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Combating Type II Diabetes Employing Biodegradable Transdermal Microneedles

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KEYWORDS

Transdermal delivery, 3D printed Microneedles, Sitagliptin, Diabetes type II.

SHORT SUMMARY

Microneedles (MNs) are devices that could convey drugs transdermally, which offers an alternative route for hydrophilic drug delivery that display oral- gastrointestinal side effects. Sitagliptin was selected as the model drug, which is an antidiabetic. The work in the present study comprises formulation, in-vitro, ex-vivo & in-vivo characterization of effective non-invasive MNs for the transdermal delivery of Sitagliptin. MNs moulds were successfully fabricated using 3D printing technique. Biodegradable MNs were prepared using chitosan, PVA and hyaluronic acid (HA). Sitagliptin MNs made of PVA (SMP) and HA (SMH) showed suitable physical properties with drug content of 3.5 ± 1.4 and 3.8 ± 1.2 mg /1g, respectively. SMH exhibited superior skin penetration over that of SMP reflecting sharper and stiffer MN tips in correlation to optical microscope imaging. Ex-Vivo Drug Permeation using ventral rat skin revealed a biphasic pattern for both SMP and SMH. Sitagliptin was mainly deposited in the epidermis with ~40 & 55% for SMP and SMH, respectively. The in-vivo studies revealed that both the SMP and SMH presented similar efficacy compared to oral sitagliptin in lowering fasting blood glucose and that the SMH exhibited exceptional results in tapering postprandial blood glucose, and boosting postprandial insulin, almost touching the normal levels. Conclusively, HA biodegradable MNs are an amiable and promising tool for Sitagliptin delivery.

EXTENDED ABSTRACT

AIM OF WORK:

The main purpose of the study was to design microneedles as a delivery system to conquer the challenge of transdermally delivering a drug with such hydrophilic nature as sitagliptin to avail from its glucose lowering capabilities, meanwhile detouring it's orally accompanied serious side effects.

METHODOLOGY:

Fabrication of microneedles mould.

Fabrication of the MNs mould was *via* using stereolithography (SLA) and Computer-Aided Design (CAD) software files. MNs produced *via* UV exposure to a photosensitive resin[1]. The microneedle array was made up of 10x10 microneedles with a length of 1 mm and a base diameter of 0.5 mm

Fabrication of microneedles.

Firstly, plain MNs were prepared through making aqueous stock solutions from: 3% chitosan dissolved in 1% acetic acid solution, 15% PVA, 10 % PVP and 15% HA. Secondly, combinations between the stock solutions according to Table 1 were investigated for the MNs array. A 5% glycerol was added to all preparations. The MNs array mixture was then poured into the mould and centrifuged at 4000 rpm. Following that the packing layer was added. The MNs were dried and ejected from the mould [1]. Sitagliptin was added only in the successful MNs array combinations.

Physical Assessment & Dimensional Analysis and *In-Vivo* Skin Penetration

The physical assessment (PA) was based on the integrity and extrudability from the moulds of the MNs. The dimensions of the MN were examined using Optical Microscope with Lancer Image

Focus® Software. The MNs were inserted against the arm skin of a human volunteer, applying a pressure using thumb. The site of array application on the surface of the skin was treated with dye and the number of pores formed was counted [1].

***In vivo* animal studies**

A modified model for the induction of type II diabetes in rats was executed, using the high-fat high fructose diet (HFFD) and Streptozotocin injection technique. Six rats who received the normal fat diet served as Group 1: normal group (n=6). Diabetic rats were divided into four groups: Group 2: served as control (T2D) (n=8); Group 3: treated with sitagliptin oral (SO) (10mg/kg) (n=8), group 4: treated with equivalent dose of sitagliptin MN PVA (SMP) (n=8), and group 5: treated with sitagliptin MN HA (SMH). The treatment lasted for 6 days. Afterwards, blood glucose and insulin levels were measured fasting (8h) and 2 hours after the meals (postprandial) to evaluate the effects of all the preparations [2].

RESULTS:

The MNS mould was proficiently designed as shown in Figure 1. Also, pertaining to the findings presented in Figure 2, it could be concluded that F4 and F7 attained the optimal characteristics. This elected them to be loaded with sitagliptin to form the medicated MNs (SMP and SMH) and further investigated *via* the *ex vivo* permeation and *in vivo* studies (Figures 3).

Tables and Figures

Table 1 Combination ratios of the prepared non medicated formulae.

Formula Code	Polymers Ratio			
	PVP	Chitosan	PVA	HA
F1	1	2		
F2	0	1		
F3	1		2	
F4	0		1	
F5	1			0.5
F6	0			1
F7	1			1
F8	1			1.5

Figure 1 The fabricated microneedles mould

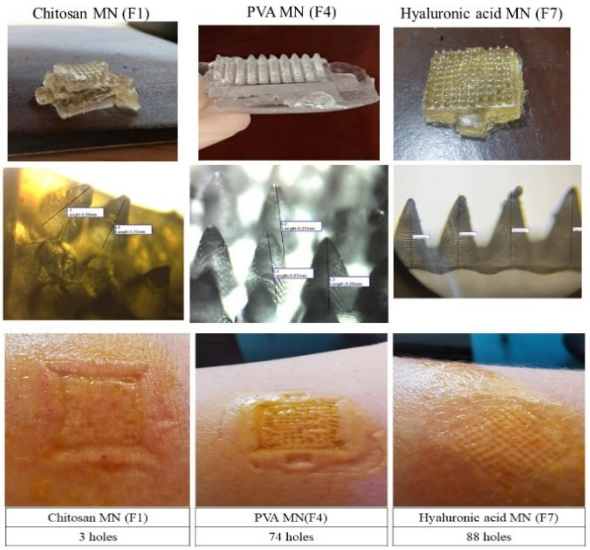

Figure 2 physical assessment and skin penetration

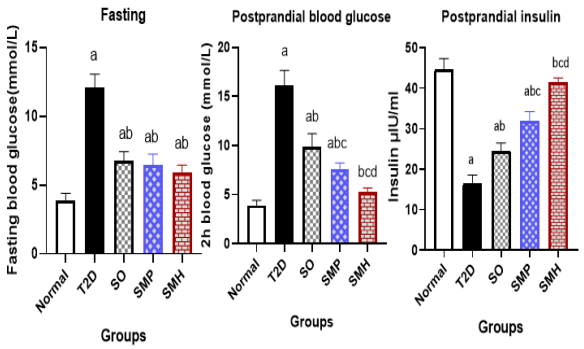

Figure 3 Effect of sitagliptin oral (SO), sitagliptin microneedle PVA (SMP), and sitagliptin microneedle hyaluronic (SMH) on 8 h fasting blood glucose levels, postprandial blood glucose and insulin levels. Statistical analysis was performed and a comparison was obtained for a normal group (a), T2D (b), SO (c), and SMP (d).

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