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Universitas Hasanuddin

Andi Dian Permana <andi.dian.permana@farmasi.unhas.ac.id>

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2 messages

Journal of Pharmaceutical Innovation <em@editorialmanager.com> Wed, Jun 23, 2021 at 3:40 PM
Reply-To: Journal of Pharmaceutical Innovation <jedjoseph.adel@springernature.com>
To: Andi Dian Permana <andi.dian.permana@farmasi.unhas.ac.id>

Dear Dr. Permana:

The PDF for your manuscript, "Dissolving microneedle formulation of ceftriaxone: Effect of polymer concentrations on characterisation and ex vivo permeation study" is ready for viewing.

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With kind regards,

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Journal of Pharmaceutical Innovation

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Journal of Pharmaceutical Innovation <em@editorialmanager.com> Wed, Jun 23, 2021 at 4:35 PM
Reply-To: Journal of Pharmaceutical Innovation <jedjoseph.adel@springernature.com>
To: Andi Dian Permana <andi.dian.permana@farmasi.unhas.ac.id>

[Quoted text hidden]

BUKTI REVIEW DARI REVIEWERS

Universitas Hasanuddin

Andi Dian Permana <andi.dian.permana@farmasi.unhas.ac.id>

Decision on your manuscript #JOPI-D-21-00295

1 message

Journal of Pharmaceutical Innovation <em@editorialmanager.com> Mon, Aug 30, 2021 at 10:10 AM
Reply-To: Journal of Pharmaceutical Innovation <jedjoseph.adel@springernature.com>
To: Andi Dian Permana <andi.dian.permana@farmasi.unhas.ac.id>

Dear Dr. Permana:

We have received the reports from our advisors on your manuscript, "Dissolving microneedle formulation of ceftriaxone: Effect of polymer concentrations on characterisation and ex vivo permeation study", which you submitted to Journal of Pharmaceutical Innovation.

Based on the advice received, your manuscript could be reconsidered for publication should you be prepared to incorporate major revisions.
When preparing your revised manuscript, you are asked to carefully consider the reviewer comments which are attached, and submit a list of responses to the comments.
Your list of responses should be uploaded as a file in addition to your revised manuscript.

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Robert A Lodder

Journal of Pharmaceutical Innovation

COMMENTS FOR THE AUTHOR:

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Reviewer #2: This study reveals the step by step preparation technique for ceftriaxone dissolving microneedle topical preparation. The flow of the experiments are well designed, but there are some drawbacks such as
1. Small number of the formulations which is 3 without using any experimental design or reducing criteria and without sharing the logic's of selecting only these three compositions.
2. The final designated use of the microneedle topical preparation in pneumonia treatment seems too far from its clinical feature.
3. The logics in selecting drug dosage at 15% (not in mg in each patch) are not available.

4. Stability studies have not been performed or even mentioned. No shelf life prediction is made.
5. The manufacturer or in-house designation of the mold (Mould) and the centrifuge tube are not available.
6. The conclusion regarding the percentage of PVA to PVP in reducing drug release is not an unknown and surprising finding because the hydrophilic nature of PVP is a an evident phenomenon.
7. It's not clear what the net effect of the dissolving microneedles is in only 10 minutes in providing effective permeation of drug to the derm layer, Compared to drug in polymer matrix with no microneedles?

Reviewer #3: Article entitled "Dissolving microneedle formulation of ceftriaxone: Effect of polymer concentrations on characterisation and ex vivo permeation study"
My observation on article as follow.
1. In abstract: Purpose is not meeting the title claim.
2. In Material & Methods : Instruments are missing please include in it.
3. The methodology applied for this study is acceptable.
4. Ceftriaxone belong to class 3 of Biopharmaceutics Classification System high aqueous solubility and low permeability. It is poorly absorbed through mucosal membranes, Authors tried to enhance permeability of Ceftriaxone by using PVP and PVA combination through rat skin.
5. One of the critical point in this study lacks stability studies data which is more important in characterization. A formulation of ceftriaxone contains more than 2.4% w/w water leads to degradation (Ceftriaxone is hygroscopic as well PVA). In this study authors employed water for dissolving PVP AND PVA and Ceftriaxone in different ratios. This needs to be answered in the MS.
6. The term "Research conducted by" is frequently used, which needs to be modified.
7. MS needs to be checked thoroughly for Language.
8. PVA and PVP combination of MNs stability at room temperature data is required as part of characterization.
9. Page 7 Line number 171 - Dissolving Time Test: The method is not clear? Did you applied 5G pressure? Or did you use 5G skin tissue? How many needles were used for study? In Reference 22 explains differently.

10. 2.10 Ex vivo Permeation Test: The method is not clear? Did you applied 5G pressure? Or did you use 5 gram skin tissue? How many needles /what quantity (G) are used for study? Reference 22 shows bit different explain clearly.
11. The skin size mm/cm and quantity or number of needle(s) applied on the skin needs to be mentioned clearly.
12. Please check all references

Reviewer #5: Run a spelling checker on the manuscript and make the necessary corrections (for example, "microneeldes." in the abstract should be "microneedles".)

Stability data should be included in the manuscript.

The number of formulations tested is small. No particular experimental design is described, and no rationale provided for selecting only these three compositions.

Why did the author's select the drug dosage that was used?

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Universitas Hasanuddin

Andi Dian Permana <andi.dian.permana@farmasi.unhas.ac.id>

Acknowledgement of Receipt of #JOPI-D-21-00295R1

1 message

Journal of Pharmaceutical Innovation <em@editorialmanager.com> Fri, Oct 1, 2021 at 6:24 PM
Reply-To: Journal of Pharmaceutical Innovation <jedjoseph.adel@springernature.com>
To: Andi Dian Permana <andi.dian.permana@farmasi.unhas.ac.id>

Dear Dr. Permana:

We acknowledge, with thanks, receipt of the revised version of your manuscript, "Dissolving microneedle formulation of ceftriaxone: Effect of polymer concentrations on characterisation and ex vivo permeation study", submitted to Journal of Pharmaceutical Innovation. The manuscript number is JOPI-D-21-00295R1.
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Journal of Pharmaceutical Innovation

Dissolving microneedle formulation of ceftriaxone: Effect of polymer concentrations on characterisation and ex vivo permeation study

--Manuscript Draft--

Manuscript Number:	JOPI-D-21-00295R1
Full Title:	Dissolving microneedle formulation of ceftriaxone: Effect of polymer concentrations on characterisation and ex vivo permeation study
Article Type:	Original Article
Keywords:	ceftriaxone; dissolving microneedle; polymer; skin permeation
Order of Authors:	Hamita Esa Putri
	Rifka Nurul Utami
	Aliyah Aliyah
	Elly Wahyudin
	Windy Winalda Oktaviani
	Mukarram Mudjahid
	Andi Dian Permana
Corresponding Author:	Andi Dian Permana Universitas Hasanuddin Fakultas Farmasi Makassar, INDONESIA
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Universitas Hasanuddin Fakultas Farmasi
Corresponding Author's Secondary Institution:	
First Author:	Hamita Esa Putri
First Author Secondary Information:	
Order of Authors Secondary Information:	
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Abstract:	Purpose:This study aimed to develop dissolving microneedle preparations containing ceftriaxone and evaluate the effect of polymer concentrations on characterisation and ex vivopermeation study. Methods:The microneedles were prepared using centrifugation method with different ratios of PVP40% and PVA15%, namely FB1 (50:50), FB2 (60:40), and FB3 (70:30). The microneedles were also prepared with various concentrations of ceftriaxone, namely 10% w/w, 15% w/w and 20% w/w.The microneedles were evaluated for their mechanical propertiesand ex vivopermeation profiles. Results:The results showed that the microneedles were in the form of sharp pyramidalwith size ranging between 712-800 mm.The concentration of ceftriaxone was found to affect the mechanical properties of the microneedles where formulations containing 20% w/w of ceftriaxone could not be produced. To achieve high drug loading, 15% w/w of ceftriaxone was selected in this study. Following the microneedle preparations, the formulation containing 15% w/w of ceftriaxone with FB3 polymer mixture exhibited the best mechanical properties with only 12.96 ± 0.56% height reduction after the compression with 30 N pressure. Moreover, this formulation was able to penetrate 4 layers of Parafilm®layers, indicating adequate insertion properties. Importantly, the microneedles were found to dissolve completely after 10 minutes on the full thickness rat skin. Thepermeation study showed that the greater the concentration of PVA, the slower the permeation of ceftriaxone from the microneedles. The highest drug permeation was obtained by containing 15% w/w of ceftriaxone with PVP40%:PVA15% with the ratio of 70:30, with the percentage of 99.86 ±

	7.6%. The stability studies showed that the microneedles were stable for a 1-month in two humidity levels, namely RH 43% and RH 86%. Conclusion:Variation of polymer concentration exhibited a significant effect on themechanical properties of microneedles. The permeation test showed that the greater the concentration of PVA, the slower the permeation of the active substance from dissolving microneedle. Further studies should be conducted to perform in vivo pharmacokinetic studies.

JOPI-D-21-00295

Dissolving microneedle formulation of ceftriaxone: Effect of polymer concentrations on characterisation and ex vivo permeation study

Reviewers' comments:

Reviewer #2: This study reveals the step by step preparation technique for ceftriaxone dissolving microneedle topical preparation. The flow of the experiments are well designed, but there are some drawbacks such as

Response to Reviewers

We are very thankful to the reviewers for taking the time to provide helpful comments for improvements to our manuscript. We have addressed each of the reviewers' comments in detail below.

1. Small number of the formulations which is 3 without using any experimental design or reducing criteria and without sharing the logic's of selecting only these three compositions.

Response to Reviewer

We thank the reviewer for the comments. As a result, we have explained that initially, different formulations were prepared to achieve maximum drug loading of ceftriaxone in the formulations. In this study, the blank formulations were mixed with three various concentrations of ceftriaxone, namely 10% w/w, 15% w/w and 20% w/w, resulting in nine different formulations, as shown in Table 2. In our preliminary study, to achieve the highest loading for the microneedles, three different concentrations (10% w/w, 15% w/w and 20% w/w) of ceftriaxone were used. The results showed that the use of 20% w/w of ceftriaxone resulted in very viscous solutions, leading to difficulty in the microneedle preparations. We have added these explanations in our revised manuscript, as well as the results obtained in the results and discussion section.

2. The final designated use of the microneedle topical preparation in pneumonia treatment seems too far from its clinical feature.

Response to Reviewer

We thank the reviewer for the comments. Indeed, our study seems too far from its clinical feature. However, the initial background behind the design of this study was to overcome the problems of ceftriaxone explained in the introduction in our manuscript. Ceftriaxone has good tolerability, but at higher doses or long-term administration, ceftriaxone may cause biliary pseudolithiasis and other quite dangerous side effects. Ceftriaxone is not readily absorbed by mucous membrane, resulting in poor absorption of this drug in the gastrointestinal tract. For that reason, ceftriaxone is not available in oral dosage form, and only given through intravenous or intramuscular injection. However, several drawbacks have been found in the administration of injection, such as patient compliance, problems surrounding needle phobia and the production of dangerous biological waste. Hence, it is essential to develop a delivery system formulation that has similar effectiveness as parenteral administration, without causing the unnecessary side effects of the injection. However, to prove its effectiveness, several studies are required. In vivo pharmacokinetic studies should further be carried out to investigate the plasma concentration of ceftriaxone following the administration of the microneedles. Afterwards, the determination of the size of the microneedle patches can be determined according the plasma level achieved. Other important studies such as skin irritation test and in vivo pharmacodynamic activity test in appropriate animal models should also be conducted. Importantly, the acceptability and usability investigations should be performed to assure the effect of this approach before reaching the clinical studies. We have added these explanations in the revised manuscript.

3. The logics in selecting drug dosage at 15% (not in mg in each patch) are not available.

Response to Reviewer

We thank the reviewer for the comments. As a result, we have explained that initially, different formulations were prepared to achieve maximum drug loading of ceftriaxone in the formulations. In this study, the blank formulations were mixed with three various concentrations of ceftriaxone, namely 10% w/w, 15% w/w and 20% w/w, resulting in nine different formulations, as shown in Table 2. In our preliminary study, to achieve the highest loading for the microneedles, three different concentrations (10% w/w, 15% w/w and 20% w/w) of ceftriaxone were used. The results showed that the use of 20% w/w of ceftriaxone resulted in very viscous solutions, leading to difficulty in the microneedle preparations. Moreover, we have calculated the amount of ceftriaxone loaded in mg, as shown in Table 5.

We have added these explanations in our revised manuscript, as well as the results obtained in the results and discussion section.

4. Stability studies have not been performed or even mentioned. No shelf life prediction is made.

Response to Reviewer

We thank the reviewer for the comments. Accordingly, we have performed stability studies of our formulations. We have included these in the revised manuscript (Section 2.11 and Section 3.10).

5. The manufacturer or in-house designation of the mold (Mould) and the centrifuge tube are not available.

Response to Reviewer

We have included these in the revised manuscript.

6. The conclusion regarding the percentage of PVA to PVP in reducing drug release is not an unknown and surprising finding because the hydrophilic nature of PVP is a an evident phenomenon.

Response to Reviewer

We thank the reviewer for the comments. Indeed, we agreed that the percentage of PVA to PVP in reducing drug release is not an unknown and surprising finding due to the reason mentioned by the reviewer. In this study, the combination of these polymers was not investigated only for the drug release, but also the mechanical properties and insertion abilities of the microneedles. We were aiming to obtain the suitable combination to produce the adequate physical property, the good permeation profile, and importantly, the good stability.

7. It's not clear what the net effect of the dissolving microneedles is in only 10 minutes in providing effective permeation of drug to the derm layer, Compared to drug in polymer matrix with no microneedles?

Response to Reviewer

We thank the reviewer for the comments. It is interesting to note that although the microneedles completely dissolved after 10 minutes, a controlled release manner was observed for 24 h. It could be potentially beneficial to provide a constant plasma level of ceftriaxone. This might be due to the poor permeability of ceftriaxone, providing slow permeability in the dermis layer to the receiver compartment although the drug has been delivered to the dermis layer using the microneedles. Additionally, we have performed additional experiment and compared the permeation profile of ceftriaxone from the microneedles with needle-free polymeric matrix containing polymeric mixture similar to F6. As shown in Figure 7B, due to the poor permeability of ceftriaxone, only 0.53 ± 0.08% of ceftriaxone permeated after 24 h. A previous study has also reported that the incorporation of the drugs into dissolving microneedles exhibited a greater skin delivery compared to the drugs incorporated into the needle-free patches

Reviewer #3: Article entitled "Dissolving microneedle formulation of ceftriaxone: Effect of polymer concentrations on characterisation and ex vivo permeation study"

My observation on article as follow.

1. In abstract: Purpose is not meeting the title claim.

Response to Reviewer

We thank the reviewer for the comments. We have rewritten the purpose to meet the claim of the title.

2. In Material & Methods : Instruments are missing please include in it.

Response to Reviewer

We thank the reviewer for the comments. We have included these in the revised manuscript.

3. The methodology applied for this study is acceptable.

Response to Reviewer

We are grateful that the reviewer thought that the methodology applied for this study is acceptable

4. Ceftriaxone belong to class 3 of Biopharmaceutics Classification System high aqueous solubility and low permeability. It is poorly absorbed through mucosal membranes, Authors tried to enhance permeability of Ceftriaxone by using PVP and PVA combination through rat skin.

Response to Reviewer

We thank the reviewer for the comments. We have added this in the introduction of the revised manuscript to enhance the clarity.

5. One of the critical point in this study lacks stability studies data which is more important in characterization. A formulation of ceftriaxone contains more than 2.4% w/w water leads to degradation (Ceftriaxone is hygroscopic as well PVA). In this study authors employed water for dissolving PVP AND PVA and Ceftriaxone in different ratios. This needs to be answered in the MS.

Response to Reviewer

We thank the reviewer for the comments. Accordingly, we have performed stability studies of our formulations. We have included these in the revised manuscript (Section 2.11 and Section 3.10).

6. The term "Research conducted by" is frequently used, which needs to be modified.

Response to Reviewer

We thank the reviewer for the comments. We have modified this term in the revised manuscript.

7. MS needs to be checked thoroughly for Language.

Response to Reviewer

We thank the reviewer for these suggestions. Following the suggestions, we have corrected the sentences. Importantly, we have re-checked the manuscript thoroughly and made significant changes in the English. We believe that the English of the revised manuscript has now been improved.

8. PVA and PVP combination of MNs stability at room temperature data is required as part of characterization.

Response to Reviewer

We thank the reviewer for the comments. Accordingly, we have performed stability studies of our formulations. We have included these in the revised manuscript (Section 2.11 and Section 3.10).

9. Page 7 Line number 171 - Dissolving Time Test: The method is not clear? Did you applied 5G pressure? Or did you use 5G skin tissue? How many needles were used for study? In Reference 22 explains differently.

Response to Reviewer

We thank the reviewer for the comments. We have rewritten this part to improve the clarity. This test was carried out using a full-thickness rat skin model with an average thickness of 2.3 cm. Microneedle was inserted into the skin using a pressure equivalent to 30 N for 30 seconds. Afterwards, a circular weight of 5 g was placed on the top of the microneedles. Afterwards, at 2 minutes, 4 minutes, 6 minutes, 8 minutes and 10 minutes, the microneedle was removed and observed using a microscope. We have included this in the revised manuscript.

10. 2.10 Ex vivo Permeation Test: The method is not clear? Did you applied 5G pressure? Or did you use 5 gram skin tissue? How many needles /what quantity (G) are used for study? Reference 22 shows bit different explain clearly.

Response to Reviewer

We thank the reviewer for the comments. We have rewritten this part to improve the clarity. Rat skin was placed in the Franz diffusion cell donor compartment (area of 4.9 cm^2) using cyanoacrylate glue with the stratum corneum facing up in the donor compartment (Figure 2.). Then, the microneedle consisting of 100 needles was applied to the skin with manual pressure for 30 seconds. A weight of 5 g was placed on top of the microneedle to hold the microneedle in place. The donor compartment was covered using Parafilm® and attached to the receptor compartment of the Franz diffusion cell. We have included this in the revised manuscript.

11. The skin size mm/cm and quantity or number of needle(s) applied on the skin needs to be mentioned clearly.

Response to Reviewer

We thank the reviewer for the suggestions. We have included these in the revised manuscript.

12. Please check all references

Response to Reviewer

We thank the Reviewer for these suggestions. Following the suggestions, we have re-checked the manuscript thoroughly and made significant changes in the references.

Additional Response:

In addition to the above-mentioned response, we thank the reviewer for the comments provided in the PDF files. We have addressed all the comments in the revised manuscript. We believe that our revised manuscript has been improved substantially.

Reviewer #5: Run a spelling checker on the manuscript and make the necessary corrections (for example, "microneeldes." in the abstract should be "microneedles".)

Response to Reviewer

We thank the reviewer for the comments. We have corrected all the wrong spelling in the revised manuscript.

Stability data should be included in the manuscript.

Response to Reviewer

We thank the reviewer for the comments. Accordingly, we have performed stability studies of our formulations. We have included these in the revised manuscript (Section 2.11 and Section 3.10).

The number of formulations tested is small. No particular experimental design is described, and no rationale provided for selecting only these three compositions.

Response to Reviewer

We thank the reviewer for the comments. As a result, we have explained that initially, different formulations were prepared to achieve maximum drug loading of ceftriaxone in the formulations. In this study, the blank formulations were mixed with three various concentrations of ceftriaxone, namely 10% w/w, 15% w/w and 20% w/w, resulting in nine different formulations, as shown in Table 2. In our preliminary study, to achieve the highest loading for the microneedles, three different concentrations (10% w/w, 15% w/w and 20% w/w) of ceftriaxone were used. The results showed that the use of 20% w/w of ceftriaxone resulted in very viscous solutions, leading to difficulty in the microneedle preparations. We have added these explanations in our revised manuscript, as well as the results obtained in the results and discussion section.

Why did the author's select the drug dosage that was used?

Response to Reviewer

We thank the reviewer for the comments. As mentioned previously, different formulations were prepared to achieve maximum drug loading of ceftriaxone in the formulations. We have

added these explanations in our revised manuscript, as well as the results obtained in the results and discussion section.

Title Page w/ ALL Author Contact Info.

Hamita Esa Putri[1], Rifka Nurul Utami[1], Aliyah[1], Elly Wahyudin[2], Windy Winalda Oktaviani[1], Mukarram Mudjahid[1], Andi Dian Permana[1*]

Dissolving microneedle formulation of ceftriaxone: Effect of polymer concentrations on characterisation and *ex vivo* permeation study

[1]Department of Pharmaceutics, Faculty of Pharmacy, Hasanuddin University, Makassar, Indonesia
[1]Department of Pharmacology and Toxicology, Faculty of Pharmacy, Hasanuddin University, Makassar, Indonesia
Corresponding author:
***Andi Dian Permana (andi.dian.permana@farmasi.unhas.ac.id)**
Department of Pharmaceutics, Faculty of Pharmacy, Hasanuddin University, Makassar, Indonesia
(+6282293273673)

ETHICAL DECLARATION

We have no ethical issue to declare

ABSTRACT

Purpose: This study aimed to develop dissolving microneedle preparations containing ceftriaxone and evaluate the effect of polymer concentrations on characterisation and *ex vivo* permeation study.

Methods: The microneedles were prepared using centrifugation method with different ratios of PVP40% and PVA15%, namely FB1 (50:50), FB2 (60:40), and FB3 (70:30). The microneedles were also prepared with various concentrations of ceftriaxone, namely 10% w/w, 15% w/w and 20% w/w. The microneedles were evaluated for their mechanical properties and *ex vivo* permeation profiles.

Results: The results showed that the microneedles were in the form of sharp pyramidal with size ranging between 712-800 μm. The concentration of ceftriaxone was found to affect the mechanical properties of the microneedles where formulations containing 20% w/w of ceftriaxone could not be produced. To achieve high drug loading, 15% w/w of ceftriaxone was selected in this study. Following the microneedle preparations, the formulation containing 15% w/w of ceftriaxone with FB3 polymer mixture exhibited the best mechanical properties with only 12.96 ± 0.56% height reduction after the compression with 30 N pressure. Moreover, this formulation was able to penetrate 4 layers of Parafilm® layers, indicating adequate insertion properties. Importantly, the microneedles were found to dissolve completely after 10 minutes on the full thickness rat skin. The permeation study showed that the greater the concentration of PVA, the slower the permeation of ceftriaxone from the microneedles. The highest drug permeation was obtained by containing 15% w/w of ceftriaxone with PVP40%:PVA15% with the ratio of 70:30, with the percentage of 99.86 ± 7.6%. The stability studies showed that the microneedles were stable for a 1-month in two humidity levels, namely RH 43% and RH 86%.

Conclusion: Variation of polymer concentration exhibited a significant effect on the mechanical properties of microneedles. The permeation test showed that the greater the concentration of PVA, the slower the permeation of the active substance from dissolving microneedle. Further studies should be conducted to perform *in vivo* pharmacokinetic studies.

Keyword(s): ceftriaxone, dissolving microneedle, polymer, skin permeation

1. INTRODUCTION

Pneumonia is a respiratory infectious disease that is still considered globally as the main cause of death in children under five. The global record showed that around 808.694 children under five died in 2017 due to pneumonia amounting to 15% of total under-five deaths [1]. Meanwhile, in Indonesia, 32 out of 1,000 children under five died out of this disease based on data from BPS-Statistics of Indonesia in 2017 [2]. Specifically, in South Sulawesi Province in the same year, there were 31.759 cases of pneumonia with 26 deaths. Pneumonia can be caused by bacteria, viruses, fungi or other parasites. However, because of its fatality, bacterial pneumonia is believed to be the major cause of morbidity and mortality [3, 4].

Ceftriaxone is a broad-spectrum, third-generation cephalosporin antibiotic used for the treatment of Gram-positive and Gram-negative bacterial infections. Thus, this drug is usually used for severe infections, such as pneumonia at a dose of 50mg - 2g/kgBW/day [5, 6]. Ceftriaxone has good tolerability, but at higher doses or long-term administration, ceftriaxone may cause biliary pseudolithiasis and other quite dangerous side effects [7]. Ceftriaxone is not readily absorbed by mucous membrane, resulting in poor absorption of this drug in the gastrointestinal tract. This drug is categorised as class 3 of Biopharmaceutics Classification System, possessing high aqueous solubility and low permeability. For that reason, ceftriaxone is not available in oral dosage form, and only given through intravenous or intramuscular injection [8, 9]. Hence, it is essential to develop a delivery system formulation that has similar effectiveness as parenteral administration, without causing the unnecessary side effects of the injection.

One of the alternative delivery systems that can replace injection delivery is the microneedle delivery system. Microneedle is a novel drug delivery system with a needle-like shape and micron-range size from 100 to 1000 µm. This system can be used as an alternative to the parenteral route because it can penetrate the stratum corneum to blood circulation in the dermis without reaching the nerve endings, so it does not cause pain [10–15]. Among several types of microneedles, the dissolving microneedle is the one that is most often used to deliver active substances [16]. A previous study has shown that gentamicin formulated in the form of dissolving microneedle has a higher AUC than the intramuscular injection, and can deliver 75% gentamicin in 24 hours with constant plasma levels, thereby increasing the duration of gentamicin in the body and can reduce the frequency of gentamicin administration [17]. Accordingly, this system could potentially be used as an approach to deliver ceftriaxone transdermally to the systemic circulation.

Dissolving microneedles can be prepared from materials that are readily soluble and biodegradable [18], such as polymers, for example, methyl cellulose, polyvinyl pyrrolidone (PVP) and polyvinyl alcohol (PVA) or sugars such as dextrin, galactose, and many more [19]. Based on a previous study [20], the use of PVP as a microneedle polymer without being combined with other polymers resulted in poor mechanical properties of the microneedle. Meanwhile, the microneedle using a mixture of PVP and PVA as a polymer combination showed adequate mechanical strength. Indeed, in another study reported by Permana et al. [21], it was found that the mechanical properties of microneedles containing a mixture of PVA and PVP were found to be better than microneedles containing only one PVA or PVP polymer.

Based on the aforementioned reasons, this study focused on the formulation of ceftriaxone dissolving microneedles using different concentrations of PVA and PVP. In this study, we also evaluated different drug concentrations to achieve the highest drug loading in the microneedle preparations. Afterwards, the microneedles were characterised for their morphology, mechanical strength, drug loading, and dissolving time. Lastly, the skin

permeation study was carried out using a rat skin model to observe the potential of these microneedle formulations to be developed for transdermal delivery.

2. MATERIALS AND METHODS

2.1. Materials

Ceftriaxone was purchased from Alfa Aesar (Lancashire, UK). Polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), potassium chloride, sodium chloride, potassium dihydrogen phosphate, and disodium phosphate were obtained from Sigma-Aldrich (Singapore). All other reagents used were analytical grade.

Microneedle moulds (Micropoint Technologies, Singapore), Centfrifuge, (LC-04S Centrifuge, Zenith Lab (Jiangsu) Co., LTD.), microscope (Olympus CS33, Olympus Corporation), HPLC (Shimadzu Prominence, Shimadzu, Kyoto, Japan) and column C18 (ODS1) (150 mm x 4.6 mm, with a particle size of 5 µm) (Phenomenex Luna C18 (ODS1)) were used in this study.

2.2. Formulation Design and Manufacture of Ceftriaxone Dissolving Microneedle

Initially, blank microneedles were prepared by dispersing 40 g of PVP in 60 g of water at room temperature and 15 g PVA in 85 g of water at 80 ºC to obtain the concentration of 40% w/w and 15% w/w of PVP and PVA, respectively. The polymer solutions were then mixed with the ratio shown in Table 1 to achieve the final weight of 10 g.

Table 1. Design of dissolving microneedle blank formulas

Material	Ratio		
	FB1	**FB2**	**FB3**
PVP 40% w/w	50	60	70
PVA 15% w/w	50	40	30

The microneedle preparations were made by centrifugation method using a silicone mould. In this study, the specifications of the moulds were needle density of 10 × 10, pyramidal needles; 700 µm height and 200 µm width at the base and 200 µm interspacing (Micropoint Technologies, Singapore). Each mould contained 1 g of formula. The moulds were placed into the centrifuge holder and centrifugation was carried out at 3,500 rpm for 30 minutes (LC-04S Centrifuge, Zenith Lab (Jiangsu) Co., LTD.). Then, the microneedles were dried at room temperature for 1 x 24 hours at 37 ºC for another 1 x 24 hours without being removed from the mould.

Different formulations were prepared to achieve maximum drug loading of ceftriaxone in the formulations. In this study, the blank formulations were mixed with three various concentrations of ceftriaxone, namely 10% w/w, 15% w/w and 20% w/w, resulting in nine different formulations, as shown in Table 2. The microneedles containing the active substance ceftriaxone were prepared by mixing ceftriaxone with the polymer mixture. After that, they were sonicated until clear dispersion with no air bubbles was obtained. Then, the polymer-drug mixture was placed on the mould and centrifuged with a similar procedure with the blank microneedles. After the centrifugation was completed, the excess polymer mixture at the top of the mould was removed and replaced with a blank polymer mixture. Lastly, the obtained microneedles were dried at room temperature for 1 x 24 hours at 37ºC for 1 x 24 hours without being removed from the mould. Figure 1 describes the preparation of dissolving microneedles and the dimension of the needles.

Table 2. Design of dissolving microneedle formulas containing ceftriaxone

Formula	Concentration (%w/w)			
	PVP40%:PVA 15% (50:50)	PVP40%:PVA 15% (60:40)	PVP40%:PVA 15% (70:30)	Ceftriaxone
F1	90	-	-	10
F2	-	90	-	10
F3	-	-	90	10
F4	85	-	-	15
F5	-	85	-	15
F6	-	-	85	15
F7	80	-	-	20
F8	-	80	-	20
F9	-	-	80	20

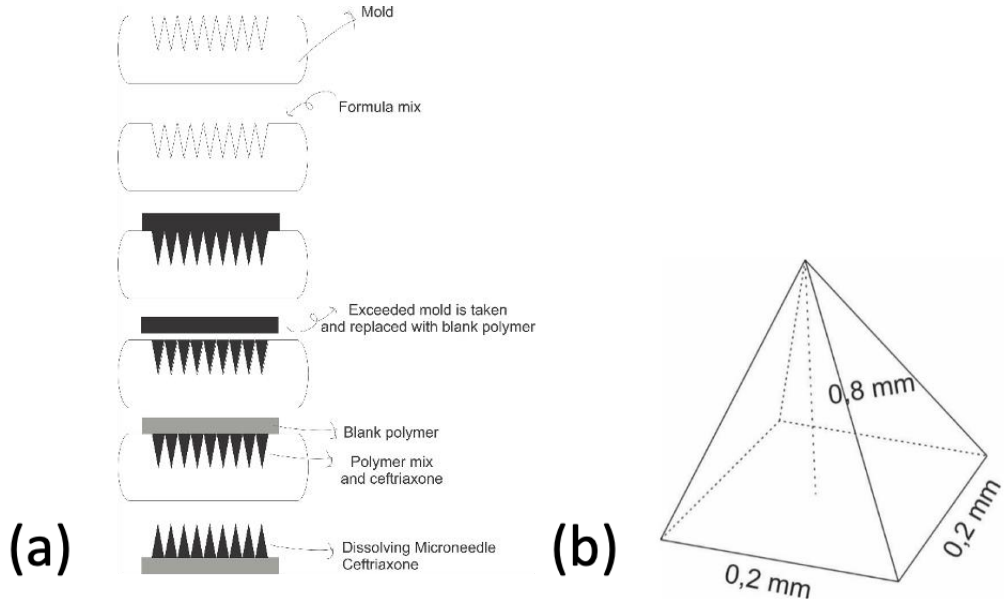


Figure 1. (a) Dissolving microneedle manufacturing scheme; (b) Microneedle dimensions

2.3 Morphological Test

This test was performed to determine the shape and size of the needle. The microneedles were observed using a microscope (Olympus CS33, Olympus Corporation) that has been calibrated with an Optilab® camera with a magnification of 4x.

2.4 Mechanical Strength and Penetration Ability Test

Mechanical strength and penetration ability tests were carried out to ascertain the strength of the microneedle against the applied pressure. This evaluation was carried out by measuring the ability of the microneedle to penetrate 8 layers of Parafilm®, possessing the same thickness as the human skin layer. Microneedle was applied under a pressure equivalent to 30 N for 30 seconds. To achieve this pressure, a weight of 3.06 kg was applied on the top of the microneedles. It is important to note that all sides of microneedles received the same pressure during the study. Then, the number of holes formed was observed in each Parafilm® layer and

the microneedle shape and size were observed using a microscope according to method 2.3 [22]. The percentage of mechanical strength and microneedle penetration ability is calculated using the following equation [17]:

$$\%compression = \frac{initial\ height - height\ after\ pressure\ applied}{initial\ height}\ x\ 100\% \quad \text{(Equation 1)}$$

$$\%penetration\ of\ n\ layer = \frac{number\ of\ holes\ in\ n\ layer}{total\ number\ of\ holes}\ x\ 100\% \quad \text{(Equation 2)}$$

2.5 Density Determination

First, the polymer mixture was moulded in a mould in the form of a flat block, then weighed and dried. The dry mould was weighed again, and the length, height and width were measured to determine the volume of the block, then its density (ρ) was calculated using the following equation:

$$\rho = \frac{weight}{volume} \quad \text{(Equation 3)}$$

2.6 Determination of LOD and Percentage of Total Ceftriaxone in Dry Mass

The percentage of total water lost (LOD) after drying was calculated using the following equation:

$$\%loss\ on\ drying\ (LOD) = \frac{weight\ in\ wet\ form - weight\ in\ dry\ form}{weight\ in\ wet\ form}\ x\ 100\% \quad \text{(Equation 4)}$$

while the percentage amount of ceftriaxone in dry mass was calculated using the equation:

$$\%amount\ of\ ceftriaxone\ in\ dry\ mass = \frac{ceftriaxone\ weight}{100\% - \%LOD}\ x\ 100\% \quad \text{(Equation 5)}$$

2.7 Determination of Volume, Needle Weight, and Weight of Ceftriaxone

The determination of the volume of the needle was calculated using the following equation:

$V = \frac{1}{3}$ x length x width x height (Equation 6)

V_{total} = V x 100 needles (Equation 7)

Then the needle weight was calculated using the density equation. Furthermore, the weight of ceftriaxone in dry mass was calculated using the following equation:

Total weight of ceftriaxone = %ceftriaxone in dry mass x weight of 100 needles (Equation 8)

2.8 Determination of Drug Content in the Microneedle System

2.8.1 Preparation of Phosphate Buffer Saline (PBS) pH 7,4

KCl, NaCl, KH_2PO_4, and Na_2HPO_4 were weighed with the amount of 0.2 g, 8 g, 2.4 g, and 1.44 g, respectively. The salts were then placed in a beaker glass and dissolved with ±800 mL CO_2-free water. After that, the pH of the solution was adjusted to 7.4. Next, the volume of the solution was made up to 1 litre with CO_2-free water [23].

2.8.2 Preparation of Ceftriaxone Stock Solution

Ceftriaxone (10 mg) was placed into a 100 mL fluidized flask, then dissolved and filled with PBS solution pH 7.4 to the limit mark, achieving 100 µg/mL of ceftriaxone stock solution [24].

2.8.3 Preparation of Ceftriaxone Standard Curve

Stock solution of ceftriaxone (100 µg/mL) was pipetted as much as 50, 100, 200, 400, 600, 800, and 1600 µL then put each into a 10 mL flask and the volume was add up to the mark using PBS, so that the solutions were obtained with concentrations of 0.5, 1, 2, 4, 8, 16, and 32 µg/mL. Then, the solutions were filtered using Millipore®. The standard solutions were injected into HPLC (Shimadzu Prominence, Shimadzu, Kyoto, Japan)

with a stationary phase of column C18 (ODS1) (150 mm x 4.6 mm, with a particle size of 5 µm) (Phenomenex Luna C18 (ODS1)), the mobile phase was a mixture of acetonitrile and trifluoracetic acid in 0.1% v/v water (40:60) with a flow rate of 1.0 mL/minute. The detector used was a UV detector with a wavelength of 220 nm. After that, each concentration was taken as much as 20 µL and injected into the injector. Lastly, curve of the relationship between concentration and area was plotted [24].

2.8.4 Determination of Drug Content in the Dissolving Microneedle

The needle was taken out by dredging, then weighed (as theoretical weight) and dissolved in distilled water up to 50 mL. After that, 1 mL of the solution was taken and made up to 5 mL, then the solution was filtered using Millipore®. Furthermore, 20 µL of this solution was analysed using HPLC as in the standard curve (2.8.3) then determined the amount of ceftriaxone contained in the needle. The percentage of drug content in the needle was calculated using the following equation:

$$\%drug\ content = \frac{analysed\ drug\ concentration}{theoretical\ drug\ concentration}\ x\ 100\% \qquad \text{(Equation 9)}$$

2.9 Dissolving Time Test

This test was carried out using a full-thickness rat skin model with an average thickness of 2.3 cm. Microneedle was inserted into the skin using a pressure equivalent to 30 N for 30 seconds. Afterwards, a circular weight of 5 g was placed on the top of the microneedles. Afterwards, at 2 minutes, 4 minutes, 6 minutes, 8 minutes and 10 minutes, the microneedle was removed and observed using a microscope [22].

2.10 *Ex vivo* Permeation Test

This test was conducted to determine the permeation of drug released from dissolving microneedles on the skin. The test was carried out using a full-thickness rat skin model with an average thickness of 2.3 cm. Rat skin was placed in the Franz diffusion cell donor compartment (area of 4.9 cm^2) using cyanoacrylate glue with the stratum corneum facing up in the donor compartment (Figure 2.). Then, the microneedle consisting of 100 needles was applied to the skin with manual pressure for 30 seconds. A weight of 5 g was placed on top of the microneedle to hold the microneedle in place. The donor compartment was covered using Parafilm® and attached to the receptor compartment of the Franz diffusion cell.

The medium used in the receptor compartment was PBS solution pH 7.4 and the temperature was maintained at 37 ± 0.5ºC under constant stirring at 600 rpm. Samples (1 mL) were taken through Millipore® at 15, 30 and 45 minutes as well as 1, 2, 3, 4, 6, 8 and 24 hours. At each sampling, the medium in the receptor compartment was refilled with the same volume and temperature of PBS. Furthermore, the samples were analysed using HPLC as described in (2.8.4) [17].

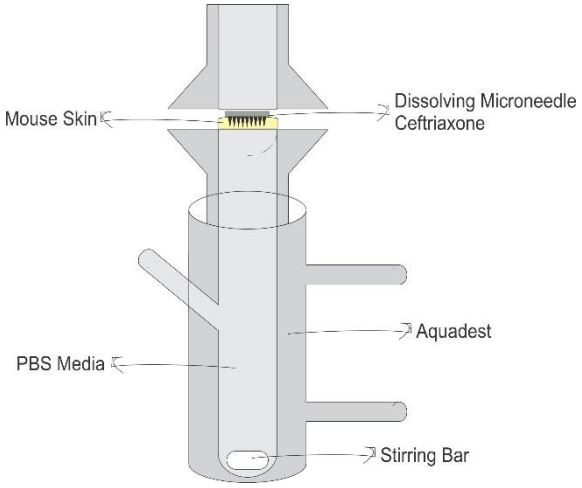


Figure 2. *Ex vivo* permeation test scheme

2.11 Stability study

The stability studies of microneedles containing ceftriaxone were carried out at controlled room temperature (25ºC) with two different relative humidity (RH), namely RH 43%, produced using a saturated solution of potassium carbonate, and RH 86%, produced using a saturated solution of potassium chloride [25]. The microneedles were placed into these conditions for a 1-month period in an airtight container. The mechanical properties and drug recovery were assessed and compared to the initial properties.

2.12 Data Analysis

The research data were collected, tabulated and then analysed using a statistical approach. Data were analysed using the One-sample Kolmogorov-Smirnov Test (1 sample K-S) to determine the normality of the data distribution. If the data distribution was normal, then one-way ANOVA analysis was performed for data with more than 2 groups and independent t-test or paired t-test analysis for data consisting of 2 groups. If the data distribution was not normal, then the Kruskal-Wallis test analysis was performed for data with more than 2 groups and the Mann-Whitney U test analysis for data consisting of 2 groups.

3. RESULTS AND DISCUSSION

3.1 Morphological and Mechanical Tests

Morphological tests were conducted to determine the shape and size of the blank dissolving microneedle. The morphology of the dissolving microneedle was conical and sharp like a needle with a very small size as shown in Figure 3a-c which shows a homogeneous mixture of PVA and PVP polymers.

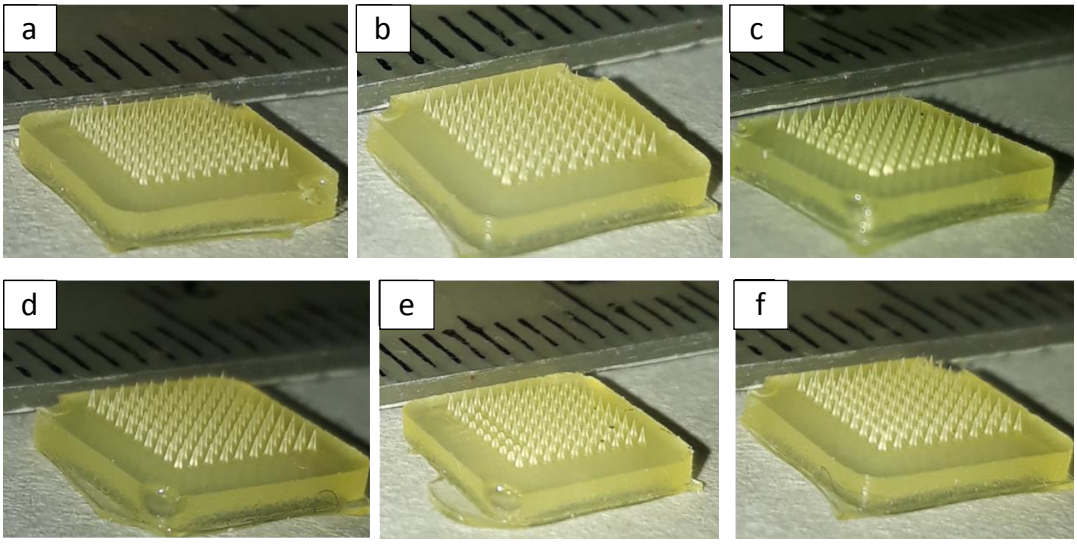


Figure 3. Morphology of blank dissolving microneedle (a) FB1; (b) FB2; (c) FB3; (d) F4; (e) F5; (f) F6

The morphology of the dissolving microneedles following the incorporation of ceftriaxone was also assessed. In our preliminary study, to achieve the highest loading for the microneedles, three different concentrations (10% w/w, 15% w/w and 20% w/w) of ceftriaxone were used. The results showed that the use of 20% w/w of ceftriaxone resulted in very viscous solutions, leading to difficulty in the microneedle preparations. No change in the visual of the microneedle was observed following the addition of the active substance. Additionally, the microneedles showed a homogenous mixture of polymer and the drug as shown in Figure 3d-f.

These results are in accordance with an investigation reported previously by Permana et al. [20], showing that microneedles have sharp edges like needles. With such a shape, it is hoped that the microneedle can penetrate the stratum corneum, obstruct the skin and form holes up to the epidermis or upper dermis [20, 26]. Figure 5 shows that the addition of ceftriaxone in the formula did not affect the physical appearance of dissolving microneedle when 15% w/w of ceftriaxone was used, seen from the colour of the microneedles that did not change.

Table 3. Size reduction of dissolving microneedle (blank and with ceftriaxone) (mean ± SD, n =3)

	Formula	Before mechanical strength test (μm)	After mechanical strength test (μm)	Size reduction of *needle* (%)
Blank	FB1	716.66 ± 1.88	258.77 ± 9.59	63.89 ± 1.30
	FB2	725.00 ± 1.09	635.78 ± 2.11	12.31 ± 0.41
	FB3	749.04 ± 1.05	689.45 ± 0.93	7.96 ± 0.22
With ceftriaxone	F1	736.67 ± 9.02	264.32 ± 8.89	64.15 ± 1.64
	F2	762.33 ± 9.29	614.33 ± 9.07	19.41 ± 1.35
	F3	793.33 ± 7.09	694.32 ± 3.62	12.52 ± 10.6
	F4	734.36 ± 4.83	253.12 ± 3.23	65.53 ± 0.66
	F5	755.24 ± 0.65	614.77 ± 8.93	18.60 ± 1.11
	F6	798.07± 1.64	694.64 ± 5.34	12.96 ± 0.56

Table 3 shows that the height of the microneedles obtained increased with the higher PVP to PVA ratio. FB3, with the highest PVP40% to PVA15% ratio, produced the highest microneedles. This shows that the concentration of the polymer affects the size of the resulting microneedles. The statistical analysis found that the initial heights of the blank microneedles are significantly different (p<0.05). Following the addition of ceftriaxone, there were no significant differences between mechanical properties between microneedles containing 10% w/w and 15% w/w of ceftriaxone. Accordingly, to achieve higher drug loading, formulations containing 10% w/w (F4, F5, and F6) were selected for further studies. After incorporation of the active substance ceftriaxone, the formula F4, F5, and F6 also showed a similar pattern of height increase. However, it was interesting to note that the addition of ceftriaxone also caused a height increase in all three formulas compared to blanks. It is possible that the addition of 15% ceftriaxone to each formulation caused an increase in viscosity, thus affecting the ability of the mixture to enter each mould hole even though it had been centrifuged. Based on the results of ANOVA analysis, it was found that each formula had a significant difference in microneedle height compared to others (p<0.05). The size of the microneedle is in accordance with the length of the needle required to penetrate the skin. The average microneedle is made with a length of 150-1500 µm [27]. This size is adjusted to the thickness of the skin to the dermis without reaching the nerve endings, so it does not cause pain [28]. Therefore, the possible needle length of microneedles obtained were not considered to result in painful when administered.

The mechanical strength of dissolving microneedles is an initial formulation study conducted to determine the ability of microneedles to effectively penetrate the *stratum corneum* for effective drug delivery [20]. Evaluations of mechanical strength and penetration ability were carried out to ensure the strength of the microneedle against the applied pressure. The condition of the needle of each formula after being given a load equivalent to 30 N is shown in Figure 4.

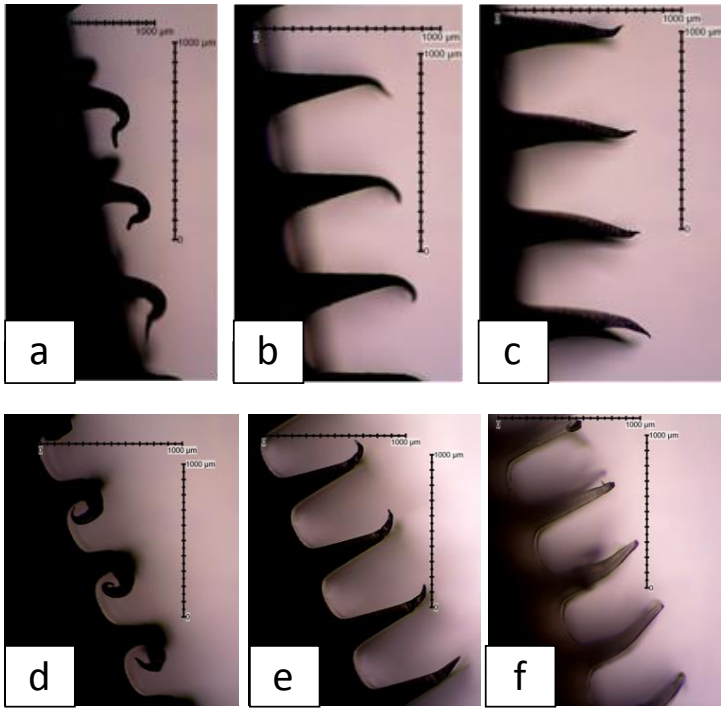


Figure 4. Morphology of dissolving microneedle formulations (a) FB1; (b) FB2; (c) FB3; (d) F4; (e) F5; (f) F6 after mechanical strength test

Figure 4a-c show all the blank needles of each formula were found to bend, especially FB1 following the application of the pressure. This was probably due to the low mechanical strength of each needle, so it was not able to penetrate the Parafilm® layer and could only penetrate a few layers. The mechanical strength of the dissolving microneedle was measured by the percentage reduction in needle height after the application of the pressure of 30 N.

Table 3 shows that the greatest percentage of the reduction in needle height was found in FB1 with reduction percentage of 69.41 ± 4.25%. On the other hand, the reduction in needle height of FB3 was the lowest, which was 7.95 ± 0.22%, suggesting the greatest mechanical strength of FB3. FB1 was prepared with PVP 40%: PVA 15% with a ratio of 50:50 while FB3 was made of PVP 40%: PVA 15% with a ratio of 70:30. This shows the possibility that the more PVA used, the worse the mechanical strength of the microneedle. The results of this study are in accordance with a study reported by Wang et al. [29], which stated that microneedles containing only PVA as a polymer had a large reduction in mechanical strength when stored in areas with high humidity because PVA is a hygroscopic polymer. Therefore, FB3 which contained only 30% PVA, had the highest mechanical strength among other formulations. In addition, PVA also has a low flexural modulus which causes PVA to be flexible and cannot withstand the external pressure applied. Accordingly, microneedles containing a higher PVA concentration tend to bend more easily when pressure was applied [30]

From Figure 4d-f, a similar pattern in terms of the correlation between PVP to PVA ratio and the mechanical strength of the resulting microneedles was observed in those containing ceftriaxone when compared to blanks, showing that no significant difference was found between blank microneedles and microneedles containing ceftriaxone ($p > 0.05$). Table 3 also shows that F4, F5 and F6 had a percentage reduction in needle height of 58.39 ± 0.53%, 18.60 ± 1.11% and 12.96 ± 0.55%, respectively. It was important to note that the height

reduction values of formulations containing 10% w/w of ceftriaxone were not statistically different compared to 15% w/w. Therefore, 10% w/w was chosen for further characterizations. Specifically, the formula with the greatest mechanical strength was F6 with the lowest height reduction. Based on the Kruskal-Wallis Test analysis, the height reduction in F6 was significantly different compared to other formulations ($p < 0.05$). Interestingly, comparing the needle height reduction in ceftriaxone dissolving microneedles to that of the blanks, the mechanical strength of all the formulas seemed to decrease following the incorporation of the active ingredient.

The mechanical strength test was also carried out to observe changes in the microneedle base plate after applying pressure. The microneedle base plate did not experience any change after being stressed, which indicated that the microneedle base plate had good mechanical strength. This is in accordance with a research reported by Permana et al. [20] that mechanical tests on several formulas containing PVA and PVP as polymers and did not find any changes in the microneedle base plate. The combination of PVA and PVP in the manufacture of microneedle could potentially improve the mechanical properties of the formulation, due to the interaction of hydrogen bonds between the hydroxyl group (-OH) of PVA and the carbonyl group (C=O) of PVP. This bond creates a strong and robust structure of the microneedle [31].

3.2 Penetration Ability Test

Penetration ability test was carried out to confirm the results of the mechanical strength test and determine the depth of the hole produced by the microneedle. This test was based on observing the holes formed in each Parafilm® layer. The results of the percentage of penetration test for dissolving microneedle ceftriaxone are presented in Table 4.

Table 4. The percentage of penetration test for dissolving microneedle formulas (blank and with ceftriaxone)

Layer	%penetrated					
	FB1	FB2	FB3	F4	F5	F6
1	100	100	100	100	100	100
2	100	100	100	93	98	100
3	79	82	92	61	73	98
4	0	0	69	0	0	62
5	0	0	0	0	0	0
6	0	0	0	0	0	0
7	0	0	0	0	0	0
8	0	0	0	0	0	0

FB1 and FB2 could penetrate up to the third layer by forming 79 holes (79%) and 82 holes (82%). Moreover, FB3 could penetrate up to the fourth layer by forming 69 holes (69%). This result is in accordance with the mechanical strength test which showed that FB3 had the greatest mechanical strength among the blank microneedle formulas. Following the addition of ceftriaxone, it was found that F4 and F5 could penetrate up to

the third layer by forming 61 holes (61%) and 73 holes (73%), respectively. While F6 could penetrate up to the fourth layer by forming 62 holes (62%) in that layer. However, F4, F5 and F6 showed a reduction in the number of holes formed in the second layer. This is in accordance with the mechanical strength test of dissolving microneedle ceftriaxone which experienced a reduction in mechanical strength due to the addition of 15% ceftriaxone.

The average thickness of each parafilm® layer is around 126 µm. Accordingly, 8 parafilm® layers has a thickness of 1008 µm which is equivalent to the thickness of the skin layer from the *stratum corneum* to the upper dermis [21, 32]. Thus, FB1 and FB2 could penetrate up to 378 µm and FB3 could penetrate up to 504 µm. F4 and F5 can penetrate up to 378 µm and F6 can penetrate up to 504 µm. This means that all formulations could penetrate the skin until the upper dermis. In this part, there are no nerve endings. Therefore, all the microneedle formulations were most likely to be painless but still able to deliver the drug to the blood vessels. Similar results were also shown in studies by Permana et al. [21] and Volpe-Zanutto et al. [26]

3.3 Density of Dissolving Microneedle

Before determining ceftriaxone content in the needle, the theoretical amount of ceftriaxone should be determined first. This determination required the density value of each formula. Based on the calculation results, F4, F5, and F6 respectively have a density of 1.14 ± 0.04 mg/mm^3, 1.17 ± 0.06 mg/mm^3 and 1.24 ± 0.05 mg/mm^3. Furthermore, based on the density, the dry weight of the microneedle was calculated. The results of the calculation of the density and dry weight of microneedle can be seen in Table 5.

Table 5. Density, LOD, percentage of ceftriaxone in dry weight, weight of 100 needles and ceftriaxone weight in 100 needles of dissolving microneedles formulations containing ceftriaxone (mean ± SD, n =3)

Formula	Density (mg/mm^3)	LOD (%)	Percentage of ceftriaxone in dry weight (%)	Weight of 100 needles (mg)	Ceftriaxone in 100 needles (mg)
F4	1.14 ± 0.04	57.60 ± 1.75	35.44 ± 1.46	1.08 ± 0.05	0.39 ± 0.01
F5	1.17 ± 0.06	57.10 ± 1.50	35.01 ± 1.20	1.08 ± 0.05	0.39 ± 0.02
F6	1.24 ± 0.05	57.80 ± 1.19	35.57 ± 1.00	1.15 ± 0.06	0.39 ± 0.02

3.4 Loss on Drying and Percentage of Ceftriaxone in Dry Weight

LOD needs to be determined to calculate the percentage of ceftriaxone in dry weight. The LOD values of F4, F5, and F6 were 57.6 ± 1.75%, 57.1 ± 1.50% and 57.8 ± 1.19%, respectively. From that, the calculated percentage of ceftriaxone in dry weight was found to be 35.44 ± 1.46%, 35.01 ± 1.20%, and 35.57 ± 1.00% for F4, F5, and F6, respectively.

In addition to calculating the percentage of ceftriaxone in dry weight, the LOD value was also related to mechanical strength because during drying, each monomer unit of PVP provides intermolecular stiffness so that dissolving microneedles can harden well during drying and increase the mechanical strength of dissolving microneedles [33]. Therefore, in the mechanical strength test, the dissolving microneedle which had the best mechanical strength was F4 with the highest LOD value.

3.5 Volume, Needles Weight and Ceftriaxone Weight

It was necessary to know the volume and weight of the needle before calculating the theoretical weight of ceftriaxone. The theoretical weight of ceftriaxone in the needle would be used to calculate the percentage of ceftriaxone contents in the dissolving microneedles. Each needle has a volume of 0.00934 mm^3, so that for 100 needles, the volume is 0.934 mm^3. Each F4, F5, and F6 contained 0.39 ± 0.01 mg of ceftriaxone, 0.39 ± 0.02 mg

and 0.39 ± 0.02 mg, respectively. Based on statistical analysis using one-way ANOVA, it was found that the amount of ceftriaxone in F4, F5, and F6 was not significantly different (p > 0.05), showing the reproducibility of the preparation method.

3.6 Ceftriaxone Content in the Dissolving Microneedle Formulations

Following the theoretical calculations, the ceftriaxone content was determined using HPLC. Initially, the standard curve solution of ceftriaxone was prepared. The standard curve equation obtained was y=335.05x-24.559 with linearity (R^2) of 0.999 (Figure 5). Due to the excellent linearity obtained, the resulting standard curve could be used as a reference in determining ceftriaxone content.

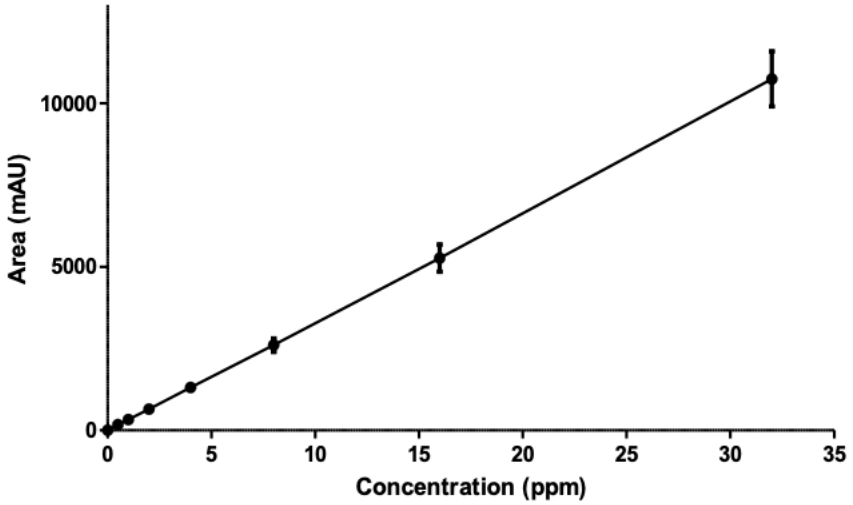
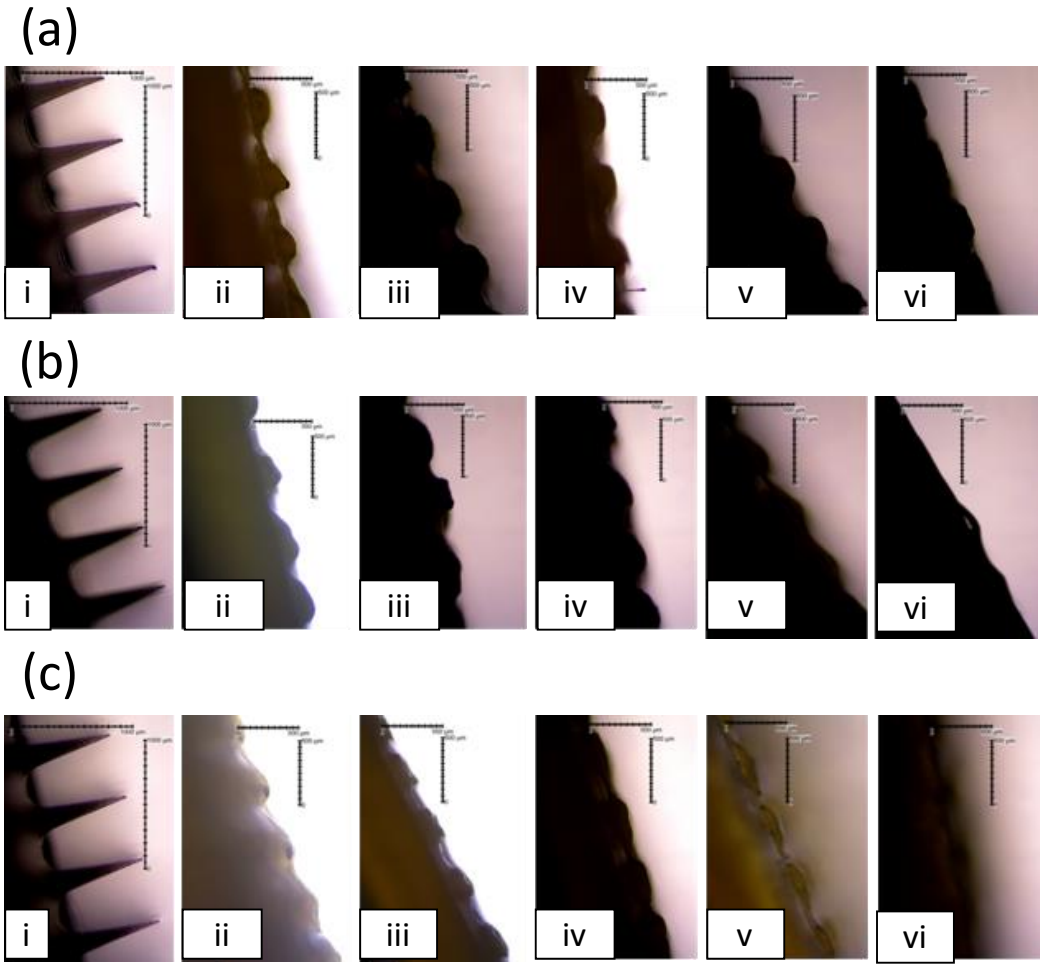


Figure 5. Standard curve of ceftriaxone (mean ± SD, n =3)

The results of determination of ceftriaxone content in the dissolving microneedle formulations using Equation 9 showed that F4, F5, and F6 contained 99.79 ± 4.50%, 99.28 ± 4.68% and 99.72 ± 4.75% ceftriaxone, respectively. Thus, it confirms good homogeneity during the mixing process. This content can be used as a reference in the use of microneedle according to the dose to be used and the development of the size of the base plate and the number of needles for the unit dose of dissolving microneedle containing ceftriaxone.

3.8 Dissolving Time Test

Dissolving time test was conducted to determine the time required for the microneedle to completely dissolve in the skin after application. The results of the dissolving time test are depicted in Figures 6 and Table 6.



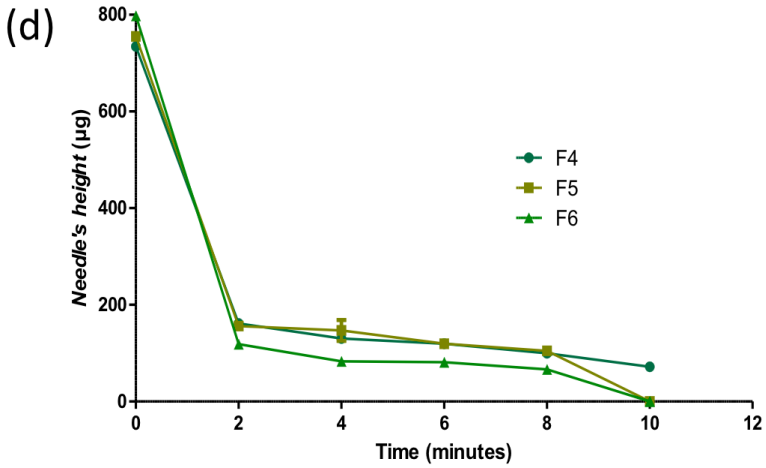


Figure 6.(a) Morphology of dissolving microneedle containing ceftriaxone F4 at (i) 0 minutes; (ii) 2 minutes; (iii) 4 minutes; (iv) 6 minutes; (v) 8 minutes; dan (vi) 10 minutes; (b) Morphology of dissolving microneedle containing ceftriaxone F5 at (i) 0 minutes; (ii) 2 minutes; (iii) 4 minutes; (iv) 6 minutes; (v) 8 minutes; dan (vi) 10 minutes; (c) Morphology of dissolving microneedle containing ceftriaxone F6 at (i) 0 minutes; (ii) 2 minutes; (ii) 4 minutes; (iv) 6 minutes; (v) 8 minutes; dan (vi) 10 minutes; (d) Dissolving time profile of F4, F5, and F6

Table 6. The height of dissolving microneedle containing ceftriaxone at several time intervals (mean ± SD, n =3)

Formula	Height of dissolving microneedle of ceftriaxone at (μm)					
	0 minute	2 minutes	4 minutes	6 minutes	8 minutes	10 minutes
F4	34.36 ± 4.83	161.34 ± 3.76	130.24 ± 1.29	126.83 ± 12.56	99.84 ± 6.46	71.94 ± 3.14
F5	755.24 ± 0.65	155.97 ± 8.89	147.03 ± 21.61	119.77 ± 2.44	104.84 ± 5.29	0
F6	798.07± 1.64	118.83 ± 7.73	83.27 ± 3.70	81.28 ± 6.05	66.41 ± 1.55	0

After 10 minutes, F4 has not dissolved completely in rat skin tissue, while F5 and F6 have, evidenced by the absence of needle residue located at the base of the microneedle plate. However, F6 showed a faster dissolving time than F4. Accordingly, it could be concluded that F6 is a formula that may dissolve well when applied to biological tissues.

PVP and PVA are polymers that can dissolve well in body fluids. This is due to the hygroscopicity and absorption of moisture from PVP and PVA. When PVP and PVA are applied to the skin, PVA and PVP would immediately absorb the surrounding interstitial fluid and then dissolve [17]. However, PVA in the semi-crystalline form dissolved more slowly than PVP. Thus, F4, containing a higher concentration of PVA, dissolved slower than F5 and F6. The results of this study are in accordance with research conducted by Shim et al. [33] and Shu et al. [34] which showed that a formula with a high concentration of PVP resulted in an increase in the dissolution rate of the microneedle. Based on the results of the Kruskal-Wallis analysis, the three formulas had significantly different dissolving times (p <0.05).

3.9 *Ex vivo* Permeation Test

Ex vivo permeation test was carried out to determine the drug release profile from the microneedle after application to the skin. This assay describes the release of ceftriaxone from a microneedle applied to rat skin in the donor compartment into the systemic circulation, which in this case the receptor compartment. The experiment used Franz diffusion cells with time intervals of 0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8 and 24 hours. Permeation percentage of ceftriaxone was measured using HPLC with a UV detector at a wavelength of 220 nm. The results of ceftriaxone permeation from the dissolving microneedles are presented in Figure 7A.

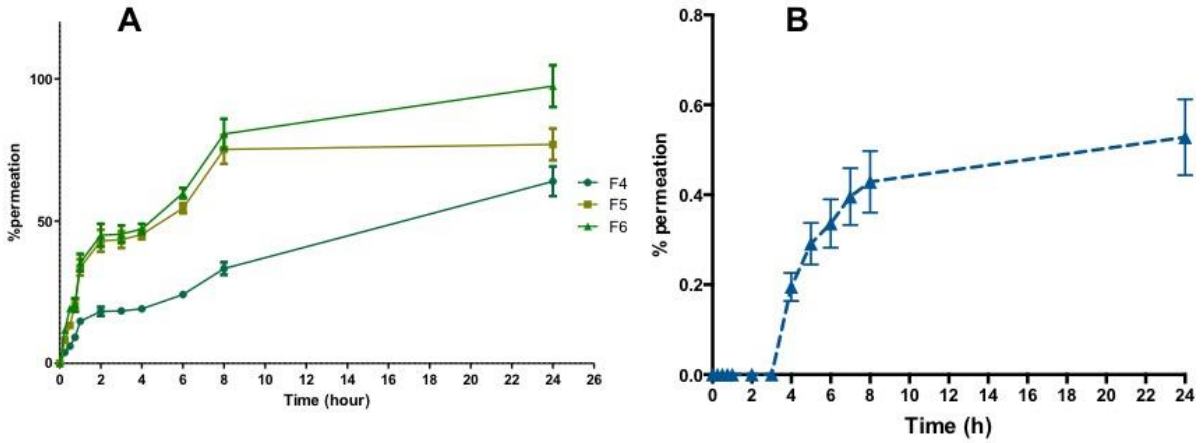


Figure 7. Ceftriaxone permeation profile from the dissolving microneedle formulations (A) and polymeric matrix (B) (mean ± SD, n =3)

Figure 7 shows the percentage of drug permeated at the sampling time interval. F4 showed a slow and relatively constant permeation rate after 2-4 hours but continued to increase up to 24 hours. While F5 and F6 showed that the permeation rate continued to increase from the beginning to 2 hours. After 24 hours, F4, F5, and F6 were permeated by 65.87 ± 5.41%, 78.86 ± 5.7% and 99.86 ± 7.61%, respectively. Based on the post-hoc one-way ANOVA analysis, the permeation percentage value of F6 was significantly different from those of F4 and F5 ($p < 0.05$).

Ceftriaxone permeated from F6 was found to be higher compared to other formulations. This was in accordance with the results of the dissolving time test which exhibited that F6 dissolves faster than other formulas due to the high concentration of PVP. The rate of dissolving of the polymer determines the amount of drug released per unit time. The faster the polymer dissolves, the faster the drug would be released. The formula with high dissolution and permeation speed allows an increase in the amount of drug in the systemic circulation. Drug delivery through dissolving microneedle depends on its ability to penetrate the stratum corneum as demonstrated by mechanical strength tests. Based on mechanical strength test and penetration ability test, F6 can penetrate the fourth Parafilm® layer which causes F6 to reach deeper layers of skin compared to F4 and F5. Accordingly, the release of ceftriaxone from F6 microneedle was faster and more abundant in comparison with other formulations. It is interesting to note that although the microneedles completely dissolved after 10 minutes, a controlled release manner was observed for 24 h. It could be potentially beneficial to provide a constant plasma level of ceftriaxone. This might be due to the poor permeability of ceftriaxone [8, 9], providing slow permeability in the dermis layer to the receiver compartment although the drug has been delivered to the dermis layer using the microneedles. Additionally, we also compared the permeation profile of ceftriaxone from the microneedles with needle-free polymeric matrix containing polymeric mixture similar to F6. As shown in Figure 7B, due to the poor permeability of ceftriaxone, only 0.53 ± 0.08% of ceftriaxone permeated after 24 h. A previous study has also reported that the incorporation of the drugs into dissolving microneedles exhibited a greater skin delivery compared to the drugs incorporated into the needle-free patches [20].

3.10 Stability Study

In the stability study, F6, containing 15% w/w of ceftriaxone and PVP40%:PVA15% with the ratio of 70:30 was selected. With respect to the mechanical strength, at RH 43%, the percentage of height reduction values of F6 were 13.43 ± 1.31%, 12.87 ± 1.28%, 13.23 ± 1.19% and 13.76 ± 1.43% after 1 week, 2 weeks, 3 weeks, and

4 weeks, respectively. At RH 86% 12.76 ± 1.22%, 13.09 ± 1.17%, 13.32 ± 1.28%, and 12.93 ± 1.32% of height reductions were found after 1 week, 2 weeks, 3 weeks, and 4 weeks, respectively. In terms of the insertion profiles, the formulations were able to penetrate 4 layers of Parafilm® after 4 weeks storage in these conditions, with the percentage penetration values between 61.43 ± 5.47% and 62.98 ± 5.39%. Analysed statically, there was no statistical difference in the mechanical and insertion properties of the microneedles in these two conditions for 4 weeks, showing the excellent stability of the formulations. Importantly, after 4-week storage, the drug recoveries were 98.78 ± 1.23% and 99.82 ± 1.18% at RH 43% and RH 86%, respectively. Accordingly, it can be concluded that ceftriaxone could maintain its stability in the microneedle formulations.

Based on the description above, it is found that the dissolving microneedle ceftriaxone formula using PVA and PVP polymers showed good mechanical strength, penetration ability, dissolving time and amount of permeation, and importantly, stability profiles. Therefore, dissolving microneedle has the potential as a new route of delivery of ceftriaxone to the systemic circulation for the treatment of pneumonia in infants. However, to prove its effectiveness, several studies are required. *In vivo* pharmacokinetic studies should further be carried out to investigate the plasma concentration of ceftriaxone following the administration of the microneedles. Afterwards, the determination of the size of the microneedle patches can be determined according the plasma level achieved. Other important studies such as skin irritation test and *in vivo* pharmacodynamic activity test in appropriate animal models should also be conducted. Importantly, the acceptability and usability investigations should be performed to assure the effect of this approach before reaching the clinical studies.

4. CONCLUSION

This study was conducted to determine the effect of variations in PVP and PVA concentrations on morphology, mechanical strength, penetration ability, dissolving time and *ex vivo* permeation profile of ceftriaxone from dissolving microneedle formulations. Based on the results of the study, it can be concluded that the microneedle is conical in shape and sharp like a needle and visually homogenous. Variation of polymer concentration showed a significant effect on mechanical strength, penetration ability and dissolving time. The permeation test showed that the greater the concentration of PVA, the slower the permeation of the active substance from dissolving microneedle. F3 which is a formula containing PVP40%:PVA15% with a ratio of 70:30 is the best formula because it has good penetration ability, dissolving time and skin permeation profile.

AUTHORS CONTRIBUTION

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript

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