Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 171 (2017) 280–286

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

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

Is it possible to find presence of lactose in pharmaceuticals? — Preliminary studies by ATR-FTIR spectroscopy and chemometrics

A. Banas [a,*], K. Banas [a], S.M.P. Kalaiselvi [a], B. Pawlicki [b], W.M. Kwiatek [c], M.B.H. Breese [a]

[a] Singapore Synchrotron Light Source, 5 Research Link, 117603 Singapore, Singapore
[b] Gabriel Narutowicz Hospital, Pradnicka 37, 31-202 Krakow, Poland
[c] Institute of Nuclear Physics PAN, Radzikowskiego 152, 31-342 Krakow, Poland

ARTICLE INFO

Article history:
Received 18 January 2016
Received in revised form 31 July 2016
Accepted 3 August 2016
Available online 04 August 2016

Keywords:
Fourier transform infrared spectroscopy
Attenuated total reflection
Lactose
Chemometrics

ABSTRACT

Lactose and saccharose have the same molecular formula; however, the arrangement of their atoms is different. A major difference between lactose and saccharose with regard to digestion and processing is that it is not uncommon for individuals to be lactose intolerant (around two thirds of the population has a limited ability to digest lactose after infancy), but it is rather unlikely to be saccharose intolerant.

The pharmaceutical industry uses lactose and saccharose as inactive ingredients of drugs to help form tablets because of their excellent compressibility properties. Some patients with severe lactose intolerance may experience symptoms of many allergic reactions after taking medicine that contains this substance. People who are specifically "allergic" to lactose (not just lactose intolerant) should not use tablets containing this ingredient.

Fourier Transform Infrared (FTIR) spectroscopy has a unique chemical fingerprinting capability and plays a significant important role in the identification and characterization of analyzed samples and hence has been widely used in pharmaceutical science. However, a typical FTIR spectrum collected from tablets contains a myriad of valuable information hidden in a family of tiny peaks. Powerful multivariate spectral data processing can transform FTIR spectroscopy into an ideal tool for high volume, rapid screening and characterization of even minor tablet components.

In this paper a method for distinction between FTIR spectra collected for tablets with or without lactose is presented. The results seem to indicate that the success of identifying one component in FTIR spectra collected for pharmaceutical composition (that is tablet) is largely dependent on the choice of the chemometric technique applied.

1. Introduction

Being disaccharides (carbohydrates) – lactose ("milk" sugar) and saccharose ("table" sugar) have the same molecular formula, however the arrangement of their atoms is different. Saccharose is made up of glucose and fructose while lactose is composed of glucose and galactose. Glucose, fructose and galactose have the same chemical formula but different chemical structures, i.e. they are isomers. Carbohydrates are one of the classes of macronutrient compounds which are required in relatively large quantities as they provide cells with energy hence they are indispensable for accurate operation of human body [1].

It is not uncommon for individuals to be lactose intolerant – around two thirds of the population has a limited ability to digest lactose after infancy, whereas being saccharose intolerant is rather unlikely. Lactose intolerance results from an inability to break into its constituent components as a result of insufficient lactase production, which is the enzyme digesting lactose. Saccharose intolerance is caused by sucrase deficiency [2].

Consumption of lactose containing products by persons who are lactose intolerant leads to transportation of undigested product to the lower intestine which may cause many allergic reactions as well as bloating or swelling of the abdomen, pain, diarrhea, nausea, production of gas [3].

Having excellent compressibility properties, lactose and saccharose are used in the pharmaceutical industry, as inactive ingredients of the drugs to help form tablets. Lactose is also used to form a diluent powder for dry-powder inhalations. The properties of lactose that contribute to its popularity as an excipient are: cost, availability, bland taste, low hygroscopicity, compatibility with active ingredients and other excipients, excellent physical and chemical stability and water solubility. Most medications do not contain enough lactose to cause lactose intolerance having no more than 12.5 to 25 mg of this substance, what is tiny on anyone's scale [4]. One glass of milk (250 ml) contains 12,000 mg of lactose.

* Corresponding author.
E-mail address: slsba@nus.edu.sg (A. Banas).

http://dx.doi.org/10.1016/j.saa.2016.08.003
1386-1425/

However, there are four classes of people who are specifically "allergic" to lactose (not just lactose intolerant) [1–9]:

1. Those who are extremely sensitive to lactose – this group includes people at the very far end of the sensitivity curve, those who became intolerant through disease or surgery (i.e. Secondary Lactose Intolerance, SLI). People in this group often have absolutely no lactase in their systems.
2. Senior citizens and others who take many pills every day. These people often have the least lactase and the most delicate intestines.
3. People with milk allergies (including the worst, life-threatening allergies).
4. Those who object to animal-derived products, such as the millions of vegans, Orthodox Jews or others with religious or ethical reasons to avoid any pills containing lactose, even if they do not get specific lactose intolerance symptoms.

People hypersensitive to various products avoid them intentionally so that not to expose their body to unwanted allergic reactions. Pharmacists perform various roles to ensure prime health outcomes for their patients. Since pharmacists know about the mode of action of a particular drug, its ingredients, and its metabolism and physiological effects on the human body in great details, they play an important role in optimization of a drug treatment for an individual; while dispensing prescription drug they have a duty to ask patient about any known allergies.

Pharmacists' knowledge relies on patient information leaflets (package insert) containing specific data about tablet including its composition (API – active pharmaceutical ingredient and all excipients). As lactose can be potential source of allergic symptoms, its presence should be also clearly marked.

Spectroscopic methods have proved to be very efficient since they allow for samples characterization by direct measurement of substances in the solid state. They involve straightforward operational steps, and deliver reliable, fast results. FTIR spectroscopy possessing a unique chemical fingerprinting capability plays an important role in providing data on identifying and characterizing analyzed samples and hence has been widely used in pharmaceutical science [10–15].

FTIR spectroscopy can be considered as a detection technique with many desirable features, such as being non-destructive and requiring no/minimal sample preparation while offering results with high chemical uniqueness. FTIR is capable of determining several sample components in a single measurement without needing physical separation. Infrared absorption causes changes in the vibrational and rotational state of molecules; the absorption frequency depends on the molecular vibrational frequency whereas absorption intensity depends on effective energy transfer to the molecule, which in turn depends on any change in the dipole moment occurring due to molecular vibration. Thus a molecule only absorbs infrared light if absorption changes the dipole moment. FTIR spectroscopy measures the vibrations of covalent chemical bonds, creating a 'spectral fingerprint'. This result can be used to identify and quantify all ingredients present in a sample [16,17].

Typical FTIR spectrum collected from tablets contains a myriad of valuable information hidden in a family of tiny peaks. FTIR characterization is complex mainly because of the high degree of overlap of infrared absorption bands. Only powerful multivariate data analysis can transform FTIR spectroscopy to an ideal tool for high volume, rapid screening and characterization of minor components in tablets. The development of statistical procedures for the fast identification and detection of all pill ingredients is an essential stage in data processing. Multivariate analysis is a powerful tool when dealing with multi-component systems and offers a valuable methodology for extracting significant differences from complicated datasets [18,19].

Further developments in FTIR interferometer architecture suggest that simpler and more compact implementations of these types of sample analysis systems will be available in the near future. New spectrometers as well as new accessories for sampling will significantly contribute to extend the application fields of the infrared techniques. Very soon FTIR spectrometers will be made as compact, relatively inexpensive and user-independent devices, making the technology available for wider group of users. Due to future advances in instrumentation and data processing techniques, infrared techniques will be invaluable tools for people – helping them, for example, to control the quality and content of consuming pills, easily discriminate not only original and illegal products but also drugs containing lactose.

In this paper a method for distinction between FTIR spectra collected for tablets with or without lactose is presented. Experiments were performed on Furazidin which is a medicine used to treat acute and chronic urinary tract infections and in long-term prevention of the recurrence of these pathological states [20]. The tablets are produced by various companies which use lactose or saccharose as a one of the excipients. The choice of this pharmaceutical was imposed by the fact that plenty of patients taking this drug complained on symptoms related to lactose intolerance even if they selected lactose-free pills (according to patients' leaflet information).

Tablets were measured mainly through placing them in direct contact with the crystal surface to collect spectroscopic data – in an attenuated total reflectance (ATR) mode. As success of identification of minor substance in FTIR spectrum collected for a mixture is largely dependent on the chemometric techniques applied for optimal data evaluation, data analysis was made by employing hierarchical cluster analysis (HCA) and principal component analysis (PCA) to ensure objective interpretation of the results [21]. Described procedure proves that FTIR coupled with chemometric methods is a prevailing technique which can be used when specific analytical questions have to be answered in a non-destructive manner. Discussed in this paper work can be valuable for people allergic to lactose, as it shows the power of method for finding dangerous from their perspective substance in the tablets what can highly assist in leading the daily lives without unpleasant symptoms.

2. Experimental

Furazidin available in Poland is produced by three pharmaceutical companies: Adamet (tablets brand names: Furaginum and uroFuraginum), TEVA Pharmaceuticals (Furaginum and neoFuraginum) and US Pharmacia (FuragiActive); each pill contains 50 mg of Furazidin as API. As is stated in the patients' leaflet information, lactose is present in TEVA and US Pharmacia products. Tablets for analysis were purchased from pharmacies in various cities within Poland in order to assure collection of pills from different batches. Pure grade lactose and saccharose were purchased from Sigma Aldrich company.

Initially, samples for experiments were prepared as thin transparent pellets (diameter 13 mm, thickness <1 mm) being a mixture of small amount (<1 mg) of analyzed substance and KBr (circa 100 mg). The mixtures were first ground into a fine powder, then placed in a standard evacuable pellet press and compressed with a clamping force of 80 kN in a hydraulic press. Taking into account the fact that testing pharmaceuticals should be very fast and at the same time highly reliable – another FTIR sampling method – ATR mode (where there is no requirement for samples to be added in KBr pellets or to undergo any pretreatment) was employed in this study. In our experiments we worked with MIRacle device (produced by PIKE) – a universal sampling accessory which is designed for both single- or multi-reflection ATR and specular reflectance measurements. Single-reflection ATR ZnSe crystal (1.8 mm diameter, cut-off wavenumber at 520 cm^{-1}) was used during experiments. The ATR crystal material, which is also called an internal reflective element, was chosen according to the sample physical properties such as pH and hardness, the spectral region of interest, and the refractive indices of both sample and crystal. The ATR method requires the sample to be in intimate contact with the sampling area. Coupled to MIRacle digital readout a high-pressure clamp enabled reproducible sampling by applying the same pressure to all samples. In order to exclude any possible contamination occurring from one sample to another, special