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The impact of chemical engineering and technological advances on managing diabetes: present and future concepts

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Monitoring blood glucose levels for diabetic patients is critical to achieve tight glycaemic control. As none of the current antidiabetic treatments restore lost functional β-cell mass in diabetic patients, insulin injections and the use of insulin pumps are most widely used in the management of glycaemia. The use of advanced and intelligent chemical engineering, together with the incorporation of micro- and nanotechnological-based processes have lately revolutionized diabetic management. The start of this concept goes back to 1974 with the description of an electrode that repeatedly measures the level of blood glucose and triggers insulin release from an infusion pump to enter the blood stream from a small reservoir upon need. Next to the insulin pumps, other drug delivery routes, including nasal, transdermal and buccal, are currently investigated. These processes necessitate competences from chemists, engineers-alike and innovative views of pharmacologists and diabetologists. Engineered micro and nanostructures hold a unique potential when it comes to drug delivery applications required for the treatment of diabetic patients. As the technical aspects of chemistry, biology and informatics on medicine are expanding fast, time has come to step back and to evaluate the impact of technology-driven chemistry on diabetics and how the bridges from research laboratories to market products are established. In this review, the large variety of therapeutic approaches proposed in the last five years for diabetic patients are discussed in an applied context. A survey of the state of the art of closed-loop insulin delivery strategies in response to blood glucose level fluctuation is provided together with insights into the emerging key technologies for diagnosis and drug development. Chemical engineering strategies centered on preserving and regenerating functional pancreatic β-cell mass are evoked in addition as they represent a permanent solution for diabetic patients.

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1. Introduction to the pathology of diabetes

Diabetes, a group of metabolic diseases defined by a chronically elevated blood glucose level (BGL), is one of the leading causes of premature mortality worldwide. While there are four types of diabetes including type 1 (T1D), type 2 (T2D), pre-diabetes and gestational diabetes, T1D and T2D account for more than 90–95% of the diagnosed forms worldwide, with T2D being the most prominent one reaching 80–85% of the total diabetes.[1]

Type 1 diabetes results from the autoimmune destruction of β-cells, the insulin producing cells within the pancreas, while T2D is characterised by insulin resistance, which corresponds to the deficiency in cellular response to insulin. In non-treated or poorly controlled T1D and T2D, hyperglycaemia and hypoglycaemia, ensue. Hyperglycaemia can lead to a variety of syndromes, notably cardiovascular and neurological complications, while hypoglycaemia results in a lack of energy and ultimately death. At the present time, none of the current antidiabetic treatments restore the functional β-cell mass, although they can manage short-term glycaemia.[2,3] As a consequence, a treatment failure leads to long-term, poor glycaemic control, which results in a progression of the disease into disabilities, infection risks and finally, premature death.[4]

The vast interest in finding treatments of people with diabetes is notably linked to the alarming projections from the world health organisation (WHO), which predicts approximately 700 million people worldwide to be affected by 2045 (Fig. 1).[5,6] Diabetes is thus becoming one of the largest public health challenges globally. Diabetes causes 5 million deaths annually in developed countries, mainly due to cardiovascular disease (50%) and kidney failure (10–20%).[6] Diabetes is also one of the leading causes of blindness, 50% of lower limb amputations, and provokes severe complications

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upon viral infections, like COVID-19.[7] In addition, diabetes increases rapidly at younger ages decreasing considerably the life expectation of the younger generation, becoming lower than that of their parents (Fig. 1).

1.1. Pathophysiology of diabetes

Diabetes is classified, according to pathophysiological mechanisms, into T1D, T2D, and gestational diabetes mellitus, a diabetes diagnosed in the second or third trimester of pregnancy (Fig. 2a).[8] To the three types of diabetes, other types of diabetes, which result from other causes (*e.g.* cystic fibrosis, drug-induced diabetes), have to be added.

In T2D, hyperglycaemia ensues as pancreatic β-cells fail to produce enough insulin to compensate for insulin resistance.[9] The β-cell dysfunction is characterized by impaired insulin secretion in response to glucose (Fig. 2b), which progressively is exacerbated by the loss of β-cell mass (BCM). The risk of developing T2D increases with age, obesity, and lack of physical activity, and is more frequently in women with prior gestational diabetes and in individuals with hypertension or dyslipidaemia.

Type 1 diabetes represents around 10% of the diabetes diagnosed forms and results from autoimmune destruction of the pancreatic β-cells. Genetic factors contribute to the risk of T1D although the environment including virus, bacteria, pollutants and nutrition is the predominant factor. More than 40 susceptible genes have been identified so far, with the gene coding for human leukocyte antigens (HLA) as the predominant one for predicting the risk of T1D. Genetic variation within the HLA gene accounts for approximately 40–50% of familial aggregation of T1D.[10] The rate of β-cell destruction is strongly variable, being rapid in infants and children, and slow in adults. At an advanced stage of T1D, insulin secretion almost vanishes.

Other forms of diabetes include familial and genetic forms of diabetes in which mutations within a single gene potentially lead to defective insulin secretion, as exemplified by Maturity Onset of

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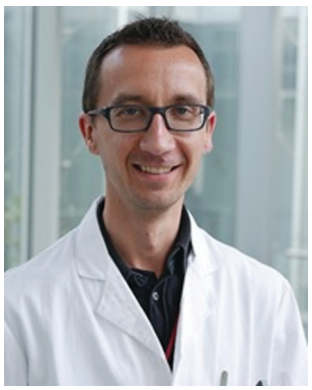

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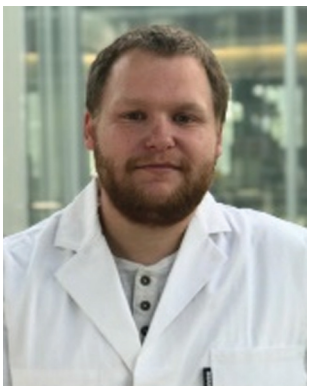

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the Diabetes of the Young (MODY), a group of inherited disorders that account for 1–5% of all cases of diagnosed diabetes and 1–6% of all paediatric diabetes cases. Usually, MODY onset ensues before 45 years of age. The disease is characterized by autosomal dominant inheritance. In other words, only one mutated gene from parents is sufficient to be affected by this type of disorder. Unlike T1D, MODY patients have no β-cell autoimmunity, whereas they have β-cell dysfunction. Mutations in genes playing a key role in β-cell function (BCF) and survival are thought to cause β-cell dysfunction and thereby the onset of MODY. To date, there are 14 types of MODYs (MODY1–14) in which mutations in 14 different genes have been reported.[11] There are other genetic forms of diabetes with congenital or acquired origins including neonatal diabetes.[12] In neonatal diabetes, mutations in genes involved in insulin secretion have been identified and cause diabetes in new-born before 6 months. There are also uncommon forms of immune-mediated diabetes including the autoimmune Stiff-man syndrome and patients with anti-insulin receptor antibodies. Patients with Stiff-man syndrome present stiffness of the axial muscles with painful spasms. These symptoms are accompanied by high glutamic acid decarboxylase (GAD) autoantibodies level, a characteristic shared with T1D. The presence of GAD autoantibodies is supposed to increase the diabetes risk. Approximately one-third of patients with Stiff-man syndrome will develop diabetes. Patients with anti-insulin receptor antibodies are rare and uncommon form of diabetes. In these patients, the anti-insulin receptor antibodies may lead to the inability of insulin to bind insulin receptor in muscle, liver and adipose tissues. The impaired insulin action results in absolute insulin resistance and ultimately diabetes. Such extreme insulin resistance also termed type B insulin resistance is also found in patients with systemic lupus erythematosus. Diabetes can be induced by drugs or chemicals.[1,6,9,13] Many drugs can impair insulin secretion or precipitate diabetes in individuals with insulin resistance. Certain vitamins, drugs and hormones such as the anti-parasite pentamidine, nicotinic acid vitamin and glucocorticoids can impair insulin action. Some patients receiving γ-interferon develop diabetes associated with islet cell antibodies, sometimes leading to severe insulin deficiency. Some endocrinopathies can lead to diabetes. Excess amounts of growth hormones, cortisol, glucagon and epinephrine can potentially lead to acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, causing diabetes.

1.2. Therapeutic strategies

To better design therapeutic strategies, one has to understand the physiological function of insulin (Fig. 3).[14–16] Insulin is produced

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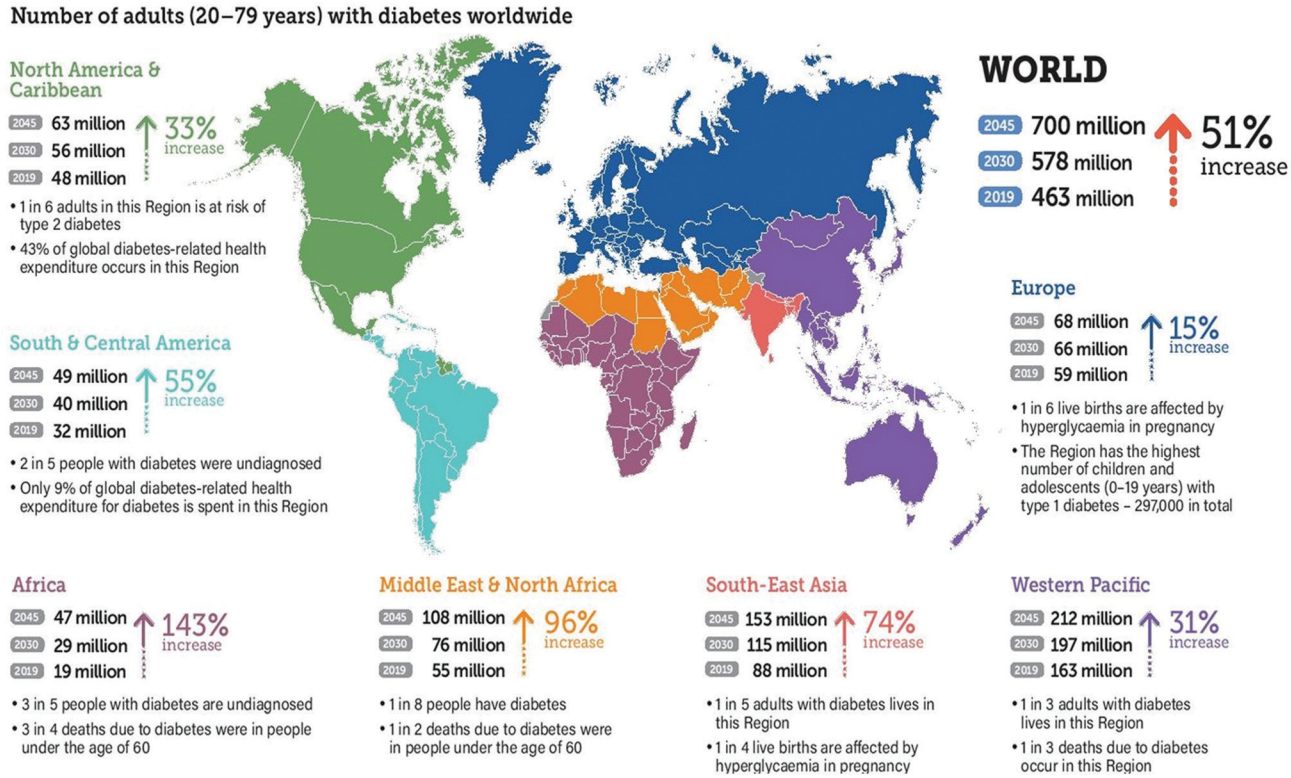

Fig. 1 Worldwide distribution of adults with diabetes. Prediction of the World Health Organisation (WHO) of diabetic patients from 2019 to 2045 in different parts of the world (reproduced from ref. 5 with permission from Elsevier, copyright 2018).

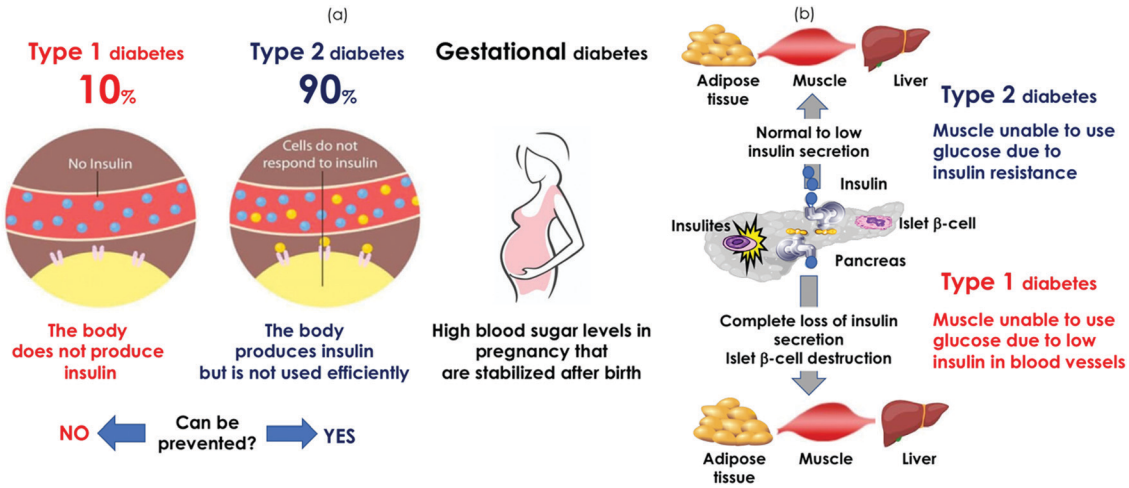

Fig. 2 Pathophysiology of diabetes. (a) Classification of diabetes according to pathophysiological mechanisms. (b) Consequences of relative and absolute deficiency of insulin production by islet β-cells. In T1D, absolute deficiency of insulin, caused by autoimmune destruction of β-cells (insulites), leads to the absence of glucose uptake and metabolism in insulin-sensitive organs including muscle, adipose tissue and liver. Therefore, glucose stays in the blood circulation, possibly leading to diabetic ketoacidosis in the case of a viral infection. In T2D, the insulin-sensitive organs become resistant to insulin action due to the impaired intracellular insulin receptor signalling. Despite the still functioning β-cells, insulin production is insufficient to compensate for insulin resistance (adapted from http://www.patiadiabetes.com/en/patia/diabetes/ and https://visual.ly/community/Infographics/health/diabetes-type-1-diabetes-vs-type-2-diabetes).

in the β-cells localized within the islets of Langerhans. Insulin is released in response to elevated BGLs. The anabolic hormone insulin enables glucose storage in liver, muscle and adipose tissue. Glucose is then transformed into glycogen (liver and muscle) and triglycerides (adipose tissue and liver). As a consequence of the insulin function, glycaemia is restored to normal level. Insulin

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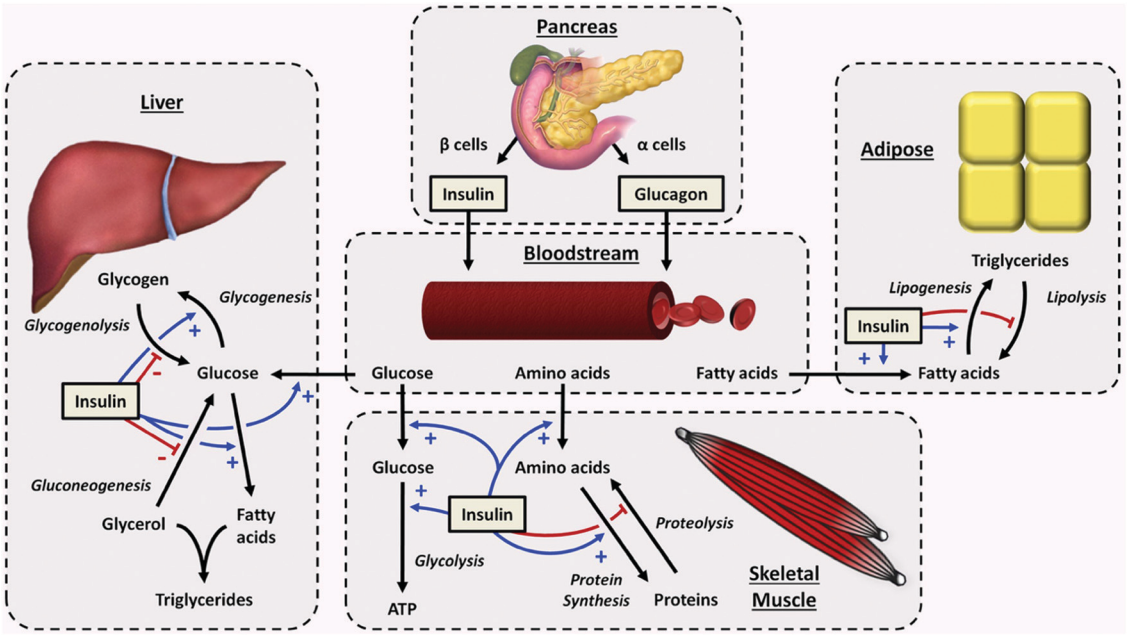

Fig. 3 Physiology of insulin and glucagon. The anabolic insulin antagonizes the catabolic effect of glucagon on the blood glucose level (BGL). When BGL raises, β-cells secrete more insulin into bloodstream. Then, insulin informs liver, muscle and adipose tissue to store the excess of glucose. Glucose anabolism enables to achieve normoglycaemia. In the opposite, glucagon produced by α-cells, promotes glucose catabolism in response to low BGLs. When insulin is stimulated, glucagon secretion is inhibited.

counterbalances the effect of glucagon that is secreted by α-cells under fasting for elevating BGLs.

As in any disease, proper and efficient treatment of diabetic patients consists in selecting the most adapted therapeutics at appropriate dose, limiting unwanted side effects. As far as diabetic treatment is concerned, a large panel of anti-diabetic drugs are available and used according to the A1c test screening (Fig. 4).[17] The A1c test result, also known under many other names such as, glycated haemoglobin, haemoglobin A1c and HbA1c, reflects the average blood sugar level of 2–3 months. The higher is the A1c level, the poorer is the blood sugar control.

In T2D, diagnosis is first followed by modification of dietary habits, accompanied by prescription of first line oral antidiabetics, which work in different ways to lower blood sugar including:[8]

(i) inhibiting the production of glucose from the liver and making tissues sensitive to insulin;

(ii) β-cell stimulation to produce insulin;

(iii) blocking the action of gastric enzymes for carbohydrate catabolism.

For T2D, metformin, an insulin sensitizer, remains the most widely prescribed oral antidiabetic worldwide. In the case of insufficiency of glycaemic control using metformin, insulin secretagogues including sulfonylurea, glinides and incretin mimetics are prescribed. The last therapeutic option of advanced T2D, when the previous therapeutic strategies do not enable appropriate glycaemic control, remains insulin injections. This happens about 12 years after the first diabetes diagnosis.

The current standard of care for T1D is the same as for advanced T2D and involves daily insulin supplementation as the only therapy or eventually pancreas or islet cells transplantation. This requires subcutaneous insulin injections and frequent finger pricks to draw blood for the measurement of BGLs. Next to being uncomfortable and resulting in patients neglection of the therapy, periodic measurement may not detect large fluctuations in the blood glucose level, which occur between points of measurements. Approaches providing continuous glucose measurements, including close-looped platforms for insulin delivery, are highly desirable and the advancements in this direction are reviewed in the following (Section 4).

2. Chemical engineering and advanced technologies for improved diabetic management

Having outlined the pathophysiology of diabetes together with testing and therapeutic options, where is the need for chemical engineering as well as advanced technologies to improve the field (Fig. 5)? Proper and if possible, continuous glucose control remains important for preventing negative complications in diabetic patients like eye and kidney diseases as well as cardiovascular problems.[18] Continuous glucose monitoring can be made possible *via* wearable and modern diagnostic devices based on advanced technological concepts.[19,20] Recent closed-loop systems that integrate continuous glucose monitoring device and triggered insulin delivery *via* insulin pumps have been introduced. The need for insulin pumps has many caveats such as insulin loading, as well as special software interface requirements. While this method is a

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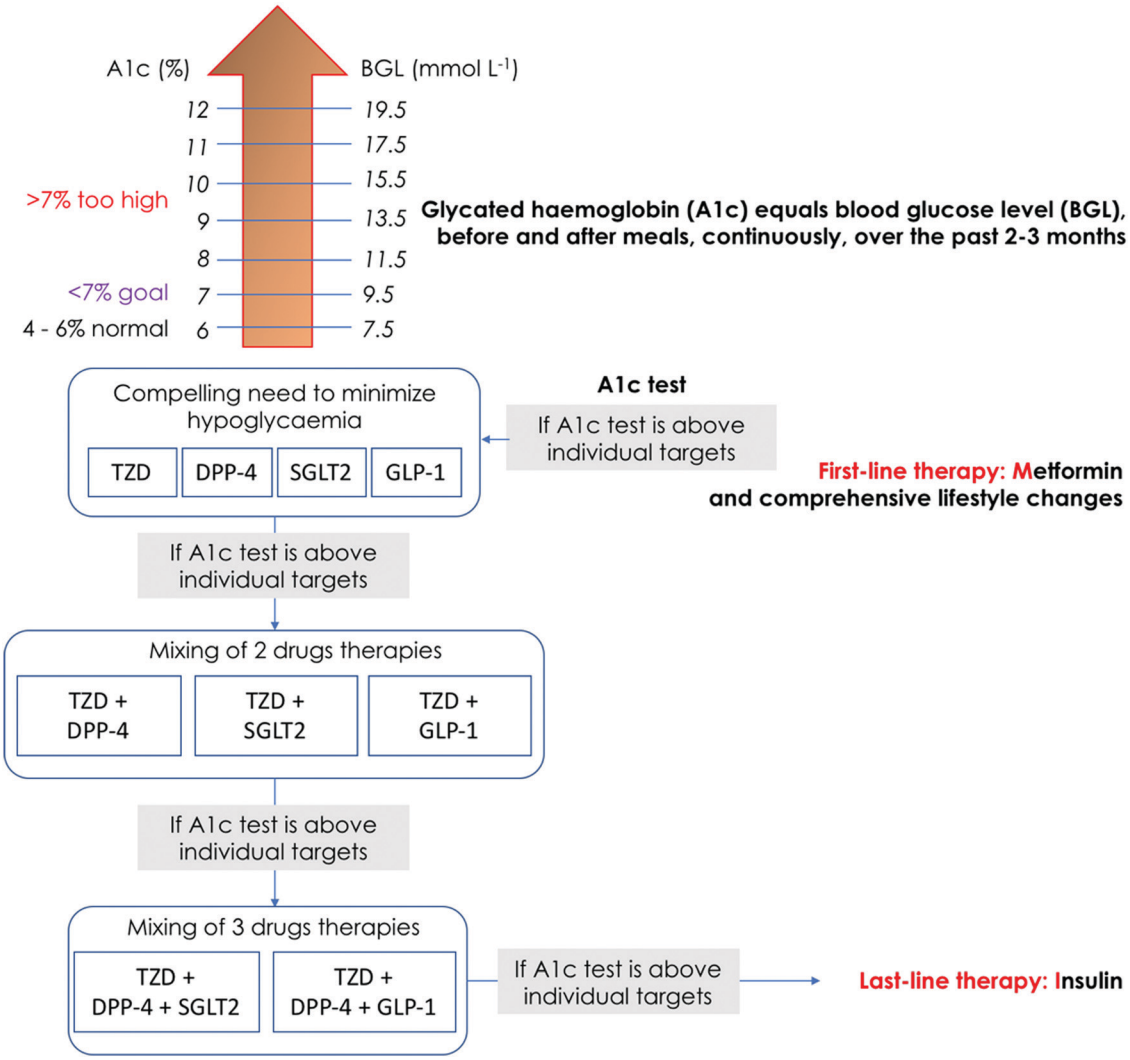

Fig. 4 Current standard of care for T1D and T2D after a positive A1c test: from oral delivery of metformin to subcutaneous injection of insulin. The exemplified drugs include thiazolidinediones (TZD), dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose cotransporter 2 (SGTL2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists (information from www.sahta.com/docs/standardsDiabetes.pdf).

large step further, glucose management with an acceptable security range remains challenging. Recent achievements in implantable nanosensors for continuous glucose monitoring can facilitate online diagnosis and is one of examples of the positive input of advanced technologies for diabetes management. Several innovations, ranging from wrist sweat bandage for continuous glucose monitoring to soft contact lens concepts, implanted glucometer where reading is performed *via* wireless monitoring to saliva glucose monitoring with an implanted mouth strip, have been set forth.[21–23] The Abbot marketed implantable biosensor can provide constant glucose monitoring for up to 10 days. These amperometric sensors are implanted subcutaneously and record an electrical current as a function of glucose concentration. To achieve improved sensitivity and efficiency for glucose monitoring, carbon-based nanomaterials such as graphene nanocomposites and carbon quantum dots have shown to be of high potential.[23] These materials are formed through chemical engineering, while their characterization is possible owing to the availability of advanced nanotechnological characterization tools.

Besides ingenious biomimetics and supramolecular chemistry schemes for blueprinting nanocarriers for drug delivery, synthesis of nanoparticles – including magnetic entities – allowed in addition to quantify subtle changes in β-cell mass facilitating early diagnoses.[24] Next to implanted continuous glucose monitoring devices, a large number of high-technology insulin delivery methods are being explored as novel therapies. Noninvasive delivery of insulin has the potential to address noncompliance issues. Insulin patches based on microneedle concepts[25] and thermal skin ablation approaches[26,27] have been reported. Injective insulin nanogels can be seen as more classical technological advance to overcome insulin delivery issues.[28] Furthermore, improved strategies to differentiate induced pluripotent stem cells into insulin-producing cells have been developed using nanofiber-based polymer scaffolds.[29]

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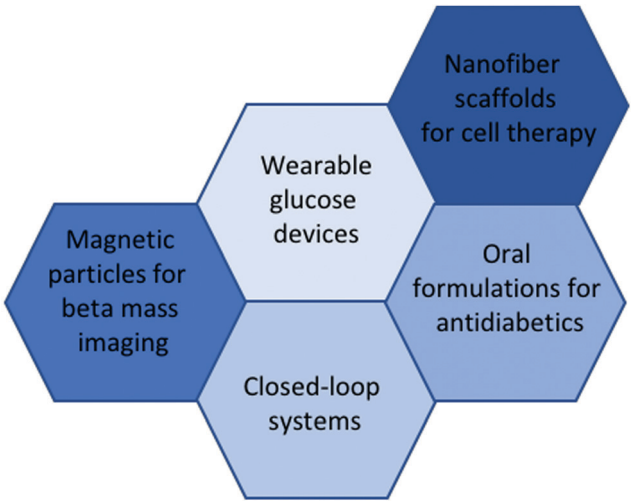

Fig. 5 Chemical engineering and enabling technologies for diabetes. Different aspects of chemical engineering and advanced technologies for diabetes management.

3. Glucose monitoring: sensing and closed-loop delivery

The diagnosis of all forms of diabetes, at an early stage, is important for the management of the disease to slow down potential complications such as diabetic nephropathy, retinopathy, neuropathy, cardiovascular diseases, diabetic foot ulcer, and viral infections.[30] The most commonly used biochemical diabetes screening and diagnostic tests are blood or plasma glucose tests. Healthcare professionals most often use the fasting plasma glucose or the random plasma glucose tests. In addition, sensing of haemoglobin A1c level is often performed.[30] Indeed, analysis of glycated haemoglobin level in blood provides evidence about an individual's average blood glucose level during the previous 2–3 months, the predicted half-life of red blood cells. Fructosamine tests can be done if the measurement of haemoglobin A1c is not reliable.[31] Drinking a 75 g sugar beverage and monitoring the body's glucose response is clinically used as the glucose tolerance test. However, diagnosis of hyperglycaemia on a personal level is mainly operated by simple blood glucose tests after overnight fasting and/or a glucose challenge (Fig. 6). These tests are based on frequent finger pricks to draw blood for the measurement of BGLs. The onset of T1D can be further diagnosed due to the presence of biomarkers of the immune destruction process of the β-cells. These include islet cell antibodies,[32] exogenous insulin antibodies (notably IgG, IgA),[33] glutamic acid decarboxylase antibodies,[34] islet-associated autoantibodies, and unique neuroendocrine-specific protein tyrosine phosphatases.[35] One and usually more of these autoantibodies are present in 85–90% of hyperglycaemic individuals.[8]

Numerous clinical trials and intense research efforts indicate that continuous metabolic monitoring holds great potential to provide early indication of diabetes. Current development in this field is thus driven by the need to replace the existing blood-based diagnostic tools, such as the glucose test strips, with implanted, portable diagnostic devices that are fast, reliable and cost effective to provide an early signal of metabolic imbalance.

Frequent self-monitoring of blood glucose, linked with intensive insulin therapy, greatly improves glycaemic control, which in turn minimizes many of the complications associated with T1D. The major drawbacks with finger-prick blood glucose self-monitoring is being painful and cannot be performed when the patient is sleeping or physically active, situations when the patient is highly exposed to hypoglycaemia. The current glucose tests are also mostly intermittent and can miss dangerous fluctuations in blood glucose concentration between tests. A large plethora of glucose monitoring systems are reported and can be roughly divided into enzymatic and non-enzymatic sensors,[36,37] as well as invasive and non-invasive ones.[38] The sensitivity of glucose sensors has to be in the mM range as for healthy patients, blood-glucose concentrations are typically between 4.9–6.9 mM, increasing to up to 40 mM in diabetics after glucose intake.

Colorimetric detection is based on the reaction of 2-methylaniline with glucose that forms a stable coloured mixture with absorption at 625 nm.[39] However, this method lacks selectivity. Using glucose oxidase (GO_x), as glucose specific enzyme, the first generation of glucose sensors was introduced in 1962 by Clark and Lyons at the Children's Hospital in Cincinnati (Fig. 7a).[40] It is an electrochemical-based glucose sensor using glucose oxidase (GO_x) as a surface ligand. While other enzymes such as glucose-1-dehydrogenase[41] were proposed for glucose measurements, GO_x shows not only high selectivity for glucose over other interfering species in blood (*e.g.* uric acid, acetic acid, dopamine, lactose, fructose and sucrose), but also tolerates extreme changes in pH, temperature and ionic strength in comparison with other enzymes

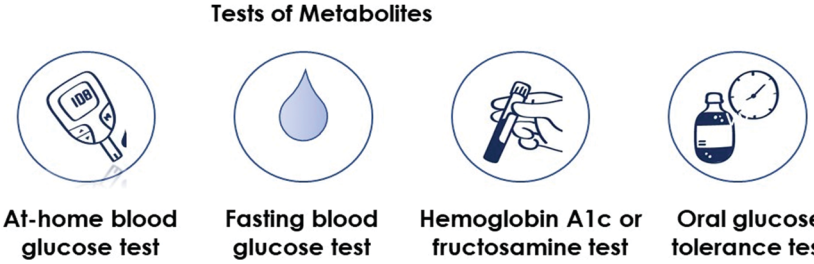

Fig. 6 Different diagnostic platforms for diabetes. Metabolic sensing currently practiced and potential biomarkers from serum samples. The test of metabolites and notable glucose can be divided into at-home glucose tests, fasting blood glucose test, oral glucose tolerance test as well as screening the level of haemoglobin A1c or fructosamine.

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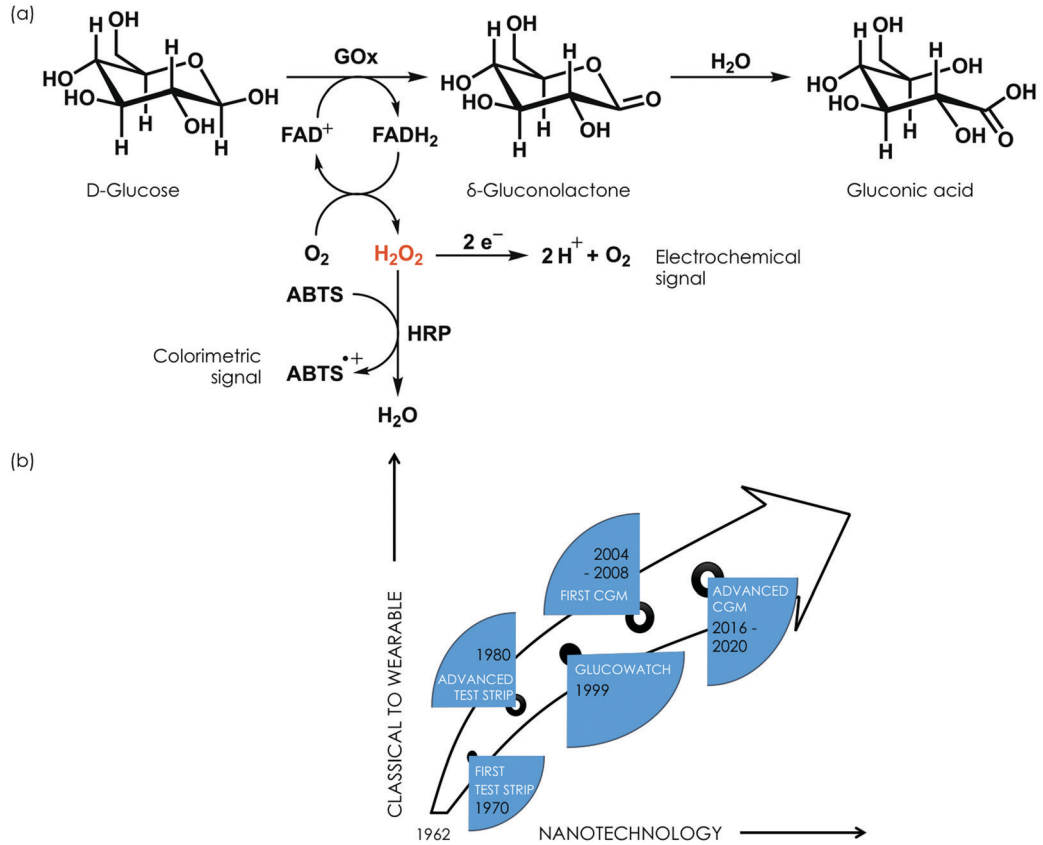

Fig. 7 Glucose monitoring. (a) Working principle of glucose oxidase (GO_x)-based glucose sensors *via* conversion of glucose to gluconic acid. (b) Time consideration in glucose sensor development: from finger pricking devices to blood samples on test strips and implanted sensors.

making it the prime candidate for glucose monitoring.[42,43] The mode of action of GO_x is to catalyze the oxidation of glucose to gluconolactone in the presence of oxygen, producing hydrogen peroxide (H_2O_2) and water as by-products (Fig. 7a). Formation of H_2O_2 is proportional to the glucose concentration. This first commercial sensor directly measures glucose concentrations by amperometric detection of H_2O_2. This type of sensor was only used in clinical settings due to the high operating potentials needed and the expensive nature of the platinum working electrode employed.

The second generation of glucose biosensors emerged in the 1980s.[38] In fact, GO_x requires a redox cofactor, flavin adenine dinucleotide (FAD^+), to carry out the oxidation process to H_2O_2, being reduced to FADH. The second generation of glucose sensors uses a synthetic electron redox mediator instead of oxygen to convert FADH back to FAD^+ and led to the development of disposable enzyme electrode strips, which could be inserted into pocket-size blood-glucose meters.[44] This second-generation glucose sensors led to the idea of self-monitored glucose management, the well-known "finger-pricking" concept.

Continuous glucose monitoring (CGM) devices consist of a tiny sensor inserted beneath the skin, which remains in place for a period of some days to access the glucose levels in tissue fluid. Technologies such as subcutaneous amperometric electrodes, microdialysers, intravenous implantable devices and micropores/microneedles have been tested, while only subcutaneous and microdialyser devices resulted in commercial products. The GlucoWatch was one of the attempts for CGM. This device was based on the principle of reverse iontophoresis. The product was, however, withdrawn in 2008 from the market due to biofouling issues and skin irritation. Indeed, the reliability of implantable systems is often undermined by biofouling and foreign body response in addition to sensor drifts and lack of temporal resolution.[45] In 1990, Medtronic introduced the first CGM system allowing for 3-day continuous glucose sensing and data recording and with the advent of DexCom-7 in 2006, the lifetime was extended to 7 days. One of the latest devices on the market, approved in 2016, is the FreeStyle Libre glycometer from Abbot using subcutaneous amperometric electrodes, which can be used for 14 days without the need for calibration.[46] The search for biocompatible and antifouling coatings including Nafion, hyaluronic acid, polyvinyl alcohol hydrogels, *etc.* was of prime importance to alleviate in part *in vivo* sensor degradation. Textured rather than smooth coatings were reported to improve further *in vivo* performance.[47] Integration of tissue response modifiers in degradable microspheres has also been considered as a possibility to reduce inflammation and suppress fibrotic encapsulation of the sensor. It is worth mentioning that the extent of foreign body response is determined by the degree of tissue damage occurring during implantation.[48]

Enzyme-less glucose sensors

The most serious problem connected with enzyme-based glucose sensors is the insufficient stability of the enzyme. The

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Concanavalin A (Con A)-based fluorescence sensor developed in 1984 was one of the first attempts in the use of an enzyme-free detection approach. Fluorescently-labeled Con A was immobilized on a hollow optical fiber and the presence of glucose tuned the florescence sensing signal.[49]

Numerous efforts have been put into the development of enzyme-free electrochemical sensors involving nanostructured electrodes. Initial research focused on the use of noble metals, such as mesoporous platinum.[50] The desire for better and cheaper electrocatalysts has resulted in the development of bimetallic systems[51,52] or in the fabrication of diamond nanowires[53] and diamond nanowires coated with nickel nanoparticles[54] for direct glucose oxidation. While being non-selective to glucose and operated in alkaline medium, these sensors exhibit numerous advantages such as fast response time, higher sensitivity and better stability than glucose oxidase-based interfaces. Copper and nickel oxide nanostructures have especially received much attention for non-enzymatic glucose sensing in alkaline media.[55–60] Some of us demonstrated (Fig. 8)[61] the interest of reduced graphene oxide (rGO) electrodes modified with $Ni(OH)_2$ using electrophoretic deposition for enzyme-free glucose sensing. The broad redox current peaks observed correspond to the $Ni(OH)_2$/NiOOH redox couple according to eqn (1) and (2):

$$Ni(OH)_2 + OH^- \rightarrow NiOOH + H_2O + e^- \quad (1)$$

$$NiOOH + \text{glucose} \rightarrow Ni(OH)_2 + \text{gluconic acid} \quad (2)$$

In the presence of glucose, the oxidation current of $Ni(OH)_2$/NiOOH redox couple is increased due to the change in the Ni^{2+}/Ni^{3+} concentration ratio (eqn (2)). Once NiOOH is formed (eqn (1)), glucose is oxidized to gluconic acid and NiOOH is reduced back to $Ni(OH)_2$. The recycling results in the increase of the oxidation current. The potential needed for this conversion is +0.6 V, where other organic substances could simultaneously oxidize.

A different approach in exploiting enzyme-less sensor designs is based on the use of boronic acid compounds.[62–67] Boronic acid derivatives recognize *cis*-diol containing molecules by forming five or six-membered cyclic esters in alkaline solutions. The 4-aminophenylboronic acid has proven to be a useful reagent for the simultaneous reduction of GO to rGO and incorporation into the rGO matrix for glucose sensing.[68] The phenylboronic acid modified rGO displayed large redox currents at neutral pH using $Fe(CN)_3^{4-}$ as a redox probe, which could be strongly modulated by the presence of glycans.

Nanotechnology-driven sensors

The field of nanofabrication together with the advent of submicron lithography techniques provide a powerful combination for miniaturized electronics. For instance, GO_x-coated semiconducting single-walled carbon nanotubes are pH sensitive and their conductance is altered upon addition of glucose.[69] Allen *et al.* proposed a glucose biosensor configuration based on organic thin film transistors,[70] while enzyme-less schemes have also been implemented (Fig. 8c).[71–73]

Closed-loop systems

Glucose-responsive insulin and delivery systems have become of great interest lately. Insulin injections depend upon real

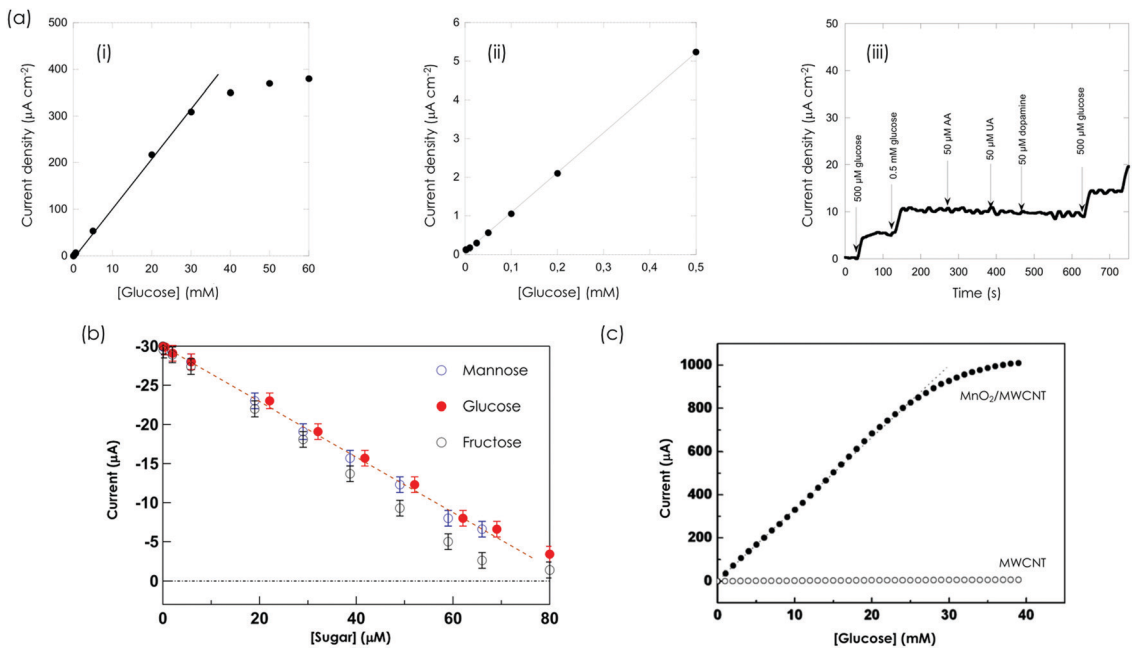

Fig. 8 Non-enzymatic glucose sensing. (a) Behavior of rGO/$Ni(OH)_2$ modified Au electrodes: (i and ii) current density calibration curves for glucose concentration [glucose] at +0.6 V bias voltage for amperometric detection, (iii) interference test at +0.6 V using 0.5 mM glucose in the presence of 0.05 mM ascorbic acid (AA), 0.05 mM uric acid (UA) and 0.05 mM dopamine. [Reproduced from ref. 61 with permission from Royal Society of Chemistry, copyright 2014.] (b) The current response as a function of sugar concentration of a biosensor based on rGO functionalized with 4-aminophenylboronic acid [glucose (pH 8.2), D-fructose (pH 7.4) D-mannose (pH 7.7)]. (c) The current response as a function of glucose concentration [glucose] for a multi-walled carbon nanotube (MWCNT) sensor and a MnO_2/MWCNT composite sensor. The applied voltage for amperometric detection is +0.3 V. Adapted from ref. 71.

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time-glucose sensing and complex algorithms to control the pattern of doses. In this respect, intelligent glucose-responsive insulin delivery (Fig. 9)[74] and wearable systems have been developed at a rapid pace in the last decade,[75–79] revealing unique opportunities, such as insulin skin-adhesive pumps[80] for basal or bolus infusions. The disposable patch pump recently introduced by EOFlow is a unique closed-loop system with minimal, secluded design but it should be worn enduringly and changed weekly – similar to the well-known MiniMed 670G system from Medtronic, in contrast to tatoo-like patches[81] that can be changed easier with smaller risks of infections. Yet, efforts are relentless into this area and CGM systems are now integrated into closed-loop systems by several key manufacturers in the field like Abbott, Dexcom and Insulet.[82] At the forefront of innovation are systems using both regular human and rapid acting insulin for delivery. Closed-loop and wearable technologies are enabled by wireless transmission of metabolic data at short and long distances *via* health apps founding inspiration in, among many other authoritative items, Dexcom, Fitbit, Google Fit, Apple HealthKit user-centric software, and with K'Watch Glucose and Glutrac being front-page wrist devices.[83,84]

Furthermore, microneedle-based closed-loop delivery systems have been developed recently.[25,85–88] Yu *et al.* reported on a novel glucose-responsive insulin delivery device using a painless microneedle array patch,[25] containing glucose-responsive vesicles with an average size of 118 nm loaded with insulin and glucose oxidase. This smart system efficiently regulated the blood glucose in a mouse model of chemically-induced T1D and was assembled from hypoxia-sensitive hyaluronic acid conjugated with 2-nitroimidazole, a hydrophobic unit that can be converted into hydrophilic 2-aminoimidazole.

The same team showed that a single removable transdermal patch, bearing microneedles loaded with insulin and a non-degradable glucose-responsive polymeric matrix, fabricated by *in situ* photopolymerization, regulated blood glucose in insulin-deficient diabetic mice and minipigs.[88]

Another interesting concept is the one proposed by Chen *et al.* using alginate-based microneedle-array patches loaded with dual mineralized protein/peptide particles for T2D therapy.[85] Different to other approaches, this patch separately encapsulated a robust glucose-sensing element and sensitive drug-release module. In this manner, a closed-loop and feedback-controlled exendin-4 (Ex4) treatment for type 2 diabetics was achieved. Hydrogen peroxide (H_2O_2) responsive vesicles were integrated into transcutaneous microneedle array path to achieve a fast response to increased glucose blood levels.[86]

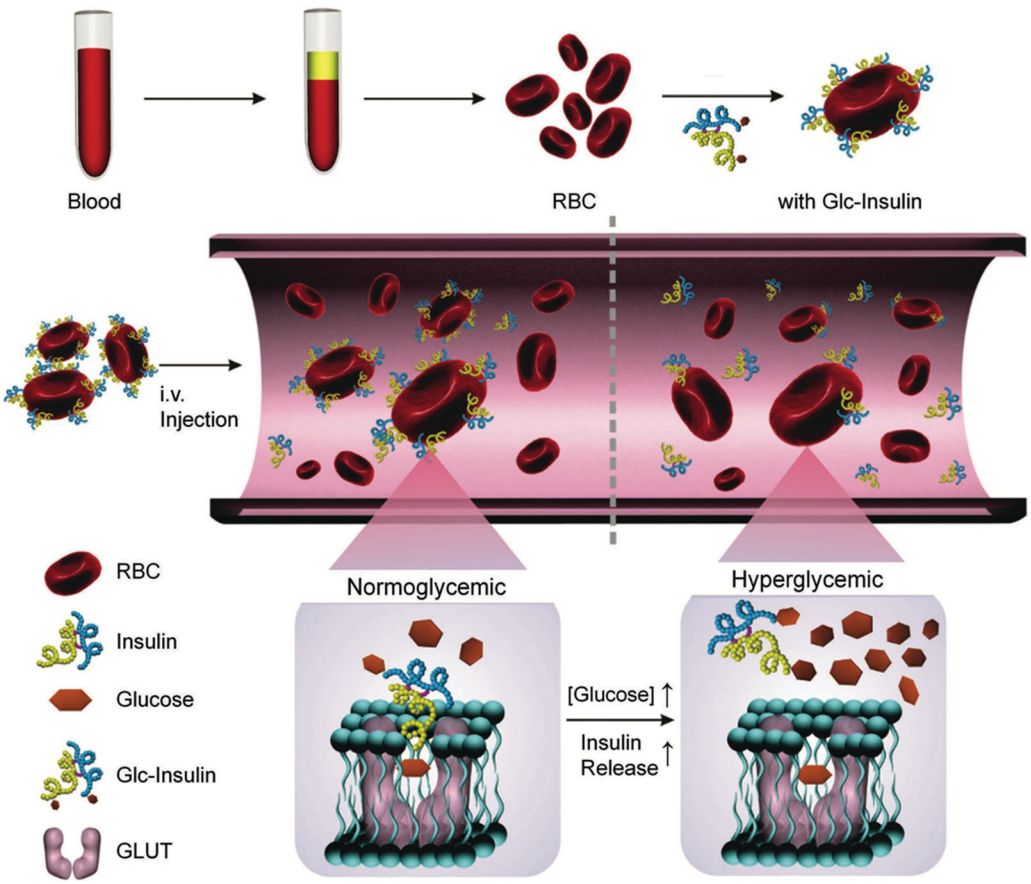

Fig. 9 Closed-loop system for insulin delivery based on red blood cells (RBCs) and glucose transporter (GLUT) protein. Synthetic glucose derivative-modified insulin (Glc-insulin) is reversibly coupled with RBCs and enables regulation of BGL in mice as animal model of T1D upon intravenous (i.v.) injection. [Reproduced from ref. 74 with permission from Wiley, copyright 2017.]

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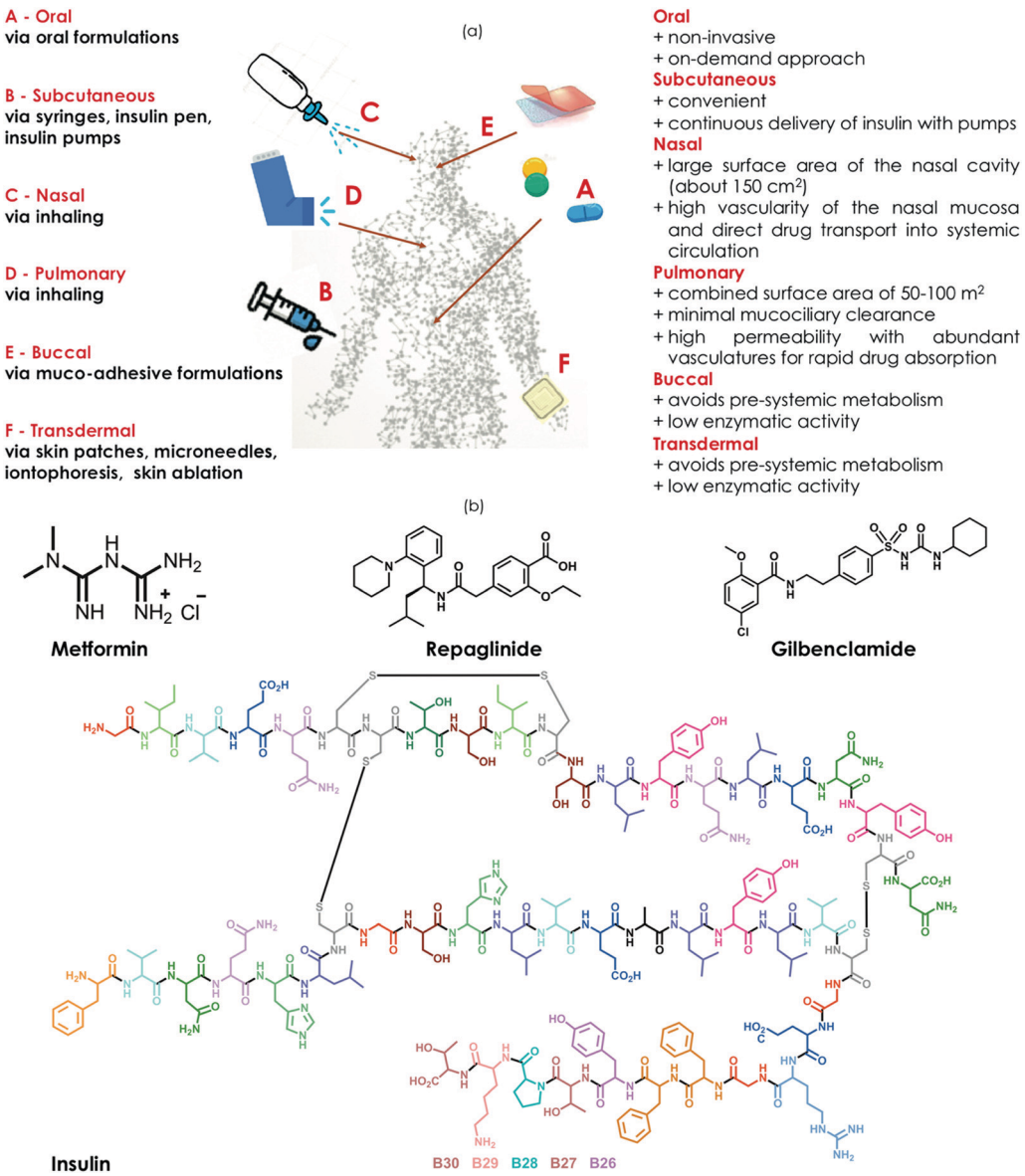

Fig. 10 Antidiabetic drugs. (a) List or currently investigated antidiabetic drug administration routes ranging from oral delivery of small organic T2D drugs (metformin, repaglidine, glibenclamide) to subcutaneous delivery of T1D therapeutics such as insulin and amylin. Their advantages and limitations are listed in addition. (b) Chemical structures of common T2D antidiabetic drugs as well as insulin, the main T1D therapeutic. The region of the insulin molecule not critical for insulin receptor recognition is labelled as B26–B30. It is in this region that amino acids are generally substituted. These insulin analogues are still recognized by and bind to the insulin receptor.

A self-adherent, bullet-shaped microneedles (MNs) patch with water-swellable tips for controlled transdermal delivery of insulin was proposed by Seong *et al.*[87] This design enabled the MNs to mechanically interlock with soft tissues by selective distal swelling after skin insertion. Additionally, prolonged release of loaded proteins by passive diffusion through the swollen tips was achieved.

4. Classical treatment of symptomatic effects of diabetes and new approaches

Together with the discovery of new antidiabetic drugs with the least side effects but with highest efficiency, different administration approaches are being relentlessly searched for (Fig. 10a) including next to the most common oral approach, nasal, buccal, pulmonary and subcutaneous administration routes. The administration method is largely dependent on the size and physico-chemical character of the antidiabetic drug to be delivered. As treatment of T2D occurs mainly with small organic molecules, therapeutic peptides such as insulin and amylin are mostly considered for T1D (Fig. 10b).

(i) Oral drug delivery

The oral delivery remains a preferential drug administration route as it is a non-invasive, on-demand approach. Most of

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small molecules such as metformin, repaglinide, glibenclamide (Fig. 10b) fall into class II (poorly soluble, but permeable to the lipid layer of biological membranes), according to the Biopharmaceutical Classification System, making oral delivery possible.

(ii) Subcutaneous drug delivery

For class III drugs such as peptides (insulin), subcutaneous drug delivery is required. These drugs can be oxidized and denatured in the acid environment of the gastrointestinal (GI) tract, losing their therapeutic activity. Next to the low pH, gastric enzymes are major barriers for antidiabetic drugs such as insulin when administered orally.[89,90] A typical absorption-enhancing excipient is sodium *N*-[8-(2-hydroxybenzoyl)aminocaprylate], which protects against enzymatic degradation *via* local buffering actions and transiently enhances absorption. While the need of higher doses to compensate the elevated level of unabsorbed drug and the associated increase in costs are considered less problematic nowadays owing to the significant decrease of the cost of peptide synthesis over the past years, the main drawback associated with oral delivery is the high inter-subject variability, which makes it often difficult to create robust methodology to define a safety margin, in particular for peptide/protein-based antidiabetic drugs. Other routes have been considered in diabetes treatment such as nasal, pulmonary, buccal, and transdermal approaches (Fig. 5).[91–104]

(iii) Nasal antidiabetic drug delivery

Nasal antidiabetic drug delivery takes advantage of the large absorption surface area of the nasal cavity (about 150 cm^2) with high vascularity of the nasal mucosa and direct drug transport into systemic circulation thus bypassing the GI tract associated low oral bioavailability (Fig. 11a).[92,94,95] Nasal administration of fine insulin powder allows the partial delivery of insulin into the lungs, where it enters the blood through tiny blood vessels. Seeming the perfect administration route, several limitations impede this approach to a certain extent.[96] One issue is the rapid (half-life of 0.25–0.5 h) clearance by the mucociliary mechanism, the primary innate defence mechanism of the lung, removing inhaled particles before

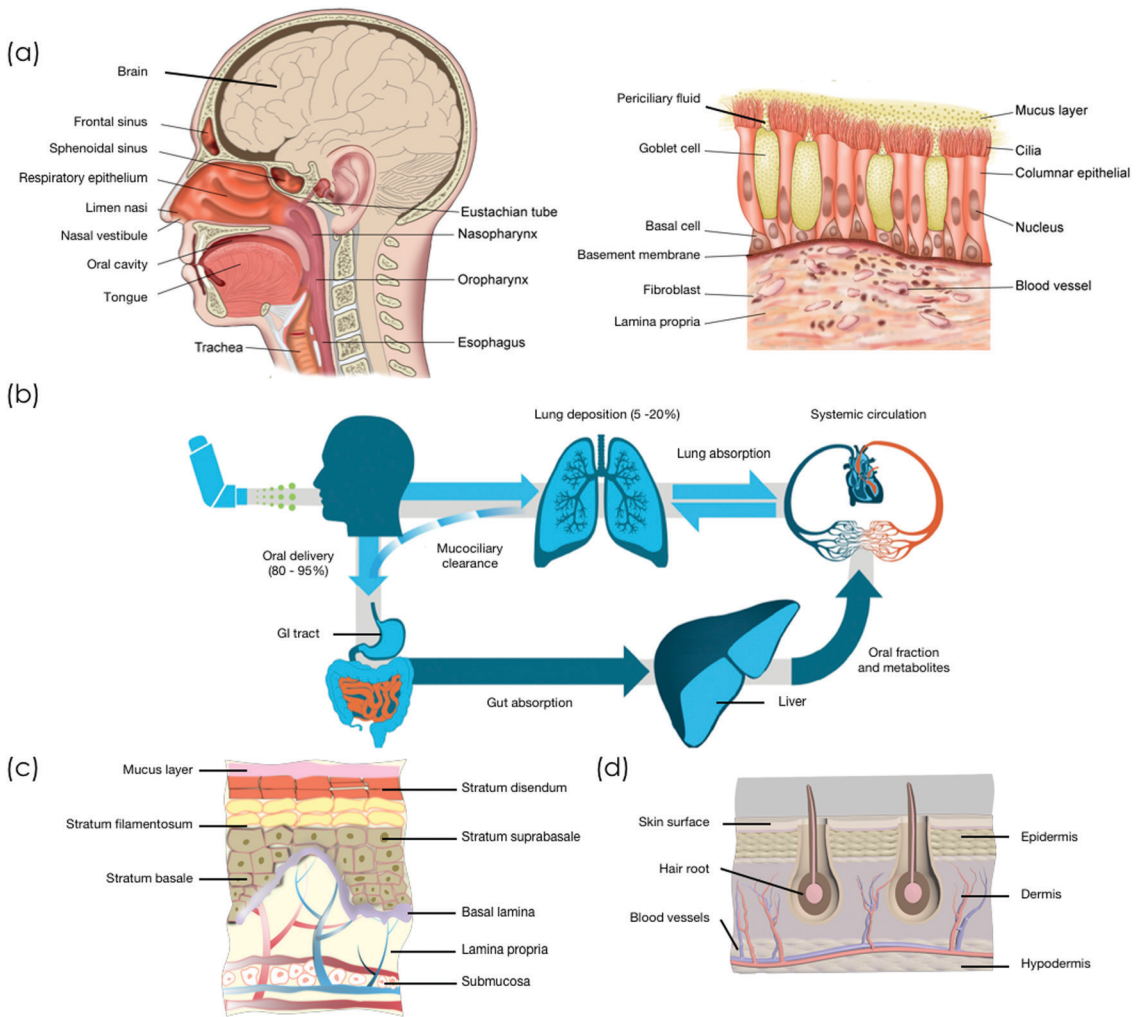

Fig. 11 Antidiabetic delivery pathways. (a) Nasal drug administration. (b) Pulmonary delivery where, in general, >20% of the drug is deposited in the lung, with the rest being swallowed orally. Deposited compounds in the lung are also cleared by mucociliary clearance and systemic absorption through lung. (c) Buccal administration. (d) Transcellular and intercellular routes of drug delivery *via* the skin. Adapted from ref. 91 and 93.

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they can reach the delicate tissue of the lungs. Only small amounts of insulin are therefore detected in the bloodstream after nasal administration.[97] Furthermore, permeation limitation across the mucus produced layer and the nasal epithelium along with enzymatic degradation similar to oral delivery impede this approach. A variety of additives including alkylglycosides were tested to enhance the absorption of nasally applied insulin into the bloodstream,[98,99] and have shown to be relatively safe with stable insulin formulations in spray flasks,[100] making this mode of insulin administration appealing for patients who need consecutive daily insulin treatment. Pre-clinical studies revealed that nasal insulin is neuroprotective for Alzheimer's disease, Parkinson's disease, and traumatic brain injury. Indeed, insulin can be detected in the central nervous system within minutes, following nasal administration.[101]

(iv) Pulmonary delivery

Human lungs (Fig. 11b) have a combined surface area of 50–100 m^2, 1000-fold larger than that of the nasal cavity and several times larger compared to the 2 m^2 of skin. Both lungs contain about 274–790 million alveoli involved in gas and liquid exchange and transport of liquids delivered from alveoli to the blood.[102] Its alveolar epithelium has a thickness of 0.1–0.2 μm with minimal mucociliary clearance and presents high permeability as well as abundant vasculatures, allowing rapid drug absorption. This makes alveoli and the associated vascular network a sought-after method for delivering antidiabetic drugs to the systemic circulation. However, while corticosteroids and other drugs might be delivered effectively, hydrophilic macromolecules such as insulin have limited permeation through the mucus layer (1–10 μm thickness) that covers the pulmonary epithelium. Furthermore, 90% of inhaled insulin is lost in its passage to alveoli to enter the blood stream. The other barriers to overcome for insulin absorption include pulmonary enzymes and macrophages. Most proteins are subjected to degradation by proteases or clearance by macrophages.

(v) Buccal delivery

In the recent years, buccal mucosa has emerged as a promising delivery site for antidiabetic drugs such as insulin.[103] Buccal mucosa offers a rich vasculature (Fig. 11c). The buccal route owns a series of advantages as it avoids pre-systemic metabolism of insulin *via* low enzymatic activity and ease of accessibility of buccal absorption site. Salivary scavenging as well as the barrier properties of mucosa and small area available for drug absorption are intrinsic limitations of this approach.

(vi) Transdermal drug delivery

Currently, about 20 drugs are approved by the Food and Drug Administration (FDA) for transdermal administration sharing several characteristics such as low molecular weight, lipophilicity and relatively low dose administration requirements. Small penetrants favour the intracellular route and move freely within the inter-cellular space. The diffusion rates are governed largely by the lipophilicity of the drug (Fig. 11d). For larger drugs such as therapeutic peptides and proteins, the skin has two important layers, the stratum corneum (SC) of about 0.01 μm in thickness, consisting of dead flattered keratinocytes surrounded by a lipid matrix, acting as the primary barrier to diffusion and penetration of drugs. The viable epidermis lining below the SC is 10-fold its thickness. However, the greater hydrating degree of this layer offers much faster diffusion for drugs. Below the epidermis is the dermis (1 mm in thickness), rich in blood capillaries for nutrient supply and temperature regulation. These small vessels also allow the diffusion of drugs into blood circulation.[104] Several approaches are currently under development to overcome the limitations of transdermal drug delivery for antidiabetic drugs taking into consideration novel polymer formulations and nanotechnology designs, as discussed in Section 4.

4.1. Treatment of T2D

Type 2 diabetes involves complex interactions of metabolic and genetic defects. Initially and often throughout their lifetime, patients with T2D do not need insulin treatment to survive. Dietary modifications and exercise accompanied by the supplementation of oral insulin sensitizers are the first line treatment for T2D.[105] Table 1 lists the different classes of used drugs.

Biguanides. The most widely prescribed antidiabetic medicines for the treatment of T2D worldwide are biguanides, notably metformin hydrochloride.[106] It lowers BGLs without causing hypoglycaemia or stimulating insulin secretion. Metformin improves insulin action by reducing gluconeogenesis, glycogenolysis and lipids production. Metformin is particularly attractive as it is orally administrated and has several relevant medical advantages.[107,108] Beyond the antidiabetic effect, there is a growing evidence pointing out the potential protective effects of metformin against neurodegeneration, fibrosis, cancer, and COVID-19.[109–111] For example, patients treated with metformin have a significantly lower risk of developing breast cancer as compared to diabetic individuals not treated with metformin.[112] However, there are still several concerns in the current use of metformin, in particular its relatively low bioavailability reaching 55%,[113,114] its short biological half-life of only 1–3 h,[115] and induced lactic acidosis.[116] Repeated applications of high doses (2.5 g daily dosage) may be required for an effective treatment, resulting in reduced patient compliance and occurrence of GI syndromes such as diarrhea and nausea, weight loss up to anorexia, and taste disturbance (Table 1).[117] These concerns have led to the search of innovative formulations for improving bioavailability, decreasing the dosing frequency and GI side effects of metformin.[118]

The prolonged metformin release tablets currently on the market are based on swellable matrix system fabricated from sodium carboxymethylcellulose and hydroxypropyl-methylcellulose, (*e.g.* glucophage). The drawback of this therapeutics is that it gives rise to unpredictable and uncontrollable variations in its release profile. Various nanostructures, like liposomes, dendrimers, and mesoporous silica nanoparticles, have been designed for enhancing drug oral bioavailability[119] and some of the concepts are applied for metformin formulations.[120–126] Rare remain studies where the nanostructures have been tested *in vivo*,

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Table 1 Different drug classes used for treatment of T2D

Drug class	Action	Dosing	Side effects
Biguanides Metformin, phenformin	Lower BGL Improve insulin-mediated glucose utilization and insulin receptor signaling	Oral Transdermal	GI syndromes Metallic taste
Thiazolidinediones (TZDs) Rosiglitazone, rioglitazone, troglitazone		Oral	Weight gain Cardiac issues
α-Glucosidase inhibitors Miglitol, acarbose, voglibose	Delay absorption of ingested carbohydrates Reduce postprandial insulin and glucose peak	Injection	GI syndromes
Sulfonylureas Tolbutamide, acetohexamide, tolazamide, chlorpropamide, carbutamine, glyburide, glibenclamine, glipizide, glimepiride, gliclazide, glyclopyramide, gliquidone	Trigger insulin release by inhibiting the potassium channel of the pancreatic β-cells	Oral	Hypoglycaemia Weight gain
Non-sulfonylurea secretagogues Meglitinide, repaglinide, nateglinide	Trigger insulin secretion by closing the potassium channel of the pancreatic β-cells and by opening calcium channels	Oral	Hypoglycaemia Weight gain
Dipeptidyl peptidase-4 (DPP-4) inhibitors Gemigliptin, linagliptin, lixisenatide, vildagliptin, sitagliptin, saxagliptin, alogliptin, septagliptin, teneligliptin	Inhibit GLP-1 degradation by DPP-4 and thus increase GLP-1 blood concentration	Oral	Increased risk of infection and headache
Glucagon-like peptide-1 (GLP-1) agonists Exenatide, liraglutide, taspoglutide, lixisenatide, semaglutide, dulaglutide	Glucose enters the bloodstream more slowly as starch digestion is slowed down	Injection	Nausea Weight loss
Sodium-glucose co-transporter-2 (SGLT2) inhibitors Canagliflozin, dapagliflozin, empagliflozin, remogliflozin	Inhibition of reabsorption of glucose in the kidney lowering the BGL	Oral	Urinary tract infections Sudden drop in blood pressure

primordial for the validation of the therapeutic effect of any nanostructure-based formulation. An interesting report is that of Wang *et al.*, who synthesized a highly intercellular stimuli-sensitive chitosan-modified metformin prodrug using imine reaction between oxidative chitosan and metformin.[122] Chitosan is a natural non-toxic cationic (pK_a = 6.5) polysaccharide, composed of glucosamine and *N*-acetyl-glucosamine units, characterized by good mucoadhesive capabilities and penetrating enhancing effects. In that work, metformin grafted chitosan was used to attach shRNA for intracellular delivery and gene therapy. The choice of shRNA was made based on its ability of silencing SREBP, a sterol regulatory element-binding protein, playing a central role in cholesterol and fatty acid metabolism. It was demonstrated that expression of SREBP mRNAs was reduced using this nanoarchitecture, improving insulin glucose and lipid homeostasis in mice (Fig. 12a).

The polyanionic calcium alginate polymer is widely used for its potential to control drug delivery in the GI tract due to its ability to decrease the acidic pH, together with mucoadhesive properties and absence of toxicity. It makes another interesting matrix for metformin formulation.[127] Maestrelli *et al.* encapsulated metformin niosomes and chitosomes in calcium alginate microspheres for oral T2D therapy. The entrapment of these colloidal dispersions in calcium alginate beads strongly reduces metformin release at the gastric level and supports sustained release into simulated intestinal fluid. *In vivo* studies on rats revealed further a significant improvement of metformin hypoglycaemic effect.

Recently, porous silicon-based microparticles (μPSip) were loaded with metformin *via* electrostatic interactions (Fig. 12b).[125] As the pH of the medium changes, the surface charge of the oxidised microparticles ($\mu PSipO_x$) can be tuned from slightly positive at pH < 2.2 to strongly negative at pH > 7.4, allowing to control metformin loading capability. The best condition for metformin binding to $\mu PSipO_x$ is in the pH range of 5–8, a window where the drug has two monoprotonated positive species and the microparticle surface is covered by siloxane and dissociated silanol groups ($Si–O^-$), both providing a strong negative charge to the porous surface. Next to intermolecular forces such as electrostatic and van der Waals, drug release was mediated by pore size dimension. Tuning both parameters resulted in a release of metformin over a period of 26 h. The delivery of metformin into the GI tract and its subsequence absorption in the blood was determined.

Selenium nanoparticles (Se NPs) alone and in combination with metformin were considered for the treatment of T2D in high-fat diet/streptozotocin (HFD/STZ)-induced mice models.[128] It was shown that treatment with mono-therapeutic-two doses Se NPs (0.1 and 0.4 mg kg^{-1}) resulted in remarkable protective antidiabetic effects, illustrated by significant decreases in fasting blood glucose and insulin levels after 8 weeks treatment. In a similar work, boronic acid modified carbon quantum dots were used as nanovehicles for delivery of metformin.[129]

Biguanides: the first transdermal delivery systems as alternatives. Next to oral delivery, some researchers have attempted the transdermal administration route for metformin to bypass the GI tract and avoid many of the unpleasant side effects.[130–133] Thermo-responsive microneedles,[133–135] where metformin is released upon needle melting, and hydrogel-based microneedles,[136,137] have been used for this aim. The team of Donnelly showed that a MNs patch, made from an aqueous blend of poly(methylvinylether-*co*-maleic acid) crosslinked by esterification with polyethylene glycol (PEG) to which a metformin drug reservoir was attached, containing 75 mg metformin HCl, delivers 28.1 ± 2.3 mg in 24 h. *In vivo*, metformin HCl was detected in rat plasma at 1 h post microneedle application at a concentration of 0.6 ± 0.5 μg mL^{-1}, increasing to 3.7 ± 2.5 μg mL^{-1} at

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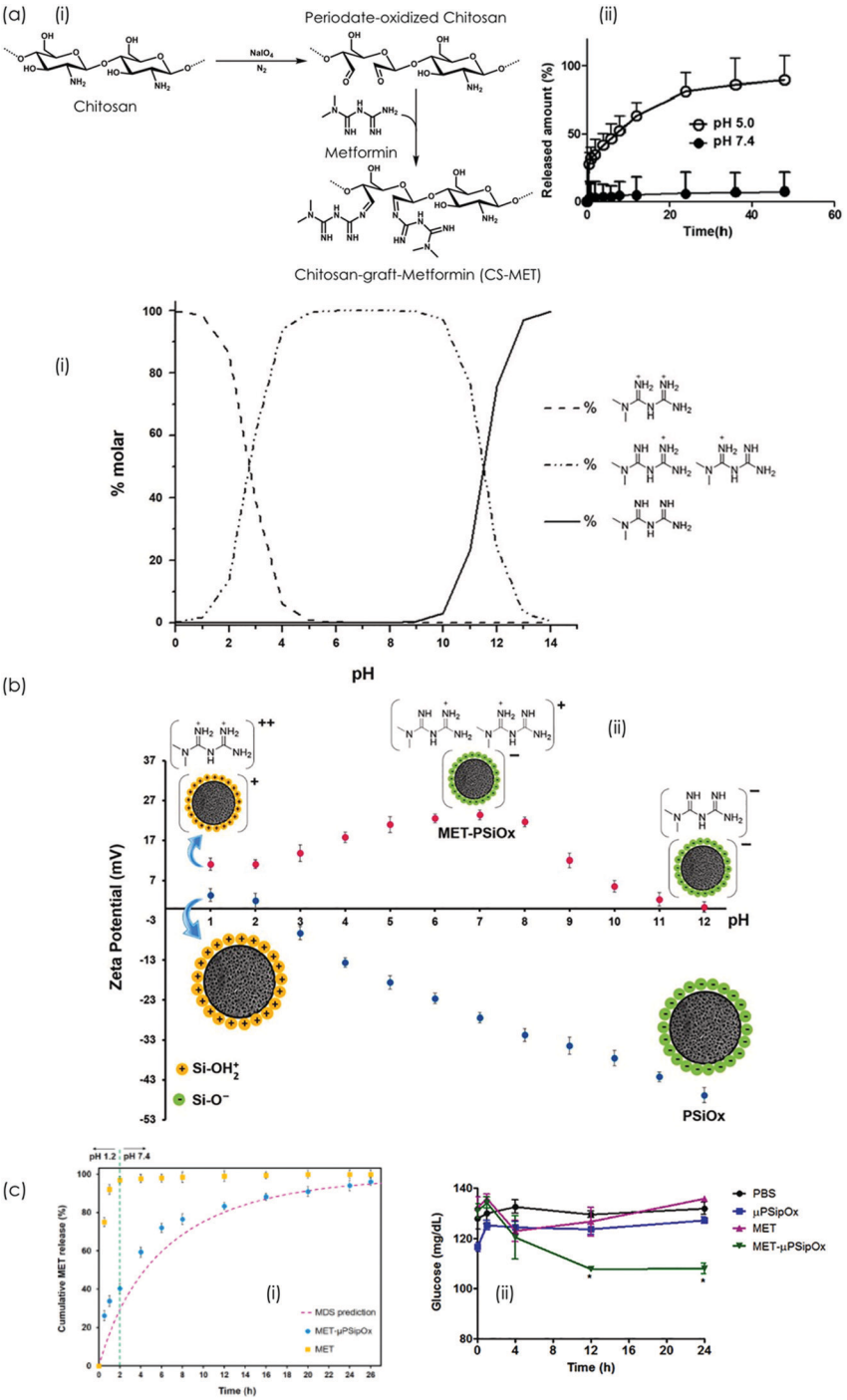

Fig. 12 Biguanides. (a) Chitosan–metformin oral formulation to improve insulin resistance: (i) reaction scheme for the synthesis of chitosan-*graft*-metformin and (ii) *in vitro* release profile of metformin under acidic (pH 5.0) and neutral (pH 7.4) condition at 37 °C. (b) Metformin–porous silicon microparticles complex (MET–μPSiPO$_x$): (i and ii) charge analysis of MET–μPSiPO$_x$ as a function of pH. (c) Metformin–porous silicon microparticles complex (MET–μPSiPO$_x$): (i) *in vitro* release profile of metformin against MET–μPSiPO$_x$ and prediction from surface diffusion model and (ii) BGL after single oral administration of phosphate buffer saline (PBS) (black), metformin (violet), μPSiPO$_x$ (blue) and MET–μPSiPO$_x$ (green). Results are expressed as means ±S.E. for 4 rats in each experimental group (*$p < 0.02$ *vs.* PBS). [Reproduced from ref. 125 with permission from Elsevier, copyright 2019.]

3 h (Fig. 13a). These needles once applied to the skin can be withdrawn and remain intact. Some of us have demonstrated lately the potential of thermo-responsive metformin gels as a transdermal controlled release system.[138] Mixing of metformin with carboxylated reduced graphene oxide (rGO–COOH) resulted in metformin gel formation driven mainly by hydrogen bonding and electrostatic interactions. Photothermal activation of such gels resulted in a stepwise dissolution of the gels and release of

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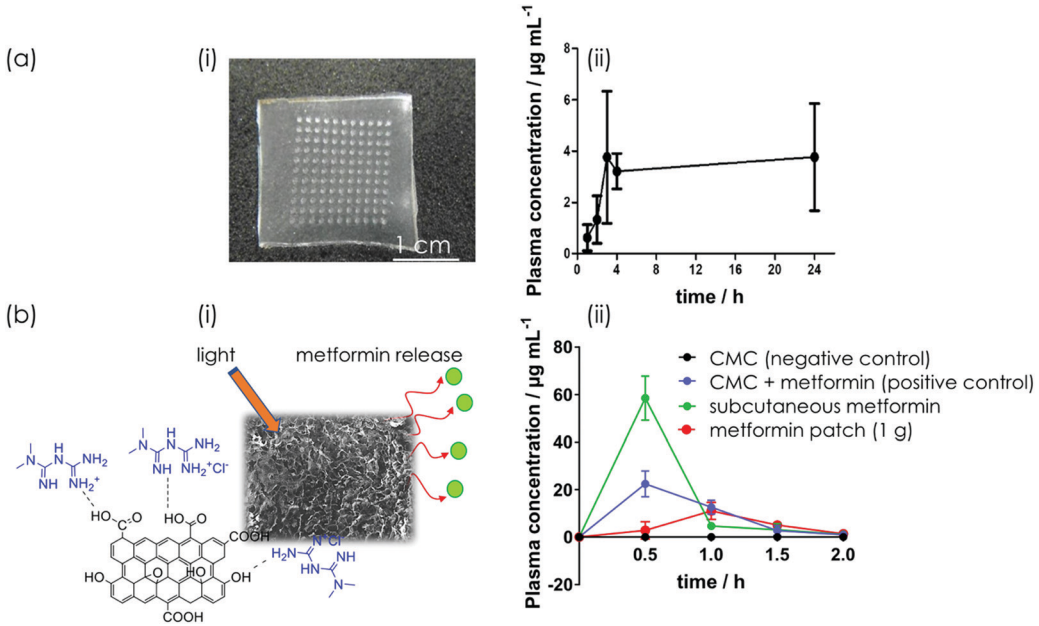

Fig. 13 Transdermal delivery of metformin. (a) (i) Digital image of hydrogel-based microneedle array in swollen state and (ii) *in vivo* plasma profile of metformin following application of hydrogel MNs and solid metformin HCl at a dose of 100 mg. [Reproduced from ref. 137 with permission from Elsevier, copyright 2018.] (b) (i) Photothermal release of metformin from COOH-enriched reduced graphene oxide matrix and (ii) *in vivo* plasma profiles of metformin, following oral administration with only carboxymethyl cellulose (CMC) solution 0.5% w:v (black) or CMC + metformin 200 mg kg^{-1} (blue), subcutaneous metformin injection (green), application of a 2 g metformin gel and activation for 10 min at 0.7 W cm^{-2} (n = 3 per group). [Reproduced from ref. 138 with permission from Royal Society of Chemistry, copyright 2019.]

active metformin in an intermittent on/off cycle with near-infrared light. *In vivo* studies indicated the rise in metformin plasma level, 1 h after patch activation (Fig. 13b).

Where do we stand with other T2D formulations? Microneedle patches have also found interest for the transdermal delivery of rosiglitazone,[139] a thiazolidinedione binding to PPARγ, a nuclear regulatory protein involved in transcription of genes regulating glucose and fat metabolism. This MNs-based patch can effectively deliver browning agents to the subcutaneous adipocytes in a sustained manner and switch on the "browning" at the targeted region. It was demonstrated that this patch was able to reduce treated fat pad size, increase whole body energy expenditure, and improve type-2 diabetes *in vivo* in a diet-induced obesity mouse model. Rosiglitazone is currently under FDA inquiry for increased risk in composite cardiovascular disease events,[140] playing a key role in myocardial dysfunction in COVID-19.

Since SGLT2 inhibitors are orally administered, patients who are injection-averse may prefer these agents over GLP-1 receptor agonists (also called GLP-1 analogues) injections. Nanostructured lipid carriers (NLCs) were considered for the oral delivery of GLP-1 analogues. Shrestha *et al.* investigated the ability of NLCs to induce endogenous GLP-1 secretion and to act as an oral carrier of exenatide and liraglutide, two GLP-1 analogues.[141] These synthetic enzyme-resistant GLP-1 analogues were used instead of the GLP-1, because of their remarkably longer half-life compared to that of GLP-1 (*ca.* 2 min). The GLP-1 analogues bind to pancreatic β-cells GLP-1 receptor, resulting in an increased release of insulin in response to glucose. The lipid composition comprises a solid lipid Precirol ATO®5, an oil phase Miglyol 812N and the peptide (*e.g.* exenatide or liraglutide). Heating the lipid and aqueous phases separately to 75 °C, followed by the formation of a pre-emulsion and cooling down to room temperature, allowed the formation of either exenatide-loaded NLCs (Exe-NLCs) or liraglutide-loaded NLCs (Lira-NLCs) (Fig. 14a). Liraglutide achieved a slightly higher encapsulation efficiency (95.4%) as compared to exenatide (87.5%), a difference which can be attributed to the lipophilic nature of the liraglutide. In that work, GLUTag cells were used as model to assess the influence of NLCs on GLP-1 secretion (Fig. 14a). *In vivo* glycaemic effect studies on non-diabetic mice, proved however to be not efficient, with no significant difference in the BGL compared to the control.

Highly specific targeting of the liver sinusoidal endothelial cells or hepatocytes after oral administration of silver-based quantum dots (QDs) coated with a formaldehyde-treated serum albumin layer was reported recently (Fig. 14b). These Ag-based QDs had an improved bioavailability and delivery of metformin to liver sinusoidal endothelial cells.[142]

A completely different strategy was proposed by Li *et al.*[143] using intraperitoneal administration of amino-acid-functionalized gadofullerene nanoparticles (GFNPs) (Fig. 14c) in diabetic mice. These structures accumulated in the pancreas and liver and decreased hyperglycaemia, along with permanently maintaining normal blood sugar levels in T2D mice even after stopping treatment. The GFNPs reversed the pancreas islets dysfunction by reducing oxidative stress and inflammation responses and fundamentally normalized the insulin secretory function of the pancreas islets.

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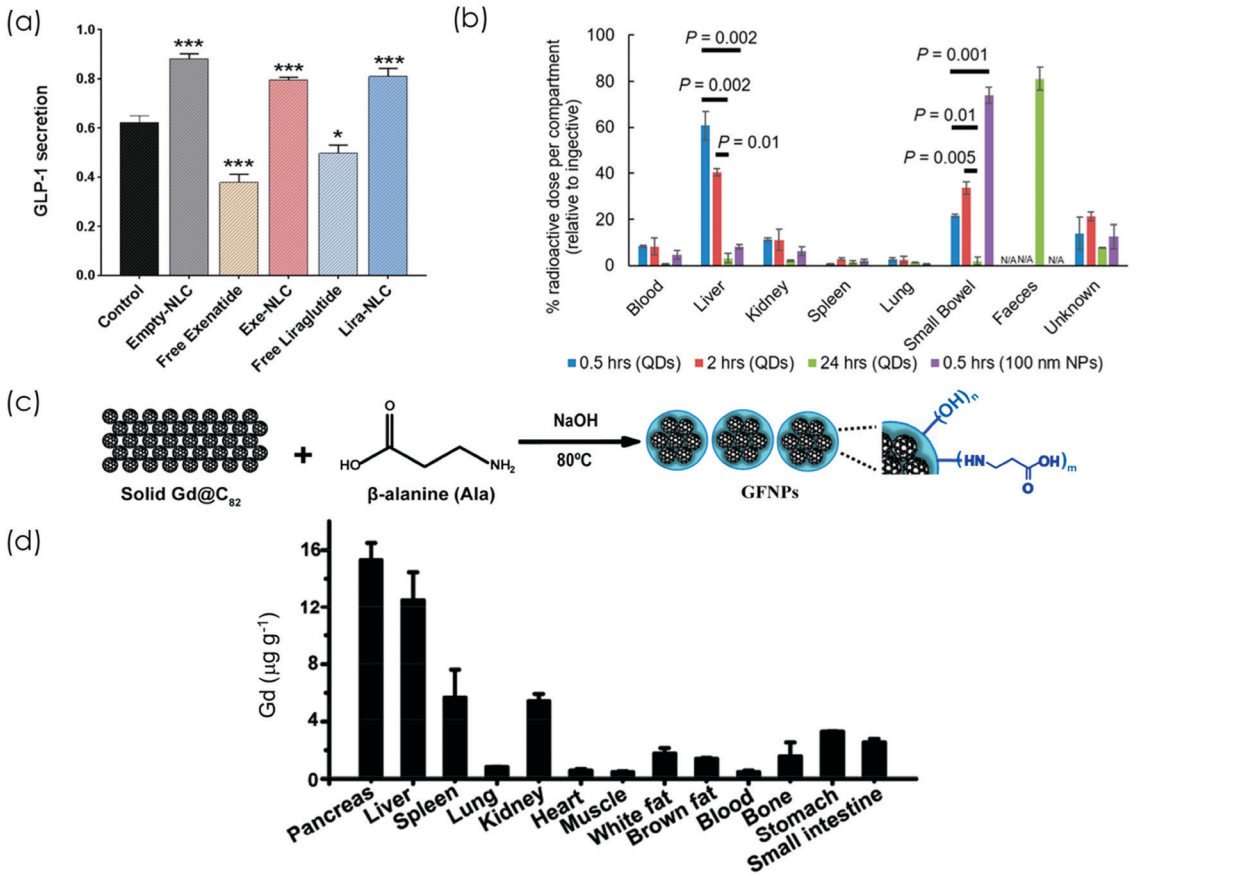

Fig. 14 Drug strategies for oral delivery. (a) Nanostructured lipid carriers (NLCs) modified with GLP-1 analogues: difference of empty-NLCs, Exe-NLCs and Lira-NLCs on GLP-1 secretion from GLUTag cells. Data in mean ± S.E.M. (N = 3, n = 12) with *$p < 0.05$, ***$p < 0.001$, as compared to the untreated control group. Reprint with permission from ref. 141. (b) Biodistribution of radiolabeled ^{3}H-QDs was measured at 30 min, 2 h, and 24 h post-gavage of 100 μL of 1 mM QDs (N = 3, n = 3). Additionally, localization was also examined for ^{3}H–Ag_2S nanoparticles (NPs) with 100 nm diameter. Reprint with permission from ref. 142. The liver demonstrated 60% accumulation of the ingested radioactive ^{3}H-QDs after 30 min, with minimal expression in other organs. (c) Use of amino-acid-functionalized gadofullerene nanoparticles (GFNPs): formulation of the NPs. (d) Biodistribution of GFNPs in mice 12 h after intra peritoneal injection at a concentration of 1 mM. Data is shown as mean ± S.D. with *$p < 0.05$, **$p < 0.01$ by Student's t-test. [Reproduced from ref. 143 with permission from American Chemical Society, copyright 2019.]

A handful of other therapies are considered in addition. Mao *et al.*[144] investigated the efficacy of chitosan/SiO_2 NPs coated with *Echinacea purpurea* ethanol extract containing phenolic acid and isobutylamides to ameliorate diabetic complications. With an average size of 218 ± 42 nm and an encapsulation efficiency of 66.9%, diabetic rats when treated with this nanovector for 7 weeks revealed improved hyperglycaemia, insulin resistance, and plasma fibroblast growth factor 21 resistance.

Sugar sponges made out of phenylboronic acid derivatives (Fig. 15) have been proposed to regulate blood glucose levels.[145] The three components in the proposed structure have unique functions, resulting in a glucose responsiveness matrix with decreased apparent pK_a of the glycopolymer. Crosslinking offered longer circulation time *in vivo*. The sugar-breathing behavior is based on the dynamic recognition between 3-acrylamidophenylboronic acid (AAPBA) and glucose in the blood or glucosyl groups in the glycopolymersomes.

Superparamagnetic iron oxide nanoparticles have also been evaluated for their anti-diabetic effect.[146] It was found that treatment with these particles normalized fasting blood glucose and lowered hyperinsulinemia level in diabetic rats compared to untreated diabetic rats. Nanoscale metal–organic frameworks were created by self-assembly of polydentate bridging ligands and metal-connecting points, showing antidiabetic effects in high-fat diet diabetic rats.[147]

Interestingly, among the antidiabetic drugs (Table 1), neither amylin, α-glucosidase inhibitors nor dipeptidyl peptidase-4 (DPP-4) or SGLT2 inhibitors have been further considered in combination with transdermal delivery or nanoparticle formulations. Amylin, a peptide hormone that is co-secreted with insulin by the pancreatic β cells and is thus deficient in diabetic people, also remains administered by subcutaneous injection. The α-glucosidase inhibitors delay carbohydrate digestion and reduce the postprandial insulin and glucose peak. Also, DPP-4 inhibitors, small molecular weight drugs, can inhibit more than 90% of plasma DPP-4 activity. As these agents increase the blood concentration of GLP-1 by inhibiting its degradation by DPP-4, these molecules present an alternative to antidiabetic drugs that stimulate insulin secretion.

On the one hand, by degrading GLP-1, DPP-4 reduces insulin secretion and partially mediates the intense inflammatory response

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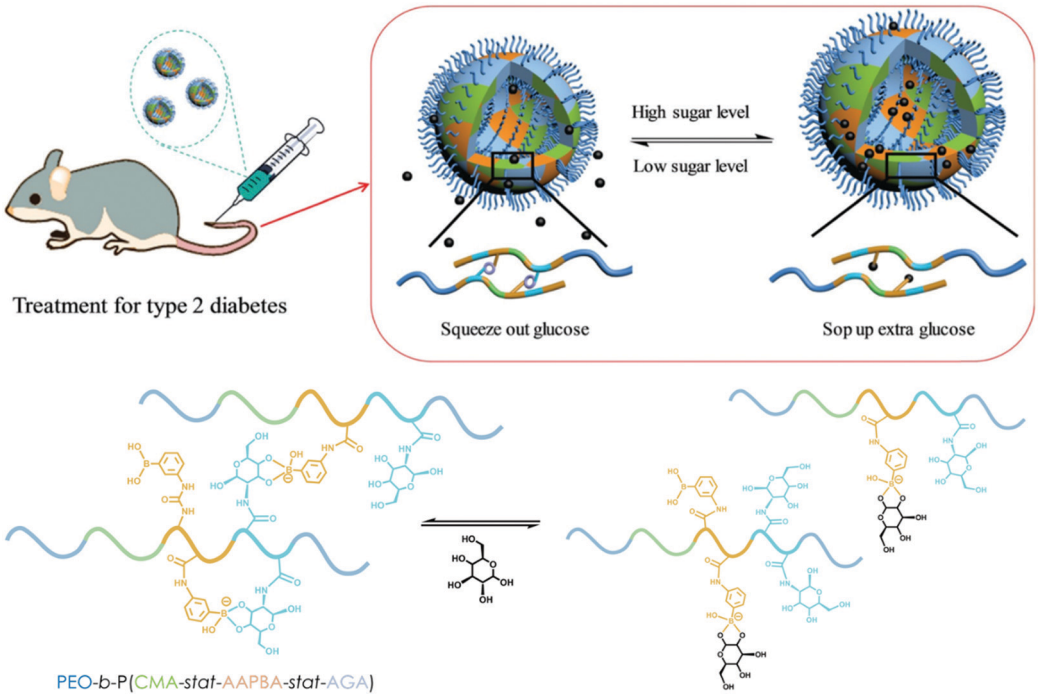

Fig. 15 Blood glucose regulation behavior of glycopolymersomes. The sugar-releasing character of the glycopolymersomes is based on the dynamic binding between the 3-acrylaminophenylboronic acid (AAPBA) units and glucose: high glucose concentration results in glucose binding to the glycopolymersomes by substituting the glucosyl on the polymer chain. When exposed to lower glucose levels, the glycopolymersomes will shrink and release the bound glucose. [Reproduced from ref. 145 with permission from Royal Society of Chemsitry, copyright 2019.]

to the virus responsible for COVID-19. Thus, evidence exists that DPP-4 inhibitors minimize the occurrence of acute respiratory complications added by T2D to the COVID-19 disease.[148] Different DPP-4 inhibitors are available in the market, like linaglipitin (Tradjenta by Boehringer Ingelheim – Eli Lilly) and sitaglipitin (Januvia by Merck). It has been advocated, recently, that these drugs should be tested in clinical trials for their capacity to reduce inflammation in hospitalized COVID-19 patients with T2D. On the other hand, studies of the T2D agent dapagliflozin (Farxiga by AstraZeneca) in patients with COVID-19 infection are currently under scrutiny, as SGLT2 inhibitors might increase the risk for diabetic ketoacidosis.[7]

4.2. Treatment of T1D

The T1D therapy is currently mainly based on two approaches: insulin replacement and islets or pancreas transplantation.

Islets transplantation is particularly attractive as it re-establishes a "physiologic insulin supply" at the appropriate time, leading to improved glucose uptake and storage into tissues, thereby resulting in tight blood glucose control and the prevention of micro- and macrovascular complication risks. Although attractive,[149] islets transplantation remains marginal because of the insufficient number of islets per donors for providing enough islets for one patient. In addition, the reduced number of islets is exacerbated by the current islet extraction and isolation procedures, in which a large number of cells do not survive. This inconvenience makes insulin administration by subcutaneous injection the most current mode of delivery. The objective of this section is to highlight the different insulin formulations currently available on the market. All of them are administered *via* subcutaneous injection. To understand the engineering aspects for this part of diabetic management, details about other administration systems are provided and discussed.

Insulin. Insulin, a peptide hormone produced by β-cells of the pancreas and responsible for allowing glucose in the blood to enter cells, providing them with the energy to function, remains the most widely used and known therapeutic agent for T1D (Fig. 10b). To alter the pharmacokinetic properties of insulin, the B26–B30 region of the insulin molecule, not critical for insulin receptor recognition (Fig. 10b) is generally substituted. For example, Wang *et al.* reported that insulin-facilitated glucose transporter inhibitor conjugate, in which insulin is rendered glucose-responsive *via* conjugation to an inhibitor of glucose transporter.[150] Commercial production of human insulin in the early 1980s enabled production of synthetic human insulin in virtually unlimited quantities and in a cost-effective way.[151] Different insulin formulations are thus marketed and classified according to their action in the body (Table 2).

At high concentration, human insulin can aggregate into dimers and hexamers, resulting in the delay of insulin monomers release into the bloodstream. Indeed, rapid-acting insulin has been formulated to overcome mainly this issue. The first rapid-acting insulin analogue, insulin lispro, has been released in the USA in 1996, followed by the introduction of insulin aspart and glulisine in Europe shortly after.[153] These rapid-acting insulin analogues improve post-prandial plasma glucose (PPG) profiles and reduce the rate of hypoglycaemia.[154]

The rapid-acting insulin aspart by Novo Nordisk Ltd is highly stable after subcutaneous administration, mimics better

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Table 2 Several types of insulin formulations currently marketed[152]

Formulations	Action	Types
Rapid-acting insulin	This type of insulin starts to work just 15 min after administration. It peaks within 30 to 90 min, and its effects last for 3 to 5 h.	Insulin glulisine (Apidra® by Sanofi, Paris, France) Insulin lispro (Humalog® by Elly Lilly Ltd, Indianapolis, USA) Insulin aspart (Novorapid® by Novo Nordisk Ltd, Bagsværd, Denmark)
Short-acting insulin	This type of insulin takes about 30 to 60 min to become active in the bloodstream. It peaks in 2 to 4 h, and its effects can last for 5 to 8 h. It is sometimes called regular-acting insulin.	Human Regular (Humulin R, Novolin R, Velosulin R)
Intermediate-acting insulin	The intermediate type of insulin takes 1 to 3 h to start working. It peaks in 8 h and works for 12 to 16 h. It is usually mixed with mealtime in the morning, before the evening meal, or both. This insulin is administered once or twice daily.	NPH (Humulin N, Novolin N, ReliOn)
Long-acting insulin	It is also named basal insulin. This type of insulin takes the longest amount of time to start working: up to 4 h to get into the bloodstream.	Insulin glargine (Lantus) – lasts up to 24 h Insulin detemir (Levemir) – lasts 18 to 23 h Insulin glargine (Toujeo) – lasts more than 24 h Insulin glargine (Basaglar) – lasts up to 24 h
Ultra-long acting insulin	This insulin reaches the bloodstream in 6 h, does not peak, and lasts about 42 h or longer.	Insulin degludec (Tresiba) – lasts up to 42 h
Insulin mixtures	A combination of two different types of insulin, one that controls blood sugar at meals and another that controls blood sugar between meals.	Humulin 70/30 (NPH/Regular by Elly Lilly Ltd, Indianapolis, USA) Humalog Mix 50/50 (Protamine/Lispro, by Elly Lilly Ltd, Indianapolis, USA) Novolog Mix 70/30 (Protamine/Aspart by Novo Nordisk Ltd, Bagsværd, Denmark)

the prandial insulin secretion profiles and is highly efficient in reducing PPG and HbA1c. Moreover, the use of this analogue significantly reduced the risk of overall hypoglycaemia. Insulin lispro and its biomimetic (SAR-Lis) exhibit improved absorption due to the modification of some amino acids[155] with high efficacy and safety in patients taking multiple daily injections and those using insulin pumps.[155–157]

Insulin delivery *via* subcutaneous injection. Currently, the most widespread mode of insulin delivery is *via* subcutaneous injection. The delivery is achieved by multiple daily injections using conventional syringes marked in insulin units (30, 50 or 100 IU) or pen-like devices as well as insulin containing cartridges.[158] It requires, in general, an injection of slow-acting basal insulin in the morning or evening and frequent dosing of a rapid-acting insulin prior to meals. This invasive mode of administration is often associated with several concerns such as needle phobia, injection pain, self-injection, lifestyle restriction, negative social stigma, poor self-efficacy, patient compliance, leading, sometimes, some patients to stop the treatment. Furthermore, the imperfect reproducibility of the insulin physiology, the risk of lipodystrophy (and potentially insulin resistance), the heat sensitivity of solutions that must be kept cool, make the need of alternative routes for insulin delivery essential.[159–161]

Despite the extensive use or artificial insulin, several problems gradually develop with insulin as a long-term clinical treatment for diabetes. Use of subcutaneous administration and/or insulin pump delivery insulin alone directly into the portal vein. Selecting the ''right'' dose and timing is crucial as injecting an increased dosage of insulin causes hypoglycaemia, a dangerous life-threatening fall in BGL.

Insulin delivery *via* insulin pumps. With the need for a more convenient method of administration and as efficient alternative for patients who are unable to administer injections, the insulin pen, with disposable insulin cartridges and external continuous-insulin pumps, is available.[162] The latter is mostly operated using electromechanical pumps with superimposed meal-related boluses, providing a constant supply of rapid-acting insulin into the subcutaneous tissue at preselected rates. Insulin delivery by pumps is more efficient than multiple daily injections for stimulating blood glucose variability. This efficiency has been monitored by measuring the mean glycated haemoglobin HbA1c. Because haemoglobin is glycated by hyperglycaemia, and remains present in blood over the past 2 to 3 months (period of the haemoglobin renewing), HbA1c has become a consistent biomarker of the average BGL.[163] High HbA1c in patients treated with antidiabetics means that glycaemic control has not been achieved and adjustment of medicines is required, whereas its decrease mirrors of BGL drop and efficient treatment. The insulin pumps diminished HbA1c by approximately 0.5% over several years, with a reduced occurrence of severe hypoglycaemia.[164]

Non-invasive or semi-invasive insulin delivery modes. To improve the quality of life of patients with diabetes, alternative approaches for controlling insulin delivery have been extensively explored (Fig. 10a), including non-invasive administration routes such as oral, nasal, pulmonary, as well as semi-invasive transdermal methods.[165–233]

Oral delivery. The literature on orally administered insulin formulations largely exceeds that of any other administration routes (Fig. 16).[165–188] Indeed, oral administration of insulin is largely preferred to other routes due to the convenience and good

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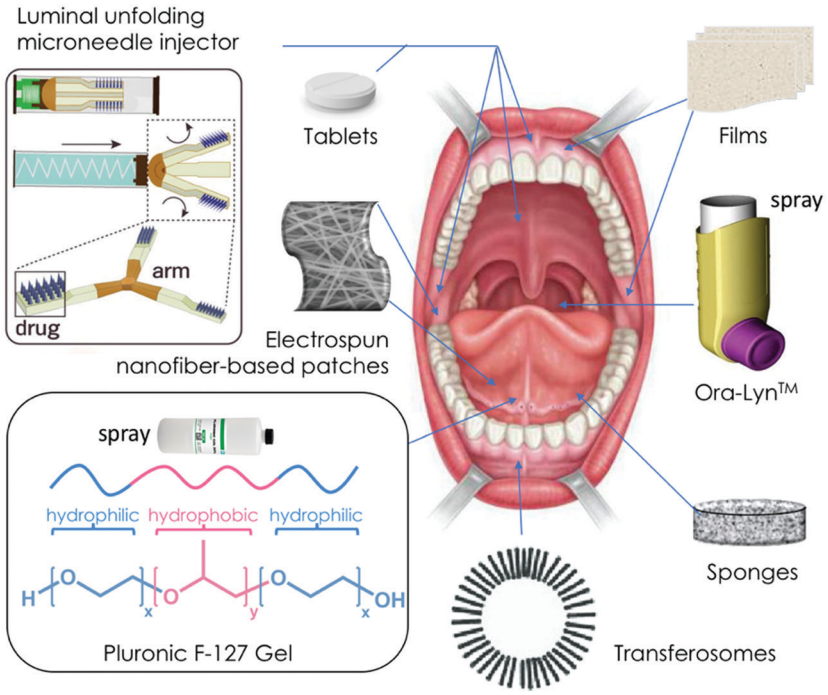

Fig. 16 Insulin delivery *via* oral cavity using different approaches. Adapted from ref. 185.

patient compliance. The hydrophilic nature of insulin and its limited ability to cross the lipid bilayer of biological membranes make oral bioavailability of insulin limited. The intestinal mucus is a robust barrier for insulin and particles alike to reach the epithelial surface, especially for cationic and hydrophobic structures. Hydrophilic and neutral mucin particles have been prepared *via* PEGylation and investigated for oral insulin delivery as proposed in seminal work by Mumuni *et al.*[188] However, this approach results in the reduction of affinity with the lipophilic and negatively charged cell membrane, leading to inefficient cellular uptake. Use of lipid nanoparticles have thus been undertaken notably for GLP-1 conjugates.[165,175]

With the first reports on the oral delivery of insulin dating in the 1970s and 1980s using liposomes and polymeric nanoparticles, we look back currently to a few decades of efforts in oral delivery of diabetic peptides and proteins. These nanoparticle-based drug delivery systems offer many advantages as they can carry and deliver the drug to a target site, increase the therapeutic benefits and minimize the side effects of the drug. These structures aimed primarily at improving the oral bioavailability of diabetic peptides and proteins by incorporating tight junctions' openers, membrane fluidizers, hydrophobic complexing agents, usually referred as permeation enhancers and/or enzyme inhibitors.[169,171]

Considerable progress has been made in the development of different nanostructures as effective vehicles for the delivery of insulin and diabetic peptides.[167–172] Polymers such as poly(lactide-*co*-glycolide) (PLGA) were found to be ideally adapted for high drug loading of insulin and used as major targets of nanoinsulin formulations with the goal to reduce the dose of insulin and help in suspended release of insulin from its nanocapsule.[173,174] Even though improvements can be significant as compared to unformulated peptides, oral insulin bioavailability remains low compared to intravenous or subcutaneous administration. Success in commercialisation for oral insulin delivery remains thus limited.[151]

The hydrophilic nature and poor ability to cross the lipid bilayer of biological membranes are the major obstacles of therapeutic proteins such as insulin preventing efficient crossing of the mucus layer and the underlying intestinal epithelium. Opposite surface charge properties are required for nanostructures for good mucus penetration and high epithelial uptake. Co-administration of insulin with sodium *N*-(8-[2-hydroxybenzoyl]amino) caprylate (SNAC), an absorption enhancer, is one widely used strategy to obtain a lipophilic complex with improved capability to cross the mucus and intestinal epithelium and is part of the rare clinical tests on oral drug delivery (Table 3). Self-gelation using chitosan and aqueous soluble snail mucin was recently proposed by Mumuni *et al.* for oral insulin delivery.[166] The mucin interacted ionically with chitosan to obtain insulin loaded nanoparticles with smooth surface and positive surface charge. To overcome the dilemma of insulin administration due to the coexistence of intestinal mucus and epithelial barriers, the team of Huang proposed the use of NPs composed of insulin, cell penetrating peptides and a mucus inert dissociable hydrophilic coating based on a *N*-(2-hydroxypropyl)methacrylamide copolymer derivative.[176] A 20-fold higher insulin absorption on mucus-secreting epithelium cells was observed, with a prominent hypoglycaemic response after oral administration and increase of serum insulin concentration in diabetic rats. The same concept was proposed by the team using zwitterionic NPs with excellent mucus penetrating properties and affinity with epithelial cells.[177] More recently, Wu *et al.*[178] demonstrated the interest of mucus-penetrating virus-inspired biomimetic

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Table 3 Clinical studies aimed at oral insulin delivery

Company	Technology	Websites or citations
Biocon Limited, Bangalore, India, IN-105	Pegylated insulin formulation with absorption enhancer to improve stability and solubility and promoting rapid absorption	https://www.businesswire.com/news/home/20080908005828en/Biocon-Limited-Presents-Human-Clinical-Data-IN-105
Novo Nordisk Ltd, Bagsværd, Denmark, GIPET technology	Enteric coated capsule containing caprate absorption enhancer (withdrawn after phase II)	https://www.pharmaceuticalonline.com/doc/merrion-pharmaceuticals-plc-signs-feasibility-0001
Novo Nordisk Ltd, Bagsværd, Denmark, Eligen technology	Insulin with SNAC absorption enhancer (phase II suspended)	https://emisphere.com/technology/
Oramed, Jerusalem, Israel, ORMD-0801	Enteric-coated capsule containing insulin with an absorption enhancer to protect insulin during transit through the stomach followed the increased absorption	https://www.oramed.com/oramed-initiates-patient-recruitment-for-a-new-clinical-trial-in-israel-of-its-oral-insulin-drug-ormd-0801-in-the-treatment-of-type-1-diabetes/

PLGA nanoparticles with cationic octa-arginine peptide and anionic phosphoserine units. The small size and neutral surface charge achieved rapid mucus penetration. Hydrolysis of anionic phosphoserine units by the intestinal alkaline phosphatase led to a positive surface potential and increased cellular uptake and transepithelial transport. The hypoglycaemic effect of released insulin was consistent with an equivalent dose of free insulin. Oral administration of these NPs generated a prominent hypoglycaemia response and induced a maximal blood glucose reduction of 32%. Another system is that proposed by Wang *et al.*,[179] where bovine serum albumin was adsorbed on cationic liposomes forming a protein corona around the liposomes. These nanostructures conquered the mucus and epithelium barriers and improved oral insulin availability. *In vivo* investigations revealed that the uptake amount and transepithelial permeability is 3.2- and 7.9-fold higher than that of free insulin, respectively. Poly(*n*-butylcyanoacrylate) NPs loaded with insulin were recently reported for their good stability in gastric fluid with controlled release in intestine; the release rate increased with increasing insulin polymer mass ratio. These particles achieved excellent mucus penetration (>60%, 10 min) and strong gastrointestinal retention (70%, 12 h) with promising hypoglycaemic effects.[180] Amylase and pH responsive nanostructures based on carboxymethyl starch/poly(2-isobutyl acrylic acid) hybrid microgels were used by Liu *et al.* as effective enteric carrier for oral insulin delivery.[181] The accelerated decomposition of the microgels in response to amylase was demonstrated by chromogenic reaction and morphology changes. Oral administration to diabetic rats led to a continuous decline in the fasting blood glucose level with 2–4 h with a hypoglycaemic effect maintained over 6 h *in vivo*.

An interesting, while technically challenging approach, has been introduced by Banerjee *et al.*[182] Intestinal iontophoresis from insulin loaded mucoadhesive patches was proposed to increase oral insulin transport. It has been shown that application of an electrical current to intestinal cells resulted in opening the tight cell junctions with a 3-fold improvement in paracellular transport of insulin. When used *in vivo*, insulin loaded mucoadhesive patches produced profound hypoglycaemia. The same team developed further an effective oral insulin formulation based on choline and ionic liquid (CAGE). When 10 IU kg^{-1} insulin-CAGE was orally delivered in enterically coated capsules using an oral gavage, a sustained decrease in blood glucose of up to 45% was observed.[183]

A glucose-responsive oral insulin delivery system based on Fc receptor-targeted liposomes with glucose-sensitive hyaluronic acid shell for postprandial glycaemic regulation has been recently proposed by Yu *et al.*[184] After oral administration, the hyaluronic acid shell detaches in the presence of high intestinal glucose concentrations due to competitive binding of glucose with the phenyl boronic acid groups conjugated with hyaluronic acid. The exposed Fc groups facilitate intestinal absorption.

Rather futuristic and technologically demanding approaches are those introduced by the team of Traverso.[185,186] The ingestible capsule, the so called luminal unfolding microneedle injector, allows for oral delivery of drugs, by rapidly propelling dissolvable drug-loaded microneedles into intestinal tissue. Using insulin as model drug, the luminal unfolding microneedle injector showed a faster pharmacokinetic uptake profile and a systemic uptake >10% of that of a subcutaneous injection over a 4 h sampling period.[185] Inspired by the leopard tortoise's ability to passively reorient, they also developed another indigestible self-orienting millimetre-scale applicator that autonomously positions itself to engage with GI tissue. Using insulin as model, the applicator exhibited active insulin delivery comparable to subcutaneous administration.[187]

Buccal delivery. Buccal insulin delivery is attracting increased attention as it is painless and holds on-demand features (Fig. 16).[189–193] One easy approach in terms of preparation is muco-adhesive insulin tablets formed by mixing insulin with carbopol 934, hydroxypropyl cellulose or hydroxypropyl methylcellulose (HPMC) and different absorption promoters.[189] These tablets can be placed in different parts of the oral cavity such as the mucosa lining of the cheek, between the lip and the gum and to the palate. A mixture of HPMC : carbopol 934 1 : 1 containing 1% polyoxyethylene-9-lauryl ether led to 26% reduction in plasma glucose levels and producing 9.4% relative hypoglycaemia.

With the aim to improve the comfort of insulin administration, thin and flexible buccal films were developed. In the work of Morales *et al.*,[193] a cationic polymethacrylate thin film based on trimethylammonioethyl methacrylate chloride (Eudragit® RLPO) was loaded with insulin-coated NPs. Insulin-loaded NPs embedded into chitosan films have shown to improve insulin absorption using a EpiOral buccal mucosa model.[190] Chitosan-based buccal films prepared from thiolated dimethyl ethyl chitosan and containing insulin NPs were tested *ex vivo* on excised rabbit buccal

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mucosa and achieved enhanced buccal delivery of insulin.[191] Bilaminated films, prepared by a simple casting procedure consisting of a muco-adhesive layer based on a chitosan-ethylenediaminetetraacetic acid hydrogel film containing insulin and a baking layer made of ethylcellulose, exhibited pronounced hypoglycaemic effects in rats following buccal administration, achieving a 17% pharmacological availability compared with subcutaneous insulin injection.[192] A new form of deformable lipid vesicle, known as a transferosome, displayed excellent buccal absorption of insulin in rabbits.[194,195] Transferosomes can minimize the defective transdermal permeation of a number of low and high molecular weight drugs.[196] Thanks to their improved structure, transferosomes can squeeze and change their form, allowing them to penetrate deeper to the skin even though the pores are much smaller than their size. Their structure is similar to liposomes and consists, in the case of buccal delivery, of soybean phosphotidylcholine, cholesterol, and sodium deoxycholate.

In addition, many studies have tested the effect of absorption enhancers to improve buccal insulin delivery, one of them being Pluronic F-127. Pluronic® is a class of commercially available hydrophilic-*block*-hydrophobic-*block*-hydrophilic copolymers of low toxicity, displaying bioadhesive nature and weak immunogenic properties.[197–199] Morishita *et al.* demonstrated[199] that a formulation of Pluronic F-127 gel containing unsaturated fatty acids, improved insulin release, caused continuous hypoglycaemic effects in normal rats, with oleic acid giving the highest pharmacological availability of 15.9 ± 7.9%.

Another approach that is used for buccal insulin administration is a spray. Oral-Lyn™ is a market available buccal insulin preparation consisting of a mixed micellar solution containing insulin and absorption enhancers developed by Generex Biotechnology Corporation. It is delivered *via* the company's RapidMist™ hand-held device. The solution enables buccal absorption of insulin due to the relatively large micelles used (>7 μm), and prevention of deposition in the lungs. Each puff delivers 10 IU and with an absorption rate of 10%, resulting in 1 IU absorbed.[200]

Sponges, highly porous and flexible materials, are ideal as they possess mucoadhesive properties. Portero *et al.*[201] prepared a sponge from a mucoadhesive chitosan layer containing insulin and an impermeable protective layer made of ethylcellulose. Closely related is the use of electrospun nanofiber mats.[202] Electrospinning is an effective technique for the cost-effective production of nanofibers from polymer solutions, which possess large surface-to-volume ratios and pore sizes in the nanometer range. Thus, nanofibers and nanofiber mats can be applied as drug delivery systems. Sharma *et al.*[202] investigated a biodegradable mucoadhesive insulin-loaded nanofiber patch composed of poly(vinyl alcohol) and sodium alginate. *In vitro* insulin release studies from the nanofiber mats showed approximately 99% cumulative drug release after 10 h, while *in vivo* experiments on male Wistar rats by the sublingual route indicated a significant decrease in the BGL in the range of 113 ± 3.1 to 117 ± 4.2 mg dL^{-1}. More recently, Lancina *et al.*[203] produced chitosan-based nanofiber mats mixed with poly(ethylene oxide) and insulin for buccal insulin delivery studies. Insulin permeation across the buccal mucosa was measured in an *ex vivo* porcine model and the nanofiber mats achieved up to 16 times higher buccal permeability compared to free insulin.

Nasal delivery. The pioneer work on the feasibility of nasal administration of insulin dates back to the 1990s from two complementary studies performed on both adults and children with diabetes.[204,205] However, it was only in 2006 when the first inhaled powder form of recombinant human insulin was approved by FDA and available in Europe and USA markets.[206] Nasal insulin formulations are based on liposomes, chitosan, cyclodextrin, gelation-like polymers and others. Chitosan, due to its high facility to nasal absorption by electrostatic attraction and nasal epithelial components for insulin to pass through the nasal membrane, has great potential for nasal delivery.[94] Sintov developed lispro-loaded microemulsions; the microemulsion spray preparation provided a bioavailability of 21.5% relative to subcutaneous insulin administration.[207] However, due to rapid clearance from the nasal cavity by the mucociliary mechanism and enzymatic degradation, this approach remains not efficient.[208,209] In fact, only small amounts of insulin are detected in the bloodstream after nasal administration of up to 160 IU.[96]

Pulmonary delivery. While corticosteroids and other drugs can be delivered effectively *via* pulmonary administration, hydrophilic macromolecules such as insulin have limited permeation through the 1–10 μm thick mucus layer that covers the pulmonary epithelium. In addition, most proteins are subjected to degradation by proteases or clearance by macrophages in the alveoli of the lung, which also secret short-lived peroxidases, and inflammatory mediators able to degrade the therapeutic protein. The issue that needs to be addressed is how to deliver insulin into the alveoli directly without being deposited on the air passages on its way to the alveoli. So far, no such method has been developed. It might stay an unreachable target due to the presence of billions of tentacles (cilia) on the surface of the cells lining the air passages that pick up any particulate matter from the breathed air that passes by.

Exubera (Pfizer) was released in 2006 as the first FDA-approved inhaled insulin on the market.[210] However, Exubera was rapidly withdrawn due to its side effects, such as the notable increased risk of hypoglycaemia for people smoking and for patients with unstable or poorly controlled lung disease such as asthma or chronic obstructive pulmonary disease. In 2015, Afrezza, an inhaled insulin product became available.[211] Afrezza is a rapid-acting inhaled insulin that is administered at the beginning of each meal. It is acting within 12 to 15 min, peaking at 30 min, and being out of the system in 180 min. However, also this formulation of inhaled insulin was taken off the market based on a failure to meet its expectations, in addition to suspected carcinogenic effects of inhaled insulin. This makes research in this domain extremely challenging.

Amidi *et al.* demonstrated that insulin loaded *N*-trimethyl chitosan powder formulations allowed efficient pulmonary delivery of insulin.[212] Indeed, while small particles (<1 μm) are predominately exhaled, particles of 1–4 μm in diameter are primarily absorbed in the alveoli or deep lung, with larger ones distributed in the tracheobronchial and oropharyngeal regions.[213] In a similar effort, PLGA spheres of 5–7 μm were used by

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Kawashima *et al.* and showed hypoglycaemic effects which lasted for 48 h.[214] Liposomes, with their enhanced pulmonary uptake of insulin, revealed improved hypoglycaemic effect compared to free insulin.[215] Liposomes, consisting of dipalmitoylphosphatidyl choline:cholesterol, showed in particular enhanced effects on insulin absorption, due to the opening of the tight junctions of the epithelial cells without damaging the mucosal cells by the liposomes.[215] Bi *et al.* reported a dry powder inhalation system based on insulin-loaded solid lipid NPs with an entrapment efficiency of about 70%, a relative pharmacological bioavailability of 44.4% and prolonged hypoglycaemic effect after intratracheal instillation into diabetic rats.[216]

Transdermal delivery. The modern age of transdermal drug delivery started in 1979, with the marketing of Transderm Scop, the first patch against motion sickness using scopolamine as drug.[217] The FDA-approved drugs for transdermal administration share several characteristic features such as low molecular weight, lipophilicity and relatively low dose administration requirements.[218] The highest selling transdermal patch remains the nicotine patch, but the transdermal delivery industry is growing worldwide with an expected market value of 8127 million USD in 2025.[219] From a physicochemical point of view, an ideal transdermal drug candidate has to meet a number of requirements: (i) low molecular weight, (ii) lipophilic character, and (iii) relatively low dose administration. Insulin is not an ideal transdermal drug candidate due to its large molecular weight, restricting its passive transdermal delivery. A number of different innovative approaches have been explored to modify the barrier properties of the *stratum corneum* (SC), evolving from passive to active methodologies (Fig. 17a). One of the first approaches is the use of chemical penetration enhancers, which increase the drug partitioning into the barrier domains of the SC without long-term skin damage. The active mode of skin permeabilization is associated with physical methods based on the formation of microcavities into the skin *via* mechanical or thermal approaches (Fig. 17b). Another advantage is that they offer more reproducible control over the delivery profile of the drug, thus overcoming lag times between the application and the drug reaching the systemic circulation when compared to the classical passive methods. What is applicable to the delivery of macromolecules such as insulin?

Iontophoresis is a promising technique for enhancing transdermal administration of charged drugs. However, conventional iontophoresis is not sufficient for effective delivery of large, hydrophilic, or electrically neutral molecules. Almost ten years ago, Chen *et al.* reported the use of unilamellar nanovesicles with membrane thickness of 3–5 nm and 89% insulin entrapment efficiency for insulin delivery through microneedle-induced skin microchannels using in addition iontophoresis for enhancing transdermal delivery.[220] The permeation rates of insulin was 713 times higher than those measured for passive diffusion. Specifically, *in vivo* studies revealed that the BGLs of diabetic rats were 33.3% and 28.3% of the initial levels at 4 and 6 h, which are comparable to those induced by subcutaneous injection of insulin. A comparable approach was used by Kajimoto *et al.*[221] employing a lipid composition of 12-dioleoyl-3(trimethylammonium)propane : egg phosphatidylcholine : cholesterol 2 : 2 : 1, a current supply of 0.45 mA cm^{-2} and a duration 1 h, liposome-encapsulated insulin was tested for transdermal delivery using a rat model of T1D. Interestingly, iontophoresis of liposome-encapsulated insulin resulted in a gradual decrease in BGLs, with levels reaching 20% of the initial value at 18 h after administration. This low BGL was maintained for up to 24 h. A significant amount of insulin was also

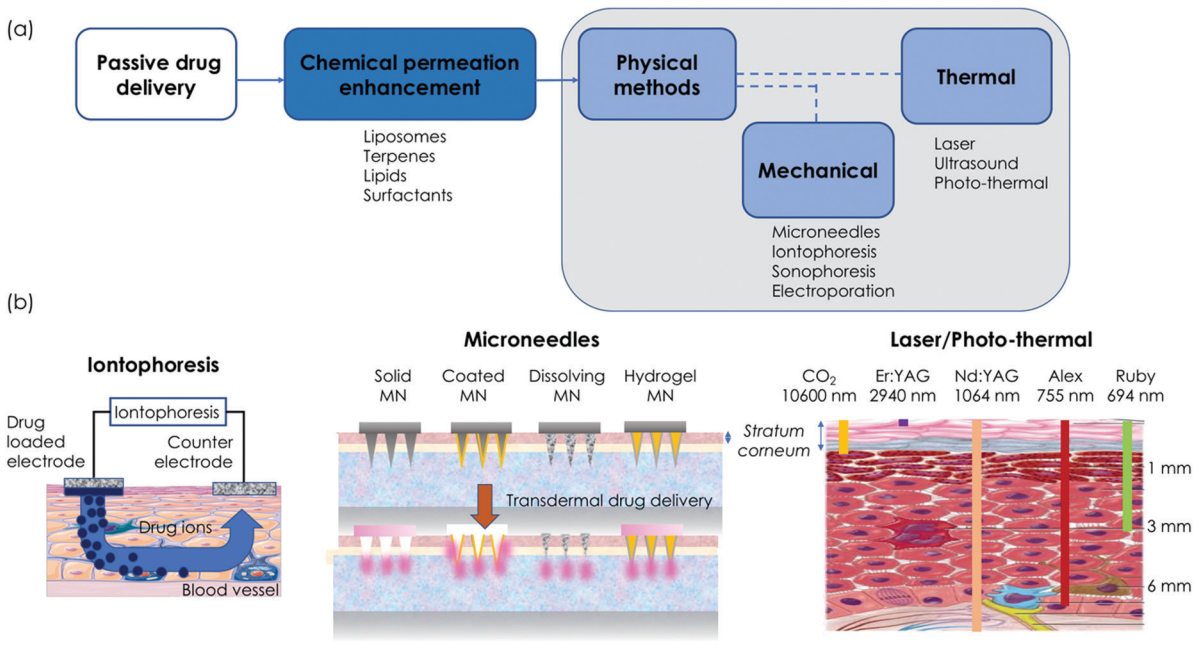

Fig. 17 Transdermal drug delivery. (a) Technology evolution from passive transdermal delivery, like in the nicotine patch, to the use of chemical permeation enhancers and the application of different physical enhancement methods based on the formation of transient micropores in the skin. (b) Different physical enhancement methods for transdermal drug delivery.

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detected in plasma 18 h after iontophoresis of liposome-encapsulated insulin.

However, the combination of skin barrier impairment using MNs coupled with iontophoresis may be the most efficient strategy. This approach has been pursued by the team of Donnelly,[222] who reported on the release of insulin from polymeric microneedles based on poly(methylvinylether comaleic acid) formed in laser-engineered silicon micromould templates.[223–226] Since the first proof-of-concept of such a device for enhanced drug delivery into the skin,[227] a large growing body of literature has investigated various microfabrication technologies.

Hydrogel-forming MN arrays based on poly(methylvinylethene) and polyethylene glycol, 15% and 7% weight, and crosslinked at 80 °C for 24 h have been first described by Donnelly *et al.* (Fig. 18a) in 2012 using aqueous blends of polymeric materials.[223] Upon skin application, the MN array swells and liberates insulin without destruction of the array. Further studies by the same group demonstrated that transdermal drug delivery can be easily controlled by modulating the crosslinking density of the hydrogel matrix.[226] This indicates that drug delivery can be tailored on a case-by-case basis to meet the requirements of various drugs with different therapeutic windows. A similar concept was validated by Yamamoto and coworkers[228] using MN arrays based on hyaluronic acid loaded with insulin.

Thermal ablation, based on the selective removal of the SC by localized microsecond heat pulses, is another promising alternative to increase the permeability of the skin's outer barrier layer while sparing deeper living tissue.[229,230] Cell ablation and the transient creation of microchannels or pores typically 50–100 μm in diameter are observed. Laser-based thermal ablation requires appropriate choice of the laser wavelength (Fig. 18b). Visible light (400–700 nm) is readily absorbed by blood and the skin surface

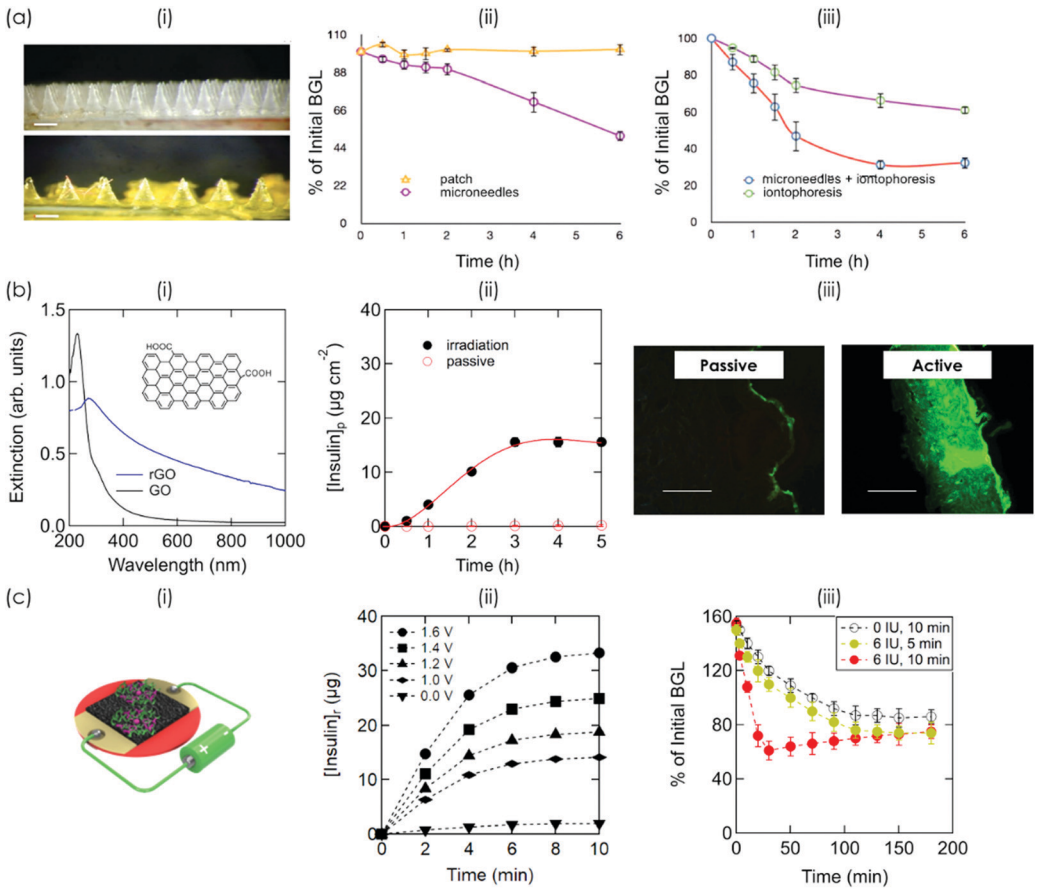

Fig. 18 Physical enhancement methods for insulin delivery. (a) Microneedle (MN) arrays for insulin delivery: (i) representative light microscopy images of hydrogel-based MN arrays based on poly(methylvinylether) and polyethylene glycol before and after insertion in rats for 12 h. Scale bars represent a length of 300 μm, (ii) % drop in BGLs following delivery of insulin from patches alone and from integrated hydrogel-forming MN arrays in rats, (iii) % drop in BGLs following application of an electric current (0.5 mA for 2 h) with the insulin-loaded patch and in combination with integrated hydrogel-forming MN arrays. [Reproduced from ref. 223 with permission from Wiley, copyright 2011.] (b) Photothermal insulin release: (i) UV-vis spectra of graphene oxide (GO) and reduced graphene oxide (rGO); (ii) *in vitro* permeation profiles of insulin, (iii) skin optical micrographs after permeation with fluorescently-labeled insulin passively and *via* photo-thermal activation for 10 min at 980 nm. Scale bars are 300 μm (passive) and 100 μm (active). Adapted from ref. 26. (c) Electrothermal insulin delivery: (i) schematics of the active side based on nano-perforated gold layers formed by colloidal lithography on polyimide substrates coupled to rGO insulin reservoirs, (ii) cumulative *in vitro* release profile from the patch $[insulin]_r$ in PBS (pH 7.4), maintained at 37 °C upon application of different heating ramps, (iii) change in BGL with time: negative control group with insulin-free patches applied and activated (1.0 V, 10 min) (black), group with insulin-loaded electrothermal patches (6 IU) and activated (1.0 V, 5 min) (red) and group with insulin-loaded electrothermal patches (6 IU) and activated (1.0 V, 10 min). Adapted from ref. 27.

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components, thereby limiting its tissue penetration to <10 mm with low heating effects and no skin ablation. Using an erbium–yttrium–aluminum-garnet (Er:YAG) laser as well as a CO_2 laser, located in the far-infrared (above 1400 nm), heating and micro-poration of the skin through water excitation and explosive evaporation of the epidermis is observed. The Er:YAG laser is preferentially used as its light is strongly absorbed by water and favored properties for enhanced transdermal drug delivery when compared to the CO_2 laser.[231] The Er:YAG laser treatment was used to study the transdermal delivery of insulin,[232] which proved that Er:YAG laser can be effective for transdermal delivery of macromolecules.

The advances made in the synthesis of nanomaterials proved to be central for recent developments in transdermal drug delivery (Fig. 18b). Photo-thermal active materials such as reduced graphene oxide (rGO)[233] revealed to be beneficial for photo-thermal skin ablation and insulin delivery. The strong optical absorption across the near infrared spectrum of rGO allows rapid temperature rise and insulin delivery *via* the skin.[26] For this purpose, a photo-thermal active hydrogel patch was developed. The 3D structured hydrogel enabled insulin loading *via* interaction with the porous hydrophilic network of the PEG-based hydrogel. The temperature reached in the patches upon light illumination was high enough to interfere with the affinity between human insulin and rGO, resulting in effective insulin release. Using such insulin-loaded photo-thermal active hydrogels (Fig. 18b), the affinity of insulin inside the hydrogel can be modulated upon near infrared irradiation with a permeation of insulin taking place at a flux of $J = 5.8 \pm 0.2$ μg cm^{-2} h^{-1} in a relatively short time scale (0–3 h).

To these thermal approaches, a novel transdermal insulin delivery patch was developed based on electrothermal activation.[27] The integration of nano-heaters into transdermal patches loaded with insulin enables efficient release, capable to reduce the BGL in mice in a comparable manner to insulin injection (Fig. 18c). The nanoporous metallic layer core offers air and moisture permeability. Application of insulin-loaded patches to the skin of mice resulted in blood glucose regulation within minutes. With the need of power densities below 200 mW cm^{-2} to reach a steady state temperature of 52 °C in a few seconds, the transdermal drug delivery device is adapted for platforms using commercially available handheld battery systems.

5. One of the emerging technologies for diabetes: gene therapy

Nucleic acids such as plasmid DNA (pDNA), antisense RNA, microRNA (miRNA), small hairpin RNA (shRNA) or small interfering RNA (siRNA) hold significant promise for developing new gene therapies, but require systemic administrations.[234] Most of synthetic nucleic acid delivery systems are obtained through self-assembly of nucleic acid molecules with cationic lipids or cationic polymers in an aqueous medium.[235,236] Lipid-based nanoparticles have been studied as systemic gene delivery carriers. The first method, described by Felgner *et al.* in 1987, used mixtures of DNA and cationic liposomes to form cationic lipid/DNA complexes.[237] *In vitro*, the high cationic charge makes these complexes efficient delivery carriers. However, gene delivery *in vivo* usually fails due to low gene transfer efficiency and their rapid clearance by the reticulo-endothelial system.[238,239] Stable DNA-containing particles could be developed using classical liposome-based systems.[240] Then, a lipid–protamine–DNA formulation was prepared for *in vivo* gene transfer and offered better protection of plasmid DNA, because protamine can condense DNA and form a virus-like structure.[241,242] In this respect, efforts have been made to enhance the stability of the complex of cationic lipid with DNA. When a PEG–lipid was used in the formulation, plasmid–lipid particles exhibited a long circulation time, reached the cell target by the enhanced permeability and retention effect, and achieved a higher gene expression than the lipoplex.[243] In recent years, new lipidoid nanomaterials based on triazinanetrione and amine mixtures along with phospholipid, cholesterol and PEG–lipids have been successfully applied for co-administration of pDNA and siRNA both *in vitro* and *in vivo*.[244] Simultaneous gene expression and silencing therapy therefore represents an attractive strategy to counteract malfunctions of multiple genes involved in autoimmune diseases such as diabetes.

In T1D, immune cell systems destroy insulin-producing β-cells in the pancreatic islets, resulting in hyperglycaemia.[245,246] In T2D, the low concentration of insulin in blood due to insufficient insulin secretion from pancreatic β-cells induces an increase of glucose level in the patients. Several strategies have been devised in order to protect β-cells from autoimmune destruction or modulate the insulin secretion from own pancreatic β-cells of patients including:

(1) insulin gene therapy,
(2) stem cell differentiation,
(3) islet transplantation,
(4) β-cell regeneration.

Insulin gene therapy introduces foreign genes in the body that can restore insulin production.[247] To do this, the choice of the carriers and the route of administration are key points to study the success of the therapy. Niu *et al.* transfected gut K-cells in the GI tract of diabetic rats with a plasmid of the human insulin gene, wrapped with chitosan NPs, revealing thus chitosan as a promising non-viral vector.[248] Similarly, orally administered pDNA coding for insulin (pDNA-insulin) to diabetic mice was studied in order to protect mice for more than 10 days from hyperglycaemia.[249] Covalently modified-chitosan with a well-known cationic polymer (polyethylenimine, PEI) was condensed with human pDNA-insulin to enhance the stability against harsh GI tract environments and transgene expression in liver. Administration of pDNA-insulin *via* oral delivery into T1D mice model significantly lowered glycaemia over a period of 36 h after three repeated doses every 24 h.[250] The highly hydrophilic coating of PEG-functionalized lipoplexes (1,2-dioleoyl-3-trimethylammonium-propane/DNA) decreases their capture by the mucus located in GI tract and facilitates higher transfection efficiency.[251]

The use of stem cells as the unlimited source for producing beta cells is considered as the best alternative of the islet cells transplantation, and thereby is seen as the best hope for T1D

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care. This idea of differentiating adipose-derived stem cells and human amniotic mesenchymal stem cells was taken up by Wang *et al.* by using interfering siRNA.[252] They exploited the ability of mesenchymal stem cells to differentiate into insulin-producing cells by silencing neuronal restrictive silencing factor (NRSF) and sonic hedgehog (SHH) with PEI-coated iron oxide NPs. Resulting expressions of NRSF and SHH were down-regulated in mesenchymal stem cells, promoting insulin secretion under glucose stimulation. At the present time, although it is possible to produce beta cells from several stem cells such as human inducible pluripotent stem cells, the experimental procedure leading to the full beta-cell differentiation including glucose competence remains a key challenge, limiting their clinical use.[253]

Pancreatic islet transplantation is the only alternative for patients with T1D having uncontrolled glycaemia with insulin injection. A large number of magnetic particles have been developed in recent years with the advantage of being able to be used not only for delivering nucleic acids, but also for noninvasive imaging such as detection by magnetic resonance imaging (MRI). This advantage can be used in the delivery of siRNA in intact pancreatic islets in order to improve transplantations.[254,255] Indeed, pancreatic islet transplantations are increasingly performed in order to restore the number of β-cells, but suffer from limitations such islet cell deaths, graft rejections and autoimmune reactions. Caspase-3 gene mediates cell apoptosis and its inhibition could result in better survival of transplanted islets. In treated islets, dextran-coated magnetic NPs associated with human Caspase-3 revealed a protective effect both *in vitro* and *in vivo*.[256] Similarly, silencing of monocytic chemokine receptor CCR2, which mediates the emergence of inflammatory monocytes, prolongs islet graft survival and may avoid recruiting inflammatory monocytes in allograft rejection.[257] As a proof of concept, another platform based on gold NPs was also successfully evaluated as an efficient and safe technique for DNA delivery in intact islets.[258]

The miRNA is one of the most interesting targets for the treatment of diabetes. The design of safe and selective nanostructures for *in vivo* delivery is needed to protect microRNA (miRNA) or miRNA inhibitors and overcome side-effects in both T1D and T2D. In order to enhance insulin secretion, Chen *et al.* designed a complementary binding DNA oligomer to the 3′-untranslated region of insulin microRNA associated to gold nanoparticles (AuNPs).[259] The AuNPs–DNA complexes uptake by the rat RIN-5F insulin-producing cells revealed a 1.7-fold increase in the translation of insulin. The overexpression of miR375 inhibits the expression of Pdk1 kinase and myotrophin, leading to impaired insulin secretion induced by glucose. The transfection of anti-miR-375 into the mouse MIN6 insulin producing cells with optimized liposome-based NPs could enhance insulin secretion after glucose induction in comparison with classical transfection agents such as Lipofectamine.[260] Similarly, the aberrant expression of miR-216a is able to influence the proliferation of insulin-secreting cells in a T1D animal model. The introduction of a miR-216a mimic conjugated to dextran-coated magnetic NPs is capable to increase β-cell proliferation and thus restore insulin production in comparison with control models.[260] More recently, co-delivery systems are emerging to improve the potential of therapeutics for diabetes. They endow the benefits of the incretin hormone GLP-1, which enhances the glucose-mediated stimulation of insulin production, either by combining siRNA specific to DPP-4 microRNA with GLP-1 in polymeric porous microparticles[261] or with DPP-4 resistant GLP-1 analogues in specific chitosan NPs.[262]

6. Overcoming islet amyloid aggregation as therapeutic approach

A growing body of evidence suggests that β-cell failure in T2D relies on the formation of pancreatic islet amyloid deposits.[263–280] The major component of islet amyloid is the islet amyloid polypeptide (IAPP) amylin, co-secreted with insulin from β-cells. In T2D, this peptide aggregates to form highly insoluble amyloid fibrils in the pancreatic islets of Langerhans that are toxic to β-cells. While the mechanism responsible for islet amyloid formation in T2D is still unclear,[263] the search for inhibitors of islet amyloid fibril formation might prevent the progression to β-cell failure in T2D. IAPP, like insulin, plays an important role in lowering the level of glucose by inhibiting glucagon secretion. Human amylin, co-secreted by pancreatic β-cells along with insulin, is composed of 37 amino acids and the fibrillation process of this native peptide results in the formation of cytotoxic fibrils with a diameter of approximately 5 to 15 nm, leading to β-cell death and disease (Fig. 19a).[264] Together with low pH, high insulin-to-hIAPP ratio and Zn concentration, amylin stays inside β-cells granules at mM concentration range without formation of amyloid aggregations.[265] While after secretion, the physiological environment changes may cause the formation of toxic aggregates, leading to β-cells death (Fig. 19b). The cytotoxicity of amyloidogenic protein aggregates may be due to interaction with the lipid membranes, oxidative or endoplasmic reticulum stress and mitochondrial signaling pathway dysfunctions.[266]

Peptides and small molecules

In recent years, research has turned to the production of inhibitors of the formation of fibrils in order to prevent the formation of amylin β-sheets and the aggregation of the peptide together with destabilization of fibrils. Among the first inhibitors tested are short peptides and small molecules with high affinity and specificity for amylin. Some hexapeptide fragments, SNNFGA and GAILSS, from the human hIAPP core amyloidogenic sequence are able to interact with full-length hIAPP and avoid fibril formation while several decapeptide fragments SNNFGAILSS with Pro-for-Ser substitution in position 28 exhibit strong amyloidogenic potential.[267,269] Recently, the design of a new pentapeptide inhibitor, FLPNF, by docking shows direct binding between the fragment FLPNF and hIAPP, which leads to inhibition of the amyloid aggregation.[270] However, intrinsic physicochemical characteristics, such as peptide aggregation propension, may limit pharmaceutical applications. The sugar-based peptidomimetics design proposed by Ongeri and co-workers combines the targeting of hydrophobic recognition interfaces with an original hydrophilic sugar β-breakage strategy.[271]

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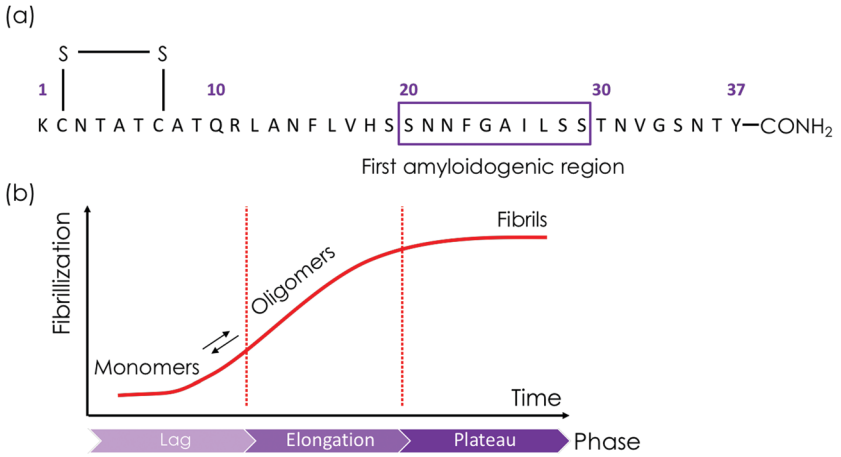

Fig. 19 Islet amyloid aggregation. (a) Human amylin sequence. Redraw from ref. 267. (b) Distinct stages of fibrillization process. [Reproduced from ref. 268 with permission from Elsevier, copyright 2020.]

A large number of natural molecules such as polyphenols (phlorotannin,[272] baicalein,[273] rosmarinic acid,[274] genistein,[275] (−)-epigallocatechin gallate,[276] oleuropein,[277] curcumin[278,279]) have demonstrated interesting properties in the inhibition of aggregation and the reduction of the hIAPP cytotoxicity.[280] The micromolar concentration range and the intrinsic aromatic structure of such compounds make pharmaceutical development difficult, particularly in terms of solubility (bioavailability), lack of binding specificity or side effect (drug interaction).

Other aromatic compounds like diazenyl-derivatives of pyridazinylpyrazolone are able to block the π-stacking between the aromatic residues of the hIAPP. These blocking molecules interfere with the formation of the β-sheet conformation and inhibit the hIAPP fibrillization *in vitro*; using thioflavin T fluorescence, an IC_{50} value of 3 μM was determined.[281] Interestingly, artemisinin and its derivatives, well known as antimalarial drugs, reveal an unexpected affinity for hIAPP at micromolar range.[282] Finally, the use of proteins as amyloid inhibitors is another possibility. In the same order of magnitude, selenium-containing phycocyanin, a pigment–protein complex, reduces the fluorescence intensity of thioflavin T by 58% at a concentration of 2.5 μM.[283] To overcome all these limitations, many strategies involving nanotechnology and the design of nanomaterials have been developed. Nanomaterials offer numerous possibilities to improve the delivery of existing drugs, to specifically target site of action or pass through biological barriers.

Complexes

By changing the metal centers (Au, Ru, V, Pt...) and associated ligands, metal complexes offer many combinations to inhibit the formation of amyloid deposits. Du and coworkers synthesized and studied two tetracoordinated gold–sulfur complexes and four tetracoordinated Au(III) complexes for their ability to inhibit the aggregation of the hIAPP or hIAPP core fragment (SSNNFGAILSSTNVGSNTY-NH_2) through metal coordination, besides hydrophobic and electrostatic interactions.[284,285] The same authors also investigated ruthenium complexes as an interesting alternative. The ruthenium complexes can inhibit hIAPP aggregation[286] and depolymerize mature hIAPP fibrils, while methionine ligands improve the biocompatibility of metal complexes.[287] In addition, ruthenium complexes are able to protect INS-1 insulin-producing cells against toxicity induced by IAPP. Bimetallic complexes such as Ru–Pt also exhibit synergistic bioactivities and reverse hIAPP aggregation with a strong binding affinity and a better inhibitory effect against amylin fibril formation than homo-binuclear Ru complexes.[288] A relatively high concentration up to 50–100 μM and the use of co-solvent such as dimethyl sulfoxide, makes this approach difficult to implement for *in vivo* applications. It is known that metallo-based pharmaceutical compounds containing vanadium may treat T1D and T2D through the development of insulin-mimetic vanadium.[289] Recently, the inhibition of hIAPP fibril formation with one oxidovanadium complex shows IC_{50} values as low as 8.5 μM.[290]

Metal oxide and metallic nanoparticles

It has been reported that in T2D, β-cells apoptosis induced by reactive oxygen species (ROS) such as hydroxyl radicals, hydrogen peroxide and Cu(II) cations correlate closely with the hyperglycaemia-induced oxidative stress. Therefore, cerium oxide (CeO) nanoparticles have a unique interest compared to the short half-life of vitamin C in antioxidative therapy.[291] It was found that CeO nanoparticles could inhibit Cu^{2+}/H_2O_2 induced hydroxyl radical production and hydrogen peroxide in oxidative stress of β-cells, suggesting an impact on glutathione metabolism.

Insulin shares with IAPP some similarities such as forming β-sheet rich fibrils. The study of amyloidosis with preformed insulin amyloid shows that negatively charged zinc oxide (ZnO) nanoflowers with hexagonal rod-like petals can degrade fibrils significantly higher, as compared to ZnO nanoparticles.[292] However, other spherical ZnO nanoparticles enhance insulin fibrillation by providing a suitable template for the nucleation

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and growth of insulin amyloids.[293] We can assume that protein fibrillation mediated by nanoparticles depends mainly on the interaction at the interface. This is why the careful analysis of size, surface charge, morphology and surface functionality are important in the design of therapeutic nanoparticles.

Due to chemical properties of gold nanoparticles (AuNPs), insulin can bind strongly the nanoparticle *via* direct gold–sulfur interaction with cysteine, leading to covalent bonds. The AuNPs and insulin interaction may delay the transition from the α-helix to the β-sheet form thus preventing self-aggregation.[294] Further surface modification could be useful for inhibition, but also for the disintegration of the preformed insulin fibrils under amyloidogenic conditions. Investigations of gold–aryl nanoparticles confirm that gold–insulin bioconjugates, synthesized from aryldiazonium gold(III) salt [HOOC-4-$C_6H_4N\equiv N$]$AuCl_4$ in presence of insulin, lead to insulin fibrils' dissociation *via* hydrophobic and hydrogen bonding interactions of benzene ring with the fibril-forming region of insulin.[295] Beside this, new strategies for differentiating the aggregation states of hIAPP were also studied more deeply by Javed *et al.* by using hyperspectral imaging and localized surface plasmon resonance.[296] The smaller sized citrate AuNPs facilitate the interactions with monomeric hIAPP and oligomeric/protofibrillar hIAPP with secondary structure changes, resulting from their larger surface curvatures and higher surface energies in comparison with the PEG_{400} or PEG_{3000} AuNPs. Accordingly, AuNPs stabilized with short ligands and moderate antifouling capabilities will be more effective reporters of protein aggregation and inhibitors against amyloid protein toxicity.

Magnetic particles

Magnetite (Fe_3O_4)-based NPs, usually synthesized by coprecipitation of Fe(II) and Fe(III) chlorides, are well-known in various medical applications (magnetic resonance imaging, hyperthermia, diagnosis, drug delivery...)[297] and are capable to reduce amyloid aggregation of insulin upon modification with bovine serum albumin (BSA).[298,299] Two other Fe_3O_4-based NPs, stabilized by $HClO_4$ (MF-pH) or by sodium oleate and further coated with BSA, are able to inhibit insulin amyloid fibrillization with IC_{50} values better than 65 μg mL^{-1} and promote disassembly of amyloid fibrils.[300] Additional coating, such as dextran of different molecular weights, was employed to modify superparamagnetic Fe_3O_4-based NPs.[301] Results revealed clearly that smaller particles coated with low molecular weight dextran (15–20 kDa) interfere with the formation of insulin amyloid aggregation with an IC_{50} of 42.8 μg mL^{-1} at a fixed insulin concentration of 10 μM. In addition, bigger NPs coated with high molecular weight dextran (70 kDa) are more efficient to destroy amyloid fibrils. Recently, optimized glycine-coated magnetic NPs destroy insulin amyloid fibrils in a concentration-dependent manner, but also lysozyme and α-lactalbumin.[302] Another advantage of magnetic nanoparticles is to have a scaffold allowing chemical modifications and their use as a probe in multimodal theranostic approaches. Xin *et al.* developed a nanoprobe based on iron oxide NPs modified with a two-photon (naphthalimide) fluorophore-labeled polymer for pH-triggered fluorescence/magnetic resonance imaging in the acidic β-cell environment.[303] Furthermore, this nanoprobe was able to completely inhibit hIAPP amyloidosis at 400 μg mL^{-1} and remove the hIAPP cytotoxicity on pancreatic BTC-6 cells at 100 μg mL^{-1}. Not only the intrinsic physicochemical properties of NPs, but even more their surface characteristics demonstrated the complexity of the interactions promoting protein aggregation. Silver and iron oxide NPs, with respectively antibacterial and magnetic properties, coated with citrate and branched polyethyleneimine for silver NPs as well as PEG and brushed phosphorylcholine for iron NPs, alter the fibrillation process of hIAPP at concentrations higher than 100 μg mL^{-1}.[304]

Others metalloid composite structures based on silica nanoparticles like chitosan-functionalized mesoporous silica nanoparticles[305] and chiral silica nanoribbons[306] are able to block or delay hIAPP aggregation, offering additional opportunities for the treatment of T2D.

Carbon nanoparticles

It is known that the interactions between carbon nanoparticles and peptides are dominated not only by hydrophobic and π–π stacking interactions, but also by the surface curvature. Numerical computation of tetramer and octamer hIAPP with or without diverse carbon nanoparticles such as graphene, single-wall carbon nanotubes (SWCNTs) and fullerene C_{60} revealed that peptides can be strongly adsorbed onto graphene and SWCNTs, while C_{60} prevents aggregation to a lesser extent.[307] Simulations have also shown that both pristine and hydroxylated fullerenes inhibit the β-sheet formation of hIAPP *via* different inhibitory mechanisms. Keeping in mind that fullerenes have low water solubility, hydroxylation or chemical surface modifications may be a way to overcome these limitations. Similar conclusions have been described for hydroxylated SWCNTs such as reduction of the β-sheet content and suppression of the three-stranded antiparallel β-sheet structure, leading to the delay of hIAPP aggregation and fibrillation.[308]

Experimentally, various GO nanosheets and graphene quantum dots (GQDs) have been widely described for inhibiting the formation of hIAPP fibrils in water.[309] The inhibition relies on the GO nanosheet surface that interacts with the IAPP amyloidogenic region. As this region accounts for aggregation and conserved in most amyloidogenic peptides, it is possible that GO nanosheets interact with other amyloidogenic peptides or proteins. To enhance selectivity and interaction of GQDs with hIAPP, Yousaf *et al.* prepared fluorinated graphene quantum dots (FGQDs) by adopting microwave hydrothermal synthesis.[310] A comparative study shows the inhibition of hIAPP aggregation in the following order: FGQDs > N-doped GQDs > bare GQDs (Fig. 20a). The main advantage is that FGQDs remain less toxic for INS-1 cells, while retaining the reduction of the cytotoxicity of the hIAPP fibrils. Up to date, the toxic effect of hIAPP with or without GQDs was studied *in vivo* using an embryonic zebrafish model.[311] Promising results suggest that GQDs significantly reduce malformation in larvae caused by hIAPP, fibril formation and other β sheet-rich forms while most embryos failed to hatch upon hIAPP microinjection (Fig. 20b). The effort to deliver bare GO nanosheets or GQDs *in vivo* needs specifically adapting the physicochemical properties of carbon derivatives and targeting the pancreatic cells, as proposed by Zhou *et al.* through a combination of an

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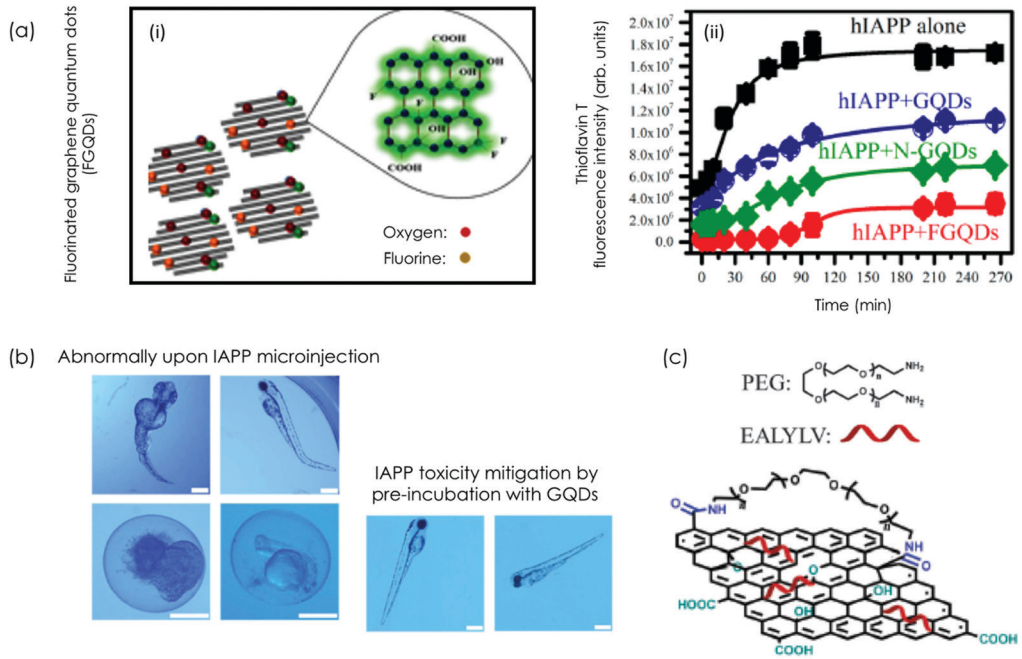

Fig. 20 Carbon nanostructures for the inhibition of hIAPP aggregation. (a) (i) Microwave-assisted hydrothermal synthesis of FGCDs. (ii) Comparison of inhibitory performance of FGQDs with inhibitory effects of GQDs and N-GQDs. [Reproduced from ref. 310 with permission from American Chemical Society, copyright 2017.] (b) Bright-field imaging of abnormality upon IAPP microinjection into the yolk of embryos and mitigation of toxicity by pre-incubating IAPP with GQDs. The scale bars are 500 μm. [Reproduced from ref. 311 with permission from Royal Society of Chemistry, copyright 2018.] (c) PEG-stabilized GO nanocomposite loaded with EAVYLV. [Reproduced from ref. 312 with permission from Royal Society of Chemistry, copyright 2015.]

insulin-derived peptide (EALYLV) loaded on PEG-stabilized nanosized GO (Fig. 20c).[312]

Polymeric and lipid-based nanoparticles

Polyamidoamine (PAMAM) dendrimers are a class of polymeric nanoparticles with a hydrophobic core and hydrophilic surface functions such as primary amines. Hydroxyl groups may replace primary amines in order to minimize the dendrimer toxicity and mimic polyphenol structure, while preserving high flexibility and good water solubility. The hydroxyl-terminated PAMAM (PAMAM-OH) displays a dose-dependent decrease of hIAPP aggregation from 0.2 to 100 μM.[313] In addition, PAMAM-OH dendrimer at a concentration of 36 μM can also protect mouse β cells against death induced by 10 μM hIAPP. Other anionic dendrimers bearing hydroxyl, carboxyl and sulfate groups also inhibit hIAPP fibrillization and associated toxicity.[314]

A counterintuitive strategy to promote fibrillization rather than inhibition was highlighted by Pilkington *et al.*[315] Star-shaped poly(2-hydroxyethyl acrylate) polymers have a promotional effect on hIAPP fibrillization and further rapid remodeling results in the "stelliform" amyloid morphology with cytoprotective properties *in vitro* and *ex vivo*. This duality was illustrated by the ability of a cationic polymethacrylate quaternary ammonium (PMAQA) to rapidly promote the formation of amorphous aggregates of β-amyloid, while PMAQA blocks the nucleation and hIAPP aggregation at sub-stoichiometric polymer concentrations.[316]

7. Novel nanotechnology approaches for *in vitro* studies and transdermal drug delivery: from microfluidic organ-on-chip models to numerical computation

Nanotechnology is the foundation of new generations of nano- and micro-electromechanical systems for controlled antidiabetic drug delivery, essentially routed in standard technologies to fabricate basic components for handling nanofluids. Microfluidic technologies are prodigiously used in the generation of drug nanocarriers[317] and are increasingly employed to assemble self-regulated therapeutics delivery platforms. Additive manufacturing encompassing automatic injection molding, soft lithography and tri-dimensional printing is gaining momentum for designing novel wearable, minimally invasive systems, with transdermal antidiabetic drug delivery driven by microneedles[25,85–88] and electrothermal[27,318,319] functionalities, as described previously.

While traditional methods for islet testing are challenged by lab-on-chip approaches (Fig. 21a),[320,321] the well-known Franz diffusion cell ubiquitously used in *in vitro* tests for transdermal drug delivery is currently replaced by microfluidic devices able to assess at lower costs drug formulations and corresponding dermal pharmacokinetics.[322–325] Effort is now directed towards the development of artificial organs for cell therapy as well as for implementing multiple tissues on a chip enabled by multi-organ approaches. Progress in technological tools needs to be matched by advances in biocompatible materials and stem cell-based

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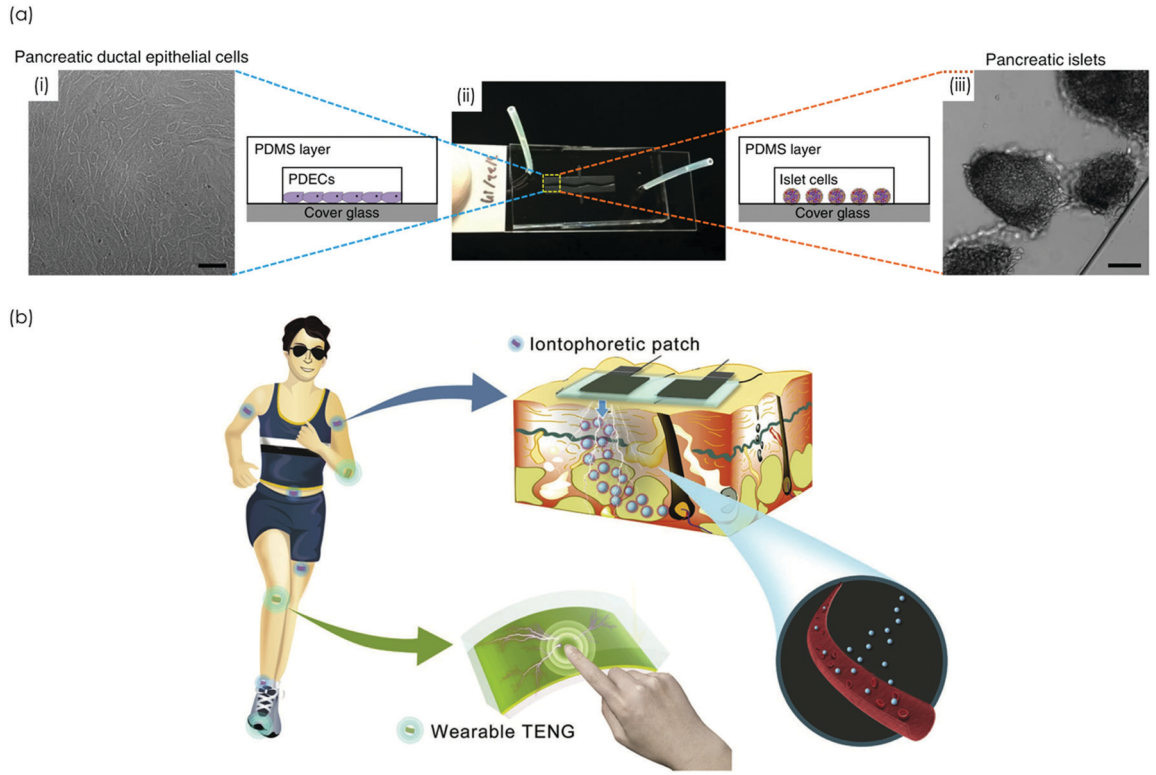

Fig. 21 Nanotechnology approaches for study pancreas-related diseases *in vitro* and for personalized transdermal drug delivery. (a) (i) Single-channel chip based on polydimethylsiloxane (PDMS) with co-cultured pancreatic ductal epithelial cells (PDECs). (ii) The device, implemented by soft lithography on glass, is mimicking the pancreatic duct-like structure. (iii) Lab-on-chip pancreatic islets. Scale bars are: (i) 50 μm and (iii) 100 μm. [Reproduced from ref. 321 with permission from Nature Publisher, copyright 2019.] (b) Illustration of a proof-of-concept self-powered iontophoretic device. [Reproduced from ref. 337 with permission from Wiley, copyright 2020.]

technologies to fabricate metabolically relevant skin-on-chip models that can minimize the deployment of *in vivo* preclinical testing. The singular disadvantage of these models to date is the absence of native extracellular matrix for realistic disease modeling.

Non-invasive transdermal protein delivery has been achieved with ultrasound decades ago,[326] and it is well-known that low-frequency (<100 kHz) sonophoresis can be efficiently used in conjunction with other physical methods, like iontophoresis. Recently, ultrasound methods regained popularity due to new formulations of biologics,[327–331] capability for glycaemic control[332] and for assessing early, asymptomatic stages of the disease,[333] especially for T1D. While imaging technologies like MRI are key in controlling diabetes, further progress into robotic manipulation offering precision imaging and *in vivo* mechanical energy harvesting[334–336] will enable the design of complex, personalised platforms for diabetes treatment. An interesting step in this direction was taken by Wu *et al.* with the introduction of an iontophoretic transdermal drug delivery device (Fig. 21b), self-powered by a wearable triboelectric nanogenerator (TENG) and tested on pig skin using dyes as simulated drugs.[337]

Certainly, the delivery ways for which the nanoengineering of drug carriers employs the colossal knowledge in building nanoblocks to exhibit emergent functions beyond the characteristics of encapsulated payloads themselves are in the center of research attention. For example, numerical simulation has been used to study drug release and absorption into the skin, helping the engineering and design optimization of patches for transdermal drug delivery.[131,338,339] The disadvantages and benefits of permeation-enhancing methods used in the treatment of diabetes can be decrypted by numerical computations, with atomic scale resolution, based on reference data for human skin. When further coupled with key physical phenomena and mechanisms of diffusion through the stratum corneum, such methods offer insight into the concentration profiles of penetration enhancers and active biologics and rapidly settle as a mainstay in the field.[340,341]

8. Diabetes management in COVID-19 era

Since the initial COVID-19 outbreak in China, much attention has focused on people with diabetes, because of poor prognosis in those with the infection. Initial reports were mainly on people with type 2 diabetes, although recent surveys have shown that individuals with type 1 diabetes are also at risk of severe COVID-19.[342] The reason for worse prognosis in people with diabetes is likely to be multifactorial, thus reflecting the syndromic nature of diabetes. Data from the U.S. Center for Disease Control and Prevention showed that more than three-quarters of people who died from

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COVID-19 had at least one preexisting condition. Overall, diabetes was noted as an underlying condition for approximately 4 in 10 patients.[343]

The causative link between COVID-19 and diabetes relies on the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which binds to angiotensin-converting enzyme 2 (ACE2) receptors. The ACE2 receptors are expressed in key metabolic organs and cells, including β cells. Binding of SARS-CoV-2 to its receptor may damage islets and thereby, can cause acute diabetes.[344,345] Thus, it is plausible that SARS-CoV-2 may cause pleiotropic alterations of glucose metabolism that could exacerbate the pathophysiology of preexisting diabetes or lead to new onset of disease. This hypothesis is further supported by the increased level in diabetes of a type-1 membrane-bound protease, belonging to the proprotein convertase subtilin/kexin family, called as Furin. The latter is involved in the entry of coronaviruses into the cell. Therefore, in patients with diabetes, the rise of Furin levels might facilitate viral replication.[346]

Furthermore, lymphocytopenia has been observed in patients with COVID-19.[347] However, most striking is the increased level of several cytokines such as IL-6 in COVID-19 infected patents as COVID-19 may accelerate insulin resistance through IL-6.[348]

Nanotechnology aspects developed for diabetic treatment might be adapted for COVID-19.[349] The large surface area, ciliated cells of lower respiratory tract may be ideal area for drug delivery as it is connected directly to systemic circulation *via* pulmonary administration with few challenges like branched nature of alveolar macrophages and pulmonary surfactant (phospholipids, proteins and mucins) decrease delivery efficiencies. However, the delivery to lower tract has to overcome muco-ciliary and cough clearance mechanisms. To address these barriers nanotechnology-based approaches can be implemented due to their characteristic features. Inhalable PLGA, polycaprolactone or polylactic acid MPs might be the way for treatment, but their uses either for development or for improvement of an antiviral have been only partly investigated.[349]

9. Conclusion and perspectives

In this review, we attempted to update the chief scientific and technical aspects of chemistry as well as micro- and nanotechnology related to diabetes, one of the leading causes of premature death with a projection of 700 million diabetics in 2030. The expectations from technology-driven medicine for diabetes are high and the potential benefits are endlessly listed. Next to conventional treatments such as lifestyle adjustment and clinical therapeutic approaches including bariatric surgeries, chemistry through the synthesis of novel drug formulations combined with high-end engineering to obtain innovative formulations are providing new vistas for diabetes treatment.[350] These new therapeutic approaches will have to meet the huge expectations, for example, to better manage the long-term glycaemic control and thereby, to stop the progression of diabetes towards other diseases such as cardiovascular diseases and infection risk, as currently exemplified by the COVID-19 sanitary crisis (Section 8). In the latter, most patients affected by COVID-19 are aged obese and/or diabetic patients with poor glycaemic control.

As the antidiabetic drug encapsulation has been considered essential to protect the therapeutic payload from degradation and improving solubility,[351] and has been motivated by patient and healthcare professionals' preference for oral drug delivery, research on ingestible systems for insulin delivery remains largely persuaded. Nanotechnology and nanomedicine have opened up new possibilities for the oral delivery of protein and peptide-based antidiabetic drugs such as insulin and GLP-1 agonists. From the large amount of work done in this field, it is evident that the interplay and fine tuning between particle size, surface charge, morphology and surface functionality are key elements to success in this area. While the integration of low molecular weight polyethylene glycol units onto insulin formulations was one of the first approaches to overcome the mucus barrier, as it created a hydrophilic and electrically neutral surface required to prevent the insulin carrier to adhere to the mucus and again access to epithelial cells, these structures strongly inhibited cellular uptake and subsequently insulin could not enter the systemic circulation. This dilemma was elegantly solved over the last years through the synthesis of various different dissociable mucus inert nanostructures, being of large potential for oral insulin delivery. Ingestible self-orientating applicators as well as unfolding microneedle injectors, as demonstrated by Traverso and co-workers,[185,186] are largely innovative platforms for oral delivery of therapeutic doses of insulin *in vivo*. It can be hoped that some of these approaches can be scaled up and quality controlled to allow their clinical testing. This stage of research is strongly biased on the acceptance of the pharma industry to oversee the different clinical trials failure on oral insulin delivery and be open minded for further adventures.

Another critical promise from nanomedicine is the development of the theranostic approach that will enable to quantify, in real-time, and to appropriately treat the BCM and BCF. While, the impaired BCF is the primary pathophysiological feature of T2D, the decrease of BCM ensues overtime, contributing to the progression of the disease towards complications and treatment failure, as mentioned in Section 1. Reduced BCM is the hallmark of T1D and none of the available treatments so far can prevent it. The possibility to diagnose BCM and BCF for patients with T1D and T2D at the early stage, will lead to prescription of the right therapeutics, and to achieve a longitudinal follow-up of both BCM and BCF. Thus, anytime, the treatment can be adapted according to the disease progression. In cancer treatment, major achievements and efforts have been achieved such that many nanoparticle-based theranostic methods are currently tested in clinical trials, progressing towards personalized cancer nanomedicine. The development of personalized diabetes nanomedicine through theranostics is currently challenging, although there is a wealth of data showing the possible application of various efficient nanoparticle-based carriers for delivering contrast agents such as magnetic nanoparticles including iron, gadolinium and manganese. The concerns are, on the one hand, that the non-invasive

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imaging of the insulin producing cells is still not possible despite the rapid progress of high sensitivity and resolutive imaging technology including MRI, positron emission tomography (PET) and single photon emission tomography (Section 7). Only two tracers for PET and one contrast agent for MRI are currently under clinical evaluation. Kang *et al.* recently proposed multimodal probes for both fluorescence and PET imaging.[352] Xin *et al.* developed lately a multimode nanoprobe for β-cell detection and amyloidosis mitigation. It uses surface-functionalized magnetic iron oxide nanoparticles with a two-photon fluorescence dye labelled polymer. The probe enables pH-triggered fluorescence and MRI properties in the β-cell acidic environment. These particles also serve as potent inhibitors against the aggregation and toxicity of human IAPP.[353] On the other hand, there are no curative therapeutics that prevent and stop the insulin producing cells dysfunction and destruction. As underlined above (Sections 2–4), all the current treatments only stimulate the residual activity of healthy and diseased cells. Some researches hold realistic hope in unveiling miRNAs as new potential therapeutic agents for theranostic purpose. For example, the use of magnetic NPs modified with miRNAs mimics involved in β-cell destruction was lately proposed by the team of Moore as a theranostic approach in T1D.[354] Evidence that miRNAs play a key role in β-cell loss in T1D is more and more provided. Identification of key miRNAs dysregulated in pancreatic islets during T1D progression and linking to MRI-based nanoformulations, such iron oxide NPs, showed increased BCM and higher insulin-producing cell activity for releasing insulin in treated animals compared to controls.

As the oral drug delivery route has still not made it to commercialisation, other approaches have been considered and developed as highlighted in Section 6. Transdermal systems are capable of not only bypassing the subcutaneous drug delivery, but also overcoming the mismatch in geometries between electronics and skin *via* advanced nano-engineering,[355] promoting multidimensional approaches for diagnosis, therapy and long-term disease management[356,357] as well as seamless integration with patient's lifestyle. To ensure reliable outcomes in diagnosis and treatment, monitoring skin status for transdermal drug delivery is essential. Biorobotic skin has been endorsed as a research mainstay in diabetes management.[358–363]

Thus, while nanomedicine remains challenging due to safety issues, it holds great potential for the future of diabetes management and, for the moment, the suggested benefits in diabetic care outweigh the possible pitfalls. It is only in its initial state, but progress is rapid. It is clear that engineering-driven medicine remains a key enabling technology for solving many of the hot issues and will be a multi-faceted technology in diabetic research, impacting on soft robotics and on the development of artificial intelligence tools for persons with diabetes.

Conflicts of interest

There are no conflicts to declare.

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