UNIVERSITY OF BUCHAREST

FACULTY OF CHEMISTRY

DOCTORAL SCHOOL OF CHEMISTRY

ABSTRACT OF THE PhD THESIS

PHYSICO-CHEMICAL STUDY OF SOME MIXTURES WITH APPLICATIONS IN PHARMACEUTICAL INDUSTRY

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The PhD thesis entitled "*Physico-chemical study of some mixtures with applications in pharmaceutical industry*" brings experimental data with important conclusions for a set of binary and ternary mixtures of active pharmaceutical ingredients and excipients. The aim of the study is to determine the compatibility between the components in order to obtain combined pharmaceutical products, based on large scale trials (combination therapy) that have established superior therapeutic effects to monotherapy for each system studied.

The thesis is divided in two parts: one part of literature that includes 3 chapters and one part with experimental data, interpretations and original comments that includes 4 chapters.

The literature part focuses mainly on the fundamental concepts encountered in the study of compounds of pharmaceutical interest, methods and theories used in their study, either singular or in mixtures. Also, are presented general concepts and methods used for obtaining the solid dispersions and respectively, active pharmaceutical ingredients and excipients that are used in the experimental part.

The original experimental data and results are grouped into two parts depending on area of pharmacological application: systems with applications in the treatment of hypertension as a single pathology or polipathology (**Chapter 4 and Chapter 5**) and systems with applications in the treatment of bacterial and viral infections (**Chapter 6 and Chapter 7**).

Chapter 4. Propafenone Hydrocloride (PP) – Metoprolol Tartrate (MT) system

The experimental study from this chapter follows two directions: the study of interactions established between Propafenone Hydrochloride and Metoprolol Tartrate (binary system) and the study of interactions established between the active pharmaceutical ingredients and two common used excipients, α-lactose monohydrate (LA) and corn starch (CS) (binary and ternary systems).

The binary mixtures formed by PP and TM of known concentrations were obtained in order to cover the full composition range (0.00-1.00), by varying the mole fraction. Several methods were employed to obtain the mixtures with the purpose to determine the optimum parameters:

- „in situ" recrystallisation in the DSC pan;
- solvent recrystallization;
- grinding and homogenization in normal lab conditions;
- prefused samples.

The DSC curves obtained for the binary mixtures (figure 19) present two endothermic peaks:

- the first peak, which appears in good approximation at the same temperature for all the mixtures studied, at 374 K, was attributed to the melting of eutectic composition;

- the second peak corresponding to the melting of compound in excess reported to the eutectic composition.

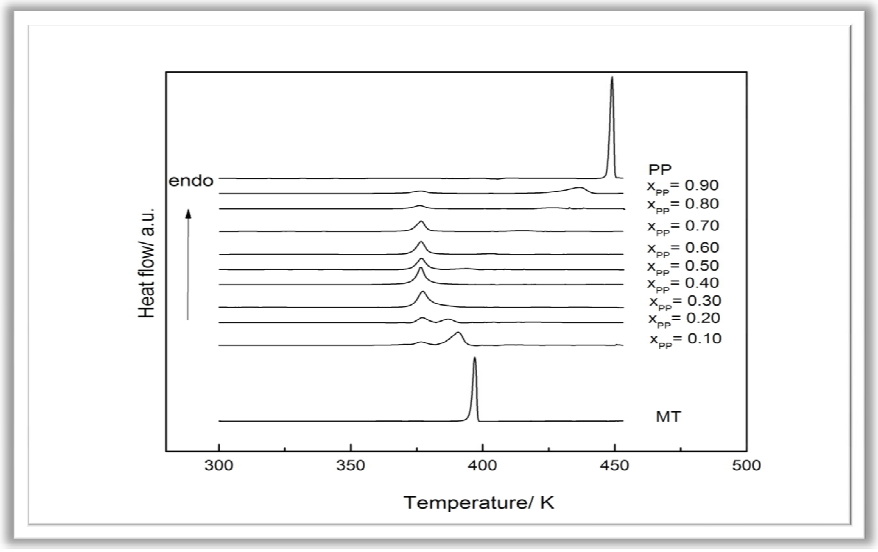

Figure 19: DSC curves for PP and MT and their binary mixtures with variable composition.

The ideal phase diagram calculated using Schroder van Laar equation and the real phase diagram obtained using the DSC data (at least three measurements), are presented in figure 20 a) as $T=T(x_i)$. The ideal phase diagram indicates an eutectic composition at $x_{PP} = 0.15$ and an eutectic temperature of 392 K.

The real phase diagram presents a simple eutectic behavior with the eutectic point at temperature 373.84 K and 0.40 mole fraction of PP.

The obtained phase diagrams indicate, for mixtures with low content of PP, $x_{PP} < 0.15$, a behavior close to the ideality, but for mixtures with $x_{PP} > 0.15$, a significant deviation from the ideal behavior is observed.

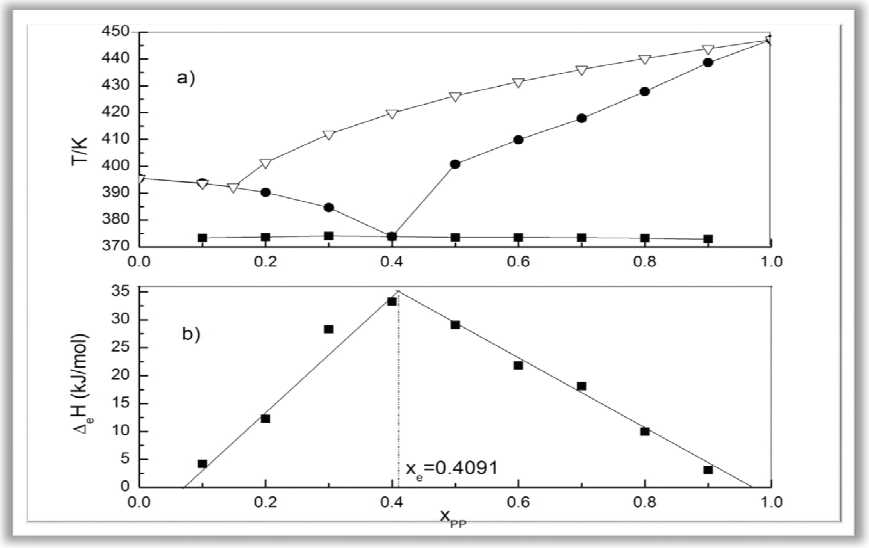

Figure 20: a) Phase diagram of binary mixture PP-MT: Δ – Ideal temperatures curve, ● Liquid temperatures curve, ■ - Solid temperatures curve; b) - Tamman's plot

Tamman's plot indicates an exact eutectic composition at $x_{PP} = 0.4091$ and suggest that solid solutions are formed at the extremities of the phase diagram below compositions of $x_{PP} \approx 0.06$ and above $x_{PP} \approx 0.96$.

The structure of the eutectic melt was determined by computing the mixing enthalpy. For the binary mixture PP-MT the mixing enthalpy obtained , $\Delta^M H$ = - 24.52 kJ·mol^{-1} is negative which suggests that clustering of molecules takes place in the eutectic melt, process favored by weak intermolecular forces.

The deviation from the ideal behavior of the studied system was determined by computing the activity coefficients and the excess thermodynamic functions values: G^E, S^E and μ_i^E:

$$G^E = RT[x_1 ln\gamma_1^l + x_2 ln\gamma_2^l]$$

$$S^E = -R[x_1 ln\gamma_1^l + x_2 ln\gamma_2^l] - RT\left[x_1 \frac{\partial ln\gamma_1^l}{\partial T} + x_2 \frac{\partial ln\gamma_2^l}{\partial T}\right]$$

$$\mu^E = RT ln\gamma_i$$

The values obtained are represented in figure 21 as function of composition and the analysis of the plot indicate that the excess free energy of mixing, G^E, decreases on either side of the phase equilibrium curves and acquires a minimal value at the eutectic composition, which is expected, since eutectic temperature is the lowest liquid temperature reached.

On the contrary, the values of the excess entropy of mixing, S^E, increase on each side of the phase diagram and show a maximal value at the eutectic composition because of the coexistence of three phases in equilibrium: two solidus phases and a liquid phase [56].

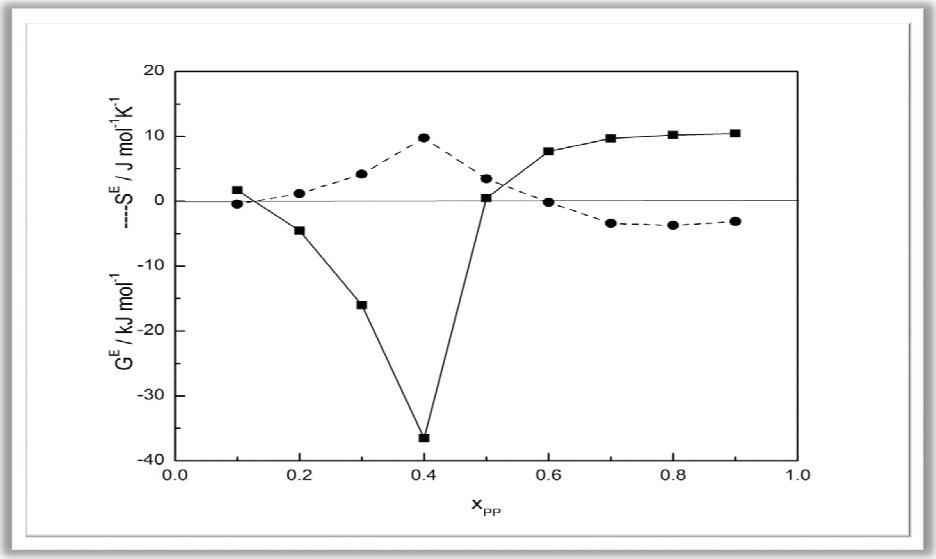

Figure 21: Variation of excess thermodynamic functions, G^E and S^E, as function of mole fraction of Propafenone Hydrochloride.

The thermonature of the system is determined by the sign of the excess thermodynamic functions, G^E and S^E respectively. For instance, $G^E>0$ and $S^E<0$ indicate the endothermic nature of the system and $G^E<0$ and $S^E>0$ indicate the exothermic nature of the system.

For the binary mixture PP-TM was observed:

- at concentrations lower than 0.50 mole fraction of PP the system is exothermic in nature, which point to strong interactions between the components that form the eutectic melt and weak associations between molecules of the same type;

- at concentrations higher than 0.50, the system is endothermic, which indicates strong interactions between molecules of the same type.

Characterization of mixtures with excipients in order determine the compatibility degree

The calorimetric study of binary and ternary mixtures with excipients showed different degrees of compatibility between the systems components, data confirmed also by FT-IR spectroscopy.

In order to determine the compatibility API (Active Pharmaceutical Ingredient) - excipient, the thermodynamic parameters were obtained from DSC curves recorded for excipients (LA and CS), API-excipient binary mixtures and API-API-excipient ternary mixtures.

In order to see if any interactions occur between the compounds, the expected enthalpy ($\Delta^{fus}H$ *calculated*) has been computed using the expression below:

$$\sum(I \cdot (\Delta^{fus} H_I)_{exp} = (\Delta^{fus} H)_{calc}$$

where I represent the mass percent of each API or eutectic mixture in the mixtures with excipients and $(\Delta^{fus} H_I)_{exp}$ represent the corresponding enthalpy value determined from DSC curves.

The study of binary mixtures of pure compounds with lactose and also of the ternary mixtures (eutectic mixture PP-MT with lactose) show enthalpy differences of almost 50%, suggesting possible weak interactions established between components, although the characteristic endothermic peaks still can be seen but are slightly displaced.

The FT-IR spectra recorded indicate that although the characteristic absorption bands of the APIs can be observed, small displacements of the absorption bands are present mainly in the region 3200-2900 cm^{-1}, related to stretching vibration of C–H functional group. The displacement to lower wavenumbers (for e.g. 2941 cm^{-1} moves to 2934 cm^{-1}) indicate the establishment of strong van der Waals interactions [115] that confirm the enthalpy change observed in the calorimetric measurements.

Using corn starch as excipient, the enthalpy values calculated and experimental, are almost the same, evidencing the absence of the incompatibility between PP and CS, MT and CS and their eutectic mixture with CS. Practically, the thermal curves of binary mixtures can be considered as a superposition of the adequate curves of each constituent. The FT-IR spectra recorded in this case are confirming the calorimetric results.

Chapter 5. Captopril (CA)-Metoprolol Tartrate (MT)

In this chapter were followed two main directions: obtaining and characterization of binary mixture Captopril-Metoprolol Tartrate and study of interactions established between the components.

Binary mixtures formed by CA and MT were obtained in order to cover the entire composition range, by varying the mole fraction in the range 0.00-1.00. Two methods were employed for the obtaining of the binary mixtures:

- grinding and homogenization in normal lab conditions;
- physical mixing (Turbula Mixer, 30 minutes mixing time).

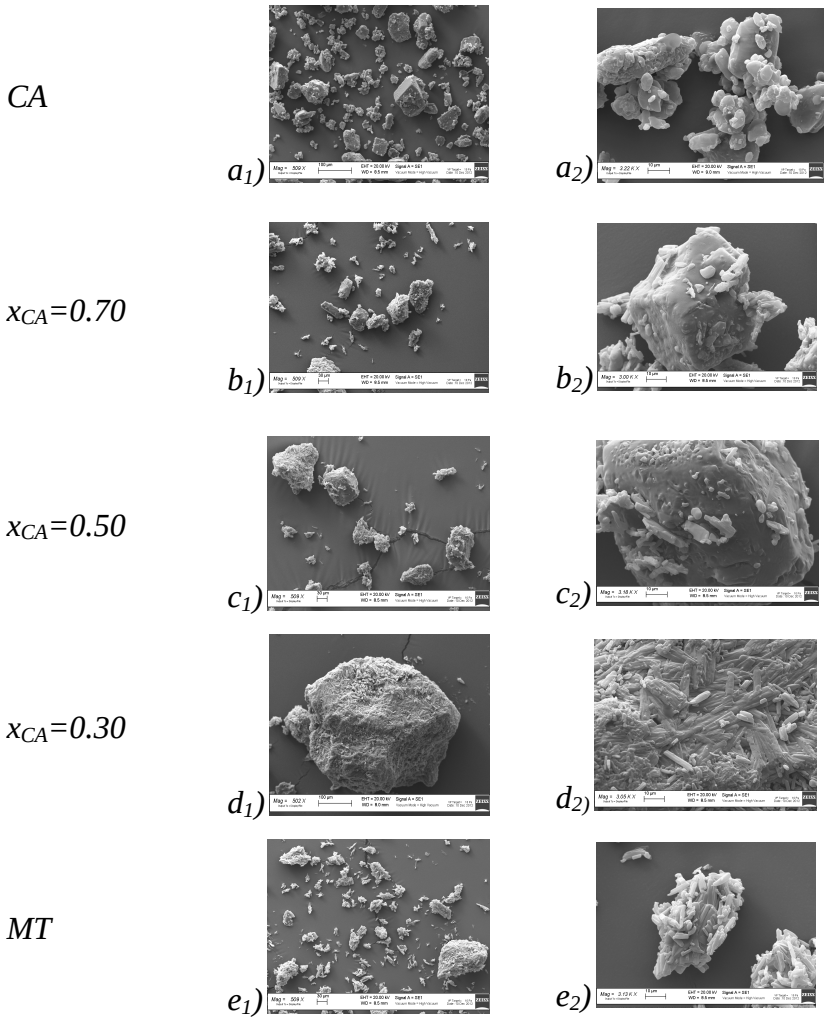

Figure 26: SEM photographs of CA a), CA:MT physical mixtures with x_{CA}=0.70 b), x_{CA}=0.50 c), x_{CA}=0.30 d) and MT e).

The lack of interaction between the two components during physical mixing was confirmed by FT-IR spectroscopy, X-ray diffraction and SEM measurements.

In the DSC curves obtained for binary mixtures two peaks are present: a broad peak, endothermic, in good approximation, at the same temperature for all compositions studied, 332 K,

corresponding to the eutectic melting and a second peak corresponding to the melting of the excess component reported the eutectic composition, with variable position depending on the composition of the sample.

Table 6: (Solid-liquid) equilibrium measured from DSC data for CA-MT binary mixture.

x_{CA}	T_e(K)	$\Delta^{fus}H_e$ (kJ·mol^{-1})	T(K)
0	-	-	395.23±0.07
0.10	333.22±0.67	2.80±0.69	392.23±0.74
0.20	333.16±0.51	4.81±0.58	390.30±0.68
0.30	332.47±0.64	7.05±0.53	388.01±0.70
0.40	333.30±0.58	9.90±0.47	385.30±0.63
0.50	332.75±0.71	11.60±0.66	382.11±0.74
0.60	333.34±0.60	13.65±0.44	377.81±0.69
0.65	333.31±0.55	15.21±0.34	371.58±0.78
0.70	332.06±0.48	16.43±0.37	-
0.75	333.58±0.61	14.51±0.59	366.08±0.75
0.80	333.46±0.69	12.73±0.70	371.03±0.64
0.85	333.38±0.47	11.31±0.51	374.91±0.72
0.90	333.37±0.39	10.08±0.29	377.17±0.48
1	-	-	378.71±0.39

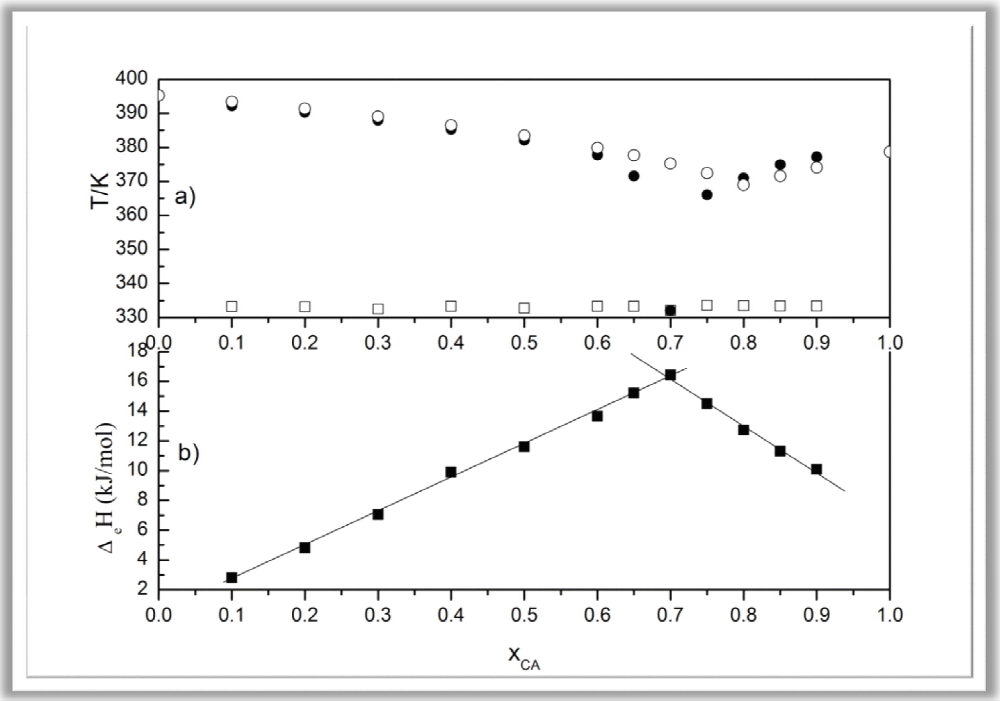

Figure 31: a) Phase diagram of CA-MT binary mixture: ○ – Ideal temperatures curve; ● Liquid temperatures curve, □ - Solid temperatures curve; b) Tamman's plot.

The ideal phase diagram [147, 148] (activity coefficients are equal to unity) reveals a simple eutectic point at a temperature of 375 K and x_{CA} = 0.80 and the real phase diagram at 332 K and x_{CA} = 0.70, respectively.

The phase diagrams obtained indicate deviation from ideal behavior on the composition range 0.60 ≤ x_{CA} ≤ 0.80 and a behavior close to the ideal case for the other regions of the composition range. Tamman`s plot, shown in figure 31 b) has a maximum at the eutectic composition (x_{CA} =0 .70).

The negative value of the enthalpy of mixing suggest the formation of molecular clusters in the eutectic melt through weak intermolecular forces that lead to a decrease in the enthalpy of eutectic melting.

$$\Delta^M H = (\Delta^{fus} H)_{exp} - (\Delta^{fus} H)_{calc} = -24.61\ kJ \cdot mol^{-1}$$

The obtained results were confirmed by HSM (Hot Stage Microscopy) experiments and the images obtained are presented in figure 32. At room temperature, the particles of the two components are aggregated and at 343 K the eutectic melting is taking place for all the samples. At a higher temperature, the melted sample (eutectic composition) can be observed together with solid particles of the component in excess, as respect to the eutectic composition.

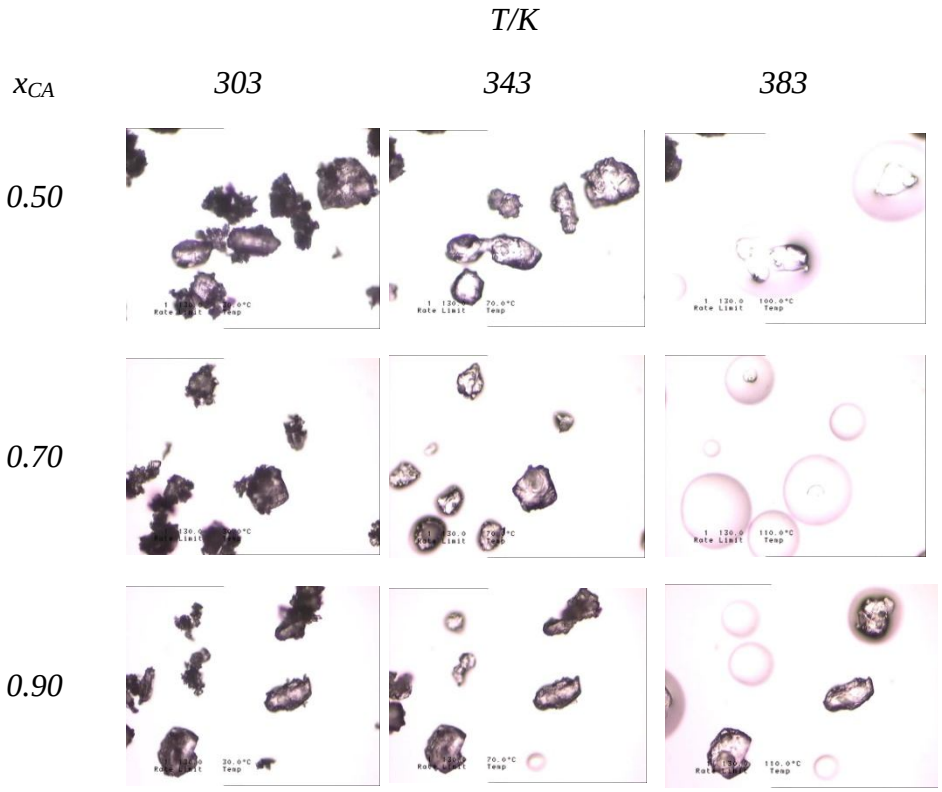

Figure 32: HSM pictures of CA-MT physical mixtures with different composition.

Trans-cis isomerisation of CA in the CA-MT binary mixture

Depending on the obtaining method, the binary mixtures CA-MT present different aspects: applying the grinding method, a sticky mass or gel, with an increased fluidity observed for the mixtures with high concentration of CA, was obtained. The DSC curves obtained in these cases present very broad endothermic peaks in the temperature range (333-353) K, for the mixtures with low concentration of CA and no thermal events for mixtures with high concentration of CA. On the contrary, the mixtures prepared using the turbula mixer, maintained the consistency of a solid mass where the particles are aggregated.

Following these results, the FT-IR spectra were recorded for the binary mixture with x_{CA}=0.50, physical mixture, ground sample and physical mixture annealed at 343.15 K, 363.15 K and 373.15K, as seen in figure 33.

An insight of the spectra indicates that while the physical mixture represents a sum of the pure compounds spectra as already mentioned, the spectrum obtained for the grounded sample and the sample annealed at 343.15 K (after the eutectic melting occurs) presents some changes: peaks at 2980 cm^{-1} and 2938 cm^{-1} assigned to CH_3 and CH_2 groups from CA move to 2979 cm^{-1} and 2936 cm^{-1}, respectively; 1632 cm^{-1} corresponding to residual content of tartaric acid becomes a shoulder; the peak at 1356 cm^{-1} assigned to CH_3 deformation in MT structure is displaced and appears at 1348 cm^{-1}. The displacement at lower wavenumbers indicates structural changes that support the clustering of molecules thought hydrogen bonds, as already mentioned and also suggests that in the grounded samples, due to the mechanical activation, the eutectic melting occurs at room temperature.

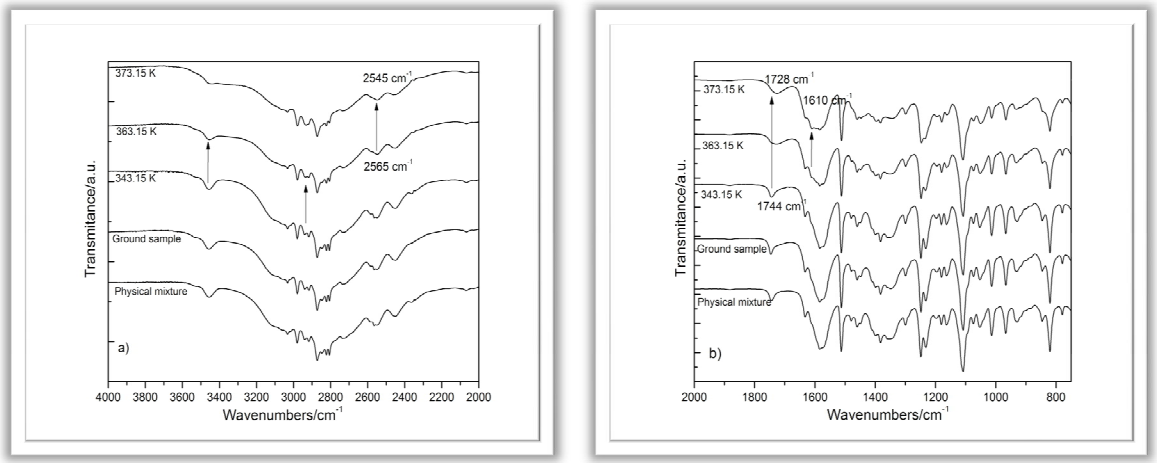

Figure 33: FI-IR spectra of CA-MT binary mixture with x_{CA}=0.50 and different obtaining methods: physical mixture, ground sample and physical mixtures annealed at different temperatures, a) (4000-2000) cm^{-1} spectral range and b) (2000-800) cm^{-1}spectral range.

From the analysis of the FT-IR spectra of the physical mixtures annealed at 363.15 K and at 373.15 K it can be observed that, during heating, the peaks already mentioned for hydrogen bonds become wider and overlapped; the peak corresponding to OH group from *MT* becomes broadened; the peak at 2565 cm^{-1} assigned to SH stretching in *CA* structure is found at 2548 cm^{-1} for the heated samples; the peak at 1744 cm^{-1} due to the C=O stretching of the COOH group of *CA* is displaced at

1728 cm^{-1} and 1726 cm^{-1}, respectively, and a new peak can be observed at 1610 cm^{-1} for the heated samples.

The formation of the eutectic mixture has a significant impact in the formulation of the dosage form containing the two active principles and can cause problems both during the technological processes and during the storage of the product. Indeed, the preparation of ground mixtures has demonstrated that the application of mechanical energy can result in the partial melting of the sample because of the eutectic behavior.

In the case of the studied system, trans-cis isomerisation of *CA* was observed for the samples annealed at high temperature, 363.15 K and 373.15 K respectively, still at a lower temperature compared to the temperature indicated in the literature for this process, an effect attributed to the presence of MT in the system.

Chapter 6. Metronidazole (MZ) –Norfloxacin (NF) system

In this chapter were studied by comparison the binary systems Norfloxacin anhydrous-Metronidazole and Norfloxacin pentahydrate-Metronidazole with the aim to determine the influence of the water content considering the fact that NF can absorb water during manufacturing or storage [111, 163]. The hydrates formed have an increased dissolution profile in comparison with the anhydrous form, but this aspect does not affect bioavailability.

For both studied systems was observed a simple eutectic point. From the diffraction patterns obtained was determined that Norfloxacin pentahydrate ($NF{\cdot}5H_20$), after the water loss undergoes a solid-solid transition to Norfloxacin anhydrous (NFanh).

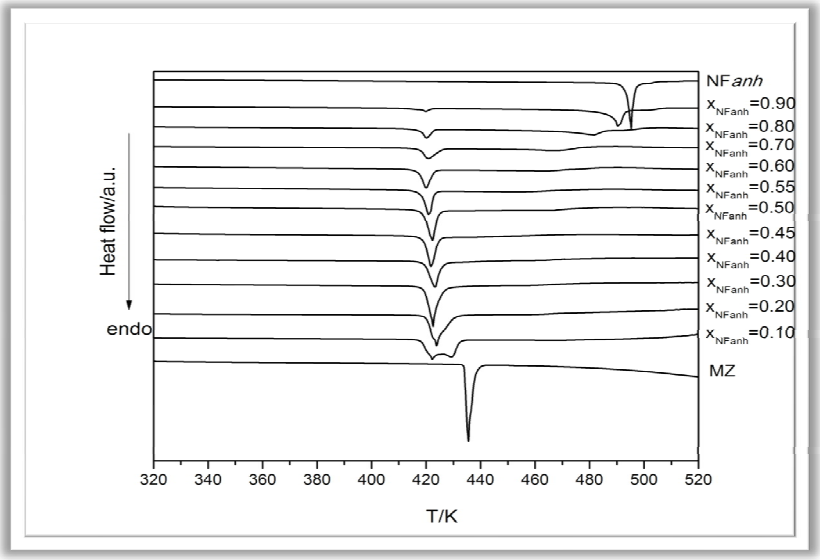

Figure 39: DSC curves of NFanh, MZ and their binary mixtures with variable composition.

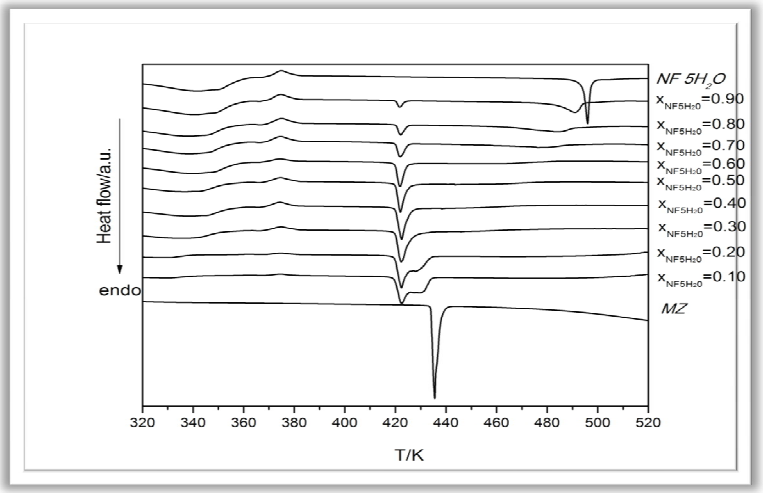

Figure 40: DSC curves of NF·5H_2O, MZ and their binary mixtures with variable composition.

The phase diagrams obtained for the ideal and real case indicate the deviation from the ideal behavior for the entire composition range and the presence of a simple eutectic point.

In the case of the studied system, for molar fractions of *NFanh* in the range 0.10 - 0.45, the eutectic peak and the peak due to the melting of the excess component are partially overlapped and reliable values of enthalpy change cannot be obtained, therefore the experimental eutectic composition has been determined using the following algorithm: the enthalpy variation of the second peak ($\Delta^{fus}H_2$) and of the first peak ($\Delta^{fus}H_e$) have been plotted versus mole fraction of *NFanh* for 0.50-1.00 composition range (the area where the two peaks are clearly separated). The representations are linear according to the equations:

$$\Delta^{fus}H_2 \text{ (kJ/mol)} = 58.07 \cdot x_{NFanh} - 29.64 \quad (30)$$

$$\Delta^{fus}H_e \text{ (kJ/mol)} = -47.62 \cdot x_{NFanh} + 46.22 \quad (31)$$

The value obtained for NFanh molar fraction in the eutectic mixture is x_{NFanh}=0.51 and the eutectic enthalpy can be determined by inserting this value in equation (31) and the obtained result is $\Delta^{fus}H_e$ = 21.91 kJ·mol^{-1}.

For NFanh-MZ binary system was obtained a negative enthalpy of mixing, $\Delta^{M}H$ = - 13.28 kJ·mol^{-1} that suggests the formation of molecular clusters in the melt. Their formation is favored if the molecules are associated together by weak intermolecular forces, which is very likely considering the structure of the two components.

Chapter 7. Acyclovir (ACV) - Fluocinolone Acetonide (FA) system

The experimental measurements from this chapter were focused on two areas: study of the interactions established between Acyclovir and Flucinolone Acetonide (binary system) and the study of interactions established between the two active pharmaceutical ingredients and the excipient β-cyclodextrin (β-CD) (binary and ternary systems).

The phase diagrams obtained indicate deviation from the ideal case and a simple eutectic point with an eutectic temperature that is influenced by the solid-solid transitions of FA (form A → B form).

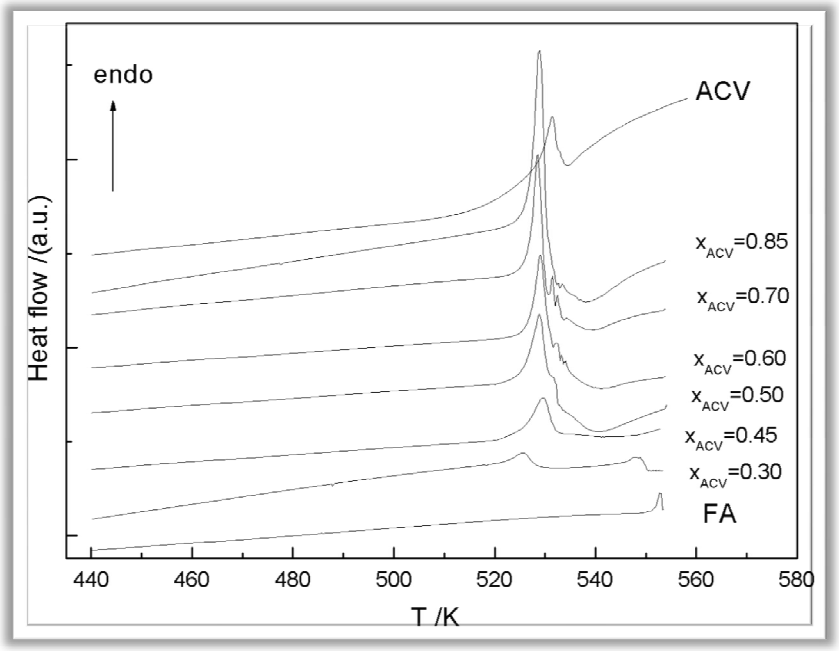

Figure 47: DSC curves obtained for ACV, FA and their binary mixtures with variable composition.

The DSC curves exhibit the melting process followed by decomposition as already seen for the pure compounds. However, a simple eutectic point represented by the first endothermic peak, located in good approximation at (525±2) K can be seen for all studied mixtures.

The following peaks in DSC curves, situated at higher temperatures, were assigned to the melting and decomposition of the component in excess reported to the eutectic composition. Due to the decomposition process, the thermodynamic parameters obtained for these peaks are approximate and can be seen from DSC curves that this process occurs very close to the eutectic melting for the mixtures with mole fraction $x_{ACV} \geq 0.50$.

The calculated phase diagram using Schröder van Laar equation and the real phase diagram obtained from DSC data (the averages of at least three determinations) are shown in figure 48) as T = T (xi). The ideal phase diagram shows a eutectic composition at $x_{ACV} = 0.72$. The experimental phase diagram indicates the deviation from ideal behavior over the entire composition range.

In the composition range $0 < x_{ACV} < 0.80$, Tamman` plot obtained for this system present two straight lines with different slope, due to the solid-solid transition of FA present in excess. For $x_{ACV} > 0.50$ composition range, the characteristic triangle shape of Tamman`s plot is retrieved, as expected for a simple eutectic system, indicating an eutectic composition of $x_{ACV} = 0.80$, were registered the higher enthalpy value, in good accordance with the value obtained from the ideal phase diagram.

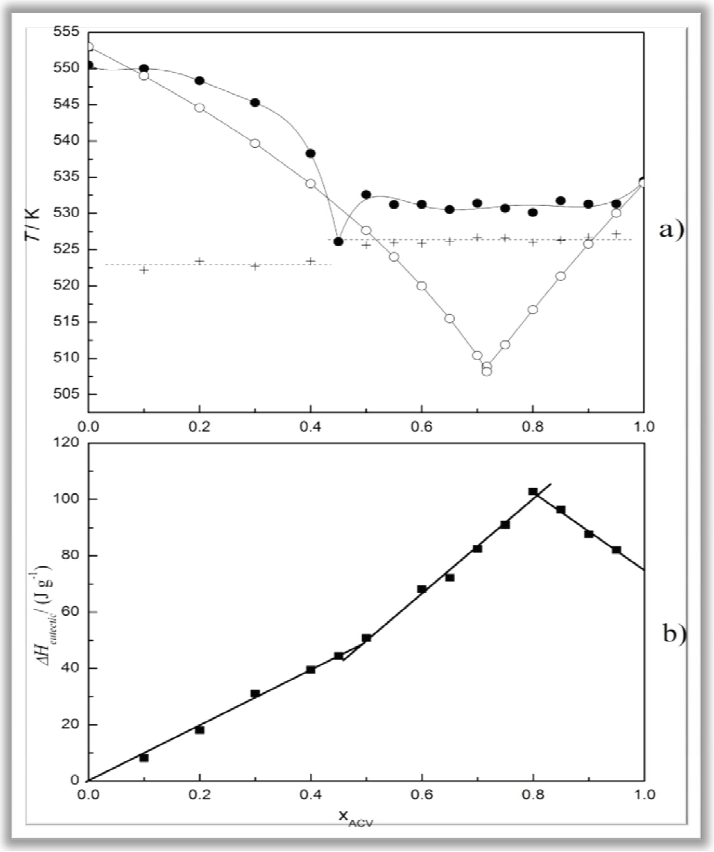

Figure 48: a) Phase diagram of binary mixture ACV – FA: a) o – Ideal temperatures curve, •- Liquidus temperatures curve, + - Solidus temperatures curve; c) ■- Tamman's plot.

In case of the binary mixtures, the FT-IR spectra were recorded before and after the dynamic temperature regime. The FT-IR spectra recorded before the dynamic temperature regime indicate that the binary mixtures spectra represent a sum of individual compounds spectra with certain variations of band intensity and position based on molar fractions of each compound, as function of sample composition.

The FT-IR spectra of binary mixtures, recorded after the dynamic temperature regime indicate certain structural changes due to partial decomposition observed also in the DSC curves, especially on frequencies $\nu_{C=C}$ = 1611 cm^{-1}, ν_{NH} = 1575 cm^{-1}, $\nu_{\text{amide, primary alcohol}}$ = (1575-1106) cm^{-1} and $\nu_{C=O}$ = 1708 cm^{-1}, whose decrease in intensity is more obvious as the value of x_{ACV} increases.

Partial decomposition of the samples at higher temperatures that the eutectic temperature is confirmed by polarized light HSM pictures obtained for ACV-FA binary mixtures with variable composition.

β-CD-APIs Inclusion Complexes

In order to determine an improvement in the solubility profile of the compounds of interest known to have a low solubility in an aqueous medium and overcome the decomposition process, the next step of this study was to encapsulate each pure API and the binary mixture of the two APIs in β-CD cavity and to characterize the interactions established between the compounds and β-CD.

The existence of interactions between the components can be obtained by thermal analysis, DSC. When guest molecules are included in the CD cavity, their melting, boiling, and sublimation points usually shift to a different temperature or disappear within the temperature range at which the CD is decomposed [176, 177].

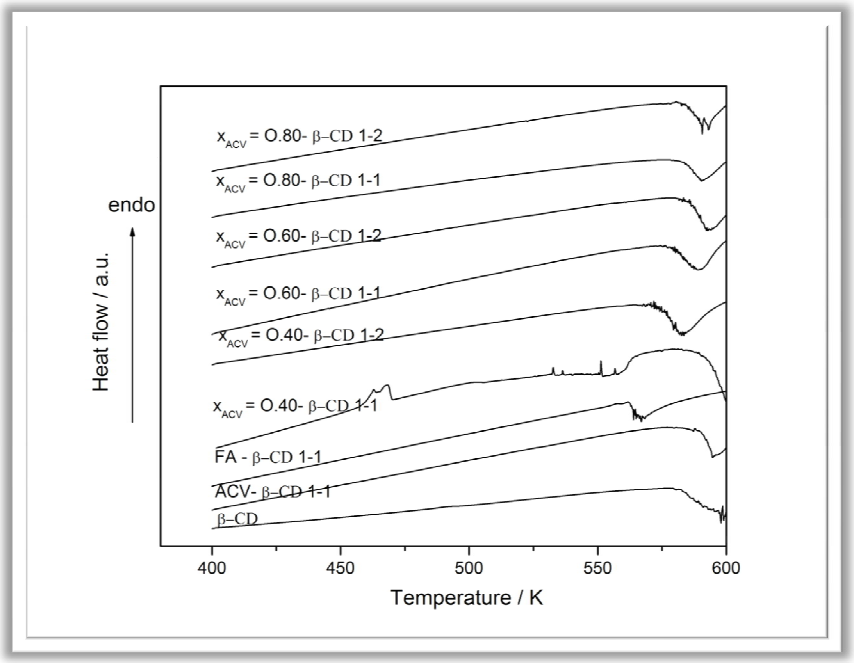

Figure 51: The DSC thermograms of β-CD, ACV and β-CD, FA and β-CD, ACV-FA binary mixture with x_{ACV}=0.40, 0.60, 0.80 and β-CD, physical mixtures with a mole ratio 1:1 and 1:2.

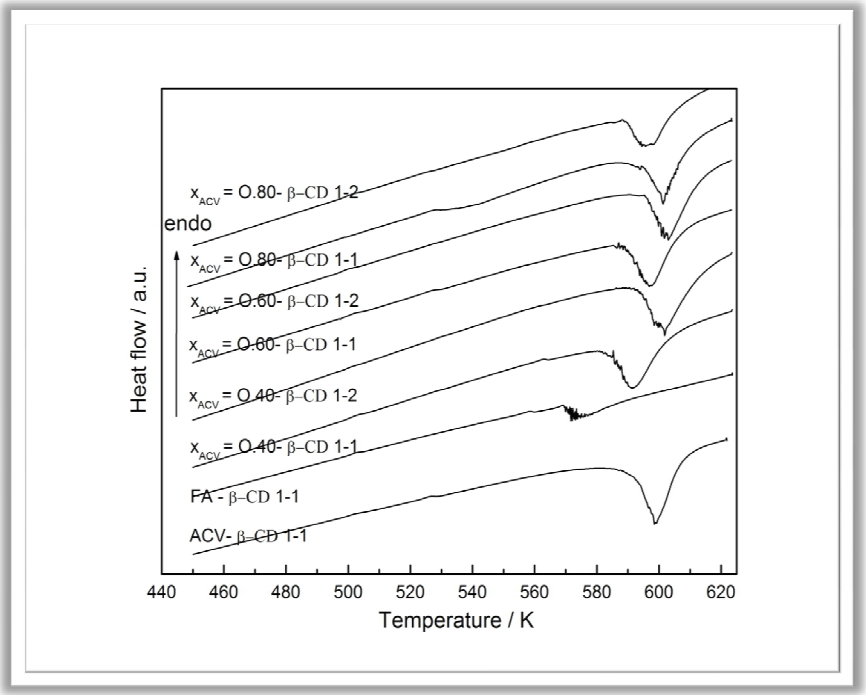

Figure 52: The DSC thermograms of ACV and β-CD, FA and β-CD, ACV-FA binary mixture with x_{ACV}= 0.40, 0.60, 0.80 and β-CD, solvent method, with a mole ratio 1:1 and 1:2.

In the case of the ternary mixtures formed by the FA-ACV binary mixture and β-CD obtained by physical mixture method (p.m.) (figure 51) can be seen some differences between the DSC curves obtained for molar ratio 1:1 and 1:2 respectively, (mole ratio is reported at mole of binary mixture of APIs).

For the physical mixture method, in the case of 1:1 mole ratio some endothermic or exothermic events can be observed, suggesting that this method does not give complete encapsulation; the phenomenon is obvious for the ternary system with 0.40 mole fraction of ACV, thus a higher concentration of FA, process determined by the structure of this compound. The complete disappearance of the two APIs characteristic features was instead observed for systems prepared with x_{ACV}= 0.60 and 0.80, 1:1 molar ratio obtained by physical mixing or for all the mixtures obtained by solvent evaporation method (s.e.) (figure 52).

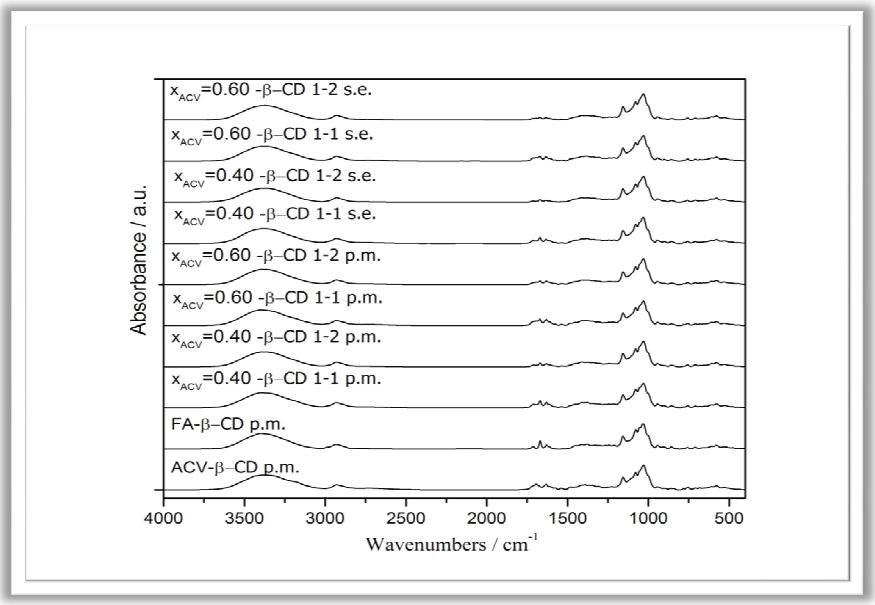

Figure 53: FT-IR spectra of ACV and β-CD, FA and β-CD, ACV-FA binary mixture with x_{ACV}= 0.40 and 0.60 and β-CD, physical mixtures (p.m.) and solvent method (s.m.), with a molar ratio 1:1 and 1:2.

The ACV-β-CD inclusion complex spectrum, (figure 53) presents shifts of the characteristic absorption bands of the components. The OH absorption band observed in the inclusion complex spectrum is shifted to a lower frequency (3369 cm^{-1}), comparing with the pure ACV spectrum. The same phenomenon is observed for NH (1575 cm^{-1}) and C=O (1693 cm^{-1}) adsorption bands and for C-H deformation vibrations of β-CD (1412, 1335, 1302, 1239 cm^{-1}) which are shifted to higher wavenumbers. The characteristic adsorption bands for primary and secondary amine form ACV (3312-3175) cm^{-1} are covered by the very intense OH band of cyclodextrin. In the case of FA and β-CD inclusion complex spectrum, comparing to the pure FA spectrum, the OH adsorption band is also shifted to lower frequencies. Meanwhile, the C=O adsorption band from pure FA is slightly shifted to higher wavenumber (from 1707 to 1709 cm^{-1}) indicating participation to a weak hydrogen bond and the C-H deformation vibrations of β-CD are shifted to higher frequencies suggesting the existence of non specific van der Waals interactions. These results indicate that the vibrations of the guest molecules are influenced by the encapsulation of ACV or FA in the β-CD cavity.

In the case of the ternary system spectra, it can be observed that the characteristic adsorption bands for primary and secondary amine, at (3312-3175) cm^{-1} and 1575 cm^{-1} are seen as very weak shoulders, C=C adsorption band is shifted to higher wavenumbers and the C-H deformation vibrations of β-CD are shifted to higher frequencies. These observations support the inclusion complex formation observed in the DSC curves but it is difficult to identify the position of the APIs molecule in the cyclodextrin cavity.

Slight differences are observed in the spectra obtained for the 1:1 and 1:2 mole ratio (one mole of binary mixture ACV-FA) and in the spectra of ternary systems obtained by physical and solvent method. In the case where excess quantity of β-CD was used, independent from the obtaining method of the ternary mixtures, the spectra are more similar to that of pure β-CD, as expected. In the light of these results we concluded that even the signals of ACV-FA binary mixture are quite completely convoluted by the β-CD signals, fact that confirm the complexation process.

General conclusions

The aim of this thesis was to obtain the physico-chemical characteristics of some binary and ternary mixtures of active pharmaceutical ingredients and excipients in order to determine the compatibility between the constituents for the development of combined pharmaceutical products.

The complete characterization of the systems was performed using a series of theoretical and experimental methods that have yield some general conclusions:

- the formation of a eutectic mixtures is very likely to occur in the mixing of the pharmaceutical powders, as observed in the study of the systems presented in the thesis;
- since in the eutectic melt have been highlighted interactions (van der Waals or hydrogen bonding) is recommended that the temperature used in the manufacture process or storage does not exceed the eutectic temperature;
- except the eutectic mixture formation, the study of Propafenone Hydrochloride-Metoprolol Tartrate system showed different degrees of compatibility of the two active ingredients with two excipients commonly used as diluents: α-lactose monohydrate and corn starch;
- in the study of the binary system Captopril-Metoprolol Tartrate was observed an eutectic mixture at low temperature, 332 K, which may lead to difficulties during the processing or storage of the pharmaceutical product containing the two active ingredients. Also, the partial melting of the sample was observed due to the formation of eutectic mixture at room temperature by applying mechanical energy and trans-cis isomerization of Captopril at a lower temperature due to the presence of Metoprolol Tartrate in the system;
- the study performed on Metronidazole-Norfloxacin system showed the formation of a simple eutectic mixture at 419 K and the fact that the water molecules from the structure of Norfloxacin does not influence the thermal behavior of binary mixture containing both active ingredients;
- for the system Acyclovir-Fluocinolone Acetonide was observed a simple eutectic point whose temperature is influenced by solid-solid transition of Fluocinolone Acetonide, for the mixtures with this component present in excess. Also, the study of binary or ternary mixtures with β-

cyclodextrin highlighted the formation of thermal stable inclusion complexes that may lead to improved solubility profiles of the two active ingredients known to have low solubility profiles;

- formation of inclusion complexes between cyclodextrin and active pharmaceutical ingredients has broad applications in the pharmaceutical industry since by complexation process the water solubility of the active principles contained can be increased;
- the determination of the interactions between the constituent elements of a possible combined pharmaceutical product is a key stage in product development;
- the formation and characterization of eutectic mixtures formed between constituents of a combined pharmaceutical product present a particular importance in obtaining and developing a new pharmaceutical product;
- in order to determine the positive or negative influence on the eutectic mixture formed in vitro and in vivo studies are needed.

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List of published and submitted articles:

1. „*Thermodynamic study of binary system Propafenone Hydrocloride with Metoprolol Tartrate: Solid–liquid equilibrium and compatibility with α-lactose monohydrate and corn starch*”, Daniela-Crina Marinescu, Elena Pincu, Viorica Meltzer, *International Journal of Pharmaceutics*, 448, 366–372, **2013** (I.F.= 3.458);

2. „*Thermal and spectral characterization of a binary mixture (acyclovir and fluocinolone acetonide): Eutectic reaction and inclusion complexes with β-cyclodextrin*”, Daniela-Crina Marinescu, Elena Pincu, Ioana Stanculescu, Viorica Meltzer, *Thermochimica Acta*, 560, 104–111, **2013** (I.F.= 1.989);

3. „*Thermal analysis of binary liquid crystals eutectic system cholesteril p-phenoxi phenyl carbamate–cholesteril p-biphenylcarbamate”*, Daniela-Crina Marinescu, Elena Pincu, Viorica Meltzer, *Journal of Thermal Analysis and Calorimetry*, 110, 2, 985-990, **2012** (I.F.= 1.982)**;**

4. „*Solid state study of Captopril and Metoprolol Tartrate binary system*”, Daniela-Crina Marinescu, Elena Pincu, Petruta Oancea, Giovanna Bruni, Amedeo Marini, Viorica Meltzer, *Journal of Thermal Analysis and Calorimetry*, - submitted.

Communications (poster presentations)

1. „*The DSC study of binary mixtures of captopril and metoprolol tartrate*”, Daniela-Crina Marinescu, Elena Pincu, Viorica Meltzer, “New Trends in Materials Science” Workshop, ID: POSDRU/89/1.5/S/58852, Romanian Academy, Bucharest, Romania, march 28-31, **2012**;

2. „*The DSC study of binary mixtures of acyclovir and fluocinolone acetonide*”, Daniela-Crina Marinescu, Elena Pincu, Viorica Meltzer, *Second International Conference on Analytical and Nanoanalytical Methods for Biomedical and Environmental Sciences IC-ANMBES,* Brașov *Romania*, may 24-27, **2012**;

3. „*The DSC study of excipients binary mixtures–tartaric acid and adipic acid*”, Daniela-Crina Marinescu, Elena Pincu, Viorica Meltzer, *Second International Conference on Analytical and Nanoanalytical Methods for Biomedical and Environmental Sciences IC-ANMBES,* Brașov *Romania*, may 24-27, **2012**.