A survey on the potential awareness for the delivery of insulin using transdermal microneedle array

A project submitted by

Anika Mahmood

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To

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Dedicated to my parents & supervisors

Certificate Statement

This is to certify that the project titled **"A survey on the potential awareness for the delivery of insulin using transdermal microneedle array"** submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy from the Department of Pharmacy; BRAC University constitutes my own work under the supervision of Dr Hasina Yasmin, Associate Professor of Department of Pharmacy, BRAC University. Throughout the project I have given appropriate credit where I have used the language, ideas or writings of another.

This is a collaborative project under the joint supervision of Professor Dr. Eva Rahman Kabir, Chairperson, Department of Pharmacy, BRAC University, Dr. Hasina Yasmin, Associate Professor, Department of Pharmacy, BRAC University and Dr. Md. Jasim Uddin, Assistant Professor, Department of Pharmacy, BRAC University.

Signed

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Counter signed by the supervisor

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I am grateful to the Almighty for giving me the strength to stay on course with determinations through all the hardships. It is only possible with His blessings and mercy that I am able to have come this far today.

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Abstract

Conventional ways of delivering anti-diabetic drugs such as insulin via injection and other means might have limitations that can affect patient compliance although having good efficacy such as pain, needle phobia, skin irritation and skin hardness etc. Use of microneedle skin patch to convey the drug via transdermal delivery system can be an innovative and successful approach to deal with the drawbacks of traditional methods. For this purpose, this study has been conducted on "A survey on the potential awareness for the delivery of insulin using transdermal microneedle array" involving a sample size of 385 diabetic patients. The survey included a questionnaire of 25 questions regarding the problems faced by patients on using injections, the introduction of microneedles and their advantages along with the most vital question of acceptance of microneedle patches in future. Data analysis was carried out using Microsoft Excel. It was found that 56% of the sample population used insulin on a regular basis and 53% was needle phobic. Insulin injection was considered inconvenient by 63% of the total sample. Lastly, 93% of the patients surveyed agreed upon acceptance of the patch for controlling blood sugar level and shared their views and apprehensions concerning this new technology. Several concerns relating to this patch were established. Finally, study findings suggested to further research on the topic and design to develop microneedle patches for the delivery of insulin.

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Chapter 1: Introduction

1.1 Introduction

Traditional drug administration system comprises of tablets, capsules, oral liquid dosage forms, ointments, intravenous solutions and eye drops etc. For decades, the oral route has been considered the most suitable for administration of drug. Yet, drug deliverance via this route has the disadvantages such as GI tract irritation, nausea and hepatic first pass metabolism. Alternatively, using injections is considerable in cases like in need of rapid absorption, impossible for oral administration or too irritating to be injected into the skin or muscles (Jin et al., 2015). The hypodermic needles used in injections have many shortcomings, such as unable to painless delivery of drug, the possibility of having infections or communicating a contagious disease, fatality from injecting the drug directly into a vein because of rapid entrance of the drug in the bloodstream (Khalid et al., 2013), it may require assistance of medical professionals, may produce medical wastes (Economidou et al., 2018).

Limitations of such traditional drug delivery systems enable the transdermal route an appealing alternative (Economidou et al., 2018). By transdermal drug delivery system (TDDS), drugs are released directly via skin recompensing the shortcomings of oral route and stratum corneum penetration, some widely used drug delivery methods (Kwon et al., 2017).

1.2 Skin

An easy accessible pathway for administration of drugs is skin fromlong-ago, which demonstrates the feasibility of systematic therapy through percutaneous drug absorption (Economidou et al., 2018). In adults,it has a surface of about 1.5 m^2 and it protects the internal organs of body (Ita, 2015). Skin takes up almost the one-third of body's blood circulation and therefore makes it one of the significant targets for drug delivery. Moreover, it also absorbs chemicals as well as bio-agents (Kwon et al., 2017).

Although skin provides a large surface area, it is difficult for the vaccines and drugs to transfer through the skin significantly asskin consists of several layers (Ita, 2015).

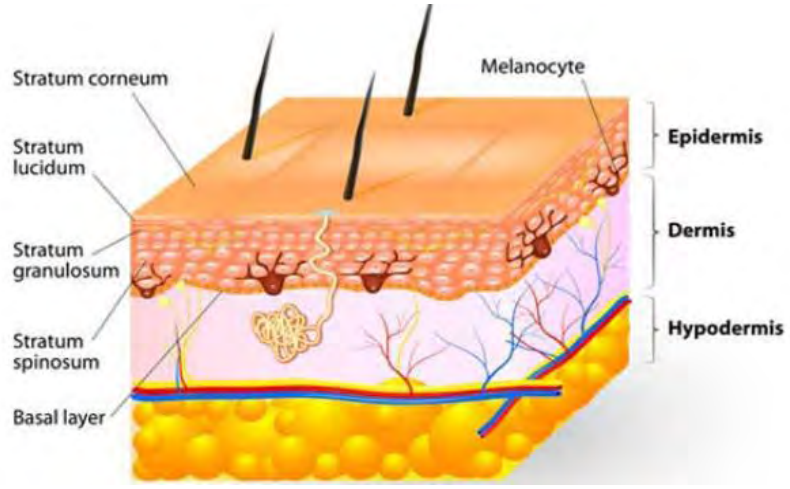


Figure 1.1 Layers of human skin (from Layers of the Dermis, 2017)

1.2.1 Stratum Corneum

The outermost part of the skin is stratum corneum (SC) which acts as a major obstacle in skin penetration. It is 10 to 15 μm in thickness that consists of 15 to 20 corneocyte layers (Ita, 2015) and its organization can be compared to a "brick-and-mortar" structure. Here, the bricks correspond to the corneocytes that are differentiated terminally and thelipid matrix between cells that surrounds the corneocytes is represented by the mortar (Danso et al., 2014).

The composition of lipids of the SC works as a barrier to the skin as the main pathway to penetrate molecules across the SC is through the matrix. Free fatty acids, cholesterol and ceremides that form two lamellar phases are the principal lipid classes in the human SC. Thephases are short periodicity phase and long periodicity phase. In the lipid lamellae, the lipids are mostly structured in a dense orthorhombic packing but a small part of lipids take up a packing of hexagonal shape (Danso et al., 2014).

1.2.2 Viable epidermis

It is an avascular cellular tissue that lies underneath the SC with a thickness of 50 to 100μm. Keratinocyes, protiens, lipids and water make up the viable epidermis (VE). Epidermal cells ofthe basal layer form the most important structural and useful association to the dermis underneath (Ita, 2015).

Full epidermis of the skin comprises of SC and VE together. It has been reported that the permeability of drugs to the total epidermis rather than only SC is more effective for drug delivery (Ita, 2015). The existance of a basement membrane at the bottom of the epidermis and rigid junctions in the VE may resist the transfer of molecule in the epidermis (Andrews et al., 2012).

1.2.3 Dermis

The dermis is in the deepest part, which is predominantly a fibrous tissue with thickness of 1 to 2 mm. Under the epidermis, lays a rich capillary bedwhich acts as the key site of drug uptake into the blood stream. Typically, the success in transdermal drug delivery involves transportation of drugs through the epidermis to the surface capillary bed (Andrews et al., 2012).

Therefore, drugs that can penetrate SC disperse through out VE and exceed to the upper fraction of papillary dermis, are expected to get to the circulation to demonstrate complete effect (Ita, 2015).

1.3 Transdermal drug delivery system

Transdermal drug delivery system (TDDS) ensures deliverance of drugs all the way through skin compensating drawbacks of subcutaneous andoral route, the most used methods for drug delivery (Kwon et al., 2017). Further advantages of this route include avoidable degradation of drug due to first pass metabolism, yielding high bioavailability, which may be utilized as a means to stimulate the controlled and sustained drug discharge in a non-invasive way (Economidou et al., 2018).

Studies have discovered three generations of TDDS (Kwon et al., 2017). The clinical setting for the lipophilic and low dose drugs delivery through the skin involves the useof the first generation TDDS. With the developmentof patch technology, first generation TDDS using traditional patches have been introduced in the market though drugs with suitable properties for such a system have depleted. Advancement into second-generation TDDS drugs was due to a vision of enhancing skin penetrability of transdermal drugs. This generation of TDDS usesbiochemical enhancers, iontophoresis and ultrasound which are non- cavitational. Yet, application of these drugs fails to balance between the increased drug deliveries crosswise the SC and protecting the deeper tissue from destruction. Hence, to provide a significant delivery of drugs, third generation

TDDS was developed in recent years. Their ability to disrupt the stratum corneum barrier and protecting the deeper tissues enables the third generation TDDS for more effective transdermal delivery. This generation of TDDS uses microneedles, microdermabrasion, electroporation, thermal ablation and cavitational ultrasound to deliver macromolecules such as vaccines and therapeutic proteins (Kwon et al., 2017).

However, in the scientific community, it is considered as a challenge to deliver Insulin by transdermal route because of the small permeation pace of the drug in the skin and as a result, it is difficult to achieve a beneficial concentration with this manner of administration (Ita, 2015).

1.4 Microneedle technology & microneedles patch

Microneedles (MNs) technology offers an appealing way to form reversible micro channels on skin, maximizing the transfer of broad range of bio therapeutics unable in infusing the intact skin (Ling & Chen, 2013). With the development of micro-fabrication manufacturing technology in the past decades, MNs are developed and are now used to deliver small as well as big molecules to the lower layers of skin effectively. When MNs are fabricated into arrays on a support that applies on skin similar to a dressing as bandage, the mechanism is termed a MNs patch (Ita, 2015). Recent studies and trials on MNs that provide a combination of a usual injection method along a patch scheme have shown their high effectiveness such as persistent drug release, user-friendliness, painlessness, convenient storage conditions, suitability for vaccination routes etc. (Kwon et al., 2017).

Silicon, metals, polymers and different types of materials can be used to manufacture MNs. The advantage of using biodegradable and biocompatible polymers is that these can provide safe application on skin and usually are cost effective. Several materials which are polymeric in nature such aspoly-dimethylsiloxane, poly-l-lactic acid, maltose, poly-lactic-*co*-glycolic acid (PLGA), poly-carbonate,poly-glycolic acid, carboxymethyl cellulose, galactoseand dextrinare used in MNs fabrication (Alkilani et al., 2015).

MNs are categorized in four typesdepending on their delivery techniques of drug: solid MNs, coated MNs, dissolving/ polymer MNs and hollow MNs (Ita, 2015).

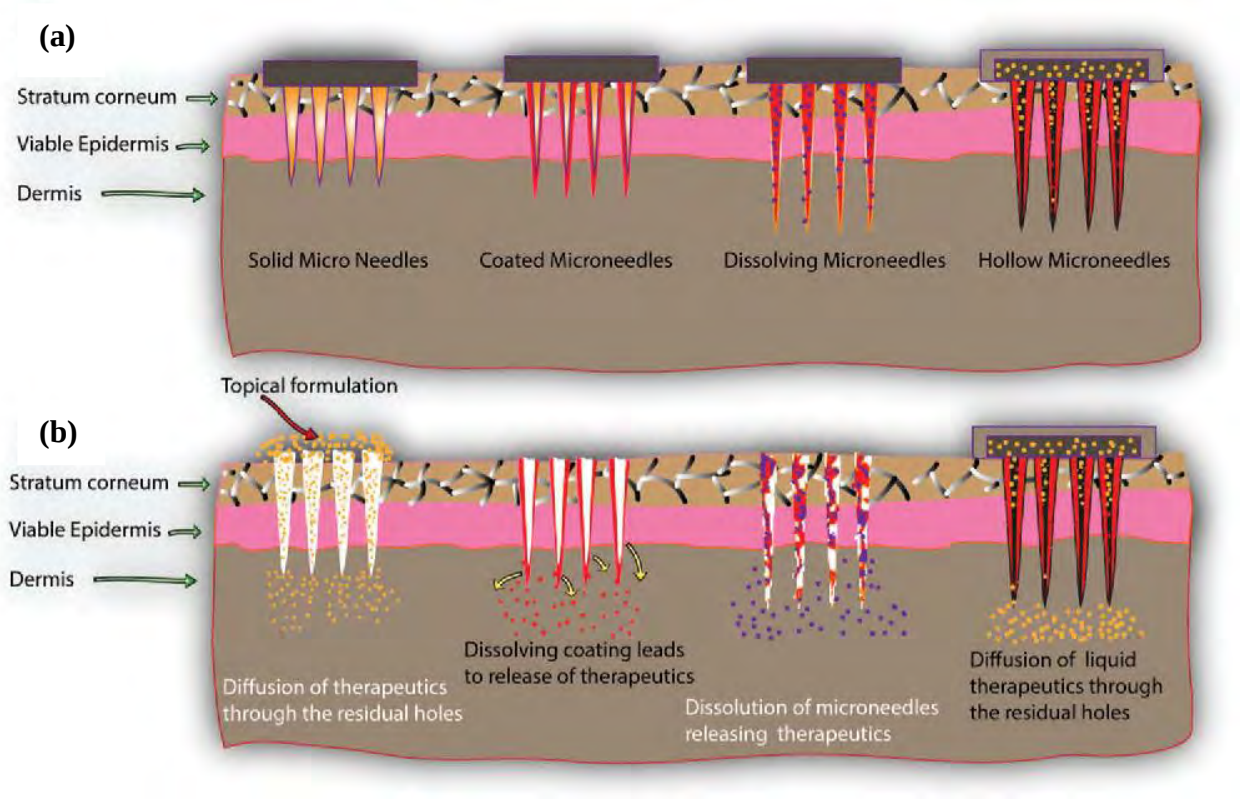


Figure 1.2 (a) Classes of MNs: solid MNs, coated MNs, dissolving MNs and hollow MNs and **(b)** Mode of actions of MNs (Rejinold et al., 2015)

1.4.1 Solid MNs

Solid MNs are applied to the skin layer as it attaches to the surface of skin, allowing the preparationin slow infusion through holes. It is useful to prevent pathogenic infections though the drug delivery is not high (Kwon et al., 2017). Solid MNs increase skin permeability as they transport drugs by diffusion that is passive by forming micro channels and the use of a patch, which is drug-loadedin channels (Ita, 2015).

Some metals, for example, titanium and stainless steel have proved to be structural material used for fabrication of solid MNs along with various approaches. Laser cutting (stainless steel) and photochemical etching (titanium) is already employed to fabricate solid MNs (Tuan-Mahmood et al., 2013).

The first study on clinical studies in human was carried out in the year of 2008 in order to reveal a solid MNs delivery of naltrexone (NTX), an opioid blocker. Another study in 2012 reported the

treatment of skin with solid MNs of silicon and using iontophoresis to improve skin penetration of insulin, which were fused into transdermal patches. This resulted into the maintenance of a basal dose of insulin that was sustained for continual decrease of blood glucose level and ensured on demand bolus dosing for the mealtime coverage via iontophoresis "switch on" effect (Tuan-Mahmood et al., 2013).

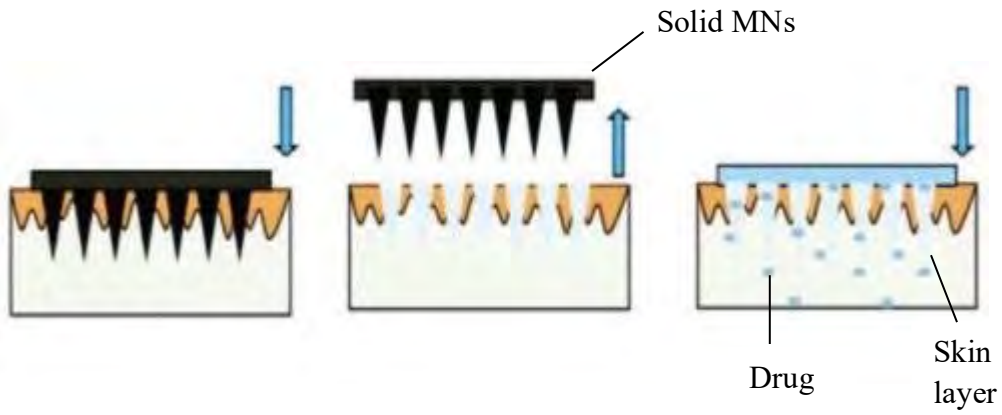


Figure 1.3 Solid MNs create micro-holes on the skin that increase the permeability of drug (Tuan-Mahmood et al., 2013)

1.4.2 Coated MNs

MNs that are coated withdispersion that contain drug are referred to as coated MNs (Ita, 2015). These needles have the benefit of rapidly delivering fixed and very small quantity of drugs but the residual MNs tips can be unsafe as there is the possibility of infecting others (Kwon et al., 2017).

ZosanoPharma of the United States has been successful in developing a patch comprising an arrangement of MNs (titanium) that is parathyroid hormone (PTH) coated which attaches to an adhesive patch. This patch involves application with the help of an applicator that is reusable on human skin. Another reseach involved the Zosano titanium MN patch system that was carried out in the year of 2014 to assess the likelihood of using titanium MN to deliver recombinant human growth hormone. Moreover, the 3M Microneedles Technologies developed coated MNs in order to deliver molecules that are polar, water-soluble and ionic like lidocaine, via skin. This

technique is successful in not only delivering drugs within seconds but also providing rapid onset of local analgesics (in 1 min) that eases emergency or routine processes (Alkilani et al., 2015).

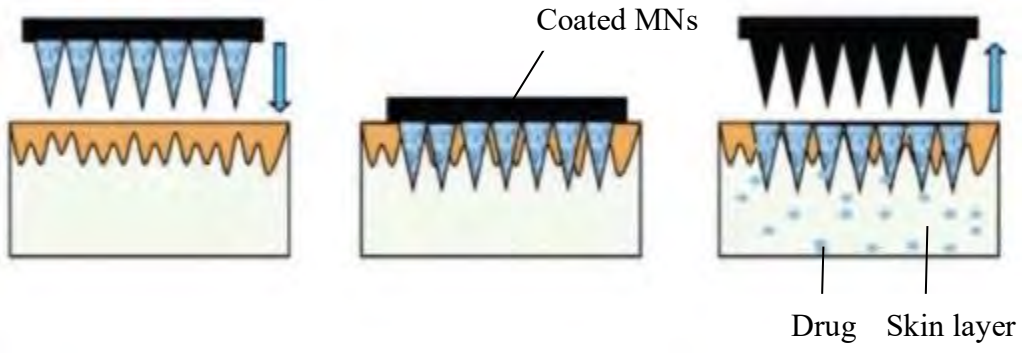


Figure 1.4 Rapid dissolution of drug into skin via coated MNs (Tuan-Mahmood et al., 2013)

1.4.3 Dissolving MNs

Dissolving MNsare composed of water-soluble material that causes the needle to melt in skin once pushed and release the drug contained in it. This one-step application process is also known as 'poke and release' principle (Ita, 2015). These MNs can deliver a large amount of drug and are unable to provide a small fixed amount of drug as the coated MNs (Kwon et al., 2017).

Dissolving MNs patch has been testified to deliver small (MW 500 Da) and macro (MW 500 Da) molecules both successfully (Alkilani et al., 2015). For instance, these MNs have been recently shown to improve dermal and transdermal delivery of numerous drug substances including 5-aminolevulinic acid, insulin, sulforhodamine B, low molecular weight heparin, ovalbumin, adenovirus vector, vaccine antigens (Tuan-Mahmood et al., 2013).

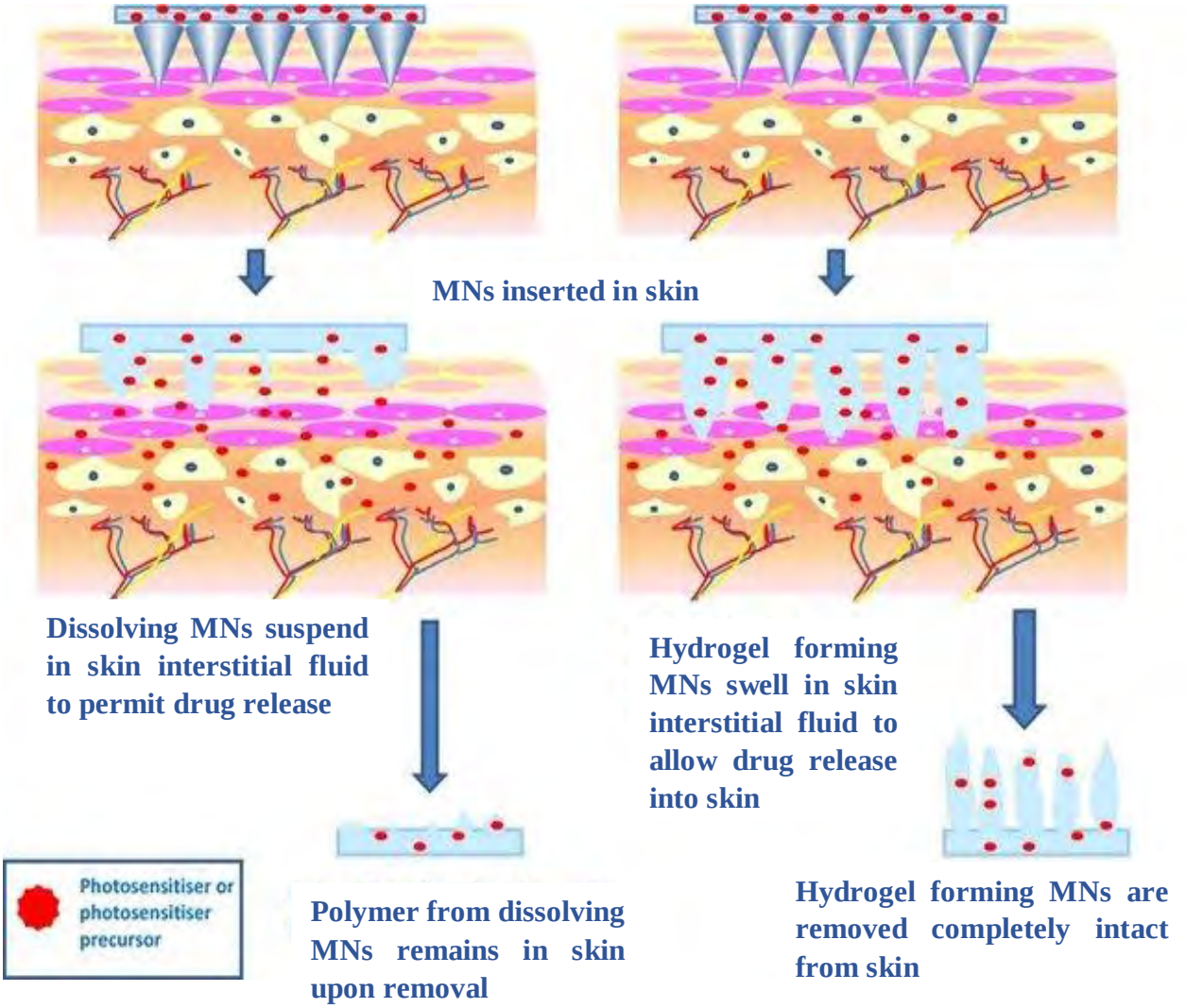


Figure 1.5 Schematic illustration of the mechanism of drug delivery from dissolving and hydrogel-forming MN arrays with attached bio adhesive patch-type drug reservoirs (Donnelly et al., 2013)

1.4.4 Hollow MNs

Hollow MNs are shorter in length than the regular hypodermic needles. In these needles, the liquid form of the drug is filled in through bore. Hollow MNs can avoid the SC to deposit a drug into VE directly or in the dermis. Thus, this type of MNs plays a significant role in the delivery of compounds with high molecular weight including vaccines, oligonucleotides, proteins etc. (Ita, 2015).

The effectiveness of such MNs has been examined in humans. For instance, according to a study conducted in 2009, the efficacy of hollow MNs was observed in case of insulin delivery needed in adults with Type 1 diabetes. The hypothesis established was the rapid incorporation of insulin, which administered at 1mm depth, was due to the MNs insertion in close proximity to blood capillary in papillary region of dermis (Tuan-Mahmood et al., 2013).

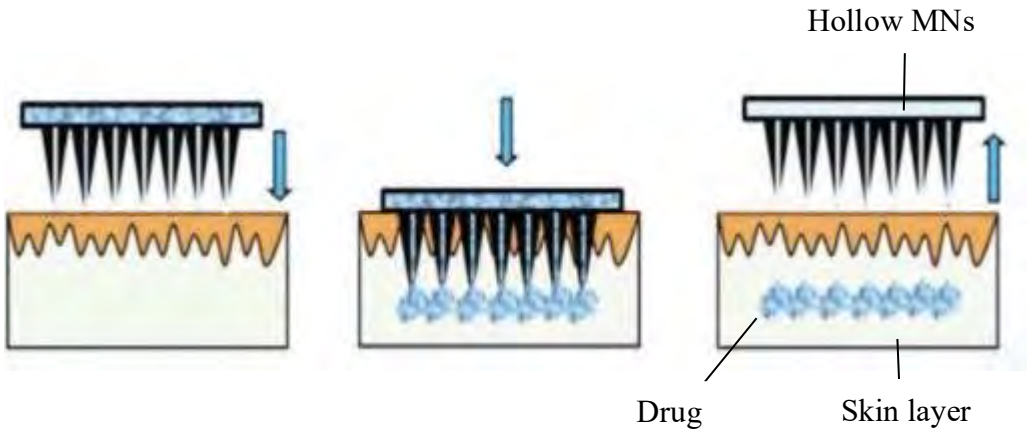


Figure 1.6 Hollow MNs are used to penetrate into skin and allow liquid drug release following active infusion or active diffusion of the formulation via the needle bore (Tuan-Mahmood et al., 2013)

1.5 Diabetes and anti-diabetic treatment

Being acknowledged since 2000 B.C, diabetes mellitus (DM) is illustrated by the high blood glucose concentration primarily due to the shortage of insulin production internally. Insulin is the chief hormone that suppresses the increase of the blood glucose level by turning it into core energy that the human body requires. Blood glucose is a useful energy to function muscles, brain and other tissues. However, too much concentration of blood glucose can lead to numerous complications (Takahashi et al., 2007).

1.5.1 Worldwide diabetes prevalence

One of the major global health problems that are prevalent worldwide is DM, by which 382 million of people are affected, which accounts for death of 5.3 million people in 2013 (Rahman et al., 2015). Current studies have shown that among the Southeast Asian population, 72.1 million people or 8.2% of the adult population have diabetes. Moreover, it is estimated to

boostup to 123 million by 2035 because of the growing urbanization, changes in lifestyle etc. On the other hand, there are about 24.3 million people having pre-diabetes and it is estimated to raise to 38.8 million within 2035 (Islam et al., 2016).

1.5.2 Diabetes prevalence in Bangladesh

Among the countries of South Asia, Bangladesh is second with the highest number of adult diabetic population (Rahman et al., 2015). Islam et al. (2016) reported that The International Diabetes Federation (IDF) has anticipated 7.1 million diabetic people in Bangladesh. In addition, this estimation is predicted to be doubled within the year 2025. The findings also show that in every ten Bangladeshi adults, onewasdiabetic (9.2%) (Rahman et al., 2015).

Table 1.1 General data on prevalence of diabetes in Bangladesh according to International Diabetes Federation's Diabetes Atlas, 2015 (Mahbub, 2016)

At a glance: Diabetes in Bangladesh (in 2015)	
Total adult population (20-79 years) (1000s)	95947
Total cases of adults (20-79 years) with diabetes (1000s)	7138.9
Prevalence of diabetes in adults (20-79 years) (1000s)	7.4
Cost per person with diabetes (USD)	41

Prevalence of diabetes is ever increasing in both rural and urban areas and it is an alarming issue for Bangladesh. Some common risk factors behind this situation include lifestyle change, adverse dietary pattern like increased consumption of salt and chemical-rich food, obesity and environmental exposure (Biswas et al., 2016).

1.5.3 Commonly used anti diabetic drugs

The most common anti diabetic drugs used for blood sugar level control can be categorized as oral hypoglycemic and insulin therapy.

Oral hypoglycemic

According to a study on prescription pattern of anti-diabetic drugs, about 41% of patients were only prescribed Metformin and 31.4% were prescribed a combination of Metformin and Sitagliptin. Other drugs commonly prescribed as oral hypoglycemics are Glimepiride, Gliclazide and Pioglitazone (Ahmed et al., 2016). Another study on the current trends in the prescription pattern of anti-diabetic drugs revealed the categories of common oral hypoglycemic agents according to their predominant prescription that are respectively:

- Sulfonylurease
- Biguanides
- Dipeptidyl peptidase-4 inhibitors
- Thiazolidinediones
- Alpha Glucosidase inhibitors.

However, as stated in the study, the highest rate of commonly prescribed drug group for diabetes mellitus (DM) was sulfonylureas, but alone use of metformin (biguanide) was the most common drug among oral hypoglycemic agents (Chowdhury et al., 2017).

Biguanides

This class of drug possesses hepatic effects that direct its basis of action (Bösenberg & Zyl, 2008). In other words, the anti-hyperglycemic activity of the biguanides is a result of decreased glucose production due to the liver gluconeogenesis inhibition and probably to a slighter extent, amplified glucose uptake that is insulin-mediated in skeletal muscle (Pernicova & Korbonits, 2014).

The anti-diabetic activity of metformin is not the consequence of high insulin levels but rather it is linked to reduced concentration of insulin in blood circulation. Conversely, this system might be effective less in type 2 DM patients and itcouldmake upunusual cases of hypoglycemia inDM patients who receive monotherapy of metformin. Therefore, combining dipeptidyl peptidase 4 and metformin showed improvement in glycaemic management intype 2 DM patients (Pernicova & Korbonits, 2014).

Sulfonylureas

Sulfonylureas can be categorized into two generations. They are the first generation sulfonylureas includingtolazamide, chlorpropamide, tolbutamide and the second generation including glimepiride, glipizid, and glyburide. Recently, this class of drugs is prescribed as second line option for the treatment of Type II DM. They exhibit their action in lowering blood glucose concentration by escalating secretion of insulin in pancreas by K_{ATP} channels blocking. Moreover, in liver they limit gluconeogenesis (Chaudhury et al., 2017). Sulfonylureas are effective anti-hyperglycemic agents, which lessen HbA1C in monotherapy regimen by greater than 1% (Alhadramy, 2016).

Thiazolidinediones

By binding to the peroxisome proliferator, activated receptor, which is, expressed predominantly in the adipocytes, thiazolidinediones (TZDs) mediate their function. Similar as metformin, TZDs require insulin presence to mediate a blood glucose lowering effect. On other note, the expression of TNF-α by adipocytes is also suppressd by TZDs (Bösenberg & Zyl, 2008).

Alpha-glucosidase inhibitors

Acarbose, which got approval by the FDA in 1995, was the first member of this group. Acarbose blocks alpha-glucosidases on the border of the intestinal brush. This reduces the absorption of carbohydrate as well as postprandial glucose in blood. Moreover, these drugs have a modest effect as a monotherapy in controlling diabetes (Alhadramy, 2016).

Dipeptidyl peptidase-4 inhibitors

This class of compounds ismainly based on incretin effect where insulin secretion is modulated by a substance that is released from intestine in response to food ingestioninto the circulation. Severalenzymes (DPP- 4I) inhibitors are synthesized. The FDA approved the first inhibitor, sitagliptin, in 2006. Saxagliptin, vildagliptin, linagliptinetc are other enzyme inhibitors (Alhadramy, 2016).

Insulin dependent diabetes therapy

According to Kochba et al. (2016), the most effective blood glucose-lowering agent in diabetes is insulin. In other words, insulin delivery is highly desirable for patients with diabetes among

various drug formulations. Due to the reliable therapeutic effect exhibited, subcutaneous insulin administration using hypodermic needles, catheters connected to insulin pumps and insulin pens are prevalent. Another substitute is inhaled insulin but it has certain limitations and requires basal insulin to be combined using conventional methods (Resnik et al., 2018).

Insulin and insulin analogues

Intravenous insulin injection

By this method, insulin is provided using needle of an injection, penetrating the skin and directly delivering the drug in veins that will ultimately lead to the bloodstream. Despite the benefit of quick drug delivery, injections have shortcomings such as irritation of blood vessel because the catheter should be put into vein. In case of long-time infusion of insulin, the catheter may have to be kept away from vein or blocked (Parker et al., 2001).

Subcutaneous insulin injection

This is a simpler way of delivering insulin with less risk of infection. Although it demonstrates a better glycemic profile than IV injections, intermittent infusion of insulin subcutaneously is inadequate for reversing diabetic complication, because of the limitations in glycemic control (Takahashi et al., 2008).

Intra peritoneal insulin injection

Limited number of experiments showed the efficacy of this method in diabetic patients receiving peritoneal dialysis. Although there is advantage of moderate absorption of insulin in blood, there are possible risks of peritonitis infection and tissue degradation on the site of the catheter (Albisser & Spencer, 1982).

Insulin pump

One of the devices for introducing insulin to body is the insulin pump that consists of a processing module along with a display small in size, a disposable insulin reservoir and an insulin syringeand batteries. The quantity of insulin supply can be externally controlled depending on blood glucose amounts (Takahashi et al., 2008).

Insulin pen

Since the introduction of insulin pens in 1985, they have been user-friendly. Some of insulin pen models are intuitively usable, requiring less instruction. In spite of the progress, there are inconsistencies in insulin pens access to diabetic people in many countries. However, continuous progress has been made to deal with patient needs such as more convenientand less painful; easy to use and more accurate for small insulin doses, memory function etc and these contribute to a device that allows patients to manage their diabetes better at any time and in any place, without the problem of carrying a syringe and vial (Pearson, 2014).

MicronJet (MJ) needle for insulin delivery

Intradermal injection for insulin with a MicronJet needle resulted in a Tmax that is compared to subcutaneous one. Studies revealed the improvement in pharmacokinetic profile of such delivery system for insulin by MJ in type 2 diabetic patients which also reduces the risk of postprandial hypoglycemia (Kochba et al., 2016).

1.6 Literature review

A huge number of surveys have been done on patients with diabetes mellitus since the onset of this physical condition. One example is that Rahman et al., (2015) claimed first effort to approximate the rate of understanding, control and treatment of diabetes in Bangladesh using national survey data. It was found that this health condition was predominant in people aged 55 to 59 years for both genders and it was dominated in urban residents. Moreover, diabetes prevalance has increased in association to socio-economic condition. A noticeable data found in this study was that in Bagladesh, one in ten adults is affected with diabetes.

A cross-sectional study on diabetes management in Bangladesh found that diabetes in majority of patients (92.3%) was managed by receiving treatment for diabetes where 58% patients were on insulin treatment (either alone or combination with oral hypoglycemic). The most commonly prescribed oral hypoglycemics were metformin (81.8%) and sulphonylureas (52.6%) (Latif et al., 2017).

Patients, who have type 1 DM, require insulin every day one or more than one time by SC injections normally which has the drawbacks such as pain, local tissue necrosis, bacterial

infection, nerve damage caused by repeated use of insulin injection with usual needles. This led to more research on alternative therapies (Kim et al., 2009). If oral administration was available to deliver insulin, it would be veryhelpful for patients, because of the routes conveniences but unfortunately, the bioavailability of oral insulin is still dissatisfactory. Transdermal MN delivery of insulin offers a great route in comparison with the hypodermic injection and oral route, not only because it can by-pass the harshness of gastrointestinal tract, but also because it ensures a delivery of therapeutics in a minimally invasive manner. Recent researches have shown that insulin administered through MNs can be almost completely absorbed in the systemic circulation from skin and thereby achieve higher bioavailability than the traditional injection (Ling & Chen, 2013). Another study showed the use of solid MNs in rats was effective and safe for administrating transdermally of drugs hydrophillic in nature (Liu et al., 2018).

Limited number of survey study is available related to MNs and MN patches. In particular, a survey on application of MN patches on human skin revealed that the volunteers who participated in the study were positive regarding use of MN technology and they revealed insertion or application of larger MN patches and the individual MN array are painless. However, this was a very small-scale study including only ten volunteers and the MN patches did not contain any drugs. The study suggested that use of MN patches (larger than 1-2cm^2 can be successful in patients' use and it can open up the potential possibility in the greater extension of the market size for TDDS (Ripolin et al., 2017).

1.7 Purpose of the study

According to International Diabetes Federation (IDF), the prevalence of diabetes will set Bangladesh amid the top 10 countries with regard to the population having diabetes within 2025 (Chowdhury et al., 2017). This chronic disease certainly depends on lifestyle and other important factors and is treated to control the blood sugar level by the use of oral hypoglycemic and insulin therapy. Nonetheless, these two routes of administration have limitations of their own. GI irritation or intolerance, limited bioavailability of drug, swallowing problem, first pass metabolism and so on are common problem for oral route. For insulin administration by injection, there are limitations such as skin irritation, pain, needle phobia, skin hardness etc. Hence, a novel drug delivery system of MN patches could be introduced which can overcome the limitations of the traditional therapy.

The development of MN patches for transdermal delivery of drugs and their advantages over the traditional intravenous methods is a burning topic in today's science. The aim of this study is to conduct a survey among diabetic patients on the acceptance of transdermal MN patches containing insulin. As survey related to patients' acceptance or knowledge about MNs, mainly related to insulin delivery through MNs has not been done until now, this study is a comprehensive research regarding this matter.

Chapter 2: Methodology

2.1 Research design

The future aspects of MNs and the existent drawbacks of insulin injection led to the design of this study aiming for a survey analysis. The survey mainly contributed to the acquaintance of insulin delivery by MNs. The objective of the study was to highlight the potential benefits of novel MN technology to the patients over insulin injection for controlling blood glucose level. The rationale for selecting this subject was to evaluate the acceptance of MN patches as an alternative of insulin injection. Moreover, another purpose of the study was to gather the common perspectives of using insulin injection by diabetic patients in general.

Prior designing the survey, an extensive research was first carried out on both research and review articles for explaining the potential use of MNs. As a result, it was concluded that there is no work similar to the topic that has been carried out so far. Hence, the topic of the study could get more attention to the scientific community and patients.

The participants of this survey (diabetic patients) were randomly selected. The essential point and objective of the survey was explained to the participants and consent was taken prior to the survey. It was ensured that their name will not appearat any means. Cumulative data will be either presented or displayed in the scientific seminar, conference etc.

2.2 Determination of the sample size

The participants of this study were patients who are diagnosed with diabetes mellitus (Type I and II) and currently take prescribed anti-diabetic drugs at any form.The study included a sample size of three hundred and eighty-five (385 in number) to represent a certain percentage of total diabetic population of the country. This population was decided prior the survey as the total diabetic population of Bangladesh is approximately 6.9 million according to the International Diabetes Federation (IDF). By using online-based software named Raosoft, the sample size was decided. Each participant gave his or her consent on continuing the survey.

2.3 Development of the questionnaire

A 25 question based questionnaire was prepared for the diabetic patients with the prior information about MN patch to satisfy the goals and objective of the survey. This study was

conducted on a pilot basis. It provided questions both in English and Bengali (native) language for the ease of understanding of the general population of our country. The survey questionnaire forms were distributed amongst the respondents where all survey participants were well informed about the purpose of this survey, and the consent was obtained from all participants.

The contents of the questionnaire for the patientsare described in general below.

2.3.1 Information about MN patches

At the beginning of the questionnaire, a brief introduction of MNs and MN patches was provided for the convenience of the subject to understand or get an idea of this newer technology. Such information included the process of easy administration of MN patches on skin, the needle size, the difference between conventional injection needle and MNs etc. as well as the benefits of delivering anti-diabetic drugs mainly insulin through this process.

2.3.2 Basic information of the participant

Gender, age, habitat, highest level of education, information about any occurring disease and regularly taken medications etc. were filed.

2.3.3 Yes/no answers, charts & comment box

Participants were provided with questions to answer yes or no as well as comment if they wanted. Charts containing some potential concerns & advantages of MNs were presented to fill out according to their importance to the patient.

2.4 Statistical method used for data analysis

For this purpose, a database was developed by using MS Excel in order to record the information in submitted survey forms. Graphical statistics were also applied to the gathered information. Graphs and pie charts along with the percentage needed for data analysis were obtained by this method.

Chapter 3: Results and Discussion

3.1 Results

3.1.1 Demographic details

Demographic details of the patients who participated in the study are presented in the Table 3.1. All the patients were diabetic. It is noticeable that the percentage of male and female patients who participated in the survey is 44% and 56%, respectively. In addition to that, the patients were divided by certain age groups from 25 to more than 60 years, where the highest number of patients was within the age between 46 to 52 years old, which is 29% of the total sample size.

Turning to the next information that is about in which division the patient lives in, it was found that Dhaka has the highest number of inhabitants (77%). Correspondingly, in case of academic background of the patients, the highest education level was Under Graduation.

Table 3.1 Demographic information of the patients: RQ 1-4 (Sample size= 385)

Variables	Percentage
Gender	
Male	170(44%)
Female	215 (56%)
Age	
25-31	3%
32-38	8%
39-45	22%
46-52	29%
53-59	23%
60+	15%

Division	
Dhaka	297 (77%)
Chittagong	23 (6%)
Khulna	11 (3%)
Rajshahi	25 (6%)
Sylhet	5 (1%)
Barisal	18 (5%)
Rangpur	3 (1%)
Mymensingh	3 (1%)
Education level	
SSC	89 (23%)
HSC	101 (26%)
Undergraduate	102 (27%)
Postgraduate	42 (11%)
Ph.D.	1 (0%)
Others	50 (13%)

3.1.2 General perception and data on insulin injection

In this study, the patients were asked about how they control their irregular blood sugar levels. While 54% of the patients need insulin at a daily basis, 46% of the patients control it by taking oral hypoglycemic. In addition to that, 51% of patients said that they use injection to administer

insulin by themselves, whereas the rest need help of others or do not require injection intake (49%). However, they also mentioned about controlling diet and regular exercise as the other mechanisms of controlling blood sugar level.

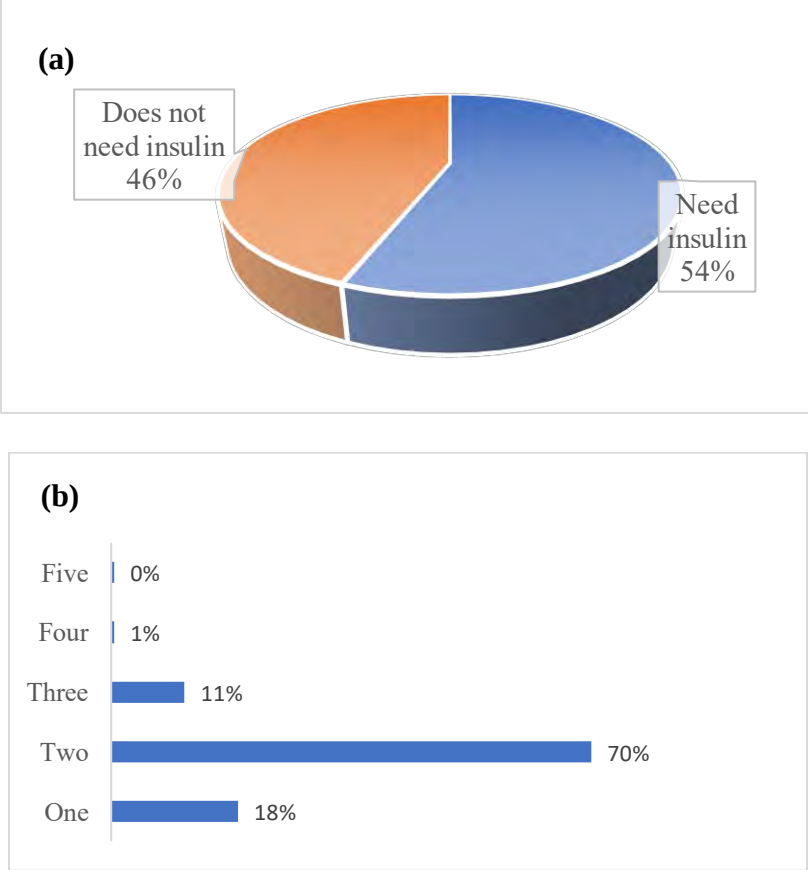
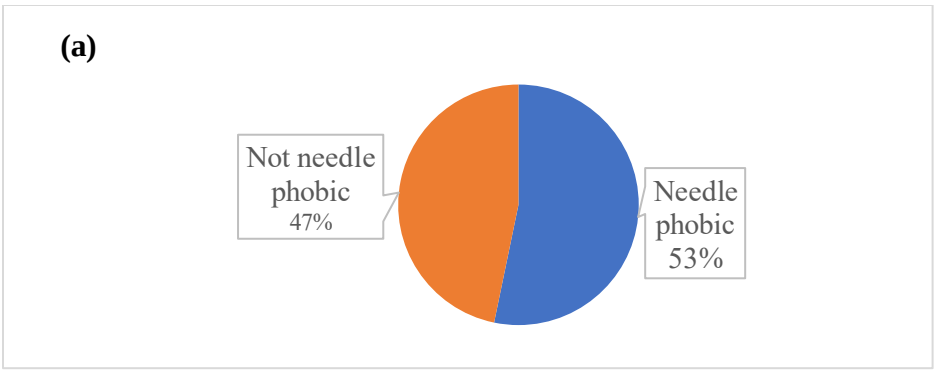
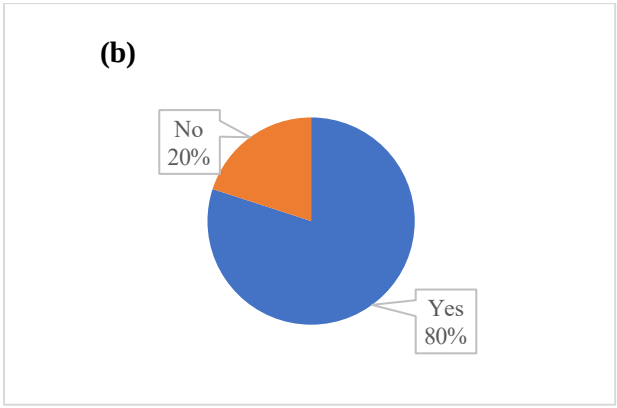


Figure 3.1 (a) Requirement of insulin injection and **(b)** Frequency of insulin intake per day (RQ 6)

It was seen than the most common answer for frequency of insulin intake per day was twice which consisted of 70% of the patients.RQ 7-11 include questions regarding fear of needles and suitability of insulin taken by injections.





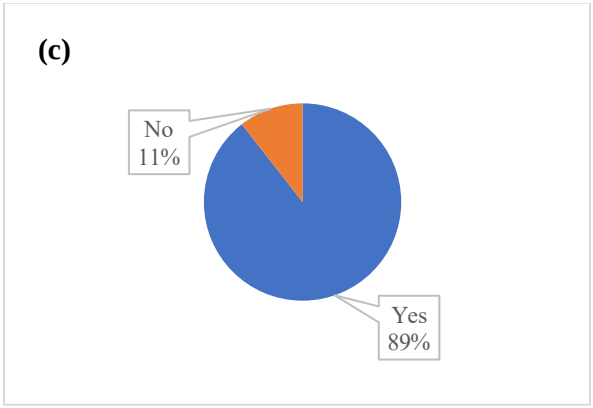
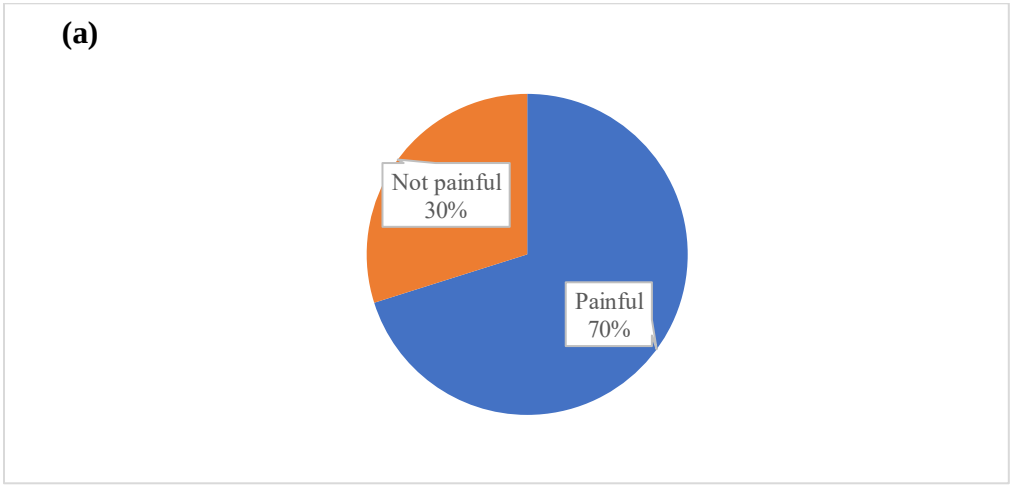


Figure 3.2 (a) Percentage of needle phobias among patients, **(b)** If needle phobic, was/ is this problem when injecting insulin? And **(c)** If not needle phobic, do you believe that a fear of needles is a significant problem in patients who require regular insulin injections? (RQ 7)

Among the total 385 patients who responded to this survey, 205 mentioned that they are needle phobic while 180 patients are not. Nevertheless, most patients think that needle phobia or fear of needles can create a problem while injecting insulin for them as well as for others.



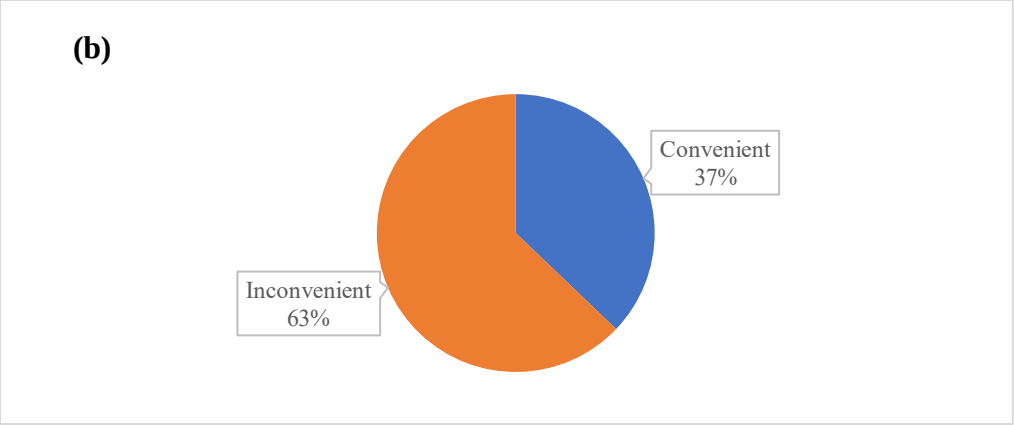


Figure 3.3 Patients' opinions on: **(a)** painfulness of insulin injection and **(b)** convenience of insulin injection (RQ 8-9)

When patients were asked whether they find insulin injection painful or uncomfortable, 270 patients responded affirmatively which consisted about 70% of the answers. Similarly, when asked if they found injection by needle convenient or not, the highest answer was negative (63%).

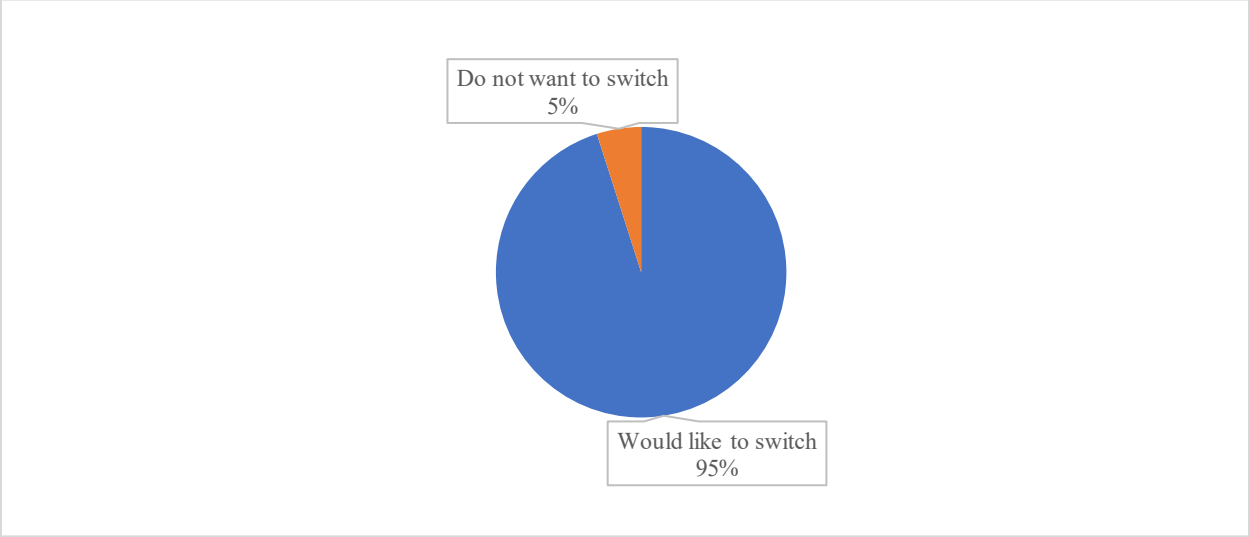


Figure 3.4 Consideration of switching from injectionsto a convenient alternative (RQ 10)

RQ 10 dealt with the question if the patients would consider switching to a painless or more convenient option of injecting if available and the response was 95% positive. However, 5% of the patients said they were satisfied and habituated with the process of injection and hence they would not switch.

RQ 11 is concerned about any other comments on injections for insulin administration and it is found that different patients had the similar and different opinions. For instance, some patients think that insulin injections are uncomfortable, painful and inconvenient and so some of the oral medication-taking patients never want to use insulin injections. Moreover, hassle of regular administration, scarring, needle phobia, multiple pricking, patient noncompliance, problem with self-administration (especially in elderly patients) are some issues they are concerned about. In addition, most patients think that doctor's prescription is necessary to switch to any other option from insulin injections. Lastly, while administering the injection by themselves, many patients feel the need of a dose indicator.

3.2 Discussion

The results gained from each individual patient of the survey were analyzed and interpreted to relate to the foremost research questions.

Firstly, when asked about controlling irregular blood sugar level, the higher percentage of patients (54%) responded that they take regular insulin to cope up with it and the frequency of insulin intake is more than one time per day for more than 80% of those patients. However, according to Latif et al. (2017), a cross-sectional study on diabetes management in Bangladesh found that diabetes in majority of patients was managed by receiving treatment for diabetes where 58% patients were on insulin treatment (either aloneor combination with oral hypoglycemic). Furthermore, in the current study for most patients, fear of needles or needle phobia is a common phenomenon among them and therefore, the perception of taking insulin by injection is opposed by most. To explain more, when patients were asked whether they find insulin injection painful or uncomfortable, 270 out of 385 patients responded affirmatively which consisted about 70% of the answers. Similarly, when asked if they found injection by needle convenient or not, the highest answer was negative (63%). As the traditional way of insulin intake is pen and injection, patients confirmed that they would switch to an alternative if available to get rid of the problems of such application processes such as pain, scarring, skin hardness, needle phobia etc.

Secondly, when asked about the knowledge of MN and MN patches, it was found that only 5% of the total population of the survey knew or heard about them. For others, it seems to be a completely new concept. Figure 3.5 shows that patients among the 5%, most patients have read about MNs in the internet. With regard to this, opinions were obtained about the potential advantages and potential concerns of MN patches relating to their importance to the patients. Figure 3.6 and 3.7 reflect the data regarding this where most advantages and concerns were marked as “very important” and “important”. The idea of delivering insulin via MNs seems attractive to 93% of the total sample population as they found it promising enough to overcome the limitations of traditional methods of insulin delivery and they agreed to switch from insulin injections to skin patch if possible.

Thirdly, the majority of patients (98%) agreed strongly that they need instructions on the usage of MN patches, in which 70% feel the need of personal training with a doctor. In the last part of

the survey questionnaire, patients were asked if they administered injections by themselves. In response to this, about 51% agreed and the rest responded negatively. Among those who stated that they do not administer injections, 84% believed that other patients would find it easier administering anti-diabetic drugs via MNs than injections. Similarly, patients showed their concerns on the subject of MNs and MN patches apart from their valuable response to the questionnaire. Although this idea gets the attention in a positive way, some patients worried about the frequency of intake of the patch in comparison to insulin injections. Patients with sensitive skin and prone to allergic condition had concerns about the application time of the patch. In addition to that, an issue rose concerning the price of the patches. On one hand, more patients want the patch to be of less price and more cost effective while on the other hand, there were some patients who showed willingness to buy and use the patch regardless of the costing factor only if the patch ensures efficacy in drug delivery, is safe to use and tested well in clinical trials to be established as beneficial comparing to insulin injections and other analogues.

However, the concept of MNs was still vague among a large proportion of the patients as it is a newer and more advanced technology in Bangladesh and patients have not come in association with this directly till now. The likelihood of their acceptance of the MN patches depends on several factors including doctor's prescription, further information on it and so forth.

Chapter 4: Conclusion

4.1 Conclusion

Diabetes mellitus is a non-communicable disease, which is an important health concern in lower income countries such as Bangladesh (Rahman et al., 2015). The management of diabetes is available in forms of oral hypoglycemic and insulin analogues. However, the ways of the traditional methods of delivery for insulin have some limitations that led to the urge of an easier and convenient route of delivery such as transdermal route. Hence, the concept of MN skin patches comes in attention and already has become an appealing method of insulin delivery. Recent researches on MN patches have shown supremacy in drug release, user-friendliness, painlessness, convenient storage conditions, suitability for vaccination routes etc. (Kwon et al., 2017). If insulin to control diabetes can be provided in such transdermal patch method, it will be of prodigious usage for people in Bangladesh and hold a market share over injections and other devices in future. This study shows the survey results on a portion of diabetic patients in Bangladesh where it was found that people are in approval of such skin patch to be developed soon which should be effective as well as safe to use. The views and concerns that they have shared will stimulate the path for designing and conveyance this technology to patients.

4.2 Future aspects

Further research would be planned by a questionnaire survey with medical professionals such as doctors or physicians for further analysis of the project in a large to design and develop MN patches.

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