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Influence of the cohesive behaviour of small particles on the solid-state photolytic degradation of furosemide

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Abstract

The effect of the cohesive behaviour of small particles on the solid-state photochemical degradation of furosemide is reported. Samples of agglomerated and recrystallised separated particles were exposed to direct sunlight for up to 240 hours, and the furosemide content measured with time. The solid-state photolytic degradation of furosemide proceeds from a nucleation period, through a growth period and eventual deceleration of the reaction. The kinetic process was best described by a power law dependence of the fraction degraded on time for the nucleation period and first order kinetics with asymptote, Prout-Tompkins equation, for the growth of the nuclei. The first order rate constants for the degradation of the agglomerated and the separated particles were 1.20×10^{-2} hour^{-1} and 1.48×10^{-2} hour^{-1} respectively for the nucleation period and 2.85×10^{-2} hour^{-1} and 2.45×10^{-2} hour^{-1} for the growth period. Although the mean particle size of the particles which made up the agglomerates was significantly smaller (2.5 μm) than the separated

particles (22 μm), the separated particles degraded more than the agglomerates. The maximum, infinite, fraction degraded (α_∞) was 0.450 for the agglomerates and 0.660 for the separated particles. It seemed as though nucleation depended on the surface area exposed to irradiation. Agglomeration decreased the surface area available and therefore nucleation was less. Degradation during the growth period appeared to occur inside the particles and was limited by the extent of nucleation.

Introduction

The work presented in this paper is part of a wider investigation into the effect the cohesive behaviour of small particles of some poorly water soluble and water wettable drugs have on their solid-state characteristics. These drugs are usually micronised to ensure the maximum surface area is available for dissolution. However, small particles are usually very cohesive and stick together to form agglomerates that decrease the surface area.

Matsuda and Tatsumi[1] studied the solid-state physicochemical photostability of furosemide polymorphic forms by following the progress of darkening as determined on the basis of colour difference. Striking differences in the degree of coloration were observed among the three polymorphs. They concluded that solid-state photochemical reactions for polymorphic drugs are less well understood and that it remain unclear as to whether the differences in coloration is correlated with the extent of chemical stability of furosemide. They compressed the powders into tablets to obtain a uniform surface presented to irradiation but form II could not be compressed and the powder was distributed on a glass slide. This meant that there was a difference in the surface area exposed to irradiation. If photolytic degradation is a surface controlled process the extent of degradation would be influenced by the surface area exposed to irradiation. This could explain the large differences in coloration observed by Matsuda and Tatsumi[1].

A general kinetic expression found to be applicable to many isothermal solid-state decomposition reactions consists of a period of first order behaviour with a constant rate of interface advance (normal growth) preceded by a power law obedience of the fraction degraded, α, on time[2]. Rate time curves for chemical changes in many solids exhibit a maximum value between $0.3 < \alpha_\infty < 0.8$ and any kinetic expression applicable to the greater part of the overall process must include due consideration of the deceleration (decay) period[3].

When diffusion is not significant the early stage of the nucleation process can be described by a power law dependence of α on t (equation 1), n is the power law factor

$$\alpha = k_s t^n \quad \text{.... (1)}$$

At a point t^* the amount not decomposed is sufficiently protected by the amount decomposed so that no more surface decomposition takes place. Beyond t^* the system is not subjected to surface degradation and should decompose by first order kinetics as described by the Prout-Tompkins model (equation 2) [3,4].

$$\ln[(\alpha_\infty-\alpha^*)/(\alpha_\infty-\alpha)] = k_l(t-t^*) \quad \text{.... (2)}$$

where α^* is the amount decomposed at time t^* and α_∞ the maximum amount degraded. When the total curve is plotted a S-curve results. The rate of decomposition would be the sum of the rate of decomposition of the surface, nucleation period, (rate constant, k_s time^{-1}) and the growth of the nuclei (assumed first order with rate constant, k_l time^{-1}).

The purpose of this paper concerns the elucidation of the effect that powder agglomeration behaviour have on the rate of photochemical degradation of furosemide. An attempt will also be made to describe the kinetic process involved in the solid-state photochemical degradation of furosemide.

Materials and Methods

Chemicals

The very fine furosemide powder used was extremely cohesive. (Fine Chemicals, batch number CSR 60099, South Africa). Furosemide was recrystallised from hot saturated solutions of the drug in methanol. Differential scanning calorimetric profiles of the recrystallised particles were measured to confirm the identity of the particles. The particles of the recrystallised powder were less agglomerated. The solvents and chemicals used were either HPLC or reagent grade. In figure 1 scanning electron photomicrographs of the two powders are shown.

Particle size analysis

The mean particle size of the dry supplied and recrystallised furosemide was measured with a Sympatec Helos instrument in combination with a Rodos dry dispersion apparatus (Sympatec, Germany). The dry dispersion technique was used to break the agglomerates into separate particles. The mean particle size of the supplied furosemide was 2.5 μm and the recrystallised powder 22 μm. The mean size of the powder agglomerates was measured with a Galai-Cis-1 particle inspection system. The agglomerates were suspended in a filtered saturated solution of furosemide in water. This procedure ensured that the agglomerates were not damaged during the determination. The mean size of the agglomerates were between 200 to 250 μm. The particle size distributions are shown in figure 2.

HPLC analysis of furosemide

The degradation of furosemide was analysed using a method developed by Twigge[5]. A Shimadzu model LC 6A pump equipped with a model SPD-6A variable wavelength detector, a model SIL-9A auto-injector and a model C-R3A integrator was used. A column, 250 × 4.6 mm, was packed with Nucleosil NH_2 polar bonded stationary phase with a particle size of 5 μm. The mobile phase consisted of acetonitrile : water (78:22 % v/v) and glacial acetic acid to a pH

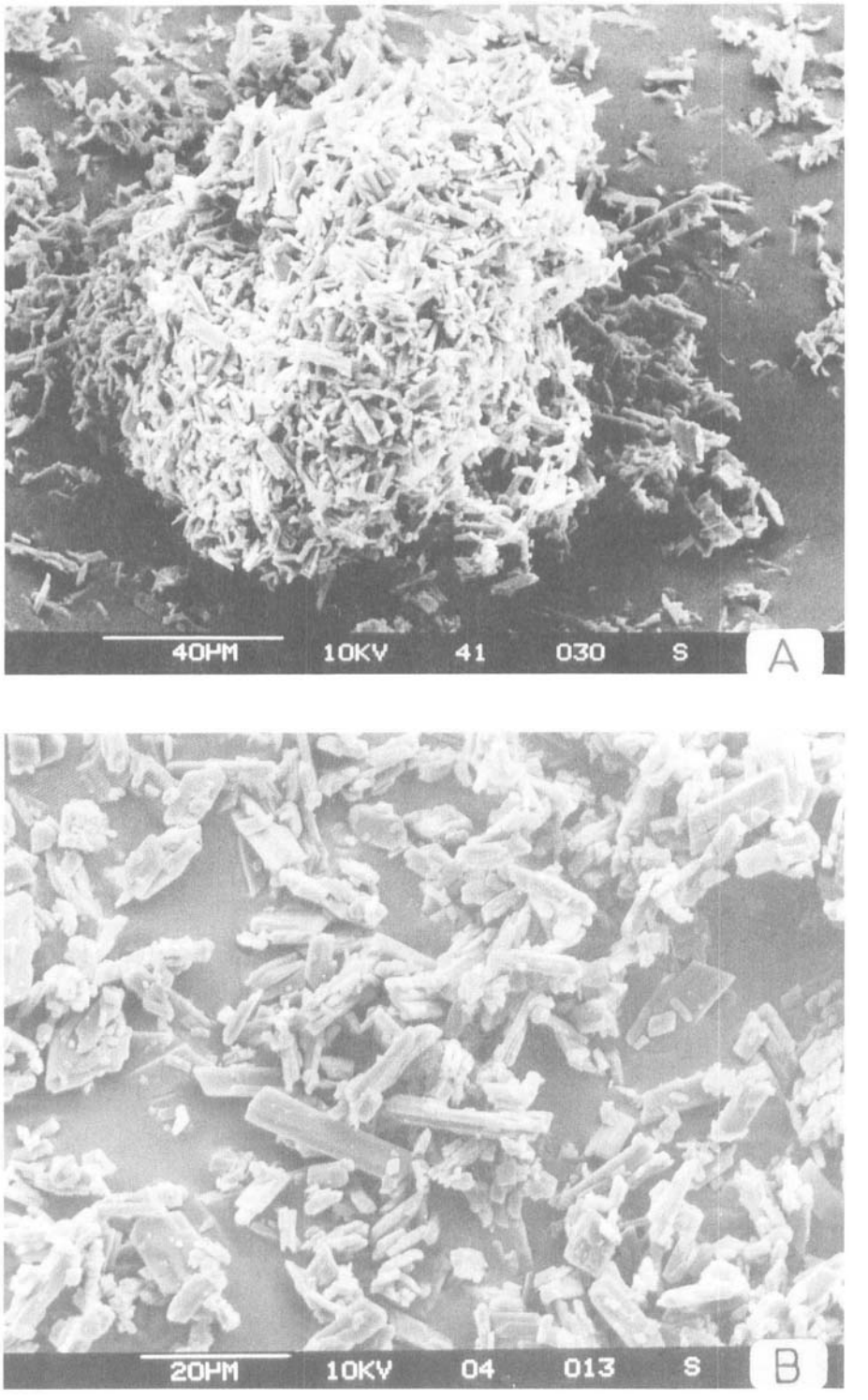

Figure 1: Scanning electron photomicrographs of (A) powder agglomerates and (B) recrystallised particles of furosemide.

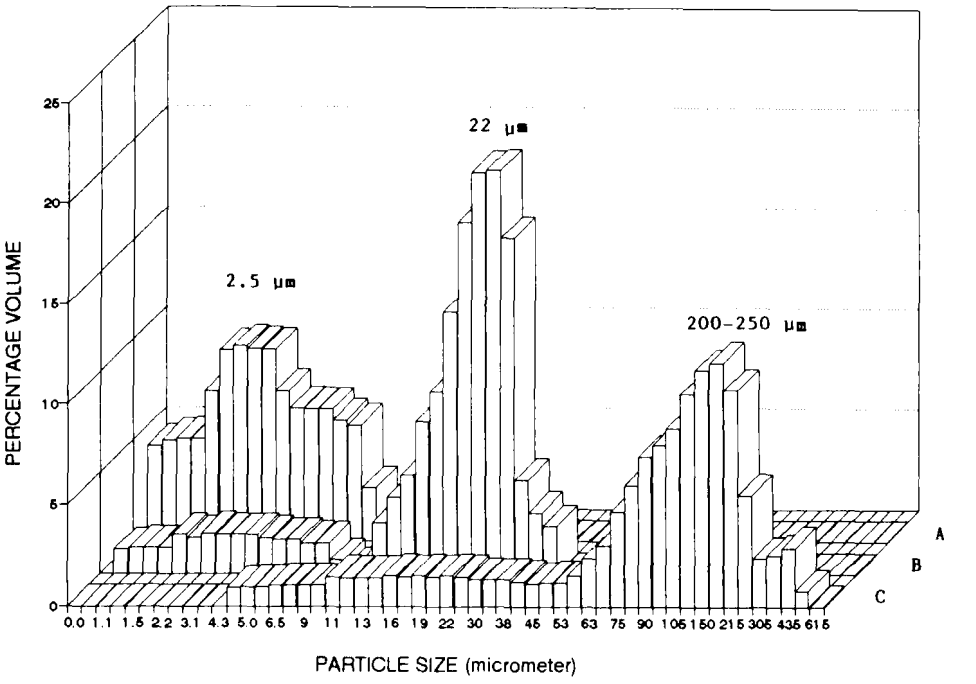

Figure 2: The volume diameter distribution of (A) the individual furosemide particles of the agglomerates (B) the recrystallised crystals and (C) the size distribution of the agglomerates.

of 4.2. The flow rate was 1 cm^3min^{-1} and the column effluent was monitored at 230 nm. Furosemide is soluble in 95 % methanol and for quantitative HPLC analysis this solvent was used to prepare solutions. Quantitative analysis of the compound was done by measuring peak areas in relation to those of standards analysed under the same conditions. Analytical plots of peak area against analyte concentration were rectilinear, the relevant data are summarised in table 1. In figure 3 liquid chromatograms of furosemide and a sample exposed to sunlight for 240 hours are shown. Results are the mean of five determinations.

Stability study

Three samples, 5 g, each of the agglomerates and the separated recrystallised particles were kept either in clear glass containers directly in sunlight or in

TABLE 1

Statistical data for analysis of furosemide.

Compound	Y-intercept	Standard error of intercept	Slope	Standard error of slope	Correlation coefficient
furosemide	-1368	0.243	5504001	25.392	0.9999

amber glass containers in the dark. The containers exposed to direct sunlight were placed beside a laboratory window. The powder was so distributed in the container as to ensure the maximum surface area was exposed to irradiation. At predetermined intervals ± 100 mg samples were removed. The average room temperature for the ten days it took to complete the experiments was 22 °C.

Calculations

The maximum, infinite, amount degraded was calculated by treating the data to a first order kinetic equation and estimating the asymptote by extrapolation[6]. A computer program (Qautro Pro) was used to treat the fraction degraded, calculated from HPLC peak areas, versus time data, according to the two equations. The time to what the power law was applicable and from when the Prout-Tompkins equation could be applied was obtained by calculating an adjusted correlation coefficient, R_a^2,

$$R_a^2 = 1-(1-R^2)[(n-1)/(n-k-1)] \quad \text{.... (3)}$$

where R^2 is the measured correlation coefficient, n the number of data points

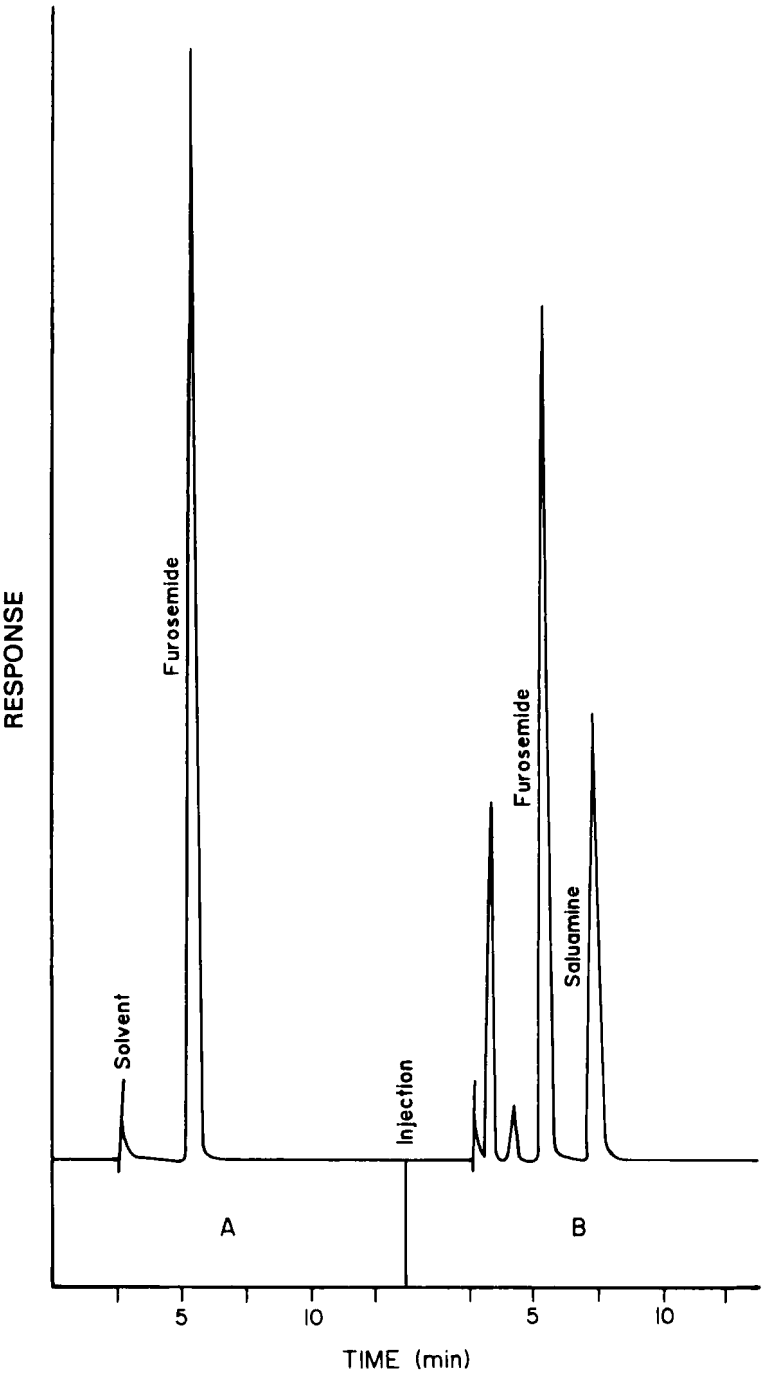

Figure 3: Liquid chromatograms of (A) furosemide and (B) a powder sample of furosemide exposed to direct sunlight for 240 hours.

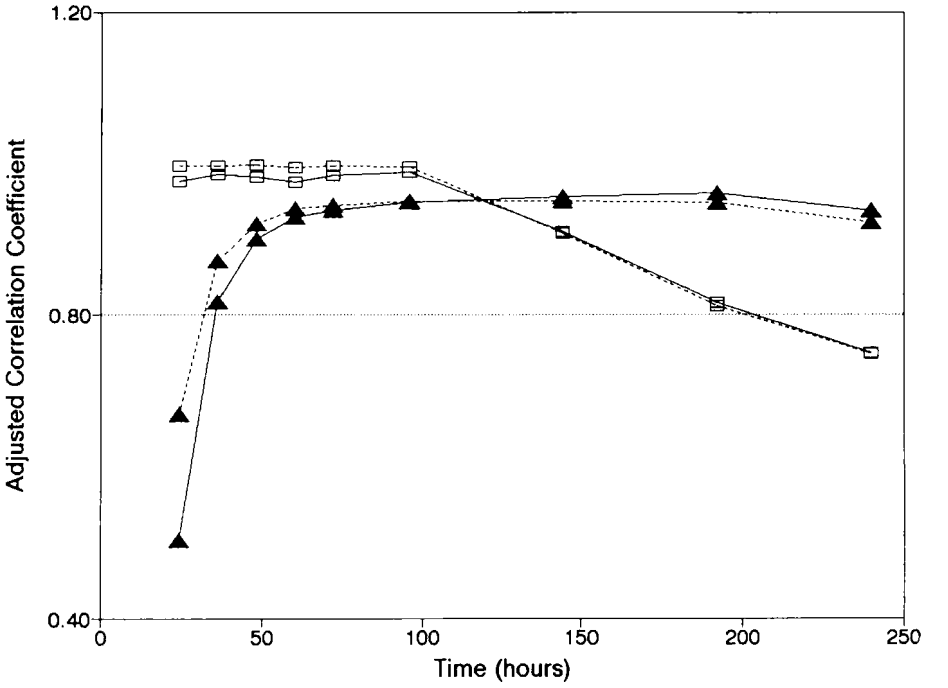

Figure 4: Adjusted correlation coefficient versus time according to the power law (□) and Prout-Tompkins (▲) equations. Solid lines represent results for the agglomerates and dashed lines the separated particles.

and k the number of parameters. From plots of R_a^2 against time the region where the kinetic process changed from a power law dependence to first order kinetics as described by the Prout-Tompkins equation was determined.

Results and Discussion

Analysis of the main chemical degradation product of furosemide, CSA, at time zero revealed no discernible purity difference between the samples, > 99 % w/w purity and CSA content 0.06-0.08 %. The samples kept in amber glass containers in the dark showed no significant photolytic degradation, mean percentage degradation 1.39 % for all the samples measured.

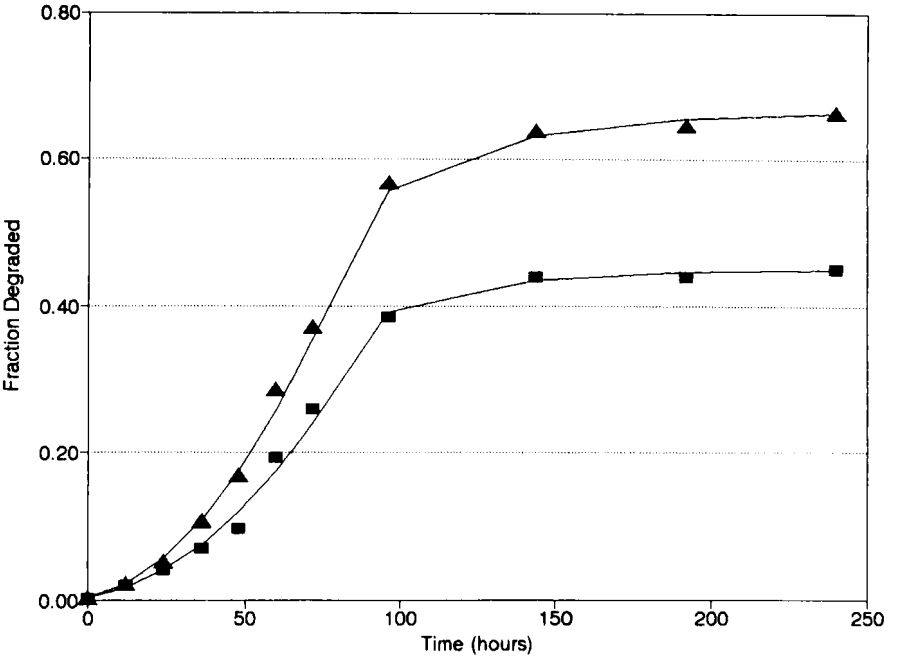

Figure 5: Apparent first order solid-state photolytic degradation of furosemide (■) agglomerates (▲) recrystallised particles. The solid lines represent the best fit, according to the proposed model, and the markers the mean measured values.

Furosemide degraded according to two simultaneous reactions. At the start a nucleation process predominates that was best described by a power law dependence ($n = 2$) of α on t thereafter the nuclei grew according to a first order kinetic process with an asymptote (Prout-Tompkins). In figure 4 the adjusted correlation coefficient versus time data according to the power law and Prout-Tompkins equations are shown. For both the agglomerates and the separated particles the power law was applicable up to 96 hours, mean correlation coefficient above 0.97. Thereafter the process followed first order kinetics as described by the Prout-Tompkins equation, mean correlation coefficient 0.95.

The apparent first order solid-state photolytic degradation of furosemide agglomerates and recrystallised particles, according to the proposed model,

TABLE 2

First order rate constants for the power law (k_s) and Prout-Tompkins (k_l), power law factor (n), maximum fraction degraded (α_∞) and regression coefficients (R) for the solid-state photolytic degradation of furosemide.

Furosemide	$k_s \times 10^{-2}$ (hour^{-1})	n	R	$k_l \times 10^{2}$ (hour^{-1})	α_∞	R
Agglomerates	1.20	2	0.995	2.85	0.450	0.969
Separated particles	1.48	2	0.998	2.45	0.666	0.978

versus time is shown in figure 5. These plots were derived from fraction degraded versus time data calculated from the amount of furosemide left in each sample. The first order rate constants for the nucleation (k_s) and growth of the nuclei (k_l), power law factor (n), regression coefficients (R) and maximum fraction degraded (α_∞) values are listed in table 2. Excellent linearity was observed, mean correlation coefficient 0.98 with a standard deviation of 0.029. Overall degradation was more rapid during the nucleation period. Nucleation was faster for separated particles but there was not a significant difference in the growth rates of the nuclei of the separated and agglomerated particles. However the total fraction degraded of the separated particles (α_∞ = 0.666) was significantly greater than for the agglomerates (0.450).

Conclusions

The solid-state photolytic degradation of furosemide followed apparent first order kinetics as described by a simultaneous kinetic process consisting of a nucleation period, followed by growth of the nuclei and eventual deceleration

of process. Overall degradation was slower during the growth period. Although the real mean individual particle size of the agglomerates was significantly smaller (2.5 μm) than the separated particles (22 μm), the separated particles were degraded more than the agglomerates. Nucleation occurred more rapidly on the surface of the separated particles. Therefore it seemed as though nucleation depended on the surface area exposed to uv irradiation. Agglomeration decreased the surface area available and therefore nucleation was less. Degradation during the growth period appeared to occur inside the particles and was limited by the extent of nucleation. There was not a significant difference in the growth rates of the nuclei for the separated and agglomerated particles.

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