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PERSPECTIVE

SGLT-2i: Nanoparticular-Based Strategies, Solutions, and Clinical Applications in Opposition to Low Bioavailability

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Abstract

Purpose Although SGLT-2i initially acquired prominence for usage in diabetes, they later emerged as the top medication class in both cardiovascular diseases and disorders. However, they still do not have the proper bioavailability (50–70%); therefore, it has different options such as using either a higher dose amount or dose frequency.

Methods The aim of this review is focusing on current trials of SGLT-2i with less side effects and improved patient compliance, which lead to different options such as using either a higher dose amount or dose frequency.

Results With the acceleration of clinical studies, it would not be surprising to witness the introduction of SGLT-2i nano-based systems as a commercial product in the upcoming years.

Conclusion Research on SGLT-2i-based systems is being conducted to facilitate the development of new drug delivery methods such as microemulsion and self-nanoemulsifying drug delivery system.

Keywords Cardiovascular disease · Bioavailability · Nanoapproaches · SGLT-2 inhibitors · New drug delivery systems · Diabetes · Side effects

Abbreviations

ADA	American Diabetes Association
BCS	Biopharmaceutical Classification System
DECLARE	Dapagliflozin Effect on Cardiovascular Events study
DM	Diabetes mellitus
DPP-4I	Dipeptidyl peptidase 4 inhibitor
EASD	European Association for the Study of Diabetes
EMA	European Medicine Agency
FDA	Food and Drug Agency
GI	Gastrointestinal system
GLP-1 RA	Glucagon-like peptide 1 receptor agonist
HF	Heart failure
LVEF	Left ventricular ejection fraction
MLNS	Multilayer nanosponge formulation
NHE_3	Sodium hydrogen exchanger
PLGA	Poly (D,L-lactide-co-glycolide)
SGLT-2i	Sodium-glucose co-transporter-2 inhibitors
SNEDD	Self-nanoemulsifying drug delivery system
T2DM	Type II diabetes mellitus

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Teaser

Nowadays, high doses, increased dosing frequency, and low bioavailability drug treatments have become paramount [1, 2]. Therefore, development of nano-based systems, low doses and increased bioavailability will end up with higher patient compliance and an improved response to treatment.

Introduction

Diabetes is recognized as an independent risk factor for cardiovascular disease in both men and women. The rate of cardiovascular disease progression in diabetic patients is three times higher than in non-diabetic patients. Cardiovascular diseases have been reported as the cause of death in approximately 65% of people with diabetes [3]. T2DM is the most diagnosed DM type worldwide. Regarding the 2017 diabetes epidemiology study, 485 million people were affected by diabetes, which corresponds to 6.82% of the entire world

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population. So, prevalence is shown to enhance the ratio to 7.3% dramatically by 2050 [3, 4].

One of the antidiabetic drugs used to ensure glycemic control, which is one of the agents suitable for use in all stages of diabetes independent of insulin, is SGLT-2i which is grouped as "glucoretics" or "gliflozins" [1]. SGLT-2i is one of the most frequently used oral antidiabetic agents, which has a mechanism of action to reduce glucose absorption via SGLT2 in the renal proximal tubules, increasing the amount of glucose excreted in the urine as well [5].

Likewise, SGLT-2i are not only effective in T2DM treatment; it has also been proven that SGLT-2i have an effect on reducing the risk of heart failure (HF) and cardiovascular mortality in 2020. In a study conducted on 6243 patients (HF with left ventricular ejection fraction (LVEF)) in 20 countries, half of the patients were given dapagliflozin (SGLT-2i) and half of them were given a placebo as well. While cardiovascular mortality was recorded as 8.3% and 7.4%, heart failure was recorded as 14.5% and 11.3% for placebo and dapagliflozin, respectively. Furthermore, the rate of adverse effects was found to be 5.8% in both [6]. After this clinical study, SGLT-2i have been added to the treatment guidelines of the American College of Cardiology/American Heart Association on critical practice as the first choice of HF with LVEF patients [7].

Present Situation

SGLT-2 is co-located in the proximal tubule with renal sodium hydrogen exchanger 3 (NHE3), which is largely responsible for sodium reabsorption, and SGLT-2i cross-reacts with NHE3, inhibiting NHE3 and enhancing natriuresis. In addition, SGLT-2i have not only positive effects on ventricular filling, cardiac metabolism, and ventricular remodeling, but they also have reduced diabetic retinopathy, cardioprotective, and antiarrhythmic effects (Fig. 1) [8–10]. Besides, the positive effects of SGLT2 on hyperglycemia, studies have observed positive effects on weight loss in patients who use SGLT-2i. Even though the weight loss initially expressed is secondary to diuresis, studies have subsequently reported that approximately 2/3 of the weight loss is through adipose tissue. Whereas the presence of SGLT-2i has positive aspects, for instance, weight loss, lowering blood pressure, decreasing uric acid level, and decreasing urinary albumin loss, they have side effects such as urinary system infections, polyuria, hypovolemia, and increased risk of diabetic normoglycemic ketoacidosis [11, 12].

Additionally, 90% of the medications in research and 40% of all pharmaceutical industry-developed medications have low solubility. A scientific categorization method called the Biopharmaceutical Classification System (BCS) is used to categorize a pharmaceutical dosage form's solubility and permeability. The rationale behind this classification is that drug permeability and solubility in dosage forms both have a significant impact on how well a drug is absorbed from the GI tract and the permeability of the drug substance on absorption from the GI tract [2].

Canagliflozin was used in the study by Devineni and Polidori to determine the drug's pharmacokinetic characteristics. Even though canagliflozin (0.053 mg/mL) is rapidly absorbed when taken orally and reaches peak plasma concentrations in 1–2 h, the oral bioavailability presented a very low profile [1] (Fig. 2).

In this context, the existence of the signal which is light on the pros and cons of SGLT-2i indicates required evolving of the new drug delivery systems.

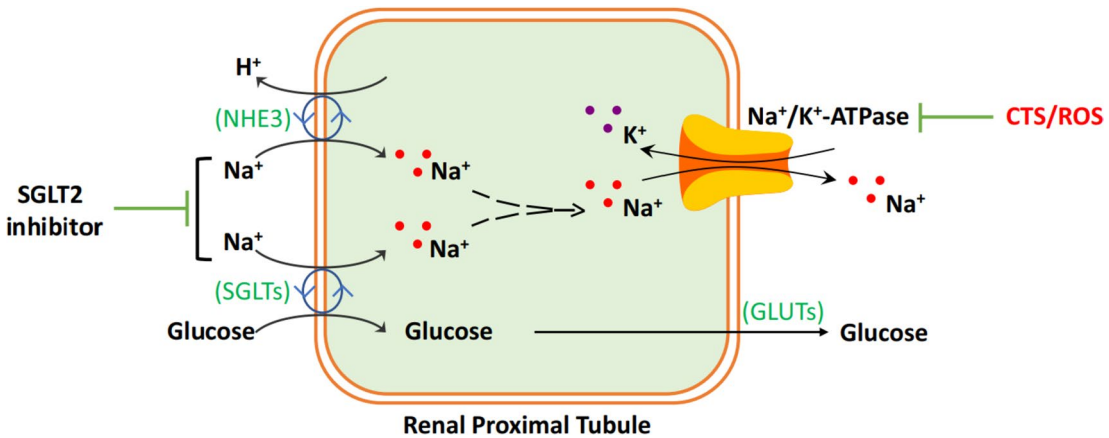

Fig. 1 A schematic image exhibiting the relation between NH3 and SGLT-2 [13] (the right of use belongs to the corresponding author and permission to use was taken from Jiang Liu—permission date: 11/01/2022)

Studies Ongoing to Develop New Drug Delivery Systems

Ikeda et al. have prepared B-cyclodextrin complexes to boost the solubility of nateglinide (SGLT-2i). According to study, planning that the solubility of nateglinide will increase, this will cause both dosage amount and side effects to reduce. Hereby, the β-cyclodextrin complexes allowed the rising resolution from 0.18 to 1.08 mM by increasing the solubility approximately 60% ratio [14].

Zhang et al. have produced biodegradable poly (D,L-lactide-co-glycolide) (PLGA) nanoparticles of saxagliptin (SAX)-dapagliflozin (DAPA) with 455.9 ± 11.4 nm mean size by the coaxial electrospray method. This cutting-edge approach was not only applied to DAPA; SAX has been also involved in the same nanoparticle. There is also one more critical property regarding application of this perspective which is one layer will contain one of these two drugs. So, each layer had one drug substance (SAX or DAPA). Furthermore, the particles' mean zeta potential was found to be -44.5 ± 2.03 mV, and the % yielding was obtained among 89–91. Besides, in vitro release kinetic model observed that burst release is available; MTT test which was not observed any significant cytotoxic effect was performed with mouse fibroblast cells (NIH3T3) against the control group (marketed product of SAX and DAPA) ($p > 0.05$) [15].

There is also one more study available with empagliflozin. Multilayer nanosponge formulation (MLNS) of linagliptin and empagliflozin (combined drug existence in the same carrier) was prepared by Hammadi et al. MLNS's ingredients' ratios were determined facilitating the factorial design model (design of experiment) as a percentage. The optimal MLNS's (30% lipid composition phospholipid to cholesterol, 1:3 w/w) average size was 40.03 ± 4.17 nm, and the buccal film of optimal MLNS reached T_{max}, two times faster than the marketed tablet formulation at in vivo rabbit study with fewer side effect profile (no cytotoxic effects observed based on histopathology study) [2].

Finally, Kazi et al. have worked on dapagliflozin's self-nanoemulsifying drug delivery system (SNEDD). Dapagliflozin (DAP) SNEDD's average droplet size, PDI, and zeta potential were found to be 60.12 ± 4.33 nm, below 0.2, and -17.29 ± 0.41 mV, respectively. Meanwhile, DAP-SNEDD preserved their formation for 3 months at room temperature. DAP-SNEDDS was tested on diabetic mice toward a marketed product, and it was found to be 16.23% more effective than the market product, while it reduced the ratio to 65.32% bringing down to the healthy glucose level compared to the negative control group within 3 h [16].

Clinical Trials

The SGLT-2i bring its advantages along with the side effect profile mentioned above. Hence, the requirement for alternative drug delivery systems has increased. In addition, the use of glucagon-like peptide 1 receptor agonist (GLP-1 RA) together with SGLT-2i is also indicated in the guidelines in order to increase the positive effect on the lipid profile, providing glycemic control as well. There are many studies conducted/completed by the NIH and FDA regarding this issue (Table 1).

The American Diabetes Association® (ADA)/European Association for the Study of Diabetes (EASD) consensus report states that especially in patients with HgbA1C level above 8.5, T2DM treatment has to initiate both with dipeptidyl peptidase 4 inhibitor (DPP-4I) and GLP-1RA [17].

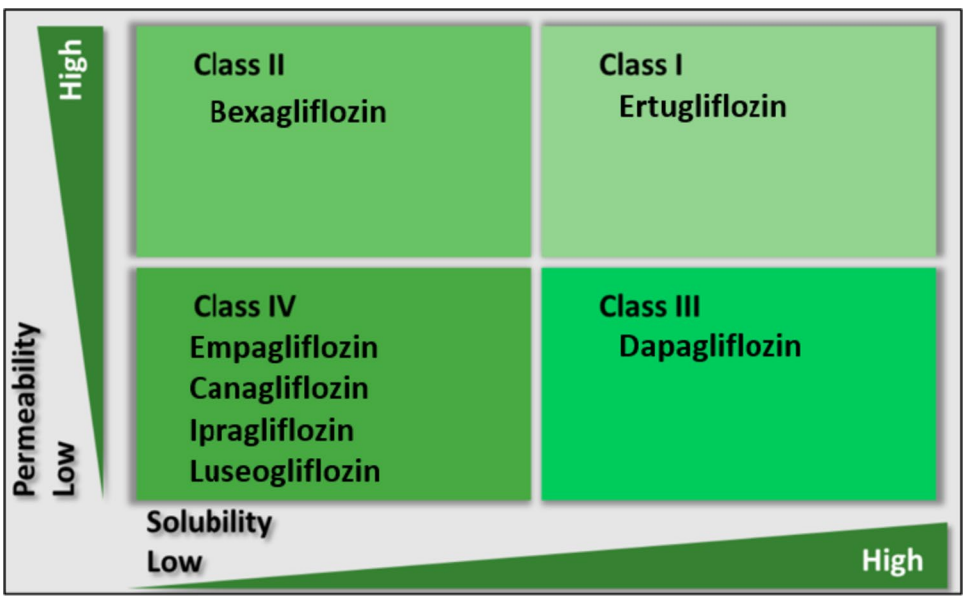

Fig. 2 BCS classification of the SGLT-2Is

The Dapagliflozin Effect on Cardiovascular Events study (DECLARE) presented at the Scientific Sessions Congress in 2018 showed that if the patient has a high cardiovascular risk, first-choice SGLT-2i should be added to DPP-4I. In spite of SGLT-2i being very suitable drugs as a second choice if the patient has no acute conditions/insulin deficiency, care should be taken when taking SGLT-2i for the risk of euglycemic diabetes ketoacidosis in the presence of vice versa situation.

According to the SGLT-2i's clinical trials, besides 12 of these trials are ongoing, 128 of these are completed (Table 1). So, related to SGLT-2i, 144 clinical trials have already been submitted and got approval within the last 2 years. Based on these clinical studies ongoing recently years are focused on combined therapy, on SGLT-2i used in the treatment of genetical disease which occurred to DM in children, and on synthesis new drug molecules. The elaboration of DM due to glycogen deficiency causes progressive disorder in a major sense, especially in infant–toddler age period children. For this reason, it is crucial that the agent used for treatment has the lowest side effect profile and the most selective one. In this context, various NIH-based studies are still carrying on [28–30]. In addition, some of the multicenter studies using SGLT-2i combined with GLP-1RA/DPP-4I have been completed and some are still in progress [19, 21, 22].

Although there are no clinical studies found in terms of the drug carrier systems (microsphere, nanoliposome, polymeric nanoparticles, exc.), several clinical studies are conducted related to the new drug molecule synthesis [3, 22].

Future Aspects

In general, the drug molecules used in the treatment of T2DM have low oral bioavailability (1–2%) due to their degradation by gastrointestinal enzymes, physical and chemical instability, short half-life, low lipophilicity, large molecular weight, and first-pass effect through the liver. In such as these studies to increase oral bioavailability, there are various approaches to chemical modification, development of mucoadhesive delivery systems, the addition of absorption enhancers and protease inhibitors to the formulation, and the development of drug delivery systems as well [31, 32].

Although no clinical study has been carried out with any drug delivery system containing SGLT-2i at present, there are many articles published based on this subject. These studies corresponded to the preliminary studies. While the number of studies published in sci-index registered journals related to diabetes was around 12,900 in 2021 [33], 17,280 studies related to drug delivery/targeted drug delivery were published until November 2022.

Therefore, the positive results of these studies would herald many clinical trial applications in accordance with this field in the very near future. The effectiveness of drug delivery systems will be high, especially in preventing serious effects such as vaginal infection, urogenital infection, and high dehydration, which are seen as common side effects of SGLT-2i [5, 34–36]. Self-nanoemulsifying drug delivery system (SNEDDS), nanoemulsions, solid lipid nanoparticles, and liposomes are among the most studied carrier systems in this field. They consist of oil, surfactant, co-solvent/co-surfactant components.

The advantages of these systems are listed as increasing oral bioavailability and thus reducing the dose, protecting the drugs from the GIS environment, reducing the changes due to food effects (motilation effect), providing high drug loading efficiency, and controlled release. Moreover, T2DM are sensitive to proteolytic enzymes in various parts of the GIS. The acidic nature of the gastric environment and the enzyme activity cause these molecules to be irreversibly digested down into smaller components; their chemical digestion in the stomach is triggered by pepsin as well. Furthermore, pancreatic enzymes such as trypsin, chymotrypsin, exopeptidase, and endopeptidases in the small intestine contribute to the degradation of these drug molecules. Chemical (low pH), biochemical (presence of enzymes), and physical (epithelial) barriers prevent the molecule from entering the bloodstream [11]. For successful absorption in the gastric environment and to prevent degradation by proteases, overcoming the chemical barrier of the GIS, ensuring diffusion through the mucus layer with drug delivery systems, facilitating paracellular transport and transcellular transport are important in overcoming the physical barrier of GIS.

Conclusion

Consequently, according to cumulative data, it is observed that even though clinical studies are focused on both the combination of GLP-1RA-SGLT-2I/DPP-4I-SGLT-2i and the usage of SGLT-2i for patients with different diseases, the individual studies' focal points are new drug delivery systems of SGLT2i. Ongoing studies include the characterization of drug delivery systems, as well as in vitro/in vivo studies of them. Considering these studies, it is being proven that drug delivery systems increased the oral bioavailability of alternative groups (GLP-1 RA, DPP-4i) used in other T2DM, including SGLT-2i as well.

It is thought that the use of the formulations alone/combination is promising. In order to develop drug delivery systems for the treatment of T2DM that can be sold as oral products, it is necessary to conduct food-effect

Table 1 Clinical trials in terms of new molecule/drug delivery/combination strategy regarding SGLT-2i

Clinical trial code	Topic	Location	Participants	Completion date	Company/institute/funders	Reference
NCT01177150	JNJ-28431754 (single escalating oral doses combination drug study)	–	67 male (ages 18–55)	08/11/2019 (6 months)	Johnson & Johnson	[3]
NCT02768220	The effect of SGLT-2I on advanced glycation end products	New York, NY	112	02/15/2020	Northwell Health	[18]
NCT03462069	SAR439954 (study to assess the intestinal, metabolic, and cardiovascular effects of SAR439954 treatment with GLP-1RA)	Berlin, Germany	110	10/20/2019	Sanofi	[19]
NCT03764631	Post-authorization safety study in type 2 diabetic patients in Saudi Arabia treated with empagliflozin to assess the incidence of severe complications	22 different study locations	1502 (ages 18 ≤)	02/10/2022	Boehringer Ingelheim	[20]
NCT05282121	Study to test whether BI 685509 alone or in combination with GLP-1 agonist have T2DM and hypertension	15 different study locations	80 (ages 18–75)	Ongoing (starting date: 11/22/2022)	Boehringer Ingelheim	[21]
NCT03152552	Assess the effect of LIK066 compared to empagliflozin in T2DM	103 different study locations	125 (18 ≤ ages)	Ongoing (starting date: 08/10/2019)	Novartis	[22]
NCT04064073	Study to evaluate drug-drug interaction of DWP16001 in combination with GLP-1RA (phase 1 study)	Peking, China	180 (ages 18 ≤)	Ongoing (starting date: 09/22/2022)	Daewoong Pharma	[23]
NCT05232071	Study to evaluate the safety and efficacy of lanifibranor alone and in combination with the IVA337 (SGLT-2I) T2DM	40 different study locations	63 (ages 18 ≤)	Ongoing (starting date: 06/29/2022)	Inventiva Pharma	[24]
NCT05081219	GLP-1 agonist and treatment with intranasal SGLT-2I (IRB00075)	Winston-Salem, North Caroline	82 (ages 55–85)	Ongoing (starting date: 09/15/2022)	Wake Forest University Health Sciences	[25]
NCT03363464	Comparative effectiveness of empagliflozin in the US	Massachusetts, Boston	230,000 (ages 18 ≤)	Ongoing (starting date: 12/06/2017)	Eli Lilly; Boehringer Ingelheim	[26]

Table 1 (continued)

Clinical trial code	Topic	Location	Participants	Completion date	Company/institute/funders	Reference
NCT03932721	Rationale and design of the expanded combination of evolocumab plus empagliflozin in diabetes: EXCEED-BHS3 trial	Sao Paulo, Brazil	110 (ages 40–70)	Ongoing (starting date: 07/19/2019)	University of Campinas	[27]
NCT04930627	Safety and efficacy of empagliflozin in GSD1b patients with neutropenia (EMPAtia)	Warsaw, Poland	20 (ages 1 month–24 months)	Ongoing (starting date: 06/23/2021)	Children's Memorial Health Institute, Poland	[28]

EMPAtia neutropenia patients related, *GLP-1RA* glucagon-like peptide 1 receptor agonist, *GSD1b* glycogen storage disease type 1B, *SGLT-2i* sodium-glucose co-transporter-2 inhibitors, *T2DM* type II diabetes mellitus

bioavailability studies and clinical studies using experimental animals.

Perspectives

Diabetes is the crucial cause of complications, mortality, and morbidity; the frequency of which is rising worldwide. One of the groundbreaking developments in the treatment of T2DM is the SGLT-2i, which have started to be among the first choices in both cardiology and nephrology guidelines with the additional benefits they provide. In addition, cardiovascular diseases are the primary cause of morbidity and mortality in people with diabetes. In order to prevent diabetes-related cardiovascular complications, glycemic control is not only important, but it is also not enough on its own. Therefore, SGLT-2i are a group of antihyperglycemic drugs with multiple effects used in the treatment of T2DM.

On the other hand, SGLT-2i reduce plasma fasting blood sugar, HbA1C, blood pressure, and plasma lipid levels and decrease body mass index; it has been shown to reduce cardiovascular (CV) death rate and significantly reduce hospitalization for heart failure (HHF) in a large population of T2DM patients as well.

SGLT-2i are related to the increased risk of urinary tract and genital tract infections. It leads to an increase in infections due to glycosuria. For this purpose, studies are being moved forward with drug delivery systems in recent years in terms of both diminishing side effects and boosting bioavailability. Consequently, an appropriate drug delivery system would be a cutting-edge discovery for SGLT-2i. Besides, they could have the potential to be used alone at lower doses, as well as given in combination with other drug groups used in the treatment of T2DM.

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Data Availability It is possible that the authors are presenting the data in accordance with specific requirements.

Declarations

Conflict of Interest The authors declare no competing interests.

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