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International Journal of Pharmaceutics 190 (1999) 129–137

international journal of pharmaceutics

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Review

Pharmaceutical applications of the Prout–Tompkins rate equation

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Received 14 June 1999; accepted 13 August 1999

Abstract

More than 50 years ago, a paper by E.G. Prout and F.C. Tompkins was published in the Transactions of the Faraday Society. The paper dealt with the kinetics of the thermal decomposition of crystals of potassium permanganate, and suggested a rate equation, which has become known as the Prout–Tompkins equation, for use in the kinetic analysis of solid state reactions. The paper has been extensively cited in the literature. Applications of the Prout–Tompkins equation in pharmaceutical stability studies are reviewed in this short review. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Kinetics; Prout–Tompkins equation; Autocatalysis; Solid state reactions; Stability

1. Introduction

A paper by E.G. Prout and F.C. Tompkins (Prout and Tompkins, 1944) dealing with the kinetics of the thermal decomposition of crystals of potassium permanganate, appeared in the Transactions of the Faraday Society in 1944. This paper not only made an important contribution to the accumulated information on the decomposition of potassium permanganate (Herbstein et al., 1994), but also focussed attention on a suggested rate equation, which has become known as the Prout–Tompkins equation, for use in the kinetic analysis of solid state reactions (Brown, 1997). Personal details of Professor Prout and the late Professor Tompkins and a more general survey of the influence of the Prout–Tompkins (PT) equation have been given (Brown, 1997). No ready method of determining the citation history of the original Prout and Tompkins (1944) paper between 1944 and 1965 was available, but a survey of the Science Citation Index from 1966 to 1996 showed 150 citations. Some of those citations directly related to pharmaceutical applications are described below.

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PII: S0378-5173(99)00292-6

2. Rate equations in solid state kinetics

The rate equations that have found application in solid state kinetic analyses (Brown et al., 1980) may be generalized in their derivative forms as: $\mathrm{d}\alpha/\mathrm{d}t = k\mathrm{f}(\alpha)$ and the corresponding integrated forms as: $\mathrm{g}(\alpha) = kt + c$, where α is the fractional extent of reaction. These expressions are grouped according to the shape of the *isothermal* α-time curves as acceleratory, sigmoid or deceleratory. Amongst the rate equations which produce sigmoid α-time curves is the Prout–Tompkins equation (often referred to as B1, but, in this paper, as the PT equation, or model):

$$\mathrm{d}\alpha/\mathrm{d}t = k_{\mathrm{B}}\alpha(1-\alpha) \tag{1}$$

which on integration under certain conditions (see below) gives:

$$\ln[\alpha/(1-\alpha)] = k_{\mathrm{B}}t + c. \tag{2}$$

The derivative form (1) shows clearly the dependence of the rate on both the amount of reactant left and the amount of product formed, known as autocatalysis. Eq. (2) was found to describe the kinetics of isothermal decomposition of potassium permanganate (Prout and Tompkins, 1944), but the results for the decomposition of silver(I) permanganate (Prout and Tompkins, 1946) were better fitted by:

$$\ln[\alpha/(1-\alpha)] = k_{\mathrm{B}}\ln(t) + c', \tag{3}$$

which is referred to as the *modified* Prout–Tompkins equation.

A more general rate equation has been proposed (Sesták and Berggren, 1971; Ng, 1975; Malek and Criado, 1991) to include most of the familiar rate equations. This equation is often referred to as the Sesták–Berggren equation:

$$(\mathrm{d}\alpha/\mathrm{d}t) = k\alpha^{m}(1-\alpha)^{n}(-\ln(1-\alpha))^{p}. \tag{4}$$

When $m = n = 1$ and $p = 0$, the general equation becomes the Prout–Tompkins equation. Ng (1975) has discussed the application, under isothermal conditions, of the more limited expression:

$$(\mathrm{d}\alpha/\mathrm{d}t) = k\alpha^{m}(1-\alpha)^{n}. \tag{5}$$

The relative values of m and n determine relative contributions from the acceleratory and decay regions.

The origin of an equation of the form of the PT equation is difficult to trace, although the equation is sometimes also referred to as the Austin–Rickett equation (Austin and Rickett, 1939). Prout and Tompkins (1944) were prompted in their choice of equation by the resemblance of the plots (Brown, 1997) to the hyperbolic function, tanh.

3. The Prout–Tompkins (PT) model

The mechanistic model on which the PT equation was originally formulated was based on the concept of 'nucleus branching', analogous to homogeneous chain reactions. The energy chain theory on which this model was based is now regarded as unacceptable because energy quanta released from reaction are expected to be dispersed as thermal energy and not specifically transferred to potential reactant species. The model that was clearly and graphically described by Prout and Tompkins (1944) involved particle disintegration, which was promoted by product generation at branching nuclei, thus exposing more surface on which decomposition proceeds. This model has been re-examined recently in considerable detail by Jacobs (1997). Unrestricted 'branching', without allowance for termination, would lead to an exponential dependence of on t:

$$\alpha = k\exp(k_{\mathrm{B}}t),$$

where k_{B} is the rate coefficient for nucleus branching. Acceleratory behaviour cannot be maintained indefinitely in any real reaction and allowance for termination can be made by including a term k_{T}, so that:

$$\mathrm{d}\alpha/\mathrm{d}t = (k_{\mathrm{B}} - k_{\mathrm{T}}\alpha)\alpha \tag{6}$$

where $k_{\mathrm{T}}\alpha$ is a measure of the probability of termination which increases with α.

Eq. (1) requires an additional term to represent the initiation of the nucleation that subsequently undergoes branching, to enable such reactions to start. α_0 is thus the extent of initial decomposition that occurs before the time t_0 when chain branching becomes dominant.

At the point of inflection (α_i, t_i), from Eq. (6):

$$d\alpha^2/dt^2 = (k_B - 2k_T\alpha_i) = 0 \tag{7}$$

and

$$k_B = 2k_T\alpha_i. \tag{8}$$

Assuming (Jacobs, 1997) that the ratio k_B/k_T is independent of α,

$$d\alpha/dt = k_B\alpha(1 - \alpha/2\alpha_i) \quad \text{for } \alpha \geq \alpha_0 \tag{9}$$

Hence:

$$\ln[\alpha/(1 - \alpha/2\alpha_i)] - \ln[\alpha_0/(1 - \alpha_0/2\alpha_i)] = k_B(t - t_0), \tag{10}$$

which Jacobs (1997) has termed the generalized Prout–Tompkins (GPT) equation.

Prout and Tompkins (1944) considered the particular case of sigmoid α-time curves, with the point of inflection at $\alpha_i = 0.50$. Eq. (10) then becomes:

$$\ln[\alpha/(1 - \alpha)] - \ln[\alpha_0/(1 - \alpha_0)] = k_B(t - t_0), \tag{11}$$

which has the same form as Eq. (2). Jacobs (1997) has discussed the assumptions made in deriving the GPT equation: (i) that the probability of termination is $k_T\alpha$, and (ii) that the ratio k_B/k_T is independent of α. The need for proper consideration of the inflection point (and the initial decomposition α_0) was illustrated by re-analysis of the data for the decomposition of $AgMnO_4$ in terms of the GPT equation. Slight adjustment of α_i from the 0.500 of the original PT equation to 0.466 for the GPT equation gave a remarkable improvement in fit of the data for whole crystals, while the data for ground crystals required $\alpha_i = 0.213$.

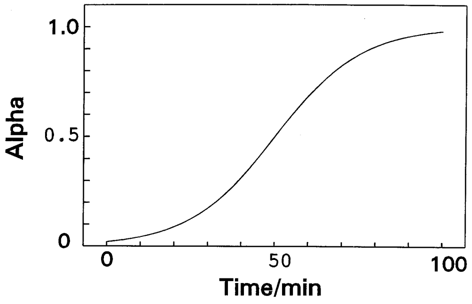

Fig. 1. Prout–Tompkins plot using $k = 0.07784$ min^{-1} and $t_0 = 50$ min.

The *modified* Prout–Tompkins Eq. (3) is obtained (Prout and Tompkins, 1946) if k_B varies inversely with time (i.e., there is a decrease in the effectiveness of branching as reaction proceeds).

Carstensen and Pothisiri (1975) also rejected the assumption that the inflection point was at $\alpha_i = 0.5$ and they developed an approach in which both the branching and termination probabilities are functions of time. Under certain conditions this resulted in the deceleratory section of an α-time curve approximating to first-order behaviour. The authors claimed that the fewer and less drastic assumptions made in the development of their equations suggested advantages in their use.

4. Distinguishability from other sigmoid models

A typical α-time plot for the Prout–Tompkins model, i.e.,

$$\alpha = [1 + \exp(-k(t - t_0)]^{-1},$$

is shown in Fig. 1, using: $k = 0.07784$ min^{-1} and $t_0 = 50$ min, so that $\alpha = 0.50$ at $t = 50$ min.

The thermal decompositions of many solids, other than permanganates, under isothermal conditions, give sigmoidal α-time curves (Prout and Tompkins, 1946; Young, 1966; Ng, 1975; Brown et al., 1980; Jacobs, 1997), e.g. mercury(II) fulminate, lead oxalate, silver oxalate, nickel formate, silver oxide, barium and calcium azides, etc., as well as some solid phase transitions, solid–solid reactions and solid–gas reactions (including heterogeneous catalytic processes) that can be described by the PT equation (Brown, 1997). In many such studies, it is difficult to decide whether the experimental results are best described by: (i) the PT equation with a single k value; (ii) the JMAEK equation with an appropriate value of n; (iii) the PT equation with two different k values; or (iv) by application of separate models to the acceleratory and decay regions. To these possibilities must now be added (Jacobs, 1997): (v) the use

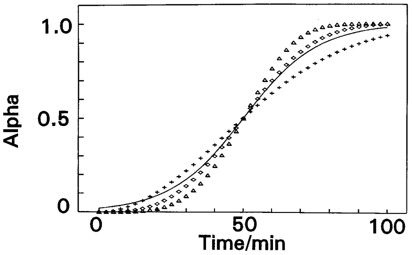

Fig. 2. Prout–Tompkins plot using $k = 0.07784$ min^{-1} and $t_0 = 50$ min (full line), compared with the plots for the A2 (+); A3 (◇); and A4 (△) models calculated so that $\alpha = 0.50$ at $t = 50$ min.

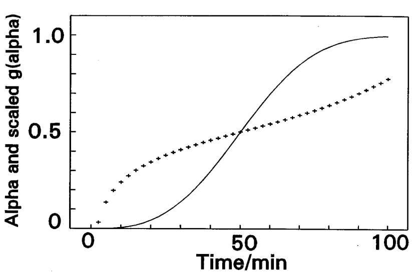

Fig. 3. The Avrami–Erofeev model A3 analysed using the linear form of the Prout–Tompkins equation g(α). This function has been scaled, (g(α)/20) + 0.5, for plotting (+) on the same axes.

of the GPT equation with appropriate values of α_i and α_0.

The sigmoid form of the α-time curve expressed by Eq. (5) is similar in shape to those derived from the Avrami–Erofeev equation (model An) (Brown et al., 1980) (also attributed to Johnson, Mehl and Kholmogorov, hence the JMAEK equation). (Useful discussion of these models of nucleation-and-growth processes is given in the review by Jacobs (1997).) Non-integer values of n in the JMAEK equation have been attributed (Hulbert, 1969) to diffusion control.

Distinguishing the fit of data to these alternative kinetic expressions is difficult (Brown and Galwey, 1979; Galwey and Brown, 1995). In Fig. 2, the PT function is compared with those of the A2, A3 and A4 models, calculated so that $\alpha = 0.50$ at $t = 50$ min. On this basis, the A3 function is closest to the PT function. This similarity is reinforced by the plots shown in Fig. 3, where the α-time curve for the A3 model has been analysed using the linear form of the PT equation (suitably scaled for plotting on the same axes). The latter plot is approximately linear over a wide range of α (about 0.05–0.95). The inflection points for the An models occur at $\alpha = 0.398$ ($n = 2$), $\alpha = 0.497$ ($n = 3$) and $\alpha = 0.545$ ($n = 4$).

Young (1966) has commented unfavourably on the practice of applying the PT equation with two different k values, above and below the inflection point. The effect of doing so, i.e., $k = k_1$ at $\alpha \leq 0.50$ and $k = k_2$ at $\alpha > 0.50$, has been illustrated (Brown, 1997) for different ratios of $k_2{:}k_1$. In practice, such a transition is likely to be more gradual. Plots of the α-time curves derived from the more general autocatalytic rate Eq. (5), for different combinations of m and n, have also been given (Brown, 1997).

Special problems of the application of the Prout–Tompkins model under *programmed temperature* conditions have been discussed by Criado et al. (1975). A comparison of kinetic results obtained from isothermal and programmed temperature experiments (Benoit et al., 1985) showed that compounds whose isothermal decompositions were describable in terms of the PT model over at least 90% of the decomposition, gave apparent first-order behaviour under non-isothermal conditions with excessively high E_a values.

5. Pharmaceutical applications

Pharmaceutical studies of stability are generally concerned mainly with initial degradation. Information is usually required on the degradation of the drug alone, on mixing with excipients, and in the presence of moisture. Accelerated degradation studies have to be extrapolated to lower temperatures, with allowance for the possibility of phase changes, and taking the estimated errors in the kinetic parameters (E_a, A and g(α)) into account. When the degradation curves are deceleratory overall, assumption of zero-order behaviour in the early stages of reaction is reasonable. This is not acceptable for sigmoidal α-time curves.

Use of the Prout–Tompkins equation in the kinetic analysis of reactions of pharmaceutical interest has been widespread, probably because of the influential and prolific publications on the subject by J.T. Carstensen and co-workers (Carstensen and Musa, 1972; Carstensen, 1974, 1995; Carstensen and Pothisiri, 1975; Carstensen and Kothari, 1981, 1983).

Bawn (1955) has discussed the thermal decomposition of organic solids in general. As a consequence of the bonding in and, hence, the crystal structures of organic solids, melting or sublimation may be expected to precede or accompany thermal decomposition. Galwey (Carr and Galwey, 1986; Galwey, 1995a,b) has discussed the possible role of melting in thermal reactions of initially solid reactants, which is not always considered in the interpretation of kinetic data and the formulation of reaction mechanisms. Formation of a liquid phase may result in increased rates of isothermal decomposition and produce sigmoid α-time curves. As a model, Bawn (1955) considered the situation where reactant A is soluble in product B with molar solubility, s. When the extent of decomposition is α, the fraction of A in the liquid phase is αs, and in the solid phase is $(1-\alpha-\alpha s)$. If the rate coefficients for reactions in the solid and in the liquid phases are k_s and k_l, respectively, then:

$$\mathrm{d}\alpha/\mathrm{d}t = k_s(1-\alpha-\alpha s) + k_l\alpha s = k_s + K\alpha,$$

where $K = k_l s - k_s s - k_s$, and:

$$\alpha = (k_s/K)[\exp(Kt) - 1]. \tag{12}$$

The expected ratio k_l/k_s can be estimated (Bawn, 1955) as follows. Using:

$$k_s = A_s \exp(-E_s/RT) \quad \text{and}$$

$$k_l = A_l \exp(-E_l/RT)$$

and assuming that the difference $E_s - E_l$ is equal to the molar enthalpy of melting, then if $A_s \approx A_l$:$k_l/k_s \approx \exp(\Delta H_{\mathrm{melting}}/RT)$.For a typical value of $\Delta H_{\mathrm{melting}} \approx 20$ kJ mol^{-1} and $T = 400$ K, $k_l/k_s = 410$.

As Carstensen (1974) has pointed out, the α-time curves for the Bawn model are sigmoidal, being acceleratory according to Eq. (12), up to the liquefaction point, where $\alpha = \alpha' = 1/(1+s)$ at $t = t'$, and deceleratory beyond according to:

$$(1-\alpha)/(1-\alpha') = \exp[-k_l(t-t')]. \tag{13}$$

Carstensen and Musa (1972) used the Bawn model in describing their results for the decomposition of a series of substituted benzoic acids.

To test the Bawn model, early stages of decomposition should give a linear plot of $\ln \alpha$ against t and the later stages a linear plot of $\ln(1-\alpha)$ against t. The same holds for the PT model, so the two models cannot readily be distinguished on kinetic grounds.

An early example of the application of the PT equation was that of Vaughan and Phillips (1946) to the sigmoid α-time curves obtained for the isothermal decomposition (50–80°C) of the solid explosive, 2-nitrobenzene-4-diazo-1-oxide. Neither the solid end products nor the gaseous products showed catalytic effects on the decomposition and microscopic examination did not indicate partial melting, so the branching mechanism suggested by Prout and Tompkins was assumed to apply.

The decomposition of *m*-nitroperoxybenzoic acid (Debenham and Owen, 1966) proceeds entirely in the solid phase at 66.5°C, but at temperatures up to 90°C the reactant melts at some stage of the decomposition. The PT expression was used to describe the symmetrical sigmoid α-time curves obtained. The fact that the reactant melts invalidates the PT model, but autocatalysis of the decomposition by *m*-nitrobenzoic acid, the principal product of decomposition, was shown to occur. Addition of other substituted benzoic acids to the reactant also catalysed decomposition.

The kinetics of the solid state transition between two crystal forms of diisopyramide, over the temperature range 37–76°C, were followed by differential scanning calorimetry (Gunning et al., 1976), and results were described by the PT equation, with $E_a = 144$ kJ mol^{-1}. The phase change was presumed to be governed by nucleation and growth but occurrence of melting could not be ruled out.

The sodium salt of amoxicillin decomposes in the solid state (Mendez et al., 1989) in a sequential reaction consisting of two pseudo first-order processes. Amoxicillin trihydrate, however, is more stable and decomposes (37–110°C) according to the PT model. Measurement of the extent of decomposition was by chemical analysis using HPLC. The limited amount of data did not give a particularly convincing kinetic analysis (see below).

Carstensen and Pothisiri (1975) chose *p*-aminosalicylic acid as a model system for studying the influence of moisture on decomposition. Kornblum and Sciarrone (1964) had earlier shown that decarboxylation in the solid state was dependent upon temperature, moisture, pressure and particle size. α-time curves for decomposition (70–80°C) of dry powder under atmospheric pressure were unsymmetrically sigmoidal. An activation energy of 172 kJ mol^{-1} was calculated. Larger crystals gave longer induction periods, and sharper acceleratory regions than the powder. Microscopic examination showed explosive cracking of crystals. Under decreased pressure the rate of degradation increased and was accompanied by sublimation of *m*-aminophenol. In a moist atmosphere, the induction period was markedly shortened and the degradation rate was increased. The apparent activation energy was decreased to 123 kJ mol^{-1} and was compared with the value of 81 kJ mol^{-1} reported for decarboxylation of *p*-aminosalicylic acid in solution (Kornblum and Sciarrone, 1964). Carstensen and Pothisiri (1975) confirmed the sigmoid form of the degradation curves for dry powder and applied a modified form of the PT model (mentioned above). Their very quantitative studies of the effect of moisture on degradation supported the Leeson and Mattocks (1958) theory that decomposition occurs in an adsorbed layer of saturated solution of the drug.

Carstensen and Attarchi (1988) studied the decomposition of aspirin in the solid state in the presence of limited amounts of moisture to test the Leeson and Mattocks (1958) model. Decomposition curves were sigmoidal. Carstensen and Attarchi (1988) explained their results in terms of model based on the Prout–Tompkins model with surface sites activated by the presence of water. Prout–Tompkins kinetics had been used by Garrett et al. (1959) to describe aspirin anhydride degradations studied at higher temperatures. Ball (1994), in a detailed kinetic study of the hydrolysis of solid aspirin (95–114°C), fitted the sigmoid curves obtained to the Avrami–Erofeev equation (Brown et al., 1980).

The kinetics of the solid state thermal decompositions of tetramethyldianilinium sulfates to give the corresponding dimethylaminobenzenesulfonic acids were described (Singh et al., 1997) using the PT equation. Activation energies for these decompositions were found to be linearly related to the $\text{p}K_{\text{a}}$ of the corresponding amine. Proton transfer was proposed to be the primary decomposition step.

Glycine hydrochloride was used as a model solute (Milton et al., 1997) to study crystallization kinetics between the glass transition region (-84°C) and the eutectic melting temperature (-28°C) by DSC. Crystallization proceeded according to the Prout–Tompkins model. The mechanism suggested was of crystal growth from nuclei formed during the freezing process. The temperature dependence of the crystallization rate constant in the temperature range studied followed Arrhenius kinetics rather than Williams–Landel–Ferry kinetics (Williams et al., 1955).

The interactions of solid drugs and excipients are of both theoretical and practical importance. Carstensen and Kothari (1983) have studied the interaction between the drug, 5-alkyloxy-2-furoic acid, and a common pharmaceutical excipient, microcrystalline cellulose. α-time curves for mixtures were sigmoidal, as had been found (Carstensen and Kothari, 1981) for the pure furoic acids. Unlike the decompositions of the pure furoic acids, the formation of a liquid phase was not observed, although this could have been masked by the microcrystalline cellulose. Applicability of the Bawn and PT models was considered, and the Bawn model gave the lower residual sum of squares. A detailed mechanism of interaction was proposed.

Leung and Grant (1997) reported on a comprehensive study of the solid state stabilities of the model dipeptides — aspartame (APM) and aspartylphenylalanine (AP). APM loses water below 150°C and at about 190°C loses methanol, through intramolecular aminolysis, to form 3-carboxymethyl-6-benzyl-2,5-dioxopiperazine (DKP) in a poorly-crystallized form which melts at 248°C. AP undergoes intramolecular cyclization at about 211°C to form DKP with release of water. The PT equation was used to describe the course of the isothermal degradations of both APM and AP to DKP. Activation energies were 268 ± 8 kJ mol^{-1} for APM and 242 ± 8 kJ mol^{-1} for AP. Similar values were obtained from programmed temperature DSC experiments at different heating rates, using the Kissinger (1957) 'model-free' method of kinetic analysis. The activation energy for the degradation of APM in solution was quoted (Leung and Grant, 1997) as 70 kJ mol^{-1}.

Leung et al. (1998) examined the hydration and dehydration behaviour of aspartame hemihydrate in greater detail. APM exists in the solid state as the hemi-hydrate in two different polymorphic forms. On exposure to water a 2.5 hydrate was formed. All hydrates dehydrated to the same crystalline anhydrous form, but the value of the activation energy for the degradation of APM to DPK (determined using the PT equation and the exponential and power law rate equations over the acceleratory region of their isothermal α-time curves) depended upon the degree of crystallinity of the anhydrous reactant.

An unusual citation of the PT equation was that of Bottom et al. (1997) who used it to describe their results for the rate of removal of formaldehyde from liquid-filled soft-shell capsules.

6. Conclusions

The Prout–Tompkins equation has achieved an interesting and unique status in solid state kinetics. Although the mathematical form of the equation was not novel, the interpretation given to its application in solid state reactions has led to developments in reaction models, including adaptation to fields outside of solid state chemistry, such as colloid and interface science (Brown, 1997).

The equation is not particularly convenient for application in kinetic analysis because of its indeterminate nature at small and large extremes of extent of decomposition, α. Its applicability is also not readily distinguishable from other rate equations (Brown and Galwey, 1979) which give sigmoidal α-time curves, i.e., the JMAEK equation (Ball, 1994), especially if non-integer values (Hulbert, 1969) of the exponent n are considered.

It is not usual to cite a specific reference to a kinetic model which *did not* apply to the reaction considered, unless the author is disputing an earlier claim of applicability, but a few of the articles (e.g. Broadbent et al., 1991) cite the Prout and Tompkins (1944) paper in indicating the difficulty of deciding between the PT and the JMAEK equations.

The main mechanisms for accounting for the applicability of the PT equation are the original model of branching nuclei (which requires that melting be excluded), autocatalysis or partial melting. Several studies support the occurrence of one or other of the first two possibilities. Other studies suggest the occurrence of possibilities two and three concurrently. If melting is a possibility, the Bawn model (Bawn, 1955; Carstensen, 1995) should be considered and evidence of melting sought by microscopy or DSC.

Obviously there are many studies of stability of pharmaceuticals where deceleratory α-time curves are obtained and hence the PT model is inappropriate. Where sigmoid α-time curves have been obtained, there has been a surprising lack of examination of alternative kinetic descriptions, with the PT equation being accepted as an empirical method of comparing this type of decomposition.

Acknowledgements

It is a pleasure to record the enthusiastic participation of Mr R. Kimber (Queen's University of Belfast) and Mrs V. Botha (Rhodes University) in the literature searches.

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