

Improving Rate of Gelatin/Carboxymethylcellulose Dissolving Microneedle for Transdermal Drug Delivery

(Penambah Baik Kadar Larutan Jarum Mikro Gelatin/Karboksimetilselulosa untuk Penghantaran Ubat Transdermal)

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ABSTRACT

Gelatin has been widely used as a nature-derived biopolymer material due to its high biocompatibility and abundance. However, multiple fabrication steps for the moulding process may limit its application to microneedle technology as biomedical application. This research focused on physical, chemical, and mechanical characteristics of gelatin-based dissolving microneedle (DMN) by adding in various concentrations of carboxymethylcellulose. Carboxymethylcellulose (CMC) derived from kenaf bast fibre were extracted by alkaline treatment and esterification process, followed by fabrication of DMN with gelatin using centrifuge-casting method. The formulation of G/CMC6 demonstrated the highest mechanical strength of 11.2 N by texture analyzer; hence, G/CMC6 was chosen for further investigate of its intra- and intermolecular bond, amorphous study, and its geometry by Fourier Transform Infrared (FTIR), X-ray Diffraction (XRD) and Scanning Electron Microscopy (SEM). FTIR showed various chemical interactions involved including hydrogen bonding, dipole-dipole and charge effect. The XRD result shows amorphous peak of gelatin decreased at $2\theta = 20 - 21^\circ$ with the addition of CMC. The height of microneedle arrays also decreased from its micromould by 36.7% due to agglomeration of CMC. Considering the biodegradability and the improvement of gelatin-based DMN mechanical properties by carboxymethylcellulose, the combination of gelatin and CMC is one of great potential for delivering drugs using microneedle.

Keywords: CMC; dissolving microneedle; gelatin; mechanical characteristics

ABSTRAK

Gelatin digunakan secara meluas sebagai sumber terbitan biopolimer semula jadi kerana sifatnya yang tinggi biokeserasian. Walau bagaimanapun, kaedah fabrikasi berganda bagi proses acuan dalam aplikasi teknologi jarum mikro adalah terhad. Kajian ini memfokus kepada sifat kimia, fizikal dan mekanikal jarum mikro terlarut (DMN) berasaskan gelatin dengan penambahan pelbagai variasi kepekatan selulosa karboksimetil (CMC). CMC yang digunakan merupakan terbitan daripada serabut kenaf yang diekstrak oleh rawatan alkali dan proses esterifikasi, kemudiannya gelatin dan variasi kepekatan CMC digunakan untuk memfabrikasikan jarum mikro terlarut dengan menggunakan kaedah tuangan-emparan. Formulasi G/CMC6 telah menunjukkan kekuatan mekanikal jarum mikro tertinggi dengan 11.2 N oleh analisis tekstur. Oleh itu, G/CMC6 dipilih untuk mengkaji ikatan intra- dan intermolekul, amorfus dan geometri menggunakan instrumentasi analisis spektroskopi transformasi Fourier infra merah (FTIR), pembelauan X-ray (XRD) dan mikroskopi imbasan elektron (SEM). FTIR menunjukkan terdapat interaksi kimia berlaku yang melibatkan ikatan hidrogen, dwikutub dan kesan cas. Keputusan XRD pula menunjukkan puncak amorfus gelatin semakin menurun pada $2\theta = 20 - 21^\circ$ dengan penambahan CMC. Panjang jarum mikro pula berkurangan semasa proses pengeringan, iaitu berkurangan sebanyak 36.7% daripada acuan atas faktor aglomerasi oleh CMC. Kajian ini telah membuktikan bahawa biodegradasi dan peningkatan mekanikal jarum mikro berasaskan gelatin dan CMC salah satu potensi untuk menghantar ubat dalam bidang farmaseutis.

Kata kunci: CMC; gelatin; jarum mikro; terlarut; sifat mekanikal

INTRODUCTION

The major problem associated with transdermal technology is that many of the drugs are not able to cross the skin due to limited permeability, which caused by

the outermost layer of epidermis of skin, called stratum corneum (SC). The ability of this 'dead' layer of tissue is to prevent the permeation of foreign compounds including drug molecules (Barry, 2001; Naik et al. 2000; Park et

al. 2014). One of the common and widely used for drug delivery in transdermal routes is topical cream. However, Prausnitz and Langer (2008) reported that the transdermal route for drug delivery using the topical cream could only permeate 10 - 20% through the skin. In addition, the conventional hypodermic needle can deliver an estimation 90 - 100% of drug loaded painfully to the patient, as it can go deep into dermis layer, which the needle reaches the pain receptor. Microneedle patch can penetrate the SC and deliver drug directly into epidermis or upper dermis layer almost 100% without pain (Dangol et al. 2017; Waghule et al. 2019).

The DMN been studied to deliver drug through the transdermal route and to overcome the limitations of transdermal conventional approaches. As it can deliver drug painlessly, patient less phobia with needles, and save cost for disposal in hospital and clinical (Tuan-Mahmood 2013; Yang 2019). The drug administration using the DMN allows the drug molecules to cross the SC layer, thus, allowing more drug molecules to enter the skin. The development of this technology creates larger transport pathway of micron size that is smaller than holes by hypodermic needles and larger than molecular dimensions. This small invasive device also faster onset of action, improved permeability, better patient compliance, and self-administration (Hu et al. 2016; Yang 2019).

Fabrication of DMN are commonly made from biopolymer such as hyaluronic acid (HA), polyvinyl pyrrolidone (PVP), gelatin (Tabari 2017), chitosan (Chen et al. 2012), polyvinyl alcohol (PVA) (Sullivan et al. 2008), carboxymethylcellulose (Naito et al. 2012; Tabari 2017), chondroitin sulfate (Ito et al. 2012) and dextran (Naito et al. 2012). Previous report shows that the preparation of DMN for lipophilic drugs delivery using HA and PVP based on drawing lithography. The phase transition of powder form of lipophilic drugs allowed the fabrication of DMN to generate a powerful transdermal drug delivery system due to interior chemical bonds between drugs and biodegradable polysaccharides and formation of nano-sized colloidal structures. The limitation of those polymer used were the mechanical property of PVP was too brittle and the robustness of HA was too low, relatively shows poor mechanical strength (Dangol et al. 2016).

Commonly, synthetic polymers are used as host face disadvantages, such as high cost and toxic to environment. There is an alternative way to obtain polymer hosts with a lower cost, also, in an environmental friendly manner and with good chemical and physical properties, natural polymers, such as cellulose, and its derivatives. CMC is a type of cellulose derivative that possess good mechanical strength (Lan et al. 2018). CMC is a natural anionic polysaccharide, which is widely used in many industrial sectors, including food, pharmaceuticals,

cosmetics, and mineral processing. It is a natural polymer that is non-toxic, cheap, renewable, available in abundance, biocompatible, and biodegradable (Ali et al. 2019; Kamath et al. 2005). Furthermore, CMC is water-soluble, that can form flexible and strong polymer by itself and it is widely applied in drug delivery application owing to its high solubility and bioavailability (Lan et al. 2018; Zhang et al. 2018). It contains a hydrophobic polysaccharide backbone and many hydrophilic carboxyl groups, hence, showing amphiphilic characteristic. Lately in Malaysia, for example kenaf was recognised as an important natural raw fibre which is capable of replacing tobacco in the manufacturing of many products. Kenaf bast fibres are chosen as desirable properties of natural fibre as reinforcement in polymer composites. The polymer matrix could hold the fibre firmly and increase interfacial properties of the composite and thus increase the mechanical properties of combined polymer (Rani et al. 2014).

In this study, we developed a transdermal drug delivery system using gelatin and CMC which were fabricated by centrifuge-casting technique. Gelatin could offer biopolymer and bioavailability properties that could be deliver therapeutic drugs transdermally, also, to fit the composition of DNM (Naito et al. 2012). The weak structure of gelatin and its low boiling point along with the low content of proline and hydroxyproline amino acids, which are mainly responsible for gel formation in gelatin, have caused it to have weak mechanical properties (Kumsah et al. 1978; Nazmi et al. 2017). To improve the properties of biopolymers, bio-composites or biodegradable composite are composed of two or more biopolymers. The addition of CMC is to improve the mechanical strength of DMN arrays (Zhang et al. 2018). To increase the mechanical strength and maintain its flexibility, plasticizers which contain materials such as water, acetone, fatty acids, and glycerol alcohols are used. They change the three-dimensional structure of the polymer and improve their mechanical property. In addition to their high efficiency, they should also be nontoxic and edible (Atef et al. 2014; Thakur et al. 2016; Tongdeesontorn et al. 2011; Tuan-Mahmood 2013).

The goal of this research was to produce DMN based on gelatin because of its biocompatibility and biodegradable properties (Lai 2010). Carboxymethyl cellulose which is extracted from Kenaf bast fibres is chosen to improve its mechanical property, which potentially could serve as an efficient device for transdermal drug delivery. Therefore, the main purpose of this present work was to improve the characteristics of gelatin DMN by adding polysaccharide of carboxymethyl cellulose. The mechanical, physical, and chemical properties of DMN were also investigated.

MATERIALS AND METHODS

CHEMICALS

Gelatin, glycerol (98%) from Sigma Aldrich (Malaysia) Sdn. Bhd., Kenaf bast fibre were obtained from Forest Research Institute Malaysia (FRIM, Malaysia). Polydimethylsiloxane (PDMS) micromould (height 850- μm , needle base 200- μm , needle base interspacing 500- μm) from Micropoint (Singapore).

PREPARATION OF CARBOXYMETHYLCELLULOSE

Kenaf bast fibres were extracted by 4% w/v of NaOH at 80 to 90 °C for 3 h. The fibres were washed and filtered by distilled water and dried overnight in room temperature. Next, the fibres undergo bleaching treatment by 1.7% w/v of NaClO₂ in acetic phosphate buffer at 80 °C for 4 h. The fibres were washed and filtered several times by distilled water (Salleh et al. 2018). Finally, the cellulose left dried overnight in room temperature. This step was repeated 3 times to make sure the fibres were completely bleached.

The extraction of CMC was continued by alkaline treatment and etherification (Bono et. al. 2009). The cellulose fibres were extracted by isopropyl alcohol and distilled water with ratio 1:1 followed by 20% w/v of

NaOH. After the alkaline treatment, sodium chloroacetate was added and heated at 50 °C for 2 h. After the etherification process, 70% of ethanol was added to stop the reaction. The fibres were washed and filtered by methanol and the fibres then, were filled in membrane tube and soaked in 0.5 M acetic acid until pH7.

FABRICATION OF DMN

The DMN formulations were prepared using centrifuge-casting method with 10% w/v gelatin, 5% w/v glycerol and different concentrations of CMC. The amount of CMC in gelatin formulation was 3, 6, and 9% w/v with the code referral as G/CMC3, G/CMC6 and G/CMC9. The formulations of gelatin with the addition of different concentration of CMC (G/CMC) were poured into micromould. Figure 1 represents the graphical abstract for fabrication of DMN. Based on Figure 1(A), the micromould carefully set in 50 mL centrifuge tube by forcep. The micromould must be perpendicularly in the centrifuge tube to ensure the formulation does not leak out. Figure 1(B) shows the micromould was subsequently centrifuged at 25 °C with the speed of 4,500 rpm for 10 min. The mould left dried in desiccator overnight. The DMN was taken out from the mould by using forcep carefully. Figure 2 represented microneedle moulds.

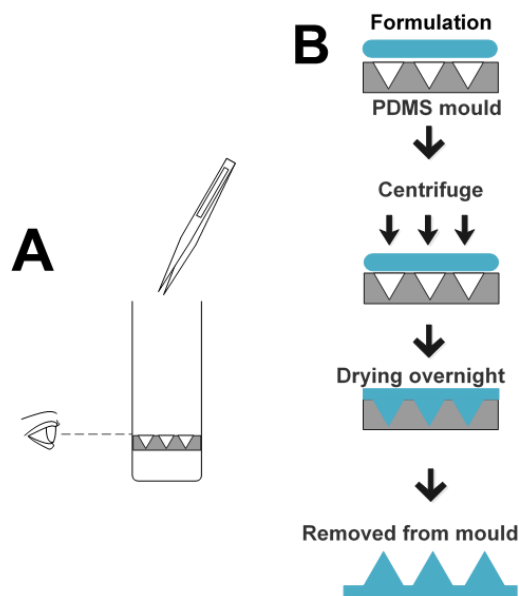


FIGURE 1. A schematic of fabrication of DMN using centrifuge-casting technique

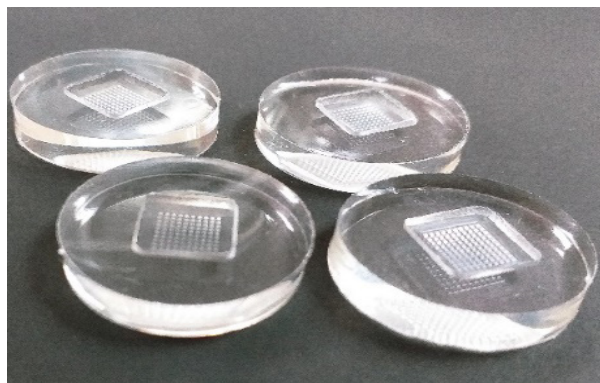


FIGURE 2. Microneedle moulds

MECHANICAL STRENGTH AND SKIN PENETRATION

An axial fracture test using a texture analyzer (CT3, Brookfield, USA) was used to determine the mechanical properties of G/CMC DMN. First, a single DMN was horizontally attached to a pin stub using an adhesive tape. The metal pin stub was fixed horizontally in an opposing position, and then moved at a rate of 0.1 mm/min. The fracture force was measured by loading until failure. The force (N) vs displacement (mm) data were measured to determine the fracture force of the DMN. To determine if the DMN could pierce skin, DMN arrays were pressed into Sprague Dawley (SD) rat skin with 4 parameter force (3, 5, 10 N and thumb press). After removing DMN from SD rat skin, puncture marks on the skin were characterized using a digital microscope.

SEM

The morphology of DMN was determined by SEM (ZEISS, Merlin Compact, Germany). The surface of DMN was coated with iridium for 30 s to ensure the electron image could magnify clearly with magnification of 20 to 200x.

XRD

X ray pattern of G/CMC DMN was analysed using X-ray diffraction (Bruker D8 Advance, Germany). X-Ray Diffractometer following a method according to Hazirah et al. (2016) with some modifications. The sample was mounted on 2 × 2 inch glass slide and secured on the X-ray platform using tape. This analysis was run with Cu K α radiation at current of 30mA and voltage of 40 kV. The sample then was scanned between $2\theta = 3$ and 80° with a scanning time 30 min per running. All DMN were tested in triplicate. The crystallinity index (CrI) was calculated using (1):

$$\text{Cr.I. (\%)} = (\text{Sc}/\text{St}) \times 100 \quad (1)$$

where Sc is the area of the crystalline domain; and St is the area of the total domain.

The amorphous index (Am) was calculated as (2):

$$\text{Am (\%)} = 100 - \text{Cr.I} \quad (2)$$

where Am is the amorphous peak.

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

Infrared spectra of the films were measured using FTIR spectrometer (Perkin Elmer Spectrum 400 FT-IR/FT-NIR & Spotlight 400 Imaging System). The sample scanning frequencies were in range of 4000 to 650 with spectra resolution of 4 cm^{-1} . The interactions among gelatin, glycerol, and CMC were determined through spectra obtained. Measurements were performed at room temperature and data were collected in triplicate. The functional group were identified by software and assigned according to the literature values.

STATISTICAL ANALYSIS

The One-way ANOVA was applied to all results using the Minitab 19 program for Windows (Minitab 213 Inc., USA). When differences between analyzed groups were significant the mean pairs were assessed on the basis of the Fisher's test with a level of significance of 0.05 ($p < 0.05$).

RESULTS AND DISCUSSION

MECHANICAL STRENGTH AND INSERTION SKIN STUDIES

The mechanical strength was characterized by presenting the force versus displacement curve of DMN arrays. Table 1 shows the mechanical strength of CMC different concentrations in gelatin.

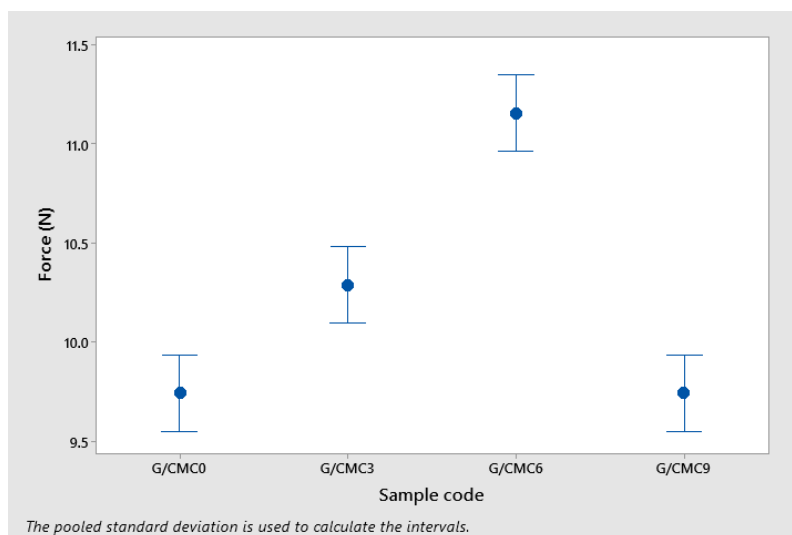


TABLE 1. Fracture force of G/CMC0, G/CMC3, G/CMC6 and G/CMC9 DMN

It can be seen the fracture force of DMN increasing significantly with the addition of CMC in gelatin DMN. It shows that the optimum fracture force is at G/CMC6. The G/CMC3 shows significantly increase with 10.3 N which is 5.3% higher than gelatin DMN. The addition of CMC in gelatin formulation improvements in their mechanical strength. This may be attributed to the long-chain CMC molecules, that contain many -OH groups that participate in strong intermolecular bonding and electrostatic interaction between gelatin and CMC which been reported in Figure 5, similarly reported by Nazmi et al. (2017). The optimum result was shown by G/CMC6 which was the highest fracture force at 11.2 N among the other DMN. Previous report by Tongdeesoontorn et al. (2011) mentioned that the addition of CMC in cassava starch-based, could enhance physical properties (high fracture

force) than pure polysaccharides formulation. However, the G/CMC9 DMN shows significantly decreases by 13.1%. The G/CMC9 DMN becomes brittle due to agglomeration of CMC which were similarly report by Ishak et al. (2010) and Serawati et al. (2010). Figure 4 represents agglomeration of CMC in G/CMC9 DMN arrays. Hu et al. (2016) believe that some of the weak polymers replace the stronger polymers, thereby weakening the internal network structure of the film, and thus causing a decrease in its strength. Besides, Atef et al. (2014) demonstrated that excessive super-hard stiffness and cracks in the film matrix are the main reasons leading to brittleness and reduced the mechanical strength of the polymer.

Skin pinhole created indicated that DMN penetrated the skin successfully. The pinhole number was calculated with the different external force of 3, 5, 10N, and thumb

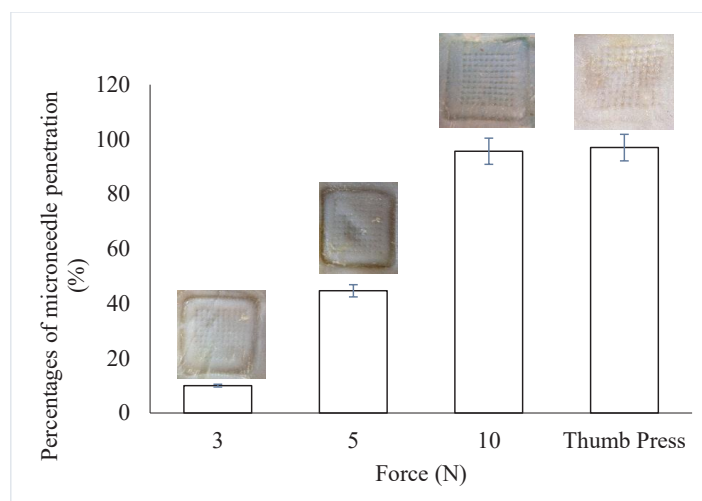


FIGURE 3. Percentages of DMN penetration into the skin with four different force

press, respectively. G/CMC6 was chosen for skin pinhole test as it shows highest mechanical property. The axial force to penetrate completely into the skin was estimated by 10 N. When the external force was 5N, only 36% needles penetrated skin. However, when the external force increased to 10 N, almost 100% needles penetrated the skin, which was almost the same results as thumb press. The higher force used creates more skin pinhole, thus, the penetration of DMN favourable with force of 10 N and onwards. The skin pinhole created indicated that DMN penetrated skin successfully by pressing of external force shows similar report to Pan et al. (2018). Therefore, the results confirmed that the G/CMC6 DMN presented enough mechanical strength to successfully puncture the 450 μm SD rat skin, and for drug delivery application. Figure 3 shows the percentages of DMN penetration into the skin.

FOURIER TRANSFORM INFRARED SPECTROSCOPY (FTIR)

The FTIR spectrum was to determine the functional group of gelatin, CMC, and G/CMC6 were summarized in Figure 4. The FTIR spectra for N–H stretching vibration in pure gelatin film shows a broad peak located around 3541 shifted to 3538 cm^{-1} (Isa 2019; Nazmi et al. 2016; Qi et al. 2015; Suhaimi & Rahman et. al. 2019; Wu et al. 2014). This was affected by the intermolecular or intramolecular hydrogen bonds, which was assigned to O-H stretching. The stretching frequency of -OH group which shows the presence of water has resulted in weak intensity (broad) at 3345 cm^{-1} (Ramli et al. 2015; Salleh et al. 2019). The addition of CMC into gelatin formulation caused the peak of O-H stretching shifted to lower wavelength from 3284 to 3274 cm^{-1} . This shows that the blends were weaker compared to the pure gelatin caused by the hydrogen bonds acting on the -OH groups (Nur Nazirah et al. 2016; Tong et al. 2008). This is due to the intermolecular interaction between hydroxyl group from gelatin and

carboxyl group from CMC, thus the amount of hydrogen bonds that can act on free hydroxyl group were reduced. The C=O stretching vibration coupled with C-N stretch, in plane NH bending modes and CCN deformation. The most sensitive spectral region to the protein secondary structural is C=O stretching absorption band. Each peak was in the same wavelength position but difference in their intensity (Kenaf 2014; Nazmi et al. 2016). The peak increased for C=O stretching band in blended formulation from 1622 to 1627 cm^{-1} which shows that the addition of CMC caused conformational changes in gelatin polypeptide chains, resulting in a decrease in the presence of single-helices, random coils and disordered structures (Esteghlal et al. 2018; Hosseini et al. 2013; Jahit et al. 2016). This also shows that the antisymmetric and symmetric vibrations of C=O and C–O bonds were enhanced. This is due to the disruption of intermolecular hydrogen bonds between the carboxylic groups that caused by the addition of CMC (Tong et al. 2008). The bending vibration of NH groups and stretching vibrations of CN groups. From the result, the stretching vibration of CN band in gelatin/CMC was shifted from 1519 to 1538 cm^{-1} . The differences observed may be due to the alteration of the secondary structure of gelatin polypeptide chains caused by the addition of CMC. The in-plane vibrations of CN and NH groups of vibrations of CH_2 groups of glycine (Nazmi et al. 2017).

From the result, bending NH group band in pure gelatin shifted to a higher wavelength, from 1229 to 1240 cm^{-1} when CMC was added to the gelatin based film. These results show that the OH group in CMC and amino groups in gelatin were consumed during the blending process which was similar report by Nazmi et al. (2017) and Su et al. (2012). The presence of glycerol as plasticizer overspread the FTIR absorption bands. The FTIR spectrum showed no covalent interaction between gelatin and CMC which is supported by Esteghlal et al.

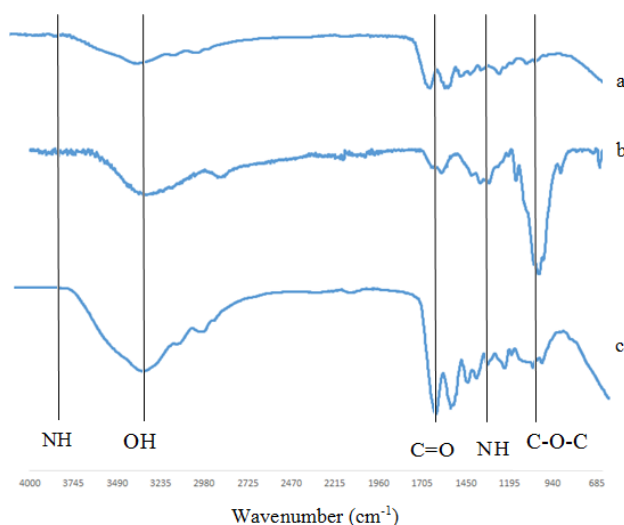


FIGURE 4. FTIR spectrum for (a) gelatin, (b) CMC and (c) G/CMC6

(2018). Blending CMC with gelatin caused minimal shifting but increased absorption in the COO- band around 1592 cm^{-1} in gelatin. This indicated that the antisymmetric and symmetric vibrations of C=O and C-O bonds were enhanced, probably due to the disruption of intermolecular H-bonds between carboxylic groups caused by added polysaccharides (Tong et al. 2008).

SEM

The geometry of G/CMC0 and G/CMC6 DMN were summarized in Table 2. The geometry and size of

microneedle shrunk due to drying process which is the same report by Zhang et al. (2018). The height of G/CMC6 DMN arrays was significantly $538.43 \pm 6.28\ \mu\text{m}$, with base of $230.87 \pm 5.7\ \mu\text{m}$, followed by the distance between arrays was $157.45 \pm 7.009\ \mu\text{m}$. The G/CMC6 DMN significantly decrease by 30.8, 12.4 and 20.5% for its height, width and width between needles from the mould. This is due to the hydration effect of CMC which is reported by Hube et al. (2017). All the patch areas and densities of DMN were constant which were 0.8 cm^2 and 100 needles.

TABLE 2. Characteristics of DMN patches. Data of DMN dimension are expressed as mean \pm SD of results from four measurements

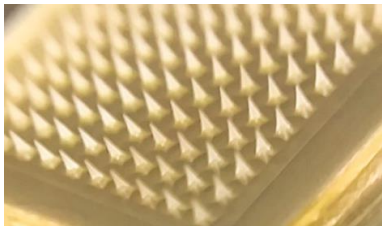
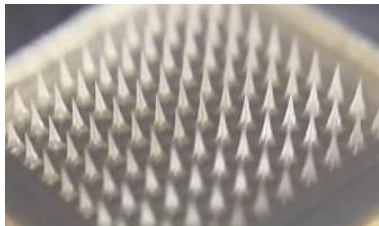
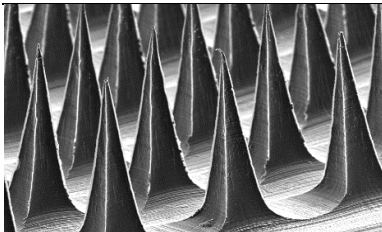
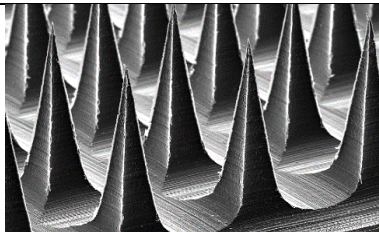
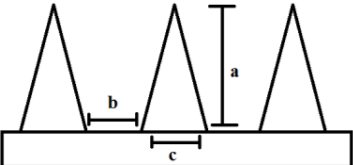
Constituents		G/CMC0 DMN	G/CMC6 DMN
Stereomicroscopic image	Patch		
	DMN		
Dimension			
		(a) 600.9 ± 0.02	(a) 538.4 ± 0.03
		(b) 225.2 ± 0.06	(b) 220.1 ± 0.04
		(c) 160.3 ± 0.03	(c) 150.7 ± 0.04

Figure 5 represents the morphology of DMNs. G/CMC0 shows amorphous surface without rough, grainy, and porous structure similar report by Wu et al. (2017). G/CMC0 DMN incorporated with CMC at G/CMC3 and G/CMC6 had relatively rough surface compared G/CMC0 DMN. The addition of CMC such as G/CMC3 and G/CMC6

DMN, caused a discontinuous and uncompact texture with sponge-like structure, with pores distributed throughout DMN arrays matrix, which became stronger at this concentration. The presence of CMC leads to the increase in roughness of DMN arrays probably due to drying process which extend over the gelatin matrix surface by reducing

it regularities. The roughness of G/CMC0 DMN visibly increased with the increasing concentration of CMC. However, cracks, cavities, and fibres agglomeration were found in G/CMC9. This was mainly related to

the agglomeration resulting from uneven dispersion of hydrophobic backbone of CMC in the fabrication process of DMN (Marques et al. 2018). This may lead to the brittleness of the needles, therefore, the mechanical strength of the needles become lower.

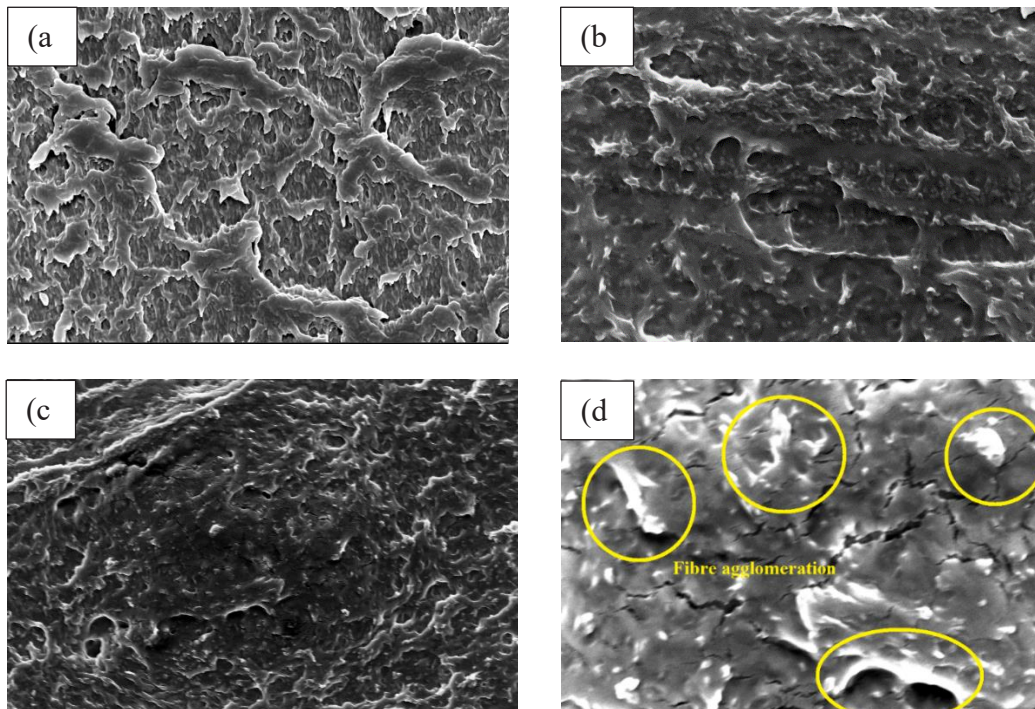


FIGURE 5. FESEM image of DMN arrays with magnification of 200 nm (a) G/CMC0, (b) G/CMC3, (c) G/CMC6, and (d) G/CMC9

XRD

Gelatin has very high amorphous peak. The addition of CMC in gelatin formulation shows the decreasing of %

A_m from 85.71 to 64.28%. CMC demonstrated a crystalline structure at peak $2\theta = 22.5^\circ$. G/CMC demonstrated a semi-crystalline structure with two major diffraction peaks: at

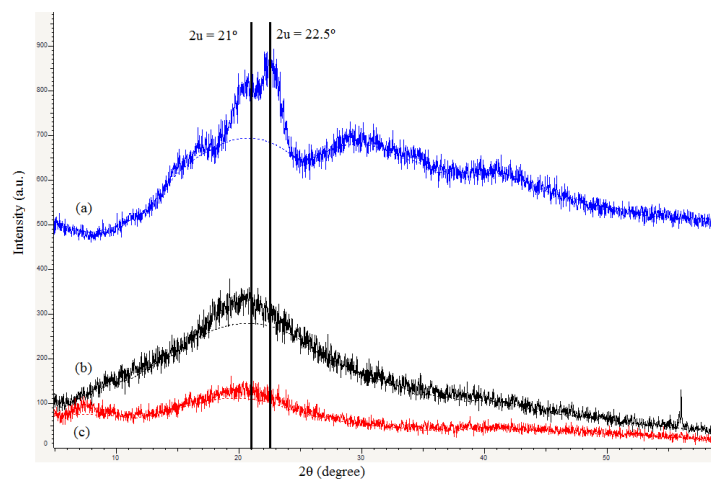


FIGURE 6. X-ray diffractogram for (a) CMC, (b) G/CMC6, and (c) gelatin

$2\theta = 21, 22.5^\circ$, showing an amorphous peak, and at $2\theta = 21^\circ$, showing a crystalline peak. A study conducted by Chai and Isa (2013) reported an amorphous peak at $2\theta = 21^\circ$ for CMC. The present study added gelatin to CMC and obtained a slight shift (to 21°) from gelatin and CMC interactions. The particularly sharp peak observed at 20° was likely due to unorganized microcrystallite molecular residue from CMC's bulkier anionic side group activities, which disrupted crystalline lattice formation during preparation of DMN formulation. These results agreed with a similar report from Martins et al. (2011). This shows, the addition of CMC in gelatin slightly decrease of its amorphous, thus, similarly with low water absorption intake. Figure 6 represents XRD spectrum for gelatin, CMC, and G/CMC.

CONCLUSION

DMN successfully prepared using PDMS micromould by centrifuge-casting technique. Mechanical strength of gelatin DMN improved 12.7% with the addition of CMC. Strong interactions between functional groups of gelatin and CMC were verified by FTIR and XRD analysis. The crosslinking and intermolecular bonding formed within gelatin and CMC functional group matrix with addition of CMC into gelatin formulation have improved some of mechanical and physical properties of G/CMC DMN. DMN has potential to offer a simple and convenient route of drug administration, while eliminating the pain associated with the use of hypodermic needles. The physicochemical characterizations of G/CMC DMN were successfully proved in this study. The addition of CMC in gelatin DMN also has the potential to deliver drug since it is able to pierce the stratum corneum. Therefore, this study highlights the need for researchers involved in the DMN field, particularly for biomedical applications, to address and consider these issues in the context of future developments.

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