Asian Journal of Pharmaceutical Sciences 15 (2020) 13–25

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/AJPS

Review

Transdermal drug delivery systems in diabetes management: A review

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ARTICLE INFO

Article history:
Received 25 November 2018
Revised 25 February 2019
Accepted 15 April 2019
Available online 22 June 2019

Keywords:
Transdermal
Diabetes
Antidiabetic
Insulin
Drug delivery system

ABSTRACT

Diabetes mellitus is a chronic disease in which there is an insufficient production of insulin by the pancreas, or the insulin produced is unable to be utilized effectively by the body. Diabetes affects more than 415 million people globally and is estimated to strike about 642 million people in 2040. The WHO reported that diabetes will become the seventh biggest cause of mortality in 2030. Insulin injection and oral hypoglycemic agents remain the primary treatments in diabetes management. These often present with poor patient compliance. However, over the last decade, transdermal systems in diabetes management have gained increasing attention and emerged as a potential hope in diabetes management owing to the advantages that they offer as compared to invasive injection and oral dosage forms. This review presents the recent advances and developments in transdermal research to achieve better diabetes management. Different technologies and approaches have been explored and applied to the transdermal systems to optimize diabetes management. Studies have shown that these transdermal systems demonstrate higher bioavailability compared to oral administration due to the avoidance of first-pass hepatic metabolism and a sustained drug release pattern. Besides that, transdermal systems have the advantage of reducing dosing frequency as drugs are released at a predetermined rate and control blood glucose level over a prolonged time, contributing to better patient compliance. In summary, the transdermal system is a field worth exploring due to its significant advantages over oral route in administration of antidiabetic drugs and biosensing of blood glucose level to ensure better clinical outcomes in diabetes management.

1. Introduction

Once known as 'honey urine', diabetes was first discovered in 1500 BCE and has been recognized as a calamitous and lethal disease for about 2000 years [1,2]. Diabetes mellitus is the general term used to describe a group of metabolic diseases characterized by chronic hyperglycemia. The pathophysiology of diabetes is due to defective insulin secretion, impaired insulin action or both. Diabetes can be classified into different types,

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Peer review under responsibility of Shenyang Pharmaceutical University.

https://doi.org/10.1016/j.ajps.2019.04.006

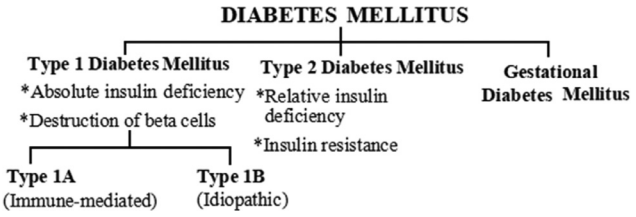

Fig. 1 – Classification of diabetes mellitus.

depending on the pathogenesis and clinical manifestations at the time of diagnosis.

Type 1 diabetes mellitus (T1DM) is attributed to the destruction of insulin-producing beta cells in the islets of Langerhans, leading to absolute deficiency of insulin. Type 1A diabetes mellitus, better known as insulin-dependent diabetes mellitus, is immune-mediated diabetes in which the immune system destroys beta cells with varying rates of destruction in different groups of patients. On the other hand, when no autoimmune mechanism of beta-cell destruction and no other known cause of insulin deficiency are identified, it is categorized as Type 1B diabetes mellitus or idiopathic diabetes. Type 2 diabetes mellitus (T2DM), previously known as non insulin-dependent diabetes mellitus, is the most common type of diabetes mellitus, accounting for about 90%–95% of diabetic patients. In this type of diabetes, relative insulin deficiency and insulin resistance arising from genetic or environmental factors are observed. Obesity is often associated with T2DM and many patients go undiagnosed for many years [3]. Gestational diabetes mellitus is characterized by glucose intolerance of any degree with onset or first recognition during pregnancy regardless of whether or not such condition continues after pregnancy. The classification of diabetes mellitus is illustrated in Fig. 1.

Looking at the global picture on epidemiology of diabetes published by the International Diabetes Federation in IDF Diabetes Atlas 7th edition, among adults aged 20–79 years, it is estimated that 415 million out of the total population of 4.72 billion globally live with diabetes. In other words, one in every 11 adults has diabetes. The figure is estimated to surge to 642 million out of the estimated total population of 6.16 billion in 2040, i.e., 1 in every 10 will have diabetes. Steering the focus to the prevalence of diabetes by region, the Western Pacific region, which comprises 27 countries, was ranked in 2015 as 4_{th} on the chart as categorized by World Health Organization, with 8.8% (7.7%–10.8%) in the region having diabetes, and the estimations indicate that it will be placed 5_{th} in 2040 with 9.0% (7.3%–11.6%), after being overtaken by South–East Asia [4]. Being one of the countries in the Western Pacific, Malaysia recorded an overall prevalence for both known and undiagnosed diabetes of 17.5% (95% CI: 16.6, 18.3) among adults aged 18 years and above in 2015, as reported in the National Health and Morbidity Survey 2015 published by Ministry of Health Malaysia. One in every five Malaysian adults has diabetes [5]. About 40%–60% of people in Malaysia die from diabetes before the age of 60 [4]. From a global perspective, a total of 5 million adults died from diabetes in 2015 [4]. As the primary clinical finding in diabetes, chronic hyperglycemia poses a high potential in incurring long-term malfunction or failure in different organs. The most pronounced organs affected are the eyes, kidneys, heart, nerves and blood vessels. There is usually an increased risk of microvascular and macrovascular complications in T2DM [3].

The International Diabetes Federation reported that 12% of global health expenditure is on diabetes, corresponding to approximately USD 673 billion in 2015, and it is expected to reach USD 802 billion in 2040 [4]. The complications that result in early death and economic burden on healthcare systems create the need to delve into the landscape of drug delivery systems to improve blood glucose monitoring and diabetes treatment to combat this 21st century challenge. T1DM requires a continuous supply of insulin which can be achieved through daily insulin injections, while T2DM is treated with hypoglycemic agents with metformin being the most commonly prescribed medication. Injectable insulin is also used in some T2DM patients.

2. Transdermal drug delivery systems

Skin, being the most extensive organ that receives one-third of the total blood supplied throughout the body, was not known to be a route of drug delivery for systemic drugs until the late 20th century [6,7]. Over the last decade, the field of transdermal drug delivery has been gaining attention owing to its advantages over conventional oral dosage forms. The global transdermal drug delivery market is estimated to grow and reach approximately $95.57 billion by 2025 [8]. Overdosing becomes a concern due to fluctuation in peak plasma concentration following oral and parenteral administration, making it a challenge in monitoring effective plasma concentration. Transdermal drug delivery systems offer several benefits because drugs administered are able to bypass hepatic first-pass metabolism and factors that alter pharmacokinetics in the gastrointestinal tract. This significantly improves systemic bioavailability with reduced risk of side effects associated with concentration. This generally improves patient compliance as it is easy and convenient to apply with a lesser dosing frequency, as the drug is released at a predetermined rate over a prolonged period [6].

This review presents the recent advances and developments in transdermal research to obtain better diabetes pharmacotherapy and management as reported in various journals from 2015 to 2017, with a few selected earlier articles. The presented research papers have been summarized in Table 1.

2.1. *Employment of microneedle in patch*

Microneedles have been extensively studied in formulating insulin patches. Different materials are used which exhibit different characteristics while the other aspects such as needle length, diameters and excipients widely vary, in order to study the differences and how the modifications can achieve optimum and desirable outcomes. Currently, the two most common treatment options for diabetes are oral agents and insulin injections. Although microneedles are being studied extensively to fabricate insulin transdermal patch, this invasive delivery system has not been widely used with many undergoing researches to review its different

Table 1 – Recent research of transdermal systems in diabetes management reported in literature.

Formulation	Subject	Ref.
Gelation and hydroxyapatite fabricated bioceramic composite microneedle	Sprague-Dawley mice	[9]
Double-layered, bullet-shaped microneedle with swellable tips patch	Male Sprague-Dawley rats and Male C57BL/6J mice	[10]
Biodegradable alginate and hyaluronate polymer microneedle patch	Sprague-Dawley rat	[11]
Poly-γ-glutamic acid microneedles with supporting structure	*In vitro*: Porcine cadaver skin/Pig cadaver skin; *In vivo*: Sprague-Dawley male rat	[12]
Alginate and maltose microneedle	Sprague-Dawley rat	[13]
Swellable microneedle patch in interstitial fluid extraction for glucose metabolic analysis	MN skin insertion: fresh porcine cadaver skin; *In vivo*: Mouse model	[14]
Patch-type 3D stainless steel microneedle array enzyme-free glucose biosensor	Guinea pig, rat and rabbit	[15]
Composite nanostructured surface electrochemical glucose sensor	–	[16]
Ultra-miniaturisation planar amperometric glucose sensor	–	[17]
Lab-on-chip with triboelectric liquid volume sensor	Rat	[18]
H_2O_2-responsive polymeric vesicle with microneedle	Mice	[19]
Insulin-loaded and H_2O_2-responsive Mesoporous Silica Nanoparticle Integrated Microneedle Patch	Male Sprague-Dawley mice	[20]
Sweat-based electrochemical patch with thermoresponsive microneedle	Mice/ Human's arm	[21]
Hypoxia and H_2O_2 dual-sensitive polymersome-based vesicles smart insulin patch	C57BL/6J mice	[22]
Permeation enhancement via proniosomal gel entrapment	*Ex vivo*: White albino rabbit; *In vivo*: Albino Wistar male rat	[23]
Proniosome carbopol-based transgel systee	Rat	[24]
Transferosomal gel with chemical enhancer 'Iodophor'	Permeation: Hairless (goat) skin; *In vivo*: Rat	[25]
Microemulsion gel	*Ex vivo*: Rat skin; *In vivo*: Sprague-Dawley rat	[26]
Transdermal nanoemulsion encapsulation	*Ex vivo*: Female Wistar rat; *In vivo*: Male Wistar rat	[27]
Nanostructured lipid carriers transdermal system	Rat	
Hyaluronic acid encapsulated CuS gel-mediated near-infrared laser nanosystem	Nude mice	[29]
Solid-in-oil gold nanorods	Mice	[30]
Choline and geranate (CAGE) deep eutectic solvent transdermal delivery vehicle	Porcine skin/ Rat	[31]
Amidated pectin hydrogel matrix patch	Rat	[32]
HPMC & PVA blend transdermal patch	Albino mice	[33]

pharmacological characteristics and grand challenges. The studies below provide insights into the different formulations of microneedle insulin patches.

2.1.1. *Gelation and hydroxyapatite fabricated bioceramic composite microneedle*

Yu et al. [9] investigated the use of biodegradable organic-inorganic bioceramic composite microneedles using gelatin and hydroxyapatite to deliver insulin transdermally. They wanted to study the biological compatibility, mechanical properties and bioactivity of this transdermal system as compared to microneedles made from pure organic systems, which are usually limited by the risk of breakage and mechanical stability. With a tip diameter of 24 μm, the microneedle should have the strength needed to penetrate into human skin using a force of <150 mN/needle. They found that this bioceramic composite microneedle system has a good cytocompatibility with low toxicity, which makes it highly suitable for *in vivo* application in insulin delivery. Skin damage following microneedle administration was healed within 1 h and did not pose any infection. As compared to subcutaneous (SC) insulin delivery in diabetic mice, insulin-loaded microneedles indicated prolonged hypoglycemic effect (blood glucose level under 200 mg/dL for 3.39, 4.21 and 5.16 h after 5, 10 and 20 IU of insulin administration respectively) by sustained release pattern of insulin, enabling insulin plasma concentration to be maintained for longer.

This study shows that the employment of microneedles is capable of providing a better surge of plasma insulin concentration in the body after administration, which is also observed in SC injection. However, microneedle delivery system exhibits an advantage in providing sustained release of insulin, which allows the insulin level to remain high in the body for longer time, providing more prolonged glucose control. This is especially useful when the glucose is shown to be better controlled over a longer time when the same dose of insulin is being administered using microneedles as compared to SC injection. However, materials used in formulating the microneedle may raise concern as hydroxyapatite and gelatin bioceramic are shown to have low cytotoxicity even though the cell viability was kept above 98% in the experiment. *In vivo* applications may have to be explored further

to make sure they are safe to be used in humans. Besides that, insulin release and glucose control when various insulin doses are administered do not seem to follow a consistent pattern, so more studies need to be carried out to look into the trend when higher and different doses of insulin are used.

2.1.2. *Double-layered, bullet-shaped microneedle with swellable tips patch*

Seong et al. [10] reported double-layered, bullet-shaped microneedles with swellable tips which are capable of loading insulin for interlocking-mediated adhesion to skin tissue and prolonged insulin delivery. The mechanical interlocking adhesion was achievable through increasing volume of swellable tips. Insulin loaded onto the tips diffuses through the swollen hydrogel into skin. *In vivo* experiments were carried out to test the insulin release behavior. Coated microneedle patches showed a burst effect by releasing greater than 90% of the coated insulin within 30 min. Interestingly, swellable microneedles released loaded insulin at a constant rate. Burst release pattern was not observed for the initial 6 h. A total of up to 241 ± 20 μg (6.04 ± 0.52 U) insulin was released over 12 h from the swollen polymer network, which corresponds to about 60% of the total insulin loaded. Hence, a controlled release of drug is possible by using this patch. *Ex vivo* tests showed that insulin loaded was equally distributed throughout the swellable layer. Hence, it is suggested that the double-layered, bullet-shaped microneedle patches are a potential candidate in the delivery of insulin in diabetes treatment owing to their controlled, prolonged insulin release, thereby controlling blood glucose level in the long term without inflammation and burst release. They also provide a good interlocking adhesion to skin tissue with the use of a swellable layer to make sure the swellable microneedle tips penetrate beneath the epidermis for the delivery of medications. The as-prepared system also does not cause any significant inflammation to the skin tissue.

2.1.3. *Biodegradable alginate and hyaluronate polymer microneedle patch*

Yu et al. [11] presented a biodegradable polymer microneedle patch fabricated from 3-aminophenylboronic acid-modified alginate (Alg-APBA) and hyaluronate (HA). This microneedle can rapidly dissolve in skin interstitial fluid after insertion. Alg-APBA can link with glucose molecule, making self-regulation of insulin feasible. *In vivo* transdermal delivery of insulin test using rat skin showed that upon loading of 10 IU of insulin into the Al-APBA/HA microneedle patch for 12 h at 37 °C, more than 90% of loaded insulin was released within 6 h in a sustainable manner. The encapsulation of insulin in the Alg-APBA/HA microneedle has no effect on the bioactivity of insulin as it is still able to preserve the secondary structure of insulin. *In vivo* test was performed by giving treatment via SC injection and Alg-APBA/HA microneedle patches. The hypoglycemic effect using Alg-APBA/HA microneedle patch was comparable to that in SC group with 10 IU of insulin, whereas the euglycemic effect post-treatment was maintained for a longer time (from 2.0 to 5.7 h) than SC group (from 1.0 to 4.3 h).

In conclusion, this system is a potentially useful model in the treatment of diabetes with several beneficial features. As alginate and hyaluronate used are naturally occurring substances, they are non-cytotoxic and biodegradable, as well as having characteristics to improve mechanical functionality. When an equivalent dose of insulin is loaded, the system shows a more prolonged release trend and avoids rapid decline in glucose level to prevent hypoglycemia. It has been demonstrated that insulin release could also be promoted and taken up rapidly through regional lymph and capillary networks. With such a formulation, the needles are formulated in a precise manner as slight deviation could potentially lead to failure in terms of insertion into skin and a fall in mechanical strength.

2.1.4. *Poly-γ-glutamic acid microneedles with supporting structure*

Chen et al. [12] proposed a microneedle patch system consisting of poly-γ-glutamic acid (γ-PGA). A supporting structure composed of polyvinyl alcohol (PVA)/polyvinyl pyrrolidone (PVP) was added to provide mechanical strength for full insertion into the skin and counteract skin deformation during skin insertion which often occurs with the microneedle system. *In vitro* drug release profile showed that all of the needles were dissolved completely in skin and encapsulated insulin was released within 4 min upon contact with skin interstitial fluid. Diffusion depth was found to be 800 μm, as shown in the *in vivo* drug release profile. These findings indicated that PVA/PVP γ-PGA microneedle is able to deliver insulin directly into dermis layer for systemic circulation absorption. The plasma concentration of insulin in diabetic rats post-administration (once daily for 2 d) of insulin-loaded microneedles was studied and found to increase rapidly and achieve maximum value after 1 h before decreasing back to normal level after 6 h. There was no significant difference between transdermal insulin delivery using SC injection and microneedles after treatment at 1 h and 24 h. γ-PGA microneedle with additional supporting structure possess the stability and accuracy in transdermal insulin delivery. As compared to other microneedle transdermal delivery systems, this system presents an additional advantage of extended needle length to counteract skin deformation during insertion and also providing sufficient mechanical strength for full insertion into skin tissue due to the extra supporting structure, to ensure drug delivery efficiency and prevent wastage of insulin being injected. However, under storage at 37 °C, the stability of encapsulated insulin will tend to decrease slightly. Nevertheless, the decrease is minimal, the system is still stable at 25 and 37 °C for at least one month, which gives it the advantages in cold chain storage and transportation. The formulation of a supporting structure combined with microneedles involves a complicated alignment and combination procedure which still has the potential to exhibit difficulty in production.

2.1.5. *Alginate and maltose microneedle patch*

Zhang et al. [13] presented a microneedle composed of alginate and maltose (Al-Mal) cross-linked by calcium ions (Ca^{2+}). The mechanical strength of alginate microneedle was improved with maltose and cross-linking with Ca^{2+}. The as-prepared microneedle demonstrated the highest failure force, around 0.41 N/needle at around 469 μm, which is better than the pure sodium alginate (0.02 N/needle at around

302 μm) and cross-linked alginate microneedle (0.04 N/needle at around 406 μm). *In vitro* drug release profile revealed that more than 80% of encapsulated insulin was able to be released within 8 min. *In vivo* experiment showed that with the same amount of insulin loaded (10 IU), the microneedle patch required a longer time to reach the lowest blood glucose level (119.1 mg/dL within 2 h) than SC injection (decreased to 200 mg/dL at 0.63 h and the lowest level at 70.2 mg/dL within 1 h). Besides, the Ca^{2+}/Al-Mal microneedle patch required a longer time to return to initial blood glucose level. Hence, it can be concluded that alginate microneedle blended with maltose and cross-linked with calcium exhibits excellent cytocompatibility, swelling and dissolution properties for painless administration, convenience and great pharmacological activity in insulin delivery for diabetes management.

In transdermal delivery of antidiabetic medication such as insulin, the use of microneedles is the most commonly and extensively studied and employed technology. The use of microneedles has been proven to deliver the medication in a sustained release pattern, which allows control of glucose level over a prolonged duration. This property is superior to that of the currently existing SC injections, which tend to cause hypoglycemia. Microneedles can be formulated using different materials, though the most commonly used are polymers. Furthermore, some polymers are biodegradable whereby the needle tips degrade in the skin of patients. Hence, it is important to further study the safety of the polymers to ensure safety for patients when using such patches. Another factor which requires further investigation to ensure the efficacy of the transdermal patch is the strength of insertion of microneedles. Failure to fully insert microneedle into the skin may result in reduced delivery of medication into the bloodstream, reducing its effectiveness. The abovementioned factors can be overcome by current knowledge of formulation. Based on the studies carried out to date, the use of microneedle patches in diabetes management appears to be promising and superior to SC injections. The system can be further improvement through medication of the length, strength of microneedles and safety issues.

2.2. *Transdermal delivery systems incorporated with biosensor*

Apart from delivering medications such as metformin and insulin, the transdermal system is also capable of biosensing for metabolic analysis. With the employment of such biosensors using transdermal delivery, we can foresee the potential in extracting biological fluids such as interstitial fluid and sweat to detect glucose levels corresponding to those present in plasma. Different approaches to this each have pros and cons, which are further elaborated below.

2.2.1. *Swellable microneedle patch in interstitial fluid extraction for glucose metabolic analysis*

Chang et al. [14] studied the use of microneedles as a tool in rapid interstitial fluid (ISF) extraction, which is the biomarker in disease diagnosis and prognosis for metabolic analysis including glucose. They developed a swellable microneedle patch using methacrylated hyaluronic acid (MeHA). It is a covalently crosslinked HA-based MN patch which is able to maintain structural integrity and possesses high water affinity in ISF extraction. The penetration of such a MeHA-MN patch into the skin using a thumb press was recorded as 1.4 mg ISF in 1 min. In an *in vivo* study using a mouse model, the MeHA-MN patch was able to extract 1.4 ± 0.3 mg and 2.3 ± 0.4 mg of ISF in 1 and 10 min, respectively. A shorter extraction time was expected in the human model due to a more abundant skin ISF. When studying the application of MeHA-MN patch in extracting ISF for detection of glucose metabolite, a similar value was observed to that measured using a traditional glucometer measurement.

In conclusion, the swellable MN patch developed by Chang et al. has the potential for the development of MN-based microdevices in managing diabetes and insulin delivery owing to its minimal invasive nature, timely ISF sampling duration, suitability for frequent administration and reduction in risk of residues post-MN insertion. Besides that, such a system is also able to extract ISF instantaneously to measure not only glucose level but also cholesterol level while maintaining structural integrity, whereby the results match the real concentrations in the plasma perfectly. However, such a system is only formulated for sensing purposes.

2.2.2. *Patch-type 3D stainless steel microneedle array enzyme-free glucose biosensor*

Lee et al. [15] fabricated an enzyme-free biosensor patch using a 3D microneedle array to investigate its use in monitoring glucose. Using an electroplating technique, the 3D microneedle array consisted of a Platinum (Pt) black sensing layer using an electroplating mixture of 1% (w/w) HCPA, 0.005% lead acetate and 0.01 M hydrochloric acid. An Ag/AgCl counter electrode was fabricated, and the microneedle was fabricated using 316 L medical grade stainless steel. The rationale of this design was to minimize pain and increase ease of use. They checked the efficiency of the microneedle array in sensing low glucose concentration by adding different glucose concentrations (50 μM–10 mM). At the first 50 μM glucose injection, a current change of 70 nA was observed, indicating the characteristic of Pt as a good electrocatalyst. *In vitro* experiment showed that this 3D microneedle array is stable in long-term use (longer than 6 d) and is able to detect glucose concentration even at extremely low values. The measured sensitivity to glucose concentration change, linearity and response time were 1.62 μA/mM, 0.9939 and within 13 s, respectively, when being measured in glucose concentrations of up to 36 mM.

The transdermal system designed by Lee et al. elucidated the role of a patch-type enzymatic-free biosensor based on a 3D stainless steel microneedle electrode array in the application of monitoring blood glucose as it exhibits excellent sensitivity and rapid response. One of the limitations found in the experiment was that the sensitivity in detecting glucose level decreased as glucose level increased due to bio-fouling around the electrodes used. Hence, further improvement in the design is required to address this issue.

2.2.3. *Composite nanostructured surface electrochemical glucose sensor*

Pu et al. [16] designed a flexible electrochemical glucose sensor consisting of a composite nanostructured surface to

monitor and measure glucose levels, which can be integrated into a wearable device to connect with skin. Using inkjet printing, *they* printed graphene onto the surface of a working electrode. Gold nanoparticles were the electrodeposited onto the graphene layer. The graphene layer is capable of improving electro-activity and providing a more uniform electrochemical active site, resulting in more sensitive glucose detection at low levels. On the other hand, gold nanoparticles can enhance the sensor's sensitivity by facilitating a better electron transfer rate between enzymes and electrode. Glucose-specified detection was achieved through immobilizing glucose oxidase onto the nanostructured surface.

Experiments carried out using amperometry on interstitial fluid, which is very similar to blood glucose, showed that the fabricated electrochemical sensor had a linear range of glucose measurements of 0–40 mg/dL and a detection limit of 0.3 mg/dL. This suggested that it is capable of detecting glucose levels within the physiological range with high accuracy. A response was obtained in <1 s when the glucose concentration was changed. These results have shown that the proposed sensor has the potential to detect glucose levels including hypoglycemic state quickly and accurately with good repeatability. Furthermore, the flexible sensor can be integrated into a microfluidic chip to extract ISF for continuous glucose sensing and monitoring. In order to obtain good sensing purpose, graphene must be present, as the absence of it will lead to failure to detect low glucose levels.

2.2.4. *Ultra-miniaturization planar amperometric glucose sensor*

Ribet et al. [17] proposed a planar amperometric device consisting of a microfabricated three-electrode enzymatic sensor with the smallest sensing area reported to date, which is less than 0.04 mm^2. This aims to achieve less invasive and uncomfortable continuous glucose monitoring in patients with diabetes mellitus. The working and counter electrodes used by Ribet et al. were made up of platinum and three polymeric membranes, together with an on-chip pseudo-reference electrode made up of iridium oxide. Iridium oxide has good biocompatibility, minimal potential drift and mechanical stability, which makes it a suitable candidate for *in vivo* application over physiological range. The three electrodes have a surface area of 0.012 mm^2 each.

In experiments carried out for longer than 8 h, the fabricated device demonstrated excellent resolution and good linearity of up to 200 mg/dL, which can be further improved by increasing PU thickness. The sensitivity is 1.51 nA/mM and a reaction time of 10 mg/dL/ min. With the rate of glucose change in humans of 3 mg dL/min, this value suggested that the sensor can be used in detecting great glycaemia changes. Thus, the smallest fully integrated planar glucose sensor fabricated by Ribet et al. has the potential to dynamically and linearly measure the physiological glucose level with higher resolution and sensitivity compared to other continuous glucose monitoring devices on the market. However, the miniaturization of this sensor faces challenges in single amplitude, stability, active materials' selection and fabrication processes. The stability of electrode may decrease following reduction in size.

2.2.5. *Lab-on-chip with triboelectric liquid volume sensor*

Wang et al. [18] developed a transdermal patch for insulin delivery from liquid volume sensor and triboelectric mechanism. This transdermal system is able to trigger delivery of drugs into the skin via a microneedle upon energy generated from gentle finger-tapping on a polymer-based micropump. Furthermore, it can monitor the delivered drug volume. *In vivo* experiment on mice treated with this patch showed continuous reduction in blood glucose level while delivering insulin into them for 5.5 h, and stabilization after 3 h. Wang et al. also carried out an experiment to determine the functionality of different components and confirmed that the liquid volume sensor made manual control drug delivery possible by monitoring insulin delivery successfully and further controlling the blood glucose level. However, *in vitro* drug delivery volume was found to be 10% lower than *in vitro* calibration when microneedles are inserted into the skin. Resistance at the microchannels was believed to account for this deviation of actual delivery volume. One of the concerns of this system is that precise fabrication of the spacing between triboelectric pair surfaces must be optimized for best accuracy to monitor the delivery volume, which is essential in the delivery of insulin.

Apart from delivering medication for diabetes management, transdermal systems can also integrate an additional biosensor to detect the glucose level. This possesses an extra functionality to the transdermal entity to allow for extraction of interstitial fluid or plasma, thereby enabling continuous detection of plasma glucose level corresponding to that in interstitial fluid or plasma. However, despite the vast variety of biosensors tested, such systems face the challenges of stability, sensitivity, accuracy and reproducibility. In conclusion, the function of the transdermal system as a biosensor is seen to be an additional property added to the main purpose of drug delivery. From the reviewer's point of view, it is not a requisite to have the biosensor functionality in the transdermal drug delivery of diabetes, as such a system is still not matured to provide consistently accurate glycemic detection, and is thus not reliable.

2.3. *Point-of-care therapy*

As discussed in the first part of this review, we understand that transdermal drug delivery could help in the therapy of diabetes mellitus via technologies such as microneedles. However, such technologies only provide benefits in delivering medications in prolonged and sustained patterns. With additional fabrication features, point-of-care therapy is made possible in which insulin is released from a transdermal patch with certain triggers that respond to changes in plasma glucose level. Hence medications are delivered according to plasma glucose with more precision.

2.3.1. *H_2O_2-responsive polymeric vesicle with microneedle*

Hu et al. [19] presented an insulin administration transdermal patch utilizing H_2O_2-responsive polymeric vesicles (PVs) with microneedles, achieving a rapid response and painless smart insulin delivery. The PVs are polymersomes assembled from block copolymers that are incorporated with polyethylene glycol (PEG) and phenylboronic ester (PBE)-conjugated polyserine, forming a hollow structure with an aqueous core and

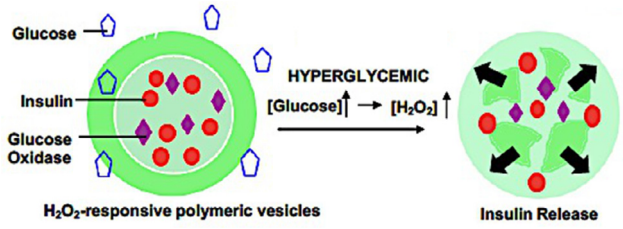

Fig. 2 – Insulin release from H_2O_2-responsive polymeric vesicle (Reprinted with permission from [19]. Copyright 2017 American Chemical Society).

a polymer bilayer membrane. The inner aqueous phase has a large drug-loading capacity, and hence, is used to load glucose oxidase (GOx) and encapsulate insulin. Upon a hyperglycemic state, insulin is released rapidly from PVs. The mechanism of drug release from this fabricated PV during hyperglycemic state is illustrated in Fig. 2 below. Microneedles with needle lengths shorter than one millimeter are integrated into this patch, along with hyaluronic acid cross-linking. Hu et al. studied the diffusion of glucose across the membrane into the patch in diabetic mice. The glucose is then oxidized to gluconic acid, forming H_2O_2.

In vivo insulin release profile using a control level (0 mg/dL), a normoglycemic level (100 mg/dL) and a typical hyperglycemic level (400 mg/dL) indicated that insulin is released rapidly when a hyperglycemic state is detected and only limited insulin release is observed at control and normoglycemic levels. At a hyperglycemic level, the insulin release rate increases, corresponding to the glucose level. Besides that, the GOx level in PV also affects the insulin release rate, giving insights into the possibility to manipulate the insulin release by varying GOx amount. Another finding from *in vivo* assessment is that this patch system is able to regulate glucose level without increased risk of hypoglycemia. No significant inflammation was reported at the application site after 2 d of administration, proving it to be biocompatible. The microneedles are stiff enough to exert an effect and the resulting microchannels after microneedle insertion are healed within 6 h.

This study shows that the microneedle insulin patch can be further innovated by encapsulating the water-soluble insulin in a polymeric vesicle. One main advantage of this approach is that the insulin release from the polymeric vesicle insulin patch is triggered by the different levels of plasma glucose in a rapid responsive manner. The release declines when the blood glucose level has achieved a normoglycemic level. This closely mimics our endogenous insulin release and action and provides a more precise control over blood glucose with less hypoglycemic risk. Another potential modification to this system is by varying the level of GOx loaded, which will provide different insulin release rates from the vesicle. However, as polymeric vesicle is the key in the release of insulin, its stability at physiological temperature needs to be investigated further to make sure the release trend and ability are similar to the temperature at which this study was carried out (4 °C). Otherwise, instability could potentially lead to hypoglycemia or failure to release insulin.

2.3.2. *Insulin-loaded and H_2O_2-responsive mesoporous silica nanoparticle integrated microneedle patch*

Xu et al. [20] fabricated a microneedle (MN) insulin delivery patch which integrates insulin-loaded and H_2O_2-responsive mesoporous silica nanoparticles (MSN) to achieve painless administration and rapid release of insulin in hyperglycemic state. 4-(imidazoyl carbamate)phenylboronic acid pinacol ester (ICBE) was used to conjugate with the conjugated amino groups on the surface of mesoporous silica nanoparticles (MSNs) to yield MSN-ICBE. Due to the host-guest complexation between ICBE and α-CD, payload insulin and gluconic oxidase (GOx) are stored in the MSN-ICBE upon addition of α-CD. The encapsulation efficiency and drug-loading capacity of this Insulin-MSN-ICBE/ α-CD were found to be 66.1% and 13.2% respectively. In the presence of glucose, GOx in the MSNs will convert glucose into gluconic acid and hydrogen peroxide (H_2O_2). Subsequently, the host-guest complexation will be destroyed and the preloaded insulin will be released. *In vitro* experiment was carried out to understand the insulin release behavior of the transdermal delivery system fabricated by Xu et al. This transdermal system exhibited an H_2O_2 concentration-dependent mechanism, as a significant rapid release of insulin was observed in the presence of H_2O_2 (72.4% of insulin release in 5 mM of H_2O_2 and 42.0% of insulin release in 1 mM of H_2O_2). On the other hand, a higher rate of insulin release was also found in the presence of a higher glucose level. These prove the rationale of using H_2O_2 as the enhancing factor and glucose as the promoting agent with the help of GOx in the fabricated transdermal system. The MNs used were in a 10×10 arrangement in a 100 mm^2 patch with both the height and space between each MN of 550 µm. This is proven to possess the mechanical strength for skin penetration.

An *in vivo* experiment was carried out using STZ-induced diabetic SD rats to investigate the transdermal delivery of insulin using this insulin-loaded and H_2O_2-responsive mesoporous silica nanoparticle integrated microneedle patch. SC injection of 24 IU and blank MNs were used in the control group whereas insulin (40 IU) was administered using the insulin-loaded MNs to two groups of rats with or without GOx. Results showed that the blood glucose level decreased rapidly in the SC group (from 510 mg/dL to ~85 mg/dL) within 2 h before increasing back to the initial level after 7 h. In the group receiving insulin treatment using Ins-MSN-ICBE/a-CD, only a little decrease of blood glucose level was observed even though higher insulin amount was loaded. A rapid decrease in the blood glucose level and slow recovery pattern were demonstrated after GOx encapsulation. A normoglycemic state can be maintained for a longer period (4.5 h) in this group as compared to SC group (2 h). These results also gave us an idea of the important role of GOx in the dissociation mechanism of such fabricated transdermal systems in facilitating the diffusion of insulin from MNs.

In conclusion, insulin release using this insulin-loaded and H_2O_2-responsive mesoporous silica nanoparticle integrated microneedle patch transdermal delivery system has glucose-mediated and H_2O_2-responsive release mechanisms which are capable of the transdermal delivery of insulin in diabetes treatment. The relative pharmacological availability and relative bioavailability are 90.1% and 92.6%, respectively, as compared to SC injection which gives this system an advantage

of natural release of encapsulated insulin from microneedles without disrupting insulin activity. A normoglycemic state can be maintained for longer. However, when a higher amount of insulin was encapsulated, it showed only a slight decrease in glucose level in comparison to SC injection. This indicates that GOx must be included in the formulation, or the loaded insulin will not be able to diffuse effectively from the microneedle into the skin tissue.

2.3.3. *Sweat-based electrochemical patch with thermoresponsive microneedle*

Lee et al. [21] designed and fabricated a disposable wearable multilayer patch that is able to monitor the glucose level with built-in sensors that work on a non-invasive sweat-based mechanism, and subsequently provide feedback to a transdermal antidiabetic through microneedles. This patch-based wearable device is claimed to achieve a multistage and precisely controlled drug release according to a patient's sweat glucose level without pain and stress. The device utilized a silicon patch to collect sweat from the wearer and any negatively charged molecules that could affect the glucose sensing were screened out by a porous and negatively charged Nafion layer. The multipoint enzyme-based glucose, pH and temperature sensors were used in measuring the correlated blood glucose level according to the sweat collected, allowing for more accurate and sensitive glucose measurement.

Two PCNs with different melting transitions ($T_{m,1} = 38\,°C$; $T_{m,2} = 43\,°C$) were loaded with metformin and built into the hyaluronic acid hydrogel microneedles. At a skin temperature of ~30 °C, no metformin was released from PCN; at 40 °C, only the drug loaded in PCN1 was released; while at 45 °C, drugs in both PCN1 and PCN2 were released. *In vivo* efficiency of this transdermal drug delivery using T2DM model on 8–12 week old diabetic mice. Diabetic mice with patches demonstrated significant blood glucose reduction as compared to diabetic mice without patch or drug-less microneedles. The amount of metformin released correlated to the reduction in blood glucose. Blood glucose of mice dosed with higher metformin was reduced to 7.6 mM (normal range: <11 mM). This sweat-based thermoresponsive microneedle has the advantage in releasing anti-diabetic medications according to sweat glucose levels which are believed to correlated with the plasma glucose levels. Only a little amount of sweat is required for the sensing (~1 μl). The multistage spatial pattern and precision in glucose sensing and release are enhanced by the detection of pH, temperature and humidity. Furthermore, it can be formulated into wearable or disposable strips, which eases application. On the other hand, this system also has a few disadvantages such as difficulty in sweat collection, temperature changes and activity variation of glucose oxidase. Enzyme stability is also a challenge with the potential of delamination upon mechanical friction and skin deformation. Precise glucose control based on patients' glucose levels, long-term stability and correlation between sweat glucose and plasma glucose in a human model are yet to be confirmed and hence require further investigation.

2.3.4. *Hypoxia and H_2O_2 dual-sensitive polymersome-based vesicle smart insulin patch*

Yu et al. [22] explored a hypoxia and H_2O_2 dual-sensitive diblock copolymer, a glucose-responsive polymersome-based vesicle (*d*-GRPs) which consists of a glucose-monitoring module and an insulin-releasing module in the treatment of diabetes. The *d*-GRPs are made up of PEG and polyserine modified with 2-nitroimidazole and are able to self-associate into a nanoscaled polymersome. The aqueous core is utilized to encapsulate recombinant human insulin and GOx. The encapsulated insulin is able to retain its secondary structure without any denaturation. In a hyperglycemic state, glucose encapsulated in the aqueous core diffuses across the polymeric bilayer membrane to interact with GOx for glucose oxidation. The oxidation process consumes oxygen, resulting in a local hypoxic environment. Meanwhile, H_2O_2 is produced as a byproduct, which has the potential to cause free radical-induced skin tissue damage. To overcome this, the H_2O_2-sensitive moiety in the *d*-GRPs was designed to scavenge the produced H_2O_2. Subsequently, the polymersomes dissociate and release the encapsulated insulin. Yu *et.al* investigated the insulin release rate of the *d*-GRPs and found that the rate is dependent on the GOx concentration. They. also integrated the *d*-GRPs with 20×20 array microneedles with a base diameter of 300 μm, tip diameter of 10 μm and height of 600 μm to fabricate a smart insulin patch (SIP). *In vivo* experiment was carried out using STZ-induced type 1 diabetes mice to investigate the efficacy of SIP and glucose control capability of the microneedles. Mice administered insulin using *d*-GRPs (encapsulated GOx + Insulin) exhibited rapid blood glucose level reduction in the first 1 h and maintained a normal state for up to 6 h without reaching a hypoglycemic state. However, when administered using *d*-GRPs (insulin) without GOx, no significant reduction in blood glucose level was observed. Mice treated with *d*-GRPs (encapsulated GOx + Insulin) SIP were able to avoid hypoglycemia as compared to free insulin-loaded microneedles. The new smart insulin patch designed by Yu et al. could be one of the options in diabetes treatment with the advantage of providing painless administration, as well as prolonged treatment efficacy with the application of more than one patch in response to a raised blood glucose level, with a reduced risk of hypoglycemia.

In conclusion, transdermal patches for diabetes management can be fabricated using more advanced technologies to incorporate entities that detect changes such as glucose level or temperature, and subsequently trigger the release of medication such as insulin. Such formulation works similarly to microneedle patches but comes together with the ability to release medication according to the varying level of glucose. A microneedle patch is promising enough in diabetes management, and with the additional ability to trigger medication release when the glucose level rises, there is an added bonus, especially for patients with uncontrolled glucose levels or with high risk of hypoglycemia. This system may provide more precise drug release.

2.4. *Employment of technologies for carrier, entrapment, penetration and release*

2.4.1. *Permeation enhancement via proniosomal gel entrapment*

Abdallah et al. [23] studied the improvement of therapeutic efficacy of glimepiride (GM), an antidiabetic using proniosomal gel entrapment via transdermal drug delivery pathway. The

proniosomal gel formulations can be formulated using Span 20, Span 60, Tween 20, Tween 60, Span 60:Tween 20 or Span 60: Tween 60 with different Cholesterol concentrations. *In vitro* drug release test revealed that proniosomal gel has the lowest drug release (about 47.5% ± 1.25% after 6 h) as compared to polymeric gel, niosomal dispersion and niosomal gel due to the need for hydration prior to drug release. The findings from *in vivo* drug release experiments on rat skin showed that GM loaded in proniosomal gel gave slow hypoglycemic effect and maximum blood glucose level reduction after 6 h (65.34% ± 6.54%) and extended to 24 h. This transdermal drug delivery profile had a longer hypoglycemic effect as opposed to oral administration of GM, which lasted only up to 6 h. These findings provide an insight into the permeation-enhancing effect of proniosomal gel with high drug release capacity in the transdermal drug delivery in diabetes treatment. In conclusion, transdermal system using proniosomal gel entrapment provides permeation effect, allowing for higher drug release capacity. This is superior to the oral route as it provides an extended effect in lowering blood glucose.

2.4.2. *Proniosome carbopol-based transgel system*

Prasad et al. [24] developed the formulation of carbopol transgel in proniosome form for diabetes management. By encapsulating pioglitazone (PZ), *in vivo* pharmacokinetic study demonstrated significant improvement of 2.26 times in bioavailability as compared to antidiabetic drugs tablet. PZ was released in biphasic pattern from noisome with diffusion-controlled mechanism. The hypothesis is that it happened through desorption of PZ from noisome surface following diffusion through swollen niosomal bilayer, that resulted in slow release. Such a release pattern might be crucial in achieving rapid drug release at the initial stage to hit a higher concentration gradient for better transdermal delivery of drugs into blood. The experiment done by Prasad et al. also showed that this transdermal system has about 4 times longer elimination half-life than oral delivery with better bioavailability (2.03 times higher than oral route) over 48 h. The observed drug release was rapid, accompanied by subsequent sustained release. Hence, carbopol-based transgel is proven to be an efficient carrier for drug penetration into skin, which leads to a better pharmacological antidiabetic effect than existing tablets on the market. In conclusion, entrapment of an antidiabetic drug in proniosomal form allows the drug to diffuse slowly into blood from the system, giving higher bioavailability as compared to conventional oral tablets.

2.4.3. *Transferosomal gel with chemical enhancer 'iodophor'*

Transferosomal gel system consisting of chemical enhancer 'iodophor' was presented by Marwah et al. [25] to investigate its use in permeation of antidiabetic agents such as insulin into skin. The transferosomes were fabricated using soya lecithin as phospholipids, sodium cholate as surfactant and insulin as drug by a conventional rotary evaporation sonication method. The study showed that the drug and excipients present in the system were compatible with each other. The entrapment efficiency of transferosomal gel increased as the concentration of drug loaded increased until it reached 10 mg, where significant reduction in entrapment efficiency was observed. 78% of insulin was successfully entrapped in the formulations with 2.5 I.U. of the drug and 25% of sodium cholate. An *in vitro* study on drug release using a cellophane membrane revealed the sustained released pattern of transferosomal gel. A transferosomal suspension was found to exhibit the highest cumulative amount of drug release as compared to transferosomal gel and plain gel. The cumulative percent drug release was found to be 83.11% ± 3.78%. On the other hand, *in vivo* study showed that transferosomal gel with iodophor is able to reduce blood glucose level initially, in a sustained manner, before the level rises steeply. This phenomenon might be attributed to the viscosity of transferosomal gel, meaning it is poor in controlling the drug release. Thus, the transferosomal gel system with chemical enhancer iodophor is proposed to have better potential for disrupting the epidermal layer to deliver insulin into the skin, thus achieving a higher bioavailability of the drug. Entrapment in transferosomal gel shows significantly higher entrapment efficiency, and hence greater drug release.

2.4.4. *Microemulsion gel*

Shinde et al. [26] studied microemulsion gel transdermal delivery of Repaglinide (RPG) in drug permeation and antidiabetic effect. Microemulsion systems were prepared by mixing oil (kept under 8%), surfactant, co-surfactant and water. 0.6% (w/w) of xanthan gum was added to the formulation to prepare a microemulsion gel with mean globule size of 36.15 ± 9.89 nm while RPG was loaded into it under ultrasonication. The rationale behind their design was based on the drug dissolution property, avoidance of first-pass metabolism, controlled and sustained drug release properties of microemulsion using transdermal route and gel. RPG microemulsion gel indicated higher *in vitro* drug permeation by exhibiting 10.97 times higher flux of drug. *In vivo* results also showed significant ($P < 0.05$) and greater hypoglycemic activity than oral suspension formulation. These data suggest that this transdermal formulation could be explored for effective T2DM treatment as it can reduce the blood glucose level in controlled manner. Similar to transferosomal gel, higher skin permeation and drug diffusion are elucidated in the use of microemulsion gels in transdermal delivery systems in diabetes management. Hence, this transdermal system demonstrated a better glucose lowering effect as compared to oral formulation.

2.4.5. *Transdermal nanoemulsion encapsulation*

Mostaga et al. [27] studied the encapsulation of fennel essential oil (FEO), an antidiabetic agent in transdermal nanoemulsions (NEs). The nanoemulsion system was formulated using distilled water as an aqueous phase, oleic acid as an oil phase and Tween 20 and propylene glycol as surfactant and co-surfactant respectively. Tween 20 and propylene glycol (Smix) were formulated in three portions: 1:9 (F1), 2.8 (F2) and 3.7 (F3). The thermodynamic stability test of NE tested using centrifugation at 5000 rpm for 20 min demonstrated the good stability of NE without the occurrence of phase separation. An *ex vivo* study revealed F1 and F2 having better cumulative drug permeation and permeation rates. In the *in vivo* study, male Wistar rats weighing 160–200 g were used as subjects and a single intraperitoneal dose of streptozotoxin (STZ) of 60 mg/kg was used to induce diabetes. At 0.5, 1, 2 and 4 h after

oral glucose administration, rats treated with FEO and FEO NEs showed a reduction in plasma glucose levels. At 4 h, the plasma glucose level was found to be lower in FEO NE than after treatment with FEO alone. Nevertheless, the difference was not significant. F1 and F3 formulation showed prolonged antidiabetic effects for up to 7 d, whereas F2 only maintained such an effect for 2 d. It was found that F1 exhibited the highest antidiabetic effect among the 3 formulations, probably due to its depot effect. A prolonged antidiabetic effect was observed when F1 with high doses of NE (120 mg/kg and 60 mg/kg) showed significant plasma glucose reduction in 7 d as compared to FEO alone at the same doses. The resulting plasma glucose levels were higher than non-diabetic control group but were still within the normal range of fasting plasma glucose. This system is able to achieve a penetration effect with oleic acid being a powerful enhancer and demonstrating a synergistic effect with surfactants used. Generally, the surfactants used in the system are considered safe. Glucose control using nanoemulsion is better and more prolonged due to higher drug permeation and permeation rate.

2.4.6. *Nanostructured lipid carriers transdermal system*

Alam et al. [28] fabricated a nanostructured lipid carrier (NLC) using high-pressure homogenization and ultrasonication to load pioglitazone (PZ) in diabetes management. An *in vivo* pharmacokinetic study elucidated that bioavailability of PZ using NLC was 2.17 times better than PZ (Piosys) tablets. A slower and sustained release pattern over a prolonged duration of about 48 h was observed. Besides that, PZ-loaded nanolipid gel showed remarkable reduction of blood sugar level up to 101.87 mg for 24 h and maintained a below-hyperglycemic level post 24 h without rising back to diabetic level. The shelf life of the NLC formulation was found to be 1.83 y. These results provide an insight into the NLC-based transdermal system for promising controlled release formulation for diabetic drugs such as PZ. Besides that, this system also proved to be potential carrier. It acts as a reservoir for long-term delivery and efficient absorption and is superior to the oral route. In conclusion, a lipid is used as the carrier (nanolipid gel) for antidiabetic drugs. Similar to the other systems mentioned above, this system allows for sustained drug release over a prolonged duration, leading to a better hypoglycemic effect.

2.4.7. *Hyaluronic acid encapsulated CuS gel-mediated near-infrared laser nanosystem*

Wang et al. [29] fabricated a hyaluronic acid encapsulated CuS nanosystem (HA-CuS) as shown in Fig. 3 for the transdermal delivery of antidiabetic drug in Type 1 Diabetes due to its excellent biocompatibility and photothermal translation efficacy. HA-CuS nanoparticles were synthesized by centrifuging the resulting solution made from 150 mg HA, 4 mM CuCl, 50 mM Na_2S and 36 mg trisodium citrate under a high temperature of 80 °C at 12 000 rpm. Cell cytotoxicity tests were performed to demonstrate safety and biocompatibility of HA-CuS nanoparticles using normal human dermal fibroblast under laser irradiation. Similar cell variability as compared to control groups were observed when the irradiation tests were conducted for 30 s until significant cell death occurred at 10 min. This shows HA-CuS nanoparticles as a prospective drug delivery candidate with good biocompatibility for short-time laser irradiation in living cells. *In vivo* biomedical application of HA-CuS transdermal drug delivery was investigated on Type 1 Diabetes nude mice using insulin as the treatment. Nude mice were pretreated with HA-Cus gel (50 µl, 100 µg/ml) on the skin (diameter ~1.5 cm) before being irradiated with NIR laser at 0.24 W/cm^2 for 30 s. Nude mice without the aforementioned pretreatment served as the control group. In the group of pretreated nude mice, human recombinant insulin solution (200 µl, 2 mg/ml)-loaded patch was added onto the treated skin area. Fig. 4 illustrates the results whereby mice receiving pretreatment and NIR laser irradiation had a gradual lowering of blood glucose to 85.7% at 2 h and to 84.2% at 8 h before increasing back to 99.6% at 10 h. On the other hand, a sudden reduction of blood glucose to 52.7% at 2 h was observed in mice receiving insulin SC injection. This blood glucose was then increased rapidly to similar to that in the HA-CuS system: 93.1%, 97.1% and 105.7% at 4, 6, 8 and 10 h, respectively.

Hence, it is shown that HA-CuS gel-mediated transdermal system is capable of sustained and controllable transdermal drug delivery to maintain blood glucose at a lower level for a longer time compared to the currently existing insulin injections, owing to its excellent biocompatibility and advanced photothermal conversion efficacy. HA-CuS nanoparticles are stable, relative to the photothermal conversion. However, this system is only proven to be safe when used for short-time laser irradiation (30 s). Significant cell death is observed when laser irradiation is increased up to 10 min. This implies that application of this system must be carried out in a controlled environment i.e., in clinical settings, and for a strict duration. In conclusion, the biocompatible hyaluronic acid encapsulated CuS nanosystem exhibits a more significant hypoglycemic effect and longer control time than SC injections. Laser irradiation acts to enhance the drug release from the nanosystem.

2.4.8. *Solid-in-oil insulin gold nanorods*

Nose et al. [30]. assessed the possibilities of using solid-in-oil insulin gold nanorods (SO-INS-GNR) in the delivery of insulin to diabetic mice. The gold nanorods (1 mM solution) complex had an edible surfactant and insulin (1 mg/ml). Processes such as homogenisation of the gold nanorods for 2 min at 26 000 rpm, rapid freezing in liquid nitrogen for 15 min and subsequent lyophilization using freeze-drying for 24 h were employed in the preparation of this system. An *in vitro* study using SO-INS-GNR along with near infrared (NIR) light on mice showed high insulin penetration stratum corneum and dermis. With the use of NIR light irradiation, the blood glucose level of treated diabetic mice had a plunging decrease at 4 h (about 58.0% ± 11.5%) as compared to diabetic mice receiving other treatments in the experiment. The glucose level showed further decreases after 6, 8 and 10 h by 37.0% ± 9.1%, 23.0% ± 4.4% and 15.0% ± 2.9%, respectively. These data indicate that SO-INS-GNR formulation could be a potential transdermal drug delivery system to allow slow release of insulin into the systemic circulation. However, such release mechanisms remain unclear. In the nanorod transdermal system, insulin is complexed into the gold nanorod. When near infrared light is irradiated, the insulin penetrates better across the skin barriers and layers. Despite the unknown drug release, such

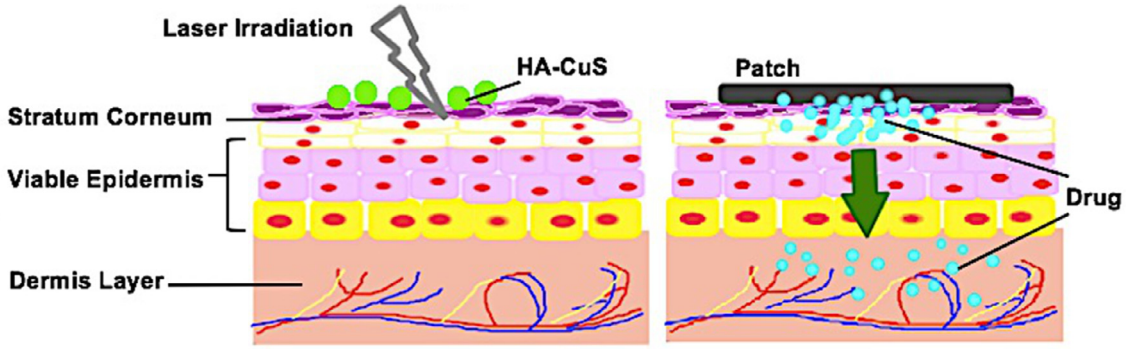

Fig. 3 – HA-CuS Near Infrared Laser Nanosystem (Reprinted with permission from [29]. Copyright 2017 American Chemical Society).

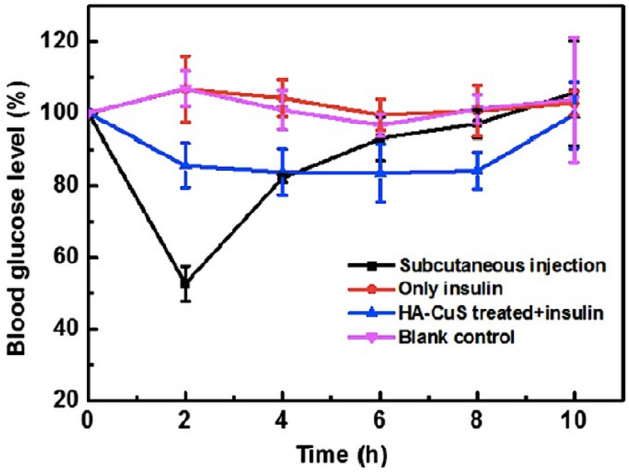

Fig. 4 – Blood glucose levels of diabetic mice in four groups: subcutaneous insulin injection (positive control); untreated+insulin; HA-CUs treated+NIR laser+insulin; and untreated diabetic mice (blank control) (Reprinted with permission from [29]. Copyright 2017 American Chemical Society).

a system has proven to provide glucose lowering over an extended duration.

2.4.9. Choline and geranate (CAGE) deep eutectic solvent transdermal delivery vehicle

Barnejee et al. [31]. investigated the application and effectiveness of Choline and Geranate (CAGE), without any physical and chemical penetration enhancer, as a transdermal delivery vehicle for proteins such as insulin to reduce the blood glucose level. They tested for the penetration of insulin across epidermis and dermis using CAGE and found that the penetration was much superior with CAGE than with commonly used chemical penetration enhancers. The penetration of insulin into dermis of non-diabetic rats was $5.46 \pm 0.04\,\mu g/cm^2$ at 24 h and $17.22 \pm 1.43\,\mu g/cm^2$ at 48 h. Circular dichroism spectra revealed the good stability of insulin in CAGE. *In vivo* topical delivery of 10 U insulin in rats using CAGE demonstrated a reduction in blood glucose level of 25% in 2 h and 40% in 4 h, and the effect was sustained and prolonged over the time of the study even though a 10% increase in the blood glucose level was observed over time.

Hence, the proposed design by Barnejee et al. is considered to be one of the options for a transdermal vehicle due to its ability to provide sustained reduction in blood glucose, resulting in better patient compliance and long-term glycemic control. Information on other aspects such as the mechanism of CAGE, long-term stability and toxicity, and application in diabetic rats are required to further investigate its use. In conclusion, skin penetration is shown to be higher than in other chemical penetration enhancers. Along with higher skin penetration of the loaded drug, the glucose control profile also proves its ability to control glucose level in a sustained and prolonged manner.

2.4.10. Amidated pectin hydrogel matrix patch

Hadebe et al. [32] explored the delivery of an insulin dermal patch using amidated pectin hydrogel matrix gel. This group tested the insulin effect on streptozotocin (STZ)-induced diabetic mice using the aforementioned system in ameliorating diabetic symptoms in tissues such as muscle and liver. The pectin matrix patch can load insulin ranging from a concentration of 76%–94%. The concentration lost 75%–89% of activity after being stored for 2 months, indicating the stability of such a patch formulation. The plasma insulin level in STZ-induced diabetic mice showed a significant increase after acute, short-term daily application of the pectin hydrogel matrix patch (6 h daily for 5 weeks) in comparison with untreated STZ-induced diabetic mice. In the treated group of mice, higher insulin-loaded patches (9.57 and 16.80 µg/kg) resulted in a higher plasma insulin level in mice, whereas a plasma insulin level was reported to be lower when lower doses of insulin-loaded patches were given (2.47 and 3.99 µg/kg). Moreover, interestingly, the plasma insulin level is higher with pectin insulin patch application than SC insulin administration. These studies show the insulin release into the blood from pectin insulin patch in a concentration-dependent pattern. Pectin insulin matrix can also prevent leakage of the drug in solution formulations. However, the downside in this study is the inability to separately investigate the effect of different insulin concentrations on plasma insulin concentration and blood glucose statistically, possibly due to the narrow range of doses used in

the experiments. Hence, to further understand the use of this system in clinical aspects, further studies with wider insulin doses are necessary and also essential in paving the development to unit dosage forms of insulin patch.

2.4.11. *HPMC and PVA blend transdermal patch*

Shaheen et al. [33] designed a formulation of a transdermal patch using HPMC and PVA, which they deemed to have the potential to be formulated into a wearable watch-belt in the future. The transdermal patch was formulated using a polymer blend of HPMC and PVA, utilizing a freezing and thawing process. In their study, 800 mg of metformin was loaded into the patch. The blood glucose level of normal and diabetic mice treated with this patch for 4 h showed significant reduction. They elucidated that metformin HCL can penetrate and cross the membrane easily into blood circulation using an HPMC-PVA based transdermal patch and provide better drug efficacy than the oral route of administration. The HPMC-PVA patch can be made to supply doses for multiple days and can be taken off if patients experience hypoglycemia symptoms. In conclusion, a HPMC and PVA-fabricated transdermal patch can be used to load an antidiabetic drug, which allows the loaded drug to penetrate across the skin membrane more easily, resulting in higher blood concentration and so better control of blood glucose.

In conclusion, all the technologies used in entrapment, penetration and release of carriers are based on gels, proniosomes, hydrogels, nanoemulsions and nanoparticles. The treatment is based on carrier (drug) delivery. In all cases high permeation is a prerequisite for the effectiveness of the technology.

3. Conclusion and future perspective

As diabetes mellitus is a chronic disease that requires long-term drug administration and glucose level monitoring, a breakthrough innovation in treatment strategies for management of the disease would be welcome. If the challenges in manufacturing the transdermal patch could be overcome, we will expect a tremendous shift in diabetes management as transdermal drug delivery systems in diabetes management are deemed to be a promising approach in providing a better clinical outcome compared to conventional dosage forms. A better drug bioavailability can be achieved, and with this, diabetic patients will then have a lesser dosing frequency as compared to twice-daily dosing of conventional oral agents and three times or even four times daily SC insulin injection. Another notable advantage would be the patients will have a much easier treatment option in which a patch with predetermined release rate can be applied to the skin. The prolonged and sustained drug release profile will also ensure better glucose control and better prediction of glucose profile. Besides that, with more sophisticated technologies, microneedles in transdermal patch are able to act as biosensor to detect glucose level and release drug accordingly. All these are exceptionally beneficial to avoid hypoglycemia which is common with some insulin injection and oral hypoglycemic agents such as sulphonylurea. As compared to SC insulin injection, transdermal patch will potentially help to reduce stigma where patients are needed to inject insulin at prescribed timing especially when they are in public areas and also reduce needle phobia.

All in all, this field is becoming an endeavor for researchers to explore and venture into, for different transdermal system approaches have shown highly desirable advantages in improving drug bioavailability, reducing dosing frequency, preventing risk of side effects and providing painless and easy administration, thus leading to improved patient compliance. More dedicated work in developing transdermal systems for antidiabetic drugs should be the focus to overcome the disadvantages associated with conventional dosage forms and the increasing size of the diabetic population.

With various technologies being employed in the fabrication of transdermal drug delivery systems in diabetes therapy, a microneedle-based approach appears to be the most commonly studied field and serves as a basis for drug penetration and dermal delivery. Most of the studies have elucidated that it could provide sustained release of medications over a prolonged duration, and avoid a rapid decrease of blood glucose in the initial phase to prevent hypoglycemic side effect. However, with only microneedle-based delivery, we are unable to control the drug release based on varying glucose levels. Additional features such as biosensors would add advantages in this respect, as the drug release will be triggered according to the glucose level. One of the challenges is the precision of measurement and correlation between results obtained from interstitial fluid or sweat and plasma or blood glucose.

With more sophisticated technologies such as carriers and laser irradiation, current studies are unable to demonstrate long-term safety profile in a human model. Nevertheless, the transdermal delivery system in diabetes therapy is opening a new avenue for a more precise and disposable wearable-type device for convenient administration and storage. The objective of future research in this field could be patch formulation for diabetes therapy in the form of a wearable belt or chip.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ajps.2019.04.006.

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