Journal of Drug Delivery Science and Technology 39 (2017) 484–489

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Effect of coexisting atorvastatin calcium on in vitro uremic-like-toxin adsorption in gastrointestinal tract model solution by spherical carbon adsorbent for chronic renal failure therapy

Yusuke Hattori, Yayoi Nitta, Makoto Otsuka*

Research Institute of Pharmaceutical Sciences, Faculty of Pharmacy, Musashino University, 1-1-20 Shinmachi, Nishi-Tokyo, Tokyo 202-8585, Japan

ARTICLE INFO

Article history:
Received 8 February 2017
Received in revised form
2 March 2017
Accepted 6 March 2017
Available online 8 March 2017

Keywords:
Spherical carbonaceous adsorbent
Adsorption kinetics
Atorvastatin
Urine-like-toxin indole-3-acetic acid
UV/Chemometrics method

ABSTRACT

Objectives: The adsorption kinetics of urine-like-toxin indole-3-acetic acid (IA) by spherical carbonaceous adsorbent (SC) was inhibited by competitive effect of atorvastatin calcium (AT).
Methods: Competitive effect of AT on the adsorption behavior of IA by SC was investigated by ultraviolet (UV) absorption/chemometrics method. In order to predict the adsorbed amounts of IA and AT to SC, the calibration models to predict drug concentrations (IA and AT) were obtained based on UV profiles of standard sample solutions by the classical least squares (CLS) method.
Key findings: The IA and AT adsorption behaviors of SC followed first-order kinetics. The drug adsorption kinetic rate constants for IA and AT (k_{IA} and k_{AT}) were obtained for the single- and multiple-drug administrations (SA and MA) by the least-squares method. In the case of the MA, the k_{IA} was 75% suppression by the coexistence of AT, but the k_{AT} was 44% suppression by the IA.
Conclusion: Adsorption rate to the SC of the IA or AT, respectively, was significantly inhibited by the presence of coexistence drug.

1. Introduction

In chronic kidney disease (CKD) patients, the concentrations of uremic toxins in the blood are higher than in healthy people [1,2]. Pharmaceutical activated carbon shows adsorption specificity for adsorbing uremic toxins of between 100 and 200 Da [3–5], and this property contributes to the efficacy expression of such compounds. Therefore, for the treatment of CKD, pharmaceutical activated carbon is given orally to improve uremic symptoms by adsorbing uremic toxins in the alimentary tract. Kremezin® is a brand product of spherical carbonaceous adsorbent (SC), which is a form of pharmaceutical activated carbon, available in Japan as a domestic medicine for therapeutics of CKD [6–13].

On the other hand, most pharmaceutical drugs used to treat CKD, and/or co-morbid diseases of CKD, were concomitantly used with SC [14]. Therefore, the adsorbing uremic toxins of SC may inhibit by the coexistence of drugs. There is a concern also that SCs may decrease the effects of co-administered drugs by adsorbing them in the alimentary tract [15], and SCs did indeed adsorb several pharmaceutical compounds (pepsin, sodium cholate and indole) in *in vitro* tests [3,11]. The bioavailability of aspirin was reduced by approximately one-third when co-administered of SC in humans [5]. So, the adsorption to the SC of the combination drug inhibited adsorption of uremic toxins, and reduced the therapeutic effect of the SC. In addition, the adsorption of the combination drug with SC reduced the therapeutic effect of chronic disease by lowering the bioavailability of the combination drug, and consequently might reduced the quality of life of patients.

On the other hand, the representatives of the Japanese Society of Nephrology has been warning that there is a highly correlation ship between CKD and hyperlipidemia [16]. And they are encouraging to CKD patients the clinical treatment of hyperlipidemia and the improvement of the diet. From this fact, there are many clinical cases of CKD patients having a combination of abnormal lipid metabolism and anti CKD drugs.

Therefore, in order to clarify co-administration drug effect to SC, competitive adsorption were analyzed when administered with SCs in a two-component coexistence model in combination with anti-hyperlipidemic drug and a model uremic toxin. However, since the uremic toxin was an unstable compound in solution, most of the toxin was degraded during a long-term in vitro adsorption test,

* Corresponding author.
E-mail address: motsuka@musashino-u.ac.jp (M. Otsuka).

http://dx.doi.org/10.1016/j.jddst.2017.03.006
1773-2247/

as reported by Nissen and Sutter et al. [17]. By therefore, the uremic toxin was not possible to accurately measure the amount of adsorption by the equilibrium adsorption method. Therefore, the adsorption kinetics of concomitant medication drug or urine toxin to SC had been investigated by using in-site ultra-violet (UV) spectroscopy with chemometrics [18].

2. Materials and methods

2.1. Materials

SC sample: as adsorbents, the brand product Kremezin®, Fine granules 2 g (KR; Kureha Corporation, Tokyo, Japan). The product was purchased from the market.

Chemicals: Atorvastatin calcium 3/2 hydrate (AT) was purchased from ZKP Co. Ltd., (Batch No.20090707, Beijing, China); Molecular weight:1209.39. Atorvastatin (AT) molecular weight is 558.6, Van der Waals radius 21.070–11.194 Å. Indole-3-acetic acid (IA), which was used as a model of uremic toxin (solubility in water, 8 mg/mL [19]), was purchased as a chemical reagent from Wako Pure Chemical Industries, Ltd. (Tokyo, Japan); molecular weight, 175.2,Van der Waals radius, 10.699–5.671 Å.

2.2. UV spectroscopy measurement

In total, 69 kinds of the standard sample solutions containing 0.9–13.9 μg/mL of AT and/or IA were prepared. UV spectral profiles from the standard sample solutions were measured in the range 200–800 nm using a UV spectrometer (Fiberspec S-2450, Soma Optics, Ltd., Tokyo, Japan) via a UV probe inserted into the solution.

2.3. Drug adsorption kinetics

The drug adsorption kinetic study was performed using 2 g of adsorbents with 10 mg of IA and/or 10 mg of AT as a model uremic toxin and a concomitant medication. The administrated amounts of SC, IA and AT were determined based on dosage amount for therapeutically treatments [20,21]. IA and/or AT powders were dissolved in 900 mL distilled water. After adding 2 g of each carbon adsorbent into the solution, adsorption tests were conducted using a dissolution test apparatus (JPXVI, NTR-3000, Toyama Sangyo Co., Ltd., Osaka, Japan) at 37 °C with the paddle method (100 rpm). UV spectra from the solutions were measured in the range 200–800 nm with a UV-spectrometer (Fiberspec S-2450, Soma Optics, Ltd., Tokyo, Japan) via a UV probe inserted into the solution continuously (time interval: 20 s). The analyses were repeated three times.

2.4. High performance liquid chromatography measurement

The IA and AT concentrations in the solution were measured by high performance liquid chromatography (HPLC; LC10ADvp, Shimadzu Co. Ltd., Kyoto, Japan) with an autosampler (SIL-10ADvp, Shimadzu Co. Ltd., Kyoto, Japan). The analysis was performed using an Inertsil ODS-3 column (250 × 4.6 mm, 5 μm particle size, GL Sciences, Inc., Tokyo, Japan). Elution was carried out using an isocratic solvent system consisting of 0.1 mol/L citric acid/ammonia buffer (pH 4.0), acetonitrile and tetrahydrofuran (57:23:20, Japanese Pharmacopoeia 16) at a flow rate of 1.8 mL/min. The sample injection volume was 20 μL. The eluate was monitored by UV-visual detector (SPD-M10Avp, Shimadzu Co. Ltd., Kyoto, Japan) at a wavelength of 319 nm. The IA and AT concentrations were calculated compared with the calibrated standard sample curves.

2.5. Chemometric analysis

In order to evaluate the function of SCs when two kinds of model compounds (AT and IA) were competitively adsorbed by SCs, the drug concentration profiles of each drug were determined in accordance with the above experimental section by UV chemometric methods. A chemometric analysis was performed using a classical least-squares (CLS) regression program contained in Pirouette Ver. 4.5 (Infometrix Co., Woodenville, WA, USA). The CLS regression is an automated data decomposition technique that is formulated as follows [22–25]:

$$\boldsymbol{D} = \boldsymbol{CK} + \boldsymbol{E} \tag{1}$$

Here, $\boldsymbol{D}$ $(n \times p)$ is a matrix of a collection of n UV spectral patterns (written row-wise) measured at p points along the frequency axis, whereas $\boldsymbol{C}$ $(n \times m)$ and $\boldsymbol{K}$ $(m \times p)$ depict quantities of m independent chemical components and the spectral patterns of independent components, respectively. In short, the measured the spectral pattern, $\boldsymbol{D}$, is made of a linear combination of pure-components of the spectral patterns of the independent components, $\boldsymbol{K}$, with weighting factors, $\boldsymbol{C}$, excluding experimental error, **E**.

With the CLS regression model, $\boldsymbol{C}$ (or $\boldsymbol{K}$) can be predicted using Eq. (2) from $\boldsymbol{D}$ by using a priori knowledge of $\boldsymbol{K}$ (or $\boldsymbol{C}$) no matter what experimental error, $\boldsymbol{E}$, is involved in $\boldsymbol{D}$ [22-25]:

$$\boldsymbol{C} = \boldsymbol{DK^T}\left(\boldsymbol{KK^T}\right)^{-1} \tag{2}$$

where the superscripts $\boldsymbol{T}$ and *-1* represent transpose and inverse matrices, respectively.

The best calibration model for the CLS method was determined to minimize the standard error of cross-validation by the leave-one-out cross-validation method in the CLS software, and the standard error of calibration (SEC) (Equation (3)) and correlation coefficient constants of calibration and validation values are evaluated.

$$SEC = \sqrt{\frac{PRESS}{n_v - k}} \tag{3}$$

PRESS is a prediction residual error sum of squares, n_v is the number of validation samples, and k is the number of factors in the model.

In order to predict the drug concentration, chemometric analysis was performed based on the calibration UV data set of the 69 standard sample solutions to estimate drug concentration using the CLS method. The chemometric parameters for AT and IA of CLS calibration models were determined to minimize the standard error of cross-validation (*SECV*) by the leave-one-out method. *SECV*, *SEC*, *PRESS* for calibration and validation (*Press Cal* and *Press Val*), and the r-values for calibration and validation (*r-Cal* and *r-Val*) were evaluated as chemometric parameters of the calibration models. To determine the accurate calibration CLS model in order to predict the drug concentration, the models were confirmed using an external validation UV data set and HPLC data.

Adsorption kinetic constant k based on the model drug concentration profiles (IA and AT) was calculated using equation (4):

$$\log C_t = -kt + \log C_0 \tag{4}$$

where C_t is the drug concentration C at any time t, C_0 is original concentration of C at initial time, and k is a rate constant.