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Effect of crystal form, cortisone alcohol and agitation on crystal growth of cortisone acetate in aqueous suspensions

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Particle size distribution in aqueous suspensions of stable and unstable crystal forms of cortisone acetate under conditions of agitation and different degrees of saturation with cortisone alcohol is described. Agitation accelerated the diffusion-controlled processes of dissolution and crystallization, leading to the formation of a high proportion of large particles. Cortisone alcohol inhibited the polymorphic transformation necessary for the crystal growth and formation of the water-stable form. The mechanism of action is discussed.

THE standard particle size distribution changes in aqueous suspensions of cortisone acetate have been described by Carless, Moustafa & Rapson (1968). Dissolution and crystal growth under special conditions which are relevant to the polymorphic system of cortisone acetate (Carless, Moustafa & Rapson, 1966) are now examined.

In a review on dissolution rates, Wurster & Taylor (1965) outlined the factors influencing the dissolution rate. Temperature and agitation were mentioned as factors affecting the total physical system, other factors arise from changes in the solute particles or dissolution medium. These factors should also apply to the reverse process of crystallization, both processes—dissolution and crystallization—being considered as heterogeneous reactions in which mass transfer is effected through the net result of escape and deposition of solute molecules at a solid surface.

Polderman, Bloo & Fokkens (1958) found that addition of small quantities of cortisone alcohol could completely prevent crystal growth in suspensions of the acetate. Qualitative experiments showed that there was a retardation of the rate of growth which was approximately proportional to cortisone concentration. This was coupled by a similar retardation of the polymorphic transformation leading ultimately to the water-stable Form IV* (Moustafa, 1967). The quantitative aspect of the effect of cortisone alcohol and its mechanism of action were thought to be worth further investigation.

Therefore, the factors to be examined that would affect the cortisone acetate system, are the use of the water-stable Form IV* (Moustafa, 1967), the effect of agitation, and the introduction of additives such as cortisone alcohol.

Experimental

APPARATUS AND MATERIAL

The cortisone acetate, Coulter Counter and its method of use were described previously (Carless & others, 1968). Cortisone alcohol, shown to be of high purity by thin-layer chromatography (Moustafa, 1967), was also used.

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PREPARATION OF SUSPENSION AND COUNTING TECHNIQUE

When the effect of cortisone alcohol was examined, 10 and 20 mg amounts were dissolved in 100 ml of 0·9% sodium chloride solution by shaking for 48 hr then filtering through filter paper and a number 3 sintered glass Pyrex filter. These solutions will be referred to as being half and fully saturated with respect to cortisone. The preparation of the suspension and the counting technique adopted were the same as described by Carless & others (1968), except when the effect of crystal form was examined. In this instance the suspension was prepared in 0·9% sodium chloride solution and left standing for a time sufficient to ensure transformation to the water-stable Form IV* (about 15 hr). The supernatant solution was decanted and the residue was ground under a little of this solution in an agate mortar for 10 min and then diluted with fresh 0·9% sodium chloride solution.

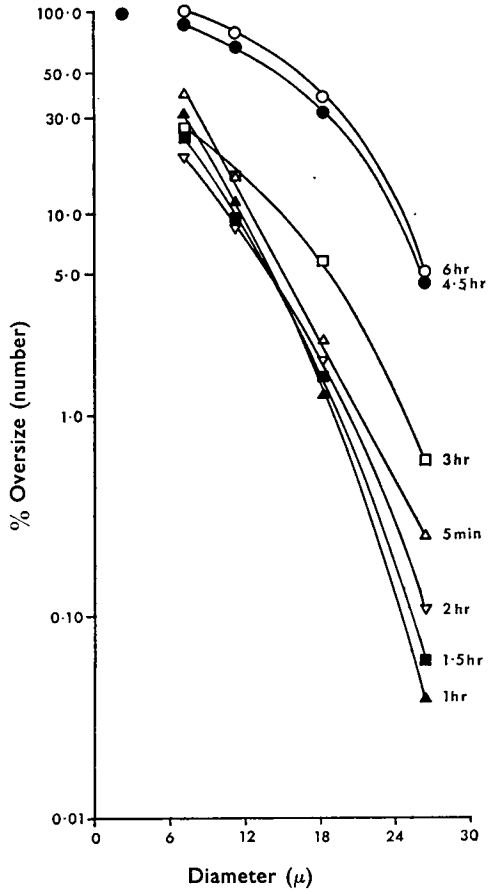

FIG. 1. Change in particle size distribution with time of suspension of cortisone acetate (Agitation at 100 rev/min).

Suspensions were kept undisturbed at 25° ± 1·5° and shaken briefly before taking a sample for analysis. To investigate the effect of agitation, the weighing bottle containing the suspension was rotated at a constant speed of 100 rev/min.

Microscopical and infrared examinations were also made at various stages of the process to observe any changes in shape, size or crystal form of the solid cortisone acetate.

Results

Data recorded for the different experiments were found to be best expressed as plots of percentage number cumulative frequency oversize on a log scale, against the equivalent particle diameter (Carless & others, 1968).

EFFECT OF AGITATION

The effect of time of agitation (100 rev/min) on size distribution is shown in Fig. 1. Compared with the non-agitated suspension (Carless & others, 1968), there was an acceleration in growth rate. This growth can be seen from the increase in cumulative count with time (Fig. 2). Agitation

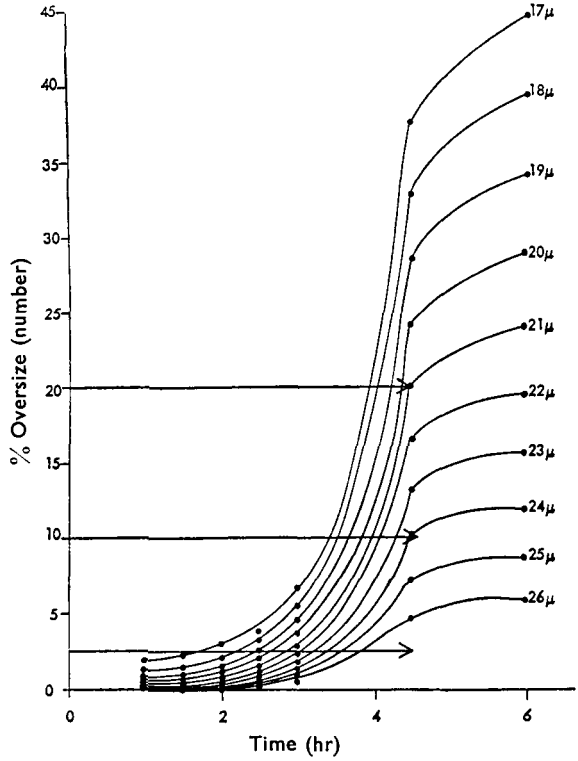

FIG. 2. Change in cumulative count with time of suspension of cortisone acetate (Agitation at 100 rev/min). Curves from top downwards represent diameters of 17–26μ.

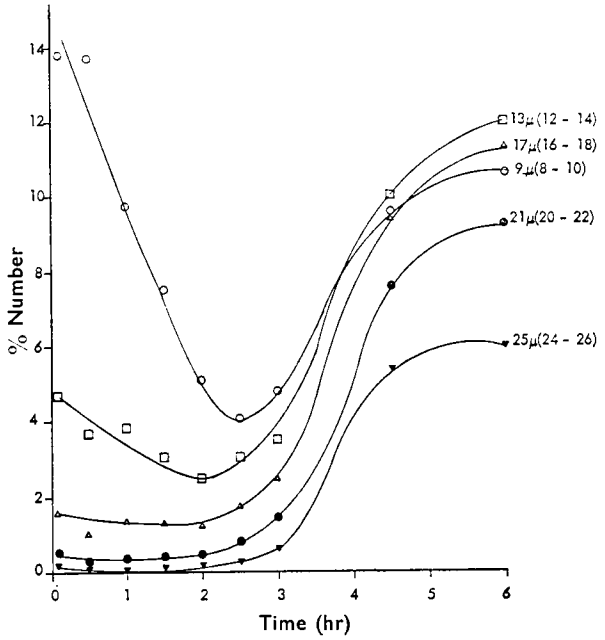

FIG. 3. Change in frequency percentage with time of suspension of cortisone acetate (Agitation at 100 rev/min).

also favours the formation of large particles, thus leading to a situation where towards the end of the growth process, almost equal numbers of particles of various diameters are present. This is demonstrated in Fig. 3. This graph was derived from the cumulative frequency curves (Fig. 1) by finding the frequency at equal diameter intervals of 2 μ each by difference and plotting it against time. Rates of growth (Carless & others, 1968) above a cumulative frequency of 10 and 20% were 6·62 and 7·17 μ/hr respectively.

EFFECT OF CORTISONE ALCOHOL

The presence of cortisone alcohol retarded the crystal growth in aqueous suspensions of cortisone acetate. Fig. 4 compares the rate of growth (Carless & others, 1968) in the presence and absence of cortisone alcohol. Calculations on basis of this plot using the method of least squares showed that the rates of growth for the standard growth experiment, and the half and full saturation with respect to cortisone experiments were 2·87, 0·43 and 0·35 μ/hr respectively.

EFFECT OF CRYSTAL FORM

Very little change in size distribution of the ground material was observed when cortisone acetate was previously allowed to change to the water-stable form.

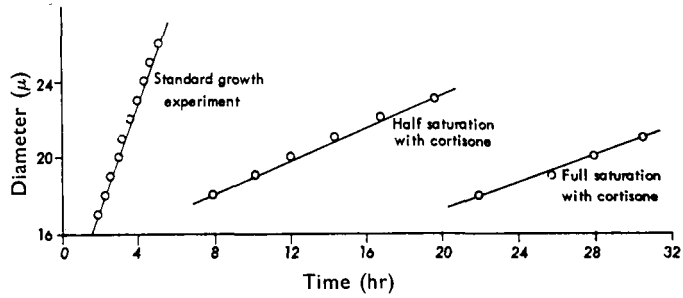

FIG. 4. Comparison of rates of growth (increase of diameter with time) in aqueous suspensions of cortisone acetate above 1% cumulative count.

No change in crystal form was observed by infrared spectroscopy when aqueous suspensions of the water-stable Form IV* were examined. Cortisone alcohol retarded both the crystal growth and polymorphic transformation from Form II to III. Agitation did not appear to shorten the time necessary for the polymorphic transformation to occur, although more large crystals were observed microscopically compared with growth under standard conditions.

Discussion

Results of the present investigation confirm the conclusions reached by Carless & others (1968) namely, that dissolution and crystal growth in the cortisone acetate system are mainly initiated by polymorphic transformation. Ostwald ripening in aqueous suspensions of the water-stable Form IV* of cortisone acetate was not significant.

To understand the mechanism of action of inhibiting agents such as cortisone alcohol and accelerating factors such as agitation, graphs of Fig. 3 type were established for both cases. The decrease in count with time in this type of plot was interpreted by Carless & others (1968) to represent mainly dissolution, whereas the increase in count represents predominant crystal growth on nuclei of the water-stable form. Curves representing similar diameters on different graphs were compared. For example, Fig. 5 shows the changes in count at 9 μ with time, for the growth under standard conditions and half and full saturation with respect to cortisone. From examination of this graph, it can be seen that there is a prolongation in the time necessary for the polymorphic process to proceed to an extent sufficient to provide enough nuclei to cause the inflexion in the curve. This agrees with qualitative results obtained from infrared spectroscopic identification of the forms and microscopical observation of the accompanying changes in shape and size. The question still remaining is whether cortisone inhibits the dissolution or the polymorphic process (and consequently the growth), or both. To answer this question, the rates at which the count decreases with time were calculated from the smooth curves in Fig. 5 at various time intervals and

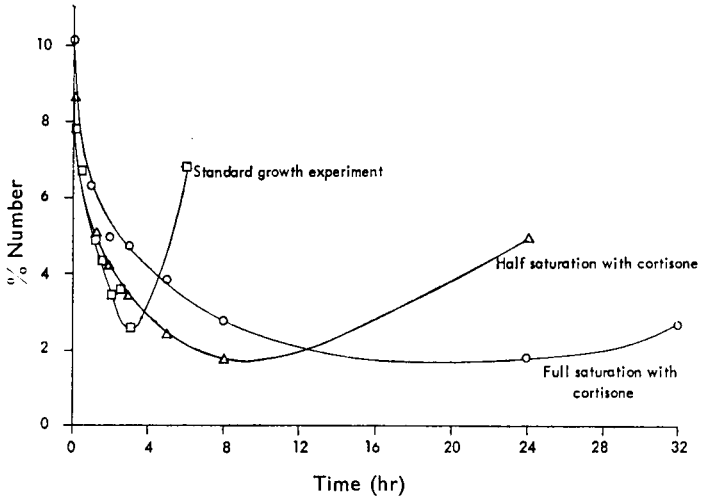

FIG. 5. Comparison of changes in frequency percentage at 9μ (8–10) with time of suspension of cortisone acetate.

plotted against the time representing the middle of the time interval on a double log grid. The straight lines thus obtained were extrapolated back to what is very nearly zero time, where they met (Fig. 6). Assuming that at this very short time there was practically very little growth, then this finding would be taken to mean that rates of dissolution were the same at near zero time. A difference was only observed when significant growth occurred in the system and this must therefore be the part of the process which is affected by cortisone alcohol. It was also possible to reproduce the same result for other diameters. On these grounds, it is

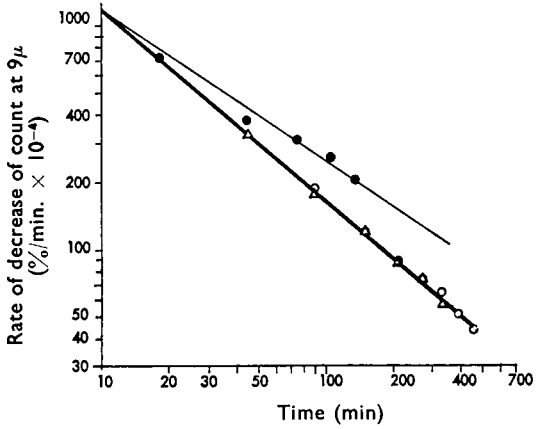

FIG. 6. Comparison of rates of dissolution of cortisone acetate in presence and absence of cortisone alcohol. ● —— ● Standard growth experiment, ○ —— ○ Half saturation with cortisone. △ —— △ Full saturation with cortisone.

reasonable to assume that cortisone is adsorbed onto particles of the stable form and prevents the arrival of new molecules of cortisone acetate which would result in crystal growth. It is noticeable that particles change their shape while growing to long needles, hence it could also be explained that the lattice arrangement of Form IV* is such that the molecular dimensions of cortisone alcohol fit into those of the most dense lattice plane of the cortisone acetate crystal, and the adsorbed cortisol alcohol thus stops the preferential growth on that face. This mechanism, which assumes competitive inhibition by cortisone, receives further support from the fact that a saturated solution of cortisone alcohol inhibits the rate of increase in diameter of cortisone acetate particles by a factor of about 10, which is roughly the ratio of the longer to the shorter axis of crystals which grow in absence of cortisone. Allen, Milosovich & Mattocks (1965) also studied a similar phenomenon and found that the effect of surface-active agents in retarding the growth of the needle habit of sodium acid urate could be one of adsorption or of competitive inhibition.

When a Fig. 6 type of plot was attempted for the effect of agitation, a similar result was obtained. Therefore, agitation is also affecting only the growth part of the process. In Fig. 3, the minimum does not appear to be significantly shifted along the time scale, and therefore agitation does not seem to enhance the polymorphic transformation. The most likely effect would be acceleration of the deposition of molecules of cortisone acetate onto nuclei of the stable form and consequently the formation of bigger crystals. The frequency of occurrence of these bigger crystals would approach that of various other sizes and consequently lead to the situation seen in Fig. 3. The diffusion-controlled process of dissolution and deposition of molecules will be affected by agitation and if this is sufficiently great then diffusion is unlikely to be the limiting factor in the growth process. If the rest of the component processes involved, for example the polymorphic transformation, are mainly controlled by the surface-area of the particles, then, according to Higuchi & Lau (1962), the rate of change of diameter with time will be independent of the diameter. The rough similarity of the figures representing rates of growth above 10 and 20% cumulative counts would suggest that this is so, therefore the above explanation appears to be adequate for agitated cortisone acetate suspensions.

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