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RELATION BETWEEN POLYMORPHIC TRANSFORMATION PATHWAY DURING GRINDING AND THE PHYSICOCHEMICAL PROPERTIES OF BULK POWDERS FOR PHARMACEUTICAL PREPARATIONS

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ABSTRACT

The polymorphic transformation pathway during grinding of cephalexin (CEX), chloramphenicol palmitate (CPP) and indomethacin (IMC) were investigated. CEX was converted into noncrystalline solid at room temperature. The meta-stable forms B and C CPP was transformed into stable form A at room temperature. IMC was transformed into noncrystalline solid during grinding at 4°C, but it transformed into meta-stable form a during grinding at 30°C. The melting point (mp) of CPP and IMC were about 90°C and 160°C, respectively. CEX does not have the mp, but have the decomposition point at 190°C. The mp of CEX is higher than the decomposition point. The order of the mp for these drugs is CPP < IMC < CEX. The proportional relation between the mp and the glass transition point of the drugs had reported, therefore, in general the higher mp material has the higher glass transition point. The order of the stability for a noncrystalline solids of these drugs is CPP < IMC < CEX. The

noncrystalline solid of CEX is very stable at 35°C under lower than 66% of relative humidity. The noncrystalline solid of CPP was very unstable at about 20°C, therefore, it transformed into a crystalline form very rapidly. The noncrystalline solid of IMC was stable at 4°C, but it was unstable at 30°C, therefore, after grinding it transformed into a form. These results suggest that there is a very important relation between the transformation pathway of the crystalline form during grinding and the physicochemical properties. The transformation pathway is controlled by the stability of noncrystalline solid and the presence of meta-stable crystalline form.

INTRODUCTION

Grinding is often carried out as means to reduce the particle size of powders and to mix drugs. The particles size and the physicochemical properties of drug powders affect the bioavailability of preparations through their effects on the dissolution rate,[1] therefore, the mechanical treatment such as grinding and tabletting are important process for making the pharmaceutical preparations. However, there are few reports on the effect of mechanical treatment on the physicochemical properties of medical drugs.[2,3]

We investigated the mechanochemical effect on the characters of typical commercial drugs such as cephalexin (CEX),[4,5] chloramphenicol palmitate (CPP)[6-8] and indomethacin (IMC).[9] In this study, we investigate the relation between the physicochemical properties of these drug powder and the pathway of crystalline form during grinding.

EXPERIMENTAL

Samples (10 g) were ground in an agate centrifugal ball mill with 350 ml of inside capacity (diameter and number of balls, 10 x 20, 15 mm x 10, 20 mm x 4) using a grinding apparatus (Fritsch Co. Ltd.) at 200 rpm. The ground samples were stored in closed containers at -20°C.

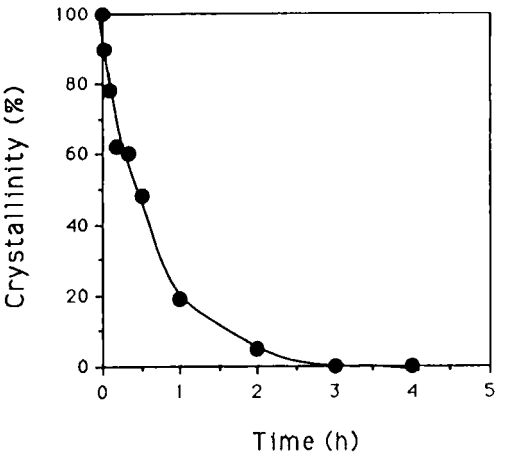


Fig. 1 Effect of Mechanical Stress on Crystallinity of CEX During Grinding

RESULTS

Cephalexin

Figure 1 shows the changes in the crystallinity of CEX during grinding in an agate centrifugal ball mill at 20°C.[1] The peak intensities of CEX decreased with increase grinding time; after 4 h grinding the ground CEX had a halo pattern. The crystallinity of ground CEX decreased with increase of grinding time; after 10 min grinding it was about 60%, and after 2 h grinding it was 0%, that is, crystalline CEX was converted into a noncrystalline solid.[4]

Chloramphenicol palmitate

Figure 2 shows the changes of the crystallinity of form B during grinding at 20°C.[6] The X-ray diffraction pattern of form B showed no change up to 130 min of grinding time, but form B ground for 150 min showed diffraction peaks attributable to form A. In grinding of form B the products ground for 5 to 130 min were transformed into form A to extents of less than about 5%, but the product ground for 150 min contained about 80 % form A, and the values stayed approximately content at 80 % on further grinding.

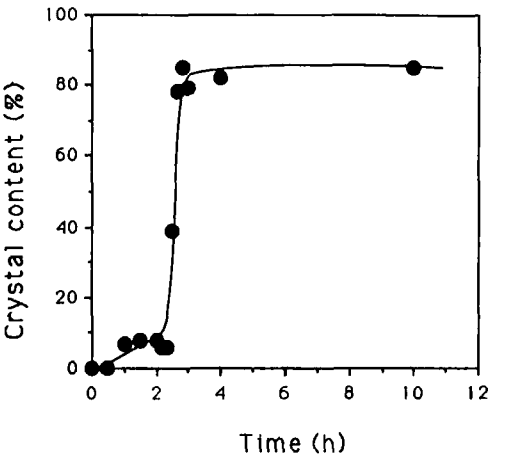


Fig. 2 Effect of Mechanical Stress on Crystalline form B CPP During Grinding

Figure 3 shows the changes of the crystallinity of form C during grinding at 20°C.[6] After grinding for 10 min, form C was transformed into form B. Further, form C ground for 150 min showed the diffraction peak attributable to form A. After grinding for 160 min, the X-ray diffraction profiles of ground form C showed a typical diffraction pattern of form A and the diffraction peaks attributable to form B had disappeared. 100% of form C was transformed into form B after 18 min of grinding a and the product ground for 160 min contained about 80% form A.

Figure 4 shows the changes of the crystallinity of form A (stable form) which are therapeutically inactive, during grinding at 20°C.[7] After 10 min of grinding form A showed very broad X-ray diffraction profiles, but even after prolonged grinding until 10 h the diffraction pattern showed no change. The broad X-ray diffraction profile of the ground form A suggested that part of form A was converted into a noncrystalline solid or that considerable disorder was produced in the crystal lattice of form A.

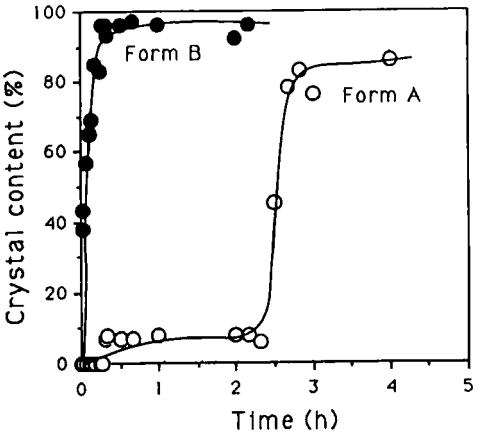


Fig. 3 Effect of Mechaincal Stress on Crystalline form of from C CPP During Grinding

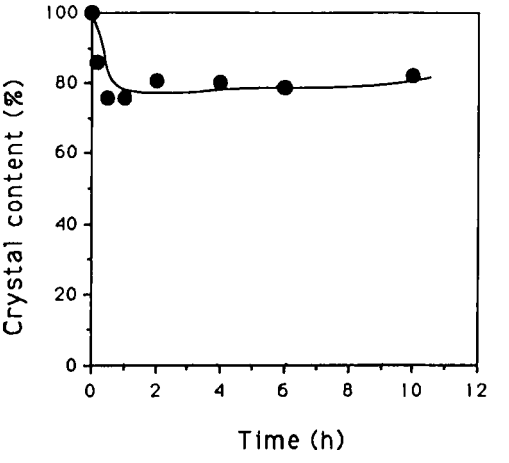


Fig. 4 Effect of Mechanical Stress on Crystalline form A CPP During Grinding

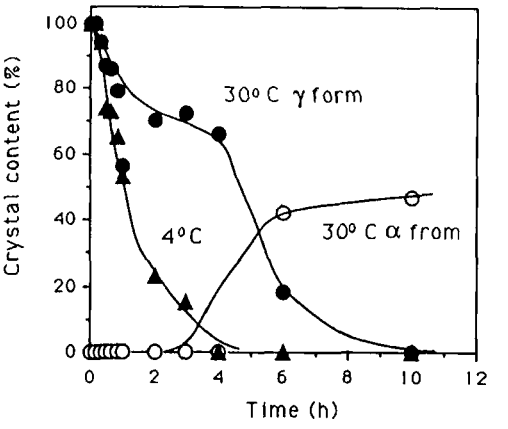


Fig. 5 Effect of Mechanical Stress on Crystallinity of γ form IMC During Grinding at 4 and 30 ℃

Indomethacin

Figure 5 shows the changes of the crystallinity of the γ form (stable form) of IMC during grinding at 4°C and 30°C.[9] The X-ray diffraction profiles of the ground product showed the halo pattern after grinding for 4 h at 4C because the γ form converted to a noncrystalline solid by grinding for 4 h, but in the case of grinding at 30C the γ form did not converted to a noncrystalline solid and after 6 h grinding the profile of ground product showed the diffraction peaks due to the α form, and the γ form transformed into α form (meta-stable form).

Figure 6 shows the change of the crystallinity of the α form. The X-ray diffraction profiles of the ground α form showed the halo pattern after grinding for 2 h at 4°C, but in the case of grinding at 30°C the ground α form showed the profiles of a form after grinding for 2 - 10 h. The a form converted to a noncrystalline solid by grinding for 2 h at 4°C, but after grinding for 10 h at 30°C the α form did not converted to a noncrystalline solid.

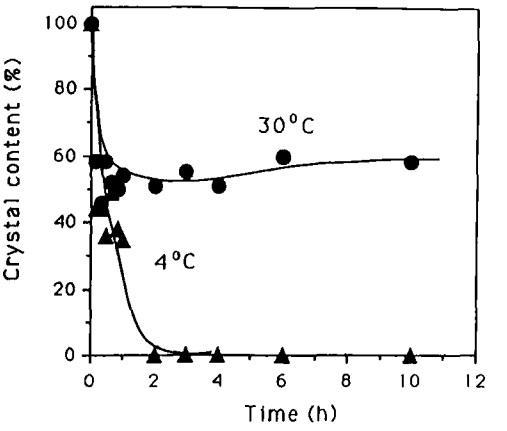


Fig. 6 Effect of Mechanical Stress on Crystallinity of α form IMC During Grinding at 4 and 30 ℃

DISCUSSION

Polymorphic transformation of drug during grinding

The noncrystalline solid of CEX was very stable at 35°C under lower than 66% of relative humidity. CEX was converted into a noncrystalline solid during grinding at 20°C, this is the most simple case as shown in Fig. 7 because CEX dose not have the meta-stable form and the crystal growth rate was negligible.

The other hand, the polymorphic transformation of CPP during grinding at 20°C were more complex, the meta-stable forms B and C were converted into a noncrystalline solid by mechanical stress. However, the crystal growth rate of form B was not negligible, beaches the noncrystalline solid of CPP was very unstable at about 20°C, therefore, it transformed into a crystalline form very rapidly. Therefore, the crystal content value reached an equilibrium until appearing nuclei of form A. After the nuclei of form A come out, the form B disappear, and the equilibrium reach a constant value between form A and a noncrystalline solid. The crystalline path way of CPP was shown in Fig. 8, and it seems that this path way was controlled by the nucleation process.

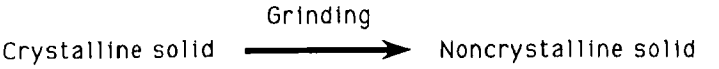


Fig. 7

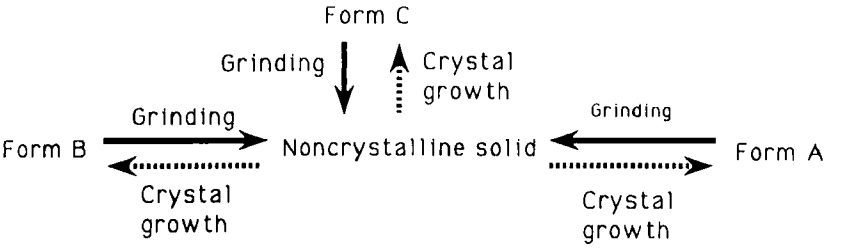


Fig. 8

The polymorphic transformation of IMC during grinding have intermediate character between CPP and CEX, because the α and γ forms were converted to a noncrystalline solid at 4°C, but the grinding at 30°C the γ form was converted to meta-stable α form and the α form remained the crystal form and unchanged. The crystalline path way during grinding was shown in Fig. 9. The mp of glassy IMC[11,12] was at 55°C to 58°C, but the noncrystalline solid obtained by grinding crystallized at 20°C after induction period for 1020 min[14]. The noncrystalline solid of IMC was stable at 4°C, but it was unstable at 30°C, therefore, after grinding it transformed into α form. These finding suggest that the α and γ forms were converted to a noncrystalline solid by mechanical stress during grinding. The conversion was irreversible at 4°C because the noncrystalline solid was stable at 4°C, but the solid was unstable at 30°C, and crystallized to α form. The crystal content of α form reached an equilibrium state because the rate of crystallization is equal to the rate of destruction of IMC crystal by grinding.

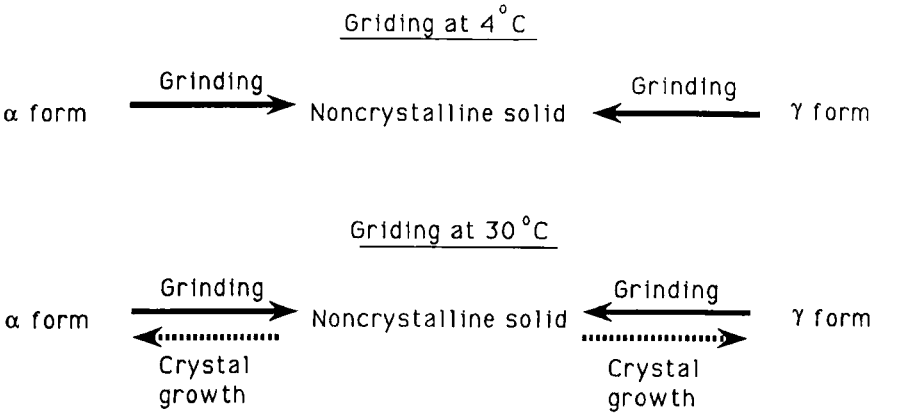


Fig. 9

The relation between melting point and the pathway of crystalline form during grinding

Fukuoka et al.,[13] reported on the proportional relation between the mp and the glass transition point of the drugs, therefore, in general the higher mp material has the higher glass transition point. The mp of CEX, CPP and IMC summarized in Table 1. The mp of CPP and IMC were about 90°C and 160°C, respectively. CEX does not have the mp, but have the decomposition point at 190°C. CEX is decomposed at lower temperature than its melting point because CEX have very strong intermolecular binding force due to the polar amino and the polar carbonate groups (Fig. 10), but the β lactam ring which is very unstable molecular structure. Therefore, the mp of CEX is higher than the decomposition point. The intermolecular binding force was affected by the molecular structure, CEX has two polar groups and IMC has a polar carbonate groups, but CPP does not have any polar group in the molecule structure as shown in Fig. 16. Therefore, the order of the mp for these drugs is CPP < IMC < CEX. The order of the stability for a noncrystalline solids of these drugs is CPP < IMC < CEX.

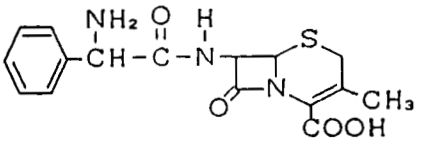
Figure 11 shows the pathway of crystalline form during grinding. The crystal growth rate is no negligible, therefore, the

Table 1

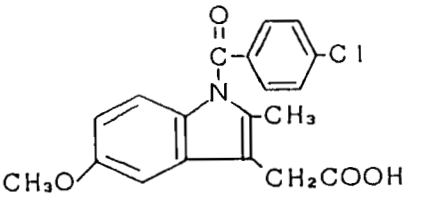
Melting point (mp) and heat of fusion (H) of CEX, CPP and IMC

Sample	mp (°C)	H ± S.D. (kcal/mol)
CEX	190	-
CPP		
form A	90.3	15.70 ± 0.52
form B	86.7	11.08 ± 0.21
form C	64.5	0.40 ± 0.11
IMC		
α form	148	7.49 ± 0.27
β form	158	8.64 ± 0.13

CEPHALEXIN



INDOMETHACIN



CHLORAMPHENICOL PALMITATE

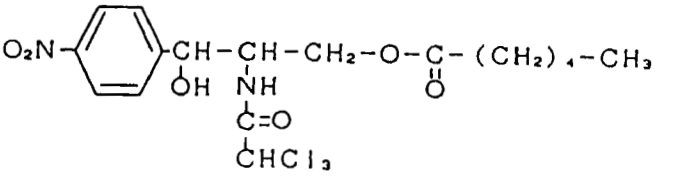


Fig. 10

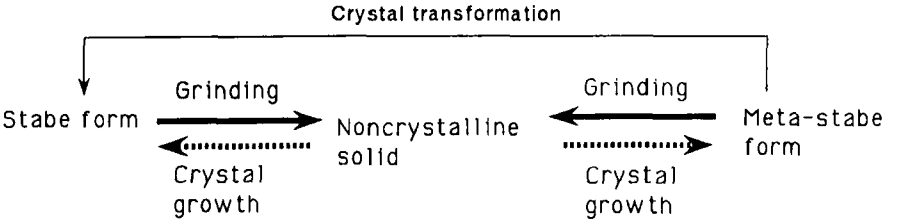


Fig. 11

crystallinity shows almost constant value since the rate of crystal growth from the noncrystalline solid became equal to the rate of loss of the crystallinity by grinding and equilibrium was established. These results suggest that there is a very important relation between the transformation pathway of the crystalline form during grinding, because the stability of noncrystalline solid depend on the mp of the drug.

CONCLUSION

We might conclude that the transformation pathway during grinding is though a noncrystalline solid and is controlled by the stability of noncrystalline solid and the presence of the meta-stable form.

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