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DECOMPOSITION PROFILES OF OXYGEN SENSITIVE DRUGS IN THE PRESENCE OF ANTIOXIDANT

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ABSTRACT

It is shown that sodium bisulfite, when used in aqueous preparations of p-amino-N-(2-diethylaminoethyl)-benzamide prevents oxidation for a given length of time. At a point of exhaustion, oxidation of the active substance commences. Both phases are first order in degrading substance. Since oxygen solubility in aqueous media is a function of temperature, an ordinary Arrhenius type extrapolation is not possible. A rational method for extrapolation of accelerated data to room temperature of oxygen sensitive solutions is presented.

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not voluminous. A partial listing is given in the references. As examples: Ventura et al.[1] studied the oxidation of propildazine, Schroeter[2] studied the oxidation of sodium sulfite and bisulfite and found them to be first order with respect to oxygen, Kassem[3]

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studied the effect of metals on ascorbic acid oxidation, Brown and Leeson[4] studied oxidation by means of loss of oxygen in the headspace; Asker et al.[5] studied the mechanism of ascorbic acid oxidation in solution; Wrona and Dryhurst studied the oxidation of 5-hydroxytryptamine[6] and Al-Turk et al. studied the oxidation of nifedipine[7].

In spite of the paucity of publications, oxidation of pharmaceuticals is a field which is attracting more attention of late, and one of the practical formulations problems is, of course, finding a method of slowing down or preventing the oxidation. One such means is the use of antioxidants.

Sodium bisulfite is an antioxidant frequently used and acts in a consumptive capacity, in that it oxidizes more rapidly than the drug substance, and protects the latter as long as it is not exhausted. Hence, as long as the sodium bisulfite is in excess it will protect the product. Use of plastics limits the length of time of protection because most plastics are permeable to oxygen.

The mode of decomposition in a system consisting of (a) water, (b) oxidizable drug substance, (c) sodium bisulfite and (d) dissolved oxygen has been investigated using p-amino-N-(2-diethylaminoethyl)-benzamide dissolved in an aqueous solution of maltilol.[c]

MATERIALS AND METHODS

An aqueous system containing the following ingredients per mL: p-amino-N-(2-diethylaminoethyl)-benzamide[d1] 50 mg; sodium bisulfite 1 mg; maltilol[e] 750 mg; methyl paraben 1 mg; propyl paraben 0.2 mg; sachharin 1 mg; sodium acetate/acetic acid q.s. ad pH 5; flavors and water q.s.

The solution was transferred into 4 oz amber bottles. Samples were kept at temperatures of 40, 50, 60 and 70°C. All samples were assayed for the initial drug content. Samples were withdrawn at specific time intervals and the percent drug remaining was determined using the HPLC procedure described below:

A 1.0 mL sample was diluted 1:2500 the final solution also containing the internal standard solution. The solution was filtered

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[c] This was selected to mimic a pharmaceutical system. A sugar syrup was also investigated and showed the expected Shiff's base reaction, but that was not the point of major investigation of this study.

[d] Obtained via Danbury Pharmacal, Danbury CT 06810, Lot # 02794C
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[e] Lycasin (Roquette Corp. Gurnee, IL 60031, lot No. 4672

through a 0.45 μm Millipore filter. A 20 μL sample was then injected into the HPLC system for analysis.

The HPLC system consisted of a Beckman 110B solvent delivery system, Beckman system organizer injecter fitted with a 20 μL loop; a model 420 system controller programmer[f] , a spectrophotometric UV detector[g] and an integrator[h] .

The column was a 10 μm, C-18 Partsil ODS-3 (250 x 4.6 mm) column[j]. The chart speed was maintained at 10 cm/min. The flow rate was set at 1.2 mL/min. The column pressure varied from 1500-2000 psi. The detector was operated at 254 nm and 0.04 AUFS. The column was operated at ambient temperature (22±2°C).

The mobile phase was aqueous 15% acetonitrile, 2% triethanolamine in aqueous sodium acetate/glacial acetic acid (4.72:1.8). The pH of the mobile phase was (adjusted to) 4.5 (with glacial acetic acid). The mobile phase was filtered through a 0.45 μm membrane filtration system[k] to remove any particulate matter.

RESULTS AND DISCUSSION

p-amino-N-(2-diethylaminoethyl)-benzamide is a fairly stable compound[8], and hence elevated temperatures and long storage times were employed. The system studied[c] is one in which p-amino-N-(2-diethylaminoethyl)-benzamide, denoted A in the following, is dissolved in a sugar alcohol, maltilol which provides no possibility for a Schiff's base reaction as would be the case in a sucrose syrup. The system also contains sodium bisulfite, denoted N in the following, as an antioxidant. The general degradation pattern in the aqueous sugar alcohol solution is shown in Fig. 1.

The profile is characteristic of the pattern established at all temperatures, and it is noted that the curves are biphasic. For a certain lag period (t(i)) the p-amino-N-(2-diethylaminoethyl)-benzamide content does not drop (Section AB in Fig. 1). After this time period there is a first order (exponential) decay of the p-N-(diethylaminoethyl)-benzamide.

In the following, the former period is denoted the lag period and the the latter the decay period. When the rate constants from

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[f] Beckman Instruments Inc., San Ramon, CA 94583

[g] Knauer Corp. Berlin W. Germany No 731.7100000

[h] Shimadzu Corp. Kyoto, Japan, C-R3A Chromatopac Integrator

[j] Supelco Inc., Supelco Park, Bellfonte, PA 16823-0048

[k] Millipore Corp., Milford, MA 01757

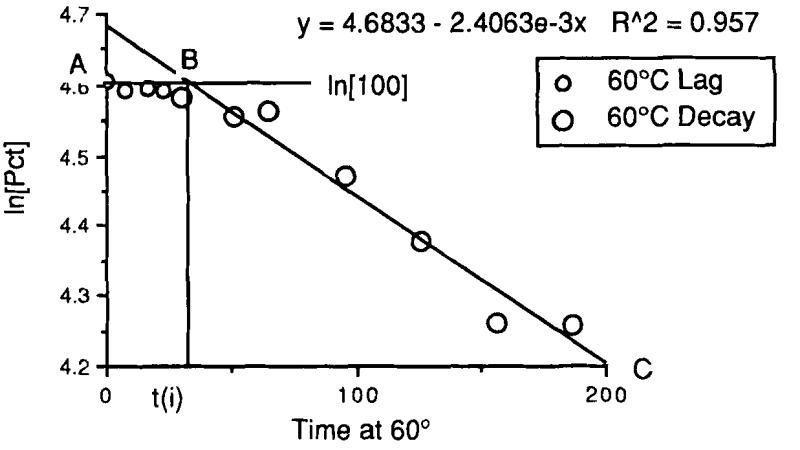

Fig. 1 Complete decomposition profile of p-amino-N-(2-diethylaminoethyl)-benzamide in aqueous sugar alcohol solution containing sodium bisulfite. Temperature 60°C. Time is in units of days.

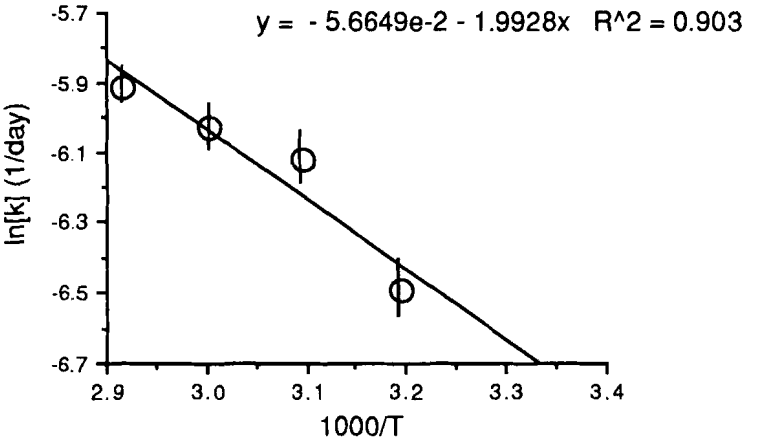

Fig. 2 Arrhenius plot of the rate constants from the decay periods.

the decay periods are plotted via an Arrhenius equation, then a straight line results as shown in Fig. 2.

The reason for the lag period may, at first, simply be thought of as the length of time in which there is sodium bisulfite present. As long as this is the case, it is the bisulfite which will decompose and not the p-amino-N-(2-diethylaminoethyl)-benzamide.

Once the sulfite is "exhausted", then the active ingredient will decompose. In reality the rate of decomposition of the drug substance will become noticable when the sulfite concentration has reached a certain, low level, e.g. $C/C_0 = ß^m$. The value of ß is not a priori known, but it may be assumed that it is temperature independent. It follows that the length of time required for a fraction $(1-\beta)$ of the sulfite to be used up would be t(i) given by

$$\ln[ß] = -k't(i) \quad \text{or} \quad t(i) = -\ln[ß]/k' = Q/k' \qquad (1)$$

where k' is the oxidation rate constant for sulfite and where it is recalled that $Q = -\ln[ß]$ is a positive number ($C/C_0 < 1$). Hence, taking logarithms:

$$\ln[t(i)] = \ln Q - \ln[k'] = \ln Q + (E/RT) + \ln Z \qquad (2)$$

where E is the energy of activation of oxidation of sulfite in solution exposed to atmospheres of 22% oxygen and Z is the (temperature independent) collision number. R is the gas constant and T is the absolute temperature.

An Arrhenius plot of t(i) is shown in Fig. 3, and the plot shows reasonable linearity. It should be noted that t(i) is obtained as the intersection of two lines, and, hence, is associated with a certain lack of precision.

The above line of argumentation is quite practical, because estimated temperature constants and lag times can be obtained by extrapolation of the Arrhenius plots for k (to k_{25}) and of t(i) (to $t(i)_{25}$), and an estimated percent retention after t months at room temperature can then be calculated as:

$$100\ (C/C_0) = 100 \exp[-k_{25}\{t-t(i)_{25}\}] \qquad (3)$$

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[m] Decomposition of the p-amino-N-(2-diethylaminoethyl)-benzamide substance might, for instance, not occur with a measurable rate until e.g. less than 5% of the sulfite is left. In that case $\beta = 0.05$

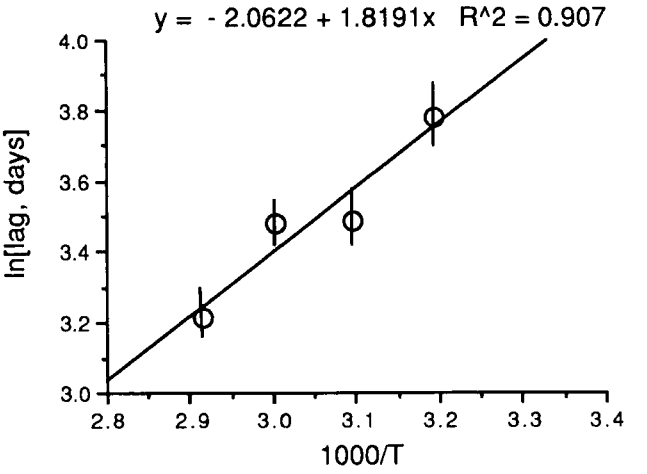

Fig. 3 Arrhenius plot of the lag times obtained from the intersection betweeen the horizontal parts of curves of the type in Fig. 1 (y = ln[100] = 4.6052) and the decay portion (ln[Pct] = -kt + q)

or, if the time required to reach C/C_0 = 0.9 (90% of p-amino-N-(2-diethylaminoethyl)-benzamide retained) is desired, then:

$$\ln[0.90] = -k_{25}\{t-t(i)_{25}\}$$

Matters are not quite that simple on a theoretical plane. First of all, the value of ß has been assumed to be the same at all temperatures, and this may not be the case, so a perusal of the theoretical profile is in order. For simplicity the reactions in question are considered to be[9]:

$$A + [O_2] \rightarrow \text{products} \quad (4)$$

$$B + [O_2] \rightarrow \text{sulfate} \quad (5)$$

The kinetic equations governing these two parallel reactions are given by:

$$dN/dt = - k_1[N][O_2] \quad (6)$$

$$dA/dt = - k_2[A][O_2] \quad (7)$$

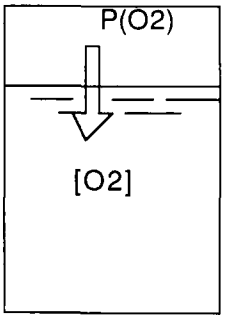

Fig. 4. Schematic of oxygen diffusion.

It is noted that the oxygen concentrations referred to are concentrations of oxygen in solution. Were there no reaction, then the oxygen concentration would be dictated by Henry's law, viz:

$$[O_2]_s = KP(O_2) \qquad (8)$$

where $P(O_2)$ is the partial oxygen pressure, $[O_2]_s$ is the saturation oxygen concentration at the given partial pressure, usually 0.22 atm, and K is the Henry's law constant. However, oxygen is being consumed by reactions (4) and (5) so that the oxygen concentration during the course of the reaction will be less than $[O_2]_s$, and oxygen will therefore continually diffuse into the solution from the supernatant atmosphere. The rate with which this will happen is assumedly Ficksian, so that:

$$\text{Rate of oxygen diffusion} = \phi\{[O_2]_s - [O_2]\} \qquad (9)$$

where ϕ is a diffusion coefficient which also depends on the geometry of the situation (e.g. the surface area and the agitation). The kinetic equation governing the oxygen concentration in solution is expressed in Eqs. 5, 6 and 9 which, combined, yield:

$$d[O_2]/dt = - k_1[O_2][N] - k_2[O_2][A] + \phi\{[O_2]_s - [O_2]\} \qquad (10)$$

Eqs. 6, 7 and 10 constitute three differential equations with three unknowns, and although theoretically solvable, a solution in closed form does not exist. Rather than seek approximate or generated solutions to this, the following approach is taken here.

A steady state in oxygen is assumed, and this is probably correct both in the beginning, when there is substantial amounts of sulfite present, and at the end, where there is virtually no sulfite present. This assumption leads to a zero accumulation of oxygen in solution, i.e.:

$$\text{Zero} = -k_1[O_2][N] - k_2[O_2][A] + \phi[O_2]_s - \phi[O_2] \quad (11)$$

$$\text{or} \quad [O_2] = \phi[O_2]_s/\{k_1[N] + k_2[[A] + \phi\} \quad (12)$$

Inserting Eq. 12 in Eqs. 6 and 7 give:

$$dN/dt = -k_1[N]\phi[O_2]_s \,/\, \{k_1[N] + k_2[[A] + \phi\} \quad (14)$$

$$dA/dt = -k_2[A]\phi[O_2]_s \,/\, \{k_1[N] + k_2[[A] + \phi\} \quad (15)$$

At the onsent, $k_1[N] >> k_2[A]$ and Eq. 9 becomes:

$$dN/dt = -k_1[N]\phi[O_2]_s/\{k_1[N] + \phi\} = -\phi[O_2]_s\{[N]/\{[N] + (\phi/k_1)\} \quad (16)$$

or:

$$dN\{([N] + (\phi/k_1))/[N]\} = -\phi[O_2]_s\, dt \quad (17)$$

Conventional integration of this[n] gives:

$$N - (\phi/k_1)\ln\{[N] + (\phi/k_1)\} = \gamma_1 - \phi[O_2]_s\{t\} \quad (18)$$

$$\text{where } \gamma_1 = N_o - (\phi/k_1)\ln\{[N_o] + (\phi/k_1)\} \quad (19)$$

and N_o is the initial concentration of sulfite.

An exactly similar equation holds for late time periods, where N is so small that now $k_1N << k_2A$. The point in time where this occurs is denoted t* in the following (and is conceptually the same as t(i)).

After t* the equation for A will be:

$$A - (\phi/k_2)\ln\{[A] + (\phi/k_2)\} = \gamma_2 - \phi[O_2]_s\{t\} \quad (20)$$

[n] Integral #32, pg. A-193, Handbook of Physics and Chemistry, 48th Ed., 1968

where $\gamma_2 = A_o - (\phi/k_2)\ln\{[A_o] + (\phi/k_2)\}$ (21)

The equations of type 20 will appear either zero or first order depending on the magnitudes of the various constants. It is noted that the steady state concentration of oxygen before and after t* may not be the same.

Although these equations are more exact than Eqs. 2 and 3, the latter are quite adequate in describing the decomposition of p-amino-N-(2-diethylaminoethyl)-benzamide, and presumably other substances as well. The proposed method is to plot the final decomposition profile, by appropriate order, at different temperatures and obtain rate constants and lag times, obtained as the intersection of the two decomposition lines. By Arrhenius plotting one may then obtain the room temperature rate constant and lag time and calculate the percent retained at a given, desired room temperature storage time, based on these two figures (e.g. using Eq. 3).

SUMMARY

The method proposed in this paper is both practical and theoretically challenging. It refers to the oxidation of an oxygen sensitive compound in the presence of an antioxidant. Methods for determining both lag time and rate constant by Arrhenius plotting, allows for determining the theoretical, extrapolated oxidation curve at room temperature.

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