Determination of Drug–Polymer Binding Constants by Affinity Capillary Electrophoresis for Aryl Propionic Acid Derivatives and Related Compounds

ZHONGJIANG JIA, DUK SOON CHOI, HITESH CHOKSHI

pRED, Pharma Research and Early Development, Pharmaceutical and Analytical R&D, Hoffmann-La Roche, Nutley, New Jersey

Received 22 June 2012; revised 8 October 2012; accepted 28 November 2012

Published online 26 December 2012 in Wiley Online Library (wileyonlinelibrary.com). DOI 10.1002/jps.23424

ABSTRACT: The binding constants (K_bs) of 17 aryl propionic acid derivatives (APADs) and related compounds with polyvinylpyrrolidone (PVP K30) and vinylpyrrolidone–vinyl acetate copolymer (Kollidon VA64) in aqueous media were determined by affinity capillary electrophoreses (ACE). The K_bs of APAD to polymers increase with octanol–water partition coefficients of the compounds. Kollidon VA64 is a stronger binder than PVP K30 to APAD compounds. The K_bs are greater at pH 4 than at pH 9. Both hydrophobic interaction and hydrogen bonding may be involved. However, hydrophobic interaction appears to be dominant. The ACE method is simple and fast, which could be used to study drug–polymer interaction in aqueous media. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:960–966, 2013

Keywords: aryl propionic acid derivatives; polyvinylpyrrolidone; vinylpyrrolidone–vinyl acetate copolymer; polymers; interaction; drug–polymer binding constant; capillary electrophoresis (CE); octanol–water partition coefficient; log *P*; solubility

INTRODUCTION

Polymers are widely used as solubility enhancers and crystallization inhibitors in supersaturatable drug delivery systems such as self-emulsifying drug delivery system (SEDDS)[1] and solid dispersion (SD)[2–4] to improve solubility, dissolution, and oral bioavailability of poorly water-soluble drugs.[5] However, the mechanisms of crystallization inhibition by polymer and mechanism of drug release from polymer matrix are complex and not well understood.[6–11] For hydroxypropyl-methylcellulose-acetate-succinate (HPMC-AS)-based spray-dried dispersions, Friesen et al.[10] proposed that the formation of drug–polymer colloids are critical to provide supersaturation and increase bioavailability. It has been suggested that the stabilization of itraconazole supersaturated solutions by polymers (cellulose acetate phthalate and polyvinyl acetate phthalate) was primarily due to the increase in solution viscosity.[12,13] Numerous evidences of interactions between drugs and polymers have been reported, which could be one of the important factors in stabilizing the formulations and improving bioavailability.[8,14–21] Therefore, measurement of drug–polymer binding constants (K_bs) could provide insight information about the roles of polymers in the stability and performance of the formulations.

Interactions between drug and polymer can be classified into three major modes: electrostatic, hydrogen binding, and hydrophobic.[22,23] The strength and mode of interactions depend on the properties of polymer and drug. Drug–polymer interactions are usually characterized in solid-state by traditional solid-state techniques [X-ray diffraction (XRD), infrared spectroscopy (IR), differential scanning calorimetry (DSC), scanning electron microscope (SEM), hot-stage microscopy, and nuclear magnetic resonance (NMR)] and in solution state by spectroscopic methods (ultraviolet-visible spectroscopy (UV–VIS), IR, fluorescence, and NMR) for any changes in physicochemical properties.[24] K_bs in aqueous solution can be measured by determining the free drug concentration using spectroscopic methods and equilibrium dialysis.[22,23,25–27] For compounds that are poorly aqueous soluble or weakly bond to polymer, it could be difficult and time consuming in determining the

Correspondence to: Zhongjiang Jia (Telephone: +973-235-7584; Fax: +973-235-3769; E-mail: zhongjiang.jia@roche.com)

Journal of Pharmaceutical Sciences, Vol. 102, 960–966 (2013)

free drug concentration. Therefore, there is a lack of simple and fast screening technique for drug–polymer K_bs.

Affinity capillary electrophoresis (ACE) has been widely used in studying non-covalent interactions and measuring binding and dissociation constants [e.g., drug–protein binding, drug-cyclodextrin complex, acid dissociation constant (pK_a)].[28–31] However, it has rarely been applied for the binding studies of drugs and pharmaceutical polymers.[32] In this work, a list of 17 aryl propionic acid derivative (APAD) and related compounds were selected as the model compounds. All of these compounds have one carboxyl group, but different lipophilicity or log *P*. The K_bs of these compounds with two polymers, polyvinylpyrrolidone (PVP K30) and vinylpyrrolidone–vinyl acetate copolymer (Kollidon VA64), are measured by ACE at different pH conditions. The chemical structure of the compounds and polymers are shown in Figure 1. The K_bs will be correlated to the octanol–water partition coefficients (log *P*s) of the compounds.

The measurement of K_bs by ACE is based on the changes in effective electrophoretic mobility (M_e) of the drug upon binding to the polymer. The M_e values of the drug are determined at different polymer concentrations using Eq. 1, where V is the applied voltage, L_d is the effective capillary length to the detector, L_t is the total capillary length, t_m is the migration time of the drug, and t_o is the migration time of the neutral marker [e.g., dimethyl sulfoxide (DMSO)]. The neutral marker was used to correct any changes in electroosmotic flow (EOF) because of the addition of polymer in the CE run buffer. Interaction between the drugs and PVP polymers have been proposed and confirmed to be 1:1 stoichiometry in the literature.[22,23,33] However, deviation from 1:1 stoichiometry is possible because of the fact that polymers are built from uniform monomers. For simplicity, 1:1 stoichiometry is assumed in this work. The K_b can be obtained from nonlinear curve fitting of M_e as a function of total polymer concentration $[P]_t$ according to Eq. 2, where M_d and M_c are the M_e of drug in the absence of polymer and the M_e of drug–polymer complex, respectively.[28,29]

$$M_e = \frac{L_d L_t}{V}\left(\frac{1}{t_m} - \frac{1}{t_o}\right) \quad (1)$$

$$M_e = \frac{M_d + M_c K_b [P]_t}{1 + K_b [P]_t} \quad (2)$$

In order to detect the changes in M_e of the drug by ACE, at least one of the polymer or drug has to be charged in the CE run buffer and the drug–polymer complex should have different charge/size ratio or M_e from the drug. Only the retention time of the drug is measured not the concentration. Finally, the drug–polymer interaction should be in rapid equilibrium.

MATERIALS AND METHODS

Materials

Deionized water was used for all solution preparations. Kollidon VA64 fine [molecular weight (MW): 45,000—70,000 Da] and PVP K30 (MW: 44,000–55,000 Da) were obtained from BASF (Ludwigshafen, Germany). The 17 APAD drugs and related compounds given in Table 1 (Sigma–Aldrich, St. Louis, MO), tris(hydroxymethyl) aminomethane (TRIS) (Fisher Scientific, Fair Lawn, NJ), sodium acetate trihydrate (Fisher Scientific), glacial acetic acid (J.T. Baker, Phillipsburg, NJ), and DMSO (Sigma-Aldrich) are equivalent of analytical grade or higher grade reagents.

Sample Preparation

Buffer solutions of 100 mM TRIS (pH 9) and 50 mM acetate (pH 4) were prepared. A stock polymer solution of 2% (w/v) (~0.4 mM) was prepared by dissolving the polymer in the pH buffer. The average MW of 57,500 Da for Kollidon VA64 and 49,500 Da for PVP K30 were used for molar calculation. Then 14 solutions containing 0%–2% (w/v) polymer were prepared by diluting the stock polymer solution in the same pH buffer. These polymer solutions were used as the CE run solutions. A drug stock solution of 1–2 mg/mL containing 30%–50% (v/v) DMSO was also prepared in the same pH buffer. Fourteen injection samples containing drug–polymer–DMSO mixtures were prepared by diluting the drug stock solution 100 times into the CE run solutions containing different percentages of polymer. The final concentrations are 10–20 μg/mL for the drugs and 0.3%–0.5% for DMSO.

Affinity Capillary Electrophoresis

The CE experiments were performed on an Agilent CE system with a diode array UV–VIS detector (Santa Clara, CA). The uncoated fused silica capillary (Polymicro Technologies, Phoenix, AZ) of 32 cm L_t and 24 cm L_d (50 μm ID, 360 μm OD) was used throughout the experiments. The capillary was thermostated at 25.0 ± 0.1°C. Prior to the first run, the capillary was flushed with 0.1 M NaOH for 20 min, water for 10 min, and running buffer for 5 min.

The capillary was rinsed with the CE run solution for 5 min. Then, the injection sample of drug–polymer–DMSO mixture in the same CE run solution was injected at 25 mbar for 5 s from the injection vial. Constant voltage and external air pressure were