PHYSICO-CHEMICAL CHARACTERISATION OF DIFFERENT CLINDAMYCIN PHOSPHATE SAMPLES

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Abstract

For the majority of the pharmaceutical dosage forms, the substances that are used maintain solid state under the standard storage conditions, i.e. powders. The interactions of pharmaceutical powders (active ingredient(s) and excipients) with liquids and vapors (particularly aqueous solutions and their vapors) occur almost always during the production process. From the physical point of view, the interactions among individual components may differ from the expected because chemically identical substances obtained from different producers vary very much. These differences influence either the production process and/or the pharmaceutical form properties. In order to overcome these problems it is necessary to establish a control over the physico-chemical properties of the used materials,

The aim of this work was to determine physico-chemical properties of three powder clindamycin phosphate samples (labeled as sample S_1, S_2 and S_3) acquired through different suppliers. All the analysis were made for the purpose of establishing possible differences among the tested samples that showed variable physical stability in the solution: recrystallization of the S_3 sample in the aqueous solution has been established during storage under standard conditions. On the basis of the obtained data it was possible to recognize the differences among the tested clindamycin phosphate samples and to explain the anomalous behavior of one sample.

The surface free energy components for the investigated clindamycin phosphate samples were determined using Wu and Good- van Oss method. The investigated clindamycin phosphate samples exhibit certain differences in surface free energy values as well as in surface morphology and thermal behavior. Comparison of γ^+ and γ^- values leads to the conclusion that all three clindamycin phosphate samples perform as monopolar, more electron acceptors, i.e. Lewis acids. However, an important difference exists between samples S_1 and S_2 on one and S_3 on the other side. Sample S_3 exhibits stronger acidic behavior, what could be connected with its recrystallization during the storage.

The samples S_1, S_2 and S_3 have different melting points e.g. "onset" temperatures. When the melting points move towards 2000C, the width of the "onset" temperature peak is especially important. In the case of wider peak, the potential for recrystallization seems to be higher.

According to the stated, the sample S_1 would be the "sample of choice" for the formulation of the stable pharmaceutical dosage form and has not shown any recrystallization tendencies during the storage period.

KEY WORDS: clindamycin phosphate, contact angle, surface free energy, DSC, TGA, surface morphology, SEM, recrystallization

INTRODUCTION

Technological processes of incorporating the active pharmaceutical ingredient(s) in the appropriate pharmaceutical dosage form are often very complex, although difficulties may occur in simple processes. These difficulties could be resolved with precise scientific analysis of all processes and materials included in the production of a dosage form.

Substances used for the preparation of a pharmaceutical dosage form are, under the standard conditions of storage, in solid state, such as powders. The interactions of pharmaceutical powders (active ingredient(s) and excipients) with liquids and vapors (particularly aqueous solutions and their vapors) occur almost always during the production process. They depend on the physico-chemical properties of all the components in the process (1).

From the physical point of view, the interactions among individual components often differ from the expected because chemically identical substances obtained from different producers vary very much. It influences either the production process and/or pharmaceutical form. These substances may vary in the quantity of the impurities, different polymorphic modifications present, degree of crystallinity, particle size etc. This variability may cause more or less serious technological problems during the production process. To overcome these problems it is necessary to explain and control all relevant physico-chemical properties that influence the technological processes and stability of pharmaceutical form.

Attempts to characterize solid surfaces, such as powders, have been undertaken using descriptions of the particles morphology and the energetics of their surfaces (2).

Fowkes (3) pointed out the significance of differentiation for non-polar and polar components of surface free energy. He proposed that the solid surface free energy (γ_s) could be considered as the sum of two contributions representing dispersive (D) and polar (P) forces [1]:

$$\gamma_S = \gamma_S^D + \gamma_S^P \qquad [1]$$

where

γ_S^D -contribution from dispersive (non-polar) forces

γ_S^D -contribution from polar forces

Wu's method (4), has been frequently applied to determine the surface free energy of pharmaceutical solids (5, 6, 7). However, it has been debated whether the separation of surface free energy into polar and non-polar forces is adequate to represent practical interfacial interactions (8, 9).

Surface free energy of solids cannot be determined by direct measurement, as it is the case with liquids where the value of the surface energy is determined simply by measuring the surface tension. Therefore, for the measurement of solid surface free energy some indirect methods need to be used. These methods are based on contact angle measurement and gas adsorption.

However, an approach for determination of the surface free energy of solids was developed based on the theory of apolar and acid–base (AB) interactions by van Oss and co-workers (10,11). They described the importance of AB interactions in surface phenomena [2]:

$$\gamma^{TOT} = \gamma^{LW} + \gamma^{AB} \qquad [2]$$

where γ^{LW} is the apolar (or non-polar) component of the associated Lifshitz–van der Waals (LW) interactions which encompass London dispersion forces, Debye-polarization and Keesom forces.

The γ^{AB} component results from electron-donor and electron-acceptor intermolecular interactions referred to as Lewis acid-base interactions. The most common AB interaction results from hydrogen bonding. The term γ^{AB} is further divided into two parameters [3]:

$$\gamma^{AB} = 2\sqrt{\gamma^+\gamma^-} \qquad [3]$$

where γ^+ and γ^- are the electron-acceptor and electron-donor parameters of the AB component of the surface free energy of the substance, respectively.From Eqs. [3] and [4], it is obvious that if either γ^+ or γ^- parameter equals zero, there is no AB component contribution to the overall surface free energy ($\gamma^{TOT} = \gamma^{LW}$). This approach is recognized to provide accurate and real description of solid surface free energy components (12, 13), and has been applied to a variety of interfacial systems in many areas of surface science (14, 15, 16, 17). For low energy solids (3), the Young's equation can be written in terms of LW and AB interactions [4]:

$$(1+\cos\theta)\gamma_l^{TOT} = 2\left(\sqrt{\gamma_s^{LW}\gamma_l^{LW}} + \sqrt{\gamma_s^+\gamma_l^-} + \sqrt{\gamma_s^-\gamma_l^+}\right) \qquad [4]$$

If we assume that contact angles θ are determined with a liquid $\underline{l}$, of which we know the total surface tension γ_l^{TOT}, there are still three unknown independent variables, i.e. γ_s^{LW}, γ_s^+, γ_s^- that can be determined by solving three equations with three unknowns (11).

This LW/AB approach, which became a standard technique in the surface chemical characterization of polymers and polar materials, was applied to many interfacial systems of pharmaceutical interest with good success (9,13).

Different methods for solid surface free energy (γ_s) assessment and several methods for its calculation are available (4,11,18).

In one of them it can be assessed indirectly from wettability measurements. Usually, compacted powders are prepared to give the plates with a suitable geometry. Contact angles have to be measured with several liquids to assess the surface free energy of powder (19).

Thermal analysis methods, in which a physical property, i.e. enthalpy of transitions, is measured as a function of temperature or as a function of time while the substance is subjected to a temperature program are very valuable for the study of the properties of raw materials and drug products as well (20).

The aim of this work was to determine some physico-chemical properties (i.e. surface free energy, thermal and morphological properties) of three crystalline clindamycin phosphate samples, labeled as $\boldsymbol{S_1}$, $\boldsymbol{S_2}$ and $\boldsymbol{S_3}$ obtained by different suppliers. All the analysis were made in order to establish possible differences among the tested samples that showed variable physical stability in the solution: recrystaliization of the $\boldsymbol{S_3}$ sample in the aqueous solution was established during storage under standard conditions.

Materials and Methods

Materials

Model powder was crystalline clindamycin phosphate, obtained from three different sources (labeled as S_1, S_2 and S_3 sample). Liquids used for contact angle measurement were: bi-distilled water, glycerol, ethylenglycol (Ridel-de-Haën, Seelze-Hanover, Germany), diiodomethane and formamide (Sigma-Aldrich, Steinheim, Germany).

Methods

Contact angle measurement and surface free energy calculation

Compacts of the powders (200 mg) were prepared in a rectangular stainless steel punch and die assembly (25×10 mm) in a Specac hydraulic press (Kent, England) with a 10 s dwell time at a pressure of 2×10^8 Pa. The exact perimeter of the sample plates was measured using a micrometer. The compressed plate of powder was attached to the balance loop of the microbalance in a Krüss Tensiometer K12 (Germany). The temperature of the liquid used for contact angle measurements was controlled at 20±0,5°C, by flowing water from a circulator (Haake, Germany). The test liquid was placed in a special glass dish and raised by means of a motorized platform to contact the powder plate at the speed of 1,2 mm/min. From the force measurements, the contact angle was obtained using the Krüss tensiometer software (Krüss GmbH, 1996). At least five plates of the same powder were used for measurements with each liquid. The surface free energy parameters of the investigated clindamycin phosphate samples were calculated using the advancing contact angle data of the probing liquids. The equations were solved according to Good (21) using a numerical analysis and equation handling software program (Mathematica 3.0) with a personal computer. γ^{LW} was first obtained using the diiodomethane data. Subsequently, the two simultaneous equations, defined explicitly in terms of γ^+ and γ^-, were solved using Newton's method. The AB components were examined for consistency and subsequently averaged.

Thermal analysis

Samples were analyzed by differential scanning calorimetry and thermogravimetrical analysis. These experiments have been performed on Pyris 1, Perkin Elmer and Mettler TA 3000 System, Metler Toledo, respectively. DSC measurements were carried out under inert nitrogen atmosphere (40 ml min^{-1}) and with heating rate of 10K min^{-1}. TGA measurements were carried out under the heating rate of 5 K min^{-1}.

Scanning electron microscopy (SEM)

Powder samples were analyzed by scanning electron microscopy. The particles were Au/Pd coated and deposited on a double-sided carbon tape (diameter 12 mm, Oxon, Oxford instruments, UK). Samples were scanned at a voltage of 14 kV using secondary electron technique, with magnifications of 500 x and 2000 x. SEM analyses were performed using JSM 5800-JEOL instrument.

Liquid	SURFACE TENSION PARAMETERS		
	γ_l [mN/m]	γ_l^D [mN/m]	γ_l^P [mN/m]
Water	72,0	21,8	50,2
Glycerol	63,7	32,0	31,7
Diiodomethane	50,4	50,4	0
Ethylenglycol	48,9	33,4	15,5
Formamide	58,3	32,3	26,0

TABLE 1. Surface tension parameters of liquids [mN/m] suitable for solid surface free energy calculation according to Wu approach (23)

Liquid	SURFACE TENSION PARAMETERS				
	γ_l [mN/m]	γ^{LW} [mN/m]	γ^{AB} [mN/m]	γ^+ [mN/m]	γ^- [mN/m]
Water	72,8	21,8	51,0	25,5	25,5
Glycerol	64,0	34,0	30,0	3,92	57,4
Diiodomethane	50,8	50,8	0	0	0
Ethylenglycol	48,0	29,0	19,0	1,92	47,0
Formamide	58,0	39,0	19,0	2,28	39,6

TABLE 2. Surface tension parameters of liquids [mN/m] suitable for solid surface free energy calculation according to Good and van Oss approach (24)

Results and Discussion

The theory underlying the Young equation includes rigorous assumptions: the solid must be smooth, homogeneous and rigid, the solid must not be perturbed by chemical interaction or by adsorption due to a liquid phase, and there should be a unique contact angle. It is, however, well known that chemical heterogeneity and surface roughness of practical solid surfaces results in contact angle hysteresis. The advancing contact angle on a smooth but heterogeneous solid surface has been regarded as a reasonable estimation of the equilibrium contact angle that would be observed on an ideal surface composed of the low energy solids (21, 22). Contact angles were measured with five liquids on each solid. The surface tension parameters of liquids suitable for solid surface free energy calculation according to Wu approach are listed in Table 1. The surface tension parameters of liquids suitable for solid surface free energy calculation according to Good and van Oss approach are listed in Table 2. The reproducibility of contact angle measurements was in the range ±2,4°. The results are listed in Table 3.

	Contact angle θ[°]		
	Solid surface		
Liquid	S_1	S_2	S_3
water	64,87 ± 1,97	57,05 ± 1,51	57,78 ± 1,27
ethylenglycol	47,68 ± 2,31	58,08 ± 1,59	53,56 ± 1,95
formamide	65,30 ± 1,03	63,71 ± 1,08	54,48 ± 1,11
glycerol	83,20 ± 2,18	90,74 ± 1,55	82,96 ± 1,48
diiodomethane	57,53 ± 1,70	55,76 ± 2,02	55,60 ± 2,36

TABLE 3. Contact angle values, θ, for liquids on solid plates of the investigated clindamycin phosphate samples (S_1, S_2 and S_3).

For the two components approach (Wu method), among the appropriate combinations of liquids we decided to use water/diiodomethane, ethyleneglycol/diiodomethane, formamide/diiodomethane and glycerol/diiodomethane. Diiodomethane/ water/ethyleneglycol liquids combination was used for the three components approach (Good and van Oss method). Solid surface free energy determination according to Wu and Good-van Oss approaches was assessed and the results are listed in Tables 4 and 5. From the theoretical point of view the solid surface energy is not dependent on the liquids used for its calculation. In practice this is not the case. Some combinations gave no result and are not listed in Table 4 and Table 5. An equation system without solution is called ill-conditioned (22). It could result from the use of solvents whose polarities are too similar, or from the use of liquids with too low surface tension for contact angle measurements (25). Our results suggest that the examined samples exhibit certain differences in surface free energy values. Comparison of $\gamma^+$and γ^- values leads to the conclusion that all three clindamycin phosphate samples perform as monopolar, however, more electron acceptors, i.e. Lewis acids.

Liquids	Solid surface		
	γ_S [mN/m]	γ_S^D [mN/m]	γ_S^P [mN/m]
	S_1		
water/diiodomethane	48,04	31,69	16,35
ethyleneglycol/diiodomethane	37,44	31,69	5,75
formamide/diiodomethane	37,36	31,69	5,67
glycerol/diiodomethane	33,69	31,69	2,00
	S_2		
water/diiodomethane	52,68	32,57	20,11
ethyleneglycol/diiodomethane	35,13	32,57	2,56
formamide/diiodomethane	38,48	32,57	5,91
glycerol/diiodomethane	34,58	32,57	2,01
	S_3		
water/diiodomethane	46,62	22,32	24,30
ethyleneglycol/diiodomethane	32,40	22,32	10,08
formamide/diiodomethane	33,03	22,32	10,71
glycerol/diiodomethane	27,88	22,32	5,56

TABLE 4. Solid surface free energy parameters of the investigated samples of clindamycin phosphate calculated according to Wu [mN/m]

LIQUIDS	Solid surface γ_S [mN/m]	γ_S^{LW} [mN/m]	γ_S^{AB} [mN/m]	γ_S^{+} [mN/m]	γ_S^{-} [mN/m]
			S_1		
diiodomethane/water/ethyleneglycol	35,70	29,99	5,71	20,92	0,39
			S_2		
diiodomethane/water/ethyleneglycol	34,13	31,01	3,12	20,31	0,12
			S_3		
diiodomethane/water/ethyleneglycol	31,22	31,10	0,12	34,64	$9,67 \times 10^{-5}$

TABLE 5. Solid surface free energy parameters of the investigated samples of clindamycin phosphate calculated according to Good and van Oss [mN/m]

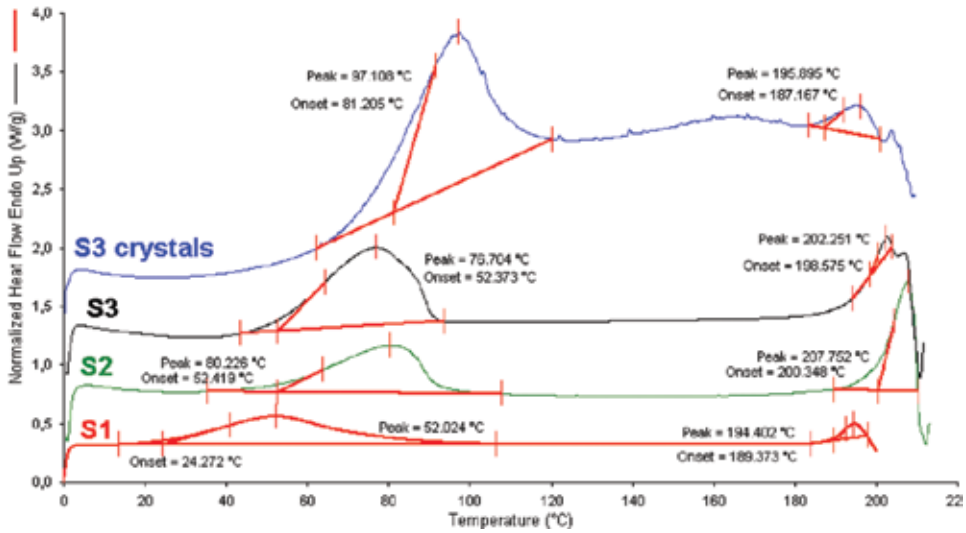

FIGURE 1. Comparison of DSC thermograms of the investigated clindamycin phosphate samples- S_1 , S_2, S_3 and recrystallized S_3 sample

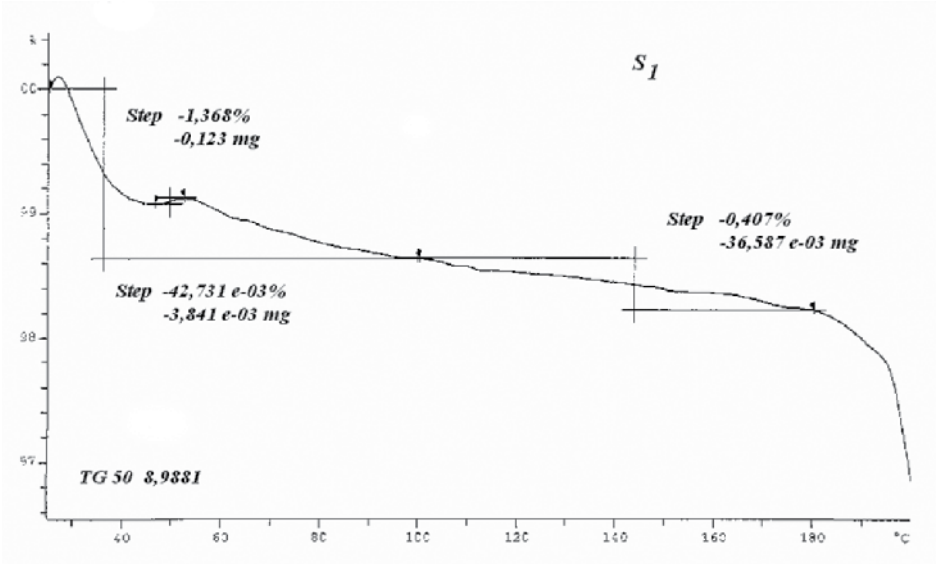

FIGURE 2. TGA thermograms of the investigated clindamycin phosphate sample- S_1

Anyway, an important difference exists between samples S_1 and S_2 on one and S_3 on the other side. S_3 sample shows much stronger acidic behavior, which might be related to its recrystallization behavior in the aqueous solution. The investigated original samples S_1, S_2 and S_3 as well as recrystallized S_3 crystals were thermally analyzed by differential scanning calorimetry and thermogravimetrical analysis. All of them contain some moisture that can be seen in their thermograms (Figure 1). The moisture is removed in the process of heating (Table 6)

Sample		
	S_1	
Δ H [J/g]	50,112	3,735
T [^{O}C]	24,272	189,373
	S_2	
Δ H [J/g]	63,732	40,173
T [^{O}C]	52,419	200,348
	S_3	
Δ H [J/g]	98,066	2,713
T [^{O}C]	52,373	198,575
	S_3 *recrystallized*	
Δ H [J/g]	174,835	14,509
T [^{O}C]	81,205	187,167

TABLE 6. Thermal changes of the investigated clindamycin phosphate samples- S_1, S_2, S_3 and recrystallized S_3 sample

(T_{onset} =24,27^{O}C). For the S_1, melting point is 189,373^{O}C. Parallel TGA experiment shows that the first peak is undoubtedly connected with the "water loss" (less than 1,4%) (Figure 2). From the detailed analysis of thermograms of S_2 and S_3 it is concluded that these two samples have different thermal properties (melting points- 200,348 ^{O}C and 198,575^{O}C for S_2 and S_3, respectively). The position of the "water" peak for S_2 and S_3 is moving towards higher temperatures, i.e. about 80^{O}C. So, the melting peak (i.e. the "onset" temperature) is similar to S_1. DSC thermograms obtained by the smaller heating rate (not shown), shows clearly the presence of additional endothermal change even before

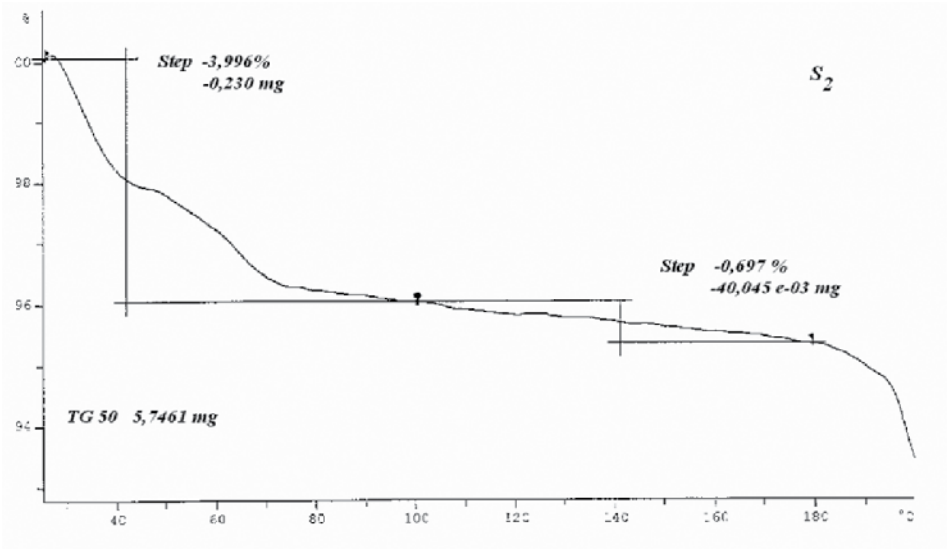

FIGURE 3. TGA thermograms of the investigated clindamycin phosphate sample- S_2

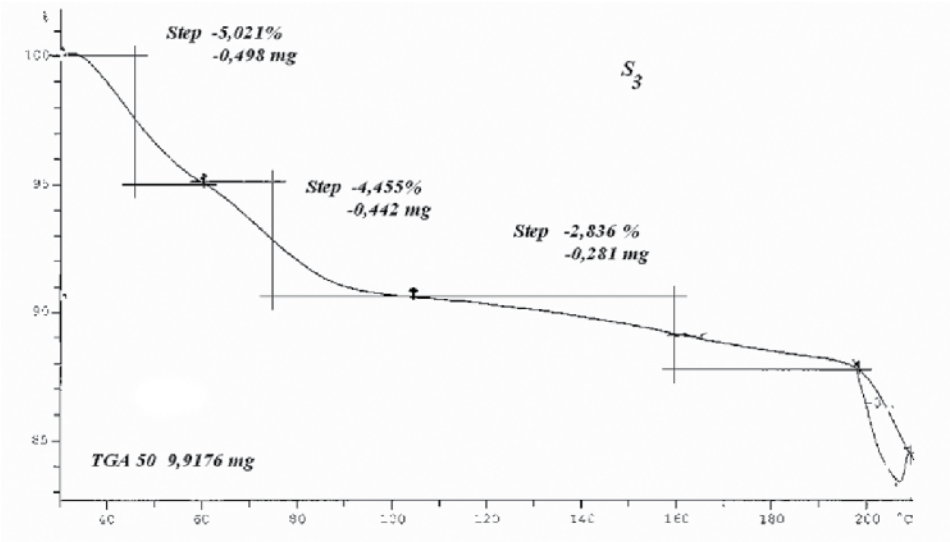

FIGURE 4. TGA thermograms of the investigated clindamycin phosphate sample- S_3

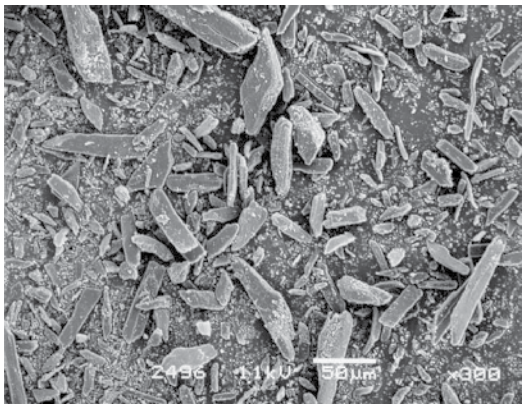

FIGURE 5a. SEM microphotography of the crystalline clindamycin phosphate (magnification 300 x)-S_1

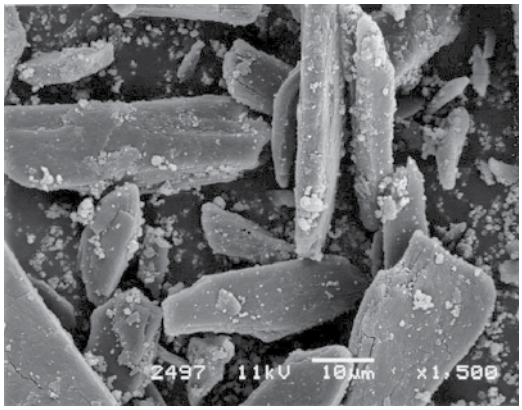

FIGURE 5b. SEM microphotography of the crystalline clindamycin phosphate (magnification 1500 x)-S_1

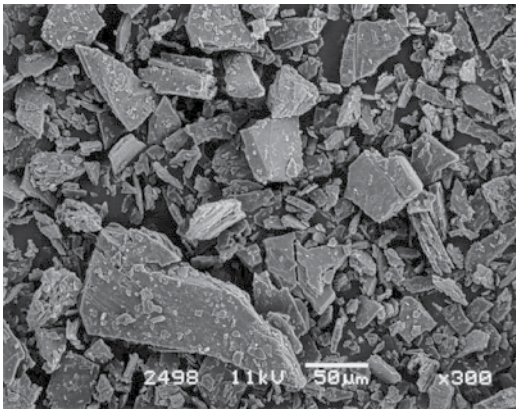

FIGURE 6a. SEM microphotography of the crystalline clindamycin phosphate (magnification 300 x)-S_2

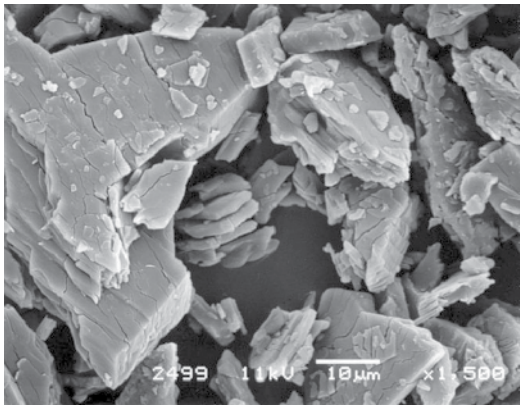

FIGURE 6b. SEM microphotography of the crystalline clindamycin phosphate (magnification 1500 x)-S_2

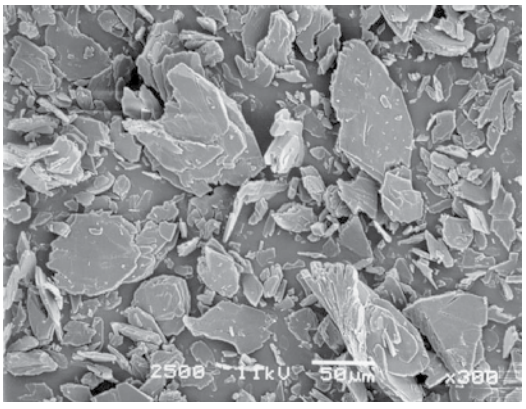

FIGURE 7a. SEM microphotography of the crystalline clindamycin phosphate (magnification 300 x)-S_3

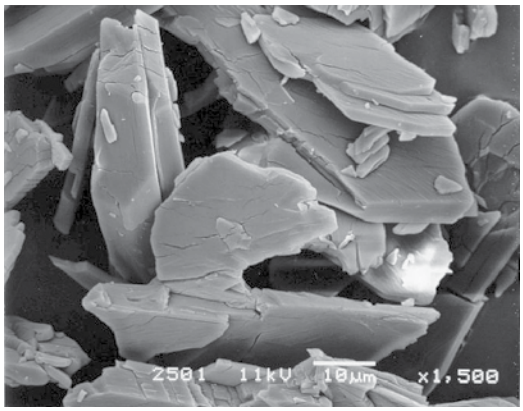

FIGURE 7b. SEM microphotography of the crystalline clindamycin phosphate (magnification 1500 x)-S_3

the melting process. What this change means is still not clear. It is possible that the presence of the new (crystal) phases initiate the recrystallization of the other dissolved parts of the clindamycin phosphate. The TGA experiment shows (Figure 3 and 4) that the appearance of additional endothermal change is not connected with the loss of the mass. That clearly shows the appearance of the new solid phase. It is possible that additional phase is represented by the mixed crystals. SEM microphotographs were analyzed and morphological differences among the investigated samples could be easily perceived visually (Figures 5, 6, 7). It could be assumed that S_1 is quite different from S_2 and especially from S_3. S_1 structure is not stratified as S_2 and S_3.

Conclusion

Based on the analysis of the obtained results we may conclude:

- The investigated samples show certain differences in surface free energy values as well as in surface morphology and thermal behavior. Comparison of γ^+ and γ^- values suggests that all the three clindamycin phosphate samples perform as monopolar, however, more electron acceptors, i.e. Lewis acids. Anyway, an important difference exists between samples S_1 and S_2 on one and S_3 on the other side. S_3 sample shows stronger acidic behavior, which might be related to its recrystallization behavior in aqueous solution.
- The samples S_1, S_2 and S_3 have different melting points e.g. "onset" temperatures- S_1-189,373 °C; 200,348 °C and 198,575°C for S_1, S_2 and S_3, respectively. When the melting points move towards 200°C, the width of the "onset" temperature peak is especially important. In the case of wider peak, the potential for recrystallization seems to be higher.
- According to the stated, the sample S_1 would be the "sample of choice" for the formulation of the stable pharmaceutical dosage form and has not shown any recrystallization tendencies during the storage period.

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