Scientia Pharmaceutica

Review

Nanotechnology for Metformin Release Systems: Nanostructures, Biopolymer Carriers, and Techniques—A Review

Eneida Azaret Montaño-Grijalva [1], Francisco Rodríguez-Félix [1,*], José Agustín Tapia-Hernández [1,*], Enrique Márquez-Ríos [1], Carmen Lizette Del-Toro-Sánchez [1], Dora Evelia Rodríguez-Félix [2], Ricardo Nalda-Molina [3,4], Elizabeth Carvajal-Millan [5], Carlos Gregorio Barreras-Urbina [1], Itzel Yanira López-Peña [6] and Cielo Estefanía Figueroa-Enríquez [1]

1 Department of Food Research and Graduate Program, University of Sonora, Blvd. Luis Encinas y Rosales S/N, Colonia Centro, Hermosillo 83000, Sonora, Mexico; eneida.azaret.mg@gmail.com (E.A.M.-G.); enrique.marquez@unison.mx (E.M.-R.); carmen.deltoro@unison.mx (C.L.D.-T.-S.); carlosgregorio.barreras@unison.mx (C.G.B.-U.); a214200337@unison.mx (C.E.F.-E.)
2 Department of Polymers and Materials Research, University of Sonora, Blvd. Luis Encinas y Rosales S/N, Colonia Centro, Hermosillo 83000, Sonora, Mexico; dora.rodriguez@unison.mx
3 Alicante Institute for Health and Biomedical Research (ISABIAL-FISABIO Foundation), 03010 Alicante, Spain; jnalda@umh.es
4 School of Pharmacy, Miguel Hernández University, 03550 San Juan de Alicante, Spain
5 Animal Origin Food Technology Coordination, Food and Development Research Center A.C. (CIAD A.C.), Hermosillo 83304, Sonora, Mexico; ecarvajal@ciad.mx
6 Vegetable Origin Food Technology Coordination, Food and Development Research Center A.C. (CIAD A.C.), Hermosillo 83304, Sonora, Mexico; itzel.lopez@ciad.mx
* Correspondence: francisco.rodriguezfelix@unison.mx (F.R.-F.); joseagustin.tapia@unison.mx (J.A.T.-H.)

Abstract

Currently, there are various approaches to the treatment of diabetes. Regarding type 2 diabetes (T2D), treatment focuses on blood glucose control. When changes in lifestyle do not achieve this glycemic control, the option is to start therapy with antidiabetic drugs such as metformin. However, long-term metformin use causes disturbances that may affect treatment approaches. This review examines recent advances in nanotechnology that have developed new forms of drug administration that can improve the efficacy of the treatment, where nanomaterials, nanostructures, and nanoparticle design are involved, so that they provide controlled and gradual release. The use of biopolymers (as drug delivery systems) has ensured biocompatibility, biodegradability, and low toxicity. There are several methods for obtaining a drug delivery system, including electrospinning, electrospraying, nanoprecipitation, etc. These systems improve drug delivery and can be used orally, transdermally, or intravenously, among means of administration. This review describes the new forms of the administration of metformin in the treatment of T2D, based on the encapsulation of metformin in polymeric matrices such as proteins, polysaccharides, and lipids, among others.

Keywords: nanotechnology; diabetes; electrospinning; electrospraying; nanoprecipitation; metformin; delivery system; biopolymer nanocarriers; polymeric nanoparticles

Academic Editors: Barbara R. Conway and Hisham Al-Obaidi

Received: 26 June 2025
Revised: 26 August 2025
Accepted: 31 August 2025
Published: 24 December 2025

1. Introduction

Diabetes is defined as a complex chronic disease that occurs when the pancreas does not produce insulin (type 1 diabetes, T1D) or when the body is unable to use it effectively (type 2 diabetes, T2D), leading to elevated blood glucose levels known as hyperglycemia [1].

The prevalence and incidence of diabetes have become major global health concerns [2]. In 2014, 8.5% of adults worldwide were reported to have diabetes, with T2D representing 95% of cases. By 2021, more than 537 million adults were living with diabetes, and this number is projected to increase to 643 million by 2030 and 783 million by 2045 [1,3,4]. Currently, there are multiple treatment options for T2D, with glycemic control being the primary therapeutic goal [5]. Preferred strategies include the use of antidiabetic drugs, lifestyle modifications, and regular physical activity [6]. Metformin remains the first line and most commonly prescribed antidiabetic drug for T2D due to its capacity to lower glucose levels in insulin-resistant tissues, support weight control, and present a low risk of hypoglycemia. However, metformin use can cause gastrointestinal intolerance (20–30%) and, in rare cases, serious adverse events such as lactic acidosis (5%), which may limit its use [6–9].

The development of nanotechnology has provided a promising avenue for improving the treatment and diagnosis of diseases. Due to their increased surface area, nanomaterials exhibit unique physical and chemical properties. Nanodrug delivery systems—one of the key applications of nanotechnology in the pharmaceutical field—have demonstrated the ability to delay drug release, improve solubility and bioavailability, and reduce side effects [10,11]. Among these nanosystems, polymer-based nanocarriers have shown significant potential due to their versatility and ability to encapsulate therapeutic compounds. These polymers may be natural (albumin, gelatin, alginate, collagen, chitosan, and cyclodextrin) or synthetic (PLGA, polyethylene, PEG, polyanhydrides, and poly-L-lysine). Such nanocarriers can deliver a variety of compounds that adhere to the polymer surface or are distributed within the polymer matrix [10,12].

Various techniques have been explored to obtain nanostructures for drug delivery. Beyond traditional methods such as electrospinning, recent studies have incorporated nanoprecipitation, electrospraying, and microfluidics. Electrospinning and electrospraying rely on electrical energy to produce nanoscale materials [13]. Control over the characteristics of the resulting materials can be achieved by adjusting parameters such as viscosity, surface tension, applied voltage, needle–collector distance, flow rate, humidity, and temperature [14]. Coaxial electrospinning/electrospraying enables the production of core–shell nanomaterials using two separate solutions, minimizing contact between organic solvents and the encapsulated biological molecules [15].

Nanoprecipitation has become widely used for polymeric nanoparticles due to its simplicity, reproducibility, and capacity to encapsulate both hydrophobic and hydrophilic drugs. Microfluidic techniques provide precise control over particle size, morphology, and drug loading efficiency—attributes that are often difficult to achieve using other methods [14,15]. Therefore, applying nanotechnology to drugs such as metformin is necessary to modulate its administration through polymeric coatings that provide sustained and controlled release, reducing adverse effects caused by prolonged use. The primary objective of this review is to summarize and analyze current advancements in the development of metformin delivery systems using nanotechnology, highlighting the design, biopolymer carriers, obtention techniques, and potential applications.

2. Methods

A comprehensive literature review was conducted across several databases, including PubMed, ScienceDirect, Scopus, and Google Scholar, to identify studies published between 2010 and 2024. A combination of keywords was used to capture specific and relevant studies on nanotechnology applied to metformin delivery systems. The terms included "metformin delivery system," "biopolymer nanocarriers," "electrospinning," "polymeric nanoparticles," and "diabetes," along with their synonyms and abbreviations These keywords were selected to encompass the scope of this review: "diabetes" to define the clinical

https://doi.org/10.3390/scipharm94010003

context, "metformin" as the first-line therapeutic agent, and "nanotechnology" to identify innovative approaches in this field. "Electrospinning," "electrospraying," and "nanoprecipitation" were highlighted as the most widely applied techniques for producing polymeric nanosystems for drug delivery. Additionally, "delivery system" was included to integrate biopolymer nanocarriers, nanostructures, and controlled-release strategies. Furthermore, current diabetes management guidelines issued by the American Diabetes Association (ADA) and the World Health Organization (WHO) were reviewed to incorporate relevant evidence-based clinical recommendations.

3. Diabetes Overview

3.1. Origin

Diabetes is a disease that has been recognized since ancient times, as evidenced by Egyptian manuscripts dating back to 1500 BC. Around the same period, Indian physicians described what is considered one of the earliest clinical diagnostic tests for diabetes. They observed that the urine of affected individuals attracted ants and flies, leading them to name the condition madhumeha ("honey urine") [16]. Within this historical context, modern diabetes management relies heavily on pharmacological intervention, with metformin remaining the first-line treatment for type 2 diabetes.

3.2. Types of Diabetes

The term "diabetes" encompasses a group of metabolic disorders characterized by persistent hyperglycemia. The underlying mechanisms differ among subtypes, which form the basis of their classification [16]. Diabetes is categorized into three main types:

- Type 1 diabetes (T1D): Caused by autoimmune destruction of β-cells, leading to absolute insulin deficiency.
- Type 2 diabetes (T2D): Characterized by insulin resistance and β-cell dysfunction.
- Gestational diabetes (GDM): Diagnosed during the second or third trimester of pregnancy.

These distinctions are crucial for determining appropriate therapeutic strategies [17–20].

3.3. Treatments

The therapeutic approach to diabetes depends on the type of the disease and individual patient characteristics. For T1D, insulin replacement therapy usually administered through multiple daily injections is the standard treatment [21–23]. Management of T2D typically focuses on lifestyle modifications combined with metformin as the first-line pharmacological therapy [23–25]. Gestational diabetes is generally managed through dietary modifications and physical activity, with medication added only when necessary [23,26].

This review focuses on the role of metformin and explores how polymeric nanocarrier systems can enhance its delivery, bioavailability, and therapeutic performance.

3.4. Metformin

Metformin (Figure 1) is derived from Galega officinalis, a plant identified in the late 19th century as being rich in guanidine compounds with hypoglycemic activity and low toxicity [27,28]. Chemically identified as 1,1-dimethylbiguanide, metformin has a molecular formula of $C_4H_{11}N_5$ and a molecular weight of 129.16 g/mol. Its solubility has been reported as 425.56 mg/mL at pH 4.6 and 348.27 mg/mL at pH 6.8 [29]. Metformin exhibits an oral bioavailability of 50–60% and, after intestinal absorption, enters the portal circulation where it accumulates primarily in the liver [30]. The recommended daily dose ranges from 1 to 2 g/day, achieving plasma concentrations of 10–40 μM [30,31]. Metformin is considered a safe, cost-effective drug that does not typically cause hypoglycemia and is associated with favorable effects on body weight [32]. Due to these characteristics, numerous authors consider metformin the first-line pharmacological treatment for T2D [33].

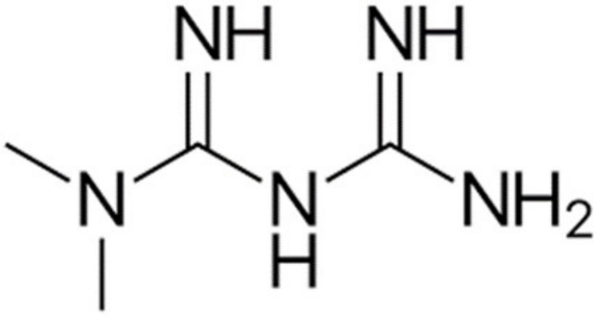

Figure 1. Metformin chemical structure.

3.4.1. Side Effects

The most common side effects of metformin include nausea, diarrhea, and abdominal discomfort, affecting 20–30% of users [34]. Therefore, it is recommended that metformin be taken with meals and that the dose be increased gradually. Although the exact mechanism behind intolerance is not fully understood, several hypotheses have been proposed, including high concentrations of metformin in the gastrointestinal tract, increased serotonin in enterochromaffin cells, and alterations to the gut microbiota that may predispose individuals to gastrointestinal infections [35,36].

A less common but more serious adverse effect is lactic acidosis, occurring in approximately 3 to 10 cases per 100,000 individuals. The proposed mechanism involves metformin increasing plasma lactate levels by inhibiting lactate clearance [37]. Historically, it was believed that patients with renal impairment should not receive metformin due to concerns about lactic acidosis, although updated evidence has reevaluated these restrictions [35].

Metformin use has also been associated with an increased risk of vitamin B12 deficiency (5.8–33%). Although the underlying mechanism is not fully understood, it is proposed that metformin interferes with calcium-dependent uptake of the intrinsic factor–vitamin B12 complex by ileal receptors, leading to impaired absorption and potential deficiency over time [23,38].

3.4.2. Challenges in Adherence and Current Advances to Improve Metformin's Bioavailability

Studies have shown that the use of antidiabetic drugs has increased in parallel with the global rise in diabetes prevalence. Adherence to medication is typically considered adequate when patients take at least 80% of the prescribed doses. Metformin is one of the most frequently used oral antidiabetic medications, with adherence rates ranging from approximately 22% to 88.6% [39].

Poor adherence to antidiabetic therapy is multifactorial. Individuals with T2D often experience challenges in achieving glycemic control, leading to multiple daily doses of metformin or polypharmacy. Gastrointestinal side effects—such as nausea, diarrhea, bloating, and abdominal discomfort—are among the primary causes of reduced adherence, especially at higher doses, prompting patients to reduce dosage frequency or discontinue treatment entirely. In addition, patients may not perceive rapid symptomatic improvement, reducing motivation to continue therapy [39,40]. Socioeconomic factors also play a significant role in adherence. Global systematic analyses have identified determinants such as occupational status, educational level, social support, and race/ethnicity as strongly associated with medication adherence in diabetes care [41,42].

To overcome these limitations, innovative drug delivery platforms have emerged. Nanoparticle-based systems are particularly promising due to their potential to enhance pharmacokinetics and therapeutic performance. These systems can improve metformin's bioavailability by increasing surface area, enhancing mucoadhesion, facilitating transport across biological barriers, and enabling controlled drug release [43].

Several strategies are currently being explored to enhance oral metformin delivery.

4. Nanotechnology for Drug Delivery Systems

4.1. Advantages and Disadvantages

Currently, one of the challenges of most drug delivery systems is low bioavailability, stability, solubility, absorption, sustained delivery, therapeutic efficiency, and the presence of side effects [39,40]. Nanotechnology has been widely used in the application of nanostructures in various fields of science, precisely in drug delivery systems [41]. These types of techniques have had an impact on the pharmaceutical industry by generating nanoparticles for a drug delivery system, because they can minimize drug degradation and loss, prevent side effects, and increase bioavailability and concentration at the required sites [40,42–44].

It might seem that nanoparticles could not have toxic effects. Nevertheless, these particles having a large surface area can cause further chemical reactions resulting in the production of reactive oxygen species. These species are mechanisms of nanoparticle toxicity that can cause oxidative stress, inflammation, and damage to proteins, cells, membranes and DNA, as well as limited biocompatibility and short action times [40,41,45,46]. Some of the advantages and disadvantages are summarized in Figure 2 [11,47].

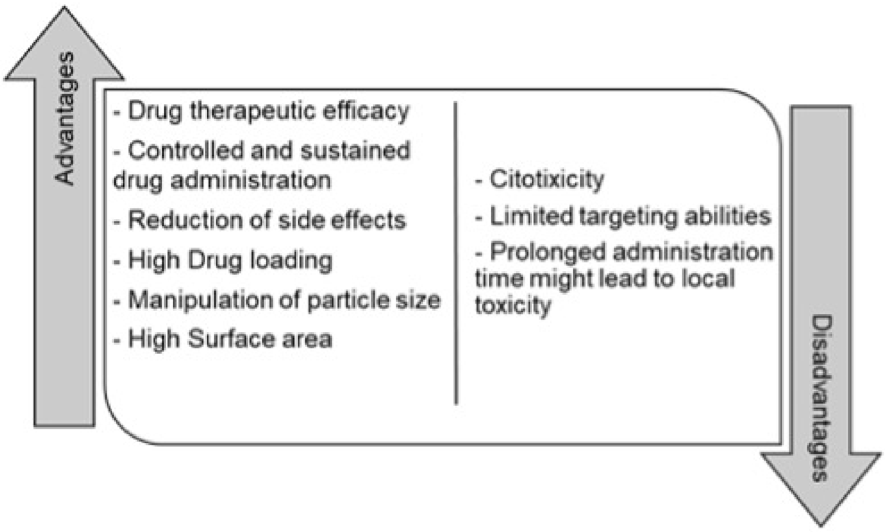

Figure 2. Advantages and disadvantages of nanotechnology applied to drug delivery systems.

4.2. Nanostructures

In recent decades, various drug delivery systems have been developed, and some are still under development. Polymeric nanoparticles, nanofibers, liposomes, micelles, dendrimers, and nanotubes are some of the materials recognized as drug delivery systems [42,48,49]. Although this review highlights biopolymer-based nanocarriers, other metformin nanostructures have been reported. Metallic nanoparticles, especially gold nanoparticles conjugated with metformin, have shown antiglycation activity [49] and anticancer activity in vitro against breast and lung cancer cell lines [50]. However, due to biocompatibility and other safety limitations, these metallic nanosystems are only briefly discussed, while the following sections are focused on describing in detail biopolymer nanocarriers as some the most widely used nanostructures in drug delivery in order to adhere to the scope of this review (Figure 3).

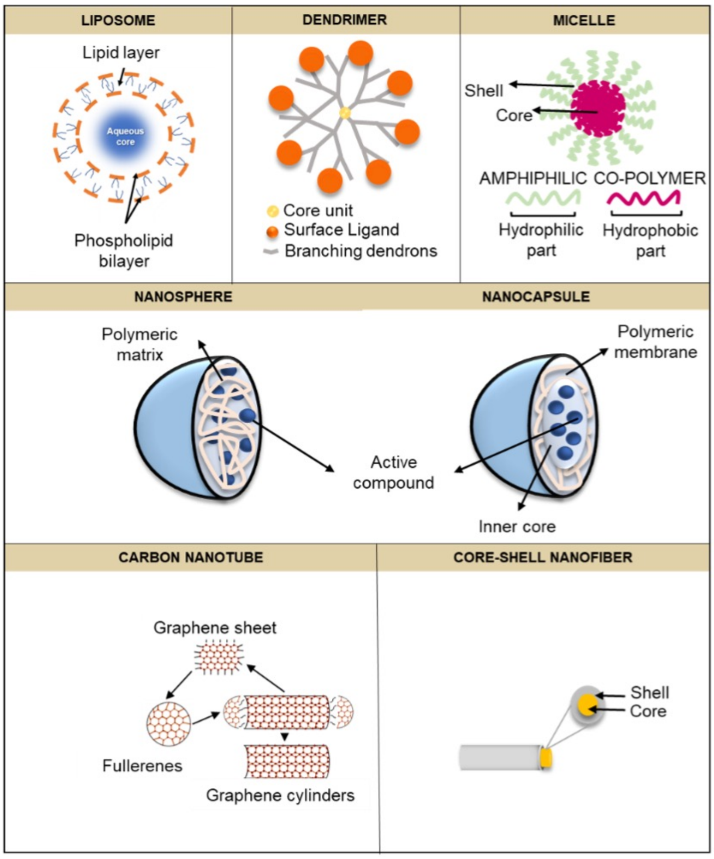

Figure 3. Schematic representation of common drug delivery nanostructure.

4.2.1. Liposomes

Liposomes were among the first nanostructures investigated as drug carriers. They are spherical vesicles composed of an aqueous core surrounded by a phospholipid bilayer. Hydrophilic molecules can be incorporated into the aqueous interior, while hydrophobic drugs can be embedded within the phospholipid membrane. This dual capacity allows liposomes to protect drugs from premature degradation and provide controlled and sustained release. Additionally, they are useful for prolonging the release of active compounds with poor water solubility [49,50]. Drugs can be loaded into liposomes using passive or active methods, including sonication, microemulsification, and membrane extrusion [51,52]. Common liposomal components include phosphatidylcholine, cholesterol, and PEGylated lipids. For metformin delivery, the hydrophilic drug can be encapsulated within the aqueous core, while PEGylation enhances circulation time and reduces clearance by the mononuclear phagocyte system. Liposomal formulations have been applied to deliver anticancer drugs, anti-inflammatory agents, and antibiotics. Drug release is typically mediated by diffusion or pH-induced destabilization of the liposomal membrane. This approach reduces off-target toxicity and improves bioavailability and therapeutic efficacy, making it a promising strategy for diabetes treatment [52].

4.2.2. Polymeric Nanoparticles

Polymers possess properties that make them ideal candidates for pharmaceutical applications [53]. Due to their chemical versatility and tunable characteristics, polymers can be engineered to control the stability, degradation, and release behavior of nanoparticles [54,55]. Polymeric nanoparticles typically range from 1 to 1000 nm in size and are most commonly spherical in morphology [53,56,57]. Based on their structural organization, polymeric nanoparticles are classified into two main types: nanocapsules and nanospheres. These nanoparticles are usually synthesized from natural or synthetic polymers such as PLGA, chitosan, PCL, and PEGylated polymers [58].

Polymeric Nanocapsules

Polymeric nanocapsules are vesicular systems consisting of a liquid or solid core surrounded by a polymeric membrane, making them suitable carriers for various therapeutic compounds [59,60]. Their core–shell architecture offers significant advantages in drug delivery, including improved drug stability, enhanced encapsulation efficiency, controlled release, and targeted distribution. The flexibility of the core allows for the encapsulation of both hydrophilic and hydrophobic drugs, including metformin and paclitaxel [56,60].

Polymeric Nanospheres

Polymeric nanospheres are matrix-type solid colloidal particles in which the active compound may be dissolved, trapped, encapsulated, or adsorbed within the polymer matrix [61]. Unlike nanocapsules, nanospheres lack a distinct core–shell structure, resulting in different release kinetics and encapsulation profiles.

4.2.3. Polymeric Micelles

Micelles are nanoscale structures formed from lipids or amphiphilic molecules, including certain polymers [62]. Polymeric micelles are characterized by their spherical shape, core–shell architecture, and diameters typically ranging from 10 to 100 nm [62–64]. These structures are formed through the self-assembly of amphiphilic copolymers in aqueous media, where the hydrophobic segments form the inner core and the hydrophilic segments form the outer shell (corona) [65,66]. One of the primary advantages of polymeric micelles in drug delivery is their ability to solubilize poorly water-soluble drugs within the hydrophobic core, while hydrophilic molecules may interact with the outer corona. Common copolymers used for micelle formation include PEG-b-PLA, PEG-b-PCL, and Pluronic block copolymers. Hydrophobic drugs such as paclitaxel and curcumin can be incorporated into the core, whereas hydrophilic drugs may associate with the corona or be chemically conjugated [66,67]. Drug release from polymeric micelles occurs mainly through core degradation, diffusion, or destabilization of the micelle structure. Their nanoscale size, biocompatibility, and enhanced solubilization capacity make polymeric micelles highly attractive platforms for drug delivery applications, including metformin nanoformulations.

4.2.4. Nanofibers

Nanofibers are defined as fibers with diameters ranging from 100 to 1000 nm [68]. They possess distinctive characteristics such as high surface area-to-volume ratio, flexibility, and excellent tensile strength, which have enabled their use in various applications, including drug delivery, biosensing, and wound dressing [69]. Structurally, nanofibers consist of an internal fiber core surrounded by an external layer known as the shell. Nanofibers are commonly produced using polymers such as chitosan, gelatin, PLGA, and PCL through electrospinning techniques [70]. The versatility of electrospinning allows for precise control over fiber morphology, porosity, and drug incorporation, making nanofibers valuable platforms for sustained and controlled drug release. These features contribute to their increasing relevance in pharmaceutical and biomedical fields.

4.2.5. Carbon Nanotubes

Carbon nanotubes (CNTs) are hollow, cylindrical nanostructures composed of rolled graphene sheets. Their unique physicochemical properties—such as exceptionally high surface area, electrical conductivity, tensile strength, and thermal stability—enable them to adsorb or conjugate a wide range of therapeutic molecules, including bioactive proteins, peptides, and drugs [71]. Due to these characteristics, CNTs have gained attention as potential nanocarriers in drug delivery applications. CNT diameters typically range from 1 to 100 nm, and their ends are often capped with hemispherical fullerene-like structures. Drugs may be associated with CNTs either through non-covalent adsorption or covalent attachment, depending on the desired release kinetics and stability. Common therapeutic agents transported using CNTs include anticancer drugs, peptides, and nucleic acids. Drug release from CNTs can be triggered by various stimuli, including pH changes or redox-responsive mechanisms, enabling targeted and controlled delivery profiles [72]. However, despite their versatility, the biocompatibility and safety of CNTs remain concerns that require careful evaluation before clinical translation.

4.2.6. Dendrimers

Dendrimers are highly branched, monodisperse macromolecules composed of three distinct structural regions: a central core, multiple layers of repeating branched units (generations), and a surface enriched with functional groups. Their unique architecture provides a large surface area, enabling the attachment or encapsulation of various therapeutic agents. Hydrophobic drugs can be encapsulated within the dendrimer's internal cavities, while hydrophilic drugs can be conjugated to the peripheral functional groups through covalent or electrostatic interactions. Common dendrimer materials include poly(amidoamine) (PAMAM), poly(propylene imine) (PPI), and PEGylated dendrimers, all of which have been extensively explored in pharmaceutical applications due to their biocompatibility, tunable surface chemistry, and controlled release capabilities [73]. The precise molecular structure and functional versatility of dendrimers make them promising nanocarriers for drug delivery, including potential use in metformin delivery systems.

5. Biopolymer Carriers for Metformin Release Systems

In recent years, the pharmaceutical industry has shown growing interest in improving drug delivery systems that offer greater versatility and enhanced therapeutic performance, including systems designed for metformin. One of the most promising advances involves the use of biopolymers to generate nanocoatings for drugs or particles. These coatings help protect the encapsulated drug as it passes through the gastrointestinal tract and enable more prolonged and controlled release profiles [74]. Biopolymers are ideal materials for drug encapsulation because of their biodegradability, biocompatibility, and ability to withstand changes in pH, temperature, surface modifications, and conjugation processes [75,76]. Their structural diversity enables them to interact with different drugs and modulate their release behavior. Depending on the desired pharmacokinetic profile, factors such as polymer concentration, crosslinking degree, and the fabrication technique can be adjusted to optimize release performance. The main biopolymers used for metformin encapsulation—including proteins, polysaccharides, and lipids—are summarized in Table 1. These nanocarriers differ in their entrapment efficiency, structural characteristics, mechanisms of action, and therapeutic outcomes, demonstrating the versatility of biopolymer-based delivery platforms.

The data summarized in Table 1, demonstrates that metformin nanoformulations such as nanofibers, nanoparticles, nanoemulsions, and micelles have shown promising outcomes in in vivo clinical models. These kind of nanosystems often offer improved glycemic control, enhances tissue targeting, and prolonged drug release compared to conventional metformin. Biopolymer-based systems including gelatin, PLGA, sodium alginate, chitosan, and bacterial cellulose ranged encapsulations efficiencies (EE) from 29.3% in solid lipid nanoparticles to 98% in cellulose acetetate nanofibers. Preclinical diabetic models with the utilization of chitosan/based nanoparticles and micelles (EE $\approx$ 92%) enhanced glycemic control and reduced gastroinstestinal irritation compared to conventional metformin. On the other hand, sodium alginate nanoparticles (EE ≈ 78%) showed sustained release and prolonged hypoglycemic action. Other metformin applications include cancer-related targeting nanoformulations, such as PLGA-PEG nanopartciles for breast cancer and cholesterol liposomes, have shown enhanced tumor uptake. Even with the high encapsulation efficiency, improved release kinetics, and high efficacy in murine models related to the therapeutic potential of nanoformulated metformin systems, clinical validation remains insufficient.

Table 1. Biopolymer-based nanocarriers for metformin hydrochloride: formulation strategies, structural characterization, mechanisms of action, and therapeutic outcomes.

Nanostructure	Biopolymer	Bioactive Ingredient	Entrapment Efficiency	Structural Characterization	Mechanism of Action	In Vitro/ In Vivo	Ref
Nanoparticle	Carboxymethyl Chitosan	Metformin hydrochloride	90%	Size ~200 nm; positive ζ-potential	Mucoadhesion, sustained release	Type II diabetes—In vivo (STZ rats), reduced blood glucose over 14 days	[77]
Nanoparticle	Lecithin and Chitosan	Metformin hydrochloride	-	Spherical particles; nano-size range	Enhanced cellular uptake, electrostatic interaction	Colorectal cancer—in vitro (HT-29), inhibited proliferation by ~40%	[78]
Nanofiber membrane	Polycaprolactone (PCL) and Chitosan	Metformin hydrochloride	-	Fiber diameter 300–500 nm	Diffusion and polymer degradation	Bone regeneration—In vitro (osteoblasts), enhanced proliferation and mineralization	[79]
Solid lipid nanoparticle	GMS, Lecithin, PVA	Metformin hydrochloride	29.3%	Size ~250 nm; stable dispersion	Lipid matrix controlled release	Colon cancer—in vitro (HCT116), increased cytotoxicity vs. free drug	[80]
Nanoparticle	Sodium alginate	Metformin hydrochloride	78%	Hydrogel-based nanoparticle; negative ζ-potential	pH-sensitive swelling and release	Type II diabetes—in vivo (STZ rats), improved glycemic control over 21 days	[81]
Solid lipid nanoparticle	Cholesterol and L-lysine	Metformin hydrochloride	60%	Size ~180 nm	Surface modification improves uptake	Dermal fibroblasts—in vitro, enhanced uptake and viability	[82]
Nanoparticle	Chitosan	Metformin hydrochloride	-	Size < 200 nm; cationic surface	Mucoadhesion and slow release	Polycystic kidney disease—in vivo (mouse), delayed cyst progression	[83]
Micelle	Chitosan	Metformin hydrochloride	92.3%	Core–shell micelle; ~100 nm	Hydrophobic core entrapment; mucoadhesion	Type II diabetes—in vivo (rats), sustained glucose reduction over 10 days	[84]
Nanocomposite (Mesoporous silica nanosphere)	Gelatin hydrogel	Metformin hydrochloride	-	Porous structure, high surface area	Diffusion-controlled sustained release	Bone regeneration—in vivo (STZ rats), prolonged release and improved glucose levels	[85]
Nanocomposite (Nanoparticle)	Chitosan, MCM-41	Metformin hydrochloride	-	Mesoporous particle, high loading capacity	Synergistic encapsulation and sustained release	Type II diabetes—in vitro (MCF-7), 30% higher cytotoxicity vs. free drug	[86]
Liposome	Cholesterol and DPPC	Metformin hydrochloride	65%	Bilayer vesicles; ~100–200 nm	Encapsulation in aqueous core/lipid bilayer	Breast cancer—in vivo (rats), significant glucose reduction	[87]
Nanoparticle	Gelatin and sodium alginate	Metformin hydrochloride	90%	Spherical nanoparticles; stable dispersion	Hydrogel-based controlled release	Type II diabetes—in vivo (rats), significant glucose reduction	[88]
Silica nanoparticle	Chitosan and alginate	Metformin hydrochloride + nettle extract	-	Porous silica with polymer coating	Synergistic inhibition of glucose absorption	Type II diabetes—in vitro, reduced glucose absorption	[89]

Table 1. *Cont.*

Nanostructure	Biopolymer	Bioactive Ingredient	Entrapment Efficiency	Structural Characterization	Mechanism of Action	In Vitro/ In Vivo	Ref
Nanoparticle	Pectin	Metformin hydrochloride	68%	Biopolymeric nanoparticle; size ~200 nm	Mucoadhesion and controlled release	Type II Diabetes—In vivo (rats), lowered fasting glucose and HbA1c	[90]
Nanofiber	PLA and PVA with fish sarcoplasmic protein	Metformin hydrochloride	-	Fiber diameter 200–400 nm	Sustained diffusion and biodegradation	Diabetes wound healing—In vivo (mice), accelerated wound closure	[91]
Nanofiber	Cellulose acetate	Metformin hydrochloride	98.41%	Fibers with uniform morphology	Sustained release from fiber matrix	Type II Diabetes—In vitro (β-cells), improved viability	[92]
Nanoparticle	Hyaluronic Acid	Metformin hydrochloride	-	Surface functionalized; size < 200 nm	HA-mediated targeting, controlled release	Type II Diabetes—In vivo (rats), improved pharmacokinetics	[93]
Nanoparticle	PVA and Sodium alginate	Metformin hydrochloride	78%	Hydrogel-based particle	Prolonged release via swelling matrix	Type II Diabetes—In vivo, hypoglycemic effect	[94]
Nanoparticle	PEG and PLGA	Metformin hydrochloride	75.15%	Spherical; 150–200 nm	Degradation-controlled release	Breast cancer—In vitro (MCF-7), enhanced cytotoxicity	[95]
Nanoparticle	PEG and PLGA	Metformin hydrochloride	75%	Nanoparticles with PEGylated surface	Improved cellular uptake and release	Breast cancer—In vitro (MCF-7), improved inhibition	[96]
Nanofiber gel	Cellulose	Metformin hydrochloride	-	Hydrogel-fiber composite	Sustained diffusion release	Melanoma—In vitro (B16F10), reduced proliferation	[97]
Nanoparticle	Bovine serum albumin	Metformin hydrochloride	-	Protein-based nanoparticles	Enzymatic degradation-controlled release	Type II Diabetes—In vivo (rats), sustained glucose lowering	[98]
Nanoparticle	PLGA and PEG with Silibinin	Metformin hydrochloride + Silibinin	75.15% (MET), 80.5% (SIL)	Polymeric core–shell nanoparticles	Dual drug encapsulation and release	Breast cancer—In vitro (MCF-7), synergistic cytotoxicity	[99]
Nanoparticle	Sodium alginate, cholesterol, folic acid	Metformin hydrochloride	82.8%	Functionalized nanoparticles	Targeted uptake via folic acid	Melanoma—In vitro (B16F10), enhanced uptake and cytotoxicity	[100]
Solid lipid nanoparticle	Cholesterol	Metformin hydrochloride	45.9%	Size ~200 nm	Lipid matrix release	Skin aging—In vitro (fibroblasts), increased collagen synthesis	[101]
Lipid vesicles	NA	Metformin hydrochloride	40.12%	Vesicles ~150 nm	Membrane-mediated diffusion	Type II diabetes—in vitro (Caco-2), improved absorption	[102]
Nanofiber	Bacterial cellulose and gelatin	Metformin hydrochloride	80%	Porous fibrous scaffold	Diffusion and biodegradation	Type II diabetes—in vivo (rats), improved wound healing and glucose control	[103]
Micelle	Casein	Metformin hydrochloride	87.42%	Self-assembled micelles	Encapsulation in hydrophobic core	Type II diabetes—in vivo (rats), sustained hypoglycemic effect	[104]
Nanoparticle	Hyaluronic Acid-coated Chitosan/Gelatin	Metformin hydrochloride	64.71%	Surface functionalized nanoparticles	HA-mediated uptake, sustained release	Melanoma—in vitro (B16F10), enhanced cytotoxicity	[105]
Nanofibers	PCL/PEG	Metformin + Glibenclamide	-	Coaxial nanofibers	Dual-drug co-release, diffusion	Type II diabetes—in vivo (rats), synergistic glucose reduction	[106]

5.1. Protein-Based Nanocarriers

Proteins have become widely used in recent years as materials for the development of nanostructures, particularly in pharmaceutical applications [105]. Their well-defined primary structure, water solubility, biodegradability, low toxicity, and natural bioavailability facilitate efficient drug incorporation. Many proteins are also generally recognized as safe (GRAS), making them suitable pharmaceutical excipients. Plant-derived proteins additionally offer a "green" label due to their renewable origin [106]. Animal-derived proteins such as keratin, collagen, gelatin, elastin, and serum albumin have been widely applied in drug delivery systems because of their biocompatibility, controlled degradation, and mucoadhesive properties. Similarly, plant-based proteins—such as zein, soy, and gliadin—serve as promising drug carriers due to their favorable interactions within biological environments and their absorption and retention capabilities [107]. Protein-based nanocarriers can be obtained in different shapes and sizes, including microspheres, nanoparticles, hydrogels, films, and minirods. These structures can be fabricated using simple, low-cost processes [108].

5.1.1. Gelatin

Gelatin is a natural, water-soluble polymer produced by the hydrolysis of collagen under alkaline or acidic conditions, or through thermal or enzymatic degradation. Its molecular weight ranges from 20 to 220 kDa, and it dissolves in water at temperatures above 35–40 °C. Commercially, gelatin is categorized as either Type A (cationic), obtained from acid hydrolysis of porcine skin collagen, and Type B (anionic), obtained from alkaline hydrolysis of bovine collagen. Its structure consists of hydrophobic, cationic, and anionic groups within a triple-helix arrangement composed primarily of glycine, proline, and alanine residues, which contribute to its stability [105]. Gelatin is widely applied in drug delivery due to its biocompatibility, biodegradability, and non-toxic nature [109].

In 2019, Shehata et al. formulated metformin-loaded gelatin/sodium alginate nanoparticles using electrospraying. The resulting nanoparticles were spherical with minimal folding, indicating that solution viscosities were optimal for electrospray processing. Entrapment efficiency exceeded 90% in all formulations. In vitro release studies showed 50% metformin release after 6 h and 84% after 24 h. In vivo testing demonstrated significant reductions in blood glucose levels at 6, 8, 12, and 24 h. These results were attributed to the mechanical stability of the gelatin/alginate nanoparticles, which provided controlled release across a wide pH range (1.2–8), simulating gastrointestinal conditions [110]. In 2020, Cam and colleagues developed a diabetic wound-healing dressing composed of electrospun gelatin/bacterial cellulose nanofibers loaded with metformin. The nanofibers exhibited smooth surfaces without visible drug crystallization, and the encapsulation efficiency was approximately 80%. The release profile was linear and sustained, with the maximum release occurring at day 15 (0.0197 mg). In vivo tests over 14 days demonstrated accelerated wound healing from day 3 onward [111].

5.1.2. Bovine Serum Albumin

Bovine serum albumin (BSA), also known as a plasma carrier protein, is a 66.5 kDa molecule consisting of 583 amino acid residues. It is commonly used in pharmaceutical applications due to its high binding affinity for both hydrophilic and hydrophobic drugs, making it an excellent encapsulation matrix. Additionally, BSA can reduce drug toxicity and enhance therapeutic efficacy [106,112,113].

In 2020, Lu et al. prepared metformin-loaded BSA nanoparticles using the nanoprecipitation technique to improve metformin dissolution. The resulting nanoparticles were spherical, non-porous, and approximately 200 nm in diameter. In vitro studies over 48 h demonstrated that the metformin-loaded BSA nanoparticles exhibited higher anticancer activity in insulin-resistant liver cancer cells compared to free metformin, highlighting the potential of protein-based carriers for targeted therapy [113].

5.1.3. Casein

Casein is the main protein found in milk and consists of a complex of four proteins (α-casein, β-casein, κ-casein). These proteins vary in their amino acid composition and their interactions with hydrophobic and hydrophilic substances, and have molecular weights of approximately 24 kDa [114]. Casein exhibits useful physicochemical properties such as emulsifying capacity, ion binding, stabilization, self-assembly, gelation, and water retention [115]. It is also cost-effective, biodegradable, non-toxic, and bioavailable, making it a promising material for encapsulating both hydrophobic and hydrophilic drugs for sustained and controlled release [116].

In 2015, Raj et al. evaluated the encapsulation of metformin in casein micelles and the sustained release behavior of the resulting formulation. The metformin-loaded micelles were fine, stable, and had an average particle size of 963.4 nm. Encapsulation efficiency was reported at 87.42%. In vitro release studies showed an initial rapid release phase—associated with desorption and diffusion of metformin from the micelle surface—followed by a sustained release phase lasting up to 15 h, achieving maximum drug release during this period [116].

5.2. Polysaccharide-Based Nanocarriers

Polysaccharides are macromolecules composed of multiple monosaccharide units. They are abundant, low-cost, renewable materials that have been widely applied in biomedical, pharmaceutical, food, and chemical industries due to their biocompatibility, multifunctionality, biodegradability, hydrophilicity, and non-toxicity [117]. These properties make them ideal materials for drug encapsulation, immobilization, and controlled or sustained drug release. Polysaccharide-based systems have demonstrated the ability to enhance drug solubility, permeability, and stability, making them highly suitable for oral and other delivery routes. Common polysaccharides used for drug delivery include pectin, hyaluronic acid, chitosan, dextran, alginate, and starch, among others [117].

5.2.1. Chitosan

Chitosan is a cationic polysaccharide derived from the deacetylation of chitin, which is found in the exoskeletons of arthropods and in fungal cell walls [117–120]. Its structure consists of β-(1→4)-linked units of glucosamine and N-acetylglucosamine. Chitosan is notable for its biocompatibility, biodegradability, gel-forming ability, high solubility at acidic pH, and low toxicity, making it an excellent candidate for pharmaceutical applications [119,121]. Its mucoadhesive properties enable strong electrostatic interactions with negatively charged mucosal surfaces, enhancing oral drug delivery and absorption. Chitosan can also form ionic crosslinks that slow drug release and enable controlled delivery [122].

In 2021, Wang et al. synthesized metformin-loaded chitosan nanoparticles via ionic gelation to evaluate their potential as an oral delivery platform for polycystic kidney disease. The nanoparticles had a mean diameter of 150 nm and high mucoadhesive efficiency. Metformin loading efficiency was 32.2%, attributed to electrostatic interactions between metformin and the crosslinker during synthesis. Degradation studies across different pH levels showed that the nanoparticles provided protection at acidic pH but released metformin at neutral pH, mimicking intestinal conditions [123].

Another study developed chitosan modified with phthalic anhydride and a RAFT agent, followed by copolymerization with acrylamide (AAm) and acrylic acid (AA), producing a CS-g-(PAAM-b-PAA) terpolymer. Nanoparticles loaded with metformin had a mean diameter of 80 nm and exhibited sustained release for up to 5 h due to strong interactions between metformin and the terpolymer's functional groups [124].

5.2.2. Pectin

Pectin is a linear heteropolysaccharide commonly found in plant cell walls. Its structure consists mainly of D-galacturonic acid units linked by α-(1→4) glycosidic bonds, with varying degrees of esterification and branching. It contains hydroxyl and carboxyl groups that enable ionization and hydrogel formation through interactions with positively charged ions. Pectin is biodegradable, biocompatible, mucoadhesive, and resistant to degradation in the upper gastrointestinal tract—properties that make it particularly useful for oral drug delivery [119,125,126].

In 2018, Chinnaiyan et al. designed pectin-based nanoparticles loaded with metformin using ionic gelation with tripolyphosphate as the crosslinker. The nanoparticles were spherical with a mean diameter of 482.7 nm and exhibited a high encapsulation efficiency of 86.74%. This was attributed to the rapid electrostatic interaction between tripolyphosphate and pectin carboxylates, forming a dense matrix that prevented premature drug release. In vitro studies showed a slow, sustained release profile, with 74.37–98.5% of metformin released over 12 h. Higher pectin concentrations resulted in slower release due to increased viscosity and stronger ionic interactions within the matrix [125].

5.2.3. Cellulose

Cellulose is a linear homopolymer composed of β-(1→4)-linked D-glucose units. It is abundant in plant cell walls and is widely recognized for its biodegradability, biocompatibility, and safety (GRAS status by the FDA) [127]. These characteristics, combined with its mechanical and chemical stability, make cellulose an attractive material for drug delivery. However, native cellulose has limitations such as low solubility in common organic solvents and limited thermoplasticity. Therefore, chemical or physical modifications—such as derivatization into cellulose acetate (CA) or carboxymethylcellulose (CMC)—are often employed to improve its functional properties [128].

Cam et al. used bacterial cellulose nanofibers crosslinked with glutaraldehyde vapor and loaded with metformin to create a material for diabetic wound treatment. The electrospun nanofibers had smooth surfaces without metformin crystals and exhibited an encapsulation efficiency of approximately 80%. Drug release was linear and sustained, demonstrating controlled delivery characteristics [122].

In another study, cellulose acetate was used as the matrix for coaxial nanofibers loaded with metformin using triaxial electrospinning. The nanofibers had an average diameter of 570 nm, uniform morphology, and a high encapsulation efficiency of 98.41%, with minimal drug loss during fabrication. In vitro release followed zero-order kinetics, achieving 95% metformin release, attributed to the coaxial structure and heterogeneous drug distribution within the core and shell [129].

5.3. Lipid-Based Nanocarriers

Lipid-based drug delivery systems—including liposomes, solid lipid nanoparticles, and nanoemulsions—are commonly used nanocarriers with particle sizes typically ranging from 100 to 500 nm [130]. Lipids offer physicochemical properties such as biocompatibility, slow water absorption, and low susceptibility to erosion, which make them ideal for improving drug solubility, stability, and bioavailability [131]. Many lipids used in these systems are dietary in origin, enhancing their biodegradability and compatibility for oral administration. Additionally, lipid nanocarriers can be engineered to interact specifically with gastrointestinal cells, increasing drug permeability and enhancing therapeutic effectiveness [132,133].

5.3.1. Lecithin

Lecithin refers to a group of phospholipids, glycolipids, and triglycerides, with phosphatidylcholine being the primary component. It is commonly extracted from plant sources such as rapeseed, rice, or soybeans. In liposomal formulations, lecithin from soy is widely preferred because it is cost-effective, safe, and more stable than lecithin derived from animal sources, which contain higher levels of polyunsaturated fatty acids that may be less stable [134].

Abd-Rabou et al. investigated the effect of lecithin and chitosan nanoparticles on metformin encapsulation and their potential in inhibiting colorectal cancer cell proliferation. The nanoparticles had an average size of 31.5 nm and a high encapsulation efficiency of 95.2%. In vitro release studies showed that 24.3% of the metformin was released within 2 h, with complete release achieved at 24 h. The combination of lecithin and chitosan produced slower release rates, likely because metformin remained embedded within the polymer chains, resulting in denser nanoparticle structures [135].

5.3.2. Glycerol Monostearate (GMS)

Glycerol monostearate (GMS) is an amphiphilic monoglyceride ester composed of a glycerol backbone and a long stearic acid chain. Its emulsifying, stabilizing, and emollient properties make it widely applicable in the food, cosmetic, and pharmaceutical industries. GMS is non-toxic, easily digestible, and suitable for developing lipid-based nanocarriers [136].

Ngwuluka et al. formulated metformin-loaded solid lipid nanoparticles using GMS and lecithin via a double-emulsion method. The resulting nanoparticles had an average size of 195 nm and an encapsulation efficiency of 29.30%. Despite metformin's high solubility and limited permeability—which negatively affect encapsulation efficiency—the lipid nanoparticles improved metformin absorption. In vitro release studies demonstrated controlled release behavior: 48% of the drug was released within 30 min, and nearly 100% was released after 8 h [137].

5.4. Nanocomposites-Based Nanocarriers

Nanocomposites are materials composed of two or more distinct phases, in which at least one component exists at the nanoscale. In these systems, the reinforcing phase (e.g., nanoparticles, fibers, and sheets) is embedded within a continuous matrix (e.g., polymers, ceramics, or metals) [138]. In the field of drug delivery, biopolymeric nanocomposites have gained significant interest because incorporating nanoparticles into a polymeric matrix can reduce premature drug release, improve drug stability, and enable controlled and sustained delivery. The performance of these systems depends on factors such as concentration, morphology, size, and the interactions between the polymeric matrix and the embedded nanomaterials [139,140].

In 2017, Shariatinia and Zahraee developed chitosan-based nanocomposite films incorporating poly(ethylene glycol)-poly(propylene glycol) blocks and mesoporous MCM-41 nanoparticles loaded with metformin. Glycerin was added as a plasticizer to modulate drug release. Morphological analysis revealed that inclusion of metformin-generated films with a rougher surface and particle sizes of approximately 50 nm. In vitro release studies showed a substantial burst release during the first 24 h, followed by a gradual and sustained release of 45% over 15 days. This biphasic profile was attributed to the mesoporous structure of MCM-41 and its strong interactions with chitosan, which slowed long-term diffusion [141].

https://doi.org/10.3390/scipharm94010003

5.5. Synthetic Polymer-Based Nanocarriers

Synthetic polymers have gained prominence in drug delivery due to their tunable physicochemical properties and high reproducibility. They enable the development of drug delivery systems with controlled and sustained release profiles. Compared with natural polymers, synthetic polymers generally offer greater purity, predictable degradation behavior, enhanced stability in physiological environments, and reduced risk of immunogenicity [142,143]. Among the most commonly used synthetic polymers in pharmaceutical applications are poly(lactide-co-glycolide) (PLGA), poly(lactide) (PLA), polyvinyl alcohol (PVA), and polyethylene glycol (PEG).

5.5.1. Poly(lactide) (PLA)

Polylactic acid (PLA) is a thermoplastic polymer derived from renewable resources such as starch. It can be synthesized from lactic acid through polycondensation or ring-opening polymerization. PLA is widely used in drug delivery systems due to its biodegradability, biocompatibility, and mechanical properties [144,145].

Sena et al. developed core–shell nanofibers using PLA as the shell material, with a core composed of polyvinyl alcohol (PVA), fish sarcoplasmic protein (FSP), and metformin, fabricated using coaxial electrospinning. The study evaluated the influence of FSP on fiber morphology and metformin release behavior. The resulting nanofibers exhibited smooth, defect-free surfaces, with mean diameters ranging from 650 to 681 nm. Metformin release showed an initial burst phase of approximately 59% within the first 24 h, followed by a slower, sustained release phase. After 21 days, approximately 96% of the encapsulated metformin had been released [146].

5.5.2. Poly(lactic-co-glycolic acid) (PLGA)

PLGA is a biodegradable copolymer composed of lactic acid (PLA) and glycolic acid (PGA) units. Its adjustable crystallinity, hydrophilic–hydrophobic balance, and tunable degradation rate make it an attractive platform for controlled drug delivery. PGA contributes hydrophilicity and high crystallinity, whereas PLA provides hydrophobicity and slower degradation [145,147]. PLGA is FDA-approved for various biomedical applications due to its safety and predictable degradation into metabolizable byproducts [148].

In a previous study, PLGA nanoparticles modified with PEG were developed for the co-release of metformin and silibinin to evaluate their antitumor potential. The nanoparticles exhibited spherical morphology with uniformly distributed sizes averaging 246 nm. Encapsulation efficiency for metformin was 75.15%. Both metformin and silibinin showed an initial burst release during the first 8 h, followed by a sustained release phase extending up to 7 days. Approximately 87% of both drugs were released within the first 72 h [149].

6. Techniques

6.1. Electrospraying

Electrospraying, also known as electrohydrodynamic atomization (EHDA), is a technique used to produce submicron-sized particles [150]. Similarly To electrospinning, the electrospray setup consists of a high-voltage power supply, a syringe containing the polymer solution, a metal needle, an injection pump, and a collector plate (Figure 4(A②)). The principle of electrospraying relies on the application of a strong electric field to the metal capillary. When the electrostatic forces exceed the surface tension of the liquid, the droplet at the needle tip destabilizes and is ejected as a fine jet, which subsequently breaks into charged droplets. Solvent evaporation leads to the formation of solid particles [151–154].

https://doi.org/10.3390/scipharm94010003

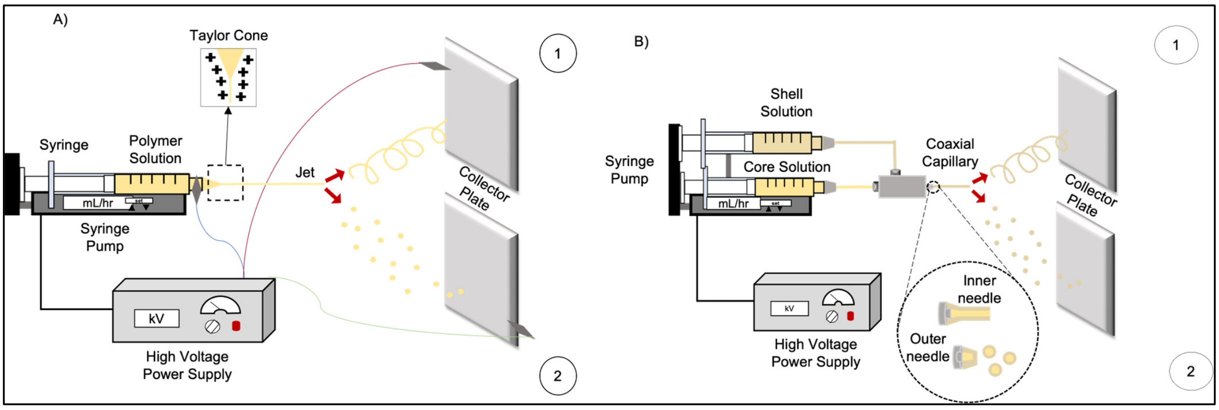

Figure 4. (**A**) Schematic representation of basic ① electrospinning and ② electrospray setups. (**B**) Schematic representation of coaxial ① electrospinning and ② electrospray setups.

Coaxial Electrospraying

Coaxial electrospraying is a variant of conventional electrospraying used to produce core–shell structures [155]. In this configuration, two immiscible or compatible polymer solutions are introduced through a concentric (coaxial) needle system, allowing for simultaneous spraying and the formation of particles with a stable core–shell architecture (Figure 4(B②)) [156,157]. Encapsulation in this system can be achieved in two ways: On the one hand, the first solution contains the polymer, while the second contains the component to be encapsulated. On the other hand, a solution can be obtained with a mixture of the polymer and the component to be encapsulated, and in the second solution only the polymer [151].

6.2. Nanoprecipitation-Based Methods

Nanoprecipitation—also known as solvent displacement—is a simple, fast, and reproducible technique developed by Fessi in 1989. It is widely used to encapsulate molecules into nanospheres or nanocapsules, typically producing polymeric nanoparticles ranging from 50 to 300 nm [156,157]. The process involves two phases: an organic solvent phase, containing the active compound and polymer, and an aqueous phase, usually water, which acts as a non-solvent. Mixing these phases causes supersaturation, leading to polymer precipitation, nucleation, and nanoparticle formation [158–162]. Surfactants may be used, although under some condition's nanoparticles form without them via the "ouzo effect" [157,160,163,164] (Figure 5).

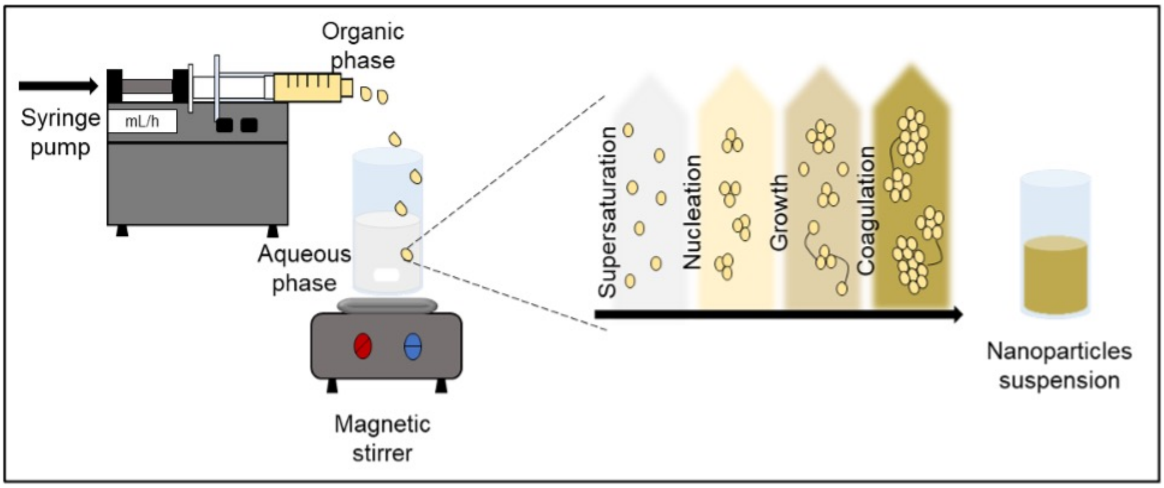

Figure 5. Schematic illustration of the nanoprecipitation mechanism.

6.2.1. Flash Nanoprecipitation

Flash nanoprecipitation produces nanoparticles by generating extremely high supersaturation levels using rapid mixing. Two liquid streams collide at high velocity inside a confined impinging jet (CIJ) mixer, resulting in instantaneous and uniform nucleation [165,166] (Figure 6A). This technique is ideal for hydrophobic compounds and amphiphilic block copolymers, yielding highly uniform particles with narrow size distributions.

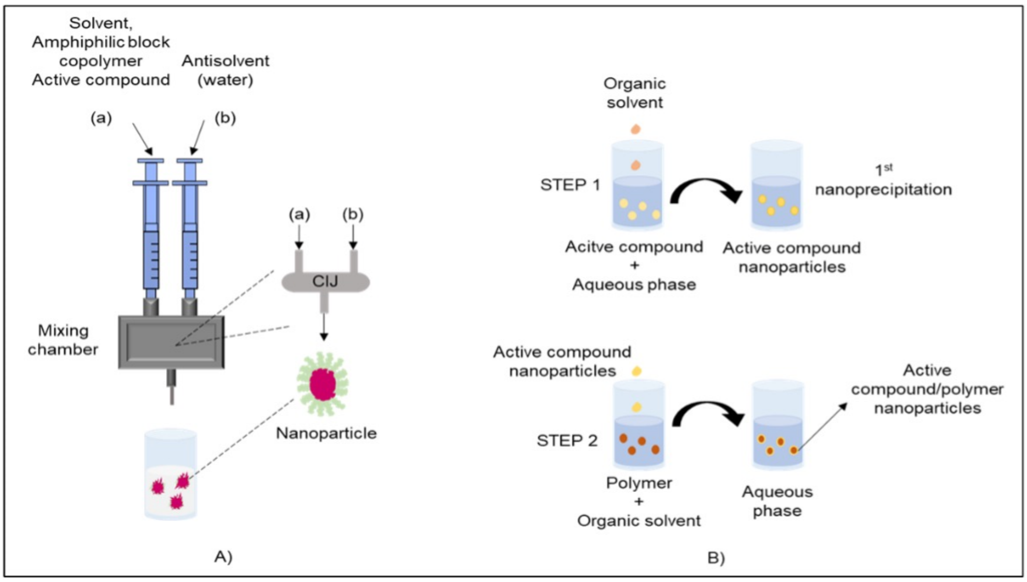

Figure 6. Schematic representation of (**A**) fast nanoprecipitation and (**B**) two-step nanoprecipitation.

6.2.2. Two-Step Nanoprecipitation

Two-step nanoprecipitation was developed to address cases in which no single solvent can dissolve both the hydrophilic polymer and hydrophobic active compound without compromising stability [167,168]. The process includes the following steps:

- Step 1: The active compound is precipitated in a suitable organic solvent to form a suspension.
- Step 2: The polymer is dissolved in a compatible solvent and added to the suspension under stirring, enabling the polymer to encapsulate the previously precipitated drug (Figure 6B) [169,170].

This method expands the applicability of nanoprecipitation to difficult-to-encapsulate compounds.

7. Methods of Administration of Metformin Delivery Systems

7.1. Oral Administration

The gastrointestinal tract (GIT) is the best-known way to administer drugs, since it has the advantage of offering a large area for systemic absorption. The challenge in the administration of drugs (especially orally) is to achieve stability when passing through the stomach, the intestinal lumen, the intestinal epithelial mucosa, and the epithelium itself [139] (Figure 7). Metformin is a hydrophilic molecule with high solubility (50 mg/mL) and poor oral absorption due to its limited saturated and poor intestinal absorption; this is why recent studies have designed various metformin delivery systems to obtain better oral absorption and a more controlled release of the drug [171].

A previous study developed nanoparticles from chitosan with the aim of improving the oral bioavailability of metformin and, in turn, the capacity for mucoadhesion and permeation through an in vitro intestinal barrier model. Metformin-loaded chitosan nanoparticles have demonstrated higher mucoadhesion efficiency at a particle size < 200 nm, with a stable morphology and drug protection capacity under acidic pH conditions found in the stomach but, upon reaching a neutral pH such as that of the small intestine and systemic circulation, they swell and release the drug. Another similar study carried out by Bhujbal and Dash [171], investigated hyaluronic acid nanoparticles loaded with metformin were synthesized by the nanoprecipitation method, in order to evaluate the mucoadhesive capacity of the polymer. Physically stable nanoparticles with a particle size of approximately 114 nm, release of metformin > 50% in 1 h, and low permeability through the intestinal membrane were obtained, thus maintaining a sustained release of metformin.

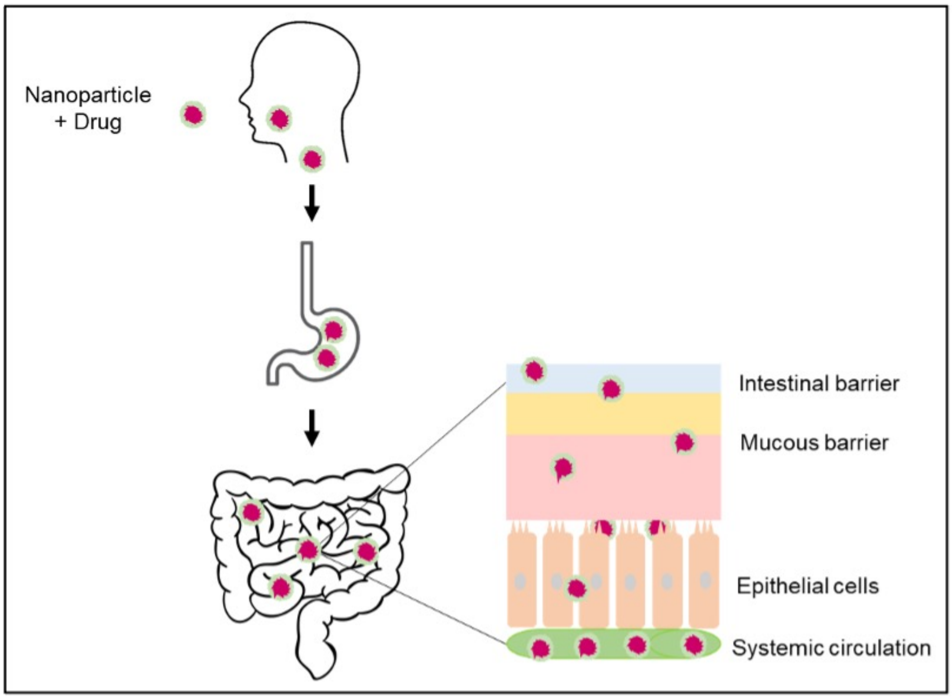

Figure 7. Gastro-intestinal barriers involved in the oral delivery of nanoparticles.

7.2. Cutaneous Administration

The skin is the largest organ in our body, covering an area of 1.8–2.0 m^2. It is composed of three layers: epidermis, dermis, and hypodermis. The stratum corneum is the outermost layer of the epidermis and is mainly composed of keratinocytes, which provide it with the skin's principal barrier properties [172]. Cutaneous administration of drugs has been proposed as an alternative to common routes such as the oral and parenteral, because the skin is considered to be an accessible organ and administration through this route does not cause pain. The main objective of this administration route is to overcome the stratum corneum barrier. The benefits that this route offers are a longer duration and a constant rhythm in terms of administration, it can be interrupted simply by removing the device and gastrointestinal incompatibility can be avoided. There are several uses for the administration of dermal drugs, among them are the treatment of burns, ulcers, wounds, inflammations, or skin diseases that require a specific drug that is released by percutaneous penetration. However, there are two routes for drug administration: dermal (Figure 8A) and transdermal administration (Figure 8B). In the first, the drug crosses the outer layer of the skin and the second requires the drug to be transported to the dermis of the skin through transepidermal (inter and intracellular) transappendicular (transfollicular and transudoripar) routes [173].

Recent research, such as that of Migdadi and collaborators [174], has studied the potential of a patch of hydrogel-forming microneedles for the administration of metformin transdermally in order to minimize the gastrointestinal side effects and variations present at the time of absorption into the small intestine that are associated with oral administration. These patches are composed of arrays of micron-sized needles made from swellable polymers, which penetrate the skin barrier and create aqueous paths for drug diffusion.

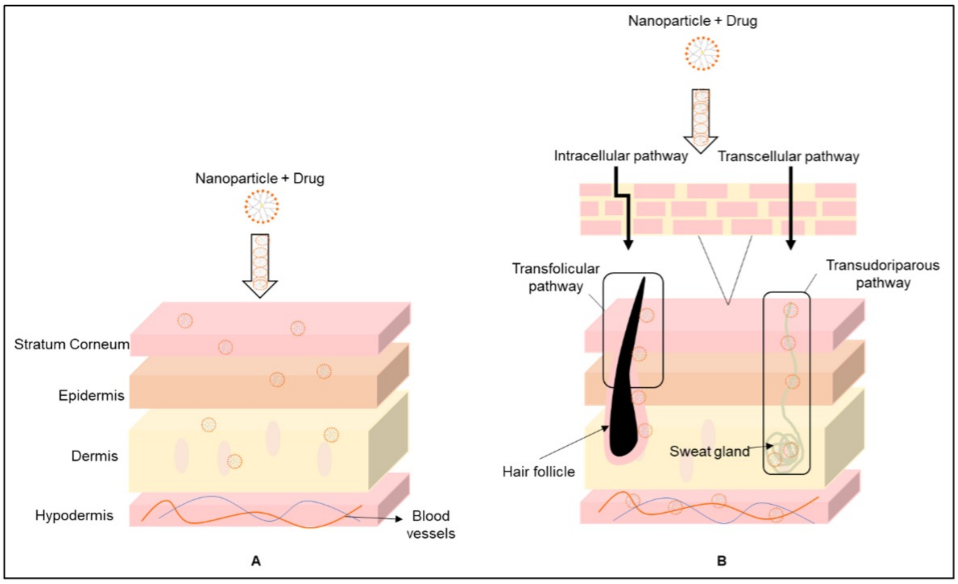

Figure 8. Dermal (**A**) and transdermal (**B**) pathways in cutaneous delivery of nanoparticles.

Regarding the mechanism of action of hydrogels, when they are inserted into the skin, they are in contact with the interstitial fluid. Hydrogels swell and create porous, aqueous channels through which the drug diffuses and reaches the dermal circulation. Moreover, the aqueous network formed by hydrogels has been reported as a suitable mechanism for the transdermal administration of drugs, with a high degree of solubility in water, such as metformin. For the purposes of the study, the permeation of metformin through porcine skin through hydrogel-forming microneedle patches was evaluated. According to the results, a transdermal bioavailability of metformin of 0.3 was obtained; that is, 30% of the drug load was released in 24 h after its application. Furthermore, in a study by Rostamkalaei [175], solid lipid nanoparticles containing metformin were obtained using the ultrasonication method; this was carried out with the aim of formulating a topical gel as a dermal delivery system to be applied to the skin to improve the administration of metformin. In vitro percutaneous absorption tests were carried out considering the ability of the nanoparticles to penetrate the different layers of the skin; the solid lipid nanoparticle gel with metformin and the gel with metformin alone were compared. The results obtained were nanoparticles with a size of approximately 203 nm with a metformin encapsulation efficiency of 32.9%. In addition, greater penetration through the different layers of the skin was achieved by the gel with the nanoparticles, which is promising in terms of the local administration of metformin and other hydrophilic drugs.

7.3. Intravenous Administration

In recent years, the parenteral route has been explored as a means of drug administration due to the complications presented in administration by other routes. Parenteral administration falls into three categories: intravenous (IV), intramuscular, and subcutaneous [176]. Nanoparticles can also be delivered through IV administration (Figure 9). IV injection is the most common parenteral route of drug administration and one of the advantages it offers is avoiding first-pass metabolism by the liver. In addition, it provides a rapid response, allows for broad control in the administration of the drug to the body, and enables complete bioavailability even at low doses. Also, it is a suitable option for those drugs that cannot be absorbed by the gastrointestinal tract or that cannot be administered via muscles or other tissues [177]. However, one of the greatest challenges in systemic intravenous injection is the interaction of the drug with components of the blood, mainly with plasmatic proteins, since they are the ones that regulate the drug's arrival at the target tissues [176]; for example, when administering nanoparticles intravenously, they are often administered without any coating, which causes their uptake by macrophages, mainly for nanoparticles < 5 nm, and thus, their rapid excretion via the kidneys [172].

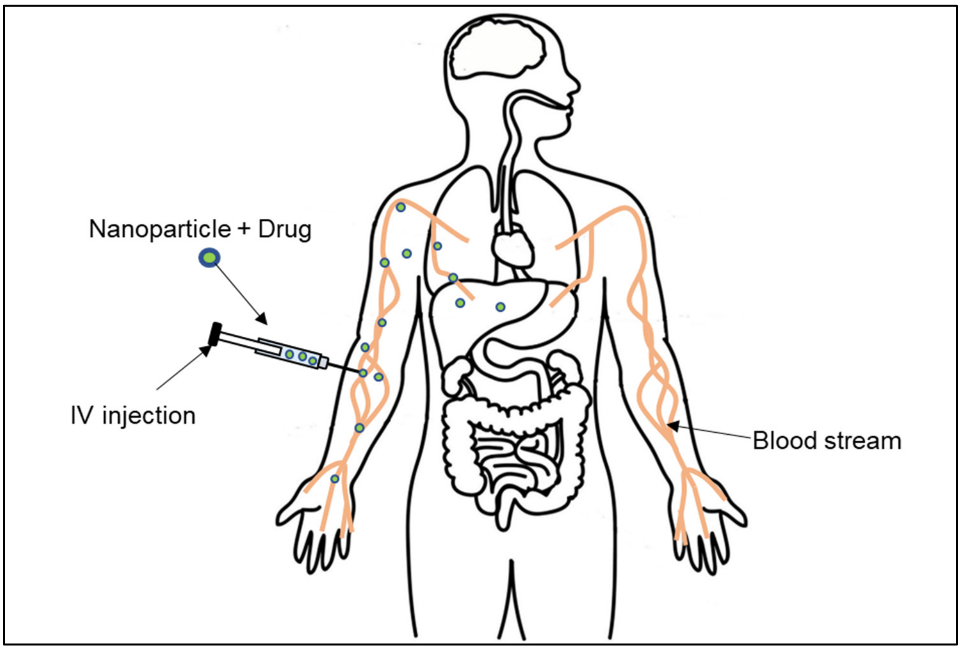

Figure 9. Systemic delivery of nanoparticles by intravenous administration.

Studies have highlighted the potential of intravenous administration of metformin-loaded nanoparticles to enhance therapeutic efficacy. PLGA nanoparticles have demonstrated a sustained plasma concentration over 72 h, with a higher area under the curve and volume of distribution (Vz/F), which suggests improved bioavailability and therapeutic effects in comparison, to conventional metformin [178]. Moreover, iron-based nanoparticles have shown improved endothelial function by enhancing endothelial nitric oxide synthase phosphorylation, which benefits cardiovascular applications [179].

8. Discussion and Future Perspectives

The application of nanotechnology to drug delivery systems represents a significant advancement in metformin therapy for T2D treatment. Although metformin's clinical application is frequently limited by gastrointestinal side effects, low bioavailability, and a narrow absorption range in the gastrointestinal tract, these challenges have driven the development of delivery strategies aimed at enhancing its therapeutic performance. The literature reviewed in this article highlights the diversity of biopolymers employed as carriers (proteins, synthetic polymers, lipids, and polysaccharides) and the versatility of obtention techniques such as electrospinning, electrospraying, and nanoprecipitation. These approaches allow for the adaptation of the physicochemical properties of metformin formulations to meet specific therapeutic requirements in T2D treatment.

Protein-based nanocarriers (e.g., gelatin, albumin, and casein) exhibit a wide range of properties relevant to drug delivery and tissue engineering, including biocompatibility, biodegradability, and binding capacity. Proteins are biomolecules present in all forms of life, contributing to their low toxicity compared with synthetic polymers. They can absorb water and inducing steric repulsion, which enhances the physical stability of nanocarriers and reduces their recognition by the immune system. Additionally, proteins are broadly available in nature and constitute renewable resources derived from plants, animals, and humans, making them easy to obtain at low cost. Importantly, the structural features, amino acid sequences, and diverse functional groups of proteins facilitate drug binding at specific sites and enable conjugation with targeting ligands on the nanoparticle surface, allowing for selective delivery to target tissues or cells [180]. Polysaccharide-based drug delivery systems are also effective in increasing the bioavailability of encapsulated molecules (proteins, peptides, and other therapeutic agents) by promoting transport through the intestinal lymphatic system and enhancing tissue permeability. Furthermore, these systems enable lower therapeutic doses, reduce systemic drug distribution, and diminish renal and hepatic clearance, leading to improved therapeutic efficacy and reduced side effects [181]. The integration of nanotechnology into metformin delivery systems holds significant promise for improving its therapeutic efficacy and overcoming the limitations associated with conventional oral administration. These nanoformulations—ranging from polymeric nanoparticles to liposomes and micelles—exhibit properties that enhance the pharmacokinetics, pharmacodynamics, and overall therapeutic effects of metformin. The drug is known for its limited oral bioavailability (~60%) due to its hydrophilic nature and restricted intestinal absorption. Multiple studies have demonstrated that nanoformulations can increase intestinal uptake and prolong gastrointestinal residence time, improving drug delivery. For example, polymer-based nanoformulations such as chitosan mucosal metformin nanoparticles developed by Lu and collaborators [182] have been designed to enhance bioavailability and prolong the hypoglycemic effect relative to conventional metformin. In intestinal adhesion studies, mucosal nanoparticle adhesion reached 67.27%, compared with only 10.52% for free metformin, suggesting strong interaction with the intestinal mucosa. In vitro release studies indicated that these nanoparticles provided sustained release for over 12 h, whereas commercial formulations released nearly all the drug within 1 h under intestinal conditions. Similarly, Jain [183] developed a jackfruit seed starch-based gastroretentive nanoparticle, which serves as a biodegradable and biocompatible excipient. In addition to optimized physicochemical properties, in vivo evaluation in a murine model demonstrated significant hypoglycemic effects. Compared with free metformin, the nanoparticle formulation maintained substantially reduced blood glucose levels for 24 h (a 50% reduction from 4 to 8 h; $p < 0.01$).

Beyond their potential therapeutic benefits in T2D treatment, metformin nanoformulations have gained attention due to the drug's pleiotropic effects, including antitumor and neuroprotective activities. One of metformin's mechanisms involves inhibiting cancer cell proliferation, as demonstrated in various cell culture models. In a study involving male and female mice with spinal cord injuries, treatment with metformin at 200 mg/kg for 14 days increased oligodendrocyte formation in both sexes. This effect was attributed to metformin's modulation of atypical protein kinase C (aPKC)-mediated phosphorylation of CREB-binding protein (CBP) [184].

In addition to their glucose-lowering and antiproliferative effects, metformin nanoparticles have demonstrated vascular protection. Mohamed et al. [185] evaluated metformin-loaded nanoMIL-89 nanoparticles, which exhibited controlled drug release over 96 h, decreased reactive oxygen species levels in vascular endothelial cells under hyperglycemic conditions, and increased phosphorylation of endothelial nitric oxide synthase, a key enzyme for vascular health maintenance.

Table 2 summarizes the potential advantages of nanotechnology-based metformin delivery systems in comparison with conventional formulations.

Table 2. Comparison between conventional metformin formulations and nanotechnology-based systems.

Characteristic	Metformin Formulation	Nanoformulated Metformin	References
Mechanism of action	Reducing hepatic glucose production, enhances intestinal absorption, and insulin sensitivity	Enhances solubility and permeability using nanostructured systems	[186]
Bioavailability	~50–60% oral bioavailability	Enhanced bioavailability (>80%)	[187,188]
Dosage	Up to 2550 mg/day	Reduced dosage due to sustained release and improved absorption	[189]
Side effects	Gastrointestinal issues and risk of lactic acidosis	Reduction in side effects due to controlled and sustained release	[187]
Limitations	Low therapeutic performance	Requires clinical validation and exhibits large-scale production limitations and high production costs	[189]

While metformin nanoformulations showed potential, not all systems achieve consistent results compared to conventional formulations. Some lipid-based nanocarriers, such as glyceryl monostearate/lecithin/PVA solid lipid nanoparticles, reported low entrapment efficiencies (~29%), reducing their drug loading capacity. Likewise, lipid vesicles and cholesterol SLNs (EE ~29%–~45.9%, respectively) demonstrated limited retention and may need higher doses to achieve therapeutic effects [190]. In some cases, prolonged and sustained release systems may not correlate with improved pharmacodynamic outcomes. Some nanoformulations (e.g., hyaluronic acid-based nanoparticles) provide prolonged release but exhibited low intestinal permeability, resulting in lower glucose effects compared to conventional metformin [191]. Other nanocarriers have demonstrated tissue accumulation in cancer models, but not a significant difference in tumor growth inhibition in comparison to conventional metformin, highlighting that even when formulations achieve better targeting, this may not result in an improved therapeutic outcome [192].

8.1. Challenges in Clinical Translation

8.1.1. Scalability

Laboratory-scale methods such as electrospinning, nanoprecipitation, or solvent-emulsification often fail to obtain a consistent particle size distribution, drug loading, and surface characteristics when scaled up, leading to reduced performance. In large-scale production, differences in shear forces and solvent evaporation requires expensive equipment and rigorous process validation [193].

8.1.2. Regulatory Hurdles

The absence of clear guidelines leads to inconsistencies in safety evaluations which delays the progression of nanocarriers to clinical trials. Engaging with agencies like the FDA (Food and Drug Administration) and EMA (European Medicines Agency) may facilitate smoother transitions through regulatory processes and accelerate clinical translation of nanomedicines [193].

8.1.3. Long-Term Toxicity Profiles

Long-term toxicity remains critical in nanomedicine development due to insufficient effects in short-term studies. Evidence indicates that prolonged exposure to nanomaterials can result in tissue accumulation, organ toxicity, and delayed redistribution. For instance, silica nanoparticles (SiO_2 NPs) have exhibited accumulation and induced chronic injury defined by elevated serum markers, fibrosis, oxidative stress, among other effects [190].

https://doi.org/10.3390/scipharm94010003

Another study related to biodegradable polymeric systems (e.g., PLGA), revealed that these nanoparticles could induce inflammation and endothelial dysfunction, which may be related to cardiovascular risks [193].

Nevertheless, despite the large quantity of preclinical evidence reported in the literature, there are certain limitations and challenges pertaining to these nanocarriers that need to be addressed in order for them to be successfully implemented. Fortunately, the field on nanomedicine is constantly innovating and evolving, and research on nanotechnology in diabetes treatment holds promise for the development of strategies that guarantee effectiveness, safety, and more personalized treatment strategies.

9. Conclusions

Diabetes is a chronic metabolic disease whose global prevalence continues to rise. Metformin remains the first-line pharmacological treatment for type 2 diabetes due to its effectiveness, safety, and affordability. However, limitations such as gastrointestinal side effects, variable absorption, and moderate bioavailability highlight the need for improved delivery strategies. Nanotechnology-based approaches have emerged as promising alternatives to enhance the therapeutic performance of metformin. Various nanostructures—including nanofibers, polymeric nanoparticles, lipid-based nanocarriers, nanocomposites, and hydrogels—offer advantages such as sustained and controlled release, improved solubility and stability, enhanced permeability, and reduced dosing frequency. Biopolymers such as chitosan, gelatin, pectin, cellulose derivatives, and protein-based matrices have shown promise due to their biodegradability, biocompatibility, and tunable physicochemical properties. Techniques such as electrospraying, electrospinning, nanoprecipitation, and ionic gelation enable the development of highly tailored metformin delivery systems. Encapsulation efficiency, release kinetics, nanostructure morphology, and polymer–drug interactions play crucial roles in determining therapeutic performance.

Overall, nanotechnology presents a versatile and effective platform for improving metformin administration, with the potential to enhance patient adherence, minimize side effects, and optimize glycemic control. Continued research focusing on biocompatibility, large-scale production, and in vivo evaluation will be essential for translating these nanocarriers into clinically applicable therapies.

Author Contributions: Conceptualization, E.A.M.-G., F.R.-F. and J.A.T.-H.; validation, F.R.-F., R.N.-M. and C.L.D.-T.-S.; formal analysis, E.A.M.-G. and E.C.-M.; writing—original draft preparation, E.A.M.-G.; writing—review and editing, J.A.T.-H., E.M.-R., C.L.D.-T.-S., D.E.R.-F., C.G.B.-U. and C.E.F.-E.; visualization, F.R.-F., E.C.-M., I.Y.L.-P., C.E.F.-E. and C.G.B.-U.; supervision, F.R.-F. and J.A.T.-H.; project administration, E.A.M.-G., F.R.-F. and E.M.-R.; funding acquisition, F.R.-F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Data Availability Statement: Data available on request due to privacy/ethical restrictions.

Acknowledgments: The authors are grateful to the University of Sonora for their support. Eneida Azaret Montaño-Grijalva would like to acknowledge SECIHTI (Secretaría de Ciencia, Humanidades, Tecnología e Innovación) for the financial support provided for her graduate studies during this study.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
GRAS	Generally Recognized As Safe

References

1. World Health Organization (WHO). Diabetes. Available online: https://www.who.int/news-room/fact-sheets/detail/diabetes (accessed on 27 February 2024).
2. Rocha, S.; Lucas, M.; Ribeiro, D.; Corvo, M.L.; Fernandes, E.; Freitas, M. Nano-based drug delivery systems used as vehicles to enhance polyphenols therapeutic effect for diabetes mellitus treatment. *Pharmacol. Res.* **2021**, *169*, 105604. [CrossRef]
3. Chatterjee, S.; Khunti, K.; Davies, M.J. Type 2 diabetes. *Lancet* **2017**, *389*, 2239–2251. [CrossRef] [PubMed]
4. Nie, X.; Chen, Z.; Pang, L.; Wang, L.; Jiang, H.; Chen, Y.; Zhang, J. Oral Nano drug delivery systems for the treatment of type 2 diabetes mellitus: An available administration strategy for antidiabetic phytocompounds. *Int. J. Nanomed.* **2020**, *15*, 10215–10240. [CrossRef]
5. Morantes-Caballero, J.; Londoño-Zapata, G.; Rubio-Rivera, M.; Pinilla-Roa, A. Metformina: Más allá del control glucémico. *Rev. Los Estud. Med. Univ. Ind. Santander* **2017**, *30*, 57–71. [CrossRef]
6. American Diabetes Association. Prevention or Delay of Diabetes and Associated Comorbidities: Standards of Care in Diabetes—2024. *Diabetes Care* **2024**, *47* (Suppl. 1), S43–S51. [CrossRef]
7. Zhou, T.; Xu, X.; Du, M.; Zhao, T.; Wang, J. A preclinical overview of metformin for the treatment of type 2 diabetes. *Biomed. Pharmacother.* **2018**, *106*, 1227–1235. [CrossRef]
8. Rena, G.; Hardie, D.G.; Pearson, E.R. The mechanisms of action of metformin. *Diabetologia* **2017**, *60*, 1577–1585. [CrossRef] [PubMed]
9. Flory, J.; Lipska, K. Metformin in 2019. *JAMA* **2019**, *321*, 1926–1927. [CrossRef] [PubMed]
10. Luo, M.X.; Hua, S.; Shang, Q.Y. Application of nanotechnology in drug delivery systems for respiratory diseases. *Mol. Med. Rep.* **2019**, *23*, 325. [CrossRef]
11. Todaro, B.; Santi, M. Characterization and Functionalization Approaches for the Study of Polymeric Nanoparticles: The State of the Art in Italian Research. *Micro* **2022**, *3*, 9–21. [CrossRef]
12. Marasini, N.; Haque, S.; Kaminskas, L.M. Polymer-drug conjugates as inhalable drug delivery systems: A review. *Curr. Opin. Colloid Interface Sci.* **2017**, *31*, 18–29. [CrossRef]
13. Liu, X.; Yang, Y.; Yu, D.G.; Zhu, M.J.; Zhao, M.; Williams, G.R. Tunable zero-order drug delivery systems created by modified triaxial electrospinning. *Chem. Eng. J.* **2019**, *356*, 886–894. [CrossRef]
14. Coelho, S.C.; Estevinho, B.N.; Rocha, F. Encapsulation in food industry with emerging electrohydrodynamic techniques: Electrospinning and electrospraying–A review. *Food Chem.* **2021**, *339*, 127850. [CrossRef] [PubMed]
15. Mohammadian, F.; Eatemadi, A. Drug loading and delivery using nanofibers scaffolds. *Artif. Cells Nanomed. Biotechnol.* **2017**, *45*, 881–888. [CrossRef] [PubMed]
16. Lakhtakia, R. The history of diabetes mellitus. *Sultan Qaboos Univ. Med. J.* **2013**, *13*, 368. [CrossRef] [PubMed]
17. Petersmann, A.; Müller-Wieland, D.; Müller, U.A.; Landgraf, R.; Nauck, M.; Freckmann, G.; Schleicher, E. Definition, classification and diagnosis of diabetes mellitus. *Exp. Clin. Endocrinol. Diabetes* **2019**, *127*, S1–S7. [CrossRef]
18. Eizirik, D.L.; Pasquali, L.; Cnop, M. Pancreatic β-cells in type 1 and type 2 diabetes mellitus: Different pathways to failure. *Nat. Rev. Endocrinol.* **2020**, *16*, 349–362. [CrossRef]
19. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: Standards of care in diabetes—2025. *Diabetes Care* **2025**, *48* (Suppl. 1), S27–S49. [CrossRef]
20. Plows, J.F.; Stanley, J.L.; Baker, P.N.; Reynolds, C.M.; Vickers, M.H. The pathophysiology of gestational diabetes mellitus. *Int. J. Mol. Sci.* **2018**, *19*, 3342. [CrossRef]
21. Katsarou, A.; Gudbjörnsdottir, S.; Rawshani, A.; Dabelea, D.; Bonifacio, E.; Anderson, B.J.; Lernmark, Å. Type 1 diabetes mellitus. *Nat. Rev. Dis. Primers* **2017**, *3*, 17016. [CrossRef]
22. Holt, R.I.; DeVries, J.H.; Hess-Fischl, A.; Hirsch, I.B.; Kirkman, M.S.; Klupa, T.; Peters, A.L. The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **2021**, *44*, 2589–2625. [CrossRef]
23. ElSayed, N.A.; Aleppo, G.; Aroda, V.R.; Bannuru, R.R.; Brown, F.M.; Bruemmer, D.; Gabbay, R.A. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in diabetes—2023. *Diabetes Care* **2023**, *46*, S140–S157. [CrossRef]
24. Padhi, S.; Nayak, A.K.; Behera, A. Type II diabetes mellitus: A review on recent drug-based therapeutics. *Biomed. Pharmacother.* **2020**, *131*, 110708. [CrossRef]

25. Top, W.M.; Kooy, A.; Stehouwer, C.D. Metformin: A narrative review of its potential benefits for cardiovascular disease, cancer and dementia. *Pharmaceuticals* **2022**, *15*, 312. [CrossRef] [PubMed]
26. Contreras-Duarte, S.; Carvajal, L.; Garchitorena, M.J.; Subiabre, M.; Fuenzalida, B.; Cantin, C.; Leiva, A. Gestational diabetes mellitus treatment schemes modify maternal plasma cholesterol levels dependent to women s weight: Possible impact on feto-placental vascular function. *Nutrients* **2020**, *12*, 506. [CrossRef]
27. Feng, J.; Wang, X.; Ye, X.; Ares, I.; Lopez-Torres, B.; Martínez, M.; Martínez, M.A. Mitochondria as an important target of metformin: The mechanism of action, toxic and side effects, and new therapeutic applications. *Pharmacol. Res.* **2022**, *177*, 106114. [CrossRef]
28. Cvijić, S.; Parojčić, J.; Langguth, P. Viscosity-mediated negative food effect on oral absorption of poorly-permeable drugs with an absorption window in the proximal intestine: In vitro experimental simulation and computational verification. *Eur. J. Pharm. Sci.* **2014**, *61*, 40–53. [CrossRef]
29. Jeong, Y.S.; Jusko, W.J. Meta-assessment of metformin absorption and disposition pharmacokinetics in nine species. *Pharmaceuticals* **2021**, *14*, 545. [CrossRef] [PubMed]
30. LaMoia, T.E.; Shulman, G.I. Cellular and molecular mechanisms of metformin action. *Endocr. Rev.* **2021**, *42*, 77–96. [CrossRef] [PubMed]
31. Zhou, J.; Massey, S.; Story, D.; Li, L. Metformin: An old drug with new applications. *Int. J. Mol. Sci.* **2018**, *19*, 2863. [CrossRef]
32. Rajasurya, V.; Anjum, H.; Surani, S. Metformin use and metformin-associated lactic acidosis in intensive care unit patients with diabetes. *Cureus* **2019**, *11*, e4739. [CrossRef]
33. Wang, Y.W.; He, S.J.; Feng, X.; Cheng, J.; Luo, Y.T.; Tian, L.; Huang, Q. Metformin: A review of its potential indications. *Drug Des. Dev. Ther.* **2017**, *11*, 2421–2429. [CrossRef]
34. Baker, C.; Retzik-Stahr, C.; Singh, V.; Plomondon, R.; Anderson, V.; Rasouli, N. Should metformin remain the first-line therapy for treatment of type 2 diabetes? *Ther. Adv. Endocrinol. Metab.* **2021**, *12*, 2042018820980225. [CrossRef]
35. Elbere, I.; Kalnina, I.; Silamikelis, I.; Konrade, I.; Zaharenko, L.; Sekace, K.; Klovins, J. Association of metformin administration with gut microbiome dysbiosis in healthy volunteers. *PLoS ONE* **2018**, *13*, e0204317. [CrossRef] [PubMed]
36. Salvatore, T.; Pafundi, P.C.; Marfella, R.; Sardu, C.; Rinaldi, L.; Monaco, L.; Sasso, F. C Metformin lactic acidosis: Should we still be afraid? *Diabetes Res. Clin. Pract.* **2019**, *157*, 107879. [CrossRef]
37. Atabi, D.F.; Qasim, A.H.; Kareem Mohammed, S.A.; Omran Al-Saadawi, A.I. Association of Metformin Use with Vitamin B12 Deficiency in Iraqi Patients with Type II Diabetes Mellitus. *Indian J. Forensic Med. Toxicol.* **2021**, *15*, 4729. [CrossRef]
38. Milićević, A.M.; Lekić, L.; Nurkić, H.; Harčinović, E.; Zahirović, I. Metformin Consumption Trends and the Impact of Adherence on the Consumption of Oral Antihyperglycemic Drugs. *Int. J. Innov. Sci. Res. Technol.* **2024**, *9*, 1837–1840. [CrossRef]
39. Lee, D.S.U.; Lee, H. Adherence and persistence rates of major antidiabetic medications: A review. *Diabetol. Metab. Syndr.* **2022**, *14*, 12. [CrossRef]
40. Studer, C.M.; Linder, M.; Pazzagli, L. A global systematic overview of socioeconomic factors associated with antidiabetic medication adherence in individuals with type 2 diabetes. *J. Health Popul. Nutr.* **2023**, *42*, 122. [CrossRef] [PubMed]
41. Ekenberg, M.; Qvarnström, M.; Sundström, A.; Martinell, M.; Wettermark, B. Socioeconomic factors associated with poor medication adherence in patients with type 2 diabetes. *Eur. J. Clin. Pharmacol.* **2024**, *80*, 53–63. [CrossRef] [PubMed]
42. Khatri, N.; Vaja, P.N.; Krishna, M.M.; BM, K.; Narapusetty, N.; Gogoi, P.; Sharma, R.K.; Jahnavi, P. Formulation and Evaluation of Metformin-Loaded Nanoparticles for Enhanced Oral Bioavailability and Antidiabetic Activity. *Int. J. Environ. Sci.* **2025**, *11*, 656–664.
43. Bahman, F.; Greish, K.; Taurin, S. Nanotechnology in insulin delivery for management of diabetes. *Pharm. Nanotechnol.* **2019**, *7*, 113–128. [CrossRef]
44. Prabhakar, P.; Banerjee, M. Nanotechnology in drug delivery system: Challenges and opportunities. *J. Pharm. Sci. Res.* **2020**, *12*, 492–498.
45. Patra, J.K.; Das, G.; Fraceto, L.F.; Campos, E.V.R.; del Pilar Rodriguez-Torres, M.; Acosta-Torres, L.S.; Shin, H.S. Nano based drug delivery systems: Recent developments and future prospects. *J. Nanobiotechnol.* **2018**, *16*, 71. [CrossRef]
46. Sahu, T.; Ratre, Y.K.; Chauhan, S.; Bhaskar, L.V.K.S.; Nair, M.P.; Verma, H.K. Nanotechnology based drug delivery system: Current strategies and emerging therapeutic potential for medical science. *J. Drug Deliv. Sci. Technol.* **2021**, *63*, 102487. [CrossRef]
47. Ahmed, F.; Khan, M.A.; Haider, N.; Ahmad, M.Z.; Ahmad, J. Recent advances in theranostic applications of nanomaterials in cancer. *Curr. Pharm. Des.* **2022**, *28*, 133–150. [CrossRef]
48. Huang, R.; Zhou, X.; Chen, G.; Su, L.; Liu, Z.; Zhou, P.; Min, Y. Advances of functional nanomaterials for magnetic resonance imaging and biomedical engineering applications. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2022**, *14*, e1800. [CrossRef]
49. Li, X.; Wang, L.; Fan, Y.; Feng, Q.; Cui, F.Z. Biocompatibility and toxicity of nanoparticles and nanotubes. *J. Nanomater.* **2012**, *2012*, 548389. [CrossRef]
50. Reise, M.; Kranz, S.; Guellmar, A.; Wyrwa, R.; Rosenbaum, T.; Weisser, J.; Sigusch, B.W. Coaxial electrospun nanofibers as drug delivery system for local treatment of periodontitis. *Dent. Mater.* **2023**, *39*, 132–139. [CrossRef] [PubMed]

51. Simonazzi, A.; Cid, A.G.; Villegas, M.; Romero, A.I.; Palma, S.D.; Bermúdez, J.M. Nanotechnology applications in drug-controlled release. In *Drug Targeting and Stimuli Sensitive Drug Delivery Systems*; William Andrew Publishing: Norwich, NY, USA, 2018; pp. 81–116.
52. Perumal, S. Polymer Nanoparticles: Synthesis and Applications. *Polymers* **2022**, *14*, 5449. [CrossRef]
53. Tiwari, S.S.; Wadher, S.J. Potential Nanomaterials for the Treatment and Management of Diabetes Mellitus. In *Nanomaterials for Sustainable Development: Opportunities and Future Perspectives*; Springer: Singapore, 2023; pp. 297–312.
54. Li, M.; Du, C.; Guo, N.; Teng, Y.; Meng, X.; Sun, H.; Li, S.; Yu, P.; Galons, H. Composition design and medical application of liposomes. *Eur. J. Med. Chem.* **2019**, *164*, 640–653. [CrossRef] [PubMed]
55. Nikezić, A.V.V.; Bondžić, A.M.; Vasić, V.M. Drug delivery systems based on nanoparticles and related nanostructures. *Eur. J. Pharm. Sci.* **2020**, *151*, 105412. [CrossRef]
56. Pawar, V.; Maske, P.; Khan, A.; Ghosh, A.; Keshari, R.; Bhatt, M.; Srivastava, R. Responsive Nanostructure for Targeted Drug Delivery. *J. Nanotheranost.* **2023**, *4*, 55–85. [CrossRef]
57. Begines, B.; Ortiz, T.; Pérez-Aranda, M.; Martínez, G.; Merinero, M.; Argüelles-Arias, F.; Alcudia, A. Polymeric nanoparticles for drug delivery: Recent developments and future prospects. *Nanomaterials* **2020**, *10*, 1403. [CrossRef]
58. Souto, E.B.; Souto, S.B.; Campos, J.R.; Severino, P.; Pashirova, T.N.; Zakharova, L.Y.; Santini, A. Nanoparticle delivery systems in the treatment of diabetes complications. *Molecules* **2019**, *24*, 4209. [CrossRef] [PubMed]
59. Wechsler, M.E.; Vela Ramirez, J.E.; Peppas, N.A. 110th anniversary: Nanoparticle mediated drug delivery for the treatment of Alzheimer's disease: Crossing the blood–brain barrier. *Ind. Eng. Chem. Res.* **2019**, *58*, 15079–15087. [CrossRef] [PubMed]
60. Khalid, M.; El-Sawy, H.S. Polymeric nanoparticles: Promising platform for drug delivery. *Int. J. Pharm.* **2017**, *528*, 675–691. [CrossRef]
61. Zielińska, A.; Carreiró, F.; Oliveira, A.M.; Neves, A.; Pires, B.; Venkatesh, D.N.; Souto, E.B. Polymeric nanoparticles: Production, characterization, toxicology and ecotoxicology. *Molecules* **2020**, *25*, 3731. [CrossRef]
62. Castro, K.C.D.; Costa, J.M.; Campos, M.G.N. Drug-loaded polymeric nanoparticles: A review. *Int. J. Polym. Mater. Polym. Biomater.* **2022**, *71*, 1–13. [CrossRef]
63. Iyisan, B.; Landfester, K. Modular approach for the design of smart polymeric nanocapsules. *Macromol. Rapid Commun.* **2019**, *40*, 1800577. [CrossRef]
64. Deng, S.; Gigliobianco, M.R.; Censi, R.; Di Martino, P. Polymeric nanocapsules as nanotechnological alternative for drug delivery system: Current status, challenges and opportunities. *Nanomaterials* **2020**, *10*, 847. [CrossRef]
65. Urrejola, M.C.; Soto, L.V.; Zumarán, C.C.; Peñaloza, J.P.; Álvarez, B.; Fuentevilla, I.; Haidar, Z.S. Sistemas de nanopartículas poliméricas II: Estructura, métodos de elaboración, características, propiedades, biofuncionalización y tecnologías de auto-ensamblaje capa por capa (layer-by-layer self-assembly). *Int. J. Morphol.* **2018**, *36*, 1463–1471. [CrossRef]
66. Matoba, T.; Koga, J.I.; Nakano, K.; Egashira, K.; Tsutsui, H. Nanoparticle-mediated drug delivery system for atherosclerotic cardiovascular disease. *J. Cardiol.* **2017**, *70*, 206–211. [CrossRef] [PubMed]
67. Lu, Y.; Zhang, E.; Yang, J.; Cao, Z. Strategies to improve micelle stability for drug delivery. *Nano Res.* **2018**, *11*, 4985–4998. [CrossRef]
68. Vardaxi, A.; Kafetzi, M.; Pispas, S. Polymeric nanostructures containing proteins and peptides for pharmaceutical applications. *Polymers* **2022**, *14*, 777. [CrossRef]
69. Simões, S.M.; Figueiras, A.R.; Veiga, F.; Concheiro, A.; Alvarez-Lorenzo, C. Polymeric micelles for oral drug administration enabling locoregional and systemic treatments. *Expert Opin. Drug Deliv.* **2015**, *12*, 297–318. [CrossRef]
70. Makhmalzade, B.S.; Chavoshy, F. Polymeric micelles as cutaneous drug delivery system in normal skin and dermatological disorders. *J. Adv. Pharm. Technol. Res.* **2018**, *9*, 2. [CrossRef]
71. Pham, D.T.; Chokamonsirikun, A.; Phattaravorakarn, V.; Tiyaboonchai, W. Polymeric micelles for pulmonary drug delivery: A comprehensive review. *J. Mater. Sci.* **2021**, *56*, 2016–2036. [CrossRef]
72. Kamble, P.; Sadarani, B.; Majumdar, A.; Bhullar, S. Nanofiber based drug delivery systems for skin: A promising therapeutic approach. *J. Drug Deliv. Sci. Technol.* **2017**, *41*, 124–133. [CrossRef]
73. Pant, B.; Park, M.; Park, S.J. Drug delivery applications of core-sheath nanofibers prepared by coaxial electrospinning: A review. *Pharmaceutics* **2019**, *11*, 305. [CrossRef] [PubMed]
74. Mahalingam, S.; Huo, S.; Homer-Vanniasinkam, S.; Edirisinghe, M. Generation of core–sheath polymer nanofibers by pressurised gyration. *Polymers* **2020**, *12*, 1709. [CrossRef]
75. Mohammadi, G.; Tahmasebi, S.; Mohajer, F.; Badiei, A. The role of carbon nanotubes in antibiotics drug delivery. *Front. Drug Chem. Clin. Res.* **2021**, *4*, 1–12. [CrossRef]
76. Kaur, J.; Gill, G.S.; Jeet, K. Applications of Carbon Nanotubes in Drug Delivery. In *Characterization and Biology of Nanomaterials for Drug Delivery*; Elsevier: Amsterdam, The Netherlands, 2019; pp. 113–135.
77. Khan, A.U.; Khan, M.; Cho, M.H.; Khan, M.M. Selected nanotechnologies and nanostructures for drug delivery, nanomedicine and cure. *Bioprocess Biosyst. Eng.* **2020**, *43*, 1339–1357. [CrossRef]

78. Chen, Y.; Shan, X.; Luo, C.; He, Z. Emerging nanoparticulate drug delivery systems of metformin. *J. Pharm. Investig.* **2020**, *50*, 219–230. [CrossRef]
79. Patiño-Herrera, R.; Louvier-Hernández, J.F.; Escamilla-Silva, E.M.; Chaumel, J.; Escobedo, A.G.P.; Pérez, E. Prolonged release of metformin by SiO2 nanoparticles pellets for type II diabetes control. *Eur. J. Pharm. Sci.* **2019**, *131*, 1–8. [CrossRef] [PubMed]
80. Kumar, S.; Bhanjana, G.; Verma, R.K.; Dhingra, D.; Dilbaghi, N.; Kim, K.H. Metformin-loaded alginate nanoparticles as an effective antidiabetic agent for controlled drug release. *J. Pharm. Pharmacol.* **2017**, *69*, 143–150. [CrossRef] [PubMed]
81. Hong, S.; Choi, D.W.; Kim, H.N.; Park, C.G.; Lee, W.; Park, H.H. Protein-based nanoparticles as drug delivery systems. *Pharmaceutics* **2020**, *12*, 604. [CrossRef]
82. Martínez-López, A.L.; Pangua, C.; Reboredo, C.; Campión, R.; Morales-Gracia, J.; Irache, J.M. Protein-based nanoparticles for drug delivery purposes. *Int. J. Pharm.* **2020**, *581*, 119289. [CrossRef]
83. Jao, D.; Xue, Y.; Medina, J.; Hu, X. Protein-based drug-delivery materials. *Materials* **2017**, *10*, 517. [CrossRef]
84. Kang, M.G.; Lee, M.Y.; Cha, J.M.; Lee, J.K.; Lee, S.C.; Kim, J.; Bae, H. Nanogels derived from fish gelatin: Application to drug delivery system. *Mar. Drugs* **2019**, *17*, 246. [CrossRef]
85. Shehata, T.M.; Ibrahima, M.M. BÜCHI nano spray dryer B-90: A promising technology for the production of metformin hydrochloride-loaded alginate–gelatin nanoparticles. *Drug Dev. Ind. Pharm.* **2019**, *45*, 1907–1914. [CrossRef]
86. Cam, M.E.; Crabbe-Mann, M.; Alenezi, H.; Hazar-Yavuz, A.N.; Ertas, B.; Ekentok, C.; Edirisinghe, M. The comparision of glybenclamide and metformin-loaded bacterial cellulose/gelatin nanofibres produced by a portable electrohydrodynamic gun for diabetic wound healing. *Eur. Polym. J.* **2020**, *134*, 109844. [CrossRef]
87. Lu, Z.; Qi, L.; Lin, Y.R.; Sun, L.; Zhang, L.; Wang, G.C.; Yu, J.M. Novel Albumin Nanoparticle Enhanced the Anti-Insulin-Resistant-Hepatoma Activity of Metformin. *Int. J. Nanomed.* **2020**, *15*, 5203. [CrossRef] [PubMed]
88. Karami, E.; Behdani, M.; Kazemi-Lomedasht, F. Albumin nanoparticles as nanocarriers for drug delivery: Focusing on antibody and nanobody delivery and albumin-based drugs. *J. Drug Deliv. Sci. Technol.* **2020**, *55*, 101471. [CrossRef]
89. Acuña-Avila, P.E.; Cortes-Camargo, S.; Jiménez-Rosales, A. Properties of micro and nano casein capsules used to protect the active components: A review. *Int. J. Food Prop.* **2021**, *24*, 1132–1147. [CrossRef]
90. Rehan, F.; Ahemad, N.; Gupta, M. Casein nanomicelle as an emerging biomaterial—A comprehensive review. *Colloids Surf. B Biointerfaces* **2019**, *179*, 280–292. [CrossRef] [PubMed]
91. Raj, J.; Uppuluri, K.B. Metformin loaded casein micelles for sustained delivery: Formulation, characterization and in-vitro evaluation. *Biomed. Pharmacol. J.* **2015**, *8*, 83–89. [CrossRef]
92. Singh, V.; Malviya, T.; Gupta, S.; Dwivedi, L.M.; Baranwal, K.; Prabha, M. Polysaccharide-based nanoparticles: Nanocarriers for sustained delivery of drugs. In *Advanced Biopolymeric Systems for Drug Delivery*; Springer: Cham, Switzerland, 2020; pp. 151–181.
93. Anda-Flores, D.; Carvajal-Millan, E.; Campa-Mada, A.; Lizardi-Mendoza, J.; Rascon-Chu, A.; Tanori-Cordova, J.; Martínez-López, A.L. Polysaccharide-Based Nanoparticles for Colon-Targeted Drug Delivery Systems. *Polysaccharides* **2021**, *2*, 626–647. [CrossRef]
94. Rizeq, B.R.; Younes, N.N.; Rasool, K.; Nasrallah, G.K. Synthesis, bioapplications, and toxicity evaluation of chitosan-based nanoparticles. *Int. J. Mol. Sci.* **2019**, *20*, 5776. [CrossRef]
95. George, A.; Shah, P.A.; Shrivastav, P.S. Natural biodegradable polymers-based nano-formulations for drug delivery: A review. *Int. J. Pharm.* **2019**, *561*, 244–264. [CrossRef]
96. Jhaveri, J.; Raichura, Z.; Khan, T.; Momin, M.; Omri, A. Chitosan nanoparticles-insight into properties, functionalization; applications in drug delivery; theranostics. *Molecules* **2021**, *26*, 272. [CrossRef]
97. Wang, J.; Chin, D.; Poon, C.; Mancino, V.; Pham, J.; Li, H.; Chung, E.J. Oral delivery of metformin by chitosan nanoparticles for polycystic kidney disease. *J. Control. Release* **2021**, *329*, 1198–1209. [CrossRef]
98. Abbasian, M.; Bighlari, P.; Mahmoodzadeh, F.; Acar, M.H.; Jaymand, M. A de novo formulation of metformin using chitosan-based nanomicelles for potential diabetes therapy. *J. Appl. Polym. Sci.* **2019**, *136*, 48037. [CrossRef]
99. Chinnaiyan, S.K.; Karthikeyan, D.; Gadela, V.R. Development and characterization of metformin loaded pectin nanoparticles for T2 diabetes mellitus. *Pharm. Nanotechnol.* **2018**, *6*, 253–263. [CrossRef]
100. Rehman, A.; Jafari, S.M.; Tong, Q.; Riaz, T.; Assadpour, E.; Aadil, R.M.; Khan, S. Drug nanodelivery systems based on natural polysaccharides against different diseases. *Adv. Colloid Interface Sci.* **2020**, *284*, 102251. [CrossRef]
101. Sun, B.; Zhang, M.; Shen, J.; He, Z.; Fatehi, P.; Ni, Y. Applications of cellulose-based materials in sustained drug delivery systems. *Curr. Med. Chem.* **2019**, *26*, 2485–2501. [CrossRef] [PubMed]
102. Oprea, M.; Voicu, S.I. Recent advances in applications of cellulose derivatives-based composite membranes with hydroxyapatite. *Materials* **2020**, *13*, 2481. [CrossRef]
103. Xu, H.; Xu, X.; Li, S.; Song, W.L.; Yu, D.G.; Annie Bligh, S.W. The effect of drug heterogeneous distributions within core-sheath nanostructures on its sustained release profiles. *Biomolecules* **2021**, *11*, 1330. [CrossRef] [PubMed]
104. Pavoni, L.; Perinelli, D.R.; Bonacucina, G.; Cespi, M.; Palmieri, G.F. An overview of micro-and nanoemulsions as vehicles for essential oils: Formulation, preparation and stability. *Nanomaterials* **2020**, *10*, 135. [CrossRef] [PubMed]

105. Shim, G.; Jeong, S.; Oh, J.L.; Kang, Y. Lipid-based nanoparticles for photosensitive drug delivery systems. *J. Pharm. Investig.* **2022**, *52*, 151–160. [CrossRef]
106. Plaza-Oliver, M.; Santander-Ortega, M.J.; Lozano, M.V. Current approaches in lipid-based nanocarriers for oral drug delivery. *Drug Deliv. Transl. Res.* **2021**, *11*, 471–497. [CrossRef]
107. Xu, Y.; Michalowski, C.B.; Beloqui, A. Advances in lipid carriers for drug delivery to the gastrointestinal tract. *Curr. Opin. Colloid Interface Sci.* **2021**, *52*, 101414. [CrossRef]
108. Le, N.T.T.; Cao, V.D.; Nguyen, T.N.Q.; Le, T.T.H.; Tran, T.T.; Hoang Thi, T.T. Soy lecithin-derived liposomal delivery systems: Surface modification and current applications. *Int. J. Mol. Sci.* **2019**, *20*, 4706. [CrossRef]
109. Abd-Rabou, A.A.; Abdelaziz, A.M.; Shaker, O.G.; Ayeldeen, G. Metformin-loaded lecithin nanoparticles induce colorectal cancer cytotoxicity via epigenetic modulation of noncoding RNAs. *Mol. Biol. Rep.* **2021**, *48*, 6805–6820. [CrossRef] [PubMed]
110. Marwah, M.; Magarkar, A.; Ray, D.; Aswal, V.; Bunker, A.; Nagarsenker, M. Glyceryl monostearate: Probing the self assembly of a lipid amenable to surface modification for hepatic targeting. *J. Phys. Chem. C* **2018**, *122*, 22160–22169. [CrossRef]
111. Ngwuluka, N.C.; Kotak, D.J.; Devarajan, P.V. Design and characterization of metformin-loaded solid lipid nanoparticles for colon cancer. *AAPS PharmSciTech* **2017**, *18*, 358–368. [CrossRef]
112. Kaurav, H.; Manchanda, S.; Dua, K.; Kapoor, D.N. Nanocomposites in controlled; targeted drug delivery systems. *Nano Hybrids Compos.* **2018**, *20*, 27–45. [CrossRef]
113. Kumar, S.; Nehra, M.; Dilbaghi, N.; Tankeshwar, K.; Kim, K.H. Recent advances and remaining challenges for polymeric nanocomposites in healthcare applications. *Prog. Polym. Sci.* **2018**, *80*, 1–38. [CrossRef]
114. Shariatinia, Z. Biopolymeric nanocomposites in drug delivery. In *Advanced Biopolymeric Systems for Drug Delivery*; Springer: Cham, Switzerland, 2020; pp. 233–290.
115. Shariatinia, Z.; Zahraee, Z. Controlled release of metformin from chitosan–based nanocomposite films containing mesoporous MCM-41 nanoparticles as novel drug delivery systems. *J. Colloid Interface Sci.* **2017**, *501*, 60–76. [CrossRef]
116. Karabasz, A.; Bzowska, M.; Szczepanowicz, K. Biomedical applications of multifunctional polymeric nanocarriers: A review of current literature. *Int. J. Nanomed.* **2020**, *15*, 8673. [CrossRef] [PubMed]
117. Avramović, N.; Mandić, B.; Savić-Radojević, A.; Simić, T. Polymeric nanocarriers of drug delivery systems in cancer therapy. *Pharmaceutics* **2020**, *12*, 298. [CrossRef] [PubMed]
118. Nagarajan, V.; Mohanty, A.K.; Misra, M. Perspective on polylactic acid (PLA) based sustainable materials for durable applications: Focus on toughness and heat resistance. *ACS Sustain. Chem. Eng.* **2016**, *4*, 2899–2916. [CrossRef]
119. Abasian, P.; Ghanavati, S.; Rahebi, S.; Nouri Khorasani, S.; Khalili, S. Polymeric nanocarriers in targeted drug delivery systems: A review. *Polym. Adv. Technol.* **2020**, *31*, 2939–2954. [CrossRef]
120. Sena, S.; Sumeyra, K.N.; Ulkugul, G.; Sema, A.; Betul, K.; Muge, S.B.; Gunduz, O. Controlled release of metformin hydrochloride from core-shell nanofibers with fish sarcoplasmic protein. *Medicina* **2019**, *55*, 682. [CrossRef]
121. Mir, M.; Ahmed, N.; ur Rehman, A. Recent applications of PLGA based nanostructures in drug delivery. *Colloids Surf. B Biointerfaces* **2017**, *159*, 217–231. [CrossRef]
122. Lagreca, E.; Onesto, V.; Di Natale, C.; La Manna, S.; Netti, P.A.; Vecchione, R. Recent advances in the formulation of PLGA microparticles for controlled drug delivery. *Prog. Biomater.* **2020**, *9*, 153–174. [CrossRef]
123. Cesur, S.; Cam, M.E.; Sayın, F.S.; Su, S.; Harker, A.; Edirisinghe, M.; Gunduz, O. Metformin-Loaded Polymer-Based Microbubbles/Nanoparticles Generated for the Treatment of Type 2 Diabetes Mellitus. *Langmuir* **2021**, *38*, 5040–5051. [CrossRef]
124. Ghosal, K.; Agatemor, C.; Špitálsky, Z.; Thomas, S.; Kny, E. Electrospinning tissue engineering and wound dressing scaffolds from polymer-titanium dioxide nanocomposites. *Chem. Eng. J.* **2019**, *358*, 1262–1278. [CrossRef]
125. Shahriar, S.M.; Mondal, J.; Hasan, M.N.; Revuri, V.; Lee, D.Y.; Lee, Y.K. Electrospinning nanofibers for therapeutics delivery. *Nanomaterials* **2019**, *9*, 532. [CrossRef]
126. Li, Y.; Zhu, J.; Cheng, H.; Li, G.; Cho, H.; Jiang, M.; Zhang, X. Developments of advanced electrospinning techniques: A critical review. *Adv. Mater. Technol.* **2021**, *6*, 2100410. [CrossRef]
127. Huang, Z.X.; Wu, J.W.; Wong, S.C.; Qu, J.P.; Srivatsan, T.S. The technique of electrospinning for manufacturing core-shell nanofibers. *Mater. Manuf. Process.* **2018**, *33*, 202–219. [CrossRef]
128. Wang, J.; Jansen, J.A.; Yang, F. Electrospraying: Possibilities and challenges of engineering carriers for biomedical applications—A mini review. *Front. Chem.* **2019**, *7*, 258. [CrossRef] [PubMed]
129. Li, H.; Chen, X.; Lu, W.; Wang, J.; Xu, Y.; Guo, Y. Application of electrospinning in antibacterial field. *Nanomaterials* **2021**, *11*, 1822. [CrossRef] [PubMed]
130. Sperling, L.E.; Reis, K.P.; Pranke, P.; Wendorff, J.H. Advantages and challenges offered by biofunctional core–shell fiber systems for tissue engineering and drug delivery. *Drug Discov. Today* **2016**, *21*, 1243–1256. [CrossRef]
131. Lu, Y.; Huang, J.; Yu, G.; Cardenas, R.; Wei, S.; Wujcik, E.K.; Guo, Z. Coaxial electrospun fibers: Applications in drug delivery and tissue engineering. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **2016**, *8*, 654–677. [CrossRef] [PubMed]

132. Han, D.; Steckl, A.J. Coaxial electrospinning formation of complex polymer fibers and their applications. *ChemPlusChem* **2019**, *84*, 1453–1497. [CrossRef] [PubMed]
133. Tabakoglu, S.; Kołbuk, D.; Sajkiewicz, P. Multifluid electrospinning for multi-drug delivery systems: Pros and cons, challenges, and future directions. *Biomater. Sci.* **2023**, *11*, 37–61. [CrossRef]
134. Tapia-Hernández, J.A.; Torres-Chávez, P.I.; Ramírez-Wong, B.; Rascón-Chu, A.; Plascencia-Jatomea, M.; Barreras-Urbina, C.G.; Rodríguez-Félix, F. Micro-and nanoparticles by electrospray: Advances and applications in foods. *J. Agric. Food Chem.* **2015**, *63*, 4699–4707. [CrossRef]
135. Rodríguez-Félix, F.; Del-Toro-Sánchez, C.L.; Javier Cinco-Moroyoqui, F.; Juárez, J.; Ruiz-Cruz, S.; López-Ahumada, G.A.; Tapia-Hernández, J.A. Preparation and Characterization of Quercetin-Loaded Zein Nanoparticles by Electrospraying and Study of In Vitro Bioavailability. *J. Food Sci.* **2019**, *84*, 2883–2897. [CrossRef]
136. Dhiman, A.; Suhag, R.; Singh, A.; Prabhakar, P.K. Mechanistic understanding and potential application of electrospraying in food processing: A review. *Crit. Rev. Food Sci. Nutr.* **2021**, *62*, 8288–8306. [CrossRef]
137. Zhou, H.; Modi, S.; Biswas, P. Controlled synthesis of charged lignin nanocarriers by electrospray. *Colloids Surf. A Physicochem. Eng. Asp.* **2022**, *648*, 129314. [CrossRef]
138. He, T.; Jokerst, J.V. Structured micro/nano materials synthesized via electrospray: A review. *Biomater. Sci.* **2020**, *8*, 5555–5573. [CrossRef]
139. Cao, Y.; Liu, F.; Chen, Y.; Yu, T.; Lou, D.; Guo, Y.; Ran, H. Drug release from core-shell PVA/silk fibroin nanoparticles fabricated by one-step electrospraying. *Sci. Rep.* **2017**, *7*, 11913. [CrossRef]
140. Gómez-Mascaraque, L.G.; Tordera, F.; Fabra, M.J.; Martínez-Sanz, M.; Lopez-Rubio, A. Coaxial electrospraying of biopolymers as a strategy to improve protection of bioactive food ingredients. *Innov. Food Sci. Emerg. Technol.* **2019**, *51*, 2–11. [CrossRef]
141. Barreras-Urbina, C.G.; Ramírez-Wong, B.; López-Ahumada, G.A.; Burruel-Ibarra, S.E.; Martínez-Cruz, O.; Tapia-Hernández, J.A.; Rodriguez Felix, F. Nano-and micro-particles by nanoprecipitation: Possible application in the food and agricultural industries. *Int. J. Food Prop.* **2016**, *19*, 1912–1923. [CrossRef]
142. Rivas, C.J.M.; Tarhini, M.; Badri, W.; Miladi, K.; Greige-Gerges, H.; Nazari, Q.A.; Elaissari, A. Nanoprecipitation process: From encapsulation to drug delivery. *Int. J. Pharm.* **2017**, *532*, 66–81. [CrossRef] [PubMed]
143. Pulingam, T.; Foroozandeh, P.; Chuah, J.-A.; Sudesh, K. Exploring Various Techniques for the Chemical and Biological Synthesis of Polymeric Nanoparticles. *Nanomaterials* **2022**, *12*, 576. [CrossRef]
144. Liu, Y.; Yang, G.; Zou, D.; Hui, Y.; Nigam, K.; Middelberg, A.P.; Zhao, C.X. Formulation of nanoparticles using mixing-induced nanoprecipitation for drug delivery. *Ind. Eng. Chem. Res.* **2019**, *59*, 4134–4149. [CrossRef]
145. Lince, F.; Marchisio, D.L.; Barresi, A.A. Strategies to control the particle size distribution of poly-ε-caprolactone nanoparticles for pharmaceutical applications. *J. Colloid Interface Sci.* **2008**, *322*, 505–515. [CrossRef]
146. Lammari, N.; Louaer, O.; Meniai, A.H.; Elaissari, A. Encapsulation of essential oils via nanoprecipitation process: Overview, progress, challenges and prospects. *Pharmaceutics* **2020**, *12*, 431. [CrossRef]
147. Yan, X.; Bernard, J.; Ganachaud, F. Nanoprecipitation as a simple and straightforward process to create complex polymeric colloidal morphologies. *Adv. Colloid Interface Sci.* **2021**, *294*, 102474. [CrossRef]
148. Bilgin, S.; Tomovska, R.; Asua, J.M. Surfactant-free high solids content polymer dispersions. *Polymer* **2017**, *117*, 64–75. [CrossRef]
149. Errezma, M.; Mabrouk, A.B.; Magnin, A.; Dufresne, A.; Boufi, S. Surfactant-free emulsion Pickering polymerization stabilized by aldehyde-functionalized cellulose nanocrystals. *Carbohydr. Polym.* **2018**, *202*, 621–630. [CrossRef]
150. Tao, J.; Chow, S.F.; Zheng, Y. Application of flash nanoprecipitation to fabricate poorly water-soluble drug nanoparticles. *Acta Pharm. Sin. B* **2019**, *9*, 4–18. [CrossRef]
151. Sharratt, W.N.; Lee, V.E.; Priestley, R.D.; Cabral, J.T. Precision Polymer Particles by Flash Nanoprecipitation and Microfluidic Droplet Extraction. *ACS Appl. Polym. Mater.* **2021**, *3*, 4746–4768. [CrossRef]
152. Nelemans, L.C.; Buzgo, M.; Simaite, A. Optimization of protein precipitation for high-loading drug delivery systems for immunotherapeutics. *Proceedings* **2021**, *78*, 29. [CrossRef]
153. Morales-Cruz, M.; Flores-Fernández, G.M.; Morales-Cruz, M.; Orellano, E.A.; Rodriguez-Martinez, J.A.; Ruiz, M.; Griebenow, K. Two-step nanoprecipitation for the production of protein-loaded PLGA nanospheres. *Results Pharma Sci.* **2012**, *2*, 79–85. [CrossRef] [PubMed]
154. Sree, S.; Patra, A.; Prasath, V.A.; Kambhampati, V.; Xiao, H.W. Innovations in Electrospinning Techniques for Nanomaterial Synthesis and its applications in the field of Active Food Packaging. *J. Future Foods* **2025**, *in press*.
155. Pereira, A.D.S.B.F.; de Souza Lima, M.L.; da Silva-Junior, A.A.; dos Santos Silva, E.; de Araújo Júnior, R.F.; Martins, A.A.; de Araújo, A.A. In vitro-in vivo availability of metformin hydrochloride-PLGA nanoparticles in diabetic rats in a periodontal disease experimental model. *Pharm. Biol.* **2021**, *59*, 1574–1582. [CrossRef] [PubMed]
156. Chenthamara, D.; Subramaniam, S.; Ramakrishnan, S.G.; Krishnaswamy, S.; Essa, M.M.; Lin, F.H.; Qoronfleh, M.W. Therapeutic efficacy of nanoparticles and routes of administration. *Biomater. Res.* **2019**, *23*, 20. [CrossRef]

157. Ciolacu, D.E.; Nicu, R.; Ciolacu, F. Cellulose-based hydrogels as sustained drug-delivery systems. *Materials* **2020**, *13*, 5270. [CrossRef] [PubMed]
158. Migdadi, E.M.; Courtenay, A.J.; Tekko, I.A.; McCrudden, M.T.; Kearney, M.C.; McAlister, E.; Donnelly, R.F. Hydrogel-forming microneedles enhance transdermal delivery of metformin hydrochloride. *J. Control. Release* **2018**, *285*, 142–151. [CrossRef]
159. Rostamkalaei, S.S.l.; Akbari, J.; Saeedi, M.; Morteza-Semnani, K.; Nokhodchi, A. Topical gel of Metformin solid lipid nanoparticles: A hopeful promise as a dermal delivery system. *Colloids Surf. B Biointerfaces* **2019**, *175*, 150–157. [CrossRef]
160. Bose, T.; Latawiec, D.; Mondal, P.P.; Mandal, S. Overview of nano-drugs characteristics for clinical application: The journey from the entry to the exit point. *J. Nanoparticle Res.* **2014**, *16*, 2527. [CrossRef]
161. Kim, J.; De Jesus, O. Medication Routes of Administration. In *StatPearls [Internet]*; StatPearls Publishing: Treasure Island, FL, USA, 2023.
162. Lari, A.S.; Zahedi, P.; Ghourchian, H.; Khatibi, A. Microfluidic-based synthesized carboxymethyl chitosan nanoparticles containing metformin for diabetes therapy: In vitro and in vivo assessments. *Carbohydr. Polym.* **2021**, *261*, 117889. [CrossRef]
163. Zhu, J.; Ye, H.; Deng, D.; Li, J.; Wu, Y. Electrospun metformin-loaded polycaprolactone/chitosan nanofibrous membranes as promoting guided bone regeneration membranes: Preparation and characterization of fibers, drug release, and osteogenic activity in vitro. *J. Biomater. Appl.* **2020**, *34*, 1282–1293. [CrossRef] [PubMed]
164. Rad, A.N.; Shams, G.; Safdarian, M.; Khorsandi, L.; Grillari, J.; Makhmalzadeh, B.S. Metformin loaded cholesterol-lysine conjugate nanoparticles: A novel approach for protecting HDFs against UVB-induced senescence. *Int. J. Pharm.* **2020**, *586*, 119603.
165. Qu, L.; Dubey, N.; Ribeiro, J.S.; Bordini, E.A.; Ferreira, J.A.; Xu, J.; Bottino, M.C. Metformin-loaded nanospheres-laden photocrosslinkable gelatin hydrogel for bone tissue engineering. *J. Mech. Behav. Biomed. Mater.* **2021**, *116*, 104293. [CrossRef]
166. Shukla, S.K.; Kulkarni, N.S.; Chan, A.; Parvathaneni, V.; Farrales, P.; Muth, A.; Gupta, V. Metformin-encapsulated liposome delivery system: An effective treatment approach against breast cancer. *Pharmaceutics* **2019**, *11*, 559. [CrossRef]
167. Esmaeili, A.; Pourkhodabakhshi, F. Loading Metformin/Nettle Extract Lamium album L. subsp. Crinitum in Porous Hollow Silica Nanoparticle Coated by the Layer-by-Layer Method. *Silicon* **2020**, *12*, 521–534. [CrossRef]
168. Bhujbal, S.; Dash, A.K. Metformin-loaded hyaluronic acid nanostructure for oral delivery. *AAPS PharmSciTech* **2018**, *19*, 2543–2553. [CrossRef] [PubMed]
169. Farajzadeh, R.; Pilehvar-Soltanahmadi, Y.; Dadashpour, M.; Javidfar, S.; Lotfi-Attari, J.; Sadeghzadeh, H.; Zarghami, N. Nano-encapsulated metformin-curcumin in PLGA/PEG inhibits synergistically growth and hTERT gene expression in human breast cancer cells. *Artif. Cells Nanomed. Biotechnol.* **2019**, *46*, 917–925. [CrossRef]
170. Javidfar, S.; Pilehvar-Soltanahmadi, Y.; Farajzadeh, R.; Lotfi-Attari, J.; Shafiei-Irannejad, V.; Hashemi, M.; Zarghami, N. The inhibitory effects of nano-encapsulated metformin on growth and hTERT expression in breast cancer cells. *J. Drug Deliv. Sci. Technol.* **2018**, *43*, 19–26. [CrossRef]
171. Nurani, M.; Akbari, V.; Taheri, A. Preparation and characterization of metformin surface modified cellulose nanofiber gel and evaluation of its anti-metastatic potentials. *Carbohydr. Polym.* **2017**, *165*, 322–333. [CrossRef]
172. Amirsaadat, S.; Jafari-Gharabaghlou, D.; Alijani, S.; Mousazadeh, H.; Dadashpour, M.; Zarghami, N. Metformin and Silibinin co-loaded PLGA-PEG nanoparticles for effective combination therapy against human breast cancer cells. *J. Drug Deliv. Sci. Technol.* **2021**, *61*, 102–107. [CrossRef]
173. Song, M.; Xia, W.; Tao, Z.; Zhu, B.; Zhang, W.; Liu, C.; Chen, S. Self-assembled polymeric nanocarrier-mediated co-delivery of metformin and doxorubicin for melanoma therapy. *Drug Deliv.* **2021**, *28*, 594–606. [CrossRef]
174. Ossai, E.C.; Madueke, A.C.; Amadi, B.E.; Ogugofor, M.O.; Momoh, A.M.; Okpala, C.O.R.; Njoku, O.U. Potential enhancement of metformin hydrochloride in lipid vesicles targeting therapeutic efficacy in diabetic treatment. *Int. J. Mol. Sci.* **2021**, *22*, 2852. [CrossRef]
175. Ebrahimnejad, P.; Rezaeiroshan, A.; Babaei, A.; Khanali, A.; Aghajanshakeri, S.; Farmoudeh, A.; Nokhodchi, A. Hyaluronic Acid-Coated Chitosan/Gelatin Nanoparticles as a New Strategy for Topical Delivery of Metformin in Melanoma. *BioMed Res. Int.* **2023**, *2023*, 3304105. [CrossRef]
176. Naghizadeh, A.; Salehi, M.A.; Mivehi, L. Response surface methodology study of extended-time metformin/Glibenclamide drug delivery system from polycaprolactone/Polyethylene glycol electrospun nanofibers. *J. Polym. Res.* **2023**, *30*, 237. [CrossRef]
177. Kianfar, E. Protein nanoparticles in drug delivery: Animal protein, plant proteins and protein cages, albumin nanoparticles. *J. Nanobiotechnol.* **2021**, *19*, 159. [CrossRef]
178. Hsu, C.Y.; Allela, O.Q.B.; Hussein, A.M.; Mustafa, M.A.; Kaur, M.; Alaraj, M.; Farhood, B. Recent advances in polysaccharide-based drug delivery systems for cancer therapy: A comprehensive review. *Artif. Cells Nanomed. Biotechnol.* **2024**, *52*, 564–586. [CrossRef]
179. Lu, W.; Yu, L.; Wang, L.; Liu, S.; Li, M.; Wu, Z.; Hao, H. Metformin hydrochloride mucosal nanoparticles-based enteric capsule for prolonged intestinal residence time, improved bioavailability, and hypoglycemic effect. *AAPS PharmSciTech* **2022**, *24*, 31. [CrossRef] [PubMed]

180. Jain, A.K.; Upadhyay, R.; Mishra, K.; Jain, S.K. Gastroretentive metformin loaded nanoparticles for the effective management of type-2 diabetes mellitus. *Curr. Drug Deliv.* **2022**, *19*, 93–103. [CrossRef] [PubMed]
181. Gilbert, E.A.; Livingston, J.; Garcia-Flores, E.; Kehtari, T.; Morshead, C.M. Metformin improves functional outcomes, activates neural precursor cells, and modulates microglia in a sex-dependent manner after spinal cord injury. *Stem Cells Transl. Med.* **2023**, *12*, 415–428. [CrossRef]
182. Mohamed, H.A.; Mohamed, N.A.; Macasa, S.S.; Basha, H.K.; Adan, A.M.; Crovella, S.; Abou-Saleh, H. Metformin-loaded nanoparticles reduce hyperglycemia-associated oxidative stress and induce eNOS phosphorylation in vascular endothelial cells. *Sci. Rep.* **2024**, *14*, 30870. [CrossRef]
183. Cheng, M.; Ren, L.; Jia, X.; Wang, J.; Cong, B. Understanding the action mechanisms of metformin in the gastrointestinal tract. *Front. Pharmacol.* **2024**, *15*, 1347047. [CrossRef]
184. Kaplan, A.B.U.; Cetin, M.; Bayram, C.; Yildirim, S.; Taghizadehghalehjoughi, A.; Hacimuftuoglu, A. In vivo evaluation of nanoemulsion formulations for metformin and repaglinide alone and combination. *J. Pharm. Sci.* **2023**, *112*, 1411–1426. [CrossRef] [PubMed]
185. Chen, N.X.; Su, X.L.; Feng, Y.; Liu, Q.; Tan, L.; Yuan, H.; Peng, Y.B. Chitosan nanoparticles for sustained release of metformin and its derived synthetic biopolymer for bone regeneration. *Front. Bioeng. Biotechnol.* **2023**, *11*, 1169496. [CrossRef]
186. Yang, X.; Lai, Q.; Yang, X.; Xie, B.; Zhang, B.; Zhang, X.; Wei, Y. Recent development and advances in the fabrication and biomedical applications of nanoparticle-based drug delivery systems for metformin. *Mater. Chem. Front.* **2022**, *6*, 128–144. [CrossRef]
187. Hu, M.; Gou, T.; Chen, Y.; Xu, M.; Chen, R.; Zhou, T.; Ye, Q. A novel drug delivery system: Hyodeoxycholic acid-modified metformin liposomes for type 2 diabetes treatment. *Molecules* **2023**, *28*, 2471. [CrossRef]
188. Đorđević, S.; Gonzalez, M.M.; Conejos-Sánchez, I.; Carreira, B.; Pozzi, S.; Acúrcio, R.C.; Vicent, M.J. Current hurdles to the translation of nanomedicines from bench to the clinic. *Drug Deliv. Transl. Res.* **2022**, *12*, 500–525. [CrossRef]
189. Metselaar, J.M.; Lammers, T. Challenges in nanomedicine clinical translation. *Drug Deliv. Transl. Res.* **2020**, *10*, 721–725. [CrossRef] [PubMed]
190. Shi, W.; Fuad, A.R.M.; Li, Y.; Wang, Y.; Huang, J.; Du, R.; Yin, T. Biodegradable polymeric nanoparticles increase risk of cardiovascular diseases by inducing endothelium dysfunction and inflammation. *J. Nanobiotechnol.* **2023**, *21*, 65. [CrossRef] [PubMed]
191. Alenazi, F.; Saleem, M.; Khaja, A.S.S.; Zafar, M.; Alharbi, M.S.; Hagbani, T.A.; Ahmad, S. Metformin encapsulated gold nanoparticles (MTF-GNPs): A promising antiglycation agent. *Cell Biochem. Funct.* **2022**, *40*, 729–741. [CrossRef] [PubMed]
192. Yeşildağ, A.; Kızıloğlu, H.T.; Dirican, E.; Erbaş, E.; Gelen, V.; Kara, A. Anticarcinogenic effects of Gold nanoparticles and Metformin Against MCF-7 and A549 cells. *Biol. Trace Elem. Res.* **2024**, *202*, 4494–4507. [CrossRef]
193. Yao, F.; Zhu, P.; Chen, J.; Li, S.; Sun, B.; Li, Y.; Zou, M.; Qi, X.; Liang, P.; Chen, Q. Synthesis of nanoparticles via microfluidic devices and integrated applications. *Microchim. Acta* **2023**, *190*, 256. [CrossRef]