Journal of Biosciences and Medicines, 2023, 11, 184-194
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Fixed-Dose Combination (FDC) Formulation of Quinine Sulphate-Doxycycline (Qidox) for Malaria Therapy

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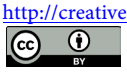
How to cite this paper: Widyati, W., Simorangkir, T.P.H., Tuba, S., Riyadi, T., Nugraha, Y.P. and Prawira, W.R. (2023) Fixed-Dose Combination (FDC) Formulation of Quinine Sulphate-Doxycycline (Qidox) for Malaria Therapy. *Journal of Biosciences and Medicines*, **11**, 184-194.
https://doi.org/10.4236/jbm.2023.111018

Received: December 9, 2022
Accepted: January 28, 2023
Published: January 31, 2023



Abstract

Background: One of the deadliest parasite infections is malaria. A combination of quinine sulphate and doxycycline is another therapeutic option for malaria that is resistant to chloroquine and is anticipated to be able to both combat the issue of anti-malarial medication resistance as well as the compliance to malaria therapy that is still raging in certain locations of Indonesia. **Aim:** This study will focus on evaluating the possibility of interaction between quinine sulphate and doxycycline followed by formulating the fixed-dose combination of both active pharmaceutical ingredients. **Method:** The study was designed as a laboratory experiment and applied some examinations. The examination from the organoleptic test of active pharmaceutical ingredients powder, crystallography analysis, and physical analysis of fixed-dose tablet including hardness, friability, and disintegration time testing. **Result:** The crystallography study reported there was no physical interaction found between quinine sulphate and doxycycline. The formula found excellent tablet printability with a composition of Quinine sulphate and doxycycline (Qidox). **Conclusion:** quinine sulphate with doxycycline can be combined into one tablet as Fixed-Dose Combination (FDC).

Keywords

Malaria, Quinine Sulphate, Doxycycline, FDC

1. Introduction

Around 219 million individuals worldwide were infected with malaria in 2017, which resulted in 435,000 fatalities. More than a century of international study

and work aimed at enhancing malaria prevention, diagnosis, and treatment has led to this burden of illness and mortality [1]. The most prevalent illness in Africa and several Asian nations with the greatest number of native cases is malaria [2]. The fatality rate from severe malaria in tropical climes is 11% - 30%, and the global malaria mortality rate is 0.3% - 2.2% [3]. The prevalence of malaria parasite infection has risen since 2015, according to numerous kinds of research [4].

Despite being used as an antimalarial for nearly 400 years, quinine is still a significant medication [5]. In 2010, the World Health Organization (WHO) advised quinine (quin) plus doxycycline (dox), tetracycline, or clindamycin as a second-line treatment for uncomplicated malaria (to be used when first-line drugs fail or are unavailable), as well as quinine plus clindamycin for the treatment of malaria in the first trimester of pregnancy [6]. Due to the higher expense of the quinine-antibiotic combination, quinine is still mostly used as a monotherapy throughout the majority of Africa, against WHO recommendations [5]. In Sub-Saharan Africa and other malaria-endemic regions, quinine still plays a significant role in the treatment of malaria, and its usage in actual practice may go beyond WHO recommendations [7].

For those traveling to Africa, 100 mg/day of doxycycline is advised as malaria preventative [8]. If ACT is not available or there has been a clinical failure with artesunate or with artesunate in the treatment of severe malaria, it is also advised for the treatment of falciparum malaria in combination with quinine [9]. Similar to tetracycline, doxycycline has a longer elimination half-life (about 20 hours), allowing for a once-daily dosage [10]. Unlike tetracycline, doxycycline cannot be administered to kids or pregnant women. Although doxycycline administration is more convenient than tetracycline administration, adherence can still be enhanced [11].

In recent years, the pharmaceutical industry has increasingly introduced products to the market that are Fixed-Dose Combinations (FDCs), single dosage forms containing two or more active ingredients [12]. These products are marketed with the expectation of optimal patient compliance, improved disease management, and lower costs [13] [14]. However, many FDC products are introduced to the market as a strategy to extend the patent life of one or more of the active ingredients in FDC [15]. Side effects are an important consideration for FDC. Another safety concern with FDCs is the difficulty in identifying which ingredients are associated with ADR adverse drug reactions. In addition, FDCs can also lead to therapeutic duplication if other prescribers ignore the fact that the product contains two ingredients, or may prescribe drugs from the same therapeutic class [16].

The most effective formulation development strategy can be chosen using decision trees and recent developments in the creation of FDC product formulations. A few specialist technologies are explored in further detail alongside specific formulation methods, such as multi-layer tablets, multiparticulate systems, active film coating, and hot-melt granulation [17]. The combination of active ingredients and excipients can cause transformations and solid-solid interactions

in physics and chemistry [16] [18]. The intermolecular interactions as a physical consequence of the binary system that occurs in the Quinine-Doxycycline combination are not clearly known [19].

The melting point of the mixture which is lower than the melting point of each of the active ingredients is a sign of physical interaction. While the reaction of hydrolysis, photolysis, isomerase, and oxidation is a mechanism of chemical interaction [19]. In-depth interaction studies are needed as a basis for designing solid dosage forms, especially tablets, because the physical and chemical interactions in solid dosage forms will have an impact on tablet formulation problems [20].

This study aims to characterize the intermolecular interactions between quinine sulfate and doxycycline hyalite and their effects on solubility and dissolution. The results of this study are expected to contribute information on the preformulating stage in the process of making drug preparations which involve a combination of these two drugs in one preparation, especially tablet preparations.

2. Materials and Method

The study was conducted from June to September 2022 in the Laboratory of Pharmaceutical Technology, the Faculty of Military Pharmacy, The Republic of Indonesia Defense University, Indonesia. The method used in this research is thermal analysis and crystallography. In conducting solid interaction analysis, there are several stages of analysis work, namely observation of crystal morphology using a polarizing microscope and Scanning Electron Microscope (SEM), thermal analysis by measuring melting temperature using Differential Scanning Calorimetry (DSC), observing structures with FTIR (Fourier Transform Infrared). NMR (Neutron Magnetic Resonance), to determine the crystal structure with Powder X-Ray Diffraction (PXRD) and X-Ray Diffraction (XRD) single crystals.

3. Result

The Dox (Doxycycline) and Quin (Quinine sulphate) raw materials used in this study were examined according to the requirements stated in the Indonesian Pharmacopoeia edition V and the United States Pharmacopeia (USP) 38. Examination results can be seen in Table 1 and Table 2.

Table 1. Dox raw material inspection results.

Parameter	Reference (CoA Kaifeng Pharmaceutical Group Co., Ltd., China)	Result
Form	Crystal Powder	Complies
Color	Yellow	Complies
Solubility	Meets Solubility Test	Complies
Water Content	1.40% - 2.80%	2.14%
pH	2.00 - 3.00	2.38
Concentration	80.00% - 92.00%	83.35%

CoA = Certificate of Analysis.

Table 2. Quin raw material inspection results.

Parameter	References (CoA PT. Sinkona Indonesia Lestari)	Result
Form	Fine Needle-Shaped Crystals	Fine Needle-Shaped Crystals
Color	White	White
Smell	No Smell	No Smell
Solubility	Difficult to Dissolve in Water	Difficult to Dissolve in Water
Water content	4.00% - 5.00%	4.61%
Concentration	99.00% - 101.00%	99.65%

CoA = Certificate of Analysis.

The first step to identify the intermolecular interactions between dox and quin is to observe the crystal habits of the two components using a polarized microscope. The method used is the fusion method because both dox and quin will decompose when heated beyond their melting point. Ethanol was chosen as the solvent used for recrystallization because both materials are soluble in ethanol. The crystal habits of dox, quin and the mixture of the two components are shown in **Figure 1**.

4. Discussion

Based on observations using a polarized microscope, the raw material dox has a crystal habit in the form of plates and quin in the form of needles. The differences in color and light intensity are affected by the orientation of the fragments, thickness and the light absorbed or transmitted by the crystal fragments [21]. Meanwhile, the results of recrystallization of the TMS-ADB mixture showed the same habit of the two constituent components [22]. The habit phenomenon in the results of recrystallization of the TMS-ADB mixture can provide initial information regarding the possibility that there will be no interaction between the two components [23].

Next, a phase diagram of the dox-quin molar mixture was made using the DSC instrument to ensure the results of the analysis using the cold contact method. The DSC thermogram of the dox-quin physical mixture with various molar ratios (10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9 and 0:10) are shown in **Figure 2**. The phase diagram obtained from the analysis using DSC shows the occurrence of eutectic interactions between dox and quin in the molar ratio (**Figure 3**).

To identify the certainty that there is no dox-quin interaction due to the effect of the treatment, the mixture of the two components is treated with slurry method. The slurry method is a method that can be used as an alternative to co-crystal production. In this method, sludge/suspension is formed by adding a small amount of solvent to the physical mixture of Active Pharmaceutical Ingredient (API) and conformer.

Formula A

Tablets were made by direct compression method but failed to achieve the expected tablet weight.

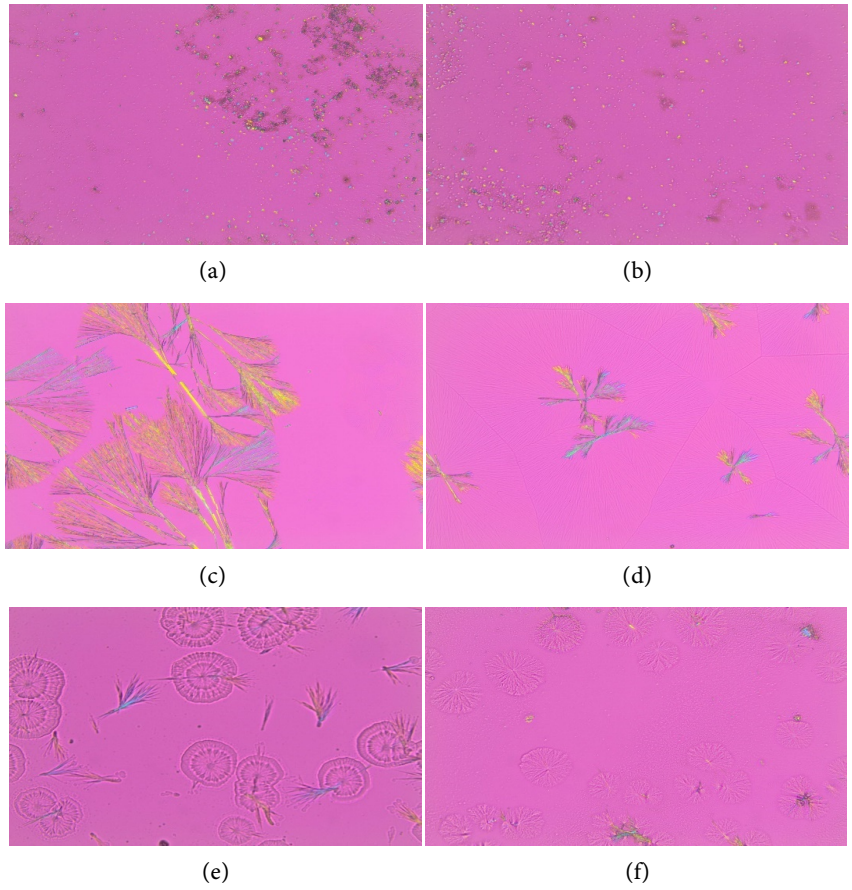
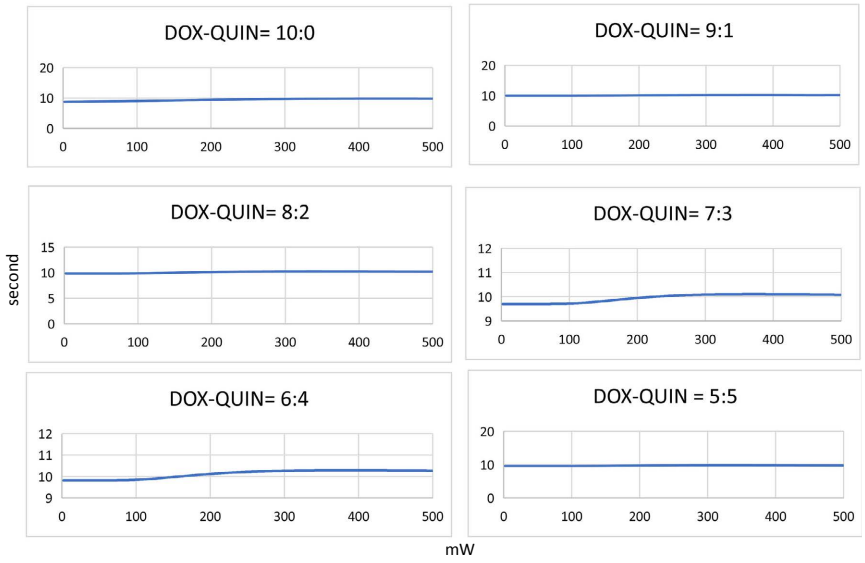


Figure 1. Recrystallisation quinine sulphate and doxycycline. (a), (b) Recrystallization of dox in ethanol; (c), (d) Recrystallization of quin in ethanol; (e), (f) Dox-quin mixture in ethanol solvent.



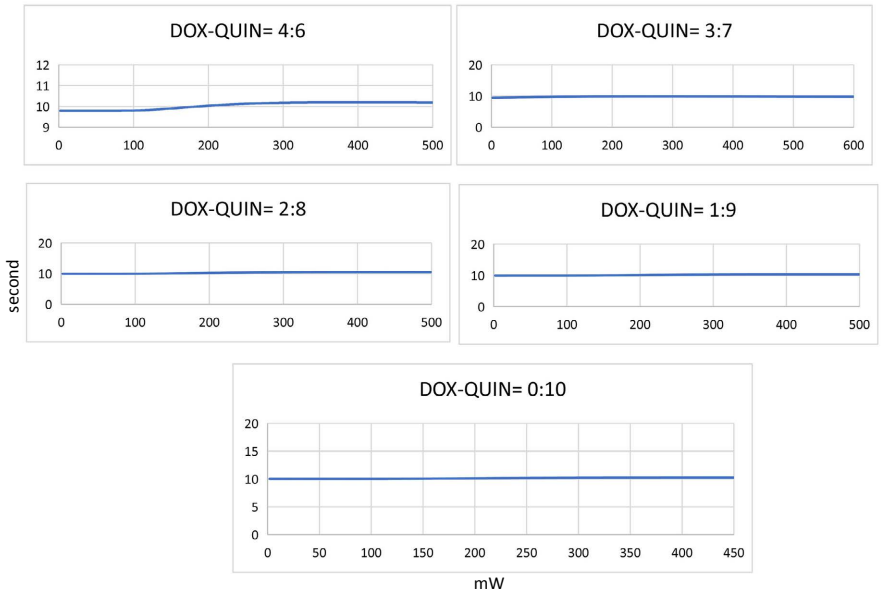


Figure 2. DSC thermogram of the dox-quin physical mixture.

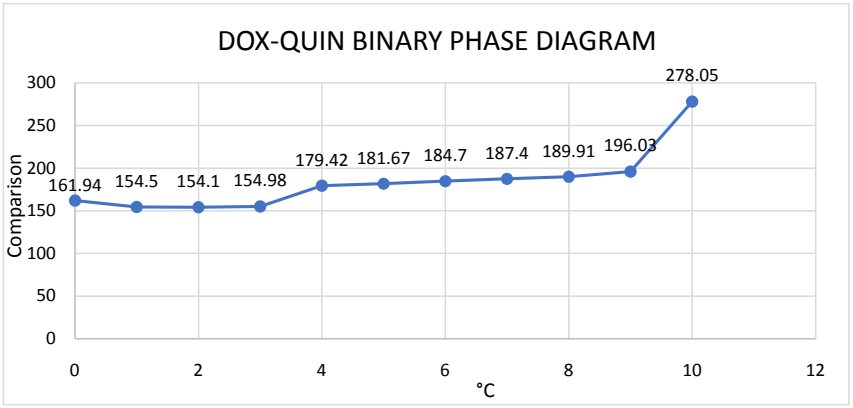


Figure 3. Graph of the phase diagram of the physical mixture of dox-quin molar fractions. 0 means doxycycline 10 and kinin 0; 1 means doxycycline 9 and quinine 1; 2 means doxycycline 8 and quinine 2; 10 means doxycycline 0 and kinin 10.

Formula B

Tablets were made by direct compression method, but failed to achieve the expected tablet weight. The method was changed to dry granulation method, but still did not reach the expected tablet weight. Besides, the tablets demonstrated capping (the tablet surface layer was loose).

Formula C (Qidox)

Tablets (**Table 3**) were made applying the wet granulation method. All excipients were mixed with water to make granules using a granulator until the granule uniform in size. The granules were then dried in an oven at 70˚C. After drying, the granules were mixed with magnesium stearate and talk to improve the flow properties of the granules during printing. The granules were printed using a single punch printing machine.

According to **Table 4**, all of the formulations produced results that were satis-

factory in terms of hardness, friability, weight variation, and disintegration time. The created formulation also showed quality in other criteria (Table 4), such as a disintegration time of no longer than 15 minutes and a friability of no more than 1%, as well as an tablet hardness within a range of 4 to 10 kg, which is in accordance with Indonesia Pharmacopoeia requirements.

Table 3. FDC quinine sulphate and doxycycline tablet formulas.

Formula A		Formula B		Formula C (Qidox)	
R/		R/		R/	
Quinine Sulphate	600 mg	Quinine Sulphate	600 mg	Quinine Sulphate	600 mg
Doxycycline	100 mg	Doxycycline	100 mg	Doxycycline	100 mg
Avicel	15%	Corn Starch	5%	xxxx	x%
Aerosol	1%	PVP	3%	xxxx	x%
Primogel	3%	Primogel	3%	xxxx	x%
Talk	1%	Talk	1%	xxxx	x%
Mg Stearates	1%	Mg Stearate	1%	xxxx	x%
Lactose Ad	850 mg	Lactose Ad	825 mg	xxxx	x mg

Table 4. Physical test results of FDC quinine sulfate-doxycycline Formula C tablets.

Tablet	Tablet Hardness (kg)	Weight Uniformity (mg)	Tablet Hardness/Friability (%)	Disintegration Time (min)
1	7.2	805		
2	7.5	810		
3	7.8	795		
4	8.2	800		
5	7.5	794		
6	7.0	812		
7	8.4	792		
8	8.2	804		
9	8.5	800		
10		806	0.2	10 ± 0.82
11		794		
12		802		
13		793		
14		797		
15		807		
16		791		
17		803		
18		810		
19		795		
20		799		
Average		800.45		
SD		6.51		
CV		0.81		
FI V	4 - 10 kg	<5%	<1	15 min

FI V: Pharmacopoeia Indonesia V; SD: Standard Deviation.

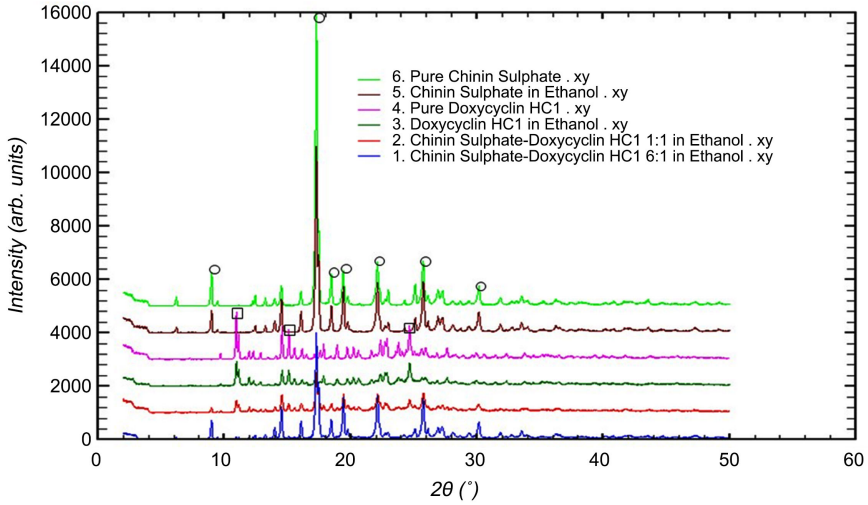


Figure 4. Powder X-Ray Diffraction (PXRD) and x-Ray Diffraction (XRD) single crystals.

Based on the diffractogram (**Figure 4**) from the PXRD (Powder X-Ray Diffraction) the specific peaks of Quinine Sulfate are at 2θ: 9.45˚, 18.75˚, 19.38˚, 19.75˚, 22.80˚ and 26.35˚. After dissolving in ethanol, the diffractogram of Quinine sulphate in ethanol still shows the same specific peak as the powder. This indicates that there is no change in the crystal habit of Quinine sulphate when it is dissolved in ethanol, this also proves that when the tablet manufacturing process is carried out using the granulation method there will be no drawback when using ethanol solvent for the wet granulation process. Moreover, doxycycline diffractogram (**Figure 4**) the specific peaks are at 2θ: 11.90˚, 17.30˚, 18.80˚, 23.10˚, and 24.90˚. After dissolving in ethanol solvent, doxycycline does not change its crystal habit and there will be complies when using ethanol solvent for the wet granulation process [24].

The physical mixture of Quinine sulphate and Doxycycline HCl (both in a 1:1 ratio and according to the expected fixed dose of tablet, namely Quin:Doxy = 6:1) dissolved in ethanol solvent and ground using the slurry method has a diffractogram with a specific peak which is a combination of specific peaks of Quinine sulphate and Doxycycline HCl. There were no additions or reductions in the diffractogram peaks of the two compounds. This indicates that if the two compounds are mixed and fixed-dose tablets are made using the wet granulation method, crystallographically they will not cause interactions that interfere with the process. On the other hand, this study has any limitations: this research has a short time and has not investigated how to determine chemical interactions in the form of fixed-dose combinations. However, in the near future, it is necessary to carry out further research to determine chemical interactions, stability, and toxicity to clinical trials.

5. Conclusion

Based on the results of material science observations using thermal and crystallographic analysis techniques, no specific interactions and fix dose tablets rela-

tively safe have been found between Quinine sulphate and Doxycycline HCl combination which will later affect the manufacturing process in the tablet dosage form.

Authors' Contribution

Conceptualizations: W.W., T.P.H.S. and S.T. Methodology: Y.P.N. and W.R.P. Writing-original draft preparation: S.T. and W.W. Visualization: W.R.P. and T.R. Funding acquisition: W.W. All authors have read and agreed to the published version of the manuscript.

Acknowledgements

We thank Professor Yahdiana Harahap (as dean of the Faculty of Military Pharmacy, RIDU) for her support with sample preparation. We thank the members of the Research Center for Nanoscience and Nanotechnology or PPNN, Bandung Institute of Technology (ITB) and the Faculty of Military Pharmacy RIDU, who gave advice and support.

Declaration

Widyati Widyati is the initiator of this project, Timbul Partogi H. Simorangkir is the evaluator of basic material science and Taufiq Riyadi is the inventor of the formulas, which served as a starting point for the formulation development.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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