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ORIGINAL ARTICLE

Chemometric technique for the optimization of chromatographic system: Simultaneous HPLC determination of Rosuvastatin, Telmisartan, Ezetimibe and Atorvastatin used in combined cardiovascular therapy

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Abstract Developed and optimized a validated isocratic reverse phase HPLC separation of Rosuvastatin, Telmisartan, Ezetimibe and Atorvastatin in pharmaceutical preparation using response surface methodology. The separation was carried out by using phenomenex C_{18} column (15 cm × 4.6 mm id, 5 μm particle size) and UV detection at 239 nm. The ranges of the independent variables used for the optimization were MeCN: 33–38%, buffer conc.: 10–20 mM and flow rate: 1–2 ml/min. The influence of these independent variables on the output responses: capacity factor of the first peak (k_1), resolutions of the 2nd and 3rd peak ($Rs_{2,3}$), and capacity factor of the fifth peak (k_5) were evaluated. Using this strategy, a mathematical model was defined and a response surface was derived for the separation. The three responses were simultaneously optimized by using Derringer's desirability functions. Optimum conditions chosen for the assay were MeCN, MeOH, 20 mM K_2HPO_4 (pH 3.0 ± 0.2) solution (34.27:20:45.73 v/v/v) and flow rate 2 ml/min. Total chromatographic analysis time per sample was approximately 10 min. The optimized assay condition was validated as per the ICH guidelines and applied for the quantitative analysis of Rosavel EZ, Avas-EZ and Lipisar 20 tablet. The developed method was simple, accurate and precise. Hence, it can be employed for the routine analysis in quality control laboratories.

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1. Introduction

High performance liquid chromatography method development and optimization is a well-known procedure exceptionally for the simultaneous determination of pharmaceutical dosage forms. Since HPLC utilizes a wide selection of several chromatographic factors, viz., the type and composition of the organic phase, column temperature, flow rate, buffer molarity, pH, type of the stationary phase, etc., optimization of the experimental conditions is a complicated process. To achieve this objective, any one of the chemometric methods

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which includes the overlapping resolution maps (Lews et al., 1996), factorial design (Valliappan et al., 2002) and response surface methodology (Myers and Montgomery, 1995; Sivakumar et al., 2007, 2007a,b, 2008) can be applied. In general, the chemometrics can be used to accomplish a variety of goals in chromatography laboratory: (i) speeding methods development, (ii) make better use of chromatographic data and (iii) explain the chromatographic process (Matthijs et al., 2004).This kind of knowledge provides important clues in the attainment of optimum experimental conditions in the development of chromatography methods (Morgan, 1991).The best experimental design approach for the purpose of modeling and optimization is the response surface design (Myers and Montgomery, 1995). However, for the HPLC method intended to be applied for the pharmaceutical or industrial environment, the analysis time is usually optimized without losing resolution (Deming, 1991).

When one needs to optimize more than one response at a time the use of multicriteria decision making (MCDM), a chemometric technique is the best choice. The different approaches of MCDM include the path of steepest ascent, constrained optimization procedure, Pareto-optimality, utility function, Derringer's desirability function. The path of steepest ascent can be employed only when all the response models are linear. Constrained optimization procedure can be used when all response models are non-linear, or when there is a mix of linear and non-linear responses. However, this method optimizes only one response by targeting all other responses to appropriate constraints. When there is a mix of linear and non-linear responses, or when all response models are linear or non-linear, Pareto-optimality, utility function or Derringer's desirability function can be used. Pareto-optimality method can basically identify the Pareto optimal region by graphical means, but requires some additional criterion or the advice of an expert to select one particular Pareto optimum point (Hadjmohammadi and Safa, 2004). The Pareto-optimal method and the Derringer's approach have their own advantages and that the decision on which method to use depends on the problem and the availability of chromatographic expertise.

There are many ways in which the individual desirability can be combined. If the combined criterion is a simple arithmetic average, it is called as utility function and if it is a geometric mean it is referred as Derringer's desirability function. The idea of combining desirabilities as geometric mean was first presented by Harrington (1965) but it was put into a more general form by Derringer (Derringer and Suich, 1980). The advantage of the Derringer's desirability function is that if one of the criteria has an unacceptable value, then the overall product will also be unacceptable, while for the utility functions, this is not the case. Further, Derringer's method offers the user flexibility in the definition of desirability functions. Derringer's desirability function was introduced in chromatography by Deming (1991), implementing resolution and analysis time as objective functions to improve separation quality. Safa and Hadjmohammadi (2005) employed Derringer's desirability function for the simultaneous optimization of resolution and analysis time in micellar liquid chromatographic separation of a group of nine phenyl thiohydantoin amino acids. Recently, Hayashi and Matsuda (1994) proposed a chemometric tool based on the Function of Mutual Information (FUMI) theory to improve prediction of the uncertainty in HPLC. Kotani et al. (2003) employed FUMI theory for the prediction of measurement R.S.D. and detection limits in HPLC-electrochemical detection of catechins without repetitive measurement of chromatograms, saving considerable amounts of chemicals and experimental time. Among the various above options, the Derringer's desirability functions were successfully employed.

We have recently employed the same MCDM approach (Derringer's desirability function) for the development and optimization of a HPLC method for the simultaneous estimation of pantoprazole and domperidone (Sivakumar et al., 2007b), amlodipine and atorvastatin (Sivakumar et al., 2007) in quality control and plasma samples.

Atorvastatin (AT) (Fig. 1), (3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-(propan-2-yl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid and rosuvastatin (RS) (Fig. 1), (3R,5R,6E)-7-[4-(4-fluorophenyl)-2-(N-methylmethanesulfonamido)-6-(propan-2-yl)pyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid belong to the statin class of drugs used to treat hypercholesterolemia both in patients with established cardiovascular disease as well as those who are at a high risk of developing atherosclerosis. These drugs inhibit the rate limiting key enzyme known as 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase involved in cholesterol biosynthesis. Until the approval of rosuvastatin in 2003, atorvastatin was the most efficacious drug in the statins class (Jones et al., 1998) but recent studies reported rosuvastatin as a potent inhibitor of HMG-CoA reductase having a higher LDL-lowering effect as compared with other statins (Jones et al., 2003; McTaggart, 2003), which demonstrates that both rosuvastatin and atorvastatin are the leading drugs in the statins class.

Ezetimibe (EZ) (Fig. 1), (3R,4S)-1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidine-2-one is a selective cholesterol absorbtion inhibitor, which potently inhibits the absorption of biliary and dietary cholesterol (Van Heek et al., 1997) from the small intestine without affecting the absorption of fat-soluble vitamins, triglyceride or bile acids. Clinical studies have shown that co-administration of ezetimibe with statins could provide significant reductions in both the low-density lipoproteins (LDL) and the total cholesterol with slight increase in the high-density lipoproteins (HDL) (Ballantyne et al., 2003; Davidson et al., 2002; Kerzner et al., 2003; Melani et al., 2003). Also co-administration of ezetimibe with statins could significantly reduce the risk of coronary heart disease (CHD) events in patients with hypercholesterolemia.

Telmisartan (TL) (Fig. 1), 2-(4-{[4-methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3-benzodiazol-1-yl]methyl}phenyl)benzoic acid is a new highly selective, non-peptide angiotensin II type 1 (AT1)-receptor antagonist angiotensin that lowers blood pressure through blockade of the renin–angiotensin–aldosterone system (RAAS) (Neutel and Smith,1998) and widely used in treatment of hypertension. It can selectively block the angiotensin type I (AT1) receptor, which is responsible for vasoconstriction and for salt and water retention. The therapy with this drug offers a good quality of life for hypertensive patients due to the absence of side effects and its once daily administration. Telmisartan has become one of the most important advances in the treatment of hypertension.

Cardiovascular therapy usually involves different combination of antihypertensive and lipid lowering drugs. Therefore the simultaneous determination of these analytes becomes motivating and significant. In the present work, a HPLC

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