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Kinetic study of the solid-state photolytic degradation of two polymorphic forms of furosemide

M.M. De Villiers [a], J.G. van der Watt [a] and A.P. Lötter [b]

[a] *Department of Pharmaceutics, Potchefstroom University for C H.E., Potchefstroom 2520 (South Africa)* and [b] *Research Institute for Industrial Pharmacy, Potchefstroom University for C H.E, Potchefstroom 2520 (South Africa)*

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Summary

In this paper some aspects influencing the solid-state photolytic degradation of two polymorphic forms of furosemide were investigated. Powder samples of the two polymorphic forms were exposed to prolonged UV irradiation, direct sunlight, in a normal and nitrogen atmosphere The solid-state photolytic degradation of furosemide followed apparent first-order kinetics as described by a model consisting of nucleation and growth periods with eventual deceleration as it reached a maximum fraction degraded. Kinetic calculations revealed that this bilateral first-order degradation process was best described by a power law dependence ($n = 2$) of the fraction decomposed (α) on time (t) for the nucleation period and first-order kinetic degradation with an asymptote for the growth and deceleration period (Prout-Tompkins model). Overall, the rate constants during the nucleation period were significantly smaller than the growth period. Form I was photochemically more stable than form II, especially under a nitrogen atmosphere ($t_{1/2}$ 50 h). The photolytic degradation of form II was not influenced by the presence of oxygen ($t_{1/2}$ 35 h under normal atmospheric conditions and 38 h in a nitrogen atmosphere). After exposure to sunlight 4-chloro-5-sulphamoylanthranilic acid (CSA) was found in significant concentrations in samples taken from both forms I and II. Photolytic degradation of furosemide form II led to the formation of mainly CSA in the presence of nitrogen and CSA and other unidentified products in the presence of oxygen.

Introduction

Several workers have studied the photolytic stability of furosemide in solution. In alkaline solutions furosemide shows a high degree of stability but is susceptible to acid-catalysed hydrolysis in acid solutions (Neil et al., 1984). According to most Pharmacopeia furosemide undergoes gradual coloration upon exposure to light and is recommended to be protected from light.

Doherty and York (1988) and Matsuda and Tatsumi (1990) prepared polymorphic forms of furosemide. These crystal forms are discrete crystal structures of furosemide. Matsuda and Tatsumi (1990) studied the physicochemical photostability of furosemide polymorphic forms by following the progress of darkening as determined on the basis of colour difference. Excellent linearity was found and the coloration process followed

Correspondence to: M M. De Villiers, Department of Pharmaceutics, Potchefstroom University for C.H.E., Potchefstroom 2520, South Africa

apparently identical kinetics. Striking differences in the degree of coloration were observed among the polymorphs. Their forms II and III were very susceptible to coloration even after short-term irradiation, but form I underwent only noticeable color changes after long irradiation (2 h).

Matsuda and Tatsumi (1990) concluded that solid-state photochemical reactions of polymorphic drugs are less well understood and it remains unclear as to whether the difference in colour is correlated with the extent of chemical stability of furosemide. However, it is important to be able to quantitatively evaluate the solid-state photostability of drugs and their crystal forms.

Theoretical considerations regarding solid-state kinetics

The purpose of any kinetic study is to obtain information concerning the reaction mechanism through comparisons of a series of measured fraction degraded (α) vs time values. The problem may be regarded as the identification of the functional relationship between α and t: $f(\alpha) = kt$, where k is the conventional rate constant. The notion of 'order of reaction' as it is understood in the fluid phase has only limited applicability to solids (Bamford and Tipper, 1980). The specific rate of solid-state degradation may be controlled by numerous factors, including both microscopic (diffusivities, defects, crystallographic surfaces, polymorphic form and reaction mechanisms) and macroscopic systems (particle size distribution, particle shape, and for agglomerates, pore size and distribution).

Rate equations are derived through integration of specific forms of a generalised expression representing a summation of the degradation process. Substitution of the appropriate functions for nucleation and growth into this equation and integration thereof yields the $f(\alpha)$-time relation

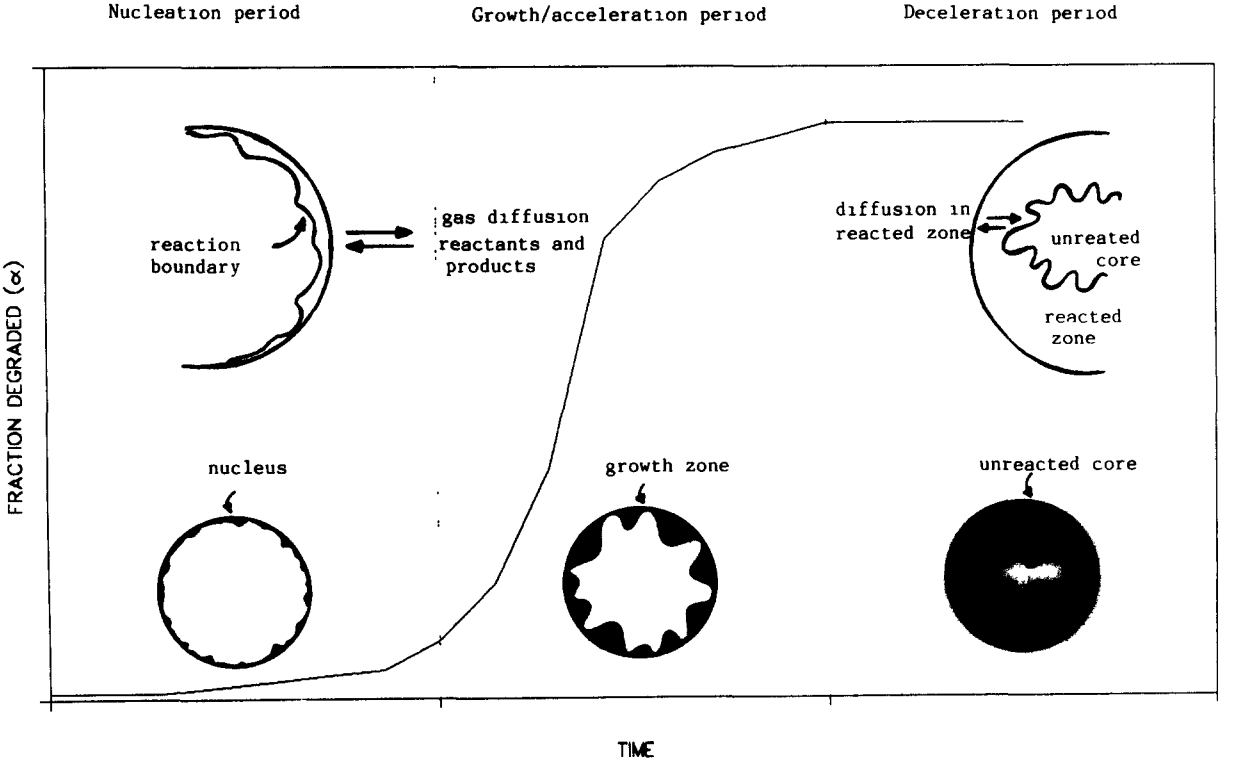

Fig 1 Details of the suggested kinetic model for the solid-state degradation of furosemide. Degradation proceeds from a nucleation period through an acceleration (growth) period to eventual deceleration of the reaction (Koga and Harrison, 1984)

corresponding to a particular geometric interface advance. In real systems plots of α against time are usually S-shaped (Fig. 1). Having identified the kinetic relationship applicable to the data for a particular reaction, it is necessary to confirm linearity of the appropriate plot of the function $f(\alpha)$ against time (Byrn, 1982).

A general expression found to be applicable to many solid-state decomposition reactions consists of a period of first-order behaviour with a constant rate of interface advance preceded by a power law obedience of α on time (Koga and Harrison, 1984). Rate-time curves for chemical changes in many solids exhibit a maximum value between $0.3\langle\alpha_\infty\rangle 0.8$ and any kinetic expression applicable to the greater part of the overall process must include due consideration of the deceleration (decay) period. Kinetic parameters (reaction constant, k, and reaction order) for the selected rate expressions are calculated, together with their experimental uncertainties (Bamford and Tipper, 1980).

According to Bawn (1990) the product of decomposition, to a certain extent, will prevent further degradation. The rate of decomposition would be the sum of the rate of decomposition of the surface (assumed first order with rate constant k_s time^{-1}) and the inside of the core (assumed first order with rate constant k_1 time^{-1}) (Bawn, 1990).

$$\ln[1 + B\alpha] = Bk_s t$$

where B is an adjustable factor estimated by the sum of the squares of deviations of the points from the ensuing line or the correlation coefficient. The line must pass through the origin. 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 such as described by the Prout-Tompkins equation.

$$\ln[(\alpha_\infty - \alpha^*)/(\alpha_\infty - \alpha)] = k_1(t - t^*)$$

where a^* is the amount decomposed at time t^* and α_∞ the maximum amount decomposed.

According to Harrison (1969), Bamford and Tipper (1980) and Koga and Harrison (1984), when a reaction is surface controlled, the behaviour of the surface with time, t, can be crudely classified into several phases. The first corresponds to formation of nuclei of the product and their growth. As shown in Fig. 1 the reaction interface increases until growing nuclei overlap extensively and then decreases, resulting in a sigmoidal dependence of extent of the reaction, α, on time. When diffusion is not significant this early stage of the nucleation process is described by a 'power law' dependence of α on t.

$$\alpha = k_s t^n$$

When nuclei start to overlap the reaction follows first-order kinetics such as described by the Avrami-Erofeev model.

$$[-\ln(1 - \alpha)]^m = k_1 t$$

where m is the extent to which the reaction takes place.

The overall resistance to the reaction (Fig. 1) is considered to consist of several steps: (i) surface reaction, (ii) gas phase mass transfer, (iii) diffusion through the porous reacted zone and (iv) chemical reaction at the boundary (Koga and Harrison, 1984). Furthermore, it is assumed that the chemical reaction is of first order with respect to the reactant, the reaction is isothermal and the shape of the particles does not change during the course of the reaction. It should be stressed that solid-state kinetics is quite complex and that it would be inadvisable to argue that if a set of data obeys certain kinetics, then the mechanism of the reaction is established (Bamford and Tipper, 1980). However, results of kinetic analysis are helpful to compare data for degradation reactions under different circumstances, if they obey the same kinetics.

The purpose of this paper concerns the elucidation of some aspects influencing the solid-state photolytic degradation of two polymorphic forms of furosemide, forms I and II (Doherty and York, 1988), this includes possible description of the kinetic process involved and determining if the

products of photolytic degradation were different for the two polymorphic forms.

Materials and Methods

Chemicals

Furosemide was generously supplied by Lennons Pty Ltd (South Africa). Solvents and sodium hydroxide used were either HPLC or reagent grade.

Preparation of 4-chloro-5-sulphamoylanthranilic acid (CSA)

The following method was used to prepare 4-chloro-5-sulphamoylanthranilic acid (Rowbotham et al., 1976): 2 g furosemide was refluxed with 50 cm^3 3 M hydrochloric acid for 3 h, which yields a brown reaction mixture. The mixture was filtered and cooled in an ice bath. Brown crystals formed which were purified by refluxing them with 50 cm^3 3 M sodium hydroxide solution containing 250 mg activated charcoal for 60 min. The yellow crystals that formed were recrystallised several times from water; melting point > 250°C; yield 1.69 g (84.5 %). The identity of CSA was confirmed by IR spectrophotometric analysis, using potassium bromide discs (Fig. 2).

Preparation of two polymorphic forms of furosemide

Two polymorphic forms of furosemide, forms I and II described by Doherty and York (1988), were prepared. Form I was generally furosemide

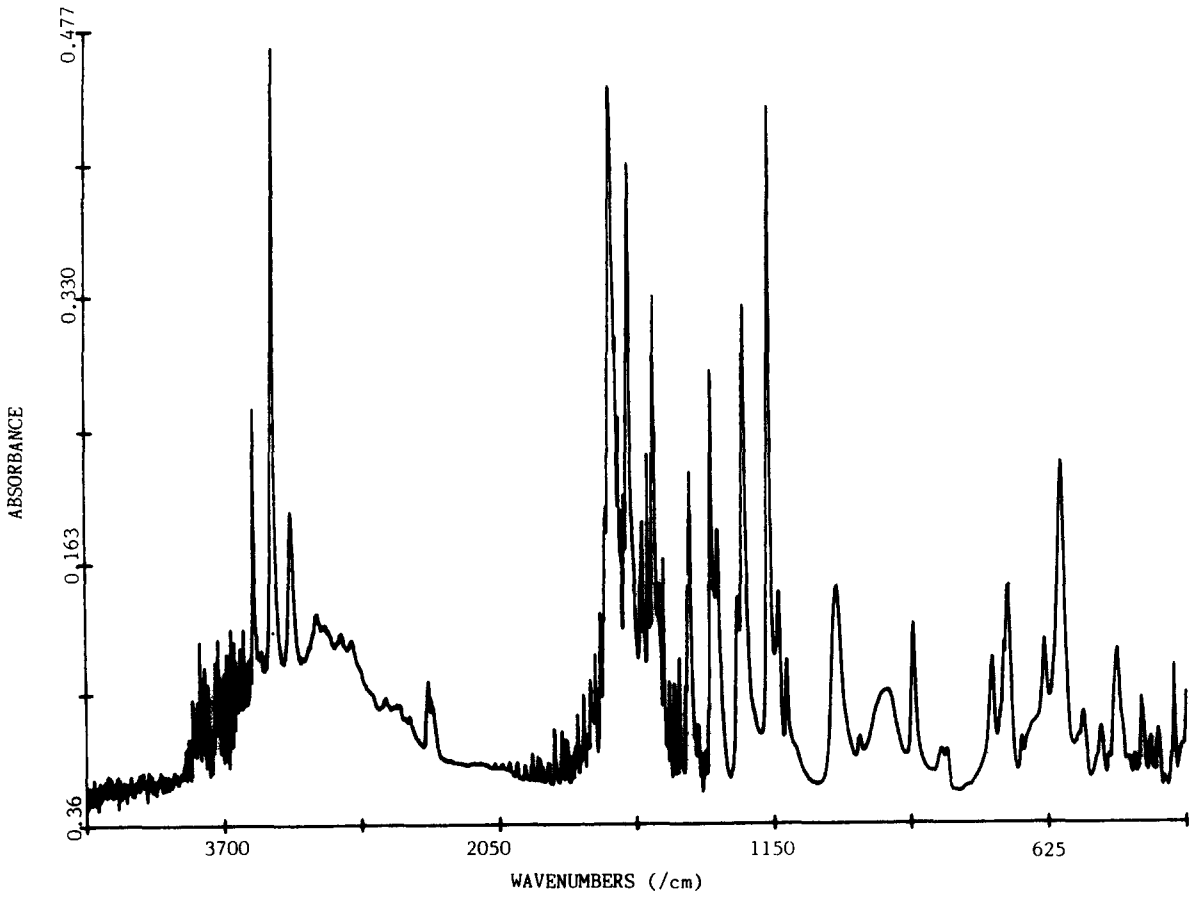

Fig 2. IR spectrum of prepared 4-chloro-5-sulphamoylanthranilic acid (CSA)

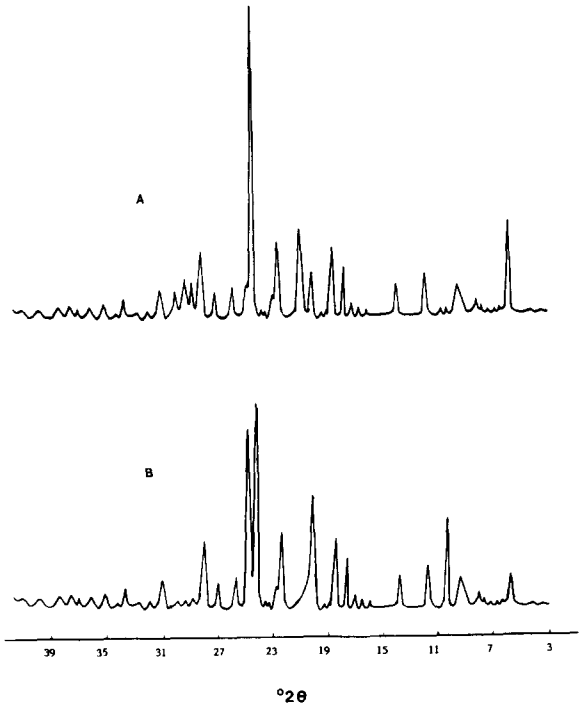

Fig 3. X-ray powder diffraction profiles of (A) form I and (B) form II of furosemide.

as supplied by the supplier. To obtain particles comparable in size to that of form II it was recrystallised from a hot saturated solution of furosemide in methanol. Form II was prepared as described by Matsuda and Tatsumi (1990). It was obtained from an acetone solution of the drug, 10 g per 200 cm^3, that was evaporated to dryness at 25°C under reduced pressure in a rotary evaporator. The two polymorphic forms of furosemide were characterised by their X-ray powder diffraction profiles (Fig. 3). X-ray powder diffraction profiles were measured at room temperature with a Philips PM 9901/00 diffractometer (20 mA, 40 kV with cobalt potassium α radiation). Samples were scanned between 2 and 40° 2θ at a speed of 2° 2θ min^{-1}. In Table 1 the main X-ray powder diffraction peak angles for the two polymorphs are listed.

TABLE 1

Main peaks in the X-ray diffraction patterns of two polymorphs of furosemide

Form I		Form II	
2° 2θ	I/I_0	2° 2θ	I/I_0
24.8	1 00	24.1	1 00
6.0	0.66	25.0	0.90
21.2	0.65	20.2	0 60
23.0	0.63	10 5	0 50

HPLC analysis of furosemide and CSA

High-performance liquid chromatography (HPLC) of furosemide and CSA was performed using a method developed by Twigge (1985). 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 were used. The column, dimensions 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 : glacial acetic acid to a pH of 4.2 (78 : 22% v/v). The flow rate was 1 cm^3 min^{-1} and the column effluent was monitored at 230 nm. Furosemide and CSA are soluble in 95% methanol and for quantitative HPLC analysis this solvent was used to prepare solutions of analytes. Quantitative analysis of the compounds was carried out by measuring peak areas in relation to those of standards analysed under the same conditions. Analytical plots of peak area against ana-

TABLE 2

Statistical data for analysis of furosemide and CSA

Compound	*y*-intercept	Standard error of intercept	Slope	Standard error of slope	Correlation coefficient
Furosemide	−1368	0.243	5504001	25.392	0.9999
CSA	−706	6.025	2780455	642.71	0.9999

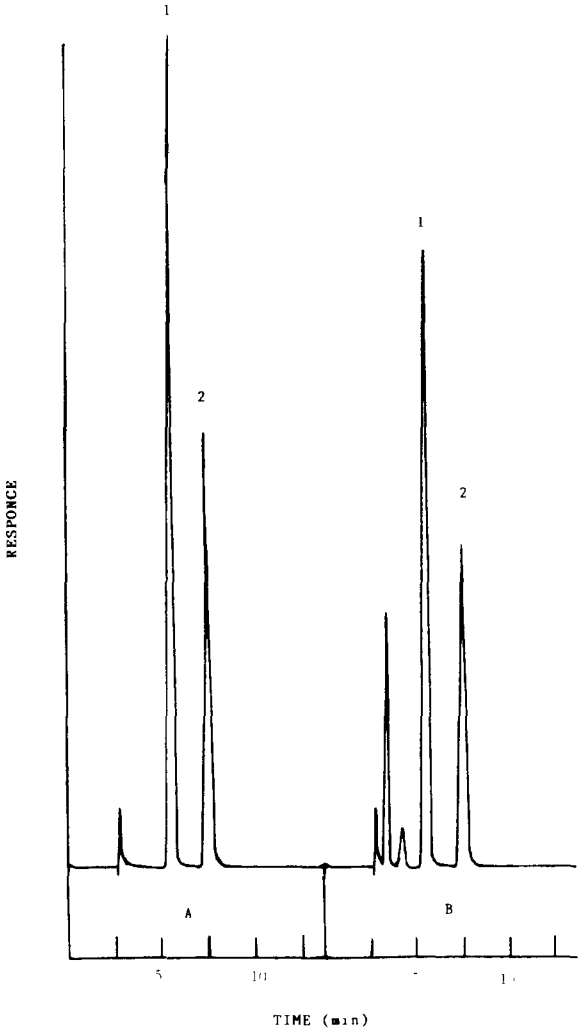

Fig. 4 Liquid chromatograms of (A) furosemide (1) and CSA (2) and (B) a powder sample of furosemide form I exposed to direct sunlight for 240 h in the presence of oxygen.

lyte concentration were rectilinear, the relevant data are summarised in Table 2 and in Fig. 4 liquid chromatograms of furosemide and CSA are shown. Results are the mean of five determinations.

Stability studies

The following stability study was conducted to examine the difference, if any, in solid-state photolytic degradation between samples of forms I and II kept in the presence and absence of oxygen. Three samples, 5 g, each of form I and form II were kept either in clear glass containers directly in sunlight or in amber glass containers in the dark. Samples were kept either under normal atmospheric conditions or in desiccators from which the air was removed and replaced with nitrogen. The powder was so distributed in the container as to ensure the maximum surface area was exposed to irradiation. At predetermined intervals samples of approx. 100 mg were removed. After removing samples from the desiccators the air was again replaced by nitrogen. The containers exposed to direct sunlight were placed beside a laboratory window. The average room temperature for the 10 days it took to complete the experiments was 22.5°C. The furosemide and CSA contents of the samples were measured.

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. A computer program (Quatro Pro) was used to treat the fraction degraded, calculated from HPLC peak areas, vs time data, according to several equations (Byrn, 1982). The fact that a straight line was not obtained meant that rate equations based on the concept of an order of reaction were mathematically inappropriate for expressing and correlating data.

Further calculations (Bawn, 1955; Harrison, 1969; Bamford and Tipper, 1980; Koga and Harrison, 1984) revealed that furosemide degraded by an apparent bilateral first-order degradation process that was best described by a power law dependence ($n = 2$) of the fraction decomposed (α) on time (t) for the nucleation period and first-order kinetic degradation with an asymptote for growth and deceleration period (Prout-Tompkins model). The apparent first-order solid-state photolytic degradation of furosemide

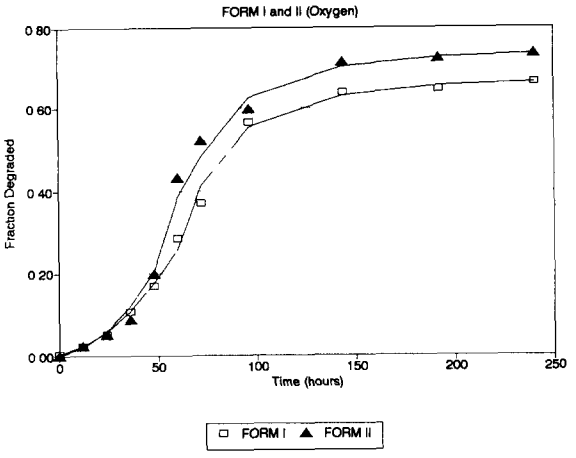

Fig 5. Apparent first-order bilateral kinetic solid-state photolytic degradation of furosemide under normal atmospheric conditions (□) form I and (▲) form II. The lines represent the best fit and the markers the mean measured values

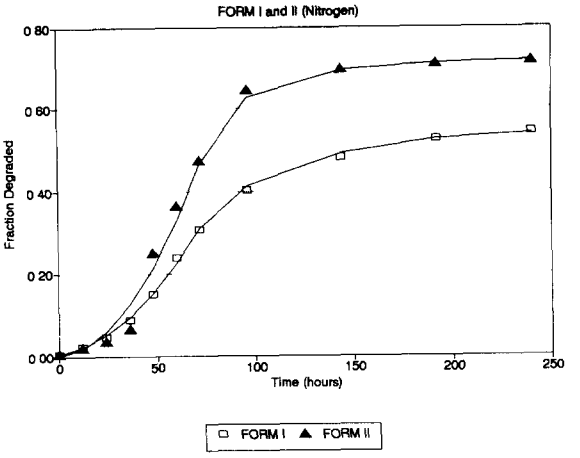

Fig. 7 Apparent first-order bilateral kinetic solid-state photolytic degradation of furosemide in the presence of nitrogen (□) form I and (▲) form II The lines represent the best fit and the markers the mean measured values

polymorphic forms, I and II, according to this hypothesis, vs time is shown in Figs 5 and 6 for degradation under normal atmospheric conditions and Figs 7 and 8 for degradation in the presence of nitrogen. Plots of the function $f(\alpha)$ against time, fitted to the proposed kinetic model, showed excellent linearity: mean regression coefficient 0.987, standard deviation 0.008. The first-order rate constants according to the power law (k_s) and Prout-Tompkins equation (k_1), power law factor (n), regression coefficients (R) and maximum fraction degraded (α_∞) values are listed in Tables 3 and 4

Overall the rate constants during the nucleation period were significantly smaller than during the growth period ($k_s < k_1$). This difference was less for form II, compared to form I, under normal atmospheric conditions. The reverse was

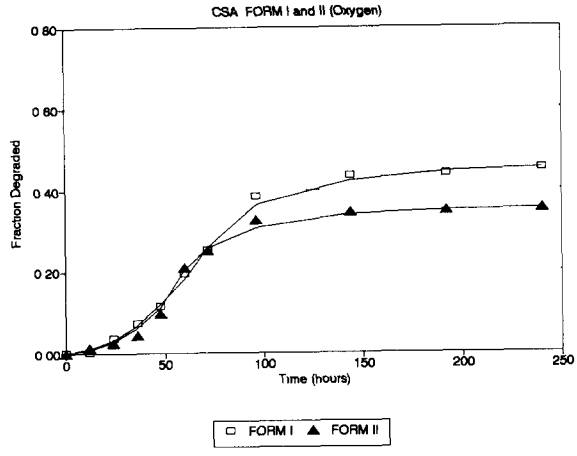

Fig 6. Apparent first-order bilateral kinetic formation of CSA under normal atmospheric conditions (□) form I and (▲) form II. The lines represent the best fit and the markers the mean measured values.

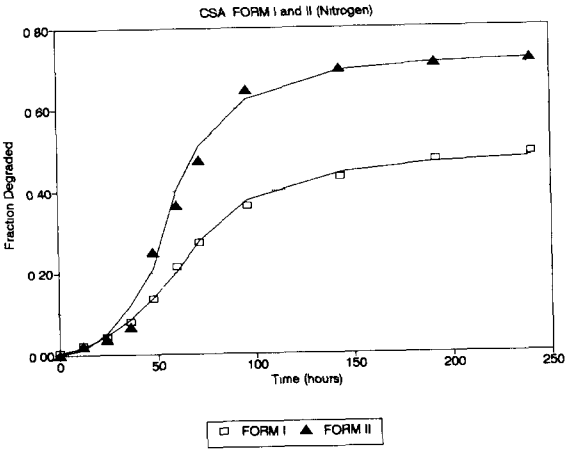

Fig 8 Apparent first-order bilateral kinetic formation of CSA in the presence of nitrogen (□) form I and (▲) form II The lines represent the best fit and the markers the mean measured values.

true in a nitrogen atmosphere. Photolytic degradation, under normal atmospheric conditions (Table 3) of form II was significantly faster during the nucleation period (k_s) but there was not a significant difference during the growth period (k_1). Under a nitrogen atmosphere the rate whereby form I was degraded, both during the nucleation and growth periods, was slower than form II. This could be the result of a significant difference in the maximum fraction degraded: α_∞ 0.550 for form I and 0.718 for form II. The photolytic degradation of form II was not influenced by the presence of oxygen ($t_{1/2}$ 35 h under normal atmospheric conditions and 38 h in a nitrogen atmosphere). Form I was more stable than form II, especially under a nitrogen atmosphere ($t_{1/2}$ 50 h).

After exposure to sunlight CSA was found in significant concentrations in samples taken from forms I and II (Table 4). The rate at which CSA was formed corresponded to the rate by which degradation took place. However, the maximum concentration of CSA measured (Table 4) was significantly more for form II kept under a nitrogen atmosphere than normal atmospheric conditions. Therefore, photolytic degradation of furosemide form II led to the formation of mainly CSA in the presence of nitrogen and CSA and other unidentified products in the presence of oxygen. According to Moore and Sithipitaks (1983), oxidation of the SO_2NH_2 of furosemide to SO_3H leads to the formation of 4-chloro-5-sulphoanthranilic acid. The difference in the rate of degradation in the presence and absence of oxygen could be because of the formation of 4-chloro-5-sulphoanthranilic acid in the presence of oxygen. Most photochemical changes are complex in that they involve subsequent reactions of the molecules or free radicals formed by photolytic degradation. This makes it difficult to determine all the products of photolytic degradation.

TABLE 3

First-order rate constants (k_s and k_1), power law factor (n), maximum fraction degraded (α_∞) and regression coefficients (R) for the solid-state photolytic degradation of furosemide polymorphic forms

Furosemide	k_s ($\times 10^{-2}$) (h^{-1})	n	R	k_1 ($\times 10^{-2}$) (h^{-1})	α_∞	R
Form I, oxygen	1.48	2	0.998	2 45	0 688	0.978
Form I, nitrogen	1 38	2	0.998	1 83	0 550	0.991
Form II, oxygen	2.01	2	0.988	2.50	0.739	0.984
Form II, nitrogen	1 83	2	0.976	2 78	0.718	0.989

TABLE 4

First-order rate constants (k_s and k_1), power law factor (n), maximum fraction CSA measured (α_∞) and regression coefficients (R) for the solid-state photolytic formation of CSA from two polymorphic forms of furosemide

Furosemide	k_s ($\times 10^{-2}$) (h^{-1})	n	R	k_1 ($\times 10^{-2}$) (h^{-1})	α_∞	R
Form I, oxygen	1.37	2	0 986	2.08	0.456	0 984
Form I, nitrogen	1.31	2	0 998	2.00	0 483	0 979
Form II, oxygen	1.40	2	0 988	2.56	0 353	0 985
Form II, nitrogen	1.97	2	0 985	2 68	0 720	0.989

The differences observed in the rates by which forms I and II were degraded were less than those reported by Matsuda and Tatsumi (1990). The solid-state photolytic degradation of furosemide followed apparent first-order kinetics as described by a model consisting of a nucleation and growth periods with eventual deceleration as it reached a maximum fraction degraded. The rate of degradation was not significantly different during the nucleation period but was markedly altered during the growth periods. Form I under a nitrogen atmosphere was the least affected by photolytic degradation. CSA appeared to be the main photolytic degradation product but other unidentified products were also present in measurable quantities (Fig. 4). Different polymorphic forms may exhibit different photochemical stability because different crystallographic faces are exposed to UV irradiation.

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