An Idea of Using Drug Combination Therapy through Dissolving Micro-needles to Treat Streptozotocin-nicotinamide Induced Diabetic Rats
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ABSTRACT

Micro-needle transport approach has been used from past few a long time as a method to break the stratum corneum layer of skin and to perform the effective transport of drug across the skin and it is especially used for delivery of peptides, protein, DNA, oligonucleotides, molecular mass medicine and inactivated viruses across the dermal layer of the skin. In this hypothetical paper, we specifically targeted on how we will develop double-layer micro-needle which can deliver drug-mixture therapy efficaciously. Because there are many diseases together with cancer, tuberculosis, diabetes, leprosy, HIV, and AIDS, which may be efficiently handled by way of drug-combination therapy however this remedy is particularly confined to the tablet, capsule or another form of dosage. If we can develop double-layered micro-needles, can an opportunity to treat these illnesses with painless delivery. In the paper, we have tried to deal with type-2 diabetes with double-layered micro needle and that is formulated with the aid of hypothetically designed capsule which has the projection in it and which may be connected with projection of primary micro-needle and can form cone-like cavities and from these cavities we will deliver our drug and materials for the development of secondary layer on a primary layer of micro-needle and this technique can be utilized in different disease remedy and it is going to reduce fee of treatment, increase in patient compliance, site directed drug-delivery, increase in bioavailability of drug in the blood stream and increase in therapeutic index with less side effects.

Keywords: Micro-needles; Double-layer micro-needles; Type-2 diabetes; Hypothetically designed capsule; Therapeutic index

INTRODUCTION

From the past few decades, the employment of syringe injection for delivery of drug particularly for delivering anti-diabetic medicine has been magnificently magnified in variety. However, we’ve got some limitations related to the standard syringe, the chance of infection and inflammation at the location of injection related to pain and anxiety. Another additional disadvantage includes manufacturing waste, the value in production, safety protocol needed for disposal and alternative disease associated with the employment of unsterilized syringe over the amount [1]. In this constraint, we tend to encourage to use micro needles over the quality of syringe and thanks to micro-needle possesses bound blessings over standard syringes like: The administration of huge molecule is feasible, Painless administration, First-pass metabolism is avoided, Compared to hypodermic/standard injection, the speed of healing at the injection web site is quicker, Ease of administration, Enhanced drug effectuality might cause dose reduction, Rapid drug delivery will be achieved by micro-needles plus associate degree electrically controlled micro-pump, The rate of drug delivery is additional manageable compared with drug delivery via the stratum [2]. Micro needles (MNs) are microscopic needles and size ranges from one to a hundred metric linear units and one micron in diameter and organized on a pad that’s robust enough too specific into the skin and transports the drug across the skin. It’s little to avoid nerve stimulation. These microstructure devices consist of microstructure projection coated with a drug or with a vaccinium and applied on the skin to supply intradermic delivery of the drug (Figure 1) [3].

MATERIALS AND METHODS

Types of Micro-needle

Solid micro-needles: These are a unit of projections with arrays which can be used for making holes in corneum and thanks to micro-needle possesses bound blessings over standard syringes like: The administration of huge molecule is feasible, Painless administration, First-pass metabolism is avoided, Compared to hypodermic/standard injection, the speed of healing at the injection web site is quicker, Ease of administration, Enhanced drug effectuality might cause dose reduction, Rapid drug delivery will be achieved by micro-needles plus associate degree electrically controlled micro-pump, The rate of drug delivery is additional manageable compared with drug delivery via the stratum [2]. Micro needles (MNs) are microscopic needles and size ranges from one to a hundred metric linear units and one micron in diameter and organized on a pad that’s robust enough too specific into the skin and transports the drug across the skin. It’s little to avoid nerve stimulation. These microstructure devices consist of microstructure projection coated with a drug or with a vaccinium and applied on the skin to supply intradermic delivery of the drug (Figure 1) [3].

Solid micro-needles: These area unit setof projections with arrays which willbe used for making holes in corneum and area unit designed for delivering drugs directly into the skin. They are typically used for the delivery of small molecules, such as peptides or drugs, and are often used in combination with other delivery systems to improve the efficacy of the treatment.
Hydrogel-forming micro-needles: These micro-needles are the most recent development within the series of micro-needles [7]. The arrays of these micro-needles comprise super-swelling polymers. This chemical compound will take an oversized quantity of water into three-dimensional compound network as a result of this chemical compound is deliquescent [10]. These arrays absorb ECF when inserted into the skin and timely to make continuous channels between dermal capillary circulation and also the drug patch-reservoir resulting in the diffusion of the drug into the skin (Figure 3) [11].

Diabetes Mellitus

We could outline DM as a bunch of metabolic diseases that are characterised by symptoms thanks to defects of endocrine secretion and/or multiplied cellular resistance to endocrine [12]. Such deformities arise because of irregular functions of the regulatory systems chargeable for the mobilization of metabolic fuels and storage of it, which incorporates the organic process and catabolism of lipids, carbohydrates, and proteins, emanating from the defective hormone secretion, hormone action, or both [13]. We can classify diabetes into 2 varieties i.e. insulin-dependent diabetes (IDDM, kind I) and ketoacidosis-resistant diabetes mellitus (NIDDM, Type II). The kind I polygenic disorder is an associate degree autoimmune disorder that’s characterised by an area inflammatory reaction in and around cells of the isle and later ends up in the destruction of insulin-secreting cells. Whereas in kind II polygenic disorders characterized by peripheral endocrine resistance and impairment of endocrine secretion [14]. Chronic and different metabolic disturbances of DM might cause long-term tissue and organ injury [12] and alternative complications like vessel diseases, peripheral tube illness, kidney failure, neuropathy,

Coated micro-needles: These micro-needles are encircled by a drug dispersion layer or with a drug resolution. The number of drugs loaded depends upon the thickness of the coating and also the size of micro-needles and these micro-needles are explored for delivery of the higher dermal layer. High-mass compounds like proteins, vaccines, and oligonucleotides are delivered by the assistance of those micro-needles [7].

Hollow micro-needles: These micro-needles contain a hollow bore within themiddle. Hollow bore bypasses the horny layer of the skin and permits the medications to taste these hollow bores and reaches the opposite lower layers of the cuticle. These micro-needles are unit the main utilised to movedrug solutions directly into the skin layer by making an immediate channel for the drug to pass [8].

Dissolving micro-needles: These micro-needles get utterly dissolved within the skin and leave no residue behind it. These micro-needles usually form up of soluble materials like polymers and sugar that are unit inert, safe and can get utterly dissolve within the skin. Medication area unit incorporated within these micro-needles to urge free into the skin [9]. Dissolution and bio-acceptability of compound within the skin create it best for semi-permanent medical care with improved patient compliance. Whereas developing dissolving micro-needles, we must always pay a lot of specialise in the drug distribution across the needle. Thus, polymer-drug mixture may be an essential step whereas developing dissolving micro-needles [7].

Figure 1: Graphical representation.

Figure 2: (a) Basic Structure of Microneedle (b) Microneedle mould (c) Bright field micrographs of dissolving Microneedle (d) SEM image of Microneedle.
We are going to use a similar quantitative relation of 1:100 for developing our micro-needles for our first-line medical care (Figure 5) [17].

**Preparation of double-layered micro-needles:** We are exploiting our base material for developing micro-needle as Hyaluronan (HA) (sodium hyaluronate, average Mw 150 kD which might be purchased from Lifecore Biomedical), a collection of mould for formation of micro-needle during which there is one special style mould, and our medication which is able to be employed in combination medical care in a very totally different proportion to see best result (glipizide and metformin) (Table 1 and Figure 6) [18].

- We have used our primary dissolving micro-needle as our base for the event of double-layer dissolving micro-needles.
- Now we’ve got opened our theoretical capsule in 2 components, one half having projection which is able to be fastened with our basic primary dissolving micro-needle and permit to develop cavities higher than primary micro-needle. Gap that is found higher than the opening of cavities from our medication and micro-needle forming material is passed with high pressure and speed through an inlet. With the assistance of pressure and speed of fabric flow, we will manage stroke, retinopathy, blindness, and amputations, etc. [14]. Drugs are available to treat type-II diabetes such as sulfonylurea (glyburide, glimepiride, glipizide), metformin, alpha-glucosidase inhibitor (acarbose, miglitol, voglibose), thiazolidinedione (pioglitazone, rosiglitazone) (Figure 4) [15]. Drug combination medical aid has bound benefits over mono-drug medical aid like two medications, every drug functioning at a separate site, block different effector pathways; thus, once two drug categories are co-administered, then there’ll be increased lowering result of blood pressure. Drug combination medical aid might increase effectiveness by countering counter-regulatory mechanisms of one drug that’s triggered by the opposite drug. Combination medical aid has fewer adverse effects as compared to high-dose mono-therapy that results in increasing patient compliance and preventing treatment failure which may result from mono-therapy. Together medical aid, adverse effects of one drug are effectively neutralized by another drug [16].

**Hypothesis**

**Drugs to be used in drug combination therapy:** Normally in oral preparation (tablets), we tend to want to offer glipizide and metformin in 2.5 mg and 250 mg severally together medical care.

**Figure 3:** Different types of micro-needles on skin layer.

**Figure 4:** Comparison between healthy, type I & type II diabetes mellitus.
Figure 5: (a) Primary mould used to form first-layer micro-needle (b) Hypothetical-design capsule for developing double-layer micro-needles.

Table 1: Overview of the different formulation composition used to prepare the double-layered dissolving micro-needles. The compositions refer to the liquid formulations before double-layered dissolving micro-needles.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Layer</th>
<th>Composition</th>
<th>Formulation approach</th>
<th>Layer</th>
<th>Composition</th>
<th>Formulation approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>First Layer</td>
<td>Metformin/Hyaluronan (% w/v)</td>
<td>24.75 mg/50 ml</td>
<td>Second Layer</td>
<td>Glipizide/Hyaluronan (% w/v)</td>
<td>0.25 mg/50 ml</td>
</tr>
<tr>
<td>B</td>
<td>First Layer</td>
<td>Metformin/Hyaluronan (% w/v)</td>
<td>49.50 mg/50 ml</td>
<td>Second Layer</td>
<td>Glipizide/Hyaluronan (% w/v)</td>
<td>0.50 mg/50 ml</td>
</tr>
<tr>
<td>C</td>
<td>First Layer</td>
<td>Metformin/Hyaluronan (% w/v)</td>
<td>69.30 mg/50 ml</td>
<td>Second Layer</td>
<td>Glipizide/Hyaluronan (% w/v)</td>
<td>0.70 mg/50 ml</td>
</tr>
<tr>
<td>D</td>
<td>First Layer</td>
<td>Metformin/Hyaluronan (% w/v)</td>
<td>99.0 mg/50 ml</td>
<td>Second Layer</td>
<td>Glipizide/Hyaluronan (% w/v)</td>
<td>1.00 mg/50 ml</td>
</tr>
<tr>
<td>Control</td>
<td>First Layer</td>
<td>Metformin/Hyaluronan (% w/v)</td>
<td>0.00 mg/50 ml</td>
<td>Second Layer</td>
<td>Glipizide/Hyaluronan (% w/v)</td>
<td>0.00 mg/50 ml</td>
</tr>
</tbody>
</table>

Figure 6: Preparation of single layer dissolving micro-needle.

the speed of formation of secondary layer on the first layer. We will fix the second part of a capsule having a holding plate that's accountable to connect our primary micro-needle structure in position and with a projection of the primary layer and making a lock condition.

- After the developing micro-needle, leave the micro-needle within the capsule for nightlong at 37°C to dry and once waterlessness then takes away micro-needle from the array.
- Now repeat the first layer and second layer process development method for developing the different variation of metformin and glipizide double layer micro-needles (Figure 7).

RESULTS AND DISCUSSION

Testing of hypothesis

Induction of experimental diabetes in Wistar rats: Rats were unbroken in a very controlled temperature and lightweight condition (i.e., 37°C and 12:12 hour light: dark cycles) [19] and permit free access to water and food more or less for two weeks to adopt the experimental conditions. Rats were fasted for twelve hours to avoid failure of induction and to avoid aldohexose competition with streptozotocin at GLUT2 transporters. Through an experiment, we are able to induce polygenic disorder in rat by giving the dose of streptozotocin through intraperitoneal route (i.e., sixty-five mg/kg weight of streptozotocin dissolved in a very 0.1 M freshly ready change state buffer having pH 4.5), once the quarter-hour we'll provide the second dose of nicotinamide (120 mg/kg body weight) and dissolved in traditional saline. To counter drug-induced hypoglycaemia, rats got a five-hour aldohexose resolution long. Blood samples were collected onceseventy-two hours of induction from the tail vein of rats by apuncture to work out the glucose with a glucometer. If the glucose level is over 250 mg/dl, then polygenic disorder is confirmed and currently we
tend to check our different quantitative relationship of metformin and glipizide double-layer micro-needles on diabetic rats (Figure 8) [20].

**Implication of hypothesis**

After, the made development of double-layered micro-needle that is comprised of metformin and glipizide and separated by two layers of hyaluronan. During this paper, we've hypothetically tried to make double-layered micro-needles by the assistance of hypothetically designed capsule which might be worked on a basis of lock and key theories, a result of its own projection which might be fitted adjacent to micro-needle projection of primary matrix. The primary micro-needle or core is able to carry single layer micro-needle and by this technique, it permits to develop cup-like cavities on top of the primary or single layer micro-needle. From these cup-like cavities our drug and material will simply flow with the assistance of a hole that is given at the cavities and by the assistance of an inlet, we are able to simplify monitor and manage the speed of drug and material, and it helps in developing the second layer on primary layer in a very controlled manner (Figure 9) [21]. We tend to create the various formulations of metformin and glipizide through variation in their formulation unit and we have hypothetically given procedure for testing on Wistar rat, once causing polygenic disease Wistar rat through intraperitoneal route by injecting streptozotocin and nicotinamide combination. Once testing each formulation on Wistar rat we are able to check the aldohexose level by glucometer and we are able to compare the results of each formulation and we are able to develop the second layer on primary layer in a very controlled manner (Figure 9) [21].

![Figure 7: Preparation of double layer dissolving micro-needle.](image7)

![Figure 8: (a) Wistar Rat (approxiamtely 150-200 g for experiment) (b) Hair removed by clipper and hair removal cream for insertion microneedles into diabetes induced wistar rat (c) Insertion of double-layer microneedle for treatment of type-2 diabetic wistar rat.](image8)

![Figure 9: Cytotoxic and protective action of streptozotocin & nicotinamide on B-cells respectively. High nicotinamide intake could result in a rise within the production of reactive element species and result in aerophilous stress and hypoglycaemic agent resistance.](image9)
to calculateserum level of total cholesterol, glyceride, and high-density lipoprotein-cholesterol by collection of blood sample from tail vein of every Wistar rat and that we will study microscopic anatomy of normal, diabetic and drug-treated exocrine gland of Wistar rat (Figure 10) [22].

CONCLUSION

In summary, until we've got a single-layer micro-needle nearly for each un-wellness however still, it's a dream to use an inspiration of drug combination medical aid in micro-needle to treat diseases like polygenic disorder, T.B., cancer, malaria, leprosy, and HIV/AIDS, rather than the pill, capsule or the other indefinite quantity forms. Size of the micro-needle may be a gift for humans owing to its size we will get painless treatment however this size is additionally a limitation for developing the second layer on the first layer of the micro-needle. Double-layer micro-needle can face a retardant owing to its size, form and double layer, the realm can become slim to carry the drug within and it’ll become tough to deliver the additional quantity of the drug to a patient and that we will improve the indefinite quantity by increasing the number of applications of the micro-needle to a patient. Within the future maybe it’ll do to develop this kind of microneedle and it’ll facilitate patients and in addition, doctor to induce additional precise and site-targeted delivery of drug and by the help of double-layer micro-needle, we’ll scale back price, medical specialty waste, and improve patient compliance.

COMPETING INTERESTS

The authors declare that they have no competing interest.

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REFERENCES


Figure 10: Mechanism of action of metformin & glipizide through double-layered micro-needle.


