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Crystallographic Characterization of Amodiaquine Hydrochloride as an Antimalarial Active Pharmaceutical Ingredient

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ABSTRACT

Solid-state properties of active pharmaceutical ingredients are important in dosage-form development because phase transformation, hydrate or solvate formation, and crystal habit modification can influence manufacturing performance and physicochemical properties. Amodiaquine hydrochloride (AQ) is an antimalarial active pharmaceutical ingredient used in artemisinin-based combination therapy and is known to occur as a hydrated crystalline form. This study evaluated the solid-state characteristics of AQ and the effects of recrystallization, heating, and milling on its crystal structure, crystallinity, thermal behavior, and morphology. AQ samples before and after treatment were characterized using powder X-ray diffraction (PXRD), thermal analysis, Fourier-transform infrared spectroscopy (FT-IR), hot-stage/polarized-light microscopy, scanning electron microscopy (SEM), and single-crystal X-ray diffraction. Recrystallization from methanol, chloroform, and acetone did not produce new PXRD peaks or meaningful changes in crystal habit. Heating at 170 °C for 1 hour produced thermal changes consistent with dehydration, without evidence of polymorphic conversion. Milling for 10, 30, and 60 minutes reduced crystallinity and thermal enthalpy, indicating lattice defects rather than formation of a new polymorph. FT-IR spectra retained the main absorption bands after thermal and mechanical treatments, suggesting that no major spectroscopic changes indicating chemical degradation were detected. Single-crystal analysis confirmed a monoclinic crystal system with space group P21/c, consistent with amodiaquine hydrochloride dihydrate. Overall, AQ maintained the same crystalline phase under the evaluated recrystallization, heating, and milling conditions, although hydration-state changes after heating should be interpreted cautiously.

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ABSTRAK

Sifat padatan bahan aktif farmasi merupakan aspek penting dalam pengembangan sediaan karena transformasi fasa, pembentukan hidrat atau solvat, serta perubahan habit kristal dapat memengaruhi proses manufaktur dan sifat fisikokimia obat. Amodiaquine hydrochloride (AQ) merupakan bahan aktif farmasi antimalaria yang digunakan dalam terapi kombinasi berbasis artemisinin dan diketahui berada dalam bentuk kristalin terhidrasi. Penelitian ini mengevaluasi karakteristik padatan AQ serta pengaruh rekristalisasi, pemanasan, dan penggilingan terhadap struktur kristal, kristalinitas, perilaku termal, dan morfologinya. Sampel AQ sebelum dan sesudah perlakuan dikarakterisasi menggunakan powder X-ray diffraction (PXRD), analisis termal, Fourier-transform infrared spectroscopy (FT-IR), hot-stage/polarized-light microscopy, scanning electron microscopy (SEM), dan single-crystal X-ray diffraction. Rekristalisasi dari metanol, kloroform, dan aseton tidak menghasilkan puncak PXRD baru maupun perubahan habit kristal yang bermakna. Pemanasan pada 170 °C selama 1 jam menghasilkan perubahan termal yang konsisten dengan dehidrasi, tanpa bukti konversi polimorfik. Penggilingan selama 10, 30, dan 60 menit menurunkan kristalinitas dan entalpi termal, yang menunjukkan terbentuknya cacat kisi, bukan pembentukan polimorf baru. Spektrum FT-IR tetap mempertahankan pita serapan utama setelah perlakuan termal dan mekanik, sehingga tidak ditemukan perubahan spektroskopik utama yang mengarah pada degradasi kimia. Analisis kristal tunggal mengonfirmasi sistem kristal monoklin dengan space group P21/c, sesuai dengan amodiaquine hydrochloride dihydrate. Secara keseluruhan, AQ mempertahankan fasa kristalin yang sama pada kondisi rekristalisasi, pemanasan, dan penggilingan yang dievaluasi, meskipun perubahan status hidrasi setelah pemanasan perlu ditafsirkan secara hati-hati.

Kata Kunci: Amodiaquine hydrochloride; Karakterisasi padatan; PXRD; Analisis termal; FT-IR; Habit kristal; API antimalaria

1. Introduction

Solid-state characterization is an important stage in preformulation because the solid form of an active pharmaceutical ingredient, including polymorphs, crystal habit, degree of crystallinity, and particle morphology, can influence physicochemical properties and formulation performance [1]. Differences in crystal form and API morphology have been shown to affect powder flow, compressibility, tablet manufacturing processes, solubility, dissolution, stability, bioavailability, and the final quality of drug products [2]. Organic crystalline solids consist of molecules arranged in a specific three-dimensional lattice and stabilized by noncovalent interactions, such as hydrogen bonding and van der Waals forces [3]. Different molecular packing arrangements may produce polymorphs, solvates, hydrates, or nonsolvated forms with distinct pharmaceutical properties [4].

During manufacturing, active pharmaceutical ingredients are frequently exposed to mechanical stress, heating, solvent-mediated recrystallization, and particle-size reduction. These treatments may disrupt the crystal lattice, reduce the degree of crystallinity, or trigger phase transformation [5]. Therefore, process-induced changes must be carefully distinguished from cocrystal formation, polymorphic transformation, or solvate/hydrate formation [6].

Amodiaquine hydrochloride (AQ) is an antimalarial active pharmaceutical ingredient used in combination with artemisinin derivatives (**Figure 1**). The compound 4-[(7-chloro-4-quinolyl)amino]-2-[(diethylamino)methyl]phenol dihydrochloride dihydrate has a molecular weight of approximately 464.8 g/mol, occurs as a yellow crystalline powder, is soluble in water and methanol, and is very slightly soluble in benzene, chloroform, and ether [7]. AQ is

of interest for solid-state investigation because it has been reported to occur in hydrated forms and to exhibit a tendency to form intermolecular hydrogen bonds in the solid state [8].

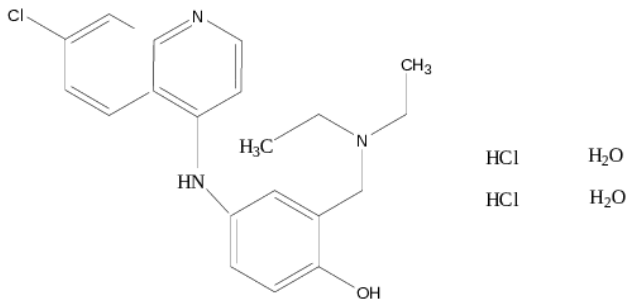

Figure 1. Chemical structure of amodiaquine hydrochloride dihydrate as the antimalarial active pharmaceutical ingredient characterized in this study.

Powder X-ray diffraction is a primary method for identifying crystalline phases because each crystalline material produces a characteristic diffraction pattern. However, PXRD interpretation should be supported by other methods [9]. Thermal analyses such as DTA or DSC provide information on dehydration and melting events, whereas FT-IR detects changes in functional-group vibrations. Microscopy, including polarized-light microscopy and SEM, provides morphological information on crystal habit and surface structure [10].

Research on amodiaquine monohydrate was previously conducted by Wiriyaporn Sirikun et al. in 2015, titled "Solid-State Characterization and Interconversion of Recrystallized Amodiaquine Dihydrochloride in Aliphatic Monohydric Alcohols." That study involved stability evaluation via heating at 190, 215, and 250°C, as well as recrystallization using polar solvents—specifically methanol, ethanol, and propanol. In contrast, the present study was conducted at lower temperatures (up to a maximum of 170°C), taking into account manufacturing processes that utilize solvents ranging from nonpolar to polar (water, methanol, chloroform, and acetone) followed by evaporation at room temperature. In this study, single-crystal identification of amodiaquine was performed.

This study aimed to characterize the solid-state properties of AQ and evaluate the effects of recrystallization, heating, and milling. PXRD, DTA/DSC, FT-IR, polarized-light microscopy, SEM, and single-crystal X-ray diffraction were integrated to assess whether these treatments caused polymorphic transformation, dehydration, crystal-lattice defects, or chemical degradation.

2. Methods

Material

Commercial amodiaquine hydrochloride (AQ) was obtained from Mangalam Drugs & Organics Ltd. (Mumbai, India) batch number AMF 113003, complay with USP monograph, purity 99,4%, with storage condition 25-30 C with RH 60% through PT Laksanawan Lestari, Jakarta, Indonesia. Analytical-grade solvents were obtained from Merck and used without further purification.

Sample preparation and recrystallization

Commercial AQ was separately dissolved in several solvents, water, methanol, chloroform, and acetone, and then evaporated at room temperature. The crystals obtained after evaporation were collected and stored in a desiccator until analysis. Each 25 mg samples of AQ were dissolved in 25 mL of water, methanol, chloroform, and acetone. The sample in

the open vial was allowed to evaporate for 1–3 days. Subsequently, the recrystallized product from each solvent was collected and result 15–20 mg. Rendement stored in a desiccator at the room temperature of 25–30°C.

To obtain the AQ melting product, 1 gram sample was placed in an open vial and heated at 170°C for one hour in a WTB Binder (Germany) oven. The cooling process was carried out for 24 hours in a desiccator. Rendement stored in a desiccator at the room temperature of 25–30°C.

To obtain the results of grinding, 3 grams of sample grounded using a Retsch Muehle apparatus, at a speed of 100 rpm, with pressure of 1 bar. Rendement stored in a desiccator at the room temperature of 25–30°C.

Powder X-ray diffraction analysis

PXRD measurements were performed at room temperature using a Panalytical (Bruker D8 Advance) diffractometer with Cu Kα radiation. The instrument was operated at a voltage of 40 kV and a current of 40 mA. Samples were scanned over a 2θ range of 5–35° with 0,02° per second in the standard slit. The powder was placed on a glass sample holder and carefully leveled to minimize excessive particle orientation. The method for estimating crystallinity is Peak Height Method.

Thermal Analysis

Thermal characterization was performed using both DTA (Mettler Toledo FP 85 Switzerland) and DSC (Rigaku Thermoplus Evo DSC 823). For DTA 5–7 mg sample was placed in a sealed aluminum pan. The DTA instrument was programmed for a temperature range of 50 to 250°C with a heating rate of 10°C per minute. Entalpy calculation method is semi quantitative with measure Δ T sampel and reference. For DSC Samples weighing 2–5 mg were placed in sealed aluminum pans. The DSC instrument was programmed for a temperature range of 50 to 250 °C with a heating rate of 10 °C per minute. Entalpy calculation method is direct measure of area under the curve divided by mass of sample.

FT-IR Spectroscopy

FT-IR spectra were recorded using the KBr pellet method over a wavenumber range of 4000–450 cm-1. Spectral profiles were compared before and after heating or milling to detect changes in functional-group vibrations.

Microscopic analysis

Small amounts of saturated sample solutions in methanol, chloroform, and CHCl3 were dropped onto microscope slides and allowed to recrystallize. The resulting crystal forms were observed under an Olympus BX-50 polarizing microscope equipped with an Olympus SC30 camera at magnification (200 x).

For SEM observation, the powder sample was placed on an aluminum sample holder and coated with a 10 nm thick layer of gold. The sample was then observed at magnifications (500 x) using an SEM (JEOL JSM-6360 LA Analytical). The accelerating voltage was set to 20 kV and the current to 12 mA.

3. Results and Discussion

Crystal Habit After Recrystallization

Polarized-light microscopy showed that the crystal habit of AQ before treatment and after recrystallization from methanol, chloroform, and acetone did not differ meaningfully (**Figure 2**). Similarity in crystal appearance alone is not sufficient to confirm or exclude the presence of a hydrate, solvate, or polymorphic change. The recrystallization process can influence crystal habit through differences in solvent polarity, hydrogen-bonding ability, and the degree of supersaturation during crystal growth. However, if the resulting crystal

structure remains the same, morphological changes are typically limited to crystal size and aspect ratio without altering the crystal lattice structure [11], [12]. Therefore, the observed similarity in crystal habits indicates that the intermolecular forces controlling AQ crystal growth remain dominant across all solvent systems used. However, morphological similarities cannot be used as definitive evidence that no change in crystal form has occurred. Some polymorphs are known to have very similar crystal habits, so confirmation is required using structural characterization techniques such as PXRD, thermal analysis, FT-IR, and SEM [13]–[16].

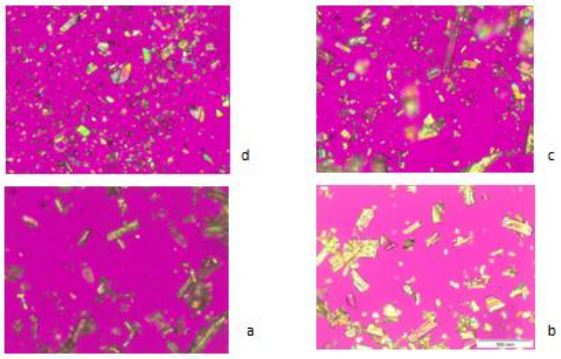

Figure 2. Polarized-light micrographs of AQ crystals before recrystallization (a) and after recrystallization from methanol (b), chloroform (c), and acetone (d). At magnification 200 x.

PXRD profile of recrystallized AQ

The PXRD patterns of untreated AQ and recrystallized samples showed the same major peaks (**Figure 3**). No new peaks or meaningful peak shifts were observed after recrystallization using methanol, chloroform, or acetone. The main peaks appeared at approximately 2θ values of 6.5°, 8.8°, 14.0°, 22.6°, and 25.5°. These results indicate that the recrystallization conditions used did not generate a new polymorphic or solvate form of AQ.

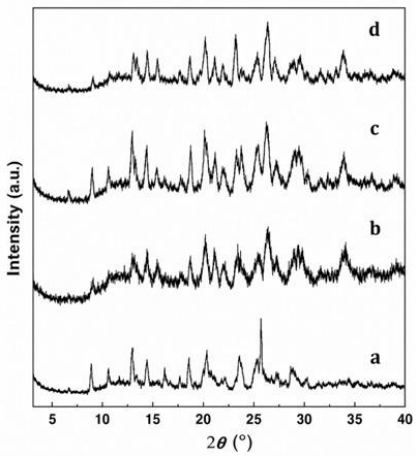

Figure 3. Powder X-ray diffraction patterns of AQ before recrystallization (a) and after recrystallization from methanol (b), chloroform (c), and acetone (d).

Effect of Heating on Thermal and Spectroscopic Characteristics

The thermal profile of untreated AQ showed a broad endothermic event followed by a sharper endothermic transition. The first endothermic event was consistent with the release of water from the dihydrate form, whereas the second event was associated with melting

behavior. After heating at 170 °C for 1 hour, the thermal profile changed in a manner consistent with the loss of crystal water. This finding suggests a dehydration-related solid-state change rather than polymorphic transformation. The absence of additional thermal events, together with the PXRD and FT-IR results, suggests that no clear new polymorphic phase was formed under the evaluated heating condition (**Figure 4**).

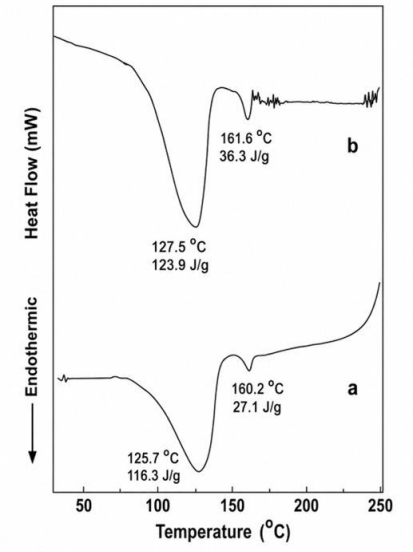

Figure 4. DSC thermal profile of AQ before heating (a) and after treatment at 170 °C for 1 hour (b).

The TG-DTA thermogram of the AQ compound indicates the presence of two H2O molecules, based on the following calculation: the molecular weight (MW) of AQ dihydrate is 464.81, and the thermogram shows a weight loss of 7.44%. This indicates that upon heating, the sample lost an amount of H2O equal to 464.81 × 0.0744 = 34.9, which corresponds to two H2O molecules (MW of two H2O molecules = 18 × 2 = 36). This result confirms that the untreated AQ starting material corresponded to the dihydrate form. However, heating-related water loss indicates that the hydration state may change during thermal treatment (**Figure 5**).

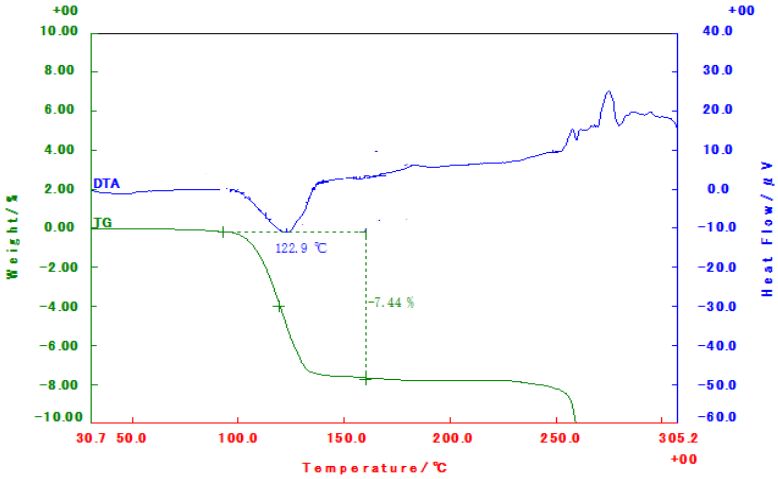

Figure 5. TG DTA thermal profile of AQ.

FT-IR analysis supported this thermal interpretation (**Figure 6**). The major peaks remained at approximately 3433 cm-1 (phenolic O-H), 3170 cm-1 (amine), 2954 cm-1 (C-H), 2654 cm-1, 1622 cm-1, and 1442 cm-1 (C-C stretching). The persistence of these peaks indicates

that the main functional groups of AQ were maintained after heating and that no degradation was spectroscopically detectable under these conditions.

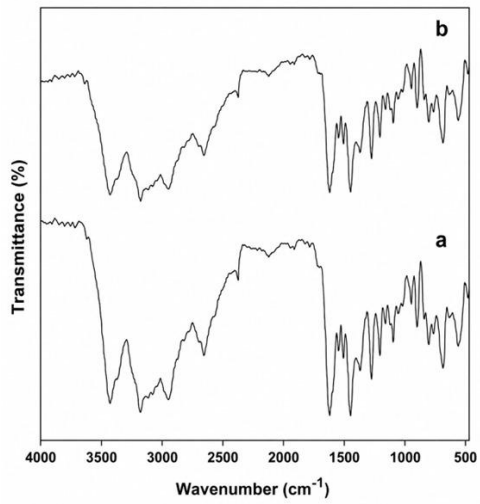

Figure 6. FT-IR spectra of AQ before heating (a) and after thermal treatment at 170 °C for 1 hour (b).

Effect of milling on crystallinity and thermal characteristics

The PXRD patterns of AQ after milling for 10, 30, and 60 minutes retained the same peak positions as the untreated sample. The main change was a decrease in peak intensity, indicating reduced crystallinity rather than formation of a new crystalline phase (**Figure 7**). The decrease in AQ crystallinity resulting from milling for 10, 30, and 60 minutes yielded crystallinity index values of 12.6%, 10.4%, and 8.7%, respectively. This finding is consistent with the formation of lattice disorder or crystal defects induced by mechanical energy during milling.

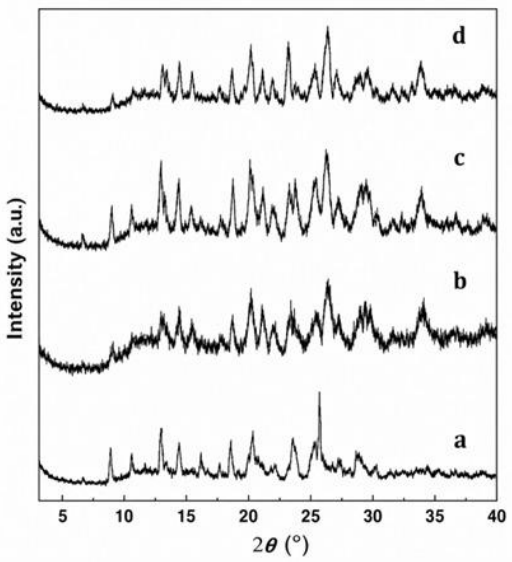

Figure 7. PXRD profiles of AQ before milling (a) and after milling for 10 minutes (b), 30 minutes (c), and 60 minutes (d).

The DTA profile further supported this interpretation (**Figure 8**). Before milling, AQ showed endothermic peaks at approximately 166.3 °C and 180.9 °C, with enthalpy values of 66.2 J/g and 50.6 J/g, respectively. After milling for 10, 30, and 60 minutes, the first

endothermic peak decreased to approximately 165.2 °C, 163.7 °C, and 162.6 °C, with enthalpy values of 62.9 J/g, 45.3 J/g, and 41.6 J/g. The second endothermic peak also decreased to approximately 179.3 °C, 178.5 °C, and 178.2 °C, with enthalpy values of 42.2 J/g, 20.1 J/g, and 19.4 J/g. The decrease in enthalpy is more appropriately explained by crystal defects and reduced lattice order caused by milling rather than polymorphic conversion.

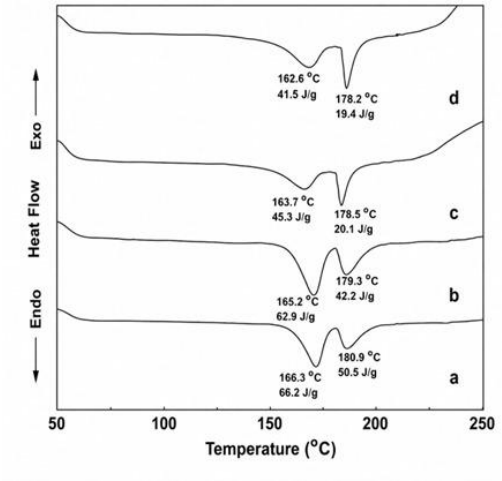

Figure 8. DTA thermograms of AQ before milling (a) and after milling for 10 minutes (b), 30 minutes (c), and 60 minutes (d).

The FT-IR spectra of AQ after milling remained comparable to those of the untreated sample and retained the major absorption peaks (**Figure 9**). The absence of new bands, disappearance of bands, or major peak shifts indicates that milling did not alter the chemical identity of AQ and did not cause detectable degradation.

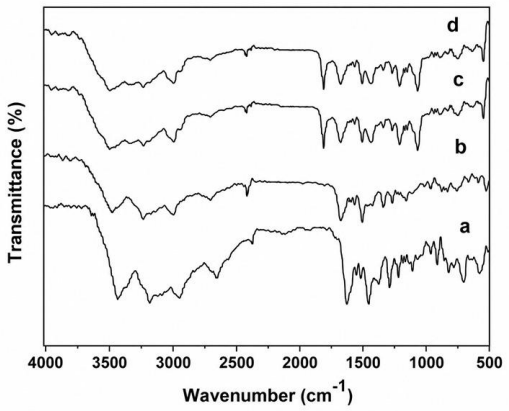

Figure 9. FT-IR spectra of AQ before milling (a) and after milling for 10 minutes (b), 30 minutes (c), and 60 minutes (d).

SEM morphology and implications for manufacturing processes

SEM analysis showed that AQ crystals had a blade-like habit with a dominant size of approximately 100 µm (**Figure 10**). Blade-like particles generally exhibit poor flowability and may complicate direct compression unless accompanied by an appropriate formulation strategy. Therefore, particle engineering or granulation should be considered in the development of solid dosage forms containing AQ [8].

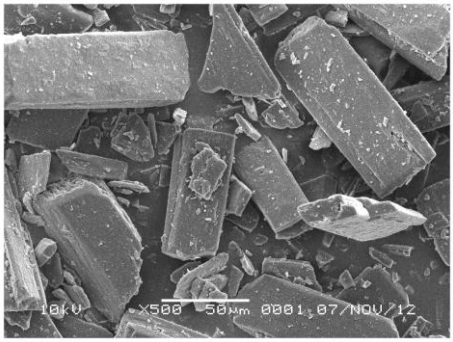

Figure 10. SEM micrograph showing the blade-like crystal habit and surface morphology of AQ. At magnification 500 x.

Single-crystal analysis

Single-crystal X-ray diffraction analysis was performed on single crystals of AQ. Crystals of suitable size and quality were selected from the sample. Crystal was mounted on a holder, and the temperature was set to -140°C. The single crystals were exposed to X-rays for approximately 24 hours. The resulting data were analyzed using WinGx, Shelx-97 (Cambridge, UK), and Mercury 3.0 software. CCDC 626826 (**Figure 11 and Table 1**).

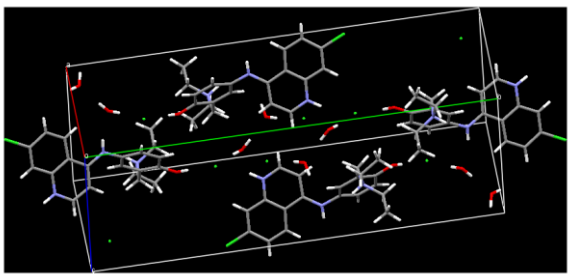

Figure 11. Three-dimensional arrangement of the AQ single crystal based on crystallographic analysis.

The diffraction analysis showed that AQ has a monoclinic crystal system with space group P21/c and Z = 4. The unit-cell parameters were consistent with the previously reported crystal form of amodiaquine hydrochloride dihydrate. Comparison between the simulated and experimental diffraction patterns supported that the untreated AQ raw material corresponded to the monoclinic dihydrate form. This finding confirms the initial solid form of AQ before processing treatments.

Table 1. Single-crystal parameters of amodiaquine hydrochloride dihydrate.

Parameter	AQ
Formula	C20H22ClN3O . 2HCl . 2H2O
Crystal size (mm)	0.39 x 0.17 x 0.15
Crystal system	Monoclinic
Space group	P21/c
a (Å)	7.839 (1)
b (Å)	26.992 (1)
c (Å)	10.808 (1)
α (degree)	90
β (degree)	92.96
γ (degree)	90
Z	4

Cell volume (Å3)	2230.91
R-factor (%)	3.70

The AQ raw material exhibits major PXRD peaks at 2θ angles (°) of 6.5, 8.8, 14.0, 22.6, and 25.5. The DSC thermogram of the AQ raw material exhibits two endothermic peaks: one at 125.7°C with an enthalpy of fusion of 116.3 J/g, and another at 160.2°C with an enthalpy of fusion of 27.1 J/g. The major peaks in the AQ FTIR spectrum of the raw material appear at the following wavenumbers (cm^{-1}): 3433 (OH group); 3170 (amine); 2954 (CH); 2654 (aldehyde); 1622 (carbonyl); and 1442 (C-C stretching). The application of mechanical energy via milling for 10, 30, and 60 minutes did not alter the crystal structure of AQ but merely resulted in a decrease in its crystallinity. The relative crystallinity index was calculated to determine the extent of this reduction. The angle at 2θ = 25.6° was used for the calculation due to its high relative intensity (I/Io). The crystallinity indices of AQ following 10, 30, and 60 minutes of milling were 12.6%, 10.4%, and 8.7%, respectively (**Table 2**).

Table 2. Powder characterization of Amodiaquine Hydrochloride.

Paramater	Result
PXRD - Main peaks	Main peaks at 2θ = 6,5°; 8,8°; 14,0°; 22,6°; and 25,5°
DSC – Endotemic peaks 1	Peak temperature 125,7°C; enthalpy of fusion (ΔH_m) = 116,3 J/g
DSC – Endotemic peaks 2	Peak temperature 160,2°C; enthalpy of fusion (ΔH_m) = 27,1 J/g
FTIR - OH	3433 cm^{-1} → OH group
FTIR – Amina	3170 cm^{-1} → amina group
FTIR – CH	2954 cm^{-1} → CH group
FTIR – Aldehida	2654 cm^{-1} → aldehida group
FTIR – Karbonil	1622 cm^{-1} → karbonil group
FTIR – C-C	1442 cm^{-1} → C-C streching
Milling effect	Milling for 10, 30, and 60 min did not induce changes in the crystal structure of AQ, but progressively reduced its crystallinity
10 minutes	12,6%
30 minutes	10,4%
60 minutes	8,7%

This study has several limitations. First, only one commercial source and batch of amodiaquine hydrochloride were evaluated; therefore, the findings may not fully represent possible variability among different suppliers or production batches. Second, although PXRD, thermal analysis, FT-IR, microscopy, SEM, and single-crystal analysis provided complementary solid-state information, chemical degradation was not confirmed using specific chemical purity methods such as HPLC, LC-MS, or NMR. Therefore, the absence of degradation should be interpreted as the absence of major solid-state or spectroscopic evidence of degradation under the evaluated conditions. Third, the hydration-state interpretation after heating remains limited because the study showed dehydration-related thermal changes, but did not further evaluate possible rehydration or long-term stability after cooling and storage. Fourth, recrystallization and milling were assessed under limited experimental conditions, including selected solvents, one heating temperature, and selected milling times. Further studies using broader stress conditions, controlled humidity, additional storage periods, and chemical purity analysis are needed to better understand the solid-state stability of amodiaquine hydrochloride during pharmaceutical processing.

4. Conclusion

The integration of PXRD, thermal analysis, FT-IR, SEM, polarized-light microscopy, and single-crystal analysis confirmed that the untreated AQ material corresponded to amodiaquine hydrochloride dihydrate. Recrystallization and milling did not produce evidence of a new crystalline phase, while heating at 170 °C caused dehydration-related changes without clear evidence of polymorphic conversion. Heating primarily caused thermal changes related to dehydration, whereas milling reduced crystallinity and enthalpy through the formation of lattice defects. No clear evidence of polymorphic transformation or major spectroscopic changes indicating chemical degradation was observed. However, the hydration-state changes after heating should be interpreted cautiously. Overall, the PXRD, TGA, and FT-IR results provided no evidence of chemical degradation of AQ under the evaluated conditions.

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Conflict of Interest:

The authors declare no conflict of interest.

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