

COMPATIBILITY STUDIES BETWEEN DRUGS AND EXCIPIENTS IN THE PREFORMULATION PHASE OF BUCCAL MUCOADHESIVE SYSTEMS

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Abstract

The main aim in the development of a pharmaceutical system is the achievement of an adequate preparation. The potential physical and chemical interactions between drugs and excipients can affect the chemical nature, the stability and bioavailability of the drugs and, consequently, their therapeutic efficacy and safety.

We present the thermal and spectroscopic study of drug/polymer physical mixtures containing ibuprofen (IB), clindamycin hydrochloride (CD), metronidazole (MZ), as the active pharmaceutical ingredient (API) and hydroxypropyl methylcellulose (HPMC K100M), Poloxamer 407, polyethylene oxide (PEO 1105) and polycarbophil (Noveon AA1) as excipients, defined as prototype formula. Differential scanning calorimetry (DSC) analysis revealed the displacement of the characteristic peaks for the prototype formulas of excipients in the case of IB and CD. A Fourier transform infrared spectroscopy (FT-IR) technique was used to confirm and to investigate the type of the possible interactions between the components. In both cases, the spectroscopic data revealed that weak intermolecular hydrogen-bond type interaction is incriminated, involving the carbonyl moiety of IB and in a lower extent the hydroxyl group of CD. The analysed excipients did not show any effect on the MZ.

Rezumat

Pentru a evalua compatibilitatea dintre substanţele medicamentoase (ibuprofen (IB), clorhidrat de clindamicină (CD), metronidazol (MZ)) şi excipienţi (hidroxipropil metilceluloză (HPMC K100M), poloxamer 407, polietilenoxid (PEO 1105) şi policarbofil (Noveon AA1)), în vederea utilizării lor la formularea unor geluri mucoadezive cu aplicare în cavitatea bucală, s-au efectuat studii de analiză termică diferenţială (DSC) şi de spectroscopie în infraroşu cu transformantă Fourier (FT-IR). Analiza DSC a evidenţiat o deplasare a picurilor caracteristice pentru formulele prototip de excipienţi în amestecurile cu IB şi CD. Studiile FT-IR, utilizate pentru a confirma rezultatele analizei DSC şi pentru a stabili tipul de interacţiuni posibile substanţe medicamentoase – excipienţi, au incriminat

prezența unor legături de hidrogen care implică grupa carbonil a IB și, într-o măsură mai mică, grupa hidroxil a CD. În cazul MZ, nu s-au observat modificări.

Keywords: FT-IR, differential scanning calorimetry, active pharmaceutical ingredient, physico-chemical compatibility

Introduction

Preformulation is the first step in the rational formulation of an active pharmaceutical ingredient (API). It is an investigation on the physical-chemical properties of the drug substance alone and in combination with excipients. Assessment of the possible incompatibilities between the drug and various excipients is an important part of the preformulation [1]. The formulation of a drug substance frequently involves it being blended with different excipients to improve manufacturability, and to maximize the product's ability to administer the drug dose effectively. Excipients are known to facilitate the administration and to modulate the release of the active component. They can also stabilize it against degradation from the environment. Most excipients have no direct pharmacological action but they can impart useful properties to the formulation. However, they can also give rise to inadvertent and/or unintended effects such as an increased degradation of the drug. The physical and chemical interactions between the drugs and excipients can affect the chemical nature, the stability and the bioavailability of the drug products, and consequently, their therapeutic efficacy and safety. The active substance/excipient compatibility studies play the role of identifying in an as short as possible time interactions between potential formulation excipients and the active substance [2,5,11].

The most frequently methods for the physical-chemical investigation with the view of detecting the possible interactions between the excipients and the active drug substance are thermal analysis (DSC, DTA, DTG, ITC), spectroscopic methods (FT-IR, X-ray diffraction, NMR), chromatographic methods (LC, LC-MS/MS), the dissolution tests etc [4,6,8,9,12,14]. The most sensitive methods for detection of the possible interaction are the thermal analytic ones, but they can be unspecific and the result are difficult to interpret and they can very frequently indicate false positive or false negative results.

Differential scanning calorimetry (DSC) is currently the leading technique in this field [3]. The main benefit of DSC, rather than stressed storage methods, is its ability to quickly screen the potential excipients for incompatibilities derived from the appearance, shifts or disappearance of peaks and/or variations in the corresponding ΔH (enthalpy of transition) [13]. Other features such as low sample consumption also make it an

attractive method. Although DSC is unquestionably a valuable technique, interpretation of the data may not be straightforward. In this method, the sample is exposed to high temperatures (up to 300°C or more), which in reality is not experienced by the dosage form. Thus, DSC results should be interpreted carefully, as the conclusions based on DSC results alone can be often misleading and inconclusive [3].

The IR spectroscopic methods are less sensitive from this point of view, but they are complementary for the thermal-analytical techniques, especially due to the detection of the atom groups involved in the excipient/API interaction and they allow the quantitative estimation of these interactions [4,7,8].

The aim of the study was to analyse by DSC and IR studies the compatibility of some excipients with potential use in binary or ternary mixtures, as vehicles for the preparation of mucoadhesive systems with antimicrobial (MZ, CD) or antiinflammatory drug substances (IB).

Materials and Methods

Materials: Poloxamer 407 (Pluronic F127, Sigma, St. Louis, MO, USA), Polycarbophil (Noveon AA1, Goodrich), hydroxypropyl methylcellulose (HPMC K100M, Colorcon, USA), polyethylene oxide (PEO Sentry Polyox 1105 NF (PEO)), ibuprofen 25 µm (BASF, Germany), metronidazole (BASF, Germany), clindamycin hydrochloride (Tokyo Industries).

Samples preparation

For the study we used polymers with the recognized bioadhesive and gelifying properties able to maintain the active substances for a longer period of time on the buccal mucosa [10,15]. For DSC analysis two prototype formulas (base) of excipients, consisting of physical mixtures of Poloxamer 407:HPMC K100M:Noveon AA1 (Base 1), Poloxamer 407:PEO 1105:Noveon AA1 (Base 2), respectively. The ratio between the components was 1:1:1 (w/w). Mixtures of these bases with the each active substance were prepared in a ratio of 1:1 (w/w) (base 1: IB 1:1, base 1:CD 1:1, etc).

For the FT-IR analysis physical mixtures of the 4 studied polymers were prepared : Poloxamer 407:PEO1105:Noveon AA1:HPMC K100M in a ratio of 1:1:1:1, w/w, mixtures of the 4 polymers with each active substance, respectively, in a ratio of 1:1:1:1:1, w/w. The polymers and drug substances in a weight ratio were mixed in a mortar to obtain a physical mixture that was sieved through 120 µm sieve.

All the samples were kept for a week at room-temperature for further analysis.

Differential scanning calorimetry (DSC)

The changes, if any, in the thermal characteristics of IB, CD and MZ in the prototype excipient mixtures formulas were studied using a differential scanning calorimeter (Mettler – Toledo DSC 822^e); the system was purged with nitrogen gas at the rate of 50mL/min to maintain an inert atmosphere; the samples were hermetically sealed in 40 μ L aluminium pans and heated between 25°C and 250°C with a heating rate of 10°C/min.

In a first stage prototype excipient mixtures were analyzed; subsequently each base in the mixture with each active substance in a 1:1 ratio.

Fourier –transform Infrared spectroscopy (FT-IR)

All the FT-IR spectra were recorded using a Jasco FT-IR 4100 spectrometer equipped with a GeSe crystal for the direct acquisition of the attenuated total reflectance (ATR) infrared spectra of solid samples. The spectra were recorded on the range of 4000 – 550 cm⁻¹ with a spectral resolution of 1cm⁻¹ and 8 readings/point, using a thermal stabilized TGS detector (Deuterated L-alanine Triglycine Sulphate).

In order to detect the possible changes due to the excipient/API interactions the subtraction of the ATR-FT-IR spectra of the mixture of the 4 excipients, components of bases 1 and 2 (Poloxamer 407:PEO1105:Noveon AA1:HPMC K100M in a ratio of 1:1:1:1 w/w) from the ATR-FT-IR spectra of the mixture of the 4 excipients and the studied active substances (in a ratio of 1:1:1:1:1, w/w) was done.

Results and Discussion

DSC analysis allows the evaluation of the possible interactions between the API and the excipients.

The analysis of the results obtained from the DSC study of the prototype polymer mixtures with the active substances selected for the formulation of the mucoadhesive buccal systems revealed that in the case of the formulation Base 1 (Poloxamer 407 : HPMC K100M:Noveon AA1) with CD, a transition of the peak base towards higher temperatures took place; also, a supplementary peak appeared, probably due to the decomposition of CD; this indicates a possible base 1 : CD interaction (Figure 1a).

Base 1 : IB – a shift of the base peak was noted, a transition towards lower melting temperatures taking place; this could be due to the impurification by the achievement of the mixture of the three polymers with IB, but it can also reflect the existence of the weak interaction effects between Base 1 and IB (Figure 1b).

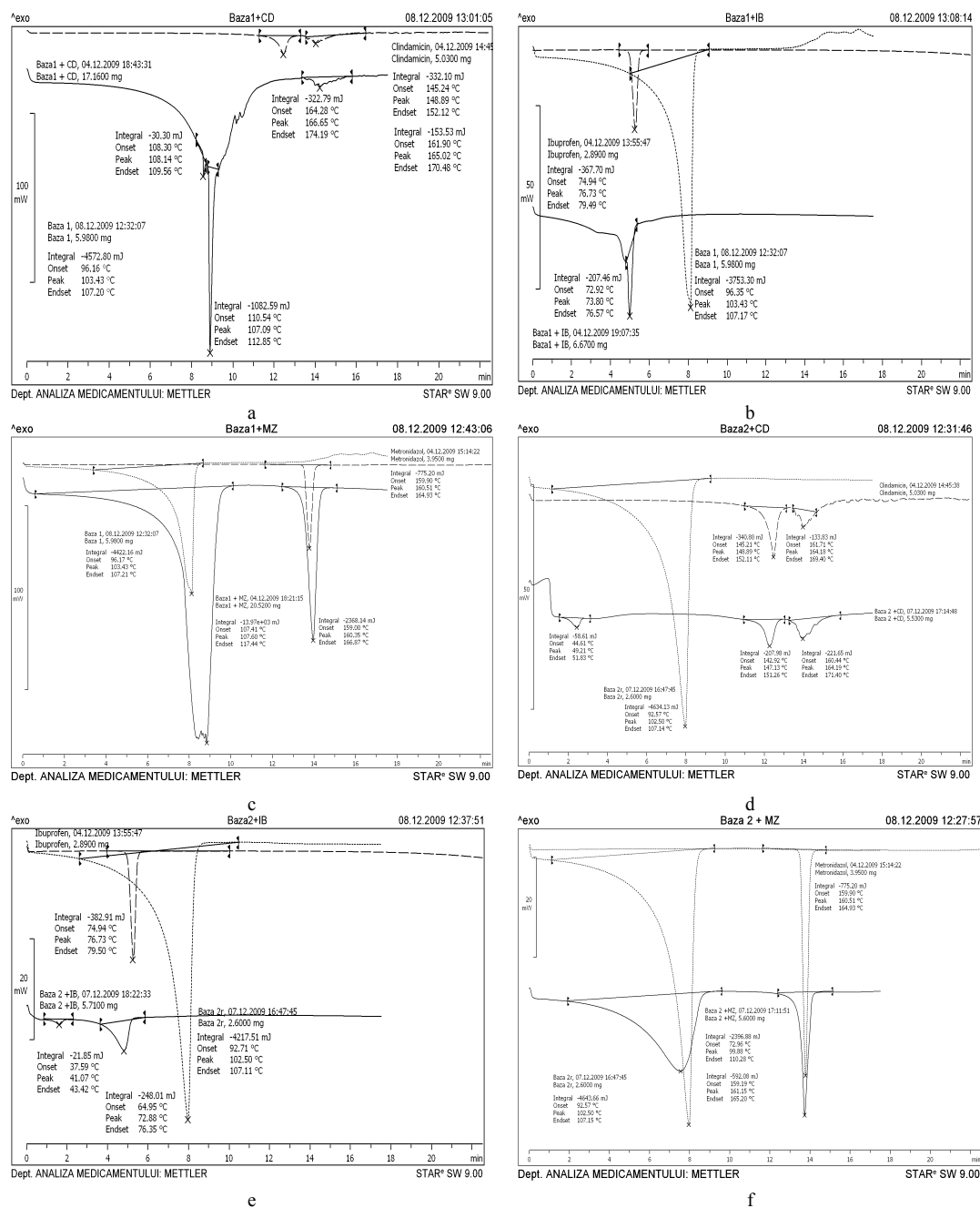


Figure 1

DSC thermograms of clindamycin hydrochloride (CD), ibuprofen (IB) and metronidazole (MZ) respectively, in combination with mixtures of polymers intended for buccal mucoadhesive system preparation (Base 1: Poloxamer 407:HPMC K100M:Noveon AA1, 1:1:1, w/w and Base 2: Poloxamer 407:PEO 1105:Noveon AA1, 1:1:1, w/w).

Analysis of Base 1:MZ mixture revealed no changes (Figure 1c). DSC analysis of base 2 with the studied active substances revealed the following aspects:

Base 2 with CD: the transition to lower temperatures of the base peak (from 102°C to 49°C) was noted (Fig. 1d). Base 2 with IB: a displacement of the base peak to a lower temperature (41°C) was noted, while the IB peak remains (Figure 1e). These results can be justified by the lowering of the melting point due to the mixing, or they can indicate some possible interaction effects. Analysis of the mixture of base 2 with MZ revealed no changes in the thermograms (Figure 1f).

To confirm the possible interactions between the API and the polymers contained in the prototype mucoadhesive formulations and most importantly to reveal their nature, infrared spectroscopy studies were required. The ATR-FT-IR spectra of IB show two characteristic strong absorption bands at 1708 cm^{-1} (stretching vibration C=O) and 2955 cm^{-1} (stretching vibration O-H). In the fingerprint region of 1500 – 550 cm^{-1} the characteristic vibration bands of the aromatic ring and the isobutyl moiety is noted.

In order to detect the possible spectral changes due to the excipients/API interactions the subtraction of the ATR-FT-IR spectrum of the mixture of the 4 excipients (ratio 1:1:1:1 w/w) from the ATR-FT-IR spectrum of the mixture of the 4 excipients with IB (ratio 1:1:1:1 w/w) was performed. The resulting spectra were compared with that of standard IB (Figure 2), where a slight shift of the vibrational band of the carbonilic moiety (from 1708 cm^{-1} to 1729 cm^{-1}) occurred which may indicate its involvement in a hydrogen bonding with one of the four excipients. No important changes were recorded in the fingerprint region of IB FT-IR spectra.

In the case of the mixture of CD with the 4 excipients, the same procedure of spectral subtraction led to a spectrum similar with that of the active substance (Fig. 3). The vibration band of the carbonylic moiety of the amide ($\nu(\text{C=O}) = 1684 \text{ cm}^{-1}$) remains unchanged, which clearly indicates the lack of interaction at this level. The significant attenuation of the absorption bands observed in the spectral range of 2800-3500 cm^{-1} assigned to the amide N-H and O-H stretching bands, as in all three cases, is most likely due to the dilution of the API in the mixture of excipients.

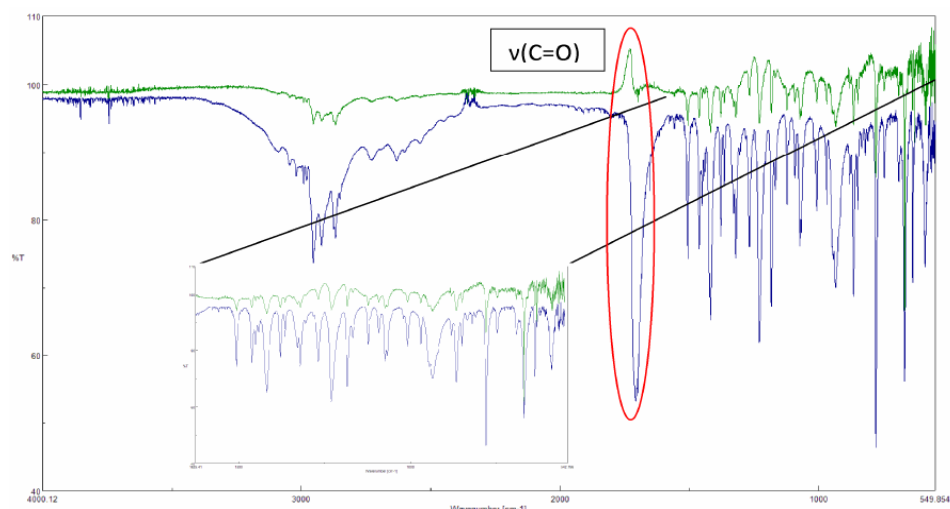


Figure 2

ATR-FT-IR spectra of standard ibuprofen (IB) (blue) and after subtracting of the spectrum of the mixture of the 4 excipients (HPMC K100M:Poloxamer 407:Noveon AA1: PEO 1105) from the ATR-FT-IR spectrum of the mixture of the 4 excipients with IB in a ratio 1:1:1:1 w/w (green). In the frame the enlarged zone of the fingerprint region of standard IB and of the residual spectra.

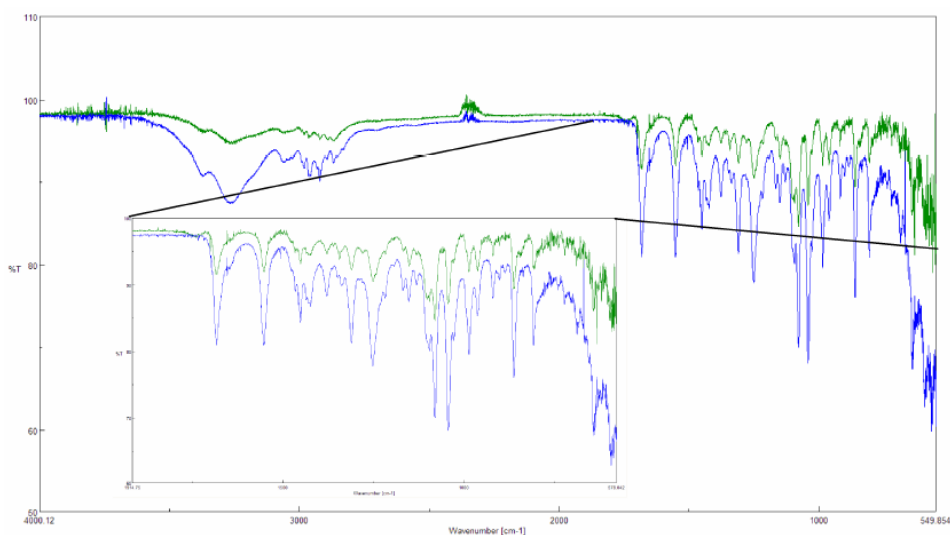


Figure 3

ATR FT-IR spectra of clindamycin hydrochloride standard (CD) (blue) and after subtracting of the spectra of the mixture of the 4 excipients (HPMC K100M:Poloxamer 407:Noveon AA1: PEO 1105) from the ATR FT-IR spectrum of the mixture of the 4 excipients with CD in a ratio 1:1:1:1 w/w (green). In the frame the enlarged zone of the fingerprint region of standard CD and of the residual spectra.

The residual spectra obtained by subtraction in the case of MZ indicates a high degree of similarity with its standard spectra (Fig. 4). The characteristic bands of MZ $\nu(\text{O-H}) = 3214 \text{ cm}^{-1}$, the asymmetric stretching $\nu_{\text{as}}(\text{NO}_2) = 1472 \text{ cm}^{-1}$ and symmetric stretching $\nu_{\text{s}}(\text{NO}_2) = 1367 \text{ cm}^{-1}$ remain unchanged, indicating the lack of interactions of the active substance with the excipients both at the level of the nitroimidazole ring and the hydroxyethyllic moiety. The decrease of $\nu(\text{O-H}) = 3214 \text{ cm}^{-1}$ in the residual spectra can only be accounted to dilution effect of MZ in the excipients, and no spectral shift or other changes can be observed.

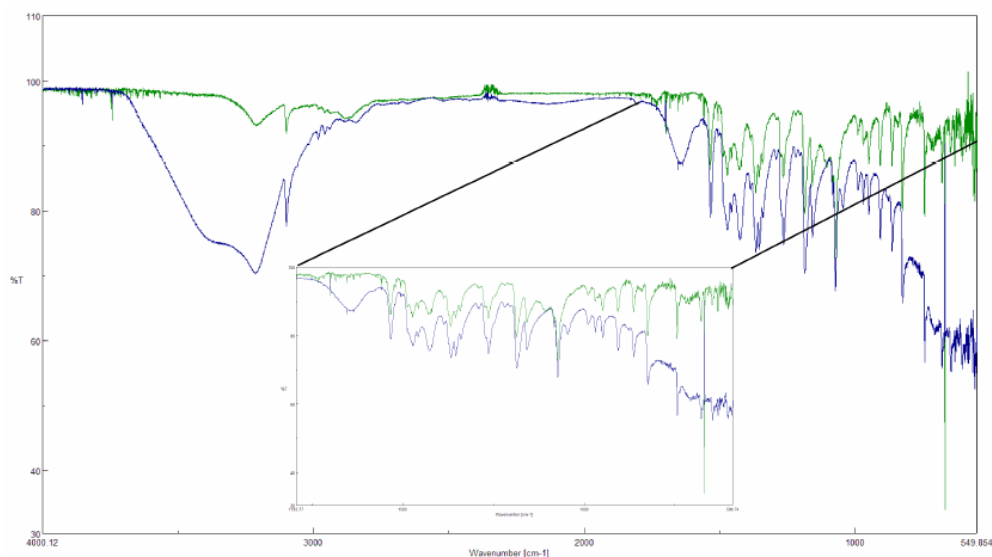


Figure 4

ATR FT-IR spectra of metronidazole standard (MZ) (blue) and after subtracting of the spectrum of the mixture of the 4 excipients (HPMC K100M:Poloxamer 407:Noveon AA1: PEO 1105) from the ATR FT-IR spectrum of the mixture of the 4 excipients with MZ in a ratio 1:1:1:1 w/w (green). In the frame the enlarged zone of the fingerprint region of standard MZ and of the residual spectra.

Conclusions

FT-IR and DSC methods were used to study drug/polymer physical mixtures that contained ibuprofen, clindamycin hydrochloride or metronidazole, as active pharmaceutical ingredients, and mixtures of hydroxypropyl methylcellulose (HPMC K100M), poloxamer 407, polyethylene oxide (PEO 1105) and polycarbophil (Noveon AA1) as possible excipients selected for the development of a mucoadhesive system intended for the local application in the oral cavity.

DSC analysis revealed the shift to lower temperatures of the characteristic peak for the prototype formulas of excipients in the case of IB and CD. IR spectroscopic data seems to be consistent with the results obtained by the thermoanalytical method, offering complementary information about the functional moieties involved in such drug-excipient interactions. In both cases, a weak intermolecular hydrogen-bond type interaction is incriminated, involving the carbonyl moiety of IB and in a lower extent the hydroxyl group of CD. According to the spectroscopic data no other type of interaction can be proven, ruling out any type of structural change of the active pharmaceutical ingredients such as hydrolysis, dimerization, complexation, condensation, etc. Therefore, based on the existing data, no real concern is formulated regarding the long-term stability of the proposed formulations. The relevance and implications of the existing hydrogen bonds between IB and one of excipients over the pharmacokinetic properties of the formulation is yet to be proven.

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