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Detection of compatibility between baclofen and excipients with aid of infrared spectroscopy and chemometry

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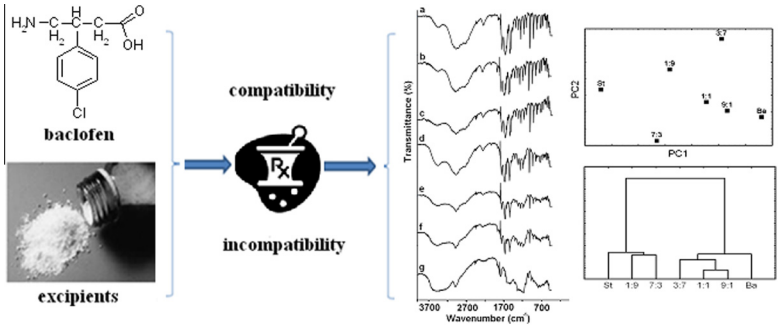
HIGHLIGHTS

- IR firstly combined with chemometry for incompatibilities detection.
- PCA and CA calculations based on transmittance values at given wavenumbers.
- Multivariate methods proved to enhance the interpretation of IR spectra.

GRAPHICAL ABSTRACT



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ABSTRACT

In the paper infrared (IR) spectroscopy and multivariate exploration techniques: principal component analysis (PCA) and cluster analysis (CA) were applied as supportive methods for the detection of physicochemical incompatibilities between baclofen and excipients. In the course of research, the most useful rotational strategy in PCA proved to be varimax normalized, while in CA Ward's hierarchical agglomeration with Euclidean distance measure enabled to yield the most interpretable results. Chemometrical calculations confirmed the suitability of PCA and CA as the auxiliary methods for interpretation of infrared spectra in order to recognize whether compatibilities or incompatibilities between active substance and excipients occur. On the basis of IR spectra and the results of PCA and CA it was possible to demonstrate that the presence of lactose, β-cyclodextrin and meglumine in binary mixtures produce interactions with baclofen. The results were verified using differential scanning calorimetry, differential thermal analysis, thermogravimetry/differential thermogravimetry and X-ray powder diffraction analyses.

Introduction

Studies of drug-excipient compatibility represent an important phase in the preformulation stage of the development of solid dosage forms. The potential physical and chemical interactions between drugs and excipients can affect the chemical nature, the stability and bioavailability of drugs and, consequently, their therapeutic efficacy and safety [1,2]. Two types of chemical incompatibilities have been described: those corresponding to intrinsic chemical drug degradation such as hydrolysis or oxidation but without significant direct covalent chemical reactions, and those corresponding to covalent reaction between the drug and the excipient [3–6]. The physical interactions can be reflected by a change in solubility, creation of eutectic mixtures, or adsorption of a drug on the surface of the excipients [6].

Numerous characterization methodologies can be employed during the preformulation stage of drug development, and each has its associated utility and function for the physical characterization of a drug substance. However, when a large amount of information is to be extracted from a small amount of sample, spectroscopic methods of analysis can be of utmost value [2].

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Infrared spectroscopy (IR) is a well-known method of drug analysis and has an exclusively great significance in investigations of interactions between drugs and excipients in pharmaceutical formulations. The occurring interactions between drug(s) and excipients are discovered and proved by IR spectroscopy with the following important characteristics: appearance of new IR absorption band(s), broadening of band(s), alteration in intensity [7]. In alleged cases of incompatibility, IR spectrum of pure drug is compared with that of drug-excipient mixture and pure excipient [8].

The proper interpretation of multidimensional data seemed to be difficult to achieve, mainly because of the complexity of processes involved in the systems with the drugs participation. As a result, the interest of pharmaceutical sciences in the use of statistical multivariate techniques for studying of enormous databases, obtained after analysis of drugs by instrumental techniques, significantly increased in the last decade [9].

IR spectroscopy associated with chemometric methods have proven to be suitable tools for simple and rapid analysis in the pharmaceutical technology. After collecting the IR spectra, the processing and interpretation of multivariate data for qualitative and quantitative analysis is performed using chemometric software. The common techniques are principal components analysis (PCA) and hierarchical methods. PCA is usually used as a first step in data analysis in order to detect patterns in multivariate data. By reducing original data dimensionality, PCA allows relevant visualization of features gained from data spectra. Hierarchical methods evaluate samples according to similarities found in their IR spectra and produce groups of clusters which can be represented graphically as a tree diagram called a dendrogram [10].

Taking into consideration all of the above, the aim of the study was to apply PCA and cluster analysis (CA), basing on the results of IR spectroscopy of baclofen and some excipients, to support the identification of potential incompatibilities that might occur in the preformulation stage of the solid dosage forms development. The spectroscopic analysis was conducted on two-component physical mixtures that contained baclofen and one of the selected excipients such as: mannitol, lactose, starch, methylcellulose, β-cyclodextrin, meglumine, chitosan, polyvinylpyrrolidone and magnesium stearate. The interpretation of IR spectra of analyzed samples involved assigning strictly defined spectral areas to particular functional groups, where distinctive absorption bands appeared. The potential incompatibilities were identified through comparison of mixtures spectra with those obtained for individual components. For chemometric calculations, transmittance values at given wavenumbers were used. Differential scanning calorimetry (DSC), differential thermal analysis (DTA), thermogravimetry (TG), differential thermogravimetry (DTG) and powder X-ray diffraction (XRPD) were employed in order to verify the results of spectrophotometric and chemometric analyses.

Materials and methods

Materials

Baclofen was supplied by Polpharma (Starogard Gdansk, Poland). Mannitol and starch were purchased from POCh (Gliwice, Poland). Lactose was provided by BUFA BV (Uitgeest, The Netherlands), and methylcellulose was obtained from Shin-Etsu Chemical Co. (Tokyo, Japan). β-Cyclodextrin, meglumine, chitosan, and polyvinylpyrrolidone were purchased from Fluka (Siegen, Germany), and magnesium stearate was donated by Faci (Carasco Genoa, Italy). Chemical formulas of the analyzed drug and excipients are shown in Fig. 1.

IR spectroscopy

The samples for recording the IR spectra of the substances tested and their physical mixtures were prepared as potassium bromide (KBr) pellets. Each pellet was prepared from 1 mg of homogenized substance and 100 mg of spectroscopy-grade KBr (Merck, Darmstadt, Germany). The IR spectra were recorded at room temperature in the 4000–200 cm^{-1} region on a Carl Zeiss Jena instrument (Specord, Model M-80, Jena, Germany). The ambient atmosphere was used as a background. The analyses of IR spectra were conducted using Spectra Manager software.

Other techniques

DSC scans were carried out with a heat-flux Mettler Toledo instrument (Model DSC 822e, Schwerzenbach, Switzerland) with application of a liquid nitrogen cooling system (Dewar vessel). Samples of approximately 4.00–5.00 mg were placed in 40 μL flat-bottomed aluminum pans with crimp-on lids, while an empty one was used as reference. Measurements were obtained at a scanning speed of 10 °C/min in the temperature range from 20 to 300 °C, using nitrogen as a purging gas at a flow rate of 70 mL/min. Indium and zinc standards were used to calibrate the DSC cell. STAR^e software was used for analysis of the DSC scans.

DTA, TG, and DTG curves for the thermal decomposition of baclofen and excipients separately and for physical mixtures of these constituents were recorded with use of a derivatograph (MOM, Model OD-103, Budapest, Hungary). Samples of 200 mg were placed in four flat-bottomed platinum pans and heated in air at a rate of 5 °C/min to a final temperature of 700 °C. α-Al_2O_3 was used as a reference material.

XRPD diffraction patterns were obtained on D2 Phaser equipment (Bruker, Karlsruhe, Germany), with tube of Cu Kα (λ = 0.154060 nm), voltage of 30 kV and current of 10 mA, in the diffraction angle range 7°–55° (2θ), using a step size of 0.02° under an exposure time of 0.10 s. Diffrac.suite software was used for diffraction data analysis.

Calculations

Multivariate statistical techniques (PCA and CA) were applied for interpretation of the results with aid of the computer program Statistica 10 (StatSoft Inc., Tulsa, OK, USA). Matrix of the data with dimensions of 7 × 402, where 7 is a number of objects (rows) and 402 is a number of variables (columns), was the starting point for calculations [11]. In the matrix, drug and excipient alone and the physical mixtures of both components were used as rows, whereas the columns included the transmittance values acquired every 4 cm^{-1} from IR spectra of the analyzed samples.

Results and discussion

Having compared IR spectra of two-component mixtures composed of baclofen and excipients it was ascertained that in some cases substantial spectral changes occurred. In IR spectrum of baclofen, characteristic absorption bands can be distinguished. They are associated with stretching vibrations of C—Cl group (1089 cm^{-1}), various vibrations of COOH group (1530 cm^{-1}) and bending vibrations of N—H group of primary amines (1625 cm^{-1}) [12–16]. Those specific bands are present in IR spectra of baclofen mixtures with mannitol, starch, methylcellulose, chitosan, polyvinylpyrrolidone and magnesium stearate. The fact that all characteristic bands for drug substance and excipients are present in IR spectra of mixtures with varying contents of both components signifies that no change occurred in chemical structure of baclofen,