Local Anesthetic Agents
III. Study of solid dosage forms with pharmaceutical excipients

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Procaine and benzocaine are widely used as anesthetic agents. The aim of this study was to evaluate the compatibility of procaine and benzocaine with pharmaceutical excipients used in formulation by differential scanning calorimetry and Fourier transform infrared spectroscopy. Binary mixtures between these anesthetic agents and pharmaceutical excipients, namely calcium stearate, colloidal silica dioxide, povidone and hydroxypropylmethylcellulose were examined. Povidone and calcium stearate mixtures with both active substances displayed some physico-chemical interactions based on the DSC results. The FT-IR study sustained some incompatibilities in the case of these four mixtures.

Keywords: anesthetic agents, excipient, DSC, compatibility

Local anesthetic agents (LA) are drugs that are implied in inducing reversible local anesthesia, namely inducing the loss of pain sensation. Local anesthetic agents can induce a nerve block, if they are used on nerve pathways or temporary muscle paralysis. Local anesthetics belong to the classes of aminoamide and aminoester derivatives. Synthetic local anesthetics are structurally related to natural occurring products, but the major difference is that they have no euphoric and addictive properties and most of them do not produce hypertension or local vasoconstriction [1].

Procaine (2-(diethylamino)ethyl 4-aminobenzoate) is a local anesthetic agent discovered by Einhorn in 1905 and used as a medical substitute for cocaine. Nowadays, procaine is mainly used as a topical anaesthetic agent, particularly in oral surgery. As pharmaceutical formulations, procaine is administered as capsules or tablet by oral route, or as a solution for infiltration and intramuscular injection. Procaine is also used pharmaceutical formulations with analgesic, geriatric and antiviral properties [2].

Benzocaine (Ethyl 4-aminobenzoate) is a surface anesthetic that acts by preventing transmission of impulses along nerve fibers and at nerve endings [3]. Benzocaine was firstly obtained before procaine (in 1890) by Ritserand and introduced to the market after 12 years under the name "Anästhesin"[4]. Benzocaine can be found in different pharmaceutical ingredients, such as products for relief of sore throat, oral ulcers, external otitis or reducing pain in orthodontic treatments. As a mixture with antipyrine, benzocaine is found in so called A/B otic drops (i.e. Antipyrine and benzocaine ear drops) indicated for the treatment of external otitis and removal of impacted cerumen [5].

It is well known that "drug discovery" involves the design of new organic molecules which possess biological activity and bioavailability [6], but as well the design of pharmaceutical formulation, being known the fact that generally the active substance is accompanied by the presents of other molecules, such as excipients. The discovery of compatibility/incompatibility of bioactive substance is an important aspect in pharmaceutical formulation and the trials normally preceded the possible interactions between a drug and different excipients. According to legislation, excipients must be biologically and chemically inert, but during the formulation step, physical and chemical interactions of the active substance can occur. The evaluation of compatibility/incompatibility for excipients with active substances are crucial for pharmaceutical formulation [7].

Several physical parameters such as the presence of water or moisture, temperature and pressure can induce different transformations of the active substance and can induce interactions between the active substance and excipient(s). These interactions can modify the behaviour of drug molecules, including the dissolution and/or bioavailability or/and their therapeutic effect and safety. The way by which the auxiliary substances such as

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excipients affect the stability of drug can involve chemical transformations, sorption of water and/or catalysis. Some pharmaceutical compatibility can be predicted, but generally the use of excipients must be realized by experimental protocols.

Reliable tools for the evaluation of physical and kinetic properties, polymorphic forms and transitions, product stability and as well the study of compatibility of active substance with excipients is the thermal analytical methods [8-11].

Differential scanning calorimetry (DSC) is considered to be an important technique for the preliminary evaluation of preformulation study of solid dosage form because detect and reveals very fast the interactions by a simple comparation of the thermal curves obtained for the active substance, for the excipients, and for their physical mixtures, in the same experimental conditions. The interaction between the active substance and the used excipient(s) can be evaluated by the appearance, shifting and/or disappearance of endothermic/exothermic peaks and/or variations in the corresponding enthalpy values obtained from thermal curves of drug–excipient mixtures.

Several techniques were previously used for evaluation of interactions or incompatibilities for drug–excipient mixtures, including isothermal stress testing and thermal analysis [9-12]. Thermal analysis has a major advantage over conventional isothermal stress testing in that that long term storage of physical mixtures and spectroscopic analysis, because only a few milligrams of sample is needed [11-13]. As a limitation, the technique has been criticized as being inconclusive because the moisture stress testing is usually not included and the temperature ranges, which are used, are not characteristic of normal storage conditions.

By the use of spectroscopic techniques, FT-IR analysis is by far the simplest, fastest and an has a high degree of accuracy in order to evaluate the interactions which take place during the mixing of active substance with pharmaceutical excipient(s). The use of FT-IR analysis relies on the tracking changes which occur in the spectra, namely the disappearance of an absorption band, modification of its intensity or position (shifting to lower/higher wavenumbers). Also, the appearance of new absorption bands is an indisputable argument that suggests that an interaction between active substance and excipient occurs. The use of FTIR analysis affords valuable information about the mechanism of interaction, by the assignment of the bands that appear or disappear in the mixture's spectra, comparative to the ones obtained for pure active substance and pure excipient. An major advantage of using UATR-FT-IR technique, compared to classic FTIR spectroscopy (the spectra acquisition is usually carried out on a pressed-dispersion of sample in KBr), is that that provides superior data quality combined with high reproducibility and has some advantages including: fastness, as no preparation of the samples is required; it is a non-destructive technique and requires small quantities of sample which can be recovered from the surface of the spectrometer's crystal after the analysis. The accuracy of UATR-FT-IR technique resides from the fact that no pressure is applied on the mixture, so no interactions induced by pressure are observed. The use of both DSC technique and Fourier Transform Infrared (FT-IR) Spectroscopy allows the evaluation and interpretation of potential interactions at the molecular level [14-19].

Our present study is following our two previous ones [14-15] regarding the solid-state characterization of two local anesthetic agents, namely procaine (Pr) and benzocaine (Bz). Our previous studies focused on the kinetic analysis of the active substances under non-isothermal conditions [14], followed by a compatibility study with some pharmaceutical excipients used in solid dosage forms, namely magnesium stearate, lactose monohydrate, talc and microcrystalline cellulose. This study was realized because the compatibility study of these two active substances, Pr and Bz have not been reported earlier, to our knowledge, for other pharmaceutical excipients, such as povidone (Kollidon 90), calcium stearate, colloidal silica dioxide (Aerosil 200) and hydroxypropylmethylcellulose (Methocel E5).

For this purpose, DSC and UATR-FT-IR spectroscopy measurements were carried out on each of the components, both in the pure form and the corresponding 1:1 (w/w) physical mixtures. The absolute value of the difference between the melting endothermic peak temperature of pure drug and that in each analyzed mixture and the absolute value of the difference between the enthalpy of the pure active ingredient melting peak and that of its melting peak in the different analyzed mixtures were chosen as indexes of the drug-excipient interaction degree. As well, the analysis of FT-IR spectra sustains the interaction which took place.

Experimental part

Materials and samples

The active ingredients, procaine hydrochloride (Pr) and benzocaine (Bz), were obtained from Sigma Chemical Co (lot No. 34D1214) and have an analytical purity. Excipients tested were: calcium stearate (StCa) (Mosselman, Belgium, lot no. 726431), Povidone-Kollidon 90 (BASF, Germany, lot no. 7491950950), colloidal silica dioxide-Aerosil 200 (Evonik Degussa, Germany, lot no. 3151010614) and hydroxypropylmethylcellulose-Methocel E5 (Dow Chemical, UK, lot no. 1F270124L1). All the compounds have an analytical purity and were used as received, without further purification.

The mixed samples consisted of equal masses of active substance and each excipient. Physical mixtures were prepared in proportion (*w:w*) 1:1 (active substance: excipient) by simple mixing of the two substances in an agate mortar with pestle for approximately 5 min. The 1:1 (*w:w*) ratio was chosen in order to maximize the probability of observing any interaction.

DSC analysis was completed using a DSC 200 F3 Maia instrument from Netzsch. The DSC curves were carried out under air atmosphere with the flow rate of 50 mL·min^{-1}. Approximately 5-6 mg of samples were weighted out and placed in a sealed aluminium crucible. The analysis was carried out from 30 to 400 °C at a heating rate $\beta = 10$ °C·min^{-1}. The DSC cell was calibrated with indium, tin, bismuth and lead.

The IR spectra were carried out using a Perkin Elmer SPECTRUM 100 device in the range of 4000-600 cm^{-1} on an UATR device, with 16 acquisitions for each spectrum.

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

The study was executed with different excipients, which have different properties and roles, namely calcium stearate as lubricant, SiO_2 as lubricant and diluent, hydroxypropylmethylcellulose and polyvinylpyrrolidone, mostly used as binders.

The DSC findings on procaine, benzocaine, excipients and the binary mixtures are shown in figures 1 and 2 and

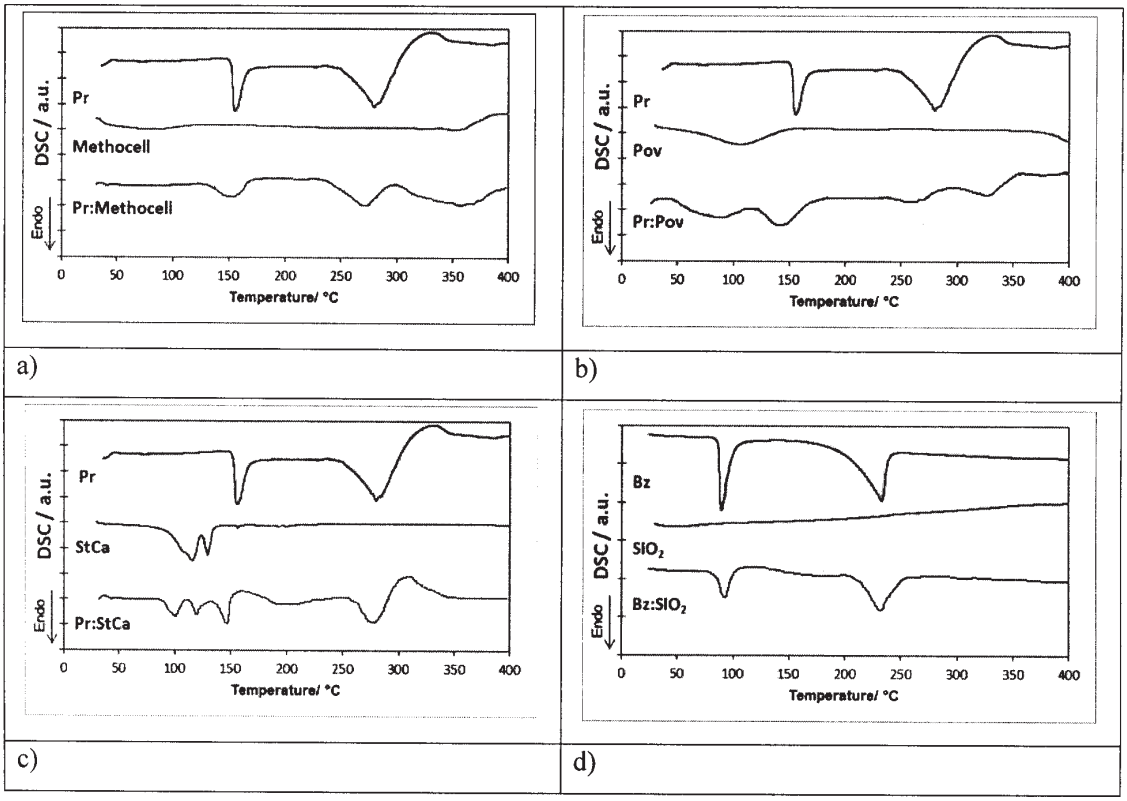


Fig. 1. The DSC curves of procaine and its 1:1 (*w:w*) binary mixtures with used excipients

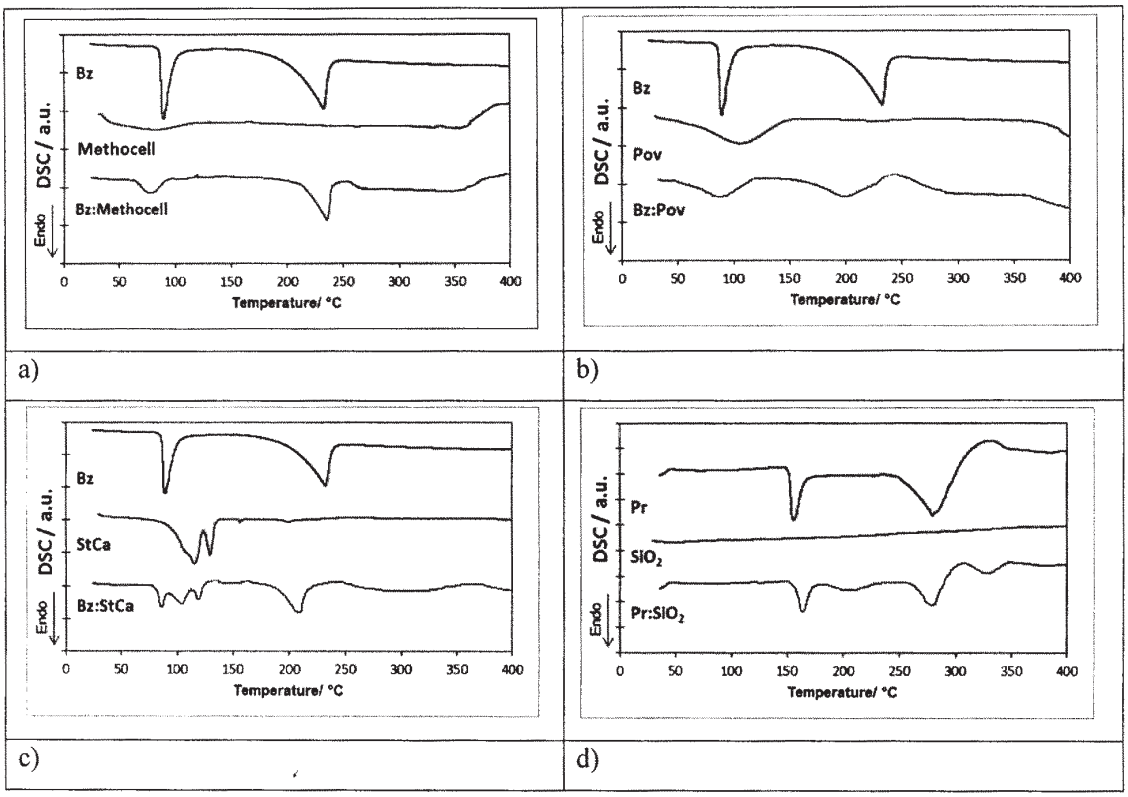


Fig. 2. The DSC curves of benzocaine and its 1:1 (*w:w*) binary mixtures with used excipients

the thermoanalytical data for two active substances and used excipients are presented in table 1.

The DSC curve of Pr (fig. 1, red curve) showed an initial sharp melting endotherm with onset at 148°C and an enthalpy value of 26.1 J·mol^{-1} (this peak is within the reported melting range (153–156°C) for this active compound [20]), which was followed by a large endotherm peak with $T_{max\ DSC}$=279 °C corresponding to the thermal destruction process of the active substance.

For the second active substance (Bz), the DSC curve showed two events (fig. 2, red curve). The first was a sharp endothermic event with maximum at 90 °C (T_{onset}= 77 °C; ΔH_{fusion}=17.8 J×mol^{-1}) indicating the melting which corresponds to the values reported in literature (88-90 °C) [21]. The second event with T_{onset}= 147 °C; T_{max}= 244 °C; T_{endset}= 249 °C; and ΔH_{fusion}=21.4 J×mol^{-1} had an endothermic nature and characterized the degradation of the benzocaine molecule.

Compatibility study with the excipients by DSC technique

Mixtures with Methocel

The DSC patterns for procaine, Methocel and their 1:1 physical mixture are presented in figure 1a, and similar records for benzocaine, Methocel and their 1:1 physical mixture in figure 2a, respectively. The DSC patterns of the

Substance	DSC curves		Nature of the process
	T_{onset}/°C	$T_{peak\ DSC}$/°C	
Procaine	148	156	Endotherm / melting
	240	279	Endotherm / degradation
Benzocaine	77	90	Endotherm / melting
	147	246	Endotherm / degradation
Aerosil 200	-	-	-
Calcium stearate	80.3	109	Endotherm /dehydration
	121	128	Endotherm /dehydration
Povidone	50	103	Endotherm /dehydration

Table 1
DSC data of the two active substances and the used excipients

mixtures of Pr and Methocel, and Bz and Methocel does not showed additional peaks, in addition to those recorded for individual drugs. The DSC profiles obtained for the physical mixtures of these components consist in the sum of representative DSC peaks of Methocel, Pr and Bz, respectively. The first event had a moderate decrease in temperatures T_{onset} from 148 to 128°C for Pr mixture ($T_{peak\ DSC}$ from 156 to 150 °C) and T_{onset} from 77 to 62 °C for Bz mixture ($T_{peak\ DSC}$ from 90 to 83 °C) respectively. As seen in figures 1a and 2a, the Methocel sample showed a large endothermic transition in the DSC curve between 50 and 110 °C corresponding to its dehydrations (unbound water). The DSC behaviour of the binary mixture of Pr and Bz, respectively with Methocel shows the endothermic characteristics of the active substance and the results indicate the presumable absence of incompatibility with this excipient.

Mixtures with Polyvinylpyrrolidone

Polyvinylpyrrolidone is a synthetic polymer consisting of a mixture of linear polymers of 1-ethenyl-2-pyrrolidinone. The DSC profile of povidone presents a broad endothermic event with T_{onset} = 50 °C and $T_{peak\ DSC}$ = 103 °C, the dehydration being finished at 142 °C. In the case of the mixture with this excipient, the observed differences are important. The DSC curves of the analyzed mixture with Pr revealed an initial dehydration peak due to loss of adsorbed water with maximum peak transition at approximately 85–88°C and a broad endothermic peak with onset at 118°C. In the case of benzocaine mixture with Pov, the temperature values are similar: the dehydration process has the maximum at 82°C and the second event is more broad and flat and begins at 150°C. The main observation of the DSC curves of the mixture with Pov is the disappereance of the melting peak of the drugs (Pr and Bz), indicating a physico-chemical incompatibility between these compounds under heating.

Mixtures with calcium stearate

The DSC behaviour of calcium stearate shows a broad endothermic peak due to the humidity loss (dehydration) at 80.3°C ($T_{peak\ DSC}$=109 °C). Between 121 and 134°C, there is an endothermic event indicated by the sharp peak ($T_{peak\ DSC}$=128 °C) corresponding to the loss of the second water molecule due to the fact that the used calcium stearate was a crystalline dihydrate.

In the DSC profiles of the physical mixture of Pr with StCa and Bz with StCa, respectively, the thermal features of drugs and excipient namely the two endothermic peaks which characterize the dehydration, the melting and degradation peaks were observed, although with a shift of approximately 7°C in melting peak of procaine and a shift of 2°C in melting peak of benzocaine, to lower temperature.

Mixtures with colloidal silicon dioxide

The DSC profile of Aerosil 200 reveals its stability, without any events in the studied temperature interval (30-400 °C). The DSC curves of the physical mixture Pr-Aerosil and Bz-Aerosil showed no change in the mixture thermal profile, which corresponds to the sum of peaks observed for the drug individually, indicating no interaction between them.

Compatibility study with the excipients by UATR-FT-IR spectroscopy

The analysis of FT-IR spectra of excipients and the ones of active substances (Pr and Bz) were comparatively analyzed with the ones obtained for studied mixtures (table 2).

Due to the fact that a complete FT-IR profile of Pr and Bz was presented in our previous studies [14-15], we present only characteristic vibrational modes of functional groups which can interact with pharmaceutical excipients during the thermal treatment (table 3).

As previously stated, FTIR bands corresponding to C-C, C-H or aromatic ring do not present interest in our study due to the fact that they present a higher stability comparative to other functional groups and their interaction with functional groups of excipients is not expected. According to this, the comparative analysis of FTIR spectra will be focused on the modification of characteristic bands for functional groups such as N-H and carbonyl groups, which present an increased reactivity compared to the one for aromatic skeleton.

The analysis of Bz and Pr mixtures with Methocel E5

Characteristic vibration bands for functional moieties (aminic and ester) for both active substances can be identified even in the FTIR spectrum of 1:1 physical mixtures. The FTIR spectra of Pr and Bz mixtures with Methocel show the presence of the characteristic band for the O-H stretching of hydroxyls at 3471 cm^{-1} as a broad signal. The C=O and C-O bands appear at the same wavenumber as in the case of pure Pr, Bz and Methocel, namely at 1693, 1251 for Pr, 1680, 1257 for Bz and 1068 cm^{-1} for Methocel. In this case, FTIR spectroscopy confirms that no interaction occurs, the FTIR spectrum of the mixture can be considered a superposition of the spectra of active substance (namely Pr and Bz) with the one of Methocel.

The analysis of Bz and Pr mixtures with Povidone-Kollidon 90

In the case of use Povidone-Kollidon 90 as excipient, for both active substances interactions occur during thermal

Band (wavenumber, cm^{-1})	Assignation
Procaine (Pr)	
3349	N-H stretching bands
3319	N-H stretching bands
3210	ammonium ions from Pr·HCl
1694	esteric C=O
1606	$-NH_2$ scissoring band
1364-1250	C-N stretching (aromatic amines)
1253	esteric C-O stretching
1172	$-N-CH_2$ stretching band (tertiary amino group)
850-750	$-NH_2$ wagging and twisting
Benzocaine (Bz)	
3344	N-H stretching
3328	N-H stretching
1682	esteric C=O
1599	$-NH_2$ scissoring band
1368-1240	C-N stretching band for aromatic amines
1255	esteric C-O stretching
850-750	NH_2 waging and twisting

Table 2
FTIR SPECTROSCOPIC ASSIGNATION OF BANDS FOR PURE PR AND BZ

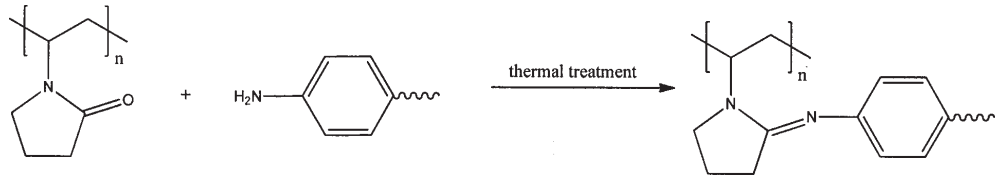
Band (wavenumber, cm^{-1})	Assignation
Methocel E5	
3472	O-H stretching band
1472	sugar ring
1068	C-O (etheric) stretching, intense
Povidone-Kollidon 90	
3483	Broad signal, -OH stretching vibrations from absorbed water
2942	stretching vibrations (symmetric and asymmetric) of the methylene group
1664	-C=O group, intense band
1430	$-CH_2$ asymmetrical vibration
1289	-CH in-plane bending
Calcium stearate	
2963, 2917, 2851	$-CH_3$ and $-CH_2$ symmetric and asymmetric stretching vibration
1577, 1541, 1471	$-COO^-$ asymmetric stretch
726	"rocking" deformation $(H-C-H)_n$ for n>3
Colloidal silica dioxide-Aerosil 200	
1093	Si-O symmetric stretching vibration
826	asymmetric Si-O stretching
680	Si-O bending

Table 3
FTIR SPECTROSCOPIC ASSIGNATION OF BANDS FOR PURE EXCIPIENTS

treatment. Corroborating the FTIR data with the ones obtained by DSC analysis, an interaction between active substances and Kollidon 90 was expected around 50 °C. In order to find an interaction, 20 mg of mixture was heated and maintained at 55 °C for 2h. Even if for the amino group from both Pr and Bz can be considered a low-reactivity moiety (an reduced basicity and nucleophilicity due to the presence of the benzene aromatic ring), under heating a modification of FTIR spectrum for the 1:1 mixture is observed. After cooling down at 25 °C, the FTIR spectra was drawn up. Several characteristic bands dissapeared (such as the broad signal 3483 cm^{-1} for stretching vibrations of -OH groups from absorbed water) or lowered the intensity (the intense band at 1664 cm^{-1} corresponding to -C=O group from Kollidon 90). Other alliteration can be noticed for the N-H stretching bands from both Pr and Bz, as well for $-NH_2$ scissoring band. These bands at 3349, 3319 and 1606 cm^{-1} (in the case of Pr) and 3344, 3328 and 1599 cm^{-1} (in the case of Bz), respectively, are no longer present in the spectra of mixtures after heating. A tentatively proposal for the interaction, according to FTIR spectroscopy analysis is presented in scheme 1.

The analysis of BZ and PR mixtures with StCa

As previously reported [15], interaction of other stearate, namely magnesium stearate with both active substances was previously found. A similar behaviour was identified in the case of using StCa. This excipient presents two intense absorption bands at 1577 cm^{-1} and 1471 cm^{-1}, respectively, corresponding to asymmetric stretch of the COO^- anion, and at higher wavenumber (2917 cm^{-1} and 2851 cm^{-1}) the ones corresponding to vibrations of C-H bonds. The FTIR spectroscopy reveals that the main modification in the structure of both active substances occurs at the ester carboxyl moiety. In both cases, a significant shifting of bands to higher wavenumbers occurs. In the case of Pr+StCa, the band is shifted up to 1723 cm^{-1}, and for Bz+StCa, is shifted up to 1731 cm^{-1}. The shifting can be a result of the fact that the esteric group suffers a chemical modification, with the transformation of the aromatic ester into an aliphatic one due to the presence of stearate anion. As in our previous study [15], in the FTIR spectra of mixtures, bands corresponding to COO^- anion from excipient are still



Scheme 1. A proposed chemical interaction between active substances and Kollidon 90

present, due to the fact that StCa is present in excess in the mixture.

The analysis of Bz and Pr mixtures with Aerosil 200

The FTIR spectra of binary systems (Pr+SiO_2 and Bz+SiO_2) is considered to be superposition of the individual spectra without major modification of characteristic wavenumbers for bands. The FTIR spectrum of SiO_2 is a relatively simply spectrum, because of its simple structure. The main bands that appear in the FTIR spectrum of SiO_2 are the ones at 1093 cm^{-1} (Si-O symmetric stretching vibration), at 826cm^{-1} (asymmetric Si-O stretching) and at 680 cm^{-1} (Si-O bending). In the case of binary mixtures, the characteristic bands for SiO_2 appear at the same wavenumbers (±1 cm^{-1}). Furthermore, no modifications are noticed for the bands corresponding to Pr and Bz leading to the conclusion that both active substances are compatible with this excipient and no interaction occurs.

Conclusions

This study was realized as a continuation to our previous investigations regarding the compatibility of two local anesthetic agents, namely procaine and benzocaine with pharmaceutical excipients. The results obtained from this study confirm that DSC and FTIR spectroscopy are simple and accurate tools in the evaluation of the compatibility between Pr and Bz respectively and the four tested excipients.

No interaction was observed between the active substances and Methocel and SiO_2. This fact was confirmed by both techniques. From the DSC data and FTIR spectroscopy, interactions were confirmed between active substances with both calcium stearate and Povidone. For each interaction observed, a possible mechanism was presented.

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