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Interconversion Kinetic Studies of Betamethasone Acetate Polymorphs in Water

Xue Ke and QiNeng Ping
Department of Pharmaceutics, China Pharmaceutical University, Nanjing 210009, People's Republic of China

ZhengGen Liao
Key Laboratory of Modern Preparation of TCM of Ministry of Education, Jiangxi Chinese Medical University, Nanchang 330004, People's Republic of China

ABSTRACT This study assessed the effect of polymers on the transformation of polymorphs of betamethasone acetate (BA) when suspended in water. The results showed that the polymers, in particular HPMC E5, retarded the transition of the forms Iα and Iβ. However, the form Iα, as the metastable form, with the aid of HPMC E5, was preferred for BA suspension preparation through kinetic studies, while the form Iβ was not suitable due to its instability in water.

KEYWORDS Betamethasone acetate, Polymorph, Kinetic study, Polymer, Metastable form, Transformation retardation

INTRODUCTION

The physical stability and the bioavailability of the various crystal forms may be affected by their interconversion, especially if such process occurs in their suspension formulation. Solvent-mediated transformation in suspension transforms the unstable polymorph to a stable polymorph via dissolution and crystal growth processes (Brittain, 1994). Unless there is inhibition, such changes may lead to marked variance in the performance of the suspension formulations. The use of various additives to stabilize drug polymorphs was first suggested by Higuchi and by Frederick (Higuchi, 1958; Frederick, 1961). Since then, the effect of the polymer on the transformation of crystalline drugs has received considerable attention.

Betamethasone acetate (BA) was selected as the drug for this study. Nurnberg and Seiller reported that BA had three polymorphic forms (form II, Iα, Iβ), and a hydrate form (Nurnberg & Seiller, 1988). We studied the transformation of these polymorphic forms of BA in water (Ke et al., 2005). According to our results, form II exhibited the most stable properties in water; whereas the other three forms were unstable which transform form II. The transformation process of each form was distinct. Form Iα changed to form II directly, while form Iβ changed to form Iα and II initially, and then to form II. In water, the hydrate transferred to form II when the temperature was above 60°C. In theory, form II is suitable for the suspension preparation, but the crystallization and purification of form II can be complicated, as shown by Nurnberg and Seiller who were unable to obtain a pure form II in their 1988 experiment (Nurnberg & Seiller, 1988). Rather, they worked with a needle

Address correspondence to QiNeng Ping, Department of Pharmaceutics, China Pharmaceutical University, Nanjing 210009, P. R. of China; Tel: +86-25-83271098; E-mail: pingqn2004@yahoo.com.cn

shaped version of form II that was not suitable for the preparation and stability of the suspension. At the same time, it's well known that the metastable forms might result in higher bioavailability (Singhal & Curatolo, 2004; Snider et al., 2004). The present study investigates the properties of metastable forms to serve for BA suspension formulation in which a suitable polymer can retard or inhibit BA polymorphs transition in water by using kinetics methods.

MATERIALS AND METHODS

Materials

Betamethasone Acetate was purchased from Shanghai Hualian Pharmaceutics Co. Ltd. HPMC (E5, Shanghai Colorcon Coating Co., Ltd, Shanghai, China), sodium carboxymethyl cellulose (CMC, Sinopharm Group, Chemical Reagent Co., Ltd, Shanghai, China), and polyvinylpyrrolidone (PVPK 12, Shanghai BASF Co., Ltd, Shanghai, China) were donated. Other reagents were of analytical grade.

Preparation and Polymorph Characterization of Samples

Nurnberg and Seiller's experiment resulted in three anhydrous phases: form II, Iα, Iβ, and a hydrate with a single water molecule. The preparation methods were reported in our previous paper (Ke et al., 2003; Ke et al., 2005). The pure form II was prepared by slowly cooling a hot, saturated acetone solution at a controlled rate. Form Iα was prepared by heating the acetone solution at 70°C until it became solid. The hydrate was derived from form Iα after grinding with water at room temperature for one hour, and the form Iβ was the transformation of the hydrate when heated in an oven maintained at 160°C for 15 min.

The melting points of forms II, Iα and Iβ were 150°C–156°C, 210°C–212°C, and 222°C–224°C, respectively. There was one water molecule in the hydrate according to the TGA profile.

Effect of Polymers on the Transformation Rate of BA Polymorphs in Water

According to our previous studies (Ke et al., 2005), form II was the most stable polymorph in water without any conversion. The remaining forms: Iα, Iβ, and hydrate were chosen for kinetic studies. Aqueous suspensions of the three polymorphs, each containing a known quantity of additive (1% HPMC E5, 0.2% CMC, or 5% PVP K12) were prepared. The suspensions were shaken at 100°C ± 0.5°C for some time in a shaking water bath (CHZ82, Changzhou Guohua Scientific Company, Changzhou, China). The samples were withdrawn, filtered and dried at 40°C for 24 hr under vacuum. The solid powder was determined by DSC and PXRD.

Preparation of Calibration Curves

A powder X-ray diffraction (PXRD) technique was developed to quantify the relative amount of crystal form in the mixture. This method is based on the pronounced differences between the PXRD patterns of the three polymorphs. The characteristic diffraction angles 2θ that distinguish the three forms are: 16.96 ± 0.06° for the form II; 12.64 ± 0.06° for the form Iα, and 13.42 ± 0.10° for the form Iβ, respectively (Ke et al., 2005).

The first series of mixtures were prepared containing various ratios of the form Iα with the form II. The PXRD values of the mixtures were recorded. The relative intensity of form Iα in mixtures with different ratios was calculated to obtain a calibration curve.

Another series of mixtures was prepared with varying quantities of the three forms. The PXRD values of the mixtures were again recorded. The relative intensity of the form Iβ in mixtures with different ratios was measured and calculated.

Kinetic Studies of Form Iα Suspended in Water

The rate of transformation was studied by preparing 1% (w/v) suspensions of form Iα in distilled water or 1% HPMC solution and placing them in a shaking water bath at 90°C, 95°C, and 100°C. The samples of each suspension were filtered at periodic intervals and dried at 40°C for 24 hr under vacuum and detected by PXRD. The residual fraction of form Iα was determined by the calibration curve.

In the seeding experiment, the form II seed corresponding to 5% by weight of the form Iα was introduced into the suspension, which was placed at 100°C, 90°C, and 80°C. The other procedures were similar.

Kinetic Studies of Form Iβ Suspended in Water

To measure the conversion rate of form Iβ in water, the form Iβ was suspended in distilled water or 1% HPMC solution at 90°C, 80°C, and 70°C. At appropriate times, the solid portion was separated by filtration and dried at 40°C for 24 hr under vacuum for PXRD analysis. The ratio of the form Iβ in the mixture was determined using the calibration curve based on PXRD data of these specimens.

X-ray Powder Diffraction

X-ray powder diffraction (PXRD) diffractograms were recorded for BA polymorphs on an automated diffractometer using CuKα radiation (MO3XHF$_{22}$, MAC Science, Japan). The powder was ground in a ball mill (QM–3P, Nanjing University Instrument Factory, Nanjing, China) for 5 min using a sample holder and ball made of agate. The samples were screened through a 250 μm sieve before being packed into standard aluminum sample holders. This eliminated the preferred orientation of crystals during analysis. The powder patterns were recorded under the following conditions: 40 kV; 40mA; range 4°–40° (2θ).

Thermal Analysis

The thermal behavior was studied by heating ±3 mg of the powdered samples at the rate of 5°C/min from 30°C to 250°C with a differential scanning calorimeter (DSC204, Netzsch Company, Germany).

RESULTS AND DISCUSSION

Effect of Polymers on the Transformation Rate of BA Polymorphs in Water

According to our previous study (Ke et al., 2005), the Iα could transform into form II when suspended in water. The effect of polymers on the transformation of form Iα in water is shown in Fig. 1. When suspended in distilled water, the three polymers retarded the transition of form Iα into the form II. HPMC was found to show the large retardation effect.

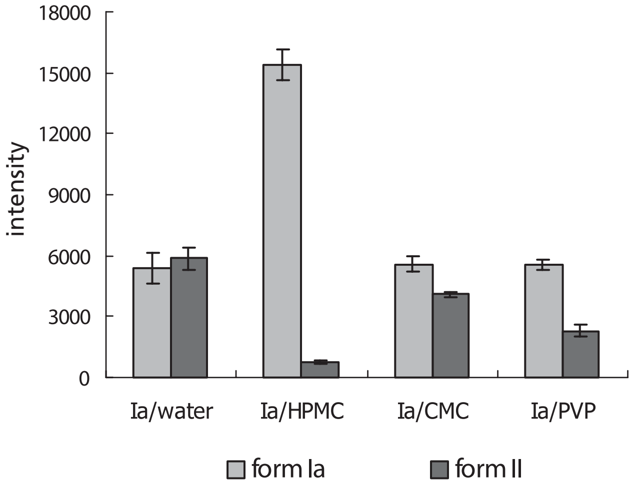

FIGURE 1 **PXRD Results of Form Iα Suspended in Polymer Solutions at 100°C for 6 hr (*n* = 3). Characteristic Diffraction Angles 2θ Are 12.64 ± 0.06° for the Quantity of Form Iα, and 16.96 ± 0.06° for Form II.**

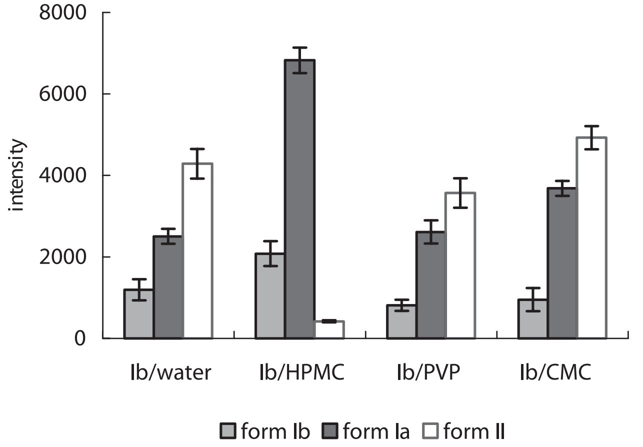

FIGURE 2 **PXRD Results of Form Iβ Suspended in Polymer Solutions at 100°C for 1 hr (*n* = 3). Characteristic Diffraction Angles 2θ Are 12.64 ± 0.06° for the Quantity of Form Iα, 16.96 ± 0.06° for Form II, and 13.42 ± 0.10° for Form Iβ.**

In our previous study, form Ib suspended in water changed to form Ia at the initial period, and then to the form II. The presence of polymers retarded the transformation of form Ib in water as shown in Fig. 2. HPMC was more effective than PVP and CMC. The conversion from form Ib to form II was completely inhibited in HPMC solution. The intensity of the characteristic peak of form Ia in HPMC solution showed a significant difference from others, which was due to complete transition inhibition to form II.

The change of the hydrate in the polymer solutions was detected by DSC. The hydrates in different polymer solutions transferred to the form II after heating at 100°C for some time through a dehydration process. Therefore, it's assumed that polymers have no retarding effect on the dehydration. PXRD gave further evidence of this phenomenon.

It is well known that the effect of polymers may be related to the relatively high viscosity of their aqueous solutions that retards the diffusion-controlled processes involved in the polymorphic transformation. This, in turn, slows down both the new nuclei formation and growth rate (Ebian, et al., 1973).

However, the viscosity of the three polymer solutions were very low (2–4 cps) in the experiments. The above results suggest that the transformation retarding effect was related to the direct absorption of the polymers on the crystal surface more than to viscous effect.

In his study on the crystal transformation of sulfathiazole (Simonelli et al., 1979), Simonelli suggested that the PVP must be strongly bound to the crystal surface in order to complete inhibition of crystal growth. A model was depicted to explain this phenomenon, in which the polymer forms a noncondensed netlike film over the crystal surface where drugs grow out through the openings of the net. The model indicated that the crystal growth would require a correspondingly larger supersaturation ratio due to the formation of the net, i.e., the crystal growth would be inhibited by the polymers attached to the crystal surface. The theory can be used to explain why the three polymers exhibited the retardation effect in the present study. At the same time, it's possible that the different retardation effect depends on the polymer's structure and the interaction between the polymer and the drug. Further work is required to validate this assumption.

In our study, the polymers showed different inhibiting or retarding transformation effects. HPMC was chosen as an effective transformation-retarding agent for forms Iα and Iβ of BA in further kinetic studies.

PXRD Calibration Curves

A good linear calibration curve was obtained (Fig. 3) by plotting the content of forms Iα and Iβ against the logarithm of the relative intensity ratios of the specific diffraction peaks. The curves were used for the quantitative analysis of forms Iα and form Iβ in the mixture.

Kinetic Studies of the Form Iα Suspended in Water

In three different solutions, the residual fraction of form Iα in suspensions was calculated according to Curve-1 by comparing the characteristic peak intensity of form Iα at different times with the initial intensity.

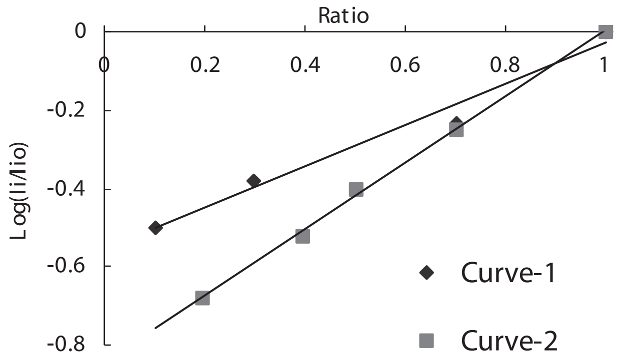

FIGURE 3 Calibration Curves for Form Iα (Curve-1) and Form Iβ (Curve-2) in the Mixture by PXRD (R^2 is 0.98 for Curve-1, R^2 is 0.998 for Curve-2).

The residual fraction of form Iα vs. time in three solutions at different temperatures were plotted as shown in Figs. 4–6

A plot of the remaining percentage of form Iα vs. time was linear by statistic treatment, suggesting that this process was approximately zero order. The zero-order rate constants and derived kinetic parameters according to the Arrhenius rule are shown in Table 1.

Form Iα was unstable in water. It took 1184 days (about three years) to transform 50% of form Iα at room temperature. Moreover, the transformation rate was highly temperature-dependent, as it may be accelerated at higher temperatures, such as a sterilization temperature, which meant that the high temperature

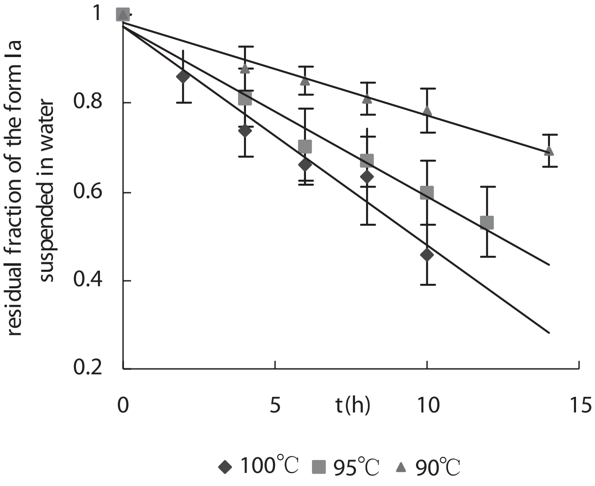

FIGURE 4 Residual Fraction of Form Iα During Transformation to Form II When Suspended in Distilled Water at Different Temperatures.

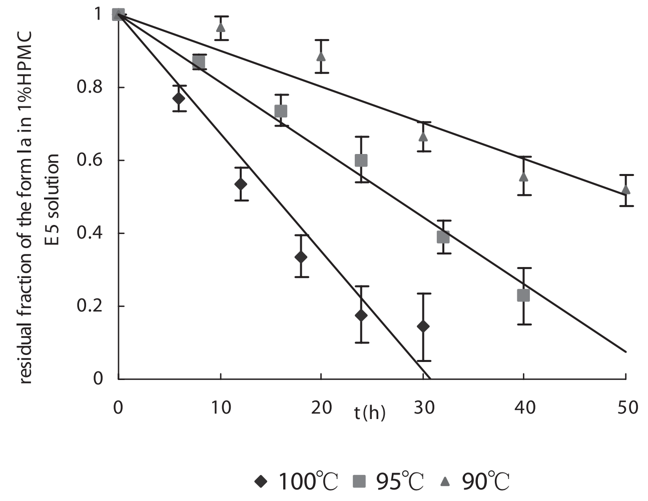

FIGURE 5 Residual Fraction of Form Iα During Transformation to Form II When Suspended in 1% HPMC E5 Solution at Different Temperatures.

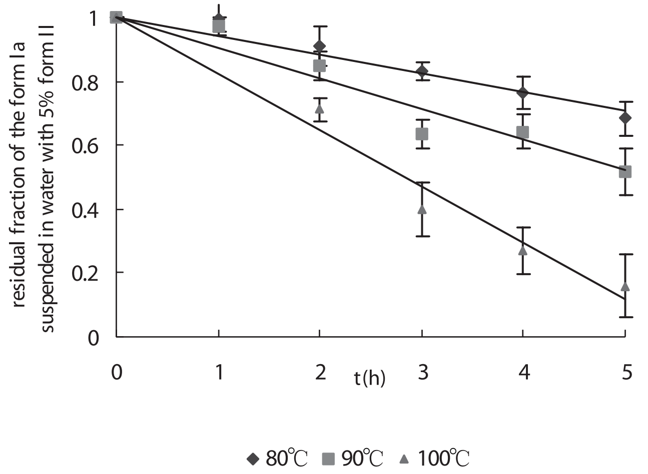

FIGURE 6 Residual Fraction of Form Iα During Transformation to Form II When Suspended in Distilled Water Seeding With Form II at Different Temperatures.

in the process of preparation would result in the transition of form Iα.

The additive-HPMC can markedly decrease the transition rate of form Iα when suspended in water (Table 1), which causes the transformation to occur very slowly at room temperature. It should be noted that the thermodynamically unstable form always tends to transform into the stable counterpart at room temperature, but the transformation may be kinetically hindered, as was the case for the example in this study.

On the other hand, the seed of form II showed the opposite effect, which was to accelerate the conversion. It takes only 22 days to convert 50% of the Iα at room temperature. It seemed that the nucleation was the rate-determining step of the transformation of form Iα to form II when suspended in water. Seeding with form II accelerates the conversion.

To summarize, although form Iα was not the most stable form in water, the addition of HPMC can apparently prevent the transformation of form Iα at room temperature, which makes it feasible for suspension formulation. Under ordinary sterilization conditions, for example, at 100°C for 0.5 hr, HPMC still effectively inhibits the transition of form Iα. However, it is important that the purity of form Iα is maintained when it is used for the suspension. A small amount of form II will obviously quicken the transition rate and affect the physical stability of suspension.

Kinetic Studies of Form Iβ Suspended in Water

The remaining percentages of form Iβ suspended in two solutions at different temperatures are shown in Fig. 7 and Fig. 8 according to Curve-2 and the transition process of form Iβ was approximately zero order by statistic treatment, similar to the transformation of form Iα in a solution.

The rate constants and the kinetic parameters for the transformation process were calculated. Results of this treatment were shown in Table 2.

Compared with form Iα, form Iβ was rather unstable in water. The calculated half-life at 25°C for form Iβ was only 80 days, which was extended to 115 days

TABLE 1 Kinetic Parameters for the Transformation of Form Iα Suspended in Different Solutions (*n* = 3)

Solution	Rate constant k, (h^{-1}) 80°C	90°C	95°C	100°C	R^2	$t_{1/2}$, 25°C (day)	Ea (kJ/mol)
Distilled water	–	0.0228 ± 0.0004	0.0412 ± 0.0024	0.0531 ± 0.0058	0.95	1184	95.35
1% HPMC E5	–	0.0099 ± 0.0005	0.0185 ± 0.0005	0.0325 ± 0.0026	0.9995	46237	133.9
Seeding with form II	0.0584 ± 0.0024	0.0958 ± 0.0094	–	0.1760 ± 0.0175	0.994	22.5	60.32

TABLE 2 **Kinetic Parameters for the Transformation of Form Iβ Suspended in Different Solutions (*n* = 3)**

	Rate constant k, (h^{-1})					
Solution	70°C	80°C	90°C	R^2	$t_{1/2}$, 25°C (day)	Ea (kJ/mol)
Distilled water	0.0653 ± 0.0095	0.2005 ± 0.0176	0.4374 ± 0.0339	0.992	80	98.97
1% HPMC E5	0.0506 ± 0.0046	0.1021 ± 0.0082	0.3383 ± 0.0088	0.97	115	98.51

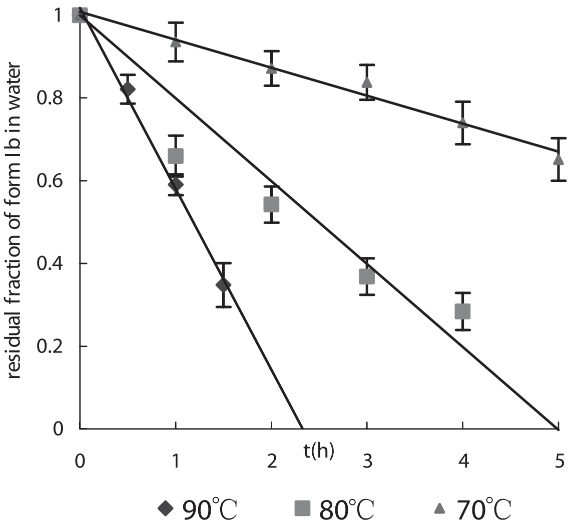

FIGURE 7 **Residual Fraction of Form Iβ Suspended in Distilled Water at Different Temperatures.**

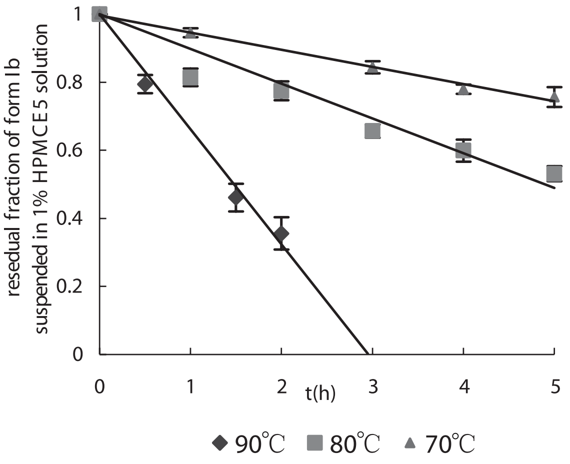

FIGURE 8 **Residual Fraction of Form Iβ Suspended in 1% HPMC Solution at Different Temperatures.**

with the aid of HPMC E5. This implied that HPMC E5 was unable to effectively retard the transition of form Iβ in water. The same result can also be observed from the data on the activation energy. The value of activation energy was very similar, 98.51 kJ/mol for the transformation of form Iβ suspended in 1% HPMCE5 solution, compared with 98.97 kJ/mol of the form Iβ. Therefore, it was concluded that form Iβ was not suitable for the preparation of the suspension of BA.

CONCLUSIONS

Through the quantitative study of BA polymorphic transformation in distilled water, the results of the present investigation would recommend the use of form Iα in pharmaceutical suspension preparations with the aid of HPMC E5 to keep it in this metastable state.

The formulation of metastable polymorphs in pharmaceutical suspensions might be desirable, provided that adequate measures are taken to keep them in such a state for the expected shelf life of the preparation. This study provides a model of the possible use of additives to stabilize a metastable polymorph of higher solubility. This method may be advantageous for the formulation design of those polymorphic drugs with the problem of bioavailability.

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