An Emerging Transdermal Drug Delivery System: Fabrication and Characterization of Natural and Biodegradable Polymeric Microneedles Transdermal Patch

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Authors' contributions

This work was carried out in collaboration among all authors. Authors SR and MJN designed the study, wrote the protocol, and wrote the manuscript. Authors MJN, DL, and SR managed the analyses of the study. Authors DL and SR managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Promising drug agents are limited by their inability to reach in systematic circulation system when applied on skin, because of the excellent barrier of biological membranes, such as the stratum corneum (SC) of the skin. It is the outermost layer of the skin, SC, the principal barrier to all the topical application applied on skin. Various strategies were employed by many research group and pharmaceutical companies worldwide, for the formulation of microneedles. Therefore, microneedles (MN's), used to puncture skin, it created the transient aqueous transport pathway and enhanced the transdermal permeability. Microneedles (MN's) fabricated with natural and biodegradable polymer, such as carboxymethyl cellulose (CMC), and dextran. Inverse replication of micro milled master mould reproduced, solid out of natural polymeric microneedles, were subsequently assembled into transdermal patch and physiochemical characterized for dissolution index.

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1. INTRODUCTION

Microneedles (MN’s) offers an alternative mechanism to the hypodermic needle for injection of drugs and blood extraction. Microneedle (MN’s) arrays designed to penetrate the skin and capillaries without causing pain and without need of medical expertise, it is concluded the diagnosis and treatment with microneedles (MN’s) can be administrated at point-of-care[1,2]. In additions, fabrication of microneedles (MN’s) method depends on the materials, manufacturing technology and application sites. Undoubtedly, polymeric materials are receiving interest from the various medical and health care sector industry because of their low cost, ease of manufacture, and provides favourable biological and mechanical properties of the system[2,3,4].

The fabrication of polymeric microneedles (MN’s) by casting method, We present a simple and versatile fabrication process directly casting polymer solution in fabricated moulds[5]. The process we have initiated involves the mechanical strength evaluation, by piercing into artificial skin, dissolution efficiency and swelling index were determined under specific environment[5,6,7]. These data were used to predict the efficient delivery of drug through transdermal patch loaded with natural polymeric microneedles[8]. If prepared microneedles were failed to penetrate the artificial skin, than evaluated mechanically.

Transdermal drug delivery system involves the transport of the drug across the stratum corneum (SC) of skin [9,10,11]. The selection of drug depends upon the physiochemical properties of the drug candidates, traditional transdermal patches can be divided into following two categories; (1) Matrix based system, and (2) Reservoir based system. This system offers advantages such as, avoidance of the first-pass hepatic metabolism, improves patient compliances, providing large surface area for the skin delivery of drugs and offers quick termination of system[12,13]. The major resistance in case of the transdermal system to cross the stratum corneum, problem of poor drug transport can be addressed by fabricating natural polymeric microneedles array, which deliver the drug painlessly through the stratum corneum, and decomposed under the skin due to the natural polymer no side effects and efficient addition[14,15].

2. MATERIALS AND METHODS

2.1 Materials

Ethyl cellulose (EC; ethoxy content 48.0 - 49.5 %, viscosity 18 to 22 mPa), Polyvinyl pyrrolidone (PVP K-30), Polyvinyl alcohol (PVA), Dibutyl phthalate (DBP) and dibutyl sebacate (DBS), Linseed oil, L-menthol, Resin, hydrates, Polylactic acid, HPMC, PEGDMA and all the other chemical of analytical reagent grade.

2.2 Method of Preparation

2.2.1 Preparation of master mould

MN’s moulds were fabricated containing 340um x 340um x 300um (LxWxH) wider, length and height and had 640 um center-to-center spacing the mould cavities (MNs holes) were prepared by mechanical method using needle top were pork into the mould surface[16,17]. Standard mould were fabricated using materials (resin and hydrate) by hand rolling method. Prepared moulds were placed for 24 hours under room temperature.

2.2.2 Preparation of polymeric microneedles arrays (MN’s)

The natural and biodegradable polymeric solution used to fabricate the microneedles transdermal patch. The polymer solution of polyvinyl alcohol (PVA) about 20% w/v was dissolved in purified water at 90°C at a ratio of 0.80 gm PVA per 1ml of purified water, stirred using magnetic stirrer for 20 minutes. Once the smooth consistency of polymer solution were prepared, allow the solution to poured in to the microneedles standard mould. Then standard mould containing
polymer solution were attached under centrifuges apparatus and allow immediately centrifuged at 1500 rpm for 15 minutes for even and uniform distribution of the solution into the mould [18,19]. After the centrifugation mould should be removed carefully and allow it to stand for 24-48 hours for complete drying of the microneedles. To take out microneedles from the mould, it kept under the freezer for 30 minutes at 4-5°C for easy removal of microneedle (MNs) (Fig. 2).

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**Fig. 1.** Three major regions of skin, epidermis, dermis, and hypodermis (thickness range)[15]

**Fig. 2.** Polymeric Microneedles (MN’s) array with 25-gauge hypodermic needle top is shown. The inset image shows a magnified view (500 um) of prepared microneedles arrays to facilitate clear imaging, blue dye (Trypan blue) used[19]
2.2.3 Fabrication of transdermal patches

Transdermal patch were fabricated using established fabrication technique with some modifications. Prepared 10% polymer solution, 0.75 gm PVP and PVA dissolved per 1ml of purified water. 1gm of dextran per 1ml of PVP/PVA solution was mixed. This Prepared polymer solution were poured in microneedle moulds arrays [20-26]. It kept for 12 hours for completely dried and removed microneedle (MN’s) arrays with supported backing layer of 10% polymer backing layer (Fig. 3).

2.3 Characterization of Microneedles Transdermal Patch

2.3.1 Scanning electron microscopy (SEM) analysis

Prepared microneedle array were investigated for magnification, tilt degree, width, spots and other imaging characteristics on SEM images. Microneedles arrays were mounted on the disc and morphological characteristic feature scanned in scanning electron microscope (SEM) in high-vacuum mode, attached ETD detector at 10-5 Torr and 15 kV, model (FEI Quanta TM ESEM, QUanta 200 FEG; FEI, Oregon).

2.3.2 Differential scanning calorimetry (DSC) analysis

The sample of microneedles were investigated under differential scanning calorimetry (DSC) system model (Netzsch 204 F1 Phoenix®; Geratebau GmbH, Bavaria). Microneedles sample were heated at a linear heating rate of about 10°C/minutes from 25 °C to 250 °C, generated graph and report were analysed with Netzsch-compatible software, parameter such as, melting peak, delta Cp of microneedle arrays.

2.3.3 Measurement of mechanical strength and swelling index

Quantitative and qualitative assessment of microneedle was observed included the experimental variability artificial skin were designed related to anatomical variation as the human skin structure, using polymer (CMC/dextran) thin film fabricated using 40:20 ratio. In contrast microneedle arrays with different geometrics delivered. On the other hand, insertion force were approximately constant, enabling deeper and more reproducible insertion with greater proportion pores. The artificial skin (CMC/PVP) thin layer were subjected to analysed under SEM analysis and depth under purified water for the determination of swelling index of the microneedle arrays.

Fig. 3. In-process fabrication of polymeric microneedle arrays using casting on mould. Image prepared MN’s, and microneedle classification. (A) Process of fabricating polymeric microneedles using polymer solution, (B) Prepared (MN’s) PVP/PVA microneedle patch, (C) Microneedle tip height 6.25 um, distance 515 um graphical elaboration.
2.3.4 Measurement of dissolution efficient of microneedle arrays

In this measurement, the application of microneedle were investigated, including the type of bioactive cargo to be dissolution time release, dissolution pH specific, dissolution by-products and estimated mechanical strength. In additions, we demonstrated six type of microneedle from different type of polymer together. We created microneedle from, (i) Carboxymethyl cellulose (CMC); (ii) Polyvinyl pyrrolidone (PVP); (iii) CMC/PVP at 60:40 dry weight ratio; (iv) PVP/PVA 20:10 at dry weight ratio; (v) CMC/dextran at 50/50 dry weight ratio; (vi) PVP/HPMC at 60:40 dry weight ratio. Microneedles from all the seven geometric polymers were fabricated and sample successfully dissolve in particular solvent for specific time and 5.4-7.2 pH buffer to demonstrate the dissolution efficient.

3. RESULTS AND DISCUSSION

3.1 Scanning Electron Microscopy (SEM) Analysis

Scanning electron microscopic analyzed the microneedles arrays, found rugged texture, uniform tip size and shape, orderly sharp tips. It was found, concentric circular features on microneedle surface, less than 1 mm in height and around 250um base thickness and tip around 20 um (Fig. 4).

3.2 Differential Scanning Calorimetry (DSC) Analysis

The structural morphology of the polymer HPMC/PVP, CMC/PVP and PVP/PVA, was analyzed, on exothermic peak (PVP/PVA MN’s) was observed at 45.5°C, that represented crystallization of the amorphous polymer material. Melting of the material occurred at approximately 198.2 °C, and crystals were observed at 240.5 °C. An exothermic peak was observed (HPMC/PVP MN’s) at 140.5 °C, with the delta Cp of 3.12 J/(g.K). Melting occurred in between 200 to 255 °C. The glass transition (Tg mid) occurred at 210.874 °C with delta Cp of 1.84 J/(g.K).

3.3 Measurement of Mechanical Strength and Swelling Index

Mechanical strength and swelling index, biodegradable polymeric PVP/PVA and PVP/HPMC MN’s proved to create pores in the skin layers (SC) without bending or breaking, promising properties such as, hard, glassy and stable at room temperature. Swelling index “poke and release” approach evaluated for enhancing the drug delivery across the skin, more efficiently (Fig.5).

The percentage of water uptake by the polymers up to 5% to 20% increased swelling after 12 hours. Microneedles (HPMC based polymer) swelling index obtained by 58.44+- 0.5 to 66.75+- 0.75%, and microneedles (PVP/PVA) swelling index obtained by 35.34+- 0.35 to 75.75+- 0.75%. This results on comparatively under effective percentages, this may obtained because of the hydrophilic property of the polymers used to fabricated the microneedles. In addition, swelling of the polymer may lead the matrix formation, and this resist the drug from the microneedles. Comparitively results showed PVP and PVA based microneedles is more suitable then HPMC blends microneedles for the transdermal drug delivery system.
Fig. 5. DSC thermogram overlay of HPMC/PVP, CMC/PVP and PVP/PVA polymers analysed glass transition (Tg mid) occurred at 210.874ºC with delta Cp of 1.84 J/(g.K).

![DSC thermogram overlay](image)

Fig. 6. Mechanical efficient of microneedles can be observed after insertion into artificial skin. A section of microneedle patch is shown as (1) before use (2) after 2 minutes (3) 10 minutes after insertion into artificial skin, imaged by bright-field microscopy. This experiment was performed at room temperature. To facilitate the imaging, blue dye (Trypan blue) used.

![Microneedle patch](image)

Table 1. Swelling index

| Polymers          | 2 hour   | 4 hour   | 8 hour   | 12 hour  |
|-------------------|----------|----------|----------|----------|
| PVP/PVA           | 25.51 +/- 0.34 | 28.51 +/- 0.16 | 30.41 +/- 0.24 | 35.34 +/- 0.35 |
| HPMC              | 33.24 +/- 0.25 | 52.50 +/- 0.34 | 55.51 +/- 0.30 | 58.44 +/- 0.50 |

PVP: polyvinyl pyrrolidone, PVA: polyvinyl alcohol and HPMC: hydroxypropyl cellulose methyl

3.4 Measurement of Dissolution Efficient of Microneedle Arrays

Sample solution were carried out in 50ml of cylindrical tube containing 40ml of phosphate buffer pH 5.4 -7.2 ranges. One of one these sample were incubated at 37 ºC in Labquake tube shaker, at pre-determined time intervals, 2 ml of sample was taken out and replaced with 2ml of phosphate buffer solution maintained at same temperature, samples; (i) Carboxymethyl cellulose (CMC); (ii) Polyvinyl pyrrolidone (PVP); (iii) CMC/PVP at 60:40 dry weight ratio; (iv) PVP/PVA 20:10 at dry weight ratio; (v) CMC/dextran at 50/50 dry weight ratio; (vi) PVP/HPMC at 60:40 dry weight ratio. Microneedles from all the seven geometric polymers were fabricated and sample successfully dissolve in particular solvent for specific time and 5.4-7.2 pH buffer solution and cumulative percentage dissolution was studied. PVP/PVA 20:10 a dried weight ratio affectively dissolve at 10 minutes of stirring (Fig. 6).
4. DISCUSSION

SEM analysed 250um base thickness with 1mm in height of microneedles, for effective delivery of drug without crossing pain sensors beneath skin structure. The studied by Su Yanping et al., drug adhesive patch for transdermal delivery of drug. It was concluded formulation which prepared 3.72% and 10% azone showed greatest potential and increased the flux, moreover sustained release achieved but microneedles can be better choice for the transdermal drug delivery[1]. 

Differential Scanning Calorimetry (DSC) analysed the morphological structure of microneedles arrays, it was obtained PVP/PVA blends microneedles melting point at 45.5°C and HPMC/PVP blends microneedles were at 140.5°C with delta Cp of 3.12J(g.K). Drug delivery through microneedles attached in transdermal drug delivery system, it is important to dissolve microneedles within body temperature and achieved drug blood plasma concentration. Comparitively Pamompathomkul B et al., studied on combined various types of microneedles permeation enhancer, this studied revealed biodegradable microneedles were greatest realized using in electrochemical anodization and delivery of drug on the top of the skin[4]. In addition, it was also concluded, their are various microneedles permeation enhancer aval with significant results, but their compared results showed dissolvable microneedles tip were significant in delivery of drug under skin without using any permeation enhancer[4]. However dissolution efficient were performed under cylindrical tube containing phosphate buffer pH 5.4 range about 40ml in quantity. About 10gm of sample were treated and these were incubated at 37°C in Labquake tube shaker at pre-determined time intervals for 10 minutes. After time intervals 2ml of samples taken out and determined the dissolution efficient in 10 minutes treated in 5.4 pH solvent using TEM. 

Transdermal delivery system for the prevention of postoperative nausea and vomiting studied by Apfel et al., the aim of their study was to explore the efficacy and tolerability of TDS in the prevention of PONV. In addition, their studied concluded TDDS were showed 68.00 +/- 24% dissolution efficiency in 30 minutes under 5.4pH phosphate solution. Transdermal drug delivery comes with the prominent drug delivery system in place of conventional system in significant rate and minimal side effect[13].

5. CONCLUSION

This studied examined the formulation and use of the novel natural and biodegradable polymer microneedles (MN’s) patch to transdermal drug delivery system. The miconeedle were easily prepared and fabricated, and can be easily inserted into the artificial skin of polymer thin layer with thumb pressure and dissolved in the medium of phosphate buffer 5.3 pH within 10 minutes. Thses findings suggest that using natural polymeric microneedle arrays may facilitate the drug delivery through transdermal patch, more efficiently and in controlled release manner in future.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not
intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Su, Yanping, et al. "Formulation and Pharmacokinetic Evaluation of a Drug-in-Adhesive Patch for Transdermal Delivery of Koumine." American Association of Pharmaceutical Scientists PharmSciTech. 2020;21(8):1-11.
2. Li QY, Jia Nan Z, Bo Zhi C, Qi Lei W, Xin Dong G. A solid polymer microneedle patch pretreatment enhances the permeation of drug molecules into the skin. RSC Advances. 2017;7(25):15408-15415.
3. Vinayakumar KB, Prachit GK, Nayak MM, et al. A hollow stainless steel microneedle array to deliver insulin to a diabetic rat. Journal of Micromechanics and Microengineering. 2016;26(6):065013.
4. Pamornpathomkul B, Wongkajornsilp A, Laiwattanapaisal W, Rojanarata T, Opanasopit P, Ngawhirunpat T. A combined approach of hollow microneedles and nanocarriers for skin immunization with plasmid DNA encoding ovalbumin. International Journal of Nanomedicine. 2017;12:885-898.
5. Li CG, Lee CY, Lee K, Jung H. An optimized hollow microneedle for minimally invasive blood extraction. Biomedical Microdevices. 2012;15(1):17-25.
6. Rodgers AM, Courtenay AJ, Donnelly RF. Dissolving microneedles for intradermal vaccination: manufacture, formulation, and stakeholder considerations. Expert Opinion on Drug Delivery. 2018;15(11):1039-1043.
7. Zhu J, Shen QI, Ying C, et al. Characterization of out-of-plane cone metal microneedles and the function of transdermal delivery. Microsystems Technologies. 2012;19(4):617-621.
8. Mulcahy A, Ye SR, Morrissey A. Process optimization and characterization of silicon microneedles fabricated by wet etch technology. Microelectronics Journal-Elsevier. 2005;36(7):650-656.
9. Pradeep Narayanan S, Raghavan S. Solid silicon microneedles for drug delivery applications. The International Journal of Advanced Manufacturing Technology-Springer. 2016;93(1-4):407-422.
10. Yan XX, Jing-Quan L, Shui-Dong J, et al. Fabrication and testing analysis of tapered silicon microneedles for drug delivery applications. Microelectronic Engineering Journal-Elsevier. 2013;111:33-38.
11. Izumi H, Aoyagi S. Novel fabrication method for long silicon microneedles with three-dimensional sharp tips and complicated shank shapes by isotropic dry etching. IEEJ Transactions on Electrical and Electronic Engineering. 2017;12(3):328-334.
12. Vinayakumar KB, Hegde GM, Nayak MM, et al. Fabrication and characterization of gold coated hollow silicon microneedle array for drug delivery. Microelectronic Engineering Journal-Elsevier. 2014;128:12-18.
13. Held J, Gaspar J, Ruther P, et al. Design of experiment characterization of microneedle fabrication processes based on dry silicon etching. Journal of Micromechanics and Microengineering. 2017;20(2):025024.
14. Chen B, Wei J, Tay FEH, et al. Silicon microneedle array with biodegradable tips for transdermal drug delivery. Microsystems Technologies-Springer. 2018;14(7):1015-1019.
15. Ashraf MW, Tayyaba S, Nisar A, et al. Design, fabrication and analysis of silicon hollow microneedles for transdermal drug delivery system for treatment of
hemodynamic dysfunctions. Cardiovascular Engineering and Technology- Springer. 2019;10(3):91-108. 16. Tahir, Muhammad Azam, Mohamed Ehab Ali, and Alf Lamprecht. "Nanoparticle formulations as recrystallization inhibitors in transdermal patches." International Journal of Pharmaceutics. 2020;575:118886.

17. Bhalerao, Rasika A., Mangesh R. Bhalekar, and Mrinalini C. Damle. Formulation and Evaluation Transdermal Patch of Hesperidin. Journal of Drug Delivery and Therapeutics. 2019;9(4):311-317.

18. Apfel, Christian C., Kun Zhang, Elizabeth George, Serena Shi, Leena Jalota, Cyrill Hornuss, Katherine E. Fero et al. "Transdermal scopolamine for the prevention of postoperative nausea and vomiting: a systematic review and meta-analysis." Clinical therapeutics. 2019;32(12):1987-2002.

19. Sun L, Cun D, Yuan B, Cui H, Xi H, Mu L, Chen Y, Liu C, Wang Z, Fang L. Formulation and in vitro/in vivo correlation of a drug-in-adhesive transdermal patch containing azasetron. Journal of Pharmaceutical sciences. 2018;101(12):4540-4548.

20. Nair SS. Transdermal patches fabricated from hyaluronic acid for the enhanced skin penetration of therapeutic entities. Journal of Drug Delivery and Therapeutics. 2019;9(1):252-256.

21. Jiang T, Xu G, Chen G, Zheng Y, He B, Gu Z. Progress in transdermal drug delivery systems for cancer therapy. Journal of Nanoparticle Research-Springer. 2020;1-15.

22. Jana BA, Wadhwani AD. Microneedle—Future prospect for efficient drug delivery in diabetes management. Indian journal of pharmacology. 2019;51(1):4.

23. Arsod NA, Amale PN, Borkar SS. Microneedle, An Innovative Approach to Transdermal Drug Delivery. Research Journal of Pharmacy and Technology. 2019;12(3):1425-1431

24. Babaie, S., Bakhshayesh, A. R. D., Ha, J. W., Hamishehkar, H., & Kim, K. H. Invasome: A Novel Nanocarrier for Transdermal Drug Delivery. Nanomaterials. 2020;10(2):341.

25. Ahmad N, Ahmad R, Al-Qudaihi A, Alaseel SE, Fita IZ, Khalid MS, Bolla SR. A novel self-nanoemulsifying drug delivery system for curcumin used in the treatment of wound healing and inflammation. 3 Biotech-Springer. 2019;9(10):360.

26. Teaima, Mahmoud H, et al. Formulation and evaluation of niosomal vesicles containing ondansetron HCL for transmucosal nasal drug delivery. Drug Development and Industrial Pharmacy. 2020;46(5):751-761.

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