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RESEARCH PAPER

Real-time Quantitative Monitoring of Synthesis Process of Clevidipine Butyrate Using Raman Spectroscopy

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Abstract: A direct synthesis process of clevidipine butyrate was used for testing the real-time detection performance of Raman spectroscopy in this study. The decrease of the reactant (Chloromethyl butyrate) and the increase of the product (Clevidipine butyrate) were used as indexes to evaluate the synthesis process using a 785-nm Raman spectrometer. Calibration models were built for the quantification of chloromethyl butyrate and clevidipine butyrate. The issue of linear regression distortions was overcome by setting solvent (acetonitrile) as internal standard. The validation results indicated that the Raman spectroscopy method was reproducible and accurate for monitoring the synthesis process. The real-time data were achieved to evaluate the esterification reaction of clevidipine butyrate under different conditions.

Key Words: Raman spectroscopy; Clevidipine butyrate; Real-time monitoring; Synthesis process

1 Introduction

The ultimate goal of a synthesis process in the pharmaceutical industry is to produce maximum amounts of end-products and to avoid the formation of by-products, with minimum time and energy consumption accompanied by improved cost-effectiveness. Process monitoring of reaction is the most significant operation during manufacture of pharmaceuticals. At present,, the main method for monitoring reaction is to collect samples at different time points during the reaction process using sampling probes, followed by analysis using traditional chromatographic methods, such as thin-layer chromatography (TLC), high performance liquid chromatography (HPLC) and gas chromatography (GC)[1–3]. However, these methods have a major disadvantage, e.g. temporal delay between sampling and analysis results. Therefore, it is necessary to develope real-time and rapid analytical methods to obtain information timely in an optimization process. Spectroscopic techniques, such as ultraviolet-visible (UV-Vis)[4], near-infrared (NIR)[5,6] and mid-infrared (IR)[7–9] spectroscopies, are alternatives for reaction monitoring. However, the problems of spectral overlapping and the difficulties in spectra data interpretation restrict their applications. The difficulties arise because the samples from the reactor are usually a complex mixture composed of reactants, products, by-products and other impurities. The complicated spectra with overlapping bands would lead to intensity changes without any correlation to the content of the components.

Compared with IR and NIR spectroscopies, Raman spectroscopy becomes popular as a quick and non-destructive monitoring tool in pharmaceutical industry[10]. Owing to the clear and selective characteristics, Raman spectral interpretation is more straightforward to the compounds[11]. Because Raman spectroscopy requires little or no sample preparation and pretreatment, it has become a preferred

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technique for real-time process monitoring during drug production process including pharmaceutical blending[12,13], chemical reactors[14–16], distillation[15], and hydrogen peroxide synthesis[17]. However, the use of Raman spectroscopy in synthesis process monitoring is rather limited. Fluorescence interference and laser instability are just some of the inherent problems associated with light scattering and these factors often influence the spectral intensities. Kuba *et al*[18] did an interesting experiment to illustrate the difficulties in real-time quantitative monitoring by Raman spectroscopy. In dealing with heterogeneous catalysis, they found that a decrease in diffusion reflectance was observed as absorption of sample increased, resulting in decrease of Raman intensities. Afterwards, Aarnoutse *et al*[19] pointed out that it was possible to use solvent (1-methyl-2-pyrrolidinone, NMP) as an internal standard for Raman monitoring to overcome the instable laser intensity and turbidity problems. Morenoa *et al*[17] utilized a solvent (water) as an internal standard. Both bands at 1646 and 3400 cm^{-1} of H_2O were included in the calibration equation. Similar problems existed in the quantitative monitoring of yeast fermentation using Raman spectroscopy by Iversen *et al*[20], when the 1627 cm^{-1} band of water was used as the internal standard.

Herein, we proposed the application of Raman spectroscopy technique with preprocessed spectral intensity to develop a fast, inexpensive and non-destructive spectroscopic method for the real-time monitoring of the synthetic process of clevidipine butyrate. The solvent (acetonitrile) was used as the internal standard for clevidipine butyrate and chloromethyl butyrate determination. The real-time monitoring of the esterification reaction was chosen to verify the setup and the calibration model.

2 Experimental

2.1 Materials

Chloromethyl butyrate (99.5%, reagent grade, Sinopharm Chemical Reagent Co., Ltd) was used to prepare a series of 20 standard solutions (2.10–42.00 mg mL^{-1}) for the quantitative calibration models. Clevidipine butyrate (99.81%, synthesized by our group) was also employed to prepare a set of 21 standard solutions (0.00–80.00 mg mL^{-1}) for the quantitative calibration models. For validation purpose, 36 composite samples of chloromethyl butyrate and clevidipine butyrate were prepared. After sample preparation, the spectra were collected immediately to reduce the possible errors caused by solvent evaporation. 4-(2,3-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-5-methoxy-carbonyl-3-pyridinecarboxylic acid (DDDMPA, 98%) was synthesized by our group. K_2CO_3 as catalyst and acetonitrile (AR) were purchased from Sinopharm Chemical Reagent Co., Ltd. In order to get the reference concentration of the samples, acetonitrile (HPLC grade, Merck), methanol (HPLC grade, Merck), sodium phosphate monobasic anhydrous (99.0%, AR, Sinopharm Chemical Reagent Co., Ltd), phosphoric acid (AR, Sinopharm Chemical Reagent Co., Ltd), and distilled water (Millipore quality) were used for HPLC.

2.2 Synthesis of clevidipine butyrate

DDDMPA (23.4 g, 66 mmol, 1.0 eq) and K_2CO_3 (11.44 g, 82.8 mmol, 1.25 eq) was firstly mixed in acetonitrile under nitrogen atmosphere. And then chloromethyl butyrate (11.71 g, 86 mmol, 1.3 eq) was added. The mixture was refluxed for 2 h, then the reaction mixture was cooled down to room temperature, the inorganic salts were filtered out and the filtrate was washed with warm acetonitrile. The scheme for the synthesis of clevidipine butyrate is shown in Fig.1.

2.3 HPLC determination

HPLC test was carried out using Agilent 1260 series HPLC system equipped with a G1311C binary pump, G1316A column heater and a G1315D diode array detector. For quantification of reactant and product, the samples were extracted, filtered and appropriately diluted with acetonitrile. Separation of the compounds was accomplished using a Waters Symmetry C_{18} column (250 mm × 4.6 mm, 5 μm). The injection volume was 10 μL, and the column temperature was 35 °C. Flow rate was kept at 1.5 mL min^{-1}. The seperation was monitored at 220 nm. The mobile phase A (MPA) was consisted of 50 mM sodium dihydrogen phosphate (Adjusted to pH 2.50 with phosphoric acid) and mobile phase B (MPB) was acetonitrile-methanol mixture (3:2, *V/V*). The gradient elution program is listed in Table 1[21]. The retention time of

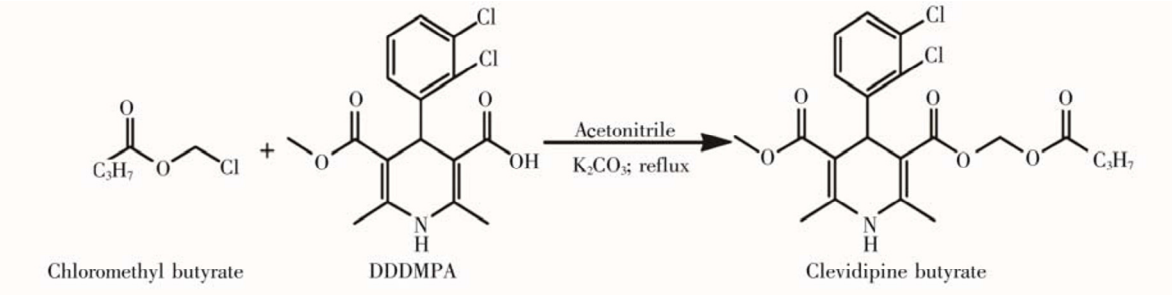

Fig.1 Schematic illustration for the synthesis of clevidipine butyrate