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SOLID STATE TRANSITIONS AND CAP AVAILABILITY IN SURFACE SOLID DISPERSIONS OF CHLORAMPHENICOL STEARATE POLYMORPHS (°)

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ABSTRACT

By grinding, chloramphenicol stearate Form III turns into Form I: then this form tends to become amorphous. So the grinding of both forms produces a "physically activated" form (FI*) with low crystallinity degree and high CAP availability.

In the presence of microcrystalline cellulose, the transition from FIII to FI is accelerated, the amorphization time does not change and the CAP availability increases.

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Therefore the results show that CAP availability may be a function of the cristallinity degree and not of the polymorphic form of the ester.

INTRODUCTION

When dissolution is the absorption limiting step, it is well known that dissolution rate of poorly soluble drugs can be increased by some techniques (1-11).

On the contrary, not much is known about the effect of some of such techniques on pro-drugs, when the therapeutic efficacy depends on drug liberation by enzymes in the gastro-intestinal tract. Therefore it seemed interesting to study the effect of grinding, with and without the presence of microcrystalline cellulose, of a pro-drug like chloramphenicol stearic ester. The polymorphic form of this ester is very important for the drug availability, because the enzyme is jugded to act according to the different crystalline structures of the ester (12).

EXPERIMENTAL

Materials

Chloramphenicol stearate (CAP-S) non polymorphous A (Carlo Erba) was purified by means of repeated crystallizations from toluene/n-hexane and from methanol/water.

Chloramphenicol stearate commercial sample ("E"),

microcrystalline cellulose (Avicel PH 102, FMC) (AV), pancreatin 4xNF (Fluka), Tween 80 (Atlas) were used as received from the manufacturers.

Equipment and methods

Pulverisette "0" mill (Fritsch): agate grinding chamber and ball (Ø 70 mm).

"Thermovar" microscope orig. Kofler (Reichert).

Spectrophotometer UV-VIS mod. 550 (Perkin-Elmer).

Spectrophotometer IR mod. 681 (Perkin-Elmer).

Powder Diffractometer PW 1050 (Philips). Experimental settings: Ni-filtered Cu radiation (λ = 1.5418 Å); tube settings 40 kV, 20 mA; angular speed 1° (2θ) per minute; 1-0.1-1 slits.

Differential Scanning Calorimeter DSC-4 (Perkin-Elmer). Heating rate: 10°C/min; dry N_2 flow (30 ml/min) and sample amounts from 4 to 5 mg were used.

Dissolution and "in vitro" enzymatic hydrolysis determination. The equipment and the conditions elsewhere described (13) were used.

Particle size determination. The microscopic method described by Speiser (14) was used.

Preparation of polymorphic forms. Form I (FI) was obtained by slow crystallization of purified CAP-S from methanol/water (15).

Form III (FIII) was obtained by slow cooling after purified CAP-S melting (16). FIII satisfies the tests reported in the Pharmacopoeias for the chloramphenicol palmitic ester, though it shows a high crystallinity degree.

Preparation of physical mixtures. Physical mixtures are mixtures of FI or FIII with AV in the (1:1), (1:3), (1:5), (1:7), (1:9) and (1:15) w/w ratios.

Preparation of ground powders and mixtures.

Ground powders : FI, FIII and AV were separately ground for variable times, until a maximum time of 85 hrs, so obtaining the corresponding FI_g, $FIII_g$ and AV_g.

Ground mixtures were obtained by the grinding of the corresponding physical mixtures, as indicated for the ground powders.

RESULTS AND DISCUSSION

Characterization and identification.

Microscopic analysis. FI appears like thin square plates (d_{50} = 7.8 μm), FIII like irregular shaped chips of different lengths (d_{50} = 8.5 μm).

After grinding, both forms appear like isotropic agglomerates of small particles (FI_g: d_{50}= 3.9 μm; $FIII_g$: d_{50}= 4.7 μm).

Thermomicroscopic analysis. FI (m.p. 96-97°C) and FIII (m.p. 92-93°C) have the same melting point after 85 hrs grinding (95-96°C).

The melting points of CAP-S in the physical or ground mixtures are difficult to evaluate owing to AV presence.

Differential Scanning Calorimetry. FI (m.p. 96.1°C) (Fig. 1,

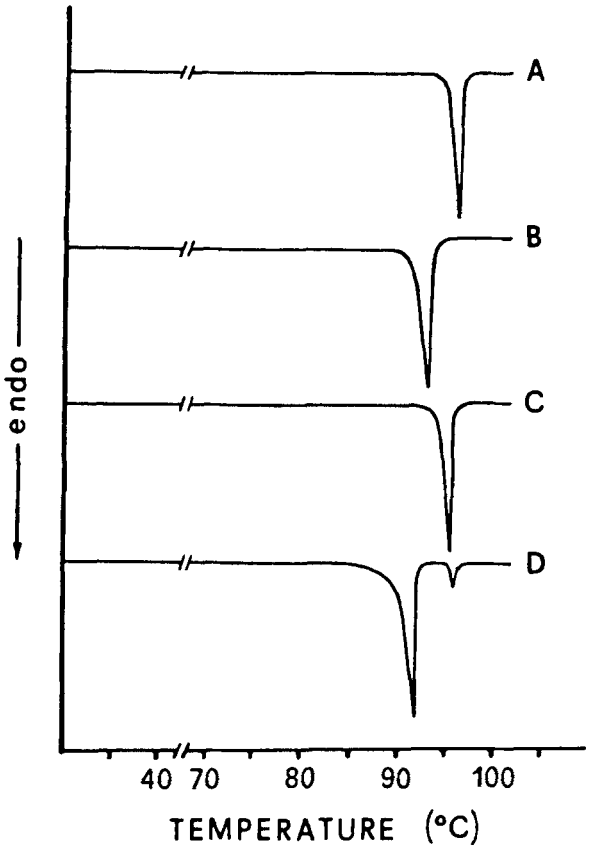

FIGURE 1

DSC Thermograms. A- FI and physical mixtures of FI; B- FIII and physical mixtures of FIII; C- FI_g, $FIII_g$ and ground mixtures of FI and of FIII; D- FIII after 5 hrs grinding.

A) and FIII (m.p. 92.9°C) (Fig. 1, B) have the same melting point also in the physical mixtures with AV.

The melting point of FI_g is 95.1°C (Fig. 1, C).

After 5 hrs grinding, the thermogram of FIII shows two endothermic peaks (Fig. 1, D): the first is the one of FIII, the second is the one of FI. This second peak is small at the

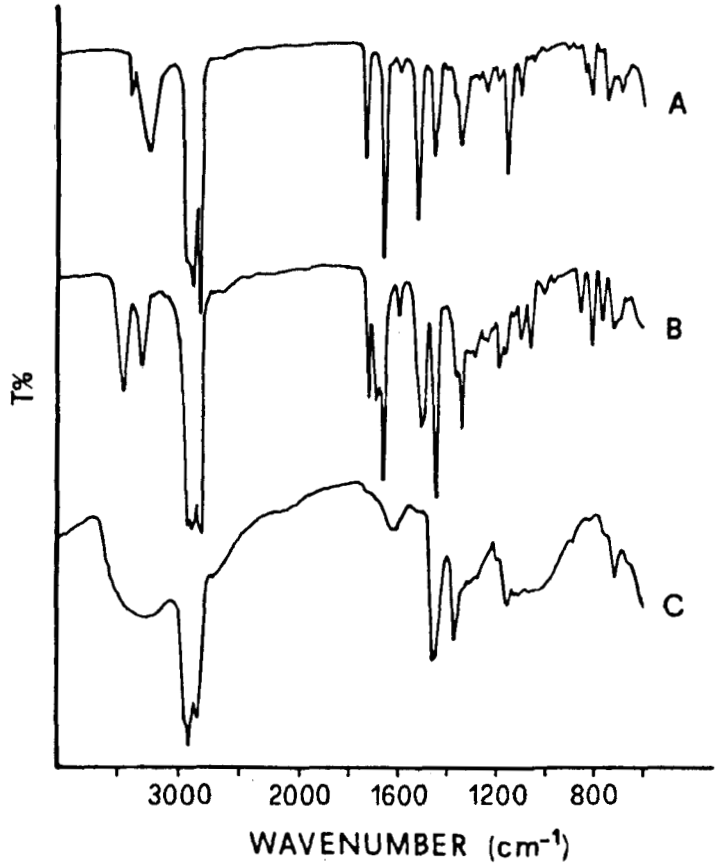

FIGURE 2
Infrared Spectra of chloramphenicol stearate polymorphs before and after grinding. A- FI, FI_g and $FIII_g$; B- FIII; C- AV and AV_g.

beginning, then, after more than 20 hrs grinding, it is the only peak present in the thermogram (Fig. 1, C).

By grinding, the physical mixtures of FIII show the same behaviour of FIII, but after 18 hrs grinding, only the endothermic peak of FI_g appears. Therefore AV produces a faster transition from FIII to FI.

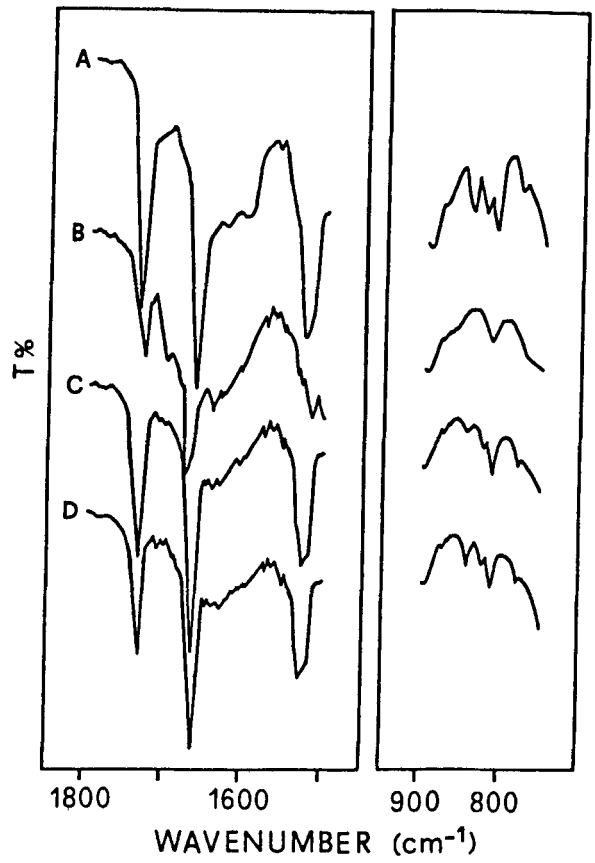

FIGURE 3
Infrared Spectra of physical and ground mixtures. A- Physical and ground mixture of FI (1:5); B- Physical mixture of FIII (1:5); C- Physical mixture of FIII (1:5) after 10 hrs grinding; D- Ground mixture of FIII (1:5).

IR spectrophotometry. The IR spectrophotometry, carried out in nujol dispersion, agrees with the thermal analysis: FI_g and $FIII_g$ show the same spectrum of FI (Fig. 2, A). Avicel shows no difference before and after grinding (Fig. 2, C).

The physical and ground mixtures of FI show the same IR spectra too (Fig. 3, A).

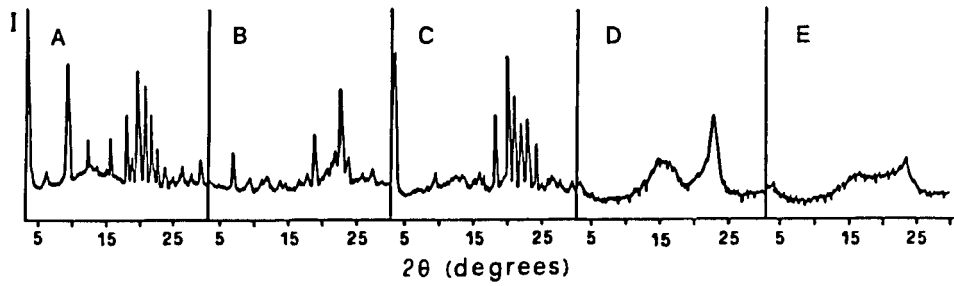

FIGURE 4

X-ray diffraction patterns of chloramphenicol stearate polymorphs before and after grinding. A- FI; B- FIII; C- FI_g and $FIII_g$; D- AV; E- AV_g.

On the contrary, the physical mixtures of FIII (Fig. 3, B) show, after grinding (Fig. 3, D), the same IR spectra of the ground mixtures of FI. This conversion from FIII to FI can be followed during the grinding time (Fig. 3, C): also by IR spectrophotometry the conversion appears faster with AV.

X-ray diffractometry. The grinding of FI (Fig. 4, A) does not produce important differences in the peaks position: only the intensity decreases (Fig. 4, C).

The grinding of FIII (Fig. 4, B) produces the same X-ray pattern of FI_g (Fig. 4, C).

This crystallinity decrease by grinding is clear for the microcrystalline cellulose too (Fig. 4, D and E).

The grinding of the physical mixtures of FI (Fig. 5, A) and FIII (Fig. 5, B) leads to mixtures (Fig. 5, C), where there is a Form I in a less crystalline state compared to FI or FIII ground without AV.

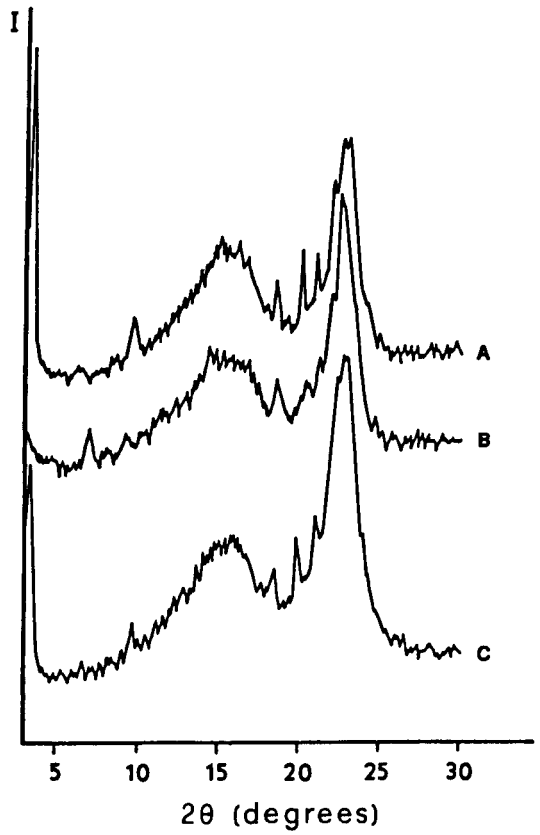

FIGURE 5
X-ray diffraction patterns of physical and ground mixtures. A- Physical mixture of FI (1:5); B- Physical mixture of FIII (1:5); C- Ground mixtures of FI and of FIII (1:5).

Then it has been confirmed that by grinding FIII with AV, FIII turns completely to FI faster.

Dissolution. The CAP-S dissolution rate in the ground mixtures studied in the present paper is strictly correlated with the ester/AV ratio. After 180 min the ground mixture (1:15) seems to show almost the same solubility of FIII and about twice the one of FI.

This solubility increase may be chiefly due to the less crystallinity degree of FI_g, to the disaggregation action of AV and to the formation of a solid dispersion on the AV surface with consequent particle size decrease and wettability increase.

Availability of chloramphenicol

"In vitro" enzymatic hydrolysis - The "in vitro" enzymatic hydrolysis rate constant values (K_{hydr}) of ground forms and ground mixtures are higher than the values of the same samples before grinding, and of the commercial product "E" (Fig. 6).

In each case this increase is higher for the ground mixtures than for the ground Forms owing to the AV presence.

For pro-drug/AV ratios higher than (1:9), the K_{hydr} decreases; the microcrystalline cellulose excess, so close to the ester surface, plays an inhibent rôle at the crystal/enzyme interface.

The K_{hydr} enhances with the grinding time too: this increase stops after 40 hrs (Fig. 7).

Stability

The CAP-S polymorphic forms ground with or without AV are chemically stable. Infact the thin-layer chromatography [silica gel G, Merck; solvent used: chloroform/ether (9:1) and methylene chloride/ether (9:1)] and the characterization tests (IR spectrophotometry, thermal analysis, X-ray diffraction) did not show a degradation process. Free

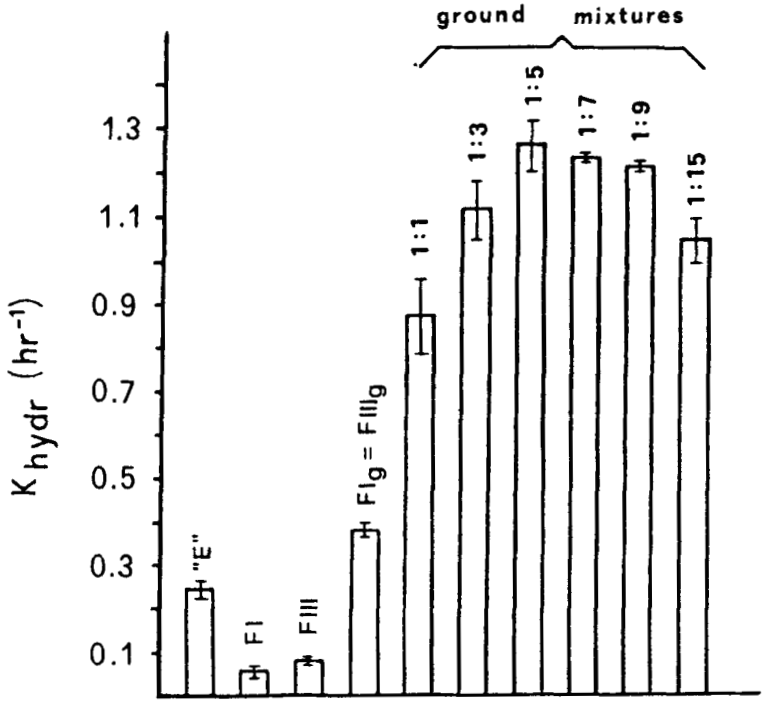

FIGURE 6

The "in vitro" enzymatic hydrolysis rate constants (K_{hydr}) of chloramphenicol stearate polymorphs before and after grinding and of ground mixtures. Bars represent standard deviation.

chloramphenicol was calculated following the method described by Andersgaard et al. (17); the amounts found after grinding were as small as the ones found in the CAP-S non polymorphous A (0.05%).

The excellent chemical and physical stability, even after time, of FI and FIII, is both the same, or before grinding or after having ground FI and FIII with or without AV. This stability was shown by tests carried out after 6 months of storage at room temperature with amounts equivalent

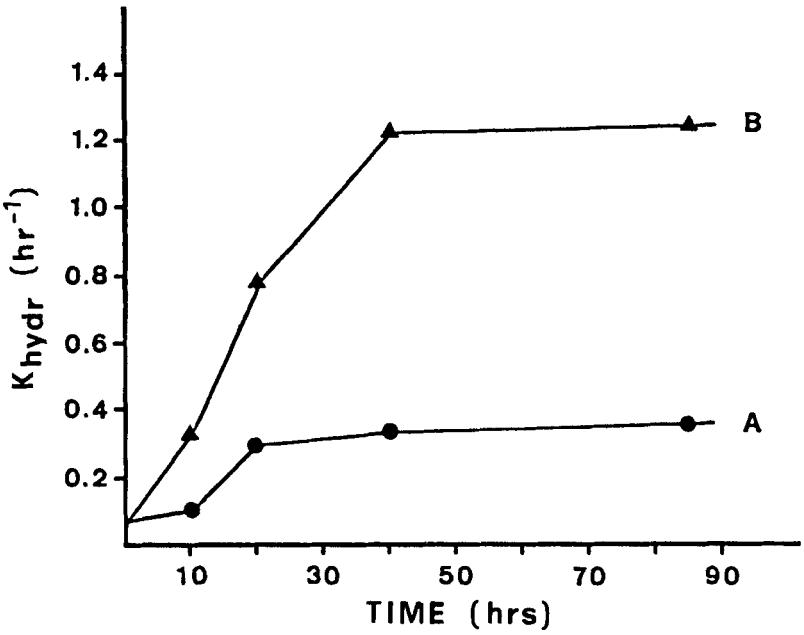

FIGURE 7
Relationship between grinding time and the "in vitro" enzymatic hydrolysis rate constants. A- FIII; B- Physical mixture of FIII (1:5).

to 5 g of ester in 100 ml of 0.05% Tween 80 acqueous solution.

In these conditions no crystallinity increase was shown and K_{hydr} values were the same ones as shown in Fig. 6.

CONCLUSIONS

By grinding with or without AV, FIII turns into FI; this transition should have a negative influence on the enzymatic hydrolysis, because FI is not biologically active (12). On

the contrary, the grinding, chiefly in the presence of microcrystalline cellulose, gives a remarkable increase of the drug release rate by pancreatic lipase, i.e. of the CAP availability, owing to the lowest crystallinity degree of the "physically activated" FI_g (FI*).

Therefore the opinion, according to which the enzyme is enable to recognize the FI structure, is not correct.

An increase of the co-grinding excipient (AV) amount improves the CAP-S dissolution rate, whereas the "in vitro" enzymatic hydrolysis rate constant increases until the ester/AV (1:5) ratio. Further AV additions do not increase the K_{hydr} until the (1:9) ratio; beyond this ratio, the K_{hydr} decreases. The "in vitro" enzymatic hydrolysis rate constant values of FI* are 1.5 times higher than K_{hydr} of "E" and 8 times higher than the one of FI, when FI* is obtained by grinding FI or FIII without AV; 5 times higher than K_{hydr} of "E" and 27 times higher than the one of FI, when FI* is obtained by grinding FI or FIII with AV in the ratios from (1:5) to (1:9).

Therefore, it is possible to emphasize that whatever the chloramphenicol stearate polymorphic form may be, the enzyme action is supported by a lowest crystallinity degree as previously suggested in some of our works (15, 16, 18).

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REFERENCES

1) W.L. Chiou and S. Riegelman, J. Pharm. Sci., 60, 1281 (1971).

2) C.F. Lerk, M. Lagas, J.T. Fell and P. Nauta, J. Pharm. Sci., 67, 935 (1978).

3) E.J. de Jong, Pharm. Weekbl., 104, 469 (1969).

4) T.R. Bates, M. Gibaldi and J.L. Kanig, J. Pharm. Sci., 55, 191 (1966).

5) T.R. Bates, M. Gibaldi and J.L. Kanig, J. Pharm. Sci., 55, 901 (1966).

6) R.G. Crounse, J. Invest. Dermatol., 37, 529 (1961).

7) K. Ventouras, J. Boucherat and P. Buri, Pharm. Acta Helv., 52, 119 (1977).

8) K. Ventouras and P. Buri, Pharm. Acta Helv., 53, 314; (1978).

9) W.L. Chiou, S.J. Chen and N. Athanikar, J. Pharm. Sci., 65, 1702 (1976).

10) H. Rupprecht, Acta Pharm. Technol., 26, 13 (1980).

11) Y. Nakai, Drug Develop. Indust. Pharm., 12, 1017 (1986).

12) L. Almirante, I. De Carneri and G. Coppi, Il Farmaco, Ed. Pr., 15, 471 (1960).

13) R. Cameroni, G. Coppi, G. Gamberini and F. Forni, Il Farmaco, Ed. Pr., 31, 615 (1976).

14) P. Speiser, Il Farmaco, Ed. Pr., 22, 181 (1967).

15) R. Cameroni, G. Gamberini, F. Forni, G. Coppi, V. Ferioli and M.T. Bernabei, Il Farmaco, Ed. Pr., 33, 141 (1978).

16) M.T. Bernabei, G. Coppi, F. Forni, R. Cameroni and E. Galli, Il Farmaco, Ed. Pr., 34, 338 (1979).

17) H. Andersgaard, P. Finholt, R. Gjermundsen and T. Hoyland, Acta Pharm. Suec., 11, 239 (1974).

18) R. Cameroni, G. Coppi, F. Forni and M.T. Bernabei, Il Farmaco, Ed. Pr., 39, 76 (1984).