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Pharmacological and Nanotechnological Insights into SGLT-2 Inhibitors for Type 2 Diabetes Management

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Abstract: Sodium-glucose cotransporter-2 (SGLT-2) inhibitors signify a novel approach in the management of diabetes, focusing on the SGLT-2 proteins within the kidneys that are responsible for the reabsorption of glucose. The main issues associated with SGLT-2 inhibitors have been inadequate solubility and limited oral bioavailability. This review elucidates the mechanism of action of SGLT-2 inhibitors. It examines preclinical investigations of these inhibitors, both alone and in combination, conducted in rat or mouse models over the past several decades. This review discusses the need to advance nanoformulations to enhance the therapeutic efficacy of SGLT-2 inhibitors. This review presents a thorough examination of nanocarrier-based drug delivery systems specifically for SGLT-2 inhibitors, emphasizing the latest developments in polymeric nanoparticles, self-microemulsifying and self-nanoemulsifying systems, nanosuspensions, solid lipid nanoparticles, and nanostructured lipid carriers. This review also provides a comprehensive update on the patent literature on SGLT-2 inhibitors over the past two years.

Keywords: canagliflozin; dapagliflozin; empagliflozin; nanotechnology; sodium-glucose cotransporter-2; type 2 diabetes Mellitus.

1. Introduction

SGLT-2 inhibitors provide an innovative approach to treat diabetes by targeting the sodium-glucose cotransporter-2 proteins in the kidneys, which are responsible for glucose reabsorption. These transporters are ideal targets for treating type 2 diabetes because they account for nearly 90% of filtered glucose reabsorption. The Food and Drug Administration has approved the four SGLT-2 selective inhibitors for the management of type 2 diabetes, which include canagliflozin (Invokana®), Dapagliflozin (Farxiga®), empagliflozin (Jardiance®), and ertugliflozin (Steglatro®) (Figure 1). Nowadays, diabetes has been a primary global cause of death and represents a significant health risk of the twenty-first century. It is expected that this condition would impact 380 million individuals worldwide by 2025 [1-3]. Over the past several decades, changes in lifestyle, culture, and social connections have led to

a marked rise in the incidence of diabetes and obesity in both developed and developing countries [4,5]. The primary consequence of diabetes progression is the development of chronic diseases, which reduce patient life expectancy, place burdens on the healthcare system, and elevate diabetes death rates [6,7]. The majority of diabetic individuals have type 2 diabetes, which is defined by insulin resistance or inadequate production of insulin. In contrast, type 1 diabetes is brought about by the absence of insulin due to pancreatic cell death. Furthermore, diabetes in pregnancy is referred to as "gestational diabetes" [8,9].

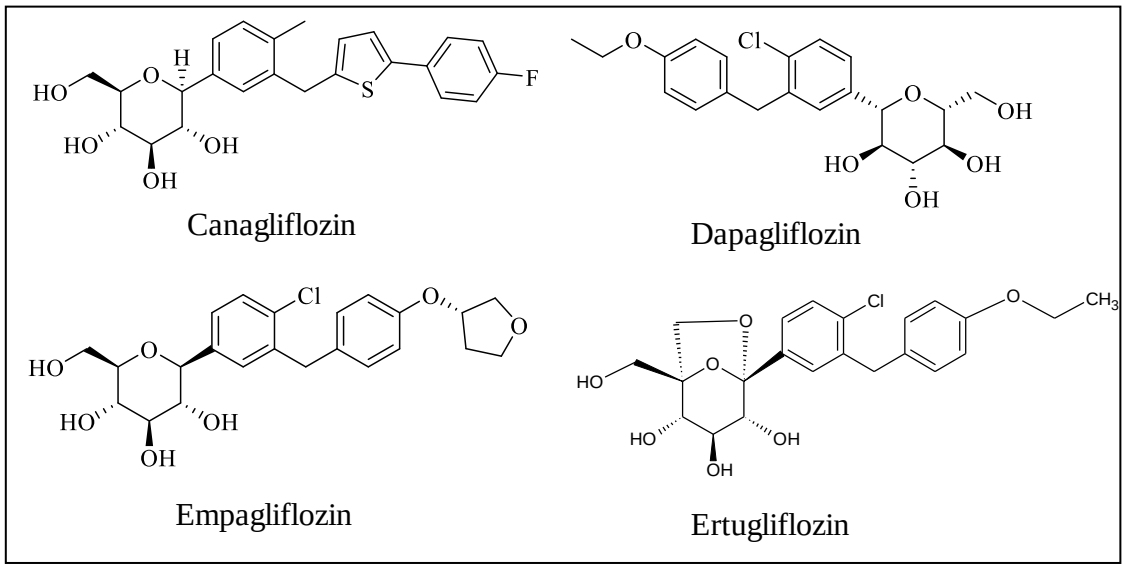

Figure 1. Chemical structures of SGLT-2 inhibitors.

This review highlights the pharmacokinetics and mechanism of action of SGLT-2 inhibitors. It also reviews preclinical investigations of SGLT-2 inhibitors, alone or in combination, conducted in rat or mouse models over the past several decades. The primary concerns with SGLT-2 inhibitors have been poor solubility and oral bioavailability. This review examines the need to develop nanoformulations to improve the therapeutic effectiveness of SGLT-2 inhibitors. This review offers a comprehensive overview of nanocarrier-based drug delivery systems for SGLT-2 inhibitors, highlighting recent advancements in polymeric nanoparticles, self-microemulsifying and self-nanoemulsifying systems, nanosuspensions, solid lipid nanoparticles, and nanostructured lipid carriers. This review also provides an update on the patent literature on SGLT-2 inhibitors over the past 2 years.

2. Role of Environmental Factors in Type II Diabetes Mellitus

Environmental factors associated with the etiopathogenesis of diabetes include pollution, dietary influences, age, genetic predispositions, and vitamin D insufficiency [10]. Endocrine disruptors can interfere with physiological processes, including hormone production and metabolism [11]. The consumption of unhealthy foods rich in refined carbs, sugars, and saturated fatty acids can cause diabetes. It has been believed that the glycated chemicals present in diet soft drinks considerably increase insulin resistance [12]. Fructose, omega-6 industrial seed oils, and cereal grains are the three principal dietary components that can induce diabetes. Excessive consumption of these chemicals increases the chance of getting diabetes, particularly in the presence of a genetic predisposition [13,14]. Ageing is a substantial risk factor for several disorders associated with insulin resistance and metabolic dysregulation [15]. Vitamin D and

its metabolites may help prevent type 2 diabetes by increasing insulin secretion and β-cell activity. It has been found that vitamin D deficiency can increase insulin resistance by elevating the p-p65/RelB ratio [16,17].

3. SGLT-2 Inhibitors: New-fangled Medicines for Diabetes Mellitus

Type II diabetes mellitus results from excessive hyperglycemia, driven by altered feedback mechanisms between insulin production and action. The body's ability to monitor physiological glucose levels is compromised when cellular dysfunction results from diminished insulin production [18-21]. β-cells detect plasma glucose levels and release insulin via the GLUT-2 transporter [22-25]. In the glomerulus's proximal convoluted tubule (PCT), glucose is rapidly filtered and reabsorbed. The filtered glucose load, which produces glycosuria, exceeds the tubular maximum for glucose in patients with poorly managed type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM). Before their blood glucose levels exceed 180 mg/dL, healthy adults do not exhibit glycosuria [26-28]. Glucose is reabsorbed via glucose transporters because it is polar and cannot pass through the PCT membrane. There are two sodium-glucose co-transporters in the apical membrane of the PCT [29]. The first segment (S1) of PCT, which contains the high-capacity/low-affinity co-transporter SGLT-2, and the second and third segments of PCT, which contain the high-affinity/low-capacity glucose/galactose transporter, are responsible for 90% of the reabsorbed glucose (proximal straight tubule) [30]. SGLT2 inhibitors function by inhibiting SGLT2 proteins in the kidneys, thereby reducing glucose reabsorption and increasing urinary glucose excretion [31-33]. The mechanisms of action of these drugs in the management of T2DM are schematically illustrated in Figure 2.

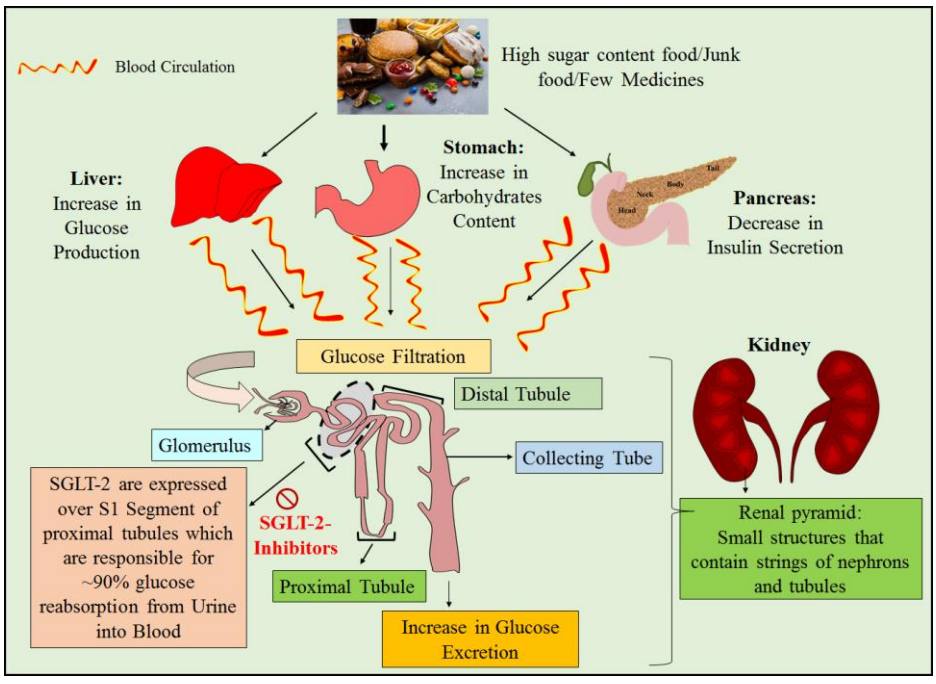

Figure 2. Schematic representation of the mechanism of action of SGLT-2 inhibitors.

The half-lives of orally administered canagliflozin at doses of 100 mg and 300 mg in healthy subjects were 10.6 hours and 13.1 hours, respectively. It showed a 150-160-fold selectivity for SGLT2 over SGLT1 [34,35]. Administration of 10 mg of dapigliflozin resulted in 78% bioavailability and a half-life of 12.9 hours. Dapigliflozin is a potent and selective

inhibitor of SGLT2, with 1,200-fold selectivity over SGLT1 [36,37]. The oral bioavailability of empagliflozin was modest in rats (31%), but excellent in mice (90-97%) and dogs (89%). The elimination half-life of empagliflozin was 13.1 hours, while it ranges from 11 to 18 hours for ertugliflozin. Empagliflozin exhibited selectivity of 2,500-fold for SGLT2 relative to SGLT1, whereas ertugliflozin demonstrates selectivity of approximately 2,200-fold [38-40]. Combining SGLT2 inhibitors with other antidiabetic drugs was highly beneficial, likely due to their additional therapeutic effects, including weight loss, blood pressure reduction, cardioprotection, and renoprotection. SGLT2 inhibitors facilitate renal glucose excretion and carry a negligible risk of hypoglycemia; consequently, they are preferred drugs for the management of T2DM and cardiovascular health [41-43].

4. Pre-clinical Status of SGLT-2 Inhibitors

The first SLGT-2 inhibitor approved in the US was canagliflozin, which has substantially lower SGLT-2 selectivity [44]. The synergies between SGLT-2 inhibitors and other antidiabetic drugs arise from their distinct, additive mechanisms of action, which target different pathways to lower blood glucose levels, enhance insulin sensitivity, and confer additional benefits such as weight and blood pressure reduction. Medications such as metformin, voglibose, and pioglitazone reduce hepatic glucose production and enhance insulin sensitivity, whereas SGLT-2 inhibitors promote renal glucose excretion through an insulin-independent mechanism [45,46]. No reports of adverse drug interactions with other drugs have been recorded. Preclinical investigations related to SGLT-2 inhibitors for T2DM have been summarized in Table 1. However, the constrained sample sizes in preclinical studies often pose substantial challenges, such as diminished statistical power and issues with data reproducibility, which frequently culminate in a high failure rate during clinical translation. Variations among species, the intricacies of human disease, and shortcomings in preclinical study design are significant contributors to clinical translation failure [47].

Table 1. Recapitulation of the preclinical investigations of SGLT-2 inhibitors in combination therapy for the management of type 2 diabetes mellitus.

Route	Drug	Dose	Research outcomes	Animal model	Ref.
Canagliflozin					
p.o.	Canagliflozin and Berberine	100 mg/kg/day alone or in combination	Significant reduction in fasting blood glucose and exhibited a marked decrease in postprandial glucose and $AUC_{0\text{-}2}$h values.	Mice	[48]
p.o.	Canagliflozin and Telmisartan	20 or 40 mg/kg/day + 5 or 10 mg/kg/day	The study revealed decreases in serum glucose levels from 257.2 mg/dL to 162.2 mg/dL and 228.5 mg/dL, and reductions in HbA1c to 7.9% and 8.4%, respectively, with canagliflozin 40 mg and telmisartan 10 mg in diabetic groups compared with controls.	Rat	[49]
p.o.	Canagliflozin and Teneligliptin	3 or 10 mg/kg + 0.3 mg/kg each alone or in combination	A study showed a 15-minute increase in basal plasma aGLP-1 levels from 0.20 pmol/L to 0.90 pmol/L, compared with the vehicle-treated group. Plasma DPP4 activity was inhibited by approximately 75%, indicating that, in combination, plasma glucose levels were suppressed, thereby improving glucose intolerance.	Rat	[50]
p.o.	Canagliflozin and Pioglitazone	10 mg/kg each alone or in combination	The study showed reductions in plasma glucose and HbA1c levels to 142.6±4.5 mg/dL and 3.4±0.11%, respectively, compared with 518.4±12.8 mg/dL and 8.1±0.17% in the control group. It showed a reduction in	Rat	[51]

Route	Drug	Dose	Research outcomes	Animal model	Ref.
			pioglitazone-induced weight gain (480.7±8.5 g vs. 533.6±5.7 g).		
p.o	Canagliflozin and Metformin	10 mg/kg +100 mg/kg	Both drugs significantly reduced elevated serum glucose levels in streptozotocin-induced obese T2DM rats.	Rat	[52]
			Dapagliflozin		
p.o.	Lansoprazole and Dapagliflozin	40 mg/kg + 0.5 mg/kg	A study showed a significant reduction in body weight with lansoprazole and dapagliflozin, alone or in combination, by 0.43-, 0.52-, and 0.58-fold, respectively, indicating that the combination improved insulin sensitivity via activation of PPARγ and Glut2 and reduced insulin resistance.	Rat	[53]
p.o.	Dapagliflozin	0.1 to 1.0 mg/kg for 2 weeks once daily	The study revealed potent SGLT2 inhibition (EC50 = 1.12 ± 0.07 nmol/L), >1200-fold selectivity over SGLT1, a 400-fold increase in urinary excretion, and a reduction in plasma glucose, indicating potential efficacy for lowering glucose levels.	Rat	[54]
p.o.	Dapagliflozin and Metformin	1 mg/kg+350 mg/kg for 6 weeks	The study showed that combination treatment reduced urinary albumin excretion by 39%, reflecting improved renal filtration, whereas dapagliflozin reduced oxidative stress by decreasing MDA levels and increasing antioxidant enzymes, with SOD increasing by 202% and GSH by 113%.	Rat	[55]
p.o.	Dapagliflozin and Voglibose	1.0 mg/kg + 0.6 mg/kg	Blood glucose levels were elevated in diabetic control rats (168.6 ± 17.9 mg/dL) compared with non-diabetic controls (94.7 ± 1.2 mg/dL) and were reduced by treatment with dapagliflozin (116.6 ± 1.7 mg/dL) and voglibose (123.3 ± 6.2 mg/dL), indicating improved glycemic control.	Rat	[56]
p.o.	Dapagliflozin	60 mg/L for 9 weeks	Exhibited improved glucose tolerance (51.6±2.3 vs 110.6±3.9 µmol/min/kg), glucose uptake in muscle (0.9±0.1 vs 1.7±0.3 µmol/min/100 g), and adipose tissue GLUT4 protein levels (0.78 ± 0.05 vs 1.20 ± 0.09 arbitrary units).	Rat	[57]
p.o.	Dapagliflozin and Exetanide	1 mg/kg + 0.03 mg/kg/day for 4 weeks	Blood glucose, HbA1c, and plasma creatinine were significantly lowered, while GFR was increased.	Mice	[58]
p.o.	Dapagliflozin and Irbesartan	2 mg/kg+ 30 mg/kg/day each alone or in combination	Showed significant reductions in kidney weights, blood glucose levels, and HbA1c, while increasing sRAGE levels, indicating improved glycemic control	Rat	[59]
p.o.	Dapagliflozin and Metformin	1 mg/kg+30 mg/kg/day for 4 weeks	The study found that plasma glucose levels during the oral glucose tolerance test were significantly higher in high-fat diet-fed rats than in non-diabetic rats. Body weight was reduced, and glucose tolerance was improved by suppressing renal glucose release.	Rat	[60]
p.o.	Dapagliflozin	50 mg/1000 g diet	Showed reduction in glucose-stimulated glucagon stimulation to 50 pg/ml, lowered HbA1c to <6%, and increased glycogen, increased glucose infusion rate by 2.9-fold. It was found to be effective in lowering glucose levels by suppressing hepatic glucagon secretion.	Rat	[61]
			Empagliflozin		
p.o.	Empagliflozin	1 or 3 mg/kg	The study showed multiple daily doses reduced fasting blood glucose by 26–39%, decreased HbA1c (from 7.9% by 0.3–1.1%), and increased urinary glucose excretion, indicating improved glycemic control.	Rat	[62]

Route	Drug	Dose	Research outcomes	Animal model	Ref.
p.o.	Empagliflozin	300 mg/kg of diet for 15 weeks	A study showed enhanced renal SGLT2 expression by 47%, reduced renal SGLT1 membrane protein expression by 33–37%, increased urinary glucose-to-creatinine ratios and absolute urinary glucose concentrations, and reduced blood glucose concentration by 60%.	Mice	[63]
p.o.	Linagliptin and Empagliflozin	3 mg//kg linagliptin + 10 mg//kg empagliflozin for 8 weeks daily alone or in combination	Empagliflozin and linagliptin alone exhibited a significant reduction in plasma glucose from 15.3±4.6 to 6.8±2.3 and 12.2±5.2 mmol/L, and HbA1c levels from 7.9±0.9% to 6.2±0.6% and 7.5±1.1%. In combination therapy, glucose levels decreased to 6.1±3.5 mmol/L and HbA1c to 5.9±0.6%.	Mice	[64]
p.o.	Empagliflozin, sibutramine, or Orlistat	10 mg/kg+5 mg/kg or 20 mg/kg	The combination treatment showed reductions in plasma glucose, insulin, and HOMA-IR of 5.73±0.31 mM, 0.82±0.12 ng/mL, and 4.67±0.72, respectively, compared with control.	Rat	[65]

p.o.: per oral

5. Prerequisite of Nanocarriers for Therapeutic Delivery of SGLT-2 Inhibitors and their Recent Advancements

According to the biopharmaceutical classification system, canagliflozin and ertugliflozin are classified as class IV and class I drugs, respectively, whereas Dapagliflozin and Empagliflozin are classified as class III drugs [66-70]. Nano-formulations have been explored to enhance therapeutic bioavailability, target-site specificity, and absorption of poorly soluble drugs [71-74]. Polymeric nanoparticles achieve high entrapment efficiency and exhibit prolonged, constant drug release, typically following zero-order kinetics. These nanocarriers tend to improve bioavailability by maintaining the drug concentrations within the therapeutic window for a prolonged period [75,76]. Self-emulsifying drug delivery systems (SEDDS) enhance dissolution by allowing the drug to dissolve within the lipid system rather than being encapsulated in a carrier matrix. SEDDS has been highly appropriate for maximizing the solubility and bioavailability of poorly water-soluble drugs [77-79]. The encapsulation efficiency of solid lipid nanoparticles (SLNs) is limited and prone to drug expulsion during storage.

In contrast, it is higher for nanostructured lipid carriers (NLCs) owing to their disordered structure and greater drug solubility in liquid lipids. The drug release from SLN is sustained and prolonged, while it is controllable and tunable for NLC with long-term stability. The bioavailability of NLC is superior to that of SLN [80-83]. Nanosuspensions primarily enhance dissolution rates due to their nanoscale particle size, thereby increasing bioavailability. In nanosuspensions, nanocrystals are suspended in a medium with stabilizers [84,85]. Figure 3 provides structural details of nanocarriers investigated for these drugs, and Figure 4 lists the benefits and drawbacks of various nanocarriers in pharmaceutical delivery.

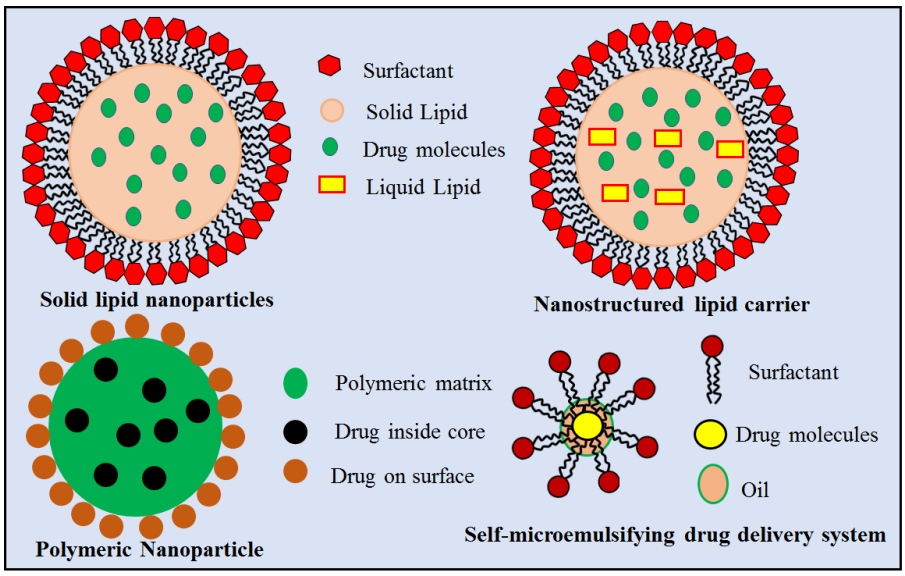

Figure 3. The pictorial representation of nanocarriers researched for therapeutic delivery of SGLT-2 inhibitors.

	Advantages	Disadvantages
Polymeric Nanoparticle	•Improves dissolution of poor soluble drugs •Provides better protection to encapsulated drugs •Provides sustained and controlled drug delivery	•Toxicity concern, use of organic solvents, stability issue
SEDDS	•Forms fine droplets that improves the absorption by lymphatic uptake •Protection from enzymatic and chemical degradation •Cost effective and simple processing make it commercially scalable	•Greater risk of oxidation and polymorphic instability due to lipid excipients
Nanosuspension	•Small particle size improves dissolution and solubility •Modified pharmacokinetics boosts drug safety and efficacy •Permits passive targeting due to nano-size	•Choice of stabilizer is challenging and not suitable for all drugs •Risk of physical instability
Solid lipid nanoparticle	•Improves bioavailability of poor soluble drugs •Improves lymphatic uptake, release, absorption and residence time •Topically, provides better sun protection	•Crystallinity changes and low drug loading can cause leakage •Agglomeration can lead to particle growth
Nanostructured lipid carriers	•Enhances stability and bioavailability of hydrophobic drugs •Improves drug loading capacity and stability •Provides excellent biocompatibility	•Instability over time leads to phase separation and precipitation

Figure 4. Overview of the merits and demerits of several nanocarriers in pharmaceutical delivery.

5.1. Polymeric nanoparticles.

These nanoparticles offer a promising approach to overcoming drug-delivery challenges, facilitating targeted and controlled drug release. These nanoparticles typically range in size from 10 to 1000 nm and can be formed as nanospheres or nanocapsules [86-88]. Various methods, including solvent evaporation, nanoprecipitation, and emulsion, are used to produce polymeric nanoparticles. Nanoparticles can be used to deliver pharmaceuticals with high drug-loading efficiency and controlled release profiles [89,90]. A study has shown that

increasing polymer concentration can enhance encapsulation efficiency, and in vitro dissolution studies have revealed sustained drug release over several hours [91].

5.2. Self-emulsifying drug delivery systems and nanosuspension.

Self-nanoemulsifying drug delivery systems (SNEDDS) are advanced formulations that enhance the oral bioavailability of poorly soluble drugs, facilitate solubilization, and promote absorption [92-94]. The study has shown that SMEDDS/SNEDDS can increase the drug release, C_{max}, and bioavailability as compared to free or marketed drugs, making them an effective method for enhanced drug delivery [95]. Nanosuspensions, or colloidal biphasic dispersions, have drug particles smaller than a nanometer and a faster dissolution rate due to their increased surface area and saturation solubility [96,97]. There are two approaches to formulating nanosuspensions, *i.e.*, top-down and bottom-up. In the bottom-up technique, the drug is precipitated by adding a nonsolvent, forming nanoparticles. Top-down technologies include high-pressure homogenization, media milling, the emulsion diffusion approach, and the supercritical fluid method [98]. These can be used to improve a drug's solubility and increase its maximum plasma levels. The reduced particle size allowed intravenous delivery of poorly soluble drugs without causing blood capillary blockage. Nanosuspensions can be converted into a solid matrix via lyophilization [99].

5.3. Solid lipid nanoparticles and nanostructured lipid carriers.

SLNs comprise a solid lipid core stabilized by surfactants and are designed to enhance drug delivery and reduce toxicity, using physiological lipids to minimize challenges. SLNs are particularly beneficial for lipophilic drugs, enhancing bioavailability and enabling targeted delivery [100-104]. Using the hot homogenization technique, SLNs of Dapagliflozin showed a significant increase in Cmax, AUC, and Tmax compared with the free and marketed drugs [105]. NLCs can be divided into distinct forms depending on lipid content and formulation factors. The lipid and surfactant components play an essential role in determining the stability, sustained-release behavior, and drug-loading capacity of NLCs. A study has indicated that dapagliflozin NLCs exhibited enhanced drug-delivery characteristics, including dual-release patterns and an initial rapid release followed by sustained release [67]. Table 2 examines the outlook on preparation techniques, excipients used, and research outcomes of nanocarrier-based formulation strategies for SGLT-2 inhibitors in the management of T2DM.

Table 2. Summary of current state-of-the-art in nanoparticle-based delivery systems for SGLT-2 inhibitors for the management of type II diabetes mellitus.

Formulation	Method of preparation	Excipients	Research outcomes	Ref.
Canagliflozin				
Solid supersaturable self-microemulsifying drug delivery system	Spray drying	Lauroglycol FCC, tween 80, transcutol-P, and Poloxamer 188	The C_{max}(ng/ml) increased from 1092.83 ± 67.43(pure drug) and 2232.14 ± 189.53(marketed product) to 3159.04 ± 198.27, Tmax (hours) was decreased from 2.42 ± 0.52 (pure drug) and 2.37 ± 0.94(marketed product) to 1.06 ± 0.35 h. Moreover, AUC0–36h (ng·h/mL) increased significantly from 7017.44 ± 1045.87 (pure drug) and 12,698.50 ± 1358.7 (marketed product) to 26,103.33 ± 1424.8 for the SS-SMEDD formulation, indicating increased oral bioavailability.	[106]
Nanosuspension	Wet media milling	Poloxamer 407, sodium starch glycolate, corn starch, Kyron T	The nanosuspension was solidified into immediate-release pellets, which released 89.59% of the drug within 10 minutes.	[68]

Formulation	Method of preparation	Excipients	Research outcomes	Ref.
		314, and microcrystalline cellulose		
Self-microemulsifying drug delivery system	Emulsification technique	Tween 80, lauroglycol FCC, labrasol, cremophor EL, labrafil M1944CS, ethyl oleate, polyethylene glycol 400	Compared with free and commercial formulations, SMEDDS showed a 2.56-fold increase in C_{max} and AUC_{0-24h}. Following oral administration, C_{max} and AUC increased by 2620 ± 983.42 and 32370.0 ± 1954.56, respectively, within 24 hours.	[107]
Dapagliflozin				
Solid lipid nanoparticles	Hot homogenization	Compritol 888 ATO and tween 80	The study showed that dapagliflozin-SLNs exhibited a more prolonged release (69.23 ± 2.35% in 8 hours) than the pure drug (37.85 ± 4.26%), and the Cmax (µg/mL) of the commercial product was 621.57 ± 0.52, increasing to 1258.37 ± 1.21 in the SLNs formulation. The AUC((mcg/mL) of SLNs-treated group increased considerably from 113.03 ± 0.19 to 6310.89 ± 0.04 when compared to the marketed product-treated group.	[105]
Nanostructured lipid carriers	High-pressure homogenization	Labrasol and tween-20	NLCs and plain dispersion of dapagliflozin exhibited %CDR of 90.01±2.01% and 31.54±1.87%, respectively, over 24 hours, indicating sustained-release behaviour required for oral delivery.	[67]
Solid self-nanoemulsifying drug delivery system tablets	Fusion method	Poloxamer 188, capryol 90, PEG 6000, polyethylene glycol 4000, and cremophore EL	The %CDR within 25 minutes from three-dimensional printed self-nanoemulsifying tablets of 8-, 10-, and 12-mm diameters was 95.27%±0.21, 89.27%±0.15, and 89.87%±0.12, respectively, indicating >75.0% drug release within 20 minutes.	[108]
Solid self-nanoemulsifying oral delivery system	Emulsification	Tween 80, polyethylene glycol 400, eucalyptus oil	The % cumulative drug released from S-SNEDDS within 10 minutes was 60.34±4.54% as compared to 38.33±1.78% released from the pure drug dispersion within 60 minutes.	[109]
Self-nanoemulsifying drug delivery systems (Dapagliflozin and Sitaglipitin)	Emulsification	Black seed oil, soybean oil, Maisen M35-1, Capmul MCM, thymoquinone, and Cremophor EL	SNEDDS showed a significant increase in C_{max} (1.99 ± 0.21 µg/ml), AUC (17.94 ± 1.25 µg/ml), and oral absorption (2-fold) of dapagliflozin compared with the marketed drug product.	[110]
Empagliflozin				
Polymeric nanoparticles	Emulsification solvent evaporation	Ethyl cellulose and Eudragit RL100, ethyl cellulose and hydroxypropyl methylcellulose K100 polymer	Encapsulation efficiency (%) of the drug polymers across different ratios ranged from 68.38 to 95.82, increasing with increasing polymer amount. *In vitro* dissolution tests over 10 hours showed that all formulations had drug release percentages ranging from 89.75% to 97.93%.	[91]
Alginate-chitosan nanocarriers	Gelatin method	$CaCl_2$, sodium alginate, and chitosan	The nanocarrier showed higher drug loading in chitosan calcium alginate than in calcium alginate and exhibited controlled release at pH 6.8 and 7.4, whereas at pH 1.2, the drug was released within 2 hours.	[111]

6. An Outlook on Patent Literature of SGLT-2 Inhibitors

The recent patents on SGLT-2 inhibitors for the management of diabetes mellitus are reviewed and organized in Table 3. These patents were governed by several patent offices, including the World Intellectual Property Organization (WIPO), the United States of America (US), China (CN), the European Patent Office (EP), and India (IN). The advantages of patenting pharmaceutical inventions include recovering research and development costs and

sharing scientific results, which benefit the broader research community and stimulate economic growth in the pharmaceutical industry. Nevertheless, rising medication costs, which reduce affordability, and delayed generic entry may pose public health risks [112].

Table 3. The enumeration of the current patent status of SGLT-2 inhibitors, either alone or in combination therapy, with reference to patent title, patent number, applicant, and publication date.

Patent title	Patent number	Applicant	Publication date	Ref.
Canagliflozin				
Use of Canagliflozin in the preparation of a drug for treating nodular sclerosis-mediated disease.	WO2022161510	Sir Run Hospital, Nanjing Medical University	04.08.2022	[113]
Use of Canagliflozin in the preparation of an antitumor drug.	US20220062316	Zhejiang University	03.03.2022	[114]
Canagliflozin for the treatment of diabetic patients with chronic kidney disease.	EP3946367	Janssen Pharmaceutical NV	09.02.2022	[115]
Application of Canagliflozin and analogs thereof in the preparation of medicine for preventing and treating male reproductive dysfunction.	CN113908152	Peking University	11.01.2022	[116]
Dapagliflozin				
A pharmaceutical composition comprising a combination of dapagliflozin and sitagliptin.	WO2023012817	Unison Pharmaceuticals Pvt. Ltd.	09.02.2023	[117]
A sachet formulation comprising Metformin and Dapagliflozin.	EP4125824	SanovelIlac Sanayi VE Ticaret Anonim Sirketi	08.02.2023	[118]
Oral complex tablet comprising Sitagliptin, Dapagliflozin, and Metformin.	EP4112047	Hanmi Pharm Ind Co Ltd	04.01.2023	[119]
Pharmaceutical composition comprising dapagliflozin.	EP4106732	Zakl Farmaceutyczne Polpharma S A	28.12.2022	[120]
Processes for preparation of dapagliflozin or its solvates or co-crystals thereof.	US20220372010	Laurus Labs Limited	24.11.2022	[121]
Effervescent tablet formulations comprising Dapagliflozin and Metformin.	EP4031122	Sanovel Ilac Sanayi VE Ticaret Anonim Sirketi	27.07.2022	[122]
Combination of Zibotentan and Dapagliflozin for the treatment of chronic kidney disease.	WO2022009163	AstraZeneca AB	13.01.2022	[123]
Application of Dapagliflozin and analogues thereof in the preparation of medicine for preventing and treating male reproductive dysfunction.	CN113893349	Peking University	07.01.2022	[124]
Empagliflozin				
Therapeutic uses of Empagliflozin.	EP4119136	Boehringer IngelheimInt	18.01.2023	[125]
Lactose-free formulation of Empagliflozin using direct compression process.	WO2022180444	Dr. Jayesh Dwivedi, Shailendra Mandge	01.09.2022	[126]
Pharmaceutical composition comprising an Empagliflozin co-crystal.	WO2022124749	Chong Kun Dang Pharmaceutical Corp.	16.06.2022	[127]
Metformin hydrochloride sustained-release, Empagliflozin quick-release pellet, and preparation method thereof.	CN114469896	Limited Responsibility Company of Jiangsu Wanbang Biochemical Medicine Group	13.05.2022	[128]

7. Conclusions and Future Perspectives

Combination therapy is often employed in the complex therapeutic approach necessary to manage type 2 diabetes. Despite the availability of anti-diabetic drugs, achieving glycemic control in patients with diabetes mellitus remains an enormous challenge. Hyperglycemia-related conditions, such as cardiovascular and renal disorders, are common in people with diabetes. Research on the application of nanotechnology to the treatment of type 2 diabetes has demonstrated improved pharmacokinetic performance. Nanocarriers, such as solid lipid nanoparticles, polymer nanoparticles, nanosuspensions, and SMEDDS, can be reshaped to alter their size and shape, thereby enhancing bioavailability and mitigating restricted solubility.

Further research on SGLT-2 inhibitors and their nanoformulations is expected to improve T2DM treatment by identifying new potential inhibitors and optimizing delivery systems.

Significant challenges in the translation of nanocarriers include large-scale development, a complex and evolving regulatory landscape, and ensuring long-term safety and biological compatibility [129,130]. Batch-to-batch variation in the manufacturing of nanoparticles with consistent size, shape, and drug encapsulation efficiency is a significant hurdle for regulatory approval. The large-scale production of nanoparticles requires expensive, specialized equipment, reducing cost-effectiveness and limiting access to nanocarrier-based therapies. The regulatory framework for nanomedicines is still evolving, and a use-case-by-case, risk-based approach to their approval creates uncertainty for organizations. The lack of standardized methods for nanoparticle characterization makes it challenging to translate research findings across various stages of development and meet regulatory requirements. Nanoparticles pose a related concern regarding long-term safety due to potential toxicity arising from accumulation in organs and tissues over time. The immunogenicity of nanoparticles remains a concern regarding long-term effects. The potential neurotoxic effects of nanoparticles crossing the blood-brain barrier require specialized risk assessments. The nanoparticles are growing a growing concern about ecological footprint and environmental hazards [131-133].

Author Contributions

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Conflict of Interest

The authors declare no conflict of interest.

Abbreviations

Abbreviation	Definition
NLCs	Nanostructured Lipid Carriers
PCT	Proximal Convoluted Tubule
PPAR	Proliferator-activated Receptor
SGLT-2	Sodium-glucose Cotransporter-2
SEDDS	Self-emulsifying Drug Delivery System
SLNs	Solid lipid Nanoparticles
SNEDDS	Self-nanoemulsifying Drug Delivery Systems
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus

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