IOP Conf. Series: Materials Science and Engineering **334** (2018) 012046 doi:10.1088/1757-899X/334/1/012046

Nanocrystal cellulose as drug excipient in transdermal patch for wound healing: an overview

S A Mohd Zuki[1], N Abd Rahman[1,2] and N F Abu Bakar[1]
[1] Faculty of Chemical Engineering, Universiti Teknologi MARA, 40450 Shah Alam, Selangor, Malaysia

E-mail: noraz695@salam.uitm.edu.my

Abstract. Wound must be carefully treated to avoid serious infection that needs costly treatment. Method to enhance the recovery of the wound is crucial to have effective wound treatment. One of the technologies in wound treatment is transdermal patch that has the benefits of being non-invasive, easy to handle and permits constant drug dosage. In order to obtain a good controlled drug release, drug excipient needs to be investigated. Recently, natural Nanocrystal Cellulose (NCC) which can be synthesized from animal, algae, microorganism or plant has been actively used in drug delivery system as excipient. The application of NCC is advantageous due to its large surface area, biodegradable, non-toxic and abundance source.

1. Introduction

Wound is a common infection that happens to human body and animal. It can occur due to mechanical, chemical or thermal injury [1]. The injury ranges from a simple skin damages or it can be dangerous damages which involves deep cut. Serious injury can penetrates deep into subcutaneous tissue and harm other structures such as tendons, muscles, vessels, nerves, parenchymal organs and bones [1]. Wound injury to critical patients such as diabetic patients, really need a good care and rapid healing rate to aid in their recovery. There are two basic principles in wound management which are; removing the impediments, and provide and maintain clean and conducive environment to heal the wound [2]. The wound has to be kept clean and the wound surface has to be insulated and protected [2].

One of the drug delivery system (DDS) for wound healing that has been used for long period of time is transdermal patch. In December 1979, the United States Food and Drug Administration has approved the first prescription patch which is scopolamine for motion sickness. The drug delivery technology for dermatology disorder has evolved from ointment and cream to the transdermal patch because of its advantages such as; it allows constant dosing which prevent the fluctuation of drug level and it is also non-invasive. Besides, it is a better alternative to be used instead of the drug delivery through the stomach which sometimes becomes problematic when there is a difficulty for the drug to be absorbed through the gastrointestinal track. The steps for transdermal permeation of drug begins

[2] To whom any correspondence should be addressed.

Content from this work may be used under the terms of the Creative Commons Attribution 3.0 licence. Any further distribution of this work must maintain attribution to the author(s) and the title of the work, journal citation and DOI.
Published under licence by IOP Publishing Ltd

with the sorption by stratum corneum, followed by the penetration of drug through viable epidermis and continued with the uptake of the drug in the dermal capillary layer.

There are four types of transdermal drug delivery system which are membrane permeation controlled, matrix diffusion-controlled, adhesive dispersion-controlled and microreservoir/microsealed dissolution controlled system. The transdermal patch is not only used for wound healing but also has been used in other treatments as shown in table 1.

Table 1. Literature review on transdermal patch.

Author	Treatment	Drug	Remarks
[3]	Wound	Ciprofloxacin (antibiotic)	-Electrospinning technique -A sustained and controlled drug release have been obtained
[4]	Wound	Vitamin B12, Curcumin and Diclofenac (anti-inflammatory, analgesic, antipyretic)	-Electrospinning technique -The resulted nanomembrane of the drug and excipient were stable -The vitamin B12 was nearly 100% -The curcumin release was up to 70% The Diclofenac release was 80%
[5]	Schizophrenia	Blonanserin (antipsychotic)	-Investigation on effect of permeation enhancer, fisopropyl myristate -The release rate of blonanserin increased with an increasing concentration of fisopropyl myristate
[6]	Pain killer	Methadone	-Film casting method -The problem of drug release onto skin has been solved by blending the methadone with the enhancer (Dimethylsulfoxide) -The permeation of the methadone was increase up to 70 %
[7]	Pain killer	Fentanyl	-Fentanyl containing geopolymer granules results in a better resistance to tampering
[8]	-	Eserine and pralidoxime chloride	-The patch resulted in a complete drug release after 72 hours - The transdermal patches were stable for 6 months at 40^0C/75% of Relative Humadity
[9]	Attention deficit/Hyperactivity Disorder (ADHD)	D-threo-methylphenidate (D-threo-MP)	-Solvent evaporation technique -Acrylic pressure sensitive adhesive used as excipient -No significant of enhancer on drug permeation -The best drug loading is resulting from 15% weight percentage of D-threo-MP
[10]	Muscle relaxant	Cyclobenzaprine	-Solvent evaporation technique -Excipient used is Cotran™ 9700 - Cotran™ 9700 give significant effect on drug release -The cumulative drug release decreasing after 7 days

From table 1, transdermal patch shows great potential to be studied as drug delivery technique and can be applied for wound healing treatment. The drug release of the antibacterial drug in the patch can be sustained and controlled. Usually, the transdermal patch consists of outer liner and matrix membrane formed by active material and excipient. Besides the active material, it is also important to study the drug excipient because it has its own role in delivering the drug into targeted cell, tissue or organ.

2. Drug Excipient

Typically, the highest content in a drug tablet, capsule, patch or liquid is not the active pharmaceutical ingredient (API) but the excipient. Excipient is an inactive material that is purposely included in formulation of drug. Usually it has been properly tested for safety and it is considered essential to include the excipient in drug formulation to improve the manufacturability and stabilization of the API. There are many type of drug excipients such as binder (povidones, polysaccharide), filler or diluent (calcium phosphate, lactose), disintegrant (sodium starch glycolate, crospovidones), lubricant (magnesium stearate, glycerides), glidant or anticaking agent (talc, colloidal silicon dioxide), colorant (titanium dioxide; food, drug and cosmetic (FD&C) colours), capsule shell (gelatin, hypromellose), coating agent (hypromellose, shellac), flavour and fragrance (peppermint, berry), release modifier (ethylcellulose, guar gum), pH modifier (citric acid and its salts, salts of phosphoric acid), wetting or solubilizing agent (sodium lauryl sulfate, polysorbates), antimicrobial preservative (glycerin, benzyl alcohol), chelating or complexing agent (ethylenediaminetetraacetic acid salts, cyclodextrins), antioxidant (ascorbic acid, butylated hydroxyanisole) and sweetening agent (sucrose, saccharin) [11].
Among the type of drug excipient that has been introduced before, polysaccharide was actively studied as an excipient in transdermal patch [12-16]). Starch, glycogen and dextrans are some of the example of polysaccharide used as an excipient and all of them are converted into energy in liver and muscles for a later use. Nowadays, there are numerous researches regarding cellulose (natural polysaccharide) as drug excipient which is discussed in next section.

3. Nanocrystal cellulose (NCC)

Nowadays, natural polysaccharide has become popular to be studied as an excipient in drug delivery system because of its properties such as highly safe, non-toxic, has abundant resources in nature, low cost in its processing, biodegradable, biocompatible, high water solubility and bioactivity [17-20]. There are many natural sources that supply polysaccharide i.e animal (chitosan, Chondroitin sulphate), plant (guar gam, pectin, cellulose, mannan), algae (alginate) and microorganism (dextran, pullulan) [21-23]. Besides, large number of reactive functional groups havehydroxyl, amino and carboxylic acid groups on their backbone which make the polysaccharide structure to be easily derived. This characteristic contribute to their structural and functional diversity [24]. From multi-functional group, it can be biochemically or chemically modified into many types of polysaccharide derivatives such as cellulose [25].

Rod-shaped cellulose with typical 10–100 nm in length and 1–100 nm in diameter is called nanocrystal cellulose (NCC) and it has potential to be investigated as drug excipient [26, 27]. There are many studies that have been done in drug delivery field using NCC as shown in table 2. NCC derived from plant has been actively studied in polymer reinforcement as a potentially new material [28]. Commonly, the plant fibre contains of cellulose (40–50%), hemicelluloses (20–30%) and lignin (10–18%). The advantages of NCC are due to its large surface area and excellent colloidal stability [29].

Table 2. Literature review on nanocrystal cellulose as drug excipient.

Author	NCC	Drug	Drug Delivery System	Remarks
[30]	Chitosan	Procaine	Transdermal	-Drug binding and release

	oligosaccharide	hydrochloride, imipramine hydrochloride	patch	are allied with the interaction nature and types that exist between the NCC and drug molecules
[31]	Carboxymethyl -β-cyclodextrin	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide, N-hydroxysuccinimide	Injection	-Drug binding resulting in stronger inhibition rate and enhanced cellular uptake through folate mediated internalization
[32]	Folic acid-conjugated NCC	Folic acid	Oral intake	-Cellular binding of the conjugate higher than non-targeted NCC
[33]	Chitosan	Doxorubicin hydrochloride, curcumin	Oral intake	-Stable microcapsules were formed after the five-layer deposition of NCC -The surface of microcapsules have the same morphologies as the thin film
[34]	Chitosan	Metformin	Injection	-The swelling of the formulated films were decrease in acidic, neutral and alkaline medium respectively - The formulated film showed potential applications as light emitting materials
[35]	Chitosan	Antofloxacin	Transdermal patch	-Drug release showed pH sensitivity - Drug release can be controlled by manipulating pH system and amount of drug encapsulated
[36]	Cotton wool	2-dimethylamino ethyl methacrylate	Transdermal patch	-Needle-like shape of NCC improve the transfection efficiencies and low cytotoxicities of drug binding
[37]	β-cyclodextrin	Polyvinyl alcohol (PVA)-styrylpyridinium	Transdermal patch	-FTIR spectra showed a successful binding between β-cyclodextrin and the drug -Average fiber diameter increased because of the swelling of nanofiber (interactions between hydroxy of PVA or β-cyclodextrin and aldehyde group)
[38]	Mucilage (Taro	Diltiazem	Transdermal	-Folding endurance and

	corms), hydroxypropyl methylcellulose	hydrochloride	patch	tensile strength of formulated patch increase as the mucilage concentration increase -The drug release controlled by addition of mucilage in formulation -Skin test shows free of potentially hazardous skin irritation
[39]	Pectin, gelatin	Testosterone	Transdermal patch	-Pectin shows important effect on rheological characteristic of formulated patch -The drug release controlled by the formulation of the patch matrix

Most of the results from previous researches showed that NCC give positive effects on the quality of the drug release. The drug release has been significantly affected by pH of solution and formulation ratio. Since it shows the potential in controlling the drug release, it will result in constant drug permeation into the targeted area. Hence, this shows that NCC is a promising drug carrier to be further studied.

4. Conclusion

In this overview, transdermal patch shows a great potential to be further studied as drug delivery system to deliver the active ingredient onto the targeted treatment area especially skin because it can give constant drug release and fulfill the patient compliance since it is a non-invasive treatment. It is easy for the patient to use the patch to treat the targeted area such as wound. Besides, other ingredient in the patch that gives important effect on drug release and permeation is the excipient. The excipient shows positive result on controlling the drug release. Nanocrystal cellulose (NCC), a type of polysaccharide extracted from natural source such as plant has been actively studied to be used as excipient and from the results, it shows that NCC has great potential to be used in improving the control of the drug release for transdermal patch application.

Acknowledgment

The authors would like to thank the financial support received from Research Management Institute of Universiti Teknologi MARA through Geran Inisiatif Penyeliaan (600-IRMI/GIP 5/3 (0015/2016)), Ministry of Higher Education, Malaysia, Faculty of Chemical Engineering, UiTM and Universiti Teknologi MARA, Malaysia.

References

[1] Mohil R "Classification of wounds" in *Principles and Practice of wound care* V. T. S. Sarabahi Eds. New Delhi, India Jaypee Brothers Medical Publishers 2012

[2] Dressings and More: Guidelines for Topical Wound ManagementDoughty D 2005 Dressings and More: Guidelines for Topical Wound Management *Nursing Clinics of North America* **40** 2 217-231

[3] In vivo wound healing performance of drug loaded electrospun composite nanofibers transdermal patchKataria K, Gupta A, Rath G, Mathur R B, and Dhakate S R 2014 In vivo wound healing performance of drug loaded electrospun composite nanofibers transdermal patch *International Journal of Pharmaceutics* **469** 1 102-110

[4] Hybrid electrospun chitosan-phospholipids nanofibers for transdermal drug deliveryMendes A C, Gorzelanny C, Halter N, Schneider S W, and Chronakis I S 2016 Hybrid electrospun chitosan-phospholipids nanofibers for transdermal drug delivery *International Journal of Pharmaceutics* **510** 1 48-56

[5] Effect of isopropyl myristate on the viscoelasticity and drug release of a drug-in-adhesive transdermal patch containing blonanserinZhao C, Quan P, Liu C, Li Q, and Fang L 2016 Effect of isopropyl myristate on the viscoelasticity and drug release of a drug-in-adhesive transdermal patch containing blonanserin *Acta Pharmaceutica Sinica B* **6** 6 623-628

[6] Design, development and characterization of transdermal patch of methadoneMuñoz M D, Castán H, Ruiz M A, and Morales M E Design, development and characterization of transdermal patch of methadone *Journal of Drug Delivery Science and Technology*

[7] Development and evaluation of a tampering resistant transdermal fentanyl patchCai B, Engqvist H, and Bredenberg S 2015 Development and evaluation of a tampering resistant transdermal fentanyl patch *International Journal of Pharmaceutics* **488** 1–2 102-107

[8] Accelerated stability testing of a transdermal patch composed of eserine and pralidoxime chloride for prophylaxis against (±)-anatoxin A poisoningBanerjee S, Chattopadhyay P, Ghosh A, Bhattacharya S S, Kundu A, and Veer V 2014 Accelerated stability testing of a transdermal patch composed of eserine and pralidoxime chloride for prophylaxis against (±)-anatoxin A poisoning *Journal of Food and Drug Analysis* **22** 2 264-270

[9] Transdermal patches for D-threo-methylphenidate (free base): Formulation aspects and in vivo pharmacokineticsZhang C, Luo H, Lin G, Zhu Z, Zhang F, Zhang J, Wu Y, Luo J, and Wang H 2016 Transdermal patches for D-threo-methylphenidate (free base): Formulation aspects and in vivo pharmacokinetics *Journal of Drug Delivery Science and Technology* **35** 50-57

[10] Effect of backing films on the transdermal delivery of cyclobenzaprine patchLv S, Quan P, Liu X, and Fang L 2016 Effect of backing films on the transdermal delivery of cyclobenzaprine patch *Asian Journal of Pharmaceutical Sciences* **11** 6 780-783

[11] Jyllian K. (2014, 3 February 2014) Eyes on Excipients : Inactive but Essential *Chemical & Engineering News*. 9-11.

[12] Effectiveness of an Oxidized Cellulose Patch Hemostatic Agent in Thyroid Surgery: A Prospective, Randomized, Controlled StudyAmit M, Binenbaum Y, Cohen J T, and Gil Z 2013 Effectiveness of an Oxidized Cellulose Patch Hemostatic Agent in Thyroid Surgery: A Prospective, Randomized, Controlled Study *Journal of the American College of Surgeons* **217** 2 221-225

[13] Fibrin Sealant Patch (TachoSil) vs Oxidized Regenerated Cellulose Patch (Surgicel Original) for the Secondary Treatment of Local Bleeding in Patients Undergoing Hepatic Resection: A Randomized Controlled TrialGenyk Y, Kato T, Pomposelli J J, Wright Jr J K, Sher L S, Tetens V, and Chapman W C 2016 Fibrin Sealant Patch (TachoSil) vs Oxidized Regenerated Cellulose Patch (Surgicel Original) for the Secondary Treatment of Local Bleeding in Patients Undergoing Hepatic Resection: A Randomized Controlled Trial *Journal of the American College of Surgeons* **222** 3 261-268

[14] Cellulose-pectin composite hydrogels: Intermolecular interactions and material properties depend on order of assemblyLopez-Sanchez P, Martinez-Sanz M, Bonilla M R, Wang D, Gilbert E P, Stokes J R, and Gidley M J 2017 Cellulose-pectin composite hydrogels: Intermolecular interactions and material properties depend on order of assembly *Carbohydrate Polymers* **162** 71-81

[15] Study of the keratin-based therapeutic dermal patches for the delivery of bioactive molecules for wound treatmentNayak K K and Gupta P 2017 Study of the keratin-based therapeutic dermal

patches for the delivery of bioactive molecules for wound treatment *Materials Science and Engineering: C* **77** 1088-1097

[16] Preparation, characterization, and in vitro diffusion study of nonwoven electrospun nanofiber of curcumin-loaded cellulose acetate phthalate polymerRavikumar R, Ganesh M, Ubaidulla U, Young Choi E, and Tae Jang H 2017 Preparation, characterization, and in vitro diffusion study of nonwoven electrospun nanofiber of curcumin-loaded cellulose acetate phthalate polymer *Saudi Pharmaceutical Journal*

[17] Synthesis of water dispersed nanoparticles from different polysaccharides and their application in drug releaseAyadi F, Bayer I S, Marras S, and Athanassiou A 2016 Synthesis of water dispersed nanoparticles from different polysaccharides and their application in drug release *Carbohydrate Polymers* **136** 282-291

[18] Polysaccharide based nanogels in the drug delivery system: Application as the carrier of pharmaceutical agentsDebele T A, Mekuria S L, and Tsai H-C 2016 Polysaccharide based nanogels in the drug delivery system: Application as the carrier of pharmaceutical agents *Materials Science and Engineering: C* **68** 964-981

[19] Millifluidic synthesis of amorphous drug-polysaccharide nanoparticle complex with tunable size intended for supersaturating drug delivery applicationsTran T-T, Nguyen M-H, Tan Y Z, Chew J W, Khan S A, and Hadinoto K 2017 Millifluidic synthesis of amorphous drug-polysaccharide nanoparticle complex with tunable size intended for supersaturating drug delivery applications *European Journal of Pharmaceutics and Biopharmaceutics* **112** 196-203

[20] Preparation and application of micro/nanoparticles based on natural polysaccharidesYang J, Han S, Zheng H, Dong H, and Liu J 2015 Preparation and application of micro/nanoparticles based on natural polysaccharides *Carbohydrate Polymers* **123** 53-66

[21] Polysaccharide biological response modifiersLeung M Y K, Liu C, Koon J C M, and Fung K P 2006 Polysaccharide biological response modifiers *Immunology Letters* **105** 2 101-114

[22] Polysaccharide-based nucleic acid nanoformulationsRaemdonck K, Martens T F, Braeckmans K, Demeester J, and De Smedt S C 2013 Polysaccharide-based nucleic acid nanoformulations *Advanced Drug Delivery Reviews* **65** 9 1123-1147

[23] Polysaccharides in colon-specific drug deliverySinha V R and Kumria R 2001 Polysaccharides in colon-specific drug delivery *International Journal of Pharmaceutics* **224** 1–2 19-38

[24] Nurunnabi M, Revuri V, Huh K M, and Lee Y-k "Chapter 14 - Polysaccharide based nano/microformulation: an effective and versatile oral drug delivery system A2 - Andronescu, Ecaterina" in *Nanostructures for Oral Medicine* A. M. Grumezescu Eds. Elsevier 2017 409-433

[25] Heterogeneous 'organoclick' derivatization of polysaccharidesHafrén J, Zou W, and Córdova A 2006 Heterogeneous 'organoclick' derivatization of polysaccharides *Macromolecular Rapid Communications* Article **27** 16 1362-1366

[26] Cellulose nanocrystals: Chemistry, self-assembly, and applicationsHabibi Y, Lucia L A, and Rojas O J 2010 Cellulose nanocrystals: Chemistry, self-assembly, and applications *Chemical Reviews* Article **110** 6 3479-3500

[27] Chemistry and applications of nanocrystalline cellulose and its derivatives: A nanotechnology perspectivePeng B L, Dhar N, Liu H L, and Tam K C 2011 Chemistry and applications of nanocrystalline cellulose and its derivatives: A nanotechnology perspective *Canadian Journal of Chemical Engineering* Review **89** 5 1191-1206

[28] Cellulose nanocrystals from acacia bark–Influence of solvent extractionTaflick T, Schwendler L A, Rosa S M L, Bica C I D, and Nachtigall S M B 2017 Cellulose nanocrystals from acacia bark–Influence of solvent extraction *International Journal of Biological Macromolecules* **101** 553-561

[29] Recent advances in the application of cellulose nanocrystalsGrishkewich N, Mohammed N, Tang J, and Tam K C 2017 Recent advances in the application of cellulose nanocrystals *Current Opinion in Colloid & Interface Science* **29** 32-45
[30] Comparative release studies of two cationic model drugs from different cellulose nanocrystal derivativesAkhlaghi S P, Tiong D, Berry R M, and Tam K C 2014 Comparative release studies of two cationic model drugs from different cellulose nanocrystal derivatives *European Journal of Pharmaceutics and Biopharmaceutics* **88** 1 207-215
[31] Carboxymethyl-β-cyclodextrin conjugated nanoparticles facilitate therapy for folate receptor-positive tumor with the mediation of folic acidSu C, Li H, Shi Y, Wang G, Liu L, Zhao L, and Su R 2014 Carboxymethyl-β-cyclodextrin conjugated nanoparticles facilitate therapy for folate receptor-positive tumor with the mediation of folic acid *International Journal of Pharmaceutics* **474** 1–2 202-211
[32] Synthesis and Cellular Uptake of Folic Acid-Conjugated Cellulose Nanocrystals for Cancer TargetingDong S, Cho H J, Lee Y W, and Roman M 2014 Synthesis and Cellular Uptake of Folic Acid-Conjugated Cellulose Nanocrystals for Cancer Targeting *Biomacromolecules* **15** 5 1560-1567
[33] Layer-by-Layer Assembled Thin Films and Microcapsules of Nanocrystalline Cellulose for Hydrophobic Drug DeliveryMohanta V, Madras G, and Patil S 2014 Layer-by-Layer Assembled Thin Films and Microcapsules of Nanocrystalline Cellulose for Hydrophobic Drug Delivery *ACS Applied Materials & Interfaces* **6** 22 20093-20101
[34] Controlled release of metformin from chitosan–based nanocomposite films containing mesoporous MCM-41 nanoparticles as novel drug delivery systemsShariatinia Z and Zahraee Z 2017 Controlled release of metformin from chitosan–based nanocomposite films containing mesoporous MCM-41 nanoparticles as novel drug delivery systems *Journal of Colloid and Interface Science* Article **501** 60-76
[35] Preparation of a novel chitosan-microcapsules/starch blend film and the study of its drug-release mechanismHuo W, Xie G, Zhang W, Wang W, Shan J, Liu H, and Zhou X 2016 Preparation of a novel chitosan-microcapsules/starch blend film and the study of its drug-release mechanism *International Journal of Biological Macromolecules* **87** 114-122
[36] Redox-Responsive Polycation-Functionalized Cotton Cellulose Nanocrystals for Effective Cancer TreatmentHu H, Yuan W, Liu F-S, Cheng G, Xu F-J, and Ma J 2015 Redox-Responsive Polycation-Functionalized Cotton Cellulose Nanocrystals for Effective Cancer Treatment *ACS Applied Materials & Interfaces* **7** 16 8942-8951
[37] Preparation and characterization of electrospun polyvinyl alcoholstyrylpyridinium/β-cyclodextrin composite nanofibers: Release behavior and potential use for wound dressingZhou J, Wang Q, Lu H, Zhang Q, Lv P, and Wei Q 2016 Preparation and characterization of electrospun polyvinyl alcoholstyrylpyridinium/β-cyclodextrin composite nanofibers: Release behavior and potential use for wound dressing *Fibers and Polymers* journal article **17** 11 1835-1841
[38] Taro corms mucilage/HPMC based transdermal patch: An efficient device for delivery of diltiazem hydrochlorideSarkar G, Saha N R, Roy I, Bhattacharyya A, Bose M, Mishra R, Rana D, Bhattacharjee D, and Chattopadhyay D 2014 Taro corms mucilage/HPMC based transdermal patch: An efficient device for delivery of diltiazem hydrochloride *International Journal of Biological Macromolecules* **66** 158-165
[39] Hydrogel blends with adjustable properties as patches for transdermal deliveryMazzitelli S, Pagano C, Giusepponi D, Nastruzzi C, and Perioli L 2013 Hydrogel blends with adjustable properties as patches for transdermal delivery *International Journal of Pharmaceutics* **454** 1 47-57