Development and Validation of a Liquid Chromatographic Method for Concurrent Assay of Weakly Basic Drug Verapamil and Amphoteric Drug Trandolapril in Pharmaceutical Formulations

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ABSTRACT

The analysis of weakly basic drugs such as verapamil by reverse-phase liquid chromatography remains a problem, particularly when present in combination with other drugs such as amphoteric compounds like trandolapril. In this study, the simple, accurate, precise and fully validated RP-LC method for the simultaneous determination of verapamil and trandolapril in combined dosage forms has been developed. The LC method allowed quantitation over the ranges of 0.50-18.00 µg/mL and 0.05-1.00 µg/mL for verapamil and trandolapril, respectively. The detection limits were found to be 0.008 µg/mL and 0.018 µg/mL for verapamil and trandolapril, respectively. Moreover, pKₐ values of verapamil and trandolapril were determined via the dependence of the retention factor on the pH of the mobile phase for ionizable substances. The effect of the mobile phase composition on the ionization constant was studied by measuring the pKₐ at different methanol-water mixtures, ranging 50-65% (v/v). It was shown that RP-HPLC was suitable for the high throughput analysis of the combination of verapamil and trandolapril. The method also allows a number of cost and time saving benefits and can be readily employed for the analysis of pharmaceutical formulations. The method has been verified, without any interference from excipients, for the concurrent analysis of these compounds in tablets.

Key words: verapamil, trandolapril, ramipril, pKₐ, HPLC, simultaneous determination

INTRODUCTION

The inhibitors of the angiotensin-converting enzyme (ACE inhibitors) are widely used for the treatment of mild to moderate hypertension and heart failure, either alone or in conjunction with other drugs(1). Trandolapril (TRA, (2S,3aR, 7aS)-1-[(S)-N-[[(S)-1-(ethoxycarbonyl)-3-phenyl propyl] alanyl] hexahydro-2-indolinecarboxylic acid), is a long acting, highly lipophilic non-peptide, ACE inhibitor with a carboxyl group but without sulphhydryl group(2) (Figure 1A). It is used for the management of hypertension and for the stable patients who have evidence of left ventricular systolic dysfunction or symptoms of heart failure within the first 2 days after acute myocardial infarction(3,4). Tablet dosage form contains 1, 2 or 4 mg TRA.

Verapamil hydrochloride(VER,(5-[3,4-dimethoxyphenethyl] methylamino)-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile hydrochloride), a slow calcium channel antagonist, inhibits the transmembrane influx of calcium ions into the heart and vascular smooth muscle cells (Figure 1B). It also enhances myocardial blood flow due to the calcium antagonistic effect on the smooth vascular muscles of coronary arteries. Therefore, it contributes to the anti-ischemic and anti-anginal efficiency in all types of coronary artery diseases and is also used as anti-hypertensive and anti-arrhythmic(5). The film-coated tablet dosage form contains 40 mg, 80 mg, or 120 mg of VER for oral administration.

The dissociation constant (pKₐ) of a drug molecule is a key parameter in absorption, distribution, metabolism, excretion and toxicity researches because it governs solubility, absorption, distribution and elimination of substances(6). Also, the pKₐ values constitute important data for thorough