N.; Akbarzadeh, I.; Ren, Q. Chitosan-based nanoniosome for potential wound healing applications: Synergy of controlled drug release and antibacterial activity. *Int. J. Biol. Macromol.* **2023**, *230*, 123185. [\[CrossRef\]](#) [\[PubMed\]](#)
150. Alhodieb, F.S.; Barkat, M.A.; Barkat, H.A.; Hadi, H.A.; Khan, M.I.; Ashfaq, F.; Rahman, M.A.; Hassan, M.Z.; Alanezi, A.A. International Journal of Biological Macromolecules Chitosan-modified nanocarriers as carriers for anticancer drug delivery: Promises and hurdles. *Int. J. Biol. Macromol.* **2022**, *217*, 457–469. [\[CrossRef\]](#)
151. Mukhtar, M.; Fényes, E.; Bartos, C.; Zeeshan, M.; Ambrus, R. Chitosan biopolymer, its derivatives and potential applications in nano-therapeutics: A comprehensive review. *Eur. Polym. J.* **2021**, *160*, 110767. [\[CrossRef\]](#)
152. Gorantla, S.; Dabholkar, N.; Sharma, S.; Rapalli, V.K.; Alexander, A.; Singhvi, G. Chitosan-based microneedles as a potential platform for drug delivery through the skin: Trends and regulatory aspects. *Int. J. Biol. Macromol.* **2021**, *184*, 438–453. [\[CrossRef\]](#)
153. Abnoos, M.; Mohseni, M.; Mousavi, S.A.J.; Ashtari, K.; Ilka, R.; Mehravi, B. Chitosan-alginate nano-carrier for transdermal delivery of pirfenidone in idiopathic pulmonary fibrosis. *Int. J. Biol. Macromol.* **2018**, *118*, 1319–1325. [\[CrossRef\]](#)
154. Talib, S.; Ahmed, N.; Khan, D.; Khan, G.M.; Rehman, A.U. Chitosan-chondroitin based artemether loaded nanoparticles for transdermal drug delivery system. *J. Drug Deliv. Sci. Technol.* **2021**, *61*, 102281. [\[CrossRef\]](#)
155. Da Silva, T.N.; Reynaud, F.; Picciani, P.H.D.S.; Silva, K.G.D.H.E.; Barradas, T.N. Chitosan-based films containing nanoemulsions of methyl salicylate: Formulation development, physical-chemical and in vitro drug release characterization. *Int. J. Biol. Macromol.* **2020**, *164*, 2558–2568. [\[CrossRef\]](#)
156. Karakurt, I.; Ozaltin, K.; Vargun, E.; Kucerova, L.; Suly, P.; Harea, E.; Minařík, A.; Štěpánková, K.; Lehocky, M.; Humpolíček, P.; et al. Controlled release of enrofloxacin by vanillin-crosslinked chitosan-polyvinyl alcohol blends. *Mater. Sci. Eng. C* **2021**, *126*, 112125. [\[CrossRef\]](#) [\[PubMed\]](#)
157. Truong, T.H.; Alcantara, K.P.; Bulatao, B.P.I.; Sorasitthyanukarn, F.N.; Muangnoi, C.; Nalinratana, N.; Vajragupta, O.; Rojsitthisak, P.; Rojsitthisak, P. Chitosan-coated nanostructured lipid carriers for transdermal delivery of tetrahydrocurcumin for breast cancer therapy. *Carbohydr. Polym.* **2022**, *288*, 119401. [\[CrossRef\]](#)
158. Engkagul, V.; Klaharn, I.-Y.; Sereemasapun, A.; Chirachanchai, S. Chitosan whisker grafted with oligo(lactic acid) nanoparticles via a green synthesis pathway: Potential as a transdermal drug delivery system. *Nanomed. Nanotechnol. Biol. Med.* **2017**, *13*, 2523–2531. [\[CrossRef\]](#) [\[PubMed\]](#)
159. Andrés Ortiz, J.; Antonella Sepúlveda, F.; Panadero-Medianero, C.; Murgas, P.; Ahumada, M.; Palza, H.; Zapata, P.A. Cytocompatible drug delivery hydrogels based on carboxymethylagarose/chitosan pH-responsive polyelectrolyte complexes. *Int. J. Biol. Macromol.* **2021**, *199*, 96–107. [\[CrossRef\]](#)
160. Castilla-Casadiago, D.A.; Carlton, H.; Gonzalez-Nino, D.; Miranda-Muñoz, K.A.; Daneshpour, R.; Huitink, D.; Prinz, G.; Powell, J.; Greenlee, L.; Almodovar, J. Design, characterization, and modeling of a chitosan microneedle patch for transdermal delivery of meloxicam as a pain management strategy for use in cattle. *Mater. Sci. Eng. C* **2020**, *118*, 111544. [\[CrossRef\]](#)
161. Bigucci, F.; Abruzzo, A.; Saladini, B.; Gallucci, M.C.; Cerchiara, T.; Luppi, B. Development and characterization of chitosan/hyaluronan film for transdermal delivery of thiocolchicoside. *Carbohydr. Polym.* **2015**, *130*, 32–40. [\[CrossRef\]](#) [\[PubMed\]](#)
162. Abioye, A.O.; Issah, S.; Kola-Mustapha, A.T. Ex vivo skin permeation and retention studies on chitosan-ibuprofen-gellan ternary nanogel prepared by in situ ionic gelation technique—A tool for controlled transdermal delivery of ibuprofen. *Int. J. Pharm.* **2015**, *490*, 112–130. [\[CrossRef\]](#) [\[PubMed\]](#)
163. Mendes, A.C.; Gorzelanny, C.; Halter, N.; Schneider, S.W.; Chronakis, I.S. Hybrid electrospun chitosan-phospholipids nanofibers for transdermal drug delivery. *Int. J. Pharm.* **2016**, *510*, 48–56. [\[CrossRef\]](#)
164. Li, B.; Wang, L.; Xu, F.; Gang, X.; Demirci, U.; Wei, D.; Li, Y.; Feng, Y.; Jia, D.; Zhou, Y. Hydrosoluble, UV-crosslinkable and injectable chitosan for patterned cell-laden microgel and rapid transdermal curing hydrogel in vivo. *Acta Biomater.* **2015**, *22*, 59–69. [\[CrossRef\]](#)
165. Chatterjee, S.; Hui, P.C.; Siu, W.S.; Kan, C.; Leung, P.C.; Wanxue, C.; Chiou, J.C. Influence of pH-responsive compounds synthesized from chitosan and hyaluronic acid on dual-responsive (pH/temperature) hydrogel drug delivery systems of Cortex Moutan. *Int. J. Biol. Macromol.* **2021**, *168*, 163–174. [\[CrossRef\]](#) [\[PubMed\]](#)
166. Takeuchi, I.; Takeshita, T.; Suzuki, T.; Makino, K. Iontophoretic transdermal delivery using chitosan-coated PLGA nanoparticles for positively charged drugs. *Colloids Surf. B Biointerfaces* **2017**, *160*, 520–526. [\[CrossRef\]](#) [\[PubMed\]](#)
167. Morad, H.; Jahanshahi, M.; Akbari, J.; Saedi, M.; Gill, P.; Enayatifard, R. Novel topical and transdermal delivery of colchicine with chitosan based biocomposite nanofibrous system; formulation, optimization, characterization, ex vivo skin deposition/permeation, and anti-melanoma evaluation. *Mater. Chem. Phys.* **2021**, *263*, 124381. [\[CrossRef\]](#)
168. Luesakul, U.; Puthong, S.; Sansanaphongpricha, K.; Muangsins, N. Quaternized chitosan-coated nanoemulsions: A novel platform for improving the stability, anti-inflammatory, anti-cancer and transdermal properties of Plai extract. *Carbohydr. Polym.* **2019**, *230*, 115625. [\[CrossRef\]](#)
169. Rubina, M.S.; Pestrikova, A.A.; Kazaryan, P.S.; Nikolaev, A.Y.; Chaschin, I.S.; Arkharova, N.A.; Shulenina, A.V.; Pigaleva, M.A. Supercritical impregnation of chitosan sponges with 17 $\beta$ -estradiol. *J. CO<sub>2</sub> Util.* **2022**, *62*, 102106. [\[CrossRef\]](#)



170. Sahu, P.; Kashaw, S.K.; Kashaw, V.; Shabaaz, J.; Dahiya, R. Synthesis and ex vivo evaluation of PLGA chitosan surface modulated double walled transdermal Pluronic nanogel for the controlled delivery of Temozolomide. *Int. J. Biol. Macromol.* **2021**, *187*, 742–754. [\[CrossRef\]](#) [\[PubMed\]](#)
171. Al-Kassas, R.; Wen, J.; Cheng, A.E.-M.; Kim, A.M.-J.; Liu, S.S.M.; Yu, J. Transdermal delivery of propranolol hydrochloride through chitosan nanoparticles dispersed in mucoadhesive gel. *Carbohydr. Polym.* **2016**, *153*, 176–186. [\[CrossRef\]](#) [\[PubMed\]](#)
172. Ye, L.; Chen, W.; Chen, Y.; Qiu, Y.; Yi, J.; Li, X.; Lin, Q.; Guo, B. Functionalized multiwalled carbon nanotube-ethosomes for transdermal delivery of ketoprofen: Ex vivo and in vivo evaluation. *J. Drug Deliv. Sci. Technol.* **2022**, *69*, 103098. [\[CrossRef\]](#)
173. Gulati, G.K.; Berger, L.R.; Hinds, B.J. A preclinical evaluation of a programmable CNT membrane device for transdermal nicotine delivery in hairless Guinea pigs. *J. Control. Release* **2018**, *293*, 135–143. [\[CrossRef\]](#)
174. Gulati, G.K.; Chen, T.; Hinds, B.J. Programmable carbon nanotube membrane-based transdermal nicotine delivery with microdialysis validation assay. *Nanomed. Nanotechnol. Biol. Med.* **2016**, *13*, 1–9. [\[CrossRef\]](#) [\[PubMed\]](#)
175. Cranford, S.W.; Buehler, M.J. In silico assembly and nanomechanical characterization of carbon nanotube buckypaper. *Nanotechnology* **2010**, *21*, 265706. [\[CrossRef\]](#)
176. Schwengber, A.; Prado, H.J.; Bonelli, P.R.; Cukierman, A.L. Development and in vitro evaluation of potential electromodulated transdermal drug delivery systems based on carbon nanotube buckypapers. *Mater. Sci. Eng. C* **2017**, *76*, 431–438. [\[CrossRef\]](#)
177. Anirudhan, T.; Nair, S.S. Development of voltage gated transdermal drug delivery platform to impose synergistic enhancement in skin permeation using electroporation and gold nanoparticle. *Mater. Sci. Eng. C* **2019**, *102*, 437–446. [\[CrossRef\]](#) [\[PubMed\]](#)
178. Guillet, J.-F.; Valdez-Nava, Z.; Golzio, M.; Flahaut, E. Electrical properties of double-wall carbon nanotubes nanocomposite hydrogels. *Carbon* **2019**, *146*, 542–548. [\[CrossRef\]](#)
179. Mohd, N.H.; Ismail, N.F.H.; Zahari, J.I.; Fathilah, W.; Kargarzadeh, H.; Ramli, S.; Othaman, R. Effect of Aminosilane Modification on Nanocrystalline Cellulose Properties. *J. Nanomater.* **2016**, *2016*, e4804271. [\[CrossRef\]](#)
180. Lunardi, V.B.; Soetaredjo, F.E.; Putro, J.N.; Santoso, S.P.; Yuliana, M.; Sunarso, J.; Ju, Y.H.; Ismadji, S. Nanocelluloses: Sources, Pretreatment, Isolations, Modification, and Its Application as the Drug Carriers. *Polymers* **2021**, *13*, 2052. [\[CrossRef\]](#)
181. Trache, D.; Tarchoun, A.F.; Derradji, M.; Hamidon, T.S.; Masruchin, N.; Brosse, N.; Hussin, M.H. Nanocellulose: From Fundamentals to Advanced Applications. *Front. Chem.* **2020**, *8*, 392. [\[CrossRef\]](#)
182. Mautner, A.; Hakalahti, M.; Rissanen, V.; Tammelin, T. Crucial Interfacial Features of Nanocellulose Materials. *Nanocellulose Sustain. Prod. Prop. Appl. Case Stud.* **2018**, *42*, 87–128. [\[CrossRef\]](#)
183. Salimi, S.; Sotudeh-Gharebagh, R.; Zarghami, R.; Chan, S.Y.; Yuen, K.H. Production of Nanocellulose and Its Applications in Drug Delivery: A Critical Review. *ACS Sustain. Chem. Eng.* **2019**, *7*, 15800–15827. [\[CrossRef\]](#)
184. Tan, T.H.; Lee, H.V.; Yehya Dabdawb, W.A. A review of nanocellulose in the drug-delivery system. In *Materials for Biomedical Engineering Nanomaterials-based Drug Delivery*; Elsevier: Amsterdam, The Netherlands, 2019; pp. 131–164.
185. George, J.; Sabapathi, S.N. Cellulose nanocrystals: Synthesis, functional properties, and applications. *Nanotechnol. Sci. Appl.* **2015**, *8*, 45–54. [\[CrossRef\]](#) [\[PubMed\]](#)
186. Lisdayana, N.; Fahma, F.; Sunarti, T.C.; Iriani, E.S. Thermoplastic Starch–PVA Nanocomposite Films Reinforced with Nanocellulose from Oil Palm Empty Fruit Bunches (OPEFBs): Effect of Starch Type. *J. Nat. Fibers* **2018**, *17*, 1069–1080. [\[CrossRef\]](#)
187. Phanthong, P.; Reubroycharoen, P.; Hao, X.; Xu, G.; Abudula, A.; Guan, G. Nanocellulose: Extraction and application. *Carbon Resour. Convers.* **2018**, *1*, 32–43. [\[CrossRef\]](#)
188. Liu, S.; Qamar, S.A.; Qamar, M.; Basharat, K.; Bilal, M. Engineered nanocellulose-based hydrogels for smart drug delivery applications. *Int. J. Biol. Macromol.* **2021**, *181*, 275–290. [\[CrossRef\]](#)
189. Quinetti, C.; Pittella, P.; Vitoria, E.M.; Francisco, G.; Junior, X. The use of bacterial nanocellulose as wound healing dressing: A scoping review. **2022**.
190. Taheri, P.; Jahanmardi, R.; Koosha, M.; Abdi, S. Physical, mechanical and wound healing properties of chitosan/gelatin blend films containing tannic acid and/or bacterial nanocellulose. *Int. J. Biol. Macromol.* **2020**, *154*, 421–432. [\[CrossRef\]](#) [\[PubMed\]](#)
191. Zainuddin, N.; Ahmad, I.; Zulfakar, M.H.; Kargarzadeh, H.; Ramli, S. Cetyltrimethylammonium bromide-nanocrystalline cellulose (CTAB-NCC) based microemulsions for enhancement of topical delivery of curcumin. *Carbohydr. Polym.* **2020**, *254*, 117401. [\[CrossRef\]](#)
192. O-Chongpian, P.; Na Takuathung, M.; Chittasupho, C.; Ruksiriwanich, W.; Chaiwarit, T.; Baipaywad, P.; Jantrawut, P. Composite Nanocellulose Fibers-Based Hydrogels Loading Clindamycin HCl with Ca<sup>2+</sup> and Citric Acid as Crosslinking Agents for Pharmaceutical Applications. *Polymers* **2021**, *13*, 4423. [\[CrossRef\]](#)
193. Thomas, D.; Latha, M.; Thomas, K.K. Synthesis and in vitro evaluation of alginate-cellulose nanocrystal hybrid nanoparticles for the controlled oral delivery of rifampicin. *J. Drug Deliv. Sci. Technol.* **2018**, *46*, 392–399. [\[CrossRef\]](#)
194. Pachuau, L. Application of Nanocellulose for Controlled Drug Delivery. In *Nanocellulose and Nanohydrogel Matrices*; Wiley: Hoboken, NJ, USA, 2017; pp. 1–19. [\[CrossRef\]](#)
195. Raghav, N.; Sharma, M.R.; Kennedy, J.F. Nanocellulose: A mini-review on types and use in drug delivery systems. *Carbohydr. Polym. Technol. Appl.* **2021**, *2*, 100031. [\[CrossRef\]](#)
196. Mina, S.K.; Maryam, Z.; Zahra, N. Application of Bacterial Nanocellulose in Cancer Drug Delivery: A Review. *Curr. Pharm. Des.* **2021**, *27*, 3656–3665.

197. Piasecka-Zelga, J.; Zelga, P.; Gronkowska, K.; Madalski, J.; Szulc, J.; Wietecha, J.; Ciechańska, D.; Dziuba, R. Toxicological and Sensitization Studies of Novel Vascular Prostheses Made of Bacterial Nanocellulose Modified with Chitosan (MBC) for Application as the Tissue-Engineered Blood Vessels. *Regen. Eng. Transl. Med.* **2021**, *7*, 218–233. [\[CrossRef\]](#)
198. Silvestre, A.J.D.; Freire, C.; Neto, C.P. Do bacterial cellulose membranes have potential in drug-delivery systems? *Expert Opin. Drug Deliv.* **2014**, *11*, 1113–1124. [\[CrossRef\]](#) [\[PubMed\]](#)
199. Stanisławska, A. Bacterial Nanocellulose as a Microbiological Derived Nanomaterial. *Adv. Mater. Sci.* **2016**, *16*, 45–57. [\[CrossRef\]](#)
200. Klemm, D.; Cranston, E.D.; Fischer, D.; Gama, M.; Kedzior, S.A.; Kralisch, D.; Rauchfuß, F. Nanocellulose as a natural source for groundbreaking applications in materials science: Today's state. *Mater. Today* **2018**, *21*, 720–748. [\[CrossRef\]](#)
201. Silva, N.H.C.S.; Mota, J.P.; de Almeida, T.S.; Carvalho, J.P.F.; Silvestre, A.J.D.; Vilela, C.; Rosado, C.; Freire, C.S.R. Topical Drug Delivery Systems Based on Bacterial Nanocellulose: Accelerated Stability Testing. *Int. J. Mol. Sci.* **2020**, *21*, 1262. [\[CrossRef\]](#)
202. Trovatti, E.; Silva, N.H.C.S.; Duarte, I.F.; Rosado, C.F.; Almeida, I.F.; Costa, P.; Freire, C.S.R.; Silvestre, A.J.D.; Neto, C.P. Biocellulose Membranes as Supports for Dermal Release of Lidocaine. *Biomacromolecules* **2011**, *12*, 4162–4168. [\[CrossRef\]](#) [\[PubMed\]](#)
203. Trovatti, E.; Freire, C.S.; Pinto, P.C.; Almeida, I.F.; Costa, P.; Silvestre, A.J.; Neto, C.P.; Rosado, C. Bacterial cellulose membranes applied in topical and transdermal delivery of lidocaine hydrochloride and ibuprofen: In vitro diffusion studies. *Int. J. Pharm.* **2012**, *435*, 83–87. [\[CrossRef\]](#) [\[PubMed\]](#)
204. Pavaloiu, R.-D.; Stoica, A.; Stroescu, M.; Dobre, T. Controlled release of amoxicillin from bacterial cellulose membranes. *Cent. Eur. J. Chem.* **2014**, *12*, 962–967. [\[CrossRef\]](#)
205. Morais, E.S.; Silva, N.H.C.S.; Sintra, T.E.; Santos, S.A.O.; Neves, B.M.; Almeida, I.F.; Freire, C.S.R. Anti-inflammatory and antioxidant nanostructured cellulose membranes loaded with phenolic-based ionic liquids for cutaneous application. *Carbohydr. Polym.* **2019**, *206*, 187–197. [\[CrossRef\]](#)
206. Chantreau, G.; Sharma, M.; Abednejad, A.; Neves, B.M.; Sèbe, G.; Coma, V.; Freire, M.G.; Freire, C.S.R.; Silvestre, A.J.D. Design of Nonsteroidal Anti-Inflammatory Drug-Based Ionic Liquids with Improved Water Solubility and Drug Delivery. *ACS Sustain. Chem. Eng.* **2019**, *7*, 14126–14134. [\[CrossRef\]](#)
207. Fonseca, D.F.; Vilela, C.; Pinto, R.J.; Bastos, V.; Oliveira, H.; Catarino, J.; Faísca, P.; Rosado, C.; Silvestre, A.J.; Freire, C.S. Bacterial nanocellulose-hyaluronic acid microneedle patches for skin applications: In vitro and in vivo evaluation. *Mater. Sci. Eng. C* **2021**, *118*, 111350. [\[CrossRef\]](#) [\[PubMed\]](#)
208. Abba, M.; Ibrahim, Z.; Chong, C.S.; Zawawi, N.A.; Kadir, M.R.A.; Yusof, A.H.M.; Razak, S.I.A. Transdermal Delivery of Crocin Using Bacterial Nanocellulose Membrane. *Fibers Polym.* **2019**, *20*, 2025–2031. [\[CrossRef\]](#)
209. Khamrai, M.; Banerjee, S.L.; Paul, S.; Ghosh, A.K.; Sarkar, P.; Kundu, P. A Mussel Mimetic, Bioadhesive, Antimicrobial Patch Based on Dopamine-Modified Bacterial Cellulose/rGO/Ag NPs: A Green Approach toward Wound-Healing Applications. *ACS Sustain. Chem. Eng.* **2019**, *7*, 12083–12097. [\[CrossRef\]](#)
210. Guccini, V.; Phiri, J.; Trifol, J.; Rissanen, V.; Mousavi, S.M.; Vapaavuori, J.; Tammelin, T.; Maloney, T.; Kontturi, E. Tuning the Porosity, Water Interaction, and Redispersion of Nanocellulose Hydrogels by Osmotic Dehydration. *ACS Appl. Polym. Mater.* **2021**, *4*, 24–28. [\[CrossRef\]](#) [\[PubMed\]](#)
211. Fukuzumi, H.; Saito, T.; Iwata, T.; Kumamoto, Y.; Isogai, A. Transparent and High Gas Barrier Films of Cellulose Nanofibers Prepared by TEMPO-Mediated Oxidation. *Biomacromolecules* **2008**, *10*, 162–165. [\[CrossRef\]](#) [\[PubMed\]](#)
212. Kolakovic, R.; Peltonen, L.; Laaksonen, T.; Putkisto, K.; Laukkanen, A.; Hirvonen, J.T. Spray-Dried Cellulose Nanofibers as Novel Tablet Excipient. *AAPS PharmSciTech* **2011**, *12*, 1366–1373. [\[CrossRef\]](#)
213. Hussin, M.H.; Trache, D.; Chuin, C.T.H.; Fazita, M.R.N.; Haafiz, M.K.M.; Hossain, S. Extraction of Cellulose Nanofibers and Their Eco-friendly Polymer Composites. *Sustain. Polym. Compos. Nanocomposites* **2019**, 653–691. [\[CrossRef\]](#)
214. Gupta, G.K.; Shukla, P. Lignocellulosic Biomass for the Synthesis of Nanocellulose and Its Eco-Friendly Advanced Applications. *Front. Chem.* **2020**, *8*, 601256. [\[CrossRef\]](#)
215. Dutta, K.; Das, B.; Orasugh, J.T.; Mondal, D.; Adhikari, A.; Rana, D.; Banerjee, R.; Mishra, R.; Kar, S.; Chattopadhyay, D. Bio-derived cellulose nanofibril reinforced poly(N-isopropylacrylamide)-g-guar gum nanocomposite: An avant-garde biomaterial as a transdermal membrane. *Polymer* **2018**, *135*, 85–102. [\[CrossRef\]](#)
216. Gencturk, A.; Kahraman, E.; Güngör, S.; Özhan, G.; Özsoy, Y.; Sarac, A.S. Polyurethane/hydroxypropyl cellulose electrospun nanofiber mats as potential transdermal drug delivery system: Characterization studies and in vitro assays. *Artif. Cells Nanomed. Biotechnol.* **2017**, *45*, 655–664. [\[CrossRef\]](#)
217. Samanta, A.P.; Ali, M.S.; Orasugh, J.T.; Ghosh, S.K.; Chattopadhyay, D. Crosslinked nanocollagen-cellulose nanofibrils reinforced electrospun polyvinyl alcohol/methylcellulose/polyethylene glycol bionanocomposites: Study of material properties and sustained release of ketorolac tromethamine. *Carbohydr. Polym. Technol. Appl.* **2022**, *3*, 100195. [\[CrossRef\]](#)
218. Sarkar, G.; Orasugh, J.T.; Saha, N.R.; Roy, I.; Bhattacharyya, A.; Chattopadhyay, A.K.; Rana, D.; Chattopadhyay, D. Cellulose nanofibrils/chitosan based transdermal drug delivery vehicle for controlled release of ketorolac tromethamine. *New J. Chem.* **2017**, *41*, 15312–15319. [\[CrossRef\]](#)
219. Shojaeiarani, J.; Bajwa, D.S.; Chanda, S. Cellulose nanocrystal based composites: A review. *Compos. Part C Open Access* **2021**, *5*, 100164. [\[CrossRef\]](#)
220. Mali, P.; Sherje, A.P. Cellulose nanocrystals: Fundamentals and biomedical applications. *Carbohydr. Polym.* **2021**, *275*, 118668. [\[CrossRef\]](#) [\[PubMed\]](#)

221. Pradeep, H.; Patel, D.H.; Onkarappa, H.; Pratiksha, C.; Prasanna, G. Role of nanocellulose in industrial and pharmaceutical sectors—A review. *Int. J. Biol. Macromol.* **2022**, *207*, 1038–1047. [\[CrossRef\]](#)
222. Aziz, T.; Ullah, A.; Fan, H.; Ullah, R.; Haq, F.; Khan, F.U.; Iqbal, M.; Wei, J. Cellulose Nanocrystals Applications in Health, Medicine and Catalysis. *J. Polym. Environ.* **2021**, *29*, 2062–2071. [\[CrossRef\]](#)
223. Ali, M.S.; Bhunia, P.; Samanta, A.P.; Orasugh, J.T.; Chattopadhyay, D. Transdermal therapeutic system: Study of cellulose nanocrystals influenced methylcellulose-chitosan bionanocomposites. *Int. J. Biol. Macromol.* **2022**, *218*, 556–567. [\[CrossRef\]](#) [\[PubMed\]](#)
224. Jeong, D.I.; Kim, S.; Kim, M.-H.; Yoon, I.-S.; Lee, S.-H.; Kim, D.-D.; Cho, H.-J. Donepezil hydrochloride-reinforced cellulose nanocrystal-aggregated gel structure for long-acting drug delivery. *Carbohydr. Polym.* **2022**, *296*, 119887. [\[CrossRef\]](#) [\[PubMed\]](#)
225. Hiranphinyopha, S.; Otaka, A.; Fujii, S.; Iwasaki, Y. Lanoconazole-loaded emulsion stabilized with cellulose nanocrystals decorated with polyphosphoesters reduced inflammatory edema in a mouse model. *Polym. J.* **2021**, *53*, 1493–1498. [\[CrossRef\]](#)
226. Banerjee, A.; Ibsen, K.; Iwao, Y.; Zakrewsky, M.; Mitragotri, S. Transdermal Protein Delivery Using Choline and Geranate (CAGE) Deep Eutectic Solvent. *Adv. Health Mater.* **2017**, *6*, 1601411. [\[CrossRef\]](#)
227. Zakrewsky, M.; Lovejoy, K.S.; Kern, T.L.; Miller, T.E.; Le, V.; Nagy, A.; Goumas, A.M.; Iyer, R.S.; Del Sesto, R.E.; Koppisch, A.T.; et al. Ionic liquids as a class of materials for transdermal delivery and pathogen neutralization. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, 13313–13318. [\[CrossRef\]](#) [\[PubMed\]](#)
228. Zakrewsky, M.; Banerjee, A.; Apte, S.; Kern, T.L.; Jones, M.R.; Del Sesto, R.E.; Koppisch, A.T.; Fox, D.T.; Mitragotri, S. Choline and Geranate Deep Eutectic Solvent as a Broad-Spectrum Antiseptic Agent for Preventive and Therapeutic Applications. *Adv. Health Mater.* **2016**, *5*, 1282–1289. [\[CrossRef\]](#) [\[PubMed\]](#)
229. Boscariol, R.; Junior, J.M.O.; Baldo, D.A.; Balcão, V.M.; Vila, M.M. Transdermal permeation of curcumin promoted by choline geranate ionic liquid: Potential for the treatment of skin diseases. *Saudi Pharm. J.* **2022**, *30*, 382–397. [\[CrossRef\]](#)
230. Tanner, E.E.; Ibsen, K.N.; Mitragotri, S. Transdermal insulin delivery using choline-based ionic liquids (CAGE). *J. Control. Release* **2018**, *286*, 137–144. [\[CrossRef\]](#) [\[PubMed\]](#)
231. Jorge, L.R.; Harada, L.K.; Silva, E.C.; Campos, W.F.; Moreli, F.C.; Shimamoto, G.; Pereira, J.F.B.; Oliveira, J.M.J.; Tubino, M.; Vila, M.M.D.C.; et al. Non-invasive Transdermal Delivery of Human Insulin Using Ionic Liquids: In vitro Studies. *Front. Pharmacol.* **2020**, *11*, 243. [\[CrossRef\]](#)
232. Islam, R.; Uddin, S.; Chowdhury, R.; Wakabayashi, R.; Moniruzzaman, M.; Goto, M. Insulin Transdermal Delivery System for Diabetes Treatment Using a Biocompatible Ionic Liquid-Based Microemulsion. *ACS Appl. Mater. Interfaces* **2021**, *13*, 42461–42472. [\[CrossRef\]](#)
233. Ali, K.; Moshikur, R.M.; Wakabayashi, R.; Moniruzzaman, M.; Goto, M. Biocompatible Ionic Liquid-Mediated Micelles for Enhanced Transdermal Delivery of Paclitaxel. *ACS Appl. Mater. Interfaces* **2021**, *13*, 19745–19755. [\[CrossRef\]](#)
234. Uddin, S.; Islam, R.; Moshikur, R.M.; Wakabayashi, R.; Kamiya, N.; Moniruzzaman, M.; Goto, M. Transdermal Delivery of Antigenic Protein Using Ionic Liquid-Based Nanocarriers for Tumor Immunotherapy. *ACS Appl. Bio Mater.* **2022**, *5*, 2586–2597. [\[CrossRef\]](#) [\[PubMed\]](#)
235. Barros, N.R.; Borges, M.C.A.; Gemeinder, F.A.; Mendonça, J.L.P.; Cilli, R.J.; Herculano, R.D. Natural rubber latex: Development and in vitro characterization of a future transdermal patch for enuresis treatment. *Int. J. Polym. Mater. Polym. Biomater.* **2017**, *66*, 871–876. [\[CrossRef\]](#)
236. Ren, X.; Barrera, C.S.; Tardiff, J.L.; Gil, A.; Cornish, K. Liquid guayule natural rubber, a renewable and crosslinkable processing aid in natural and synthetic rubber compounds. *J. Clean. Prod.* **2020**, *276*, 122933. [\[CrossRef\]](#)
237. Sivasankarapillai, V.S.; Das, S.S.; Sabir, F.; Sundaramahalingam, M.A.; Colmenares, J.C.; Prasannakumar, S.; Rajan, M.; Rahdar, A.; Kyzas, G.Z. Progress in natural polymer engineered biomaterials for transdermal drug delivery systems. *Mater. Today Chem.* **2021**, *19*, 100382. [\[CrossRef\]](#)
238. Guerra, N.B.; Pegorin, G.S.; Boratto, M.H.; de Barros, N.R.; Graeff, C.F.D.O.; Herculano, R.D. Biomedical applications of natural rubber latex from the rubber tree *Hevea brasiliensis*. *Mater. Sci. Eng. C* **2021**, *126*, 112126. [\[CrossRef\]](#)
239. Suksaeree, J.; Waiprib, R.; Kalkornsurapranee, E.; Pichayakorn, W. Lidocaine-pressure sensitive adhesive patches from STR-5L block rubber: Preparations, in vitro characterizations, and stability studies. *J. Drug Deliv. Sci. Technol.* **2021**, *67*, 102966. [\[CrossRef\]](#)
240. Suksaeree, J.; Pichayakorn, W.; Monton, C.; Sakunpak, A.; Chusut, T.; Saingam, W. Rubber Polymers for Transdermal Drug Delivery Systems. *Ind. Eng. Chem. Res.* **2014**, *53*, 507–513. [\[CrossRef\]](#)
241. Azammi, A.M.N.; Sapuan, S.M.; Ishak, M.R.; Sultan, M.T.H. Mechanical and Thermal Properties of Kenaf Reinforced Thermoplastic Polyurethane (TPU)-Natural Rubber (NR) Composites. *Fibers Polym.* **2018**, *19*, 446–451. [\[CrossRef\]](#)
242. Hao, W.; Zeng, H.H.; Chen, X.; He, W.; Zhou, R.; Li, J.; Zhang, H. Insights into the reinforcement and mechanism of silicone mold rubber co-modified with WCB and MMQ resin. *Mater. Res. Express* **2021**, *8*, 035201. [\[CrossRef\]](#)
243. Marcelino, M.Y.; Borges, F.A.; Costa, A.F.M.; Singulani, J.D.L.; Ribeiro, N.V.; Costa-Orlandi, C.B.; Garms, B.C.; Mendes-Giannini, M.J.S.; Herculano, R.D.; Fusco-Almeida, A.M. Antifungal activity of fluconazole-loaded natural rubber latex against *Candida albicans*. *Future Microbiol.* **2018**, *13*, 359–367. [\[CrossRef\]](#) [\[PubMed\]](#)
244. Silva, T.V.; de Barros, N.R.; Costa-Orlandi, C.B.; Tanaka, J.L.; Moro, L.G.; Pegorin, G.S.; Oliveira, K.S.; Mendes-Giannini, M.J.; Fusco-Almeida, A.M.; Herculano, R.D. Voriconazole-natural latex dressings for treating infected *Candida* spp. skin ulcers. *Futur. Microbiol.* **2020**, *15*, 1439–1452. [\[CrossRef\]](#)

245. Floriano, J.F.; de Barros, N.R.; Cinman, J.L.F.; da Silva, R.G.; Loffredo, A.V.; Borges, F.A.; Norberto, A.M.Q.; Chagas, A.L.D.; Garms, B.C.; Graeff, C.F.D.O.; et al. Ketoprofen Loaded in Natural Rubber Latex Transdermal Patch for Tendinitis Treatment. *J. Polym. Environ.* **2017**, *26*, 2281–2289. [[CrossRef](#)]
246. Niamlang, S.; Paradee, N.; Sirivat, A. Hybrid transdermal drug delivery patch made from poly(p-phenylene vinylene)/natural rubber latex and controlled by an electric field. *Polym. Int.* **2018**, *67*, 747–754. [[CrossRef](#)]
247. Wang, N.; Liu, Y.; Ye, E.; Li, Z.; Wang, D. Control methods and applications of interface contact electrification of triboelectric nanogenerators: A review. *Mater. Res. Lett.* **2022**, *10*, 97–123. [[CrossRef](#)]
248. Bejarano, J.; Navarro-Marquez, M.; Morales-Zavala, F.; Morales, J.O.; Garcia-Carvajal, I.; Araya-Fuentes, E.; Flores, Y.; Verdejo, H.E.; Castro, P.F.; Lavandero, S.; et al. Nanoparticles for diagnosis and therapy of atherosclerosis and myocardial infarction: Evolution toward prospective theranostic approaches. *Theranostics* **2018**, *8*, 4710–4732. [[CrossRef](#)]
249. Karam, M.; Fahs, D.; Maatouk, B.; Safi, B.; Jaffa, A.A.; Mhanna, R. Polymeric nanoparticles in the diagnosis and treatment of myocardial infarction: Challenges and future prospects. *Mater. Today Bio* **2022**, *14*, 100249. [[CrossRef](#)] [[PubMed](#)]
250. Danaei, M.; Dehghankhold, M.; Ataei, S.; Hasanzadeh Davarani, F.; Javanmard, R.; Dokhani, A.; Khorasani, S.; Mozafari, M.R. Impact of Particle Size and Polydispersity Index on the Clinical Applications of Lipidic Nanocarrier Systems. *Pharmaceutics* **2018**, *10*, 57. [[CrossRef](#)] [[PubMed](#)]
251. Carter, P.; Narasimhan, B.; Wang, Q. Biocompatible nanoparticles and vesicular systems in transdermal drug delivery for various skin diseases. *Int. J. Pharm.* **2018**, *555*, 49–62. [[CrossRef](#)]
252. Naskar, S.; Kuotsu, K.; Sharma, S. Chitosan-based nanoparticles as drug delivery systems: A review on two decades of research. *J. Drug Target.* **2018**, *27*, 379–393. [[CrossRef](#)]
253. Banerjee, R.; Jaiswal, A. Recent advances in nanoparticle-based lateral flow immunoassay as a point-of-care diagnostic tool for infectious agents and diseases. *Anal.* **2018**, *143*, 1970–1996. [[CrossRef](#)]
254. Siafaka, P.I.; Okur, N.Ü.; Karantas, I.D.; Okur, M.E.; Gündoğdu, E.A. Current update on nanoplatforms as therapeutic and diagnostic tools: A review for the materials used as nanotheranostics and imaging modalities. *Asian J. Pharm. Health Sci.* **2021**, *16*, 24–46. [[CrossRef](#)]
255. Shou, P.; Yu, Z.; Wu, Y.; Feng, Q.; Zhou, B.; Xing, J.; Liu, C.; Tu, J.; Akakuru, O.U.; Ye, Z.; et al. Zn<sup>2+</sup> Doped Ultrasmall Prussian Blue Nanotheranostic Agent for Breast Cancer Photothermal Therapy under MR Imaging Guidance. *Adv. Health Mater.* **2019**, *9*, e1900948. [[CrossRef](#)]
256. Li, X.; Schumann, C.; Albarqi, H.A.; Lee, C.J.; Alani, A.W.G.; Bracha, S.; Milovancev, M.; Taratula, O.; Taratula, O. A Tumor-Activatable Theranostic Nanomedicine Platform for NIR Fluorescence-Guided Surgery and Combinatorial Phototherapy. *Theranostics* **2018**, *8*, 767–784. [[CrossRef](#)]
257. Singh, P.; Pandit, S.; Mokkapati, V.; Garg, A.; Ravikumar, V.; Mijakovic, I. Gold Nanoparticles in Diagnostics and Therapeutics for Human Cancer. *Int. J. Mol. Sci.* **2018**, *19*, 1979. [[CrossRef](#)] [[PubMed](#)]

**Disclaimer/Publisher's Note:** The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.