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The interconversion of the polymorphic forms of chloramphenicol palmitate (CAP) as a function of environmental temperature

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Abstract

When polymorph B of chloramphenicol palmitate (CAP) is heated at 82 °C for 1600 minutes it changes completely to the less soluble and less bioavailable polymorph A. When polymorph C, the most soluble polymorph, is grinded for a prolonged period it changes to polymorph A through B. We investigated the effect of the environmental temperature on the interconversion of polymorph C. This was done to determine the effect that heat generated during grinding could have on polymorph C.

Samples of polymorph C was kept at 50 and 75 °C respectively. At predetermined intervals samples were withdrawn and differential scanning colorimetric (DSC) curves and X-ray powder diffractograms recorded.

Both samples changed to polymorph B but only the sample kept at 75 °C changed into A during the time the experiment was run. Therefore temperature control during storage and handling, especially grinding, of polymorph C and B is recommended to prevent conversion to the poorly soluble and less bioavailable polymorph A.

Introduction

Grinding is often used as a technique to reduce the particle size of powders. Frequently however, not only desired changes in physical properties such as specific area and shape, but also polymorphic transformations may occur. These changes in physicochemical properties during grinding are dependent on the energy supplied to the materials and the environmental temperature during grinding[1].

The effect of grinding on the transformation of polymorphs of chloramphenicol palmitate (CAP) were studied and it was found that when polymorph C is grinded for a prolonged period it changes to polymorph A through B[2]. The rate of interconversion depended on the presence of seed crystals of the stable form A[3]. If such crystals were present the rate of interconversion increased. When polymorph B was heated for 1600 minutes at 82 °C it changes completely to the less soluble and less bioavailable polymorph A[4].

We investigated the effect of the environmental temperature on the interconversion of polymorph C. This was done to determine if heat generated during grinding could have caused the conversion of polymorph C to polymorph A.

Experimental

Material: Chloramphenicol palmitate (Batch no. CMM 23B) supplied by Fine Chemicals (Cape Town, RSA) was used.

Preparation of polymorphic forms: Polymorph A, B and C were prepared as described by Aguiar **et al.**[5].

Identification of polymorphs: X-ray powder diffractograms and DSC curves of samples were used to identify the three forms.

X-ray powder diffractograms: The X-ray diffraction profiles were measured at room temperature with a Phillips PM9901/00 diffractometer. The measurement conditions were as follows: target, CoKα; filter, Fe; voltage, 40 kV; current, 20 mA; slit, 0.2; counting range, 2×10^2 cpm; scanning speed, 1°/min. About 100 mg of the sample was loaded into a aluminium sample holder without introducing a preferred orientation of the crystals.

Thermal analysis: Differential scanning calorimetry (DSC) curves were measured with a Du Pont 910 DSC system. The measurement conditions were as follows: sample weight, ± 5 mg; sample cell, an aluminium crimp cell; N_2 gas flow, 30 ml/min; heating rate, 10 °C/min.

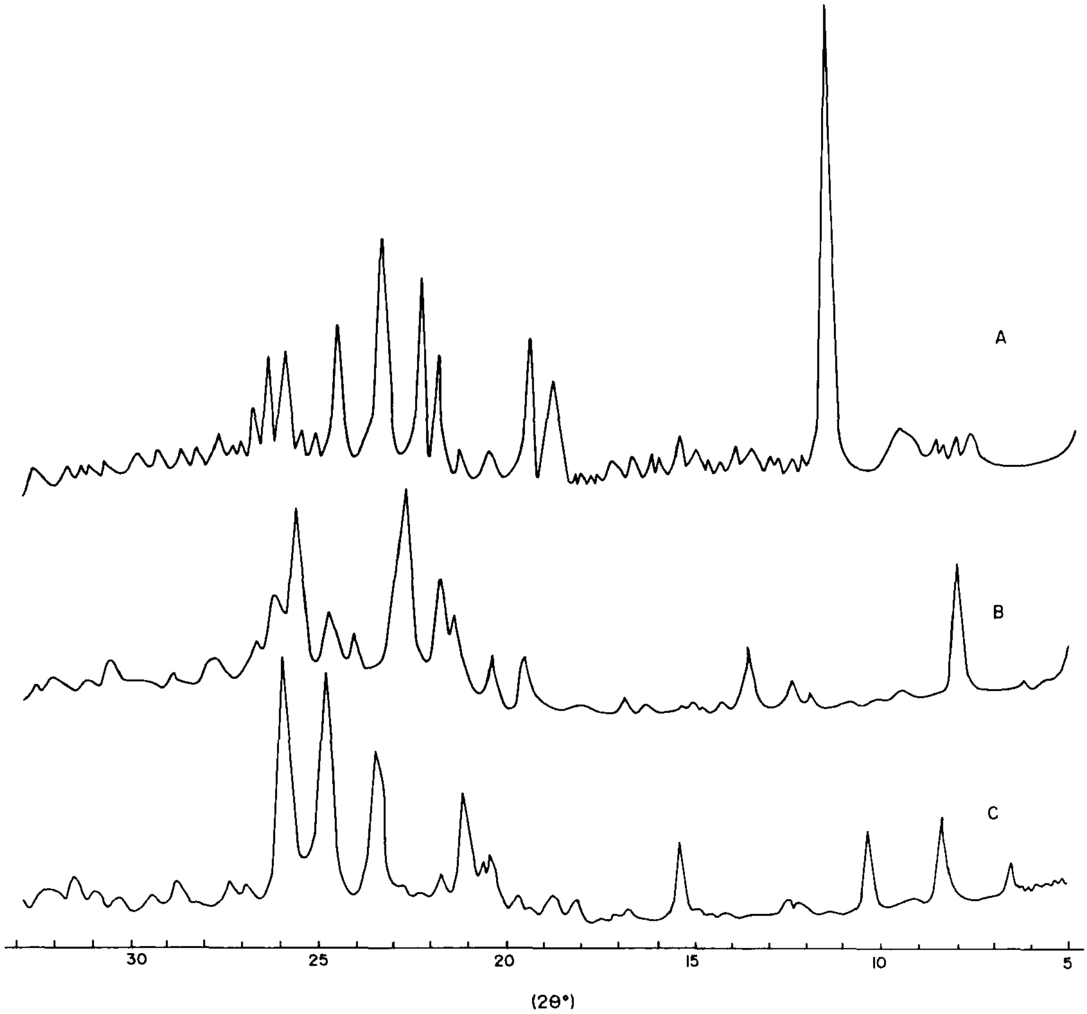

FIGURE 1

X-ray diffraction profiles of polymorphs of CAP a) form A b) form B and c) form C.

Kinetic study of isothermal transition of form C to form A: A sample, 15 g of polymorph C, was stored in a desiccator containing silica at 50 and 75 ± 1 °C. About 100 mg samples was withdrawn at appropriate intervals and the DSC curves measured. When a change in the curves was noticed the change was confirmed by recording a X-ray diffractogram of the sample.

TABLE 1

Main X-ray diffraction peak angles of polymorphs of CAP.

Form A		Form B		Form C	
2θ°	I/Io	2θ°	I/Io	2θ°	I/Io
11.6	1.00	23.0	1.00	26.2	1.00
23.6	0.57	25.8	0.92	25.0	0.94
22.5	0.48	8.3	0.72	23.7	0.65
24.8	0.40	21.9	0.64	21.3	0.49
19.5	0.34	25.0	0.50	8.7	0.39

Results and discussion

Figure 1 and Table 1 show the X-ray diffraction profiles and main diffraction peak angles of the polymorphs of CAP. The X-ray diffractograms agreed with that found in the literature. Figure 2 show the melting points of polymorphs of CAP. Form A and B showed an endothermic peak, because of fusion, at 90.6 and 86.5 °C respectively. Form C showed an exothermic peak at 65.0 °C, because of the transformation into B and an endothermic peak at 86.5 °C. The transformation of form C to B at 65.0 °C was confirmed by X-ray analysis[2].

Figures 3 and 4 shows the changes in the DSC curves with time for samples of polymorph C kept at 50 and 75 °C. When form C has transformed to form B the exothermic peak at 65.0 °C disappeared while the change of form B to form A is represented by the appearance of a endothermic peak at 90.6 °C. According to the DSC curves form C changed into form B within 600 min at 50 °C and within 240 min at 75 °C. Form B only changed completely to form A after 3200 min at 75 °C but after 600 minutes a small amount of form A was already present.

Kaneniwa and Otsuka[2] found a good linear calibration curve when they plotted the content of form B or A against the natural logarithm of the ratio in the intensity of the main diffraction peaks of the different forms. Figure 5 shows the relation between contents of polymorphs of CAP and X-ray diffraction intensity ratios at 2θ° = 23.0 and 26.2 for the relation between form B and C and at 2θ° = 11.6 and 23.0 for the relation between form A and B. The plots each gave a straight line of $r = 0.999$ and 0.998 respectively.

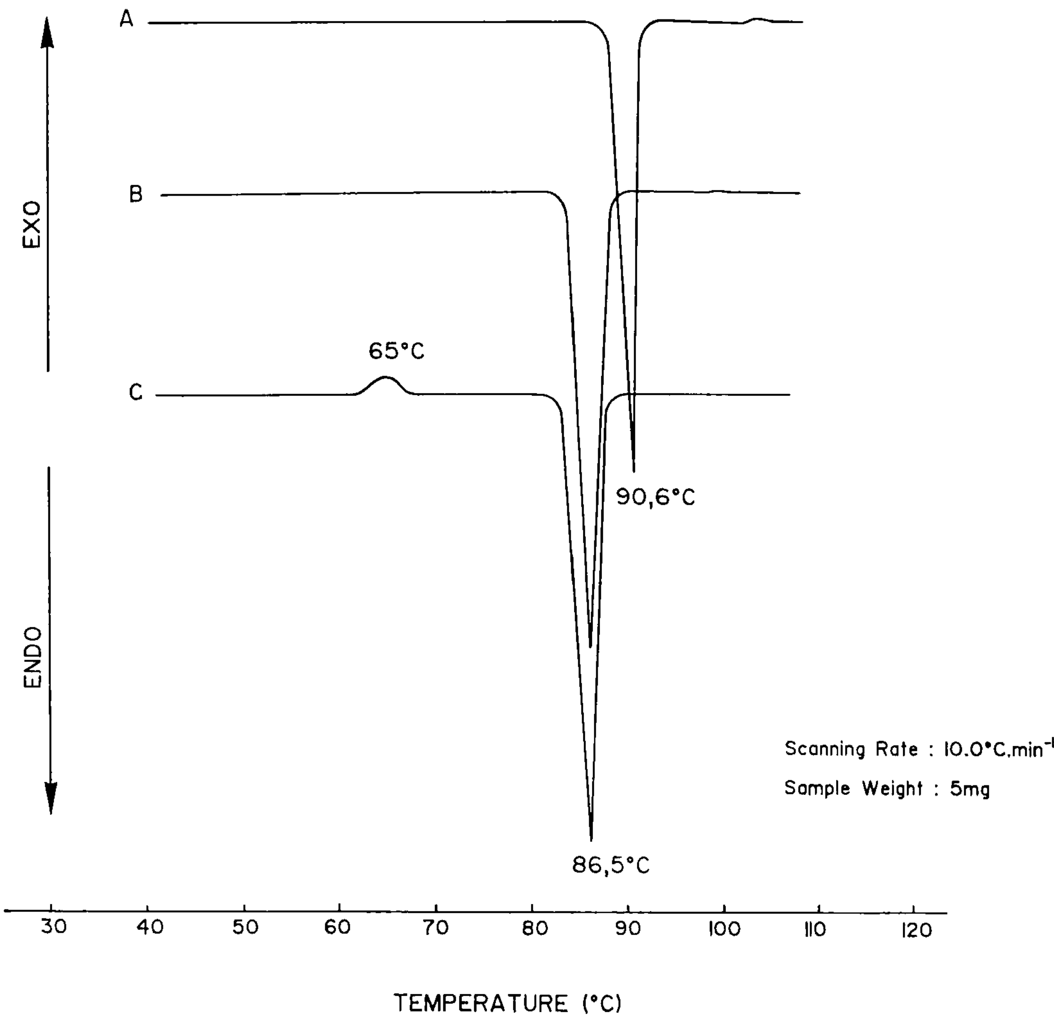

FIGURE 2

DSC curves of polymorphs of CAP a) form A b) form B and c) form C.

Table 2 shows the percentage of each polymorph present with time calculated from the data in figure 5 and the change in X-ray diffraction intensity ratios. Form C kept at 50 °C changed completely into B after 600 minutes but form B did not change to A during the 3200 minutes the sample was examined. However at 75 °C form C changed to B within 240 minutes. After 480 minutes 1.3 % of the inactive form A was present and after 3200 minutes it has changed almost completely to A.

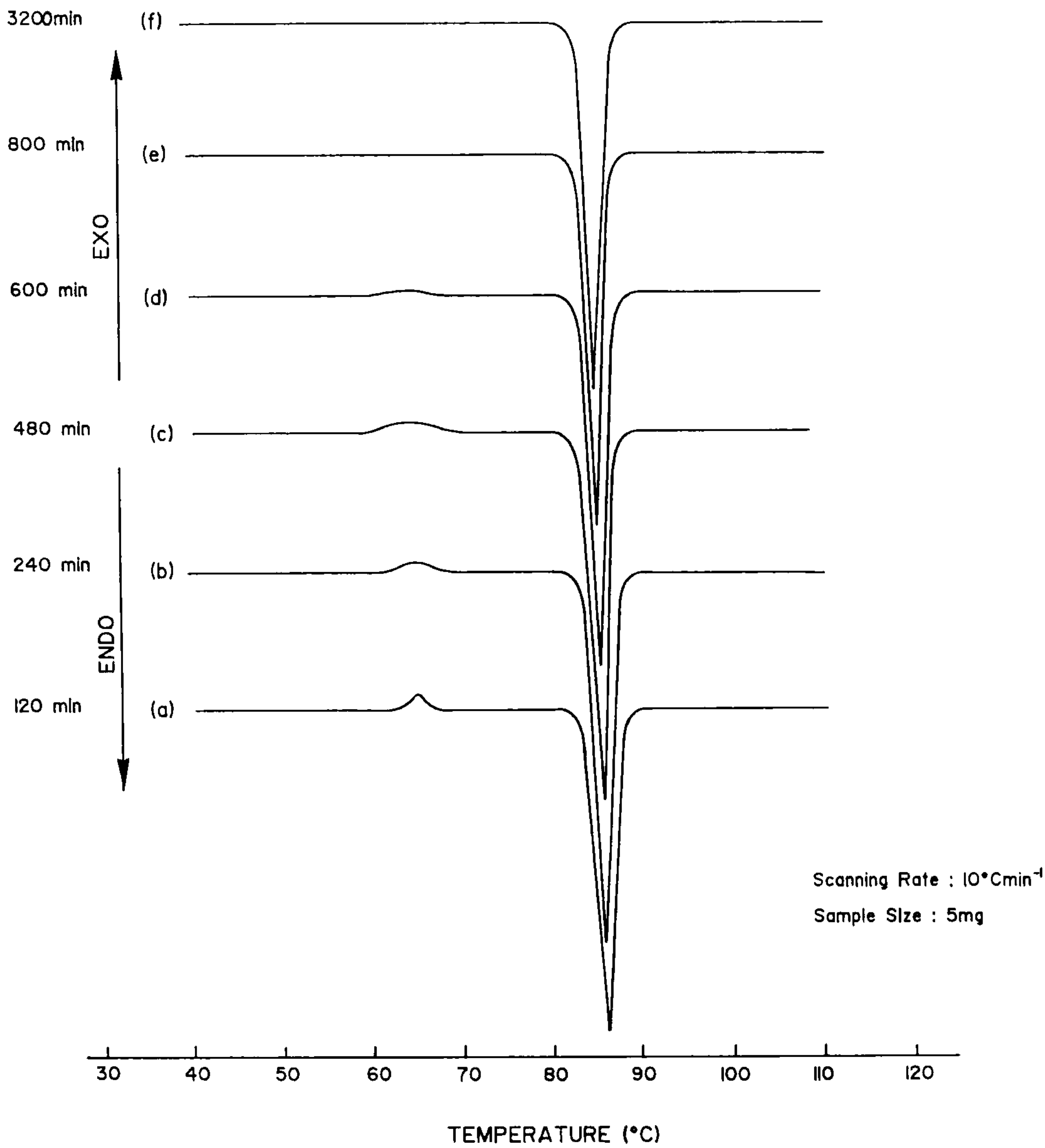

FIGURE 3

Change in DSC curves of form C when kept at 50 °C.

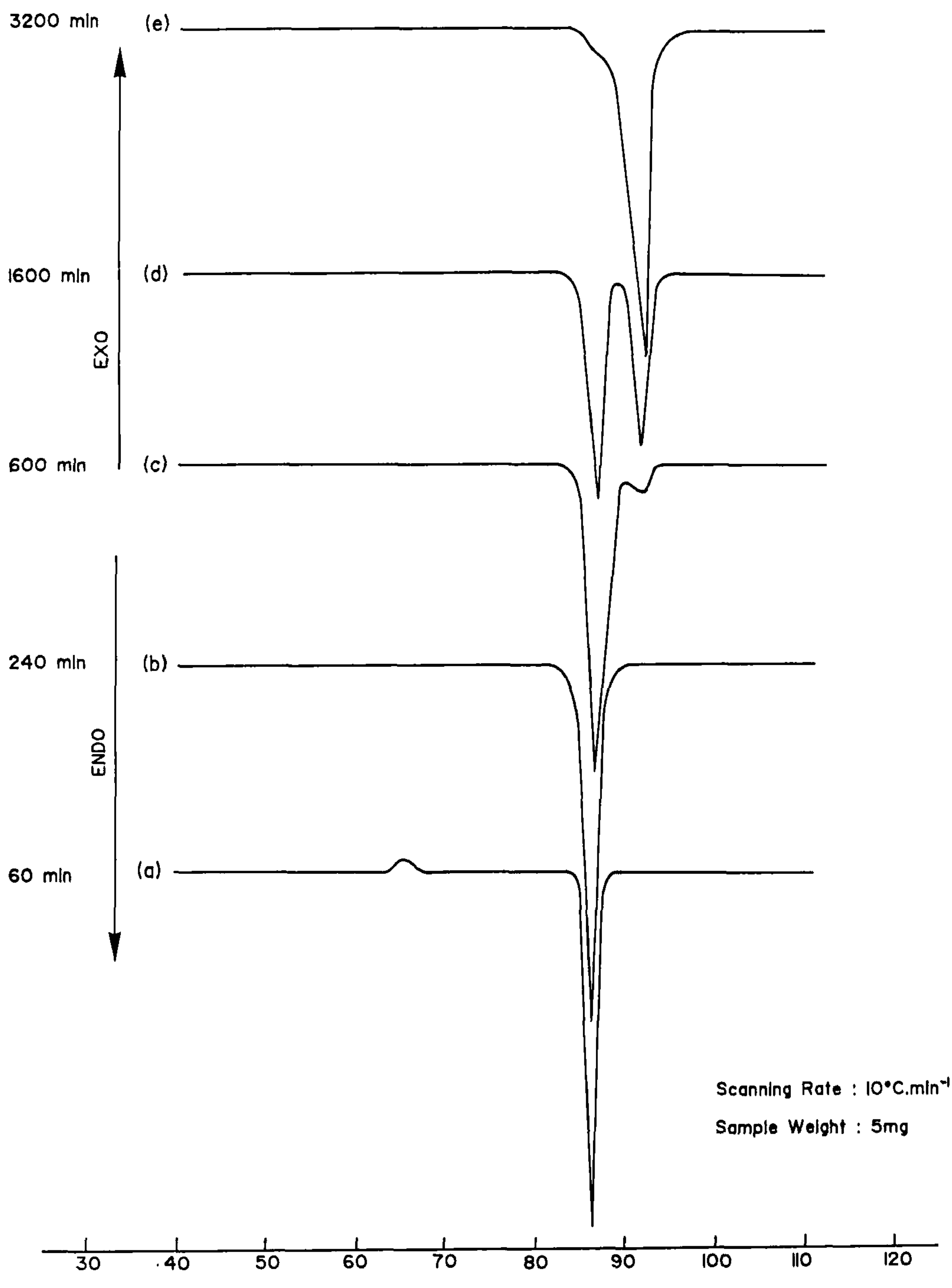

FIGURE 4

Change in DSC curves of form C when kept at 75 °C.

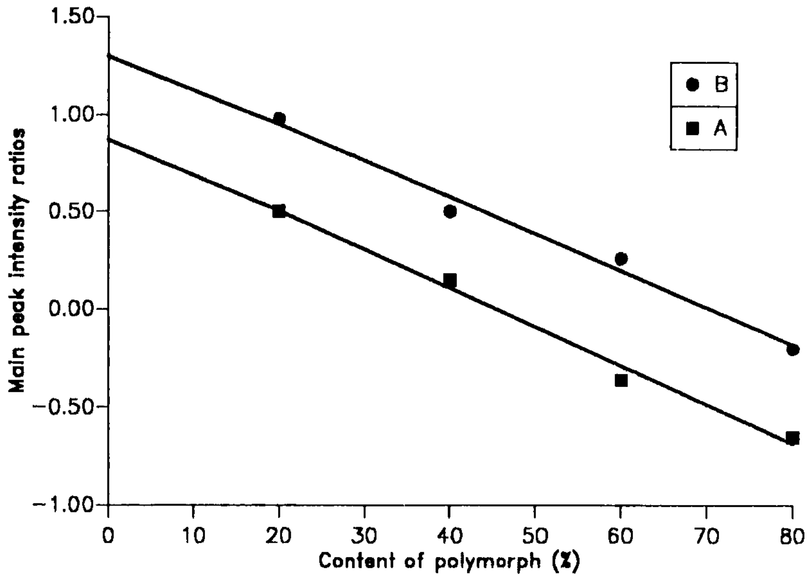

FIGURE 5

Relation between content of polymorphs of CAP and X-ray diffraction intensity ratios (I/Io) A) relation between Form C and B at $2\theta° = 26.2$ and 23.0 and B) between form B and A at $2\theta° = 23.0$ and 11.6. The markers represent measured values and the lines the best fit.

TABLE 2

The percentage of each polymorph present with time calculated from the data in figure 6 and X-ray diffraction intensity ratios.

Time		50 °C			75 °C	
(min)	A	B	C	A	B	C
60	0.0	0.0	100.0	0.0	13.0	85.0
120	0.0	38.2	61.2	0.0	54.2	42.0
240	0.0	54.7	45.3	0.0	98.2	0.0
480	0.0	92.5	7.5	1.3	95.8	0.0
600	0.0	100.0	0.0	9.8	87.1	0.0
800	0.0	100.0	0.0	29.6	65.2	0.0
1600	0.0	100.0	0.0	46.6	51.1	0.0
3200	0.0	100.0	0.0	94.2	3.0	0.0

Conclusion

When the metastable polymorphs of CAP (form C and B), which are therapeutically active, is subjected to temperatures above 65 °C for prolonged periods it changes to the therapeutically inactive form A. Below the transition temperature between C and B (65 °C) the interconversion of form B to form A do not happen that readily.

Mechanical treatment eg. by grinding may lead to an increase in the environmental temperature which in turn may cause interconversion of the polymorphic forms. During grinding the temperature inside the grinder may not rise above 65 °C but the temperature at the contact points between the mechanical parts of the grinder and the crystals may be higher than 65 °C (because of friction).

Therefore temperature control during storage and handling of polymorph C and B is recommended to prevent conversion to the poorly soluble and less bioavailable polymorph A.

References

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