Advanced Drug Delivery Reviews
Volume 173, June 2021, Pages 60-69

3D printing as a transformative tool for microneedle systems: Recent advances, manufacturing considerations and market potential

Author links open overlay panelSophia N. Economidou [a], Dennis Douroumis [b]

[a] Medway School of Pharmacy, University of Kent, Medway Campus, Central Avenue, Chatham Maritime, Chatham, Kent ME4 4TB, United Kingdom

[b] CIPER Centre for Innovation and Process Engineering Research, Kent ME4 4TB, UK

Received 25 October 2020, Revised 29 January 2021, Accepted 8 March 2021, Available online 26 March 2021, Version of Record 1 April 2021.

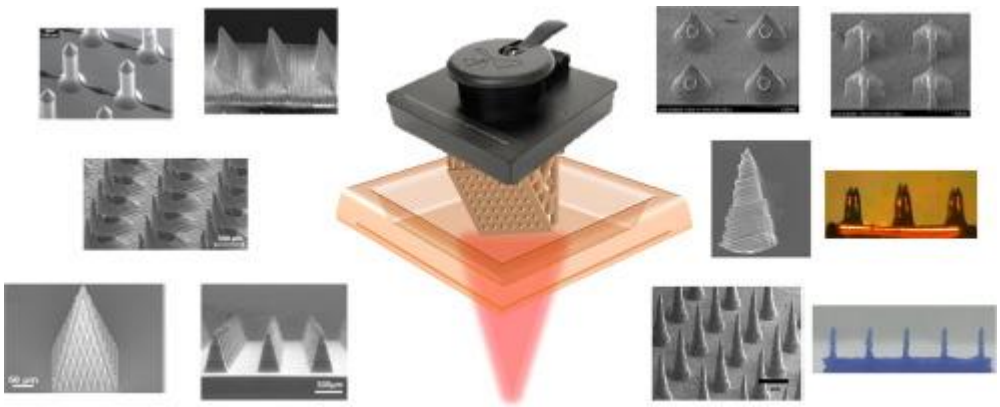
https://doi.org/10.1016/j.addr.2021.03.007Get rights and content

Abstract

The present review aims at identifying the key progress points that have been made on the use of 3D printing to manufacture microneedles in the past 3 years. The advances in the field of photopolymerization and extrusion-based 3D printing are outlined. The study revealed that the printing resolution and the material properties are the two critical parameters that have the most

influential effect on the outcome of every microneedle printing endeavour. Finally, the authors attempt to estimate the impact of 3D printing on the transdermal drug delivery market.

Graphical abstract



1. Download : Download high-res image (176KB)
2. Download : Download full-size image

Introduction

Very few newly introduced technologies have had such a universally transformative impact as 3D printing. Since its launch, 3D printing has revolutionised numerous fields, with industries abandoning lengthy, labor intensive processes in favour of rapid additive manufacturing for prototyping and production of functional parts. In the biomedical field, the use of 3D printing has already had a significant effect, with numerous products currently available in the market [1] and diverse research output, including hard tissue restorations [2], [3], [4], models for surgical preparation and educational purposes [5], [6] and tissue engineering [7], [8], [9]. In the area of pharmaceutics, only one 3D printed drug, *Spritam*, a tablet used for the treatment of epileptic seizures, has gained FDA approval [10]. Estimations of a booming market for 3D printed pharmaceuticals of up to 522$ million by 2030 [11] have ignited vast interest in these products with vivid research being conducted on the applicability of different 3D printing technologies on the development of tablets and drug delivery devices [12], [13]. Among the different drug delivery strategies, one that can be profoundly benefited by the adoption of advanced additive manufacturing techniques is the transdermal route. Transdermal Drug Delivery (TDD) has notable advantages over injection-

mediated and oral administration strategies since it is associated with potentially higher bioavailability [14], it is painless and can be self-administered [15]. Its fundamental limitation, the high impermeability of the skin, was circumvented by the introduction of microneedles, which are sharp, microsized protrusions that disrupt the skin barrier to reach the dermal microcirculation. Microneedles have permitted the delivery of macromolecules, proteins, DNA, vaccines through solid (poke-and-patch), solid coated, hollow and dissolvable systems [16]. However, despite the huge scientific interest microneedles have attracted [17], it is noteworthy that there is only a small number of products in the market, mainly for cosmetic purposes [18].

There are numerous challenges that hamper the commercialization of a broader range of microneedle products, pertaining to clinical, regulatory and technical aspects [19], [20], [21]. Important technical limitations arise by the manufacturing processes typically used for the development of microneedles, mainly micromoulding, micromachining, etching and lithography, solely or combinatorially [22]. While having been extensively used in research for the development of microneedles, they pose restrictions in terms of scalability, customizability or financial viability. Injection moulding processes for instance, due to high initial tooling and equipment costs, can only be profitable for production lines that yield large unit numbers [23]. Moreover, the need for mould fabrication or procurement introduces additional costs, which is particularly problematic in the research and development stage, wherein the tailoring of prototypes for studying and optimising of microneedle geometrical parameters (i.e. shape, length, width, tip diameter, interspace, aspect ratio) is required [24]. Other typical microfabrication methods in the range of micromachining, etching and lithography are often labor and time intensive, complex, multistep and require scientific expertise and expensive equipment [25]. Such processes are often difficult to be integrated in production lines in an economical and time-effective fashion. Replacing such methods with advanced additive manufacturing technologies can provide fast, reliable and cost-effective microneedle fabrication solutions.

The versatility, simplicity, high reproducibility and accuracy in the microscale associated by default with 3D printing have encouraged

vigorous research on its applicability on the fabrication of transdermal microneedle systems. The progress in the field until 2017 was recorded in a previous systematic review [26]. Since then, a bloom in the field has been observed with interesting new directions. Here, we discuss the state-of-the-art developments and we attempt to highlight the crucial manufacturing considerations introduced by the use of additive manufacturing technologies. We also outline the major potential benefits of adopting 3D printing for transdermal microneedle systems, in the aim to increase their accessibility and applicability in clinical practice.

Section snippets

Recent progress on 3D printed transdermal drug delivery systems

Encompassing a range of technologies, 3D printing allows the processing of various types of materials (e.g. polymeric, metallic, ceramic) by inducing the appropriate physicochemical processes. 3D printing technologies share the commonality of building a physical object through the sequential fabrication of bonded layers, that takes place into a single piece of equipment, the 3D printer. Various technologies have shown promising results, both as a direct microneedle manufacturing method (direct

Key technical considerations for microneedle 3D printing

The review of the current trends in the field of 3D printed systems for microneedle-mediated drug delivery reveals that, albeit seemingly abundant, the choices stemming from the variety of 3D printing technologies and respective materials suffer limitations, posed by the requirements of the target application. The selection of the optimal printing technology and material combination is the cornerstone of the prototyping stage and can determine the outcome of the endeavour. For microneedles, two

Regulatory framework

Microneedles that are used in the diagnosis, treatment, prevention of a disease or affect body function in any way, are viewed by regulatory bodies as medical devices [21]. In 2017, the “Regulatory Considerations for Microneedling Devices” was issued by the FDA compiling a set of guidelines on manufacturing, evaluation, testing and quality control [20]. The application of 3D printing for microneedle manufacturing introduced new challenges in the regulatory perspective and, following the

3D printing as a potential changer of the transdermal drug delivery market

Regardless of their advantages and the extensive scientific interest they have attracted, the pharmaceutical industry is still reluctant to invest in the introduction of new microneedle products. Currently, there are only 13 commercially available microneedle products for cosmetic purposes, drug and vaccine delivery [18], [21]. While the market for microneedle products is anticipated to expand at a Compound Annual Growth Rate (CAGR) of 7.1% [84], industries show a tendency to combine

Conclusions

The present review describes the progress in the field of 3D printed transdermal drug delivery systems the past 3 years. We aimed at elucidating current research directions, identifying key challenges and assessing market prospects. The advances in the field show that there has been an increasing research interest on the applicability of 3D printing for microneedle manufacturing. The variety of direct and indirect approaches and the plethora of delivered molecules tested as reported in this

References (88)

- C. Wang
  3D printing of bone tissue engineering scaffolds
  Bioact. Mater.
  (2020)
- M. Hassan *et al.*
  3D printing of biopolymer nanocomposites for tissue engineering: Nanomaterials, processing and structure-function relation
  Eur. Polym. J.
  (2019)

- M. Mao
  The emerging frontiers and applications of high-resolution 3D printing
  Micromachines
  (2017)
- L.C. Ng *et al.*
  Transdermal drug delivery systems in diabetes management: A review
  Asian J. Pharm. Sci.
  (2020)
- J. Yang *et al.*
  Recent advances of microneedles for biomedical applications: drug delivery and beyond
  Acta Pharm. Sin. B
  (2019)
- S.N. Economidou *et al.*
  3D printing applications for transdermal drug delivery
  Int. J. Pharm.
  (2018)
- C.P.P. Pere
  3D printed microneedles for insulin skin delivery
  Int. J. Pharm.
  (2018)
- I. Xenikakis
  Fabrication and finite element analysis of stereolithographic 3D printed microneedles for transdermal delivery of model dyes across human skin in vitro
  Eur. J. Pharm. Sci.
  (2019)
- N. El-Sayed *et al.*
  Customized fast-separable microneedles prepared with the aid of 3D printing for nanoparticle delivery
  Eur. J. Pharm. Biopharm.
  (2020)
- C.L. Caudill *et al.*
  Spatially controlled coating of continuous liquid interface production microneedles for transdermal protein delivery
  J. Control. Release
  (2018)
- M. Wu
  Assisted 3D printing of microneedle patches for minimally invasive glucose control in diabetes
  Mater. Sci. Eng. C

(2020)
- C. Culmone *et al.*
  Additive manufacturing of medical instruments: A state-of-the-art review
  Addit. Manuf.
  (2019)
- D. Shidid *et al.*
  Just-in-time design and additive manufacture of patient-specific medical implants
  Phys. Procedia
  (2016)
- C. Liaw *et al.*
  Current and emerging applications of 3D printing in medicine
  Biofabrication
  (2017)
- R.K. Chen, Y. an Jin, J. Wensman, A. Shih, Additive manufacturing of custom orthoses and prostheses-A review, Additive...
- D. Khorsandi
  3D and 4D printing in dentistry and maxillofacial surgery: Printing techniques, materials, and applications
  Acta Biomater. (xxxx)
  (2020)
- Q. Pan
  Investigation of bone reconstruction using an attenuated immunogenicity xenogenic composite scaffold fabricated by 3D printing
  Bio-Design Manuf.
  (2020)
- P.A. Anderson, 3D printing for education and surgical planning in orthopedic surgery, in 3D Printing in Orthopaedic...
- D.H. Ballard *et al.*
  Medical 3D printing cost-savings in orthopedic and maxillofacial surgery: cost analysis of operating room time saved with 3D printed anatomic models and surgical guides
  Acad. Radiol.
  (2020)
- D. Nesic *et al.*
  Could 3D printing be the future for oral soft tissue regeneration?
  Bioprinting
  (2020)

- L.K. Prasad *et al.*
  3D Printing technologies for drug delivery: a review
  Drug Dev. Ind. Pharm.
  (2015)
- P. Jaiswal, M. Srivastava, 3D Printed Drugs Market by Spritam (U.S. and Rest of World) and Other Drugs Potential Market...
- S.J. Trenfield
  Shaping the future: recent advances of 3D printing in drug delivery and healthcare
  Expert Opinion on Drug Delivery
  (2019)
- E. Larraneta *et al.*
  Microneedles: A new frontier in nanomedicine delivery
  Pharm. Res.
  (2016)
- A.J. Guillot *et al.*
  Microneedle-based delivery: An overview of current applications and trends
  Pharmaceutics
  (2020)
- J. Halder *et al.*
  Microneedle array: applications, recent advances, and clinical pertinence in transdermal drug delivery
  J. Pharm. Innov.
  (2020)
- R.E.M. Lutton *et al.*
  Microneedle characterisation: the need for universal acceptance criteria and GMP specifications when moving towards commercialisation
  Drug Deliv. Transl. Res.
  (2015)
- FDA, Regulatory Considerations for Microneedling Devices FDA-2017-D-4792, (301) (2017),...
- K.J. Lee, S.S. Jeong, D.H. Roh, D.Y. Kim, H.K. Choi, E.H. Lee. A practical guide to the development of microneedle...
- E. Larrañeta, R.E.M. Lutton, A.D. Woolfson, R.F. Donnelly, Microneedle arrays as transdermal and intradermal drug...
- R. Karania *et al.*
  Low volume plastics manufacturing strategies
  J. Mech. Des. Trans. ASME
  (2007)

- K.J. Krieger *et al.*
  Simple and customizable method for fabrication of high-aspect ratio microneedle molds using low-cost 3D printing
  Microsyst. Nanoeng.
  (2019)
- B. Liu
  Rapid fabrication of microneedles using magnetorheological drawing lithography acta biomaterialia rapid fabrication of microneedles using magnetorheological drawing lithography
  Acta Biomater.
  (August 2018)
- C. Schmidleithner, D.M. Kalaskar, Stereolithography, in IntechOpen, (2018),...
- Z. Faraji Rad, et al., High-fidelity replication of thermoplastic microneedles with open microfluidic channels,...
- C. Plamadeala
  Bio-inspired microneedle design for efficient drug/vaccine coating
  Biomed. Microdevices
  (2020)
- A.S. Cordeiro, et al., Two-photon polymerisation 3D printing of microneedle array templates with versatile designs:...
- A. Aksit
  In-vitro perforation of the round window membrane via direct 3- D printed microneedles
  Biomed. Microdevices
  (2019)
- B. Szeto
  Novel 3D-printed hollow microneedles facilitate safe, reliable, and informative sampling of perilymph from guinea pigs
  Hear. Res.
  (2021)
- K. Moussi, A. Bukhamsin, T. Hidalgo, J. Kosel, Biocompatible 3D printed microneedles for transdermal , intradermal ,...
- M.A. Lopez-Ramirez
  Built-in active microneedle patch with enhanced autonomous drug delivery
  Adv. Mater.
  (2020)
- R.I. Amer *et al.*
  Characterization and pharmacological evaluation of anti-cellulite herbal product(s) encapsulated in 3D-fabricated polymeric microneedles

Sci. Rep.
(2020)
- A. Kundu, T. Ausaf, S. Rajaraman, 3D printing, ink casting and micromachined lamination (3D PICL μ M): a makerspace...
- S.N. Economidou, et al., 3D printed microneedle patches using stereolithography (SLA) for intradermal insulin delivery,...