IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON TRANSDERMAL INSULIN PATCHES

Ms.Punam Mahadev Gadade*, Ms.Namrata Kathwate2,Dr.Vishal Babar3

Department of Pharmaceutics,

DKSS's Dattakala College of Pharmacy,Swami-Chincholi,Pune,Maharashtra,India 413130

ABSTRACT:

Transdermal drug delivery has made an important contribution to medical practice, but has yet to fully achieve its potential as an alternative to oral delivery and hypodermic injections. 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 antidaibetic medicaments and biosensing of blood glucose level to ensure better clinical outcomes in diabetes management.

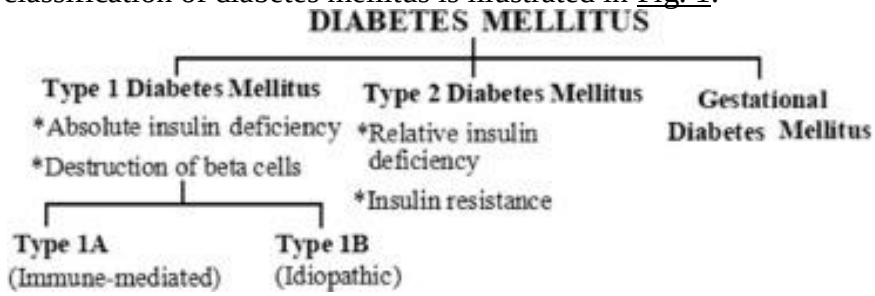
KEYWORDS: Diabeties; Insulin; Transdermal delivery system;Transdermal Patch Design;Transdermal patches.

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].Daibetes mellitus term is used to describe a metabolic diseases which are characterized by hyperglycemia. The causes of diabetes are less insulin secretion or impared insulin action or both. Diabetes can be classified into different types, 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.



Diabetes is a chronic disease and it is found that more than 415 million people globally affected by it and is estimated to stike about 642 million people in 2040, i.e., 1 in every 10 will have diabetes. Steering the focus to the prevalence of diabetes by region.

Transdermal drug delivery:

Transdermal insulin delivery allows insulin to be absorbed through the skin and can be given anywhere on the body, regardless of the body composition of the person with diabetes. Insulin patches can be potentially used with both rapid-acting and long-acting insulins[4-6]. However, no matter which insulin is put into the patch, all insulin patches have worked like basal insulin until recently[7]. Insulin patches are not yet commercially available.Transdermal drug delivery represents best alternative to oral delivery of drugs and is poised to provide an alternative to hypodermic injection too.Between 1979 and 2002, a new patch was approved on average every 2.2 years. Over the past 5 years (2003–2007), that rate has more than tripled to a new transdermal delivery system every 7.5 months. It is estimated that more than one billion transdermal patches are currently manufactured each year. Transdermal delivery also has advantages over hypodermic injections, which are painful, generate dangerous medical waste and pose the risk of disease transmission by needle re-use, especially in developing countries[8]. In addition, transdermal systems are noninvasive and can be self-administered. They can provide release for long periods of time (up to one week). They also improve patient compliance and the systems are generally inexpensive.Perhaps the greatest challenge for transdermal delivery is that only a limited number of drugs are amenable to administration by this route.

Transdermal patch design

Almost all transdermal patch designs, the drug is stored in a reservoir that is enclosed on one side with an impermeable backing and has an adhesive that contacts the skin on the other side[9]. Some designs employ drug dissolved in a liquid or gelbased reservoir, which can simplify formulations and permit the use of liquid chemical enhancers, such as ethanol. These designs characteristically are composed of four layers: an impermeable backing membrane, a drug reservoir, a semi-permeable membrane that may serve as a rate-limiting barrier and an adhesive layer. Other designs incorporate the drug into a solid polymer matrix, which simplifies manufacturing. Matrix systems can have three layers, by eliminating the semi-permeable membrane, or just two layers, by incorporating the drug directly into the adhesive.

Types of Transdermal patches

1.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. Biodegradable alginate and hyaluronate polymer microneedle patch:

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 selfregulation of insulin feasible.

3. Insulin-loaded and H2O2-responsive Mesoporous Silica Nanoparticle Integrated Microneedle Patch:

Xu et al. [11] fabricated a microneedle (MN) insulin delivery patch which integrates insulin-loaded and H2O2-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 (H2O2). Subsequently, the host-guest complexation will be destroyed and the preloaded insulin will be released.

4. Hypoxia and H2O2 dual-sensitive polymersome-based vesicles smart insulin patch:

Yu et al. [12] explored a hypoxia and H2O2 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, H2O2 is produced as a

byproduct, which has the potential to cause free radical-induced skin tissue damage. To overcome this, the H2O2-sensitive moiety in the d-GRPs was designed to scavenge the produced H2O2. 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 smartinsulin patch (SIP)

5. Amidated pectin hydrogel matrix patch:

Hadebe et al. [13] 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, shortterm 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 insulinloaded 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

6. HPMC & PVA blend transdermal patch:

Shaheen et al. [14] 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

References:

[1]

Sattley M.The history of diabetes: diabetes health; 2015. Available Google Scholar

[2]

R. Lakhtakia

The history of diabetes mellitus
SQUMJ, 13 (3) (2013), pp. 368-370

from: https://www.diabeteshealth.com/the-history-of-diabetes/.

[3]

A.D. Association

Diagnosis and classification of diabetes mellitus
Diabetes Care, 37 (Supl 1) (2014), pp. S81-S90

[4]

Rastogi R, Anand S, Koul V: Electroporation of polymeric nanoparticles: an alternative technique for transdermal delivery of insulin. Drug Dev Ind Pharm. 2010, 36: 1303-1311. 10.3109/03639041003786193.

CAS Article PubMed Google Scholar

[5]

Prelude SkinPrep system website. (available from http://www.echotx.com/drug-delivery.shtml). pp. skin prep for insulin patches

[6]

Drug delivery in diabetes: making effective treatment tolerable ONdrugDELIVERY. available from http://www.ondrugdelivery.com/publications/diabetes.pdf

[7]

Qin G, Gao Y, Wu Y, Zhang S, Qiu Y, Li F: Simultaneous basal-bolus delivery of fast-acting insulin and its significance in diabetes management. Nanomed Nanotechnol Biol Med. 2012, 8: 221-227. 10.1016/j.nano.2011.05.017.

CAS Article Google Scholar

[8]

Miller, M.A. & Pisani, E. The cost of unsafe injections. *Bull. World Health Organ.* **77**, 808–811 (1999).

CAS PubMed PubMed Central Google Scholar

[9]

Venkatraman, S. & Gale, R. Skin adhesives and skin adhesion. 1. Transdermal drug delivery systems. Biomaterials 19, 1119–1136 (1998).

[10]

Seong KY, Seo MS, Hwang DY, O'Cearbhaill ED, Sreenan S, Karp JM, et al. A self-adherent, bullet-shaped microneedle patch for controlled transdermal delivery of insulin. J Control Release 2017;265:48–56

[11]

Xu B, Jiang GH, Yu WJ, Liu DP, Zhang Y, Zhou JY, et al. H2O2-responsive mesoporous silica nanoparticles integrated with microneedle patches for the glucose-monitored transdermal delivery of insulin. J Mater Chem B 2017;5(41):8200–8.

[12]

Yu J, Qian C, Zhang Y, Cui Z, Zhu Y, Shen Q, et al. Hypoxia and H2O2 dual-sensitive vesicles for enhanced glucose-responsive insulin delivery. Nano Lett 2017;17(2):733–9

[13]

Hadebe SI, Ngubane PS, Serumula MR, Musabayane CT. Transdermal delivery of insulin by amidated pectin hydrogel matrix patch in streptozotocin-induced diabetic rats: effects on some selected metabolic parameters. PLoS ONE 2014;9(7):e101461

[14]

Shaheen SM, Jahan L, Ferdaus R. A therapeutic TDS patch of Metformin from a HPMC-PVA blend studied with a biological membrane of fish-swim bladder: an approach for dermal application in NIDDM. PJPS 2015;28(5):1619–24