CONTRIBUTIONS CONCERNING THE PREFORMULATION OF SOME BIOACTIVE COMPOUNDS USED IN MODERN PHARMACEUTICAL TECHNOLOGY

Doctoral Thesis – Summary

for obtaining the scientific title of Doctor at the
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in the field of doctoral studies Chemical engineering

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Pharmaceutical engineering is, in essence, a branch of chemical engineering that aims to design and obtain (new) formulations/preparations intended for use by human subjects, by one of the routes of administration, namely enteral (oral/per os), rectal /intrarectal, sublingual, inhalation, topical (cutaneous) and parenteral (with all the possibilities of its realization)[1–4].

Obtaining new formulations, which present both improved physico-chemical properties and an adequate biopharmaceutical profile, is the prerogative of pharmaceutical chemical engineering, usually called pharmaceutical technology, a field in which chemists and pharmacists work together. Being an interdisciplinary field, the corroboration of knowledge between specialists in the field of chemical engineering, analytical medicinal chemistry and pharmaceutical sciences is absolutely necessary, so that the results obtained can be used in the optimization of the biopharmaceutical profile of the compounds of pharmaceutical interest [5,6].

Pharmaceutical formulations contain in their composition at least one active pharmaceutical ingredient (used in the abbreviation API), along with a series of other compounds, called excipients, each of which has a certain role in formulations: binder, diluent, antioxidant, flow modulator (glidant and lubricant), disaggregatant, taste/odor improver (colorant/flavoring), preservative, film-forming agent, etc. [7,8]. The stability of APIs and corresponding pharmaceutical formulations is of great importance in pharmaceutical research and technology today. The quality of an active pharmaceutical ingredient or finished pharmaceutical products (PFF) is time dependent and influenced by several parameters such as exposure to light and air, temperature and humidity. In addition, the stability profile of an active pharmaceutical ingredient is influenced by the composition of the formulation, due to the presence of excipients or the characteristics of the packaging materials.

For the original, innovative formulations, launched on the pharmaceutical market after the expensive drug discovery process which involves huge costs and studies, when the patent expires, the manufacturers of generic formulations launch generic forms on the market, usually with different compositions in terms of regarding the selection of excipients, but for which preformulation and bioequivalence studies are not always carried out coherently [5,9–12]. Although the regulatory authorities at the level of each country authorize the clinical use of generic drug formulations based on bioequivalence studies, which consist of the evaluation of

pharmacokinetics after the administration of a single dose, there are insufficient data on the clinical equivalence between generic and original formulations, respectively on clinical efficacy and their safety [13,14].

The market demand for generic pharmaceutical products is growing exponentially globally, but especially on the Asian and African continents. Thus, in order to respond to the needs of patients, within the production laboratories of generic forms there must be the specific material and instrumental base that can satisfy the need of generic manufacturers, both in the screening of original products and for the design of generic forms produced by to them. Preformulation data, i.e. physico-chemical investigation studies on active substances and excipients published in the literature serve as a starting point in the engineering of pharmaceutical products, from the laboratory level to the industrial level [12].

As a result of these considerations, the chosen theme makes a contribution to the study of the physico-chemical characterization of some antihypertensive agents, predominantly from the class of sartans (candesartan, olmesartan, telmisartan, valsartan and losartan), respectively moxonidine, the data obtained representing an absolutely necessary portfolio in chemical and pharmaceutical engineering, from laboratory scale to production scale, facilitating the choice of safe working protocols for the preformulation and formulation of these pharmaceutical assets.

The thesis is structured in **four chapters:**

The first chapter represents a literature study that reviews the current state of knowledge in the field, starting from the importance of the topic in the current context of pharmaceutical engineering, highlighting the need to carry out preformulation studies in the current scientific context. Also, some essential aspects are presented regarding bioavailability and oral administration, solubility and the biopharmaceutical classification system of drugs, the main techniques for improving the solubility of active ingredients, hypertension therapy and classes of antihypertensive drugs (angiotensin-converting enzyme inhibitors, blockers of angiotensin receptors (sartans), calcium channel blockers, β-adrenergic antagonists, diuretics, α-adrenergic antagonists, centrally acting agents and other agents). Also in this chapter, the main physico-chemical properties of the active substances studied in the thesis (sartans - candesartan, olmesartan, telmisartan, valsartan, losartan, respectively moxonidine) are presented, as well as the instrumental working techniques used in the study: UV- VIS spectroscopic analysis, FTIR spectroscopic analysis, thermal analysis and degradation kinetics in a heterogeneous environment.

Chapter 2 presents the original contributions of the doctoral thesis, and includes the 4 subchapters (Stability in solid state and kinetics of degradation for candesartan cilexetil - pure compound and pharmaceutical formulation; Stability in solid state and kinetics of degradation for other sartans - comparative study; Thermal stability and kinetics of the degradation of moxonidine as a pure ingredient vs. pharmaceutical formulation; Obtaining and solid state characterization of binary telmisartan adducts. Dissolution behavior. Studies in solution), each subchapter being structured into four distinct parts, namely: Purpose of the study; Premises of the study; Results and discussion; Conclusions of the study.

Preformulation studies carried out on various active substances can provide valuable information related to the stability over time of pharmaceutical assets, the ways in which this

stability can be increased, but also information related to the management of formulation processes through the appropriate selection of experimental conditions, such as temperature, pressure, humidity, contact times, lighting, etc. From this point of view, thermal stability studies and data processing using the concepts of kinetics in heterogeneous media provide valuable information related to stability over time, decomposition mechanisms (in inert and/or oxidative media), as well as the stabilizing/destabilizing effect on that the auxiliary substances in the formulation (excipients) can have on the APIs.

The thermal behavior of active pharmaceutical ingredients (APIs) as pure components in binary mixtures with excipients and in pharmaceutical formulations is of great importance in drug science [15–20]. Although in the case of pharmaceuticals, the term "stability" is usually associated with the loss of the active pharmaceutical ingredient from the formulation, "solid-state stability" can also refer to the response of an API or pharmaceutical formulation to thermal stress. However, in both cases, the decomposition of the active pharmaceutical ingredient due to chemical processes or even physical transitions (phase transitions such as polymorphism and crystallization) in the presence of excipients, dictates the shelf life of the formulation [21,22]. In addition, a proper selection of excipients can lead to formulations with longer shelf life, as the presence of excipients can have a stabilizing effect on the breakdown of the active pharmaceutical ingredient in the formulation relative to the same ingredient as pure compound [23–28].

As a result of these considerations, the chosen theme makes a contribution to the study of the physico-chemical characterization of some antihypertensive agents, predominantly from the class of sartans (candesartan, olmesartan, telmisartan, valsartan and losartan), respectively moxonidine, the data obtained representing an absolutely necessary portfolio in engineering chemical and pharmaceutical from laboratory scale to production scale, facilitating the choice of safe working protocols for the preformulation and formulation of these pharmaceutical assets. The two main objectives of the doctoral thesis are:

- Instrumental and analytical investigations of selected pharmaceutical assets from the class of antihypertensive agents, using spectroscopic (FTIR), thermoanalytical and kinetic methods as working techniques;
- Obtaining and characterization in solid state of binary adducts of telmisartan. Dissolution behavior. Studies in solution.

The first study carried out consisted of evaluating solid state stability and degradation kinetics for candesartan cilexetil - pure compound and pharmaceutical formulation. The aim of this study was to evaluate the impact of the presence of excipients in a pharmaceutical formulation containing candesartan cilexetil, on the decomposition of the active pharmaceutical ingredient and to comparatively investigate the degradation kinetics during thermolysis, in an oxidative atmosphere, under controlled thermal stress. To achieve this, the samples were chosen as follows: pure candesartan cilexetil (CC) and a commercial tablet containing 32 mg API (CCTAB). As the first investigative tool, UATR-FTIR spectroscopy (Figure 1) was chosen, to confirm the purity and identity of the samples, as well as to check whether interactions between API and excipients in the tablet had occurred under ambient conditions.

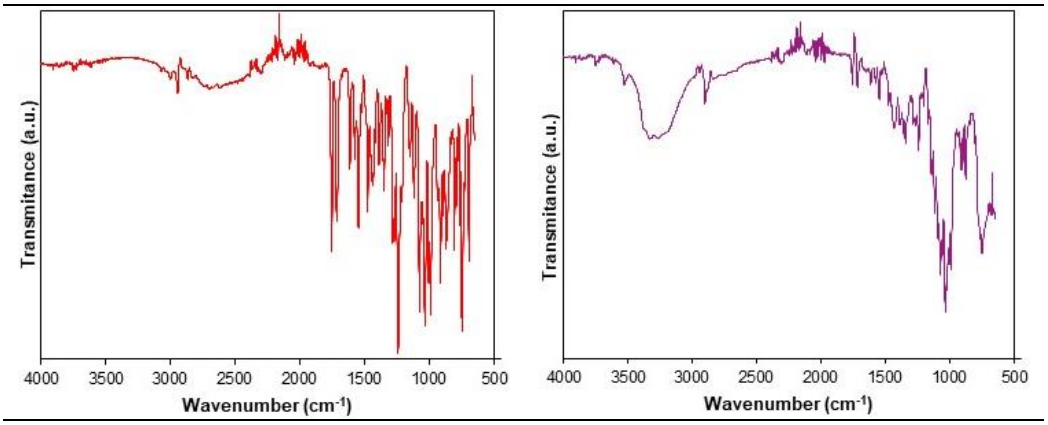


Figure 1. UATR-FTIR spectra recorded for the analyzed samples: (a) CC and (b) the tablet (CCTAB)

Subsequently, the samples were investigated by thermal analysis (Figure 2), and the elucidation of the decomposition mechanism was achieved only after conducting an in-depth kinetic study, namely the use of the modified non-parametric kinetic method (NPK, Figure 3), since the results of other kinetic methods (ASTM E698, Friedman and Flynn–Wall–Ozawa) led to inadvertences.

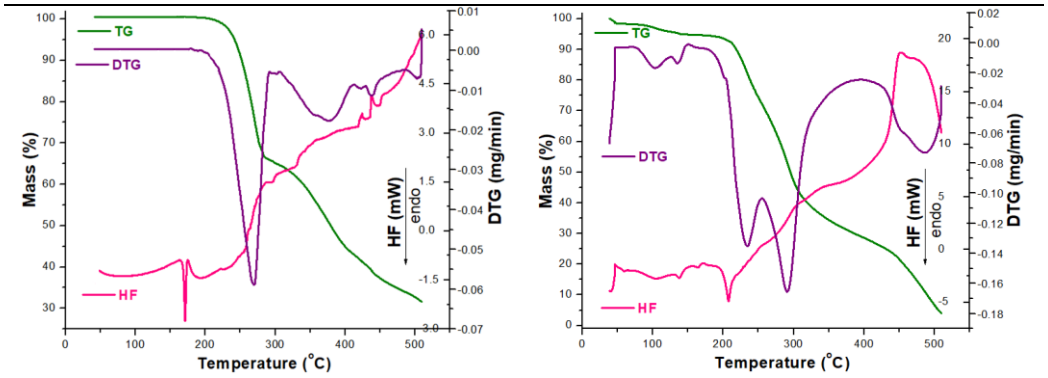
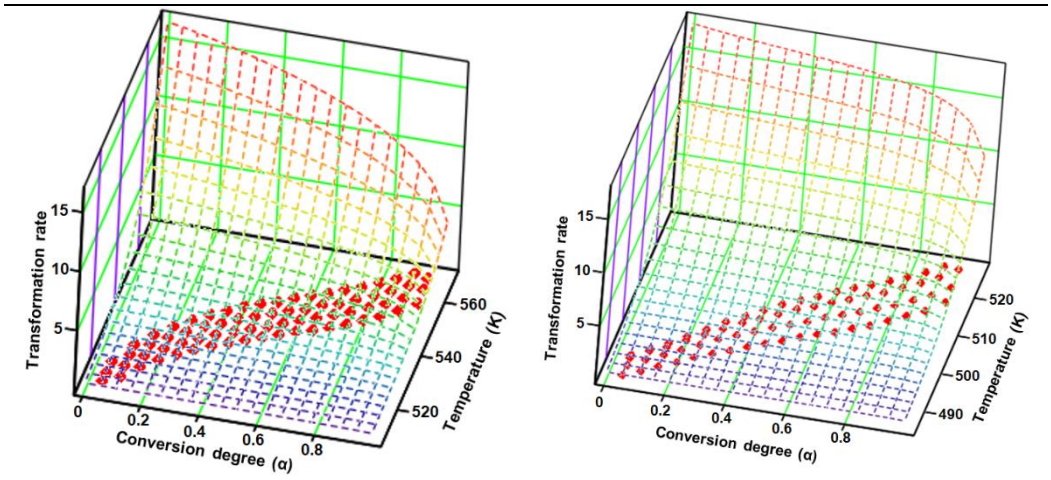


Figure 2. Thermoanalytical curves (TG/DTG/HF) recorded in oxidative atmosphere of synthetic air at $\beta = 5\ ^{\circ}C \cdot min^{-1}$ for the analyzed samples: (a) CC and (b) CCTAB.



(**a**) (**b**)

Figure 3. Experimental values (red dots) and response surface generated by kinetic parameters, according to the modified non-parametric kinetic (NPK) method, for (a) CC and (b) CCTAB.

Compared to the kinetic results provided by the previously chosen methods (ASTM E698, FR and FWO – Table 1), those provided by the NPK method were consistent for candesartan cilexetil in all cases; for CCTAB, the results confirmed the data revealed by the FWO method, namely a stabilizing effect on the decomposition of candesartan cilexetil in the pharmaceutical formulation, compared to CC, due to the presence of excipients.

Table 1. The values of apparent activation energies (Ea) vs. degree of conversion (α), obtained by isoconversion methods and the value $\overline{E_a}$.

α	**E_a (kJ/mol) = f(α) for**			
	CC		**CCTAB**	
	Fr	**FWO**	**Fr**	**FWO**
0,05	152,9	168,5	197,0	307,3
0,10	153,1	163,3	215,0	278,5
0,15	152,1	160,3	215,7	263,6
0,20	151,0	158,5	179,2	248,4
0,25	151,3	157,1	133,1	227,6
0,30	149,0	156,0	120,6	208,1
0,35	149,2	155,1	112,7	192,1
0,40	153,6	154,7	125,1	181,0
0,45	155,8	154,9	126,3	173,6
0,50	156,8	155,2	134,5	168,0
0,55	157,3	155,5	140,6	164,6
0,60	158,0	155,9	137,9	161,8
0,65	158,5	156,3	144,8	159,6
0,70	158,9	156,7	159,6	158,8
0,75	158,6	157,0	176,1	160,2
0,80	158,5	157,4	166,4	161,7
0,85	157,8	157,7	161,1	161,7
0,90	158,8	157,9	149,2	160,3
0,95	162,8	158,6	201,3	163,7
$\overline{E_a}$ (kJ/mol)	**155,5±0,9**	**157,7±0,7**	**157,7±7,2**	**194,8±10,5**

The NPK method suggested that both samples were degraded by the contribution of two steps, the main step being a chemical degradation and the secondary step being a physical transformation (Table 2). The excipients chosen in the formulation appear to have a stabilizing effect, as the apparent activation energy for tablet decomposition was 192.5 kJ/mol, and the apparent activation energy for pure API decomposition was 154.5 kJ/mol.

Table 2. Results of kinetic analysis after using the modified NPK method

Sample	Step	λ (%)	A (s^{-1})	E_a (kJ/mol)	n	m	f(α)	$\overline{E}_a$ (kJ/mol)
CC	1	87,0	$1{,}6\cdot10^{16}\pm 2{,}1\cdot10^{4}$	162,8 ± 9,1	1/3	0	$(1\text{-}x)^{1/3}$	154,5 ± 11,1
	2	8,5	$8{,}6\cdot10^{13}\pm 4{,}4\cdot10^{9}$	147,2 ± 2,0	0	1/3	$x^{1/3}$	
CCTAB	1	75,3	$9{,}6\cdot10^{20}\pm 4{,}5\cdot10^{6}$	198,2 ± 11,5	1/4	0	$(1\text{-}x)^{1/4}$	192,5 ± 16,6
	2	24,5	$4{,}6\cdot10^{18}\pm 7{,}8\cdot10^{8}$	176,1 ± 5,1	0	5/3	$x^{5/3}$	

The results of this study are disseminated in the first published ISI paper on the topic of the doctoral thesis [29].

The second study deal with solid-state stability and degradation kinetics for other sartans – a comparative study aimed at evaluating the thermal stability and degradation kinetics of telmisartan (TELM), valsartan (VLS) olmesartan medoxomil (OLM), and losartan potassium (LOS), to have an overview of the stability of the main compounds used in therapy from this class. The kinetic methods used were the preliminary ASTM E698 method, respectively the FWO and FR methods. Also, for OLM, two processes were investigated from a kinetic point of view, namely the dehydration process, respectively the first oxidative thermolysis process. As a result of the corroboration of the information obtained from the analysis of the kinetic data, it can be concluded that all the decomposition processes of the analyzed sartans are complex. Thus, the processes analyzed in this study consist of complex reaction sequences (processes involving parallel and successive reactions, processes with reversible stages and processes with transition to the diffusion regime), the curves Ea vs. α shows minima, maxima and portions where E_a is independent of the conversion.

For each sartan separately, were presented in the thesis: the linear dependencies obtained following the use of the ASTM E698 method (a), the progress of the reaction as a function of temperature on the interval of the kinetically investigated process (b), the variation of the reaction rate as a function of temperature (c), the linearized representation of the Flynn–Wall–Ozawa dependence at the five selected heating rates (d), the Friedman dependence at the five selected heating rates (e), respectively the analysis of the variation Ea vs. α for the two isoconversional methods used. Thus, in the case of OLM (Figures 4-5), two distinct processes could be identified, the first of which takes place in the range 170-195 °C and corresponds to a dehydration process (theoretical water content 0.5 mol/mol OLM, determined water content 0.52 mol/mol OLM), the result being in agreement with the hemihydrate mentioned in patent EP1801111 [30]. It is known that the dehydration of hydrates of pharmaceutical actives

generally takes place at temperatures close to the normal boiling temperature of water, considering that hydrogen bonds are formed in the molecular network which are usually defeated at this temperature [31]. In the case of this hemihydrate, it is observed that the loss of water from the network occurs at considerably higher temperatures, which indicates a strong binding of it in the crystalline network. The ASTM E698 method indicates a very high activation energy (342.9 kJ·mol^{-1}), atypical for the thermolysis processes of pharmaceutical assets.

The FR and FWO isoconversional methods suggest inexplicably higher values, as seen in Figure 4f; thus, in the case of the FWO method, a continuous decrease of Ea values is observed with the progress of the reaction, from the extreme value of 518.8 kJ·mol^{-1} (for a conversion of 5%) to 244.2 kJ·mol^{-1} (for a conversion of 95%).

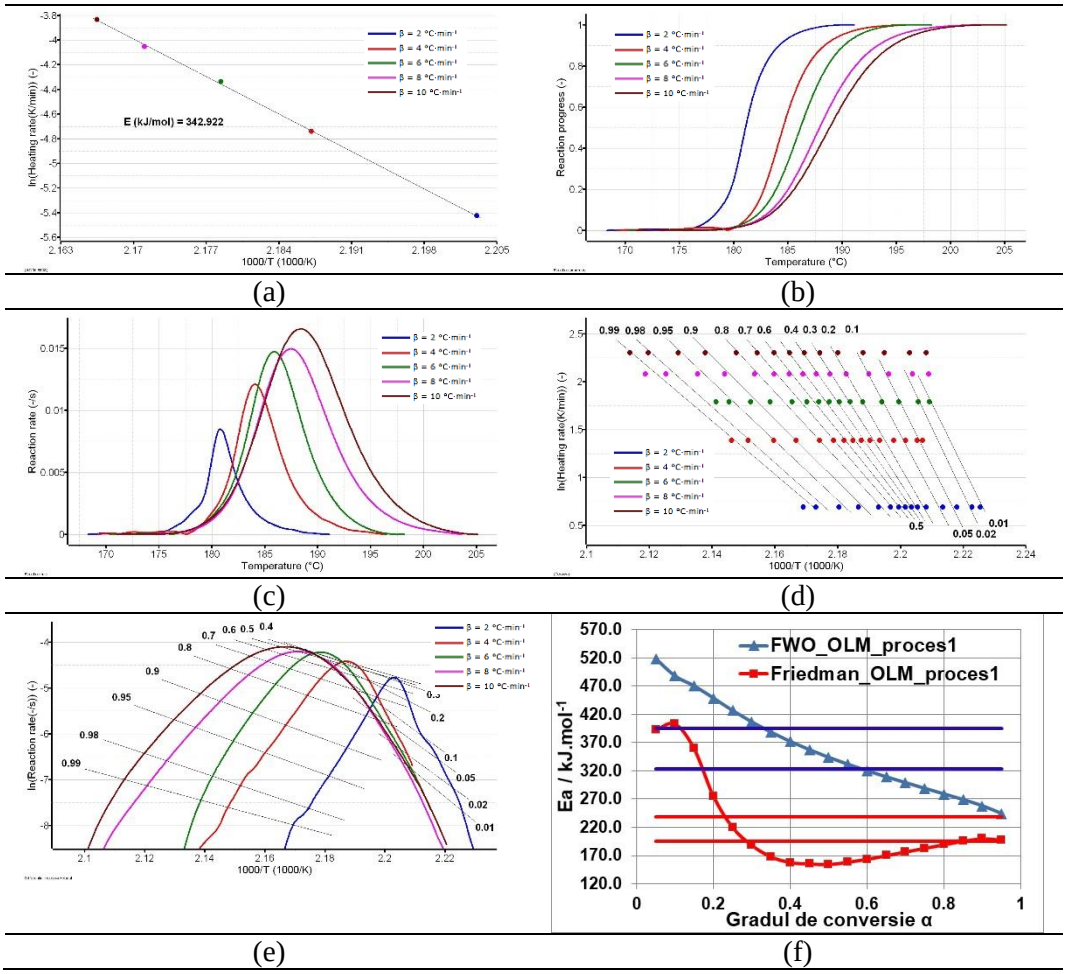


Figure 4. The results of the kinetic analysis performed on the dehydration of OLM: (a) the kinetic method ASTM E698; (b) reaction advance vs. temperature; (c) reaction rate variation vs. temperature; (d) the FWO dependence graph; (e) the FR dependence graph and (f) variation of E_a vs. α according to FWO and FR methods

This monotonous but extremely wide variation can be explained by the influence of mass and heat transfer in the case of this hemihydrate: if we analyze the olmesartan medoxomil–water system at the "macroscopic" level, we deduce that a water molecule belongs to the structure of two molecules of pharmaceutical active, or in other words, on molar scale, 18 grams of water are "bound"/"split" by 2x558.6 grams of API, i.e. 1117.2 grams of OLM. These water molecules, strongly entangled in the molecular network of the OLM, make the mass and heat transfer more difficult to initiate, requiring high energies, which "normalize" once a stationary regime of diffusion of water molecules from the solid is established. During such dehydration processes, local variations in gas water pressure and temperature occur, which can lead to distortion of the results of kinetic evaluations, as a result false dependences of activation energy with increasing conversion can appear [32,33].

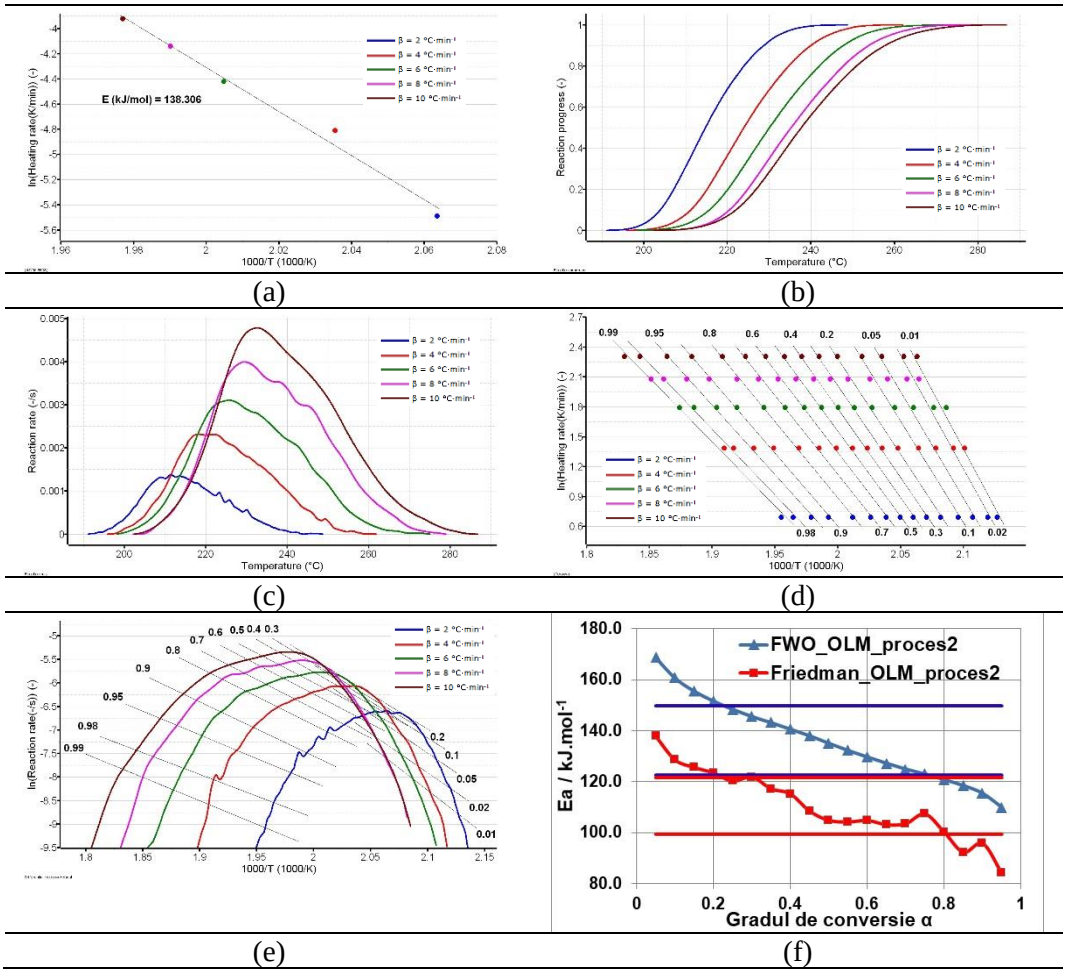


Figura 5. The results of the kinetic analysis performed on the decomposition of OLM: (a) the kinetic method ASTM E698; (b) reaction advance vs. temperature; (c) reaction rate variation vs. temperature; (d) the FWO dependence graph; (e) the FR dependence graph and (f) variation of E_a vs. α according to FWO and FR methods

In the case of the thermolysis process analyzed for OLM (Figure 5), a process that follows dehydration, a trend similar to that of dehydration can be observed in terms of the variation of activation energies by the FWO method. In the case of the decomposition of anhydrous OLM, several processes compete, which is also confirmed by the appearance of the reaction rate curves vs. T (Figure 5c). the variation observed in Figure 5f can be explained as a consequence of the water vapor diffusion process through the solid structure of the pharmaceutical active, and as a consequence, the reactant particles continuously change their reactivity as a result of the modification of the crystalline network, the appearance of gap-type defects in the network, their gap migration, etc.

The third study aimed to analyze the degradation kinetics of the antihypertensive drug moxonidine, as a pure ingredient (MOX) and in the form of two different solid mixtures, one corresponding to a pharmaceutical formulation (MOXTAB) and the other to a pharmaceutical formulation enriched in MOX (MOXMIX). Since MOXTAB contains a very small amount of API (0.4 mg of MOX) per tablet, we made a model system that mimics the behavior of the active pharmaceutical ingredient in the marketed formulation, by adding to the core of the triturated tablet a necessary amount of active substance, thus so that the final mixture contains one part API to five parts core. FTIR analysis was performed for all three samples, namely MOX in pure form, the commercially available pharmaceutical formulation, MOXTAB, which contains 0.4 mg of MOX in each film-coated tablet, and MOXMIX (5:1 mixture of MOXTAB and MOX), with the aim of characterizing the pure active pharmaceutical ingredient and identifying its presence in mixtures. The spectral profiles of MOXTAB and MOXMIX are more complex due to the presence of excipients in the analyzed mixtures (hydrated lactose, povidone K25, crospovidone and magnesium stearate). When analyzing the spectrum of the MOXTAB pharmaceutical formulation, it can be seen that the signals associated with MOX are attenuated in intensity and several bands are highlighted that can be correlated with the presence of excipients. For example, the stretching vibration of the O–H bonds found in the structure of lactose causes a broad band in the spectral range 3450–2990 cm-1 and a band at 3524 cm-1, while the well-defined band observed at 1655 cm-1 characterizes the vibration of elongation of the C=O bond present in the structure of the other three excipients. However, the addition of MOX to MOXTAB in the MOXMIX sample is noted, because in this sample, several bands characterizing pure MOX can be observed, and the intensity of the obtained signals is significantly increased.

The aim of the kinetic study was to evaluate the effect of excipients on MOX degradation. Since the thermal degradation of MOX is a heterogeneous process in the solid state, the decomposition kinetics were evaluated from the TG/DTG curves using the same protocol described previously.

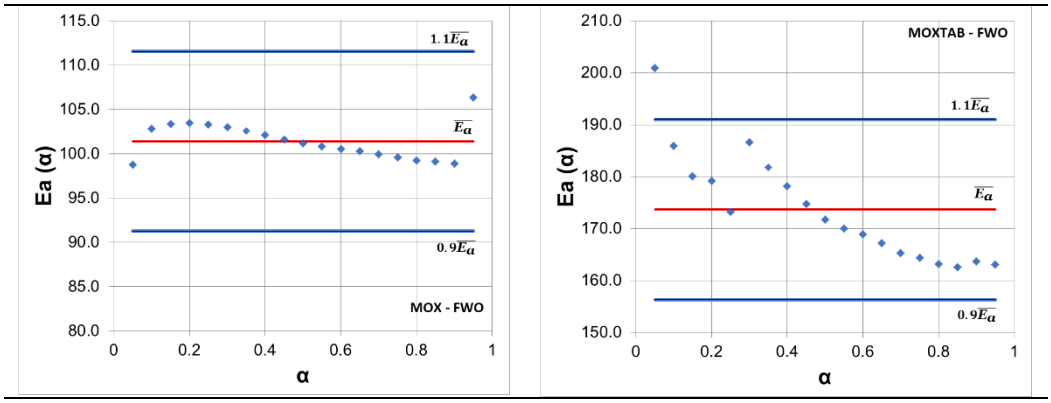
The kinetically investigated degradation process was selected based on the appearance of the TG/DTG/HF curves for MOX, and the same process was chosen for both the pharmaceutical form (MOXTAB) and the MOX-enriched sample mixture (MOXMIX) according to the DTG curves. For the analyzed samples, the degradation process that was investigated kinetically, was chosen based on the appearance of the DTG curves for each heating rate, and the temperature ranges are shown in Table 3.

Table 3 Temperature range according to DTG curves for the degradation process that was investigated by kinetic analysis.

β (°C·min^{-1})	Temperature range according to DTG curves for the degradation process for		
	MOX	**MOXTAB**	**MOXMIX**
5	174–244	187–243	150–227
7	175–247	190–248	154–231
10	175–253	193–254	165–241
15	176–260	199–259	168–243

The analysis of the obtained data (Figure 6) highlights the fact that the processing by integration of the kinetic data according to the FWO isoconversional method, suggests that the degradation of all samples is characterized by a mechanism that is not dependent on the degree of conversion, when $0.1 \leq \alpha \leq 0$,95. In the case of MOXTAB, there is only one value for Ea outside the confidence interval, at α = 5%. For all samples, the Ea values follow different trends up to α = 0.25 and for α > 0.3, suggesting the existence of complex degradation processes. This tendency is more evident for MOXTAB and MOXMIX, where the presence of excipients is the reason for this behavior.

The FR isoconversional method (Figure 6d–f) reveals a greater dispersion of Ea vs. α, outside the 10% limit. For MOX, the Ea values are higher at the beginning of the process, at lower degrees of conversion (α < 0.2) and at the end of the process (α > 0.85). Furthermore, for MOXTAB and MOXMIX, the variation of Ea vs. α is irregular, especially with extreme values for MOXMIX at α < 0.25, suggesting a complex mechanism of decomposition of these samples under thermal stress.



(**a**) (**b**)

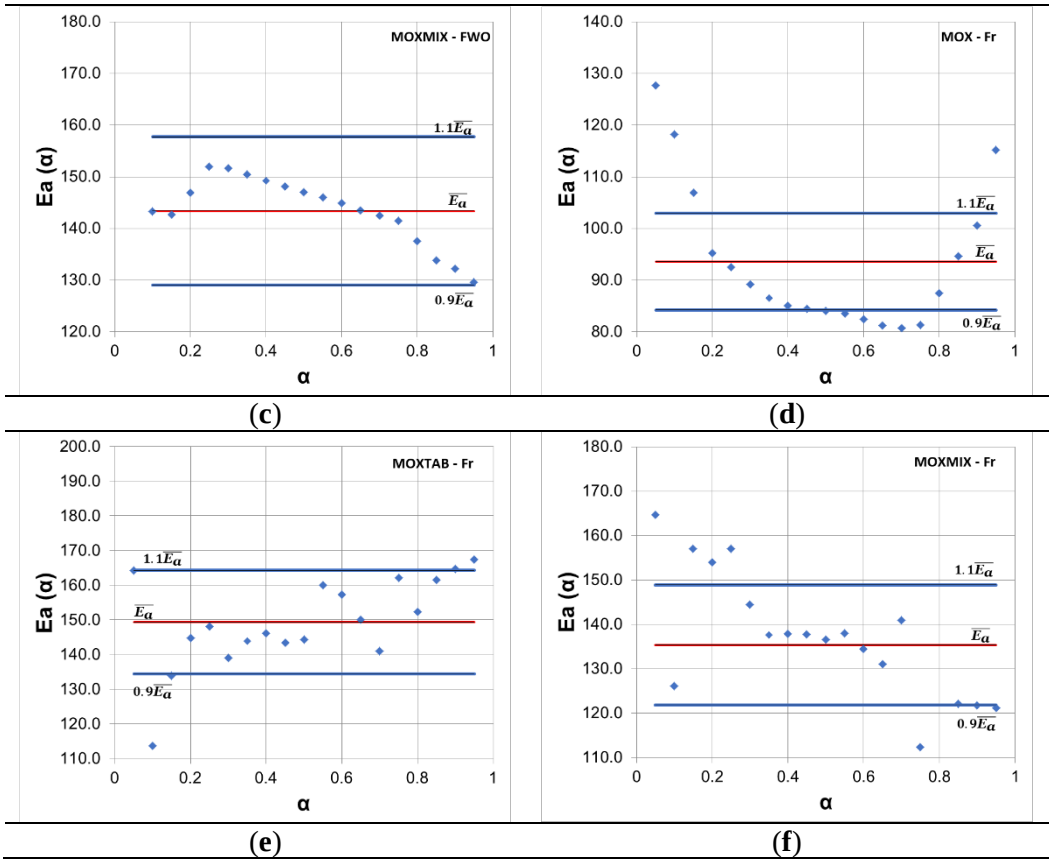


Figure 6 E_a vs. α variation according to the integral FWO isoconversional method (**a,b,c**) and differential isoconversional FR method (**d,e,f**) to the analysis of decomposition processes for: (**a,d**) MOX; (**b,e**) MOXTAB and (**c,f**) MOXMIX.

The results of this study are disseminated in the second published ISI paper on the topic of the doctoral thesis [34].

In the fourth study, we investigated the preparation and characterization of binary adducts of telmisartan with a series of amino acids, namely: glycine, L-alanine, L-aspartic acid, L-leucine, L-valine, L-cystine, L-cysteine and L-tryptophan. The binary adducts were prepared by the wet kneading method, and the samples were subsequently investigated by ATR-FTIR spectroscopy, thermal analysis (TG/DTG/DSC) and solubility studies in artificial gastric fluid (AGF), in artificial intestinal fluid (AIF) and in phosphate buffer (PB) of pH 7.4, using the UV absorption spectroscopic technique.

Analyzing the position characteristic bands of the pure TELM vs. TELM in binary adducts, it could be observed that there are a series of shifts of up to 6 cm^{-1} for the characteristic bands of functional groups that may be involved in the formation of intermolecular interactions in cocrystals (namely the COOH group through –OH, but also C=O, respectively the nitrogen atoms from the benzimidazole rings). In the case of TELM+AA binary adducts, the shifts of the bands characteristic of the "reactive" groups of TELM are not substantial, as in the case of the

formation of other cocrystals [35,36], but they exist, confirming the formation of intermolecular interactions in solid phase.

By corroborating the recorded thermal analysis data, it could be observed that the binary adducts present good thermal stability. The thermal treatment determines in the first instance the melting/decomposition of the co-forming amino acids, followed by the melting and decomposition of the active substance.

The determination of the solubility profile of TELM from binary adducts with the selected amino acids was carried out by the saturated solution method, for the quantitative determination of API, UV absorption spectrophotometry was used. For this purpose, a set of TELM aqueous solutions with concentrations in the range of 0.66-26.6 µg/mL had their absorption spectrum recorded in the spectral range 220-400 nm, at 25 °C (Figure 7). The calibration curves, with the corresponding equations, are shown in Figure 8

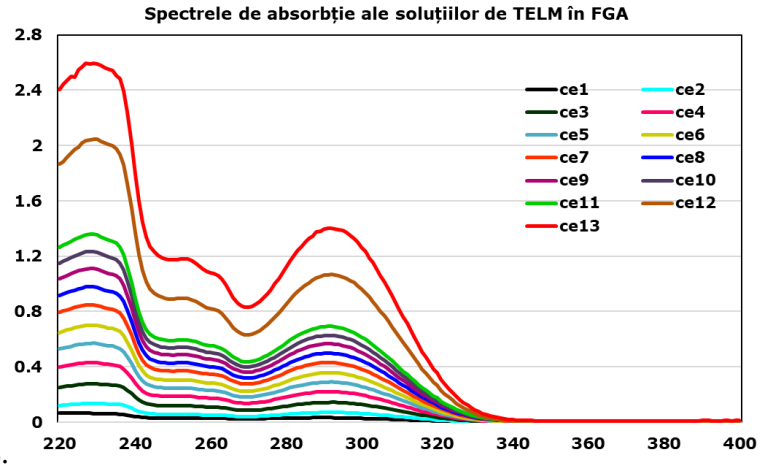


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Figure 7. Absorption spectra of TELM solutions in AGF

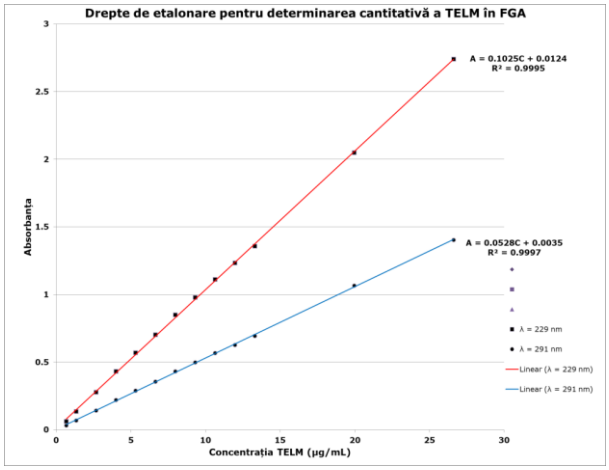

Figure 8. Calibration curves A=f(c) for TELM in AGF at 229 nm (red) and 291 nm (blue)

The solubility data obtained suggested that amino acids with short hydrocarbon chains show a strong solubilizing effect on TELM in AGF of pH 1.20, even though at this pH all amino groups are protonated in solution and repulsive ion-ion interactions between the formed cations (of amino acids, through the protonated amino group $–NH_3^+$ and of TELM, which at this pH is found mainly in the form $TELMH_3^{2+}$ and in the minority $TELMH_2^+$ [37]) are expected to appear.

The studies carried out in AIF and in PB had a simplified approach, taking into account the fact that the solubility of telmisartan in these fluids is extremely low, without the possibility of constructing calibration curves.

Chapter 3 presents the experimental part, namely the materials and methods used, the experimental protocols and the equipment used in this doctoral thesis.

Chapter 4 presents the final conclusions, which can be summarized as follows:

- The first study carried out deal with the investigation of solid-state stability and degradation kinetics for candesartan cilexetil, both as a pure compound and in a pharmaceutical formulation, in the presence of excipients. The samples were investigated by UATR-FTIR spectroscopy, which certified the identity and purity of the respective active pharmaceutical ingredient and confirmed that there were no interactions between the API and the excipients in the tablet;
- The characteristic thermoanalytical TG/DTG/HF curves for the pure ingredient (candesartan cilexetil) and the pharmaceutical formulation were recorded and discussed at $\beta = 5$ °C/min, concluding that the thermoanalytical profile of the tablet reveals some of the characteristics of candesartan cilexetil but of significantly different from that of the active pharmaceutical ingredient due to its compositional complexity;
- A comparative kinetic study was carried out, using the preliminary non-isoconversional ASTM E698 method, then the Friedman and Flynn-Wall-Ozawa isoconversional methods, the results obtained leading to some inadvertences regarding the stability of candesartan cilexetil in the pharmaceutical formulation, compared to the pure active;
- The modified NPK method was used, the only method that allowed obtaining important information regarding thermolysis, including the decomposition mechanism;
- Compared to the kinetic results provided by the ASTM E698, FR and FWO methods, those provided by the NPK method were consistent for candesartan cilexetil in all cases; for the sample obtained from the tablet, the results confirmed the data revealed by the FWO method, namely a stabilizing effect on the decomposition of candesartan cilexetil in the pharmaceutical formulation, compared to CC, due to the presence of excipients. The NPK method suggested that both samples were degraded by the contribution of two steps, the main step being chemical degradation and the secondary step being a physical transformation. The excipients chosen in the formulation have a stabilizing effect, as the apparent activation energy for the decomposition of the tablet was 192.5 kJ/mol, and the apparent activation energy for the decomposition of pure sartan was 154.5 kJ/mol;
- The second study carried out aimed at evaluating the thermal stability and degradation kinetics for other antihypertensive agents from the sartan class, namely telmisartan (TELM), valsartan (VLS), olmesartan medoxomil (OLM) and losartan potassium

(LOS), in order to have a general overview of the stability of the main compounds used in therapy in this class. The kinetic methods used were the preliminary ASTM E698 method, respectively the FWO and FR methods. Also, for OLM, two processes were investigated from a kinetic point of view, namely the dehydration process, respectively the first oxidative thermolysis process;

- As a result of the corroboration of the information obtained from the analysis of the kinetic data, it can be concluded that all the decomposition processes of the analyzed sartans are complex. Thus, the processes analyzed in this study consist of complex reaction sequences (processes involving parallel and successive reactions, processes with reversible stages and processes with transition to the diffusion regime), the curves Ea vs. α presents minima, maxima and portions where Ea is independent of conversion;
- The third study deal with the thermal stability analysis and degradation kinetics of moxonidine as a pure ingredient vs. two different solid mixtures, one corresponding to a commercialized pharmaceutical formulation (MOXTAB) and the other to a MOX-enriched pharmaceutical formulation (MOXMIX). The investigative techniques used were FTIR spectroscopy and TG/DTG/HF analysis, while thermoanalytical data were processed according to the ASTM E698 kinetic method and the isoconversional methods of Flynn–Wall–Ozawa (FWO) and Friedman (FR). Kinetic methods have highlighted the fact that the excipients have a stabilizing effect on MOX (from the point of view of Ea values), but the decomposition mechanism of the samples is complex, according to the results suggested by the analysis of the variation of Ea with the increase in the degree of conversion;
- The fourth study consisted in obtaining and characterizing some binary adducts of telmisartan with a series of amino acids, namely: glycine, L-alanine, L-aspartic acid, L-Leucine, L-valine, L-cystine, L-cysteine and L-tryptophan. The binary adducts were prepared by the wet kneading method, and the samples were subsequently investigated by ATR-FTIR spectroscopy, thermal analysis (TG/DTG/DSC) and solubility studies in artificial gastric fluid of pH 1.20, in artificial intestinal juice of pH 6.80 and in phosphate buffer of pH 7.4, using the UV absorption spectroscopic technique;
- FTIR spectroscopy indicates the existence of shifts of up to 6 cm^{-1} for bands characteristic of functional groups that may be involved in the formation of intermolecular interactions in cocrystals (namely the COOH group through –OH, but also C=O, respectively the nitrogen atoms from benzimidazole rings), therefore it is expected that the synthon from binary adducts is formed by molecular interactions between these functional groups;
- Thermal analysis data obtained under dynamic-oxidative conditions indicate that the binary adducts show good thermal stability; heating the adducts causes in the first instance the melting/decomposition of the co-forming amino acids, followed by the melting and decomposition of telmisartan;
- The determination of the solubility profile of TELM from binary adducts with the selected amino acids was carried out by the saturated solution method, for the quantitative determination of API, UV absorption spectrophotometry was employed.

From the analysis of the obtained data, it can be observed that the Bouguer-Lambert-Beer law is valid up to a concentration of 26.6 μg/mL, at both wavelengths at which telmisartan shows absorption maxima in the UV range (229 and 219 nm, respectively).

- The solubility of telmisartan at 25 °C in AGF of pH 1.2 was determined, obtaining values of 193.88 ± 21.28 μg/mL (at 221 nm), respectively 197.37 ± 12.45 μg/mL (at 291 nm).
- The analysis of the solubility of the binary adducts in artificial gastric fluid of pH 1.2 was evaluated in comparison with pure telmisartan also by UV spectroscopy, the selected amino acids being practically spectrally transparent at 291 nm, although the prepared solutions were quite concentrated (between 1 .33 and 6.61 mg/mL), except for tryptophan, which shows significant absorption due to the indole moiety in the structure.
- From the obtained solubility data, it can be observed that the amino acids with short hydrocarbon chains present a strong solubilizing effect on telmisartan in the artificial gastric fluid; also, a considerable increase in solubility (almost double) is observed when using L-aspartic acid as a co-forming agent.
- Amino acids with a longer hydrocarbon chain (VAL and LEU) cause insignificant increases in solubility for the pharmaceutical active, which would not justify their potential use in formulations.
- The studied sulfur-containing amino acids cause a drastic decrease in the solubility of telmisartan in the artificial gastric fluid, and therefore will not be considered as co-formers for the design of binary adducts.
- The studies carried out in artificial intestinal fluid and in phosphate buffer had a simplified approach, taking into account the fact that the solubility of telmisartan in these fluids is extremely low, without the possibility of constructing calibration curves.
- Considering the fact that the saturated solutions obtained as a result of the use of the saturated solution method could be dosed without dilution by UV spectroscopy, both for the artificial intestinal fluid and for the phosphate buffer, it allowed the dosing of telmisartan from binary adducts by the same method.
- Since the influence of the dissolution medium causes the bathochromic shift of the absorption maximum of the pharmaceutical active from 229 nm to 235 nm, this wavelength could no longer be used for dosing, as there was no possibility to prepare standard solutions of reasonable concentrations in the two fluids. As a result of the advantage of the fact that the absorption maximum at 291 nm is maintained even with increasing pH, dosing at this wavelength was possible. Thus, it can be concluded that all amino acids have a considerable solubilizing effect on telmisartan (up to 13-fold increase in solubility) in the artificial intestinal fluid, except for cystine, for which the increase in solubility is insignificant.
- Increasing the pH by 0.60 units in the phosphate buffer compared to the artificial intestinal fluid causes a rather pronounced increase in the solubility of telmisartan in the presence of amino acids. This could be explained both by increasing the intrinsic solubility of the pharmaceutical active, but also by the occurrence of some ionization

equilibria in which both TELM and amino acids are involved. The fact that at such a small pH variation, the increase in solubility is considerable, shows the potential of using these adducts in therapy, in the development of pharmaceutical forms with absorption at the level of the intestinal mucosa, this being the main site of absorption of pharmaceutical actives administered orally.

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