Compatibility of Ester-type Anesthetic Agents with Two Polysaccharides

JENEL PATRASCU¹, OVIDIU BEDREAG¹, MARIUS PAPURICA¹, MARIUS BIRIS¹, OANA ANCUSA¹, DANIELA ONETIU¹, GABRIELA VLASE²*, TITUS VLASE³, DOREL SANDESC¹

¹ University of Medicine and Pharmacy “Victor Babes”, Faculty of Medicine, 2 Eftimie Murgu Sq., 300041, Timisoara, Romania
² West University of Timisoara, Research Centre for Thermal Analysis in Environmental Problems, 16 Pestalozzi Str., 300115, Timisoara, Romania

* email: gvlase@cbg.uvt.ro

The paper describes the compatibility of Benzocaine (BZ) and Procaine (PR) with two pharmaceutical excipients. The results obtained from this study confirm that DSC and FTIR spectroscopy are simple, reliable, reproducible and accurate tools in the evaluation of the compatibility between active pharmaceutical ingredients and excipients. The correlated results obtained from TG, DSC and UATR-FT-IR techniques indicated that pregelatinized starch and sodium croscarmellose showed no incompatibility between PR and BZ and these excipients.

Keywords: BZ, PR, DSC, FTIR spectroscopy, starch

Ester-type anesthetic agents are one of the main two classes of local anesthetic agents, based upon the functional groups present in their structure, along amides. All of the compounds are considered “-caine” derivatives, the main representative compounds from ester-type are Procaine, Benzocaine, Chloroprocaine, Propoxycaaine and Tetracaine [1]. The “-caine” or “-ine” suffixes are historically associated with the tropane alkaloid cocaine, which was firstly used as an anesthetic for respiratory system or as toothache analgesic, now being used mainly for lacrimal duct surgery [2] or nasal surgery [3].

The mechanism of action for ester-type local anesthetic agents is associated with the blocking of both the initiation and conduction of nerve impulses, by the action over neuronal membrane permeability to Na⁺ ions. As a consequence to this, the blockade of conduction is associated with the inhibition of depolarization [4].

Benzocaine (Ethyl para-aminobenzoate) is nowadays incorporated in numerous pharmaceutical and medical formulations intended to be used as temporary relief of pain associated to pruritic dermatosis, minor burns, pruritus, in ear affections such as serous otitis media or otitis externa, swimmer’s ear, for toothache or throat pain, canker sores, rectal fissures or in lubricant formulations for the passage of catheters and endoscopic tubes [4-5].

Procaine (2-(diethylamino)ethyl para-aminobenzoate) is used as anesthetic agent in infiltration anesthesia and for diagnostic nerve blocks. It use decreased lately due to the synthesis of newer agents but is considered an low-toxic agent, which is hydrolyzed in vivo to para-aminobenzoic acid [6].

The structures of both active substances are presented in figure 1.

In the formulation step, different thermoanalytical techniques were used for the early prediction of suitable excipients for the dosage forms, in order to avoid physico-chemical interactions which appear in some drug-excipient mixture [7-8].

The most used methods for application in the pharmaceutical field are thermogravimetry (TG), differential thermal analysis (DTA), and differential scanning calorimetry (DSC) [5-13].

Differential scanning calorimetry (DSC) represents a thermal analysis technique which is more and more used for the rapid active screening of incompatibility of drug formulations which are formed by a mixture of active substance(s) and excipients [14-16]. The DSC analysis is fast, reliable and reproducible, requires a small amount of sample and the obtained results indicate the physical and/or chemical interaction(s). The compatibility study must be carried out by the use of at least two complementary techniques, and DSC can be successfully associated with the use of FT-IR spectroscopy [17].

UATR-FT-IR spectroscopy is one of the fastest techniques that can be used to evaluate the interactions which occur in the formulation step, consisting in the preparation of physical mixture of active pharmaceutical ingredient with excipient(s). The qualitative analysis of the interactions using UATR-FT-IR spectroscopy is realized by the comparison of the relative intensity, position or appearance/disappearance of absorption bands. Generally, by the use of UATR-FT-IR spectroscopy, only the qualitative analysis can be achieved, because the intensity of bands depends both on the amount of sample placed on the surface of the spectrometer crystal as well as on the pressure applied on the sample. According to this, the analysis of the spectra is realized by identifying the modification of relative intensity or position (shifting to lower/higher wavenumbers) of bands. The modifications of the number of bands in the spectrum always suggest that interactions occur, and knowing their position and the chemical structures of active substance and excipients, the reactions that took place can be identified [18-21].

The aim of this paper is to evaluate the compatibility/incompatibility of two local ester-type anesthetic agents (Benzocaine and Procaine) with two polysaccharides that are commonly used as excipients in different pharmaceutical formulations. The study is necessary because these two local anesthetics are incorporated in different types of ointments, where interactions can occur. Previous studies described the thermal behaviour of these active substances [8], the kinetic study regarding their thermal degradation [22,23], followed by several studies regarding the compatibility with pharmaceutical excipients.
This paper presents the compatibility study of both Benzocaine and Procaine with croscarmellose sodium and pregelatinized starch (Starch 1500) by the means of thermal analysis and FTIR spectroscopy.

**Experimental part**

**Materials and methods**

The analytical purity ester-type anesthetic agents, benzocaine (BZ) and procaine hydrochloride (PR), were obtained from Sigma-Aldrich Chemical and used as received. As tested excipients, sodium croscarmellose (Croscarm) and pregelatinized starch (Starch) were used. All the samples were kept in a desiccator before use, in order to avoid humidity retention. The four samples (BZ+Croscarm, BZ+Starch, PR+Croscarm and PR+Starch, respectively) consisted of equal masses of active substance and each excipient (0.1g). Physical mixtures were prepared by simple mixing of the two substances in an agate mortar with pestle for approximately 5 min. The 1:1 mass ratio was chosen in order to maximize the probability of observing any interaction.

The thermoanalytical TG curves were drawn up in an air atmosphere and under dynamic conditions at a heating rate $\beta = 10 \, ^\circ\text{C} \cdot \text{min}^{-1}$ using a Perkin-Elmer DIAMOND equipment, respectively a Netzsch differential scanning calorimeter, model DSC-204.

The DSC and TG data were recorded both under non-isothermal conditions. Samples of mass in the range of 5-7 mg were put into aluminium crucibles and heated by increasing temperature from ambient up to 500 °C (TG analysis) or up to 400 °C (DSC analysis).

The FTIR analysis was realized with the use of an UATR device on Perkin Elmer SPECTRUM 100 spectrometer, in the spectral range of 4000-600 cm$^{-1}$. Each spectrum was drawn after 16 acquisitions for each sample. In order to evaluate the accuracy of the measurements, three repetitions have been done with this experimental protocol for the samples and the obtained results were comparable.

**Results and discussions**

**Thermal analysis**

The complete thermoanalytical characterization of the two anesthetic agents was described in a previous paper [8]. The DSC curve of procaine shows a sharp endothermic peak ($T_{\text{peak}} = 155.4 ^\circ\text{C}$; $T_{\text{onset}} = 147.65 ^\circ\text{C}$; $\Delta H_{\text{fusion}} = 26.069 \, \text{Jmol}^{-1} $), corresponding to the melting event. The TG/DTG curves reveal the procaine decomposition in a single step at between 196.64-371.45 °C ($\Delta m = 90\%$, DSC$_{\text{peak}} = 232.68 ^\circ\text{C}$) (fig. 2 and 3).

For the benzocaine, the thermoanalytical curves are the same allure, the difference being $\Delta m$ which is 99.9% at 500 °C. On the DSC curve, it is shown a single sharp endothermic peak corresponding to the melting event in agreement with the literature value [8] ($T_{\text{onset}} = 79.4 ^\circ\text{C}$). The TG/DTG curve indicated thermal decomposition in the temperature range of 147.8-235.6 °C in one single step, totaling 99.9% of mass loss.

The compatibility studies were performed with binary mixtures (1:1; m/m) of BZ and PR and sodium croscarmellose and pregelatinized starch. The physical mixtures were prepared through simple mixing and then submitted to the analysis.

The first excipient used is croscarmellose sodium, which is considered as a disintegrant in the pharmaceutical formulation, as tablets and capsules. The DSC curve for PR+croscarmellose sodium mixture (fig. 3a), respectively BZ+croscarmellose sodium (fig. 3b) shows the characteristic endothermic event of the pure anesthetics melting point at 156.9 °C for the first mixture, respectively 88.1 °C for the BZ mixture.

Pregelatinized starch is an excipient commonly used as a diluent, binder, and disintegrant agent. The DSC curves for PR+starch and BZ+starch (fig. 3a) showed one endothermic peak characteristic of the procaine melting point at 154 °C, before of whose occurs the dehydration process of starch which was observed as an endothermic event in the temperature range of 100-136 °C. In the case of BZ+starch (fig. 3b), the DSC curve presents only a sharp endothermic peak at 92°C corresponding to the BZ melting point.

The thermal profiles of the mixtures procaine + croscarmellose sodium, procaine + starch, respectively benzocaine + croscarmellose sodium, and benzocaine + starch, can be considered as a superposition of the thermoanalytical curves for the two active substances and the excipients (figs. 2 and 3), demonstrating the absence of interaction.

**UATR-FT-IR spectroscopy results**

In previous studies, the FTIR spectra of both BZ and PR were discussed [8]. According to this, the maximum of
the bands from the FT-IR spectra of sodium croscarmellose, pregelatinized starch, BZ and PR were comparatively analysed with the ones obtained for studied mixtures (table 1).

UATR-FT-IR spectrum of sodium croscarmellose
Sodium croscarmellose is an internally cross-linked sodium carboxymethylcellulose. The structure of sodium croscarmellose is presented in figure 4.

A large band at 3685-2990 cm⁻¹ with a peak around 3444 cm⁻¹ can be associated with the presence of O-H stretching, and as well for the presence of adsorbed water. The bands around 2957 and 2914 cm⁻¹ are characteristic for the C–H stretching, while the band at 1670 cm⁻¹ can be associated with the bending of COH group. The peaks at 1410–1360 cm⁻¹ are associated with the OH bending, while the bands at 1037 cm⁻¹ are characteristic of the anhydroglucose ring. The polysaccharidic structure is confirmed by the peaks present in the spectral range 1156-952 cm⁻¹, signals attributed to C=C and C-O bond stretching, and for the C-H bending, respectively [25].

UATR-FT-IR spectrum of pregelatinized starch
The spectra of pregelatinized starch display the typical profile of its polysaccharide structure. A large band between 3670-3029 cm⁻¹ with a peak at 3344 cm⁻¹ can be attributed to the complex vibrational stretching, associated with free, inter and intra molecular bound hydroxyl groups, as well for the water adsorption. The bands at 2952 and 2914 cm⁻¹ are characteristic for the C–H stretching, while the band at 1670 cm⁻¹ can be associated with the bending of COH group. The peaks at 1410–1360 cm⁻¹ are associated with the OH bending, while the bands at 1085-750 cm⁻¹ are characteristic of the anhydroglucose ring. The polysaccharidic structure is confirmed by the peaks present in the spectral range 1156-952 cm⁻¹, signals attributed to C=C and C-O bond stretching, and for the C-H bending, respectively [25].

Table 1

<table>
<thead>
<tr>
<th>Sample</th>
<th>UATR-FT-IR analysis results (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ν(O-H)</td>
</tr>
<tr>
<td>BZ</td>
<td>3344(N-H); 3328(N-H)</td>
</tr>
<tr>
<td>PR</td>
<td>3349(N-H); 3319(N-H)</td>
</tr>
<tr>
<td>Croskarm</td>
<td>2957(C=H); 2914(C=H)</td>
</tr>
<tr>
<td>Starch</td>
<td>2952(C=H); 2916(C=H)</td>
</tr>
<tr>
<td>BZ+Croskarm</td>
<td>3342(N-H); 3331(N-H); 2959(C=H); 2919(C=H)</td>
</tr>
<tr>
<td>BZ+Starch</td>
<td>3343(N-H); 3329(N-H); 2959(C=H); 2919(C=H)</td>
</tr>
<tr>
<td>PR+Croskarm</td>
<td>3349(N-H); 3319(N-H); 2959(C=H); 2914(C=H)</td>
</tr>
<tr>
<td>PR+Starch</td>
<td>3349(N-H); 3319(N-H); 2954(C=H); 2917(C=H)</td>
</tr>
</tbody>
</table>

Fig. 4. The structure of sodium croscarmellose
The analysis of BZ and PR mixtures with selected excipients

The comparative UATR-FT-IR analysis results for active substances and 1:1 mixtures (Table 1) indicate the fact that the FTIR spectra of mixtures is the superposition of the spectra of active substances (BZ and PR) with the ones of excipients. All the bands identified in the spectra of the mixture appear at the same wavenumbers as in the case of pure active substances, or with an insignificant shifting of ±5 cm⁻¹. By this, UATR-FT-IR spectroscopy confirms that no interaction occurs between the four analyzed binary mixtures.

Conclusions

The thermoanalytical techniques, mainly differential scanning calorimetry, have been increasingly used in the characterization of solid state interactions of the pharmaceuticals and early detection of drug–excipient compatibility. These pre-formulation studies are an important step to obtaining a reliable and effective pharmaceutical formulation. In this study, it was presented the results of the compatibility of two anesthetic substances, procaine and benzocaine, with two excipients incompatibility between PR and BZ and these excipients. The thermoanalytical techniques, mainly differential scanning calorimetry, have been increasingly used in the characterization of solid state interactions of the pharmaceutical field. The data obtained from TG, DSC and FTIR techniques indicated that pregelatinized starch and croscarmellose showed no obtained from TG, DSC and FTIR techniques indicated that pregelatinized starch and croscarmellose showed no compatibility. These pre-formulation studies are an important step to obtaining a reliable and effective pharmaceutical formulation. In this study, it was presented the results of the compatibility of two anesthetic substances, procaine and benzocaine, with two excipients incompatibility between PR and BZ and these excipients.

References