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Investigation on the relationship between solubility of artemisinin and polyvinylpyrroli done addition by using DAOSD approach

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ABSTRACT

In this work, we investigated the influence of polyvinylpyrrolidone (PVP) on the solubility of artemisinin in aqueous solution by using quantitative ^{1}H NMR. Experimental results demonstrate that about 4 times of incremental increase occurs on the solubility of artemisinin upon introducing PVP. In addition, dipole-dipole interaction between the ester group of artemisinin and the amide group of *N*-methylpyrrolidone (NMP), a model compound of PVP, is characterized by two-dimensional (2D) correlation FTIR spectroscopy with the DAOSD (Double Asynchronous Orthogonal Sample Design) approach developed in our previous work. The observation of cross peaks in a pair of 2D asynchronous spectra suggests that dipole-dipole interaction indeed occurs between the ester group of artemisinin and amide group of NMP. Moreover, the pattern of cross peaks indicates that the carbonyl band of artemisinin undergoes blue-shift while the bandwidth and absorptivity increases via interaction with NMP, and the amide band of NMP undergoes blue-shift while the absorptivity increases via interaction with artemisinin. Dipole-dipole interaction, as one of the strongest intermolecular interaction between artemisinin and excipient, may play an important role in the enhancement of the solubility of artemisinin in aqueous solution.

1. Introduction

Over the past several decades, there have been increasing evidences accumulated supporting the rapidity, reliability, and safety of artemisinin in the treatment of malaria. Artemisinin can kill young circulating ring-stage parasites in *Plasmodium falciparum* infection, which results in a more rapid reduction in parasitaemia compared with other antimalarials. Moreover, artemisinin considerably reduces the number of parasites that mature to sequester in and block capillaries and venules. This effect explains the rapidity of clinical responses and the life-saving benefit in severe malaria compared with quinine [1,2]. In addition, artemisinin reduces gametocyte carriage which diminishes the transmission potential of the treated infection [3]. As a result, artemisinin-based combination therapies have saved lives of millions of people over the world over the past several decades [4]. Because of the great contribution in the field of artemisinin, Prof. Tu Youyou became Nobel Prize Laureate in 2015 for her great contribution in the discovery of artemisinin [5]. Furthermore, artemisinin has also clinically important activity against other parasites, such as schistosomiasis and fascioliasis [6,7]. In addition, artemisinin has anti-inflammatory properties and also inhibits angiogenesis and cell growth in several neoplastic cell lines, which suggests a potential role in cancer chemotherapy [8,9]. However, artemisinin suffers from a relatively low water solubility that leads to low bioavailability and high recrudescence rate. To break the bottleneck of artemisinin efficacy, efforts on chemical modification of artemisinin have been extensively reported in the literature. Although thousands of derivatives of artemisinin have been synthesized, only very few of them have been utilized in clinical practice [10].

An alternative way to address this problem is to introduce suitable excipient to enhance the solubility of artemisinin. The molecular structure of artemisinin is shown in Fig. 1a. Artemisinin possesses a peroxide group which was proved be a functional group in the treatment of malaria. In addition, an ester group is present at C-12 position in an

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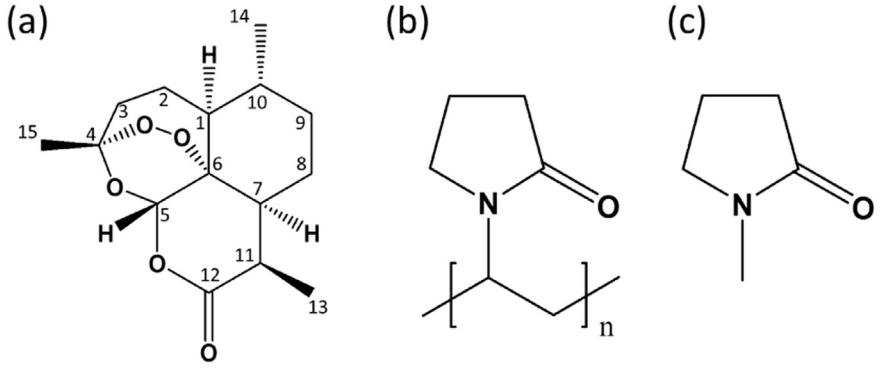

Fig. 1. Molecular structures of (a) artemisinin, (b) PVP, (c) NMP.

artemisinin molecule. The presence of an ester group confers artemisinin an opportunity to increase the solubility by specific dipole-dipole interaction. Polyvinylpyrrolidone (PVP, Fig. 1b) is a nontoxic, water-soluble polymer that has been extensively utilized as an excipient in pharmaceutical industry. PVP possesses an amide group on its pyrrolidone ring. It has been reported that the solubility of artemisinin can be gradually increased with the addition of PVP [11]. In many approaches, UV–Vis spectrometric method is utilized and the increasing of the concentration of artemisinin was proved by the increasing of the absorbance of a peak that is relevant to artemisinin. According to the Beer-Lambert's law, there are two factors that may bring about increment of the absorbance of a peak relevant to artemisinin. One is that the concentration of artemisinin indeed increases, and another is that the absorptivity of the peaks related to artemisinin increases. When an excipient is introduced, remarkable intermolecular interaction occurs between artemisinin and the excipient. In our previous work, we found that intermolecular interaction between two solutes dissolved in the solution often induces significant variations on the absorptivity of solutes [12,13]. Thus, we cannot preclude the possibility that the increment of absorptivity is the result of increment of absorptivity of the peak related to artemisinin rather than the increasing of the solubility of artemisinin.

To solve the above problem, we adopt ^{1}H NMR spectroscopic method to measure the concentration of artemisinin dissolved in aqueous solutions containing different amounts of PVP. Over the past several decades, ^{1}H NMR spectroscopic method has been extensively applied as a quantitative tool in the measurement of concentrations of various analyte [14,15]. In the ^{1}H NMR measurement, the relationship between the concentration of an analyte (C) and the area of the peak related to a specific proton (A) of the analyte can be expressed as Eq. (1).

$$C = \alpha A \quad (1)$$

where α is a proportionality coefficient. Different from absorptivity in spectrometric method such as UV–Vis, the value of α cannot be affected by solvent or interaction with other substance in the solution. Thus, ^{1}H NMR can provide a reliable evidence to reflect the change of the solubility of artemisinin under the influence of an excipient.

Based on the fact that PVP indeed increases the solubility of artemisinin in aqueous solution, we applied two-dimensional correlation FTIR spectroscopy to probe the dipole-dipole interaction between artemisinin and excipient.

Two-dimensional (2D) correlation spectroscopy, proposed by Noda in the 1980s [16], has gained extensive interests among scientists in various fields during the past thirty years [17–27]. One of the most attractive features of 2D correlation spectroscopy is that the appearance of a cross peak can be used to reflect intermolecular interactions. In our previous work, we have introduced a scheme called orthogonal sample design (OSD) approach that provides an unambiguous relationship between the cross peaks in 2D synchronous spectrum and intermolecular interaction [28–33]. Moreover, we have refined this approach by introducing double orthogonal sample design (DOSD) approach [34], asynchronous orthogonal sample design (AOSD) approach [35–38], double asynchronous orthogonal sample design (DAOSD) approach [12,13,39–47], asynchronous spectrum with auxiliary peaks (ASAP) approach [48] and other methods [49–51] in the subsequent work. The DAOSD approach turned out to be quite powerful in revealing subtle variation on the peak position, bandwidth and absorptivity of the characteristic peaks of solutes caused by intermolecular interaction. Thus, we adopt the DAOSD approach to characterize interaction between artemisinin and excipient. The description of the DAOSD approach in detail can be found in our previous paper [12]. For convenience, a brief introduction of the DAOSD is available in the 1st part of supporting information.

It should be pointed out that amide groups in PVP are linked by the polymer chain. The linkage might lead to an undesirable effect that produce interference cross peaks that does not reflect the interaction between artemisinin and excipient. To address the problem, we use *N*-methylpyrrolidone (denoted as NMP, Fig. 1c) as a model compound. The DAOSD approach is utilized to characterize interaction between the ester group of artemisinin and amide group of NMP.

2. Experimental

2.1. Reagents

Artemisinin with purity of 98% was purchased from Aladdin. *N*-methylpyrrolidone, acetonitrile and tetramethylammonium bromide were of AR grade and obtained from Beijing Chemical Company. PVP (K30) was of CP grade and purchased from Sinopharm Chemical Reagent Co. Ltd. D_2O (with >99.9% deuterium content) and C_6D_6 (with >99.9% deuterium content, containing 0.03 wt% TMS) were products of Sigma-Aldrich company.

2.2. Instrument

^{1}H NMR spectra were recorded on a Bruker-400 spectrometer operating at 400.23 MHz and 32 scans were co-added. A capillary filled with C_6D_6 (containing 0.03 wt% of tetramethylsilane (TMS)) was utilized for each experiment as the external standard. To prevent the evaporation of C_6D_6 and TMS, the capillary was sealed. C_6D_6 was also used in the shim process and all chemical shifts were corrected according to the signal of TMS. In addition, the peak area of the TMS peak was used as an external standard in the quantitative analysis. Two dimensional ^{1}H-^{13}C HSQC spectrum was recorded on the same instrument operating at same frequency and 1024 scans were co-added.

FTIR spectra were collected on a Thermo-Fischer Nicolet 6700 Fourier transform infrared spectrometer equipped with an attenuated reflection accessory. All the spectra were recorded at a resolution of 4 cm^{-1} and 32 scans were co-added. During the experiment, the FTIR spectrometer was purged by dry air to minimize the interference of water vapor.