Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 169 (2016) 50–57

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

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

Full spectrum and selected spectrum based multivariate calibration methods for simultaneous determination of betamethasone dipropionate, clotrimazole and benzyl alcohol: Development, validation and application on commercial dosage form

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ARTICLE INFO

Article history:
Received 14 February 2015
Received in revised form 7 June 2015
Accepted 1 June 2016
Available online 3 June 2016

Keywords:
Betamethasone dipropionate
Clotrimazole
Benzyl alcohol
PCR
PLS
ANN
GA

ABSTRACT

Five different chemometric methods were developed for the simultaneous determination of betamethasone dipropionate (BMD), clotrimazole (CT) and benzyl alcohol (BA) in their combined dosage form (Lotriderm® cream). The applied methods included three full spectrum based chemometric techniques; namely principal component regression (PCR), Partial Least Squares (PLS) and Artificial Neural Networks (ANN), while the other two methods were PLS and ANN preceded by genetic algorithm procedure (GA-PLS and GA-ANN) as a wavelength selection procedure. A multilevel multifactor experimental design was adopted for proper construction of the models. A validation set composed of 12 mixtures containing different ratios of the three analytes was used to evaluate the predictive power of the suggested models. All the proposed methods except ANN, were successfully applied for the analysis of their pharmaceutical formulation (Lotriderm® cream). Results demonstrated the efficiency of the four methods as quantitative tool for analysis of the three analytes without prior separation procedures and without any interference from the co-formulated excipient. Additionally, the work highlighted the effect of GA on increasing the predictive power of PLS and ANN models.

1. Introduction

Betamethasone dipropionate (BMD) is a topical steroid with an anti-inflammatory, anti-pruritic and anti-allergic activities, used for the topical management of corticosteroid responsive dermatoses [1].

Clotrimazole (CT) is an imidazole antifungal used topically in superficial candidiasis, pityriasis versicolor and dermatophytosis, also used for symptomatic relief of trichomoniasis [2]. CT is applied topically as for the treatment of fungal infections as a cream, lotion, spray, solution, powder, lozenges, pessaries and vaginal cream. CT has also been given orally but has now been substituted by other azole drugs [2].

Benzyl alcohol (BA) is used as a solubilizer and preservative. Its bacteriostatic activity mainly targets gram-positive organisms and some fungi. It is widely used in concentrations up to 3% in pharmaceutical preparations, foods and cosmetics [3].

The antifungal activity of CT works by preventing the fungal growth, while BMD possess a strong corticosteroid action that reduces swelling, redness, and itching that occurs in the skin infection and BA is added as a preservative. The three studied drugs are official drugs in British Pharmacopoeia [4]. There are reported chromatographic methods for the determination of BMD, CT or BA in different drug combinations [5–9]. Literature survey revealed a single UV-spectrophotometric method for the determination of the suggested ternary mixture by applying ratio difference method at certain wavelengths in their ratio spectra [10].

The United States Pharmacopoeia and National Formulary [11] reported an HPLC method for the determination of BMD and CT in cream formulations. Another HPLC method [12] was reported for their simultaneous determination in cream formulation. A colorimetric method has been reported [13] for determining CT without interference from BMD. A micellar electrokinetic chromatography was used for separation of BMD, CT and their derivatives in pharmaceutical dosage form [14] .

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http://dx.doi.org/10.1016/j.saa.2016.06.001
1386-1425/

Table 1
Concentrations of BMD, CT and BA in calibration and validation sets.

Calibration set				Validation set			
Mixtures	BMD	CT	BA	Mixtures	BMD	CT	BA
C1	8	120	400	**V1**	12	160	300
C2	8	200	250	**V2**	12	120	200
C3	16	140	400	**V3**	10	180	400
C4	10	200	300	**V4**	14	200	350
C5	16	160	250	**V5**	14	160	400
C6	12	140	250	**V6**	12	200	400
C7	10	140	350	**V7**	16	200	200
C8	16	180	300	**V8**	8	160	350
C9	16	120	350	**V9**	10	160	200
C10	14	120	300	**V10**	8	–	–
C11	12	180	350	**V11**	–	160	–
C12	14	140	200	**V12**	8	160	–
C13	10	120	250				
C14	8	140	300				
C15	8	160	300				

Table 2
Parameters of the genetic algorithms.

Parameter	Value
Population size	20
Maximum generations	50
Mutation rate	0.005
The number of variables in a window (window width)	2
Per cent of population the same at convergence	50
% wavelengths used at initiation	50
Crossover type	Single
Maximum number of latent variables	3
Cross validation	Random
Number of subsets to divide data into for cross validation	4
Number of iterations for cross validation at each generation	2

Chemometrics is the science that deals with extracting valuable information from the raw data [15]. Quantitative spectroscopy has been considerably enhanced by the application of different multivariate calibration methods [16–20]. Multivariate calibration methods are very helpful in spectral analysis owing to the simultaneous inclusion of multiple spectral intensities that notably increase the precision and applicability of quantitative spectral analysis [21]. Thus, the rationales for this work are:

a. Simultaneous determination of BMD, CT and BA in laboratory prepared mixtures and combined dosage form (Lotriderm® cream).

b. A comparative study between the full spectrum based chemometric models (such as PCR and PLS) and selected spectrum ones (such as PLS and ANN proceeded by genetic algorithm procedure).

c. To demonstrate the effect of genetic algorithm (GA) on increasing the predictive power of PLS and ANN models.

2. Experimental

2.1. Instruments

SHIMADZU dual beam (Kyoto/Japan) UV–visible spectrophotometer model UV-1650 PC connected to IBM compatible and an hp1020 laserjet printer. The bundle software, UV-Probe personal spectroscopy software version 2.21 (SHIMADZU) was used to process absorption and ratio spectra, the spectral slit width was 2 nm and scanning speed was 2800 nm/min.

2.2. Software

All chemometric methods were performed in Matlab® 7.0.0.19920 (R14). The *t*-test, F-test and ANOVA test were performed using Microsoft® Excel. All calculations were performed using a Dual CPU, 1.47 GHz, 2.00 GB of RAM under Microsoft Windows Vista™.

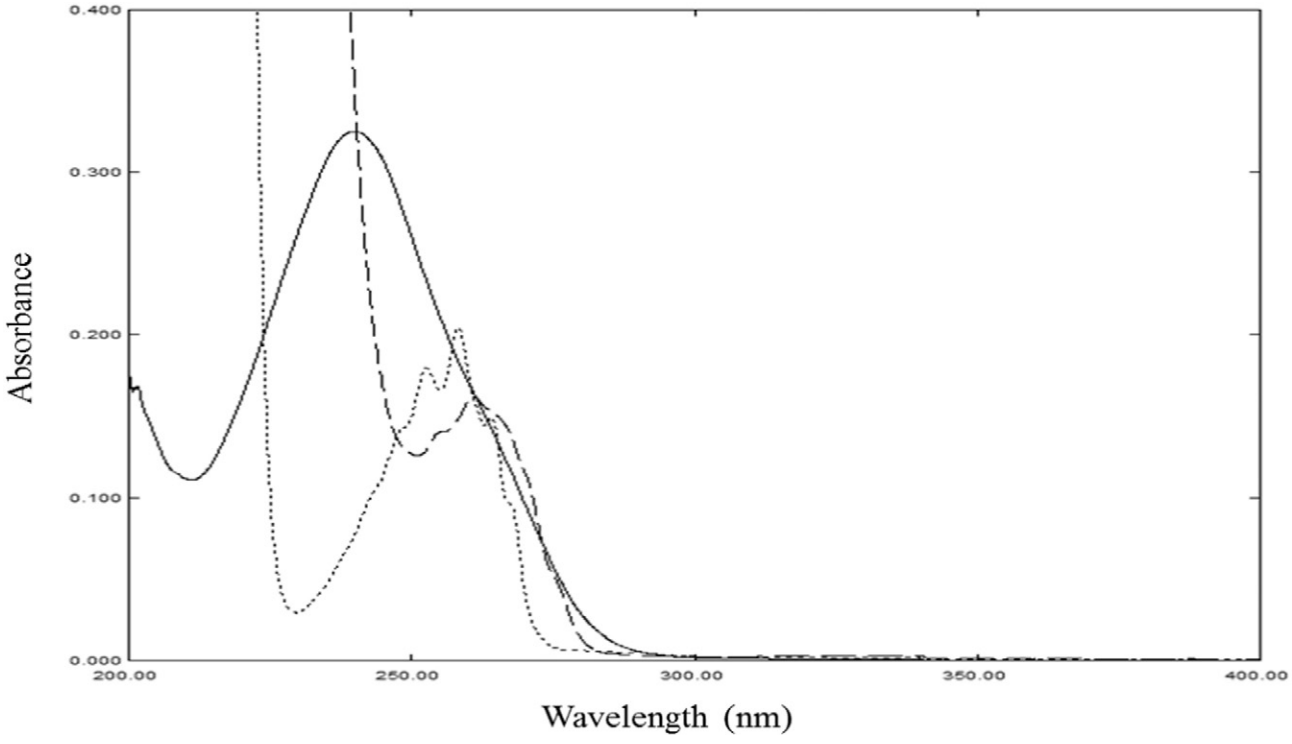

Fig. 1. The absorption spectra of BMD 8 μg/mL (__), CT 80 μg/mL (−−) and BA 120 μg/mL (….) in methanol.