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Short communication

Multi-criteria decision making approach and experimental design as chemometric tools to optimize HPLC separation of domperidone and pantoprazole

T. Sivakumar [a], R. Manavalan [a], C. Muralidharan [b], K. Valliappan [a,*]

[a] *Department of Pharmacy, Faculty of Engineering and Technology, Annamalai University, Annamalainagar, TN 608 002, India*
[b] *Department of Manufacturing Engineering, Faculty of Engineering and Technology, Annamalai University, Annamalainagar, TN 608 002, India*

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Abstract

This paper deals with multiple response simultaneous optimization using the Derringer's desirability function for the development of a reversed-phase HPLC method for the simultaneous determination of domperidone and pantoprazole in commercial pharmaceutical preparations. Twenty experiments, taking the retention factor of the first peak, the two resolutions, and three retention times as the responses with three important factors, mobile phase composition, buffer molarity and flow rate, were used to design mathematical models. The experimental responses were fitted into a second order polynomial and the six responses simultaneously optimized to predict the optimum conditions for the effective separation of the studied compounds. The optimum assay conditions were: methanol–acetonitrile–dipotassium hydrogen phosphate (pH 7.0; 15.3 mM) (20:33:47, v/v/v) as the mobile phase and at a flow rate of 1.19 ml/min. While using this optimum condition, baseline separation with a minimum resolution of 2.0 and a run time of less than 6 min were achieved. The method showed good agreement between the experimental data and predictive value throughout the studied parameter space. The optimized assay condition was validated according to ICH guidelines to confirm specificity, linearity, accuracy and precision.

Keywords: Multiple response optimization; Derringer's desirability function; Reversed-phase HPLC; Central composite design; Domperidone; Pantoprazole

1. Introduction

Reversed-phase high performance liquid chromatography (RP-HPLC) is a well-known technique exceptionally for the simultaneous determination of pharmaceutical dosage forms. Since HPLC utilizes a wide selection of chromatographic factors, viz., the type and concentration of organic modifier, pH, buffer molarity, temperature, flow rate, etc., optimization of the experimental conditions is a complicated process. Therefore, a systematic approach such as experimental design to optimize chromatographic separations is more essential [1,2]. The best experimental design approach for the purpose of modeling and optimization are the response surface design [3].

However, the HPLC method intended to be applied for the pharmaceutical or industrial environment, the analysis time is usually optimized without losing resolution [4]. When one needs to optimize more than one response at a time the use of multi-criteria decision making (MCDM), a chemometric technique is the best choice. 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 [5]. The different approaches of MCDM [6] 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

* Corresponding author. Tel.: +91 4144 239738; fax: +91 4144 238145.
E-mail address: kvalliappan@gmail.com (K. Valliappan).

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non-linear responses, or when all response models are of 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 [7]. 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 desirabilities 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 [8] but it was put into a more general form by Derringer [9]. 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 [4], implementing resolution and analysis time as objective functions to improve separation quality. Safa and Hadjmohammadi [10] 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 [11] proposed a chemometric tool based on the Function of Mutual Information (FUMI) theory to improve prediction of the uncertainty in HPLC. Kotani et al. [12] 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 function was applied to explore the user flexibility of this technique in selecting optimum chromatographic conditions for the determination of drugs in a variety of sample matrices.

Domperidone (DP) (Fig. 1) is a potent dopamine antagonist used for the treatment of nausea and vomiting, and pantoprazole (PP) (Fig. 1) is a selective and long-acting proton pump inhibitor used for the treatment of acid-related gastrointestinal disorders. Nowadays, the mixtures of these active components are present in pharmaceutical formulations as capsules and tablet forms. DP maleate is official in British Pharmacopeia [13] in which a HPLC-UV method is available for its separate determination in tablets. PP sodium is not official in any of the pharmacopoeias. On the other hand, several methods have been cited in the literature for the estimation of DP [14–17] and PP [18–20] individually. Owing to the presence of interferences or time-consuming analysis, the determination of these analytes in samples containing mixtures is not possible if analytical methods cited in the monograph and literature are followed. Therefore, the routine quality assurance of these products represents a difficult analytical task to be accomplished.

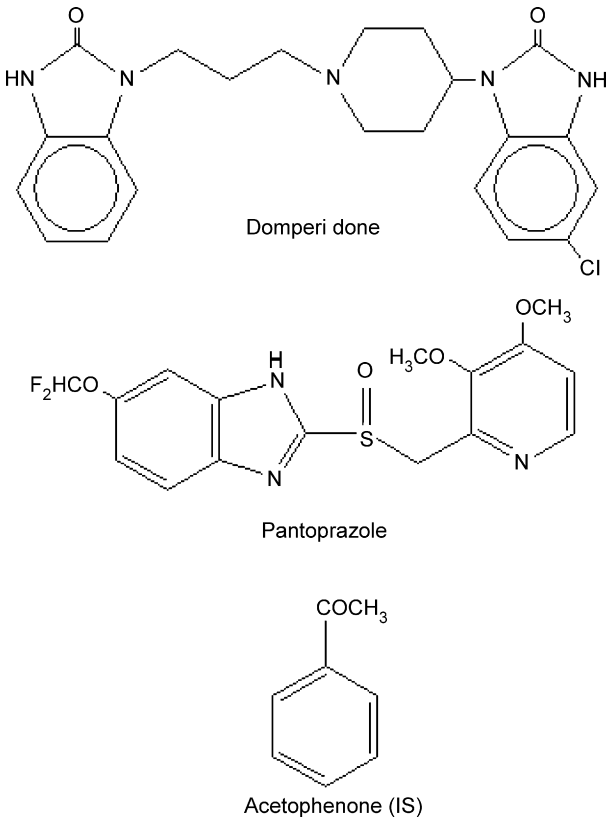

Fig. 1. The chemical structures of analytes and internal standard (IS).

Nevertheless, to the best of our knowledge, there seems to be no reports concerning methods for the simultaneous determination of DP and PP in the commercial pharmaceutical preparations.

In the present work, a HPLC method was developed, optimized and validated for the determination of DP and PP present in commercial preparations (tablets and capsules). In order to understand the sensitivity of the chromatographic factors on the separation of analytes and to simultaneous optimization of resolution and analysis time, chemometric protocols of response surface design and Derringer's desirability function were successfully employed.

2. Experimental

2.1. Apparatus

Chromatographic measurements were made on a Shimadzu (Tokyo, Japan) model which consisted of a LC10AD and LC10 ADvp solvent delivery module, SPD 10A UV–Visible detector, a Rheodyne injector (model 7125, USA) valve fitted with a 20 μl loop, and UV detector (SPD-10A). The system was controlled through a system controller (SCL-10A) and a personal computer using a Shimadzu chromatographic software (LC Solution, Release 1.11SP1) installed on it. The mobile phase was degassed using Branson sonicator (Branson Ultrasonics Corporation, USA). Absorbance spectra were recorded using an UV–Visible spectrophotometer (Model