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Accelerated stability studies of morphine injections in plastic ampoules

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Abstract

Although oxygen sensitive, morphine injections are produced in plastic ampoules. In this study, the shelf life of sodium metabisulphite stabilised morphine injections in plastic ampoules was evaluated by accelerated studies at temperatures ranging from 50 to 80°C. A derived model based on the rate equation and the Arrhenius equation was used for extrapolation. Determination of morphine and oxidation products was done by reversed phase ion pair HPLC. The concentration of morphine remained constant during the stability studies. The oxidation of morphine was partly compensated for by diffusion of water through the ampoules. A lag phase was observed for the formation of pseudomorphine. The shelf life is limited to 15 months by diffusion of water through the ampoules.

Keywords: Morphine; Plastic ampoules; Extrapolation; Shelf life; Oxidation; Accelerated studies

1. Introduction

Morphine is an oxygen senstitive drug and the most important oxidation products are morphine-*N*-oxide and pseudomorphine (Yeh and Lach, 1961). Despite the fact that most polymers used in plastic ampoules are permeable to gases (Kristensen and Møller, 1983; Florence and Attwood, 1988) and give limited protection of oxygen sensitive drugs (Pudipeddi et al., 1992), morphine injections are produced in plastic ampoules. Moreover, when stored in the presence of oxygen, morphine injections become discolorated by a yet unknown reaction (Vermeire and Remon, 1999). To remedy the situation morphine injections are frequently stabilised with the antioxidant sodium metabisulphite, protecting the drug substance from oxidation (Connors et al., 1986).

The oxidation of morphine is described by the rate equation for a second order reaction (Yeh and Lach, 1961):

$$-\frac{\mathrm{d[morphine]}}{\mathrm{d}t} = k[\mathrm{O2}][\mathrm{morphine}], \quad (1)$$

where [morphine] is the concentration of morphine, $[O_2]$ is the concentration of oxygen and k is the rate constant.

Although several stability studies of morphine and mixtures of morphine in injection and infu-

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sion devices have been performed (Holcomb et al., 1973; Deeks et al., 1983; Caute et al., 1988; Hung et al., 1988; Strong et al., 1994; Wu et al., 1995; Oustric-Medes et al., 1997; Sitaram et al., 1997; Vermeire and Remon, 1997), they have all been carried out at normal storage conditions or at slightly elevated temperatures. In particular, none of the studies have included an extrapolation of the morphine oxidation or water diffusion using the Arrhenius equation.

The Arrhenius equation is an empirical relation describing the effect of temperature on an observed rate constant for an uni- or bimolecular reaction. Since oxidation reactions consist of multiple steps, the equation is not always valid (Franchini and Carstensen, 1994). However, it is usually observed to be correct for complex reactions. The rate equation for a degradation, can be combined with the Arrhenius equation and in this way make extrapolation of accelerated stability studies possible (Nash, 1987; Ertel and Carstensen, 1990; Carstensen et al., 1992). Pudipeddi et al. (1992) have used this method and derived a model for extrapolation of oxidation of drugs in plastic ampoules. They did not use the model for extrapolation of real data.

The aim of this study was to evaluate the validity of derived models for the temperature dependence of morphine oxidation and water loss in plastic ampoules containing morphine injections stabilised with sodium metabisulphite. The model is further used for prediction of the shelf life of the product.

2. Theoretical

2.1. Oxidation of morphine in plastic ampoules

Assume a system consisting of a morphine solution with sodium metabisulphite in a plastic ampoule surrounded by an atmosphere with temperature T and relative humidity RH. The sodium metabisulphite protects the morphine from oxidation as long as it is present. This results in a complex degrading mechanism (Appendix A).

In stability studies the decrease in drug concentration is often less than 10%. Under these circumstances it is possible to assume 0 order kinetics (Connors et al., 1986) expressed by:

$$\frac{dC_{morphine}}{dt} = k_{obs} = k_{ox}[O_2], \tag{2}$$

where $C_{morphine}$ is the remaining amount of morphine, k_{obs} is the observed rate constant, k_{ox} is the rate constant for the oxidation of morphine and $[O_2]$ is the concentration of oxygen. After a lag-time t_l the sodium metabisulfite no longer protects the morphine from oxidation. If we assume that there is no degradation of morphine during the lag-time, an integration of Eq. (2) from t_l to t and $C_{morphine,0} = 100\%$ to $C_{morphine}$ gives:

$$\frac{C_{morphine} - 100\%}{[O_2](t - t_l)} = k_{ox}. \tag{3}$$

The duration of the lag-phase is given by (Tan et al., 1993):

$$\ln t_l = A_{sulphite} - \frac{E_{sulphite}}{R}\frac{1}{T}, \tag{4}$$

where $A_{sulphite}$ is a unknown frequency function, $E_{sulphite}$ is the activation energy, and R is the universal gas constant.

The temperature dependency of k_{ox} is given by the Arrhenius equation:

$$\ln k_{ox} = \ln A_{ox} - \frac{E_{ox}}{R}\frac{1}{T}, \tag{5}$$

where A_{ox} is a frequency factor and E_{ox} is the activation energy of the oxidation. Inserting Eq. (5) into Eq. (3) gives

$$\ln\left(\frac{C_{morphine} - 100\%}{[O_2](t - t_l)}\right) = \ln A - \frac{E_{ox}}{R}\frac{1}{T}. \tag{6}$$

Eq. (6) describes the degradation of morphine as a function of temperature. Degradation of morphine can thus be predicted at normal storage temperature on the basis of accelerated stability studies. The solubility of oxygen in water is temperature dependent and is given in tables.

2.2. Diffusion of water

The diffusion of water through plastic ampoules can be expressed by:

$$-\frac{dV}{dt} = k_{diff} P_{w,sat}(100\% - RH), \quad (7)$$

where V is the injection volume, k_{diff} is the diffusion rate out of the ampoules and $P_{w,sat}$ is the vapour pressure in air saturated with water. Integration of Eq. (7) from $V_0 = 100\%$ to V and $t_0 = 0$ to t gives:

$$\frac{100\% - V}{P_{w,sat}(100\% - RH)t} = k_{diff}. \quad (8)$$

The temperature dependency of k_{diff} is given by Arrhenius equation:

$$\ln k_{diff} = \ln A_{diff} - \frac{E_{diff}}{R}\frac{1}{T}, \quad (9)$$

where A_{diff} is a diffusion factor and E_{diff} is the activation energy. Inserting Eq. (9) into Eq. (8) gives:

$$\ln\left(\frac{100\% - V}{P_{w,sat}(100\% - RH)t}\right) = \ln A_{diff} - \frac{E_{diff}}{R}\frac{1}{T}. \quad (10)$$

Eq. (10) describes the diffusion of water through the ampoules as a function of temperature and relative humidity.

2.3. Concentration of morphine

For $t > t_1$, $C_{morphine}$ is given by Eq. (6), and V by Eq. (10). Combining these equations gives:

$$[\text{morphine}] = \frac{V_0 C_{morphine}}{V}, \quad (11)$$

where [morphine] is the measured concentration of morphine in the ampoule at time t. According to Eq. (11), the measured concentration of morphine depends on both oxidation of morphine and on volume.

3. Materials and methods

3.1. Materials

The stability studies employed morphine 10 mg/ml injections 'Nycomed Pharma'® (Nycomed Pharma, Oslo, Norway), a product containing morphine hydrochloride 10 mg, sodium metabisulphite 0.25 mg, sodium chloride 6.5 mg, hydrochloric acid 1 μmol and water ad 1 ml dispensed in bottlepacks. The outer package was a polypropylene box containing 10 ampoules.

The references used in the chromatographic analysis were morphini hydrochloridum ad iniectabilia (Norsk Medisinaldepot, Oslo, Norway) and morphine-*N*-oxide and pseudomorphine HCl (Vereinigde Pharmaceutische Fabrieken B.V., Apeldoorn, Holland). The mobile phase consisted of acetonitril HPLC-grade (Lab-Scan Ltd., Dublin, Eire), acetic acid 99–100% (J.T. Baker, Deventer, Holland), trietylamine 99% and 1-heptansulfonic acid sodium salt HPLC-grade (Acros organics, NJ, USA) and Milli-Q-water.

3.2. Methods

3.2.1. Chromatography

Liquid chromatography was carried out on a HP1100 system (Hewlett Packard, Waldbronn, Germany), and the column was a Hypersil C18-column (5 μm, 125–4.0 mm) (Hewlett Packard, Waldbronn, Germany). The pump was programmed to deliver a multiple segment gradient of acetonitril and a buffer consisting of heptansulphonic acid sodium salt 1.47 g/l, triethylamin 0.14% and acetic acid 1.33%:

$0 - 6$ min: composition A: acetonitril 10% and buffer 90%

$6 - 10$ min: linear gradient from composition A to composition B

$10 - 15$ min: composition B: acetonitril 18% and buffer 82%

The flow-rate was 1.5 ml/min and the injection volume was 20 μl. The substances were detected by an UV-diode-array-detector operated at 280 nm (morphine and morphine-*N*-oxide) and 254 nm (pseudomorphine).

3.2.2. Stability testing

Morphine 10 mg/ml injections 'Nycomed Pharma'® were stored at temperatures varying from 40 to 80°C and relativ humidities varying

from 40 to 75% in a Heraus Vötsch climate cabinet VLK 04/300 (Hereaus Vötsch GmbH, Baligen, Germany) for periods from 7 to 42 days. Samples were taken five times during the first week and once or twice a week thereafter.

3.2.3. Sample analysis

All samples were weighted individually before insertion and after removal from the climate cabinet. Additionally the weight of the empty plastic ampoules was measured, and the water loss was calculated.

Standard solutions were produced by dissolving reference standard in buffer yielding concentrations of morphine ranging from 700 to 1100 ng/μl and concentrations of pseudomorphine and morphine-*N*-oxide from 2 to 22 ng/μl. The samples were diluted 1:10 with buffer and assayed for morphine, morphine-*N*-oxide and pseudomorphine using liquid chromatography. The diluted sample concentrations were expected to lay within the interval of the standards.

4. Results and discussion

4.1. Chromatography

The chromatographic method was optimised for separation of morphine-*N*-oxide, morphine and pseudomorphine in a single run (Fig. 1). It was necessary to introduce a gradient in order to both separate morphine-*N*-oxide and morphine and eluate pseudomorphine as a sharp peak in reasonable time. The similarity of the hydrophilicity of morphine and morphine-*N*-oxide makes them difficult to separate. The method shows a resolution of 1.66 for morphine and morphine-*N*-oxide. Although the resolution of peaks of different heights should be 2 (Snyder et al., 1997), this was accepted because the smallest peak is eluated first.

The method accuracy, sensitivity and the linearity of the calibration curve is summarised in Table 1. Hundred percent is included in all 95% confidence intervals for the recovery of morphine and pseudomorphine except the lowest concentration of pseudomorphine. For all concentrations the precision of the method is below 1.1 and 4.1% RSD for, respectively, morphine and pseudomorphine.

We did not detect any morphine-*N*-oxide in the samples; the method accuracy for morphine-*N*-oxide was therefore not examined. The chromatogram shows several peaks in addition to morphine and pseudomorphine, examplified by Fig. 1. These peaks have not been examined, but most of them are eluated before the morphine peak and may therefore be hydrophilic sulphonate derivates. Peak purity was verified by DAD.

4.2. Stability studies

4.2.1. Water loss

The diffusion of water out of the ampoules is dependent on both temperature and relative humidity. Thus different combinations were tested.

The weight of the ampoules decreases during the entire periods examined (Fig. 2). The water-loss appears zero order, but it is not possible to differentiate between zero and first order kinetics when the water loss is below 14% (Connors et al., 1986). The water diffusion out of the ampoules increased at high temperatures and low relative humidity. This is in agreement with Eq. (10).

Eq. (10) was fitted to the experimental results by linear regression. A lack-of-fit test (Table 2) was performed. Since $F_0 > F_{25\%,3,58} = 1.42$ the models can be rejected at a 75% significance level. This is visualised in Fig. 3, which depicts a plot of Eq. (10). The figure shows a trend in the data. The decline in the water diffusion rate between 50 and 60°C exceeds the decline between 60, 70 and 80°C. This can be explained by a change in the characteristics of the amorphous polypropylen occurring at about 70°C (Martin, 1993). If the results from the 80°C experiments are left out, the model will still be rejected at a 75% significance level. This means that the model can not be used with statistical support. A possible explanation is that the model fails to take account of all relevant components. There might, e.g. be an alteration of the plastic polymers caused by relative humidity at high temperatures.

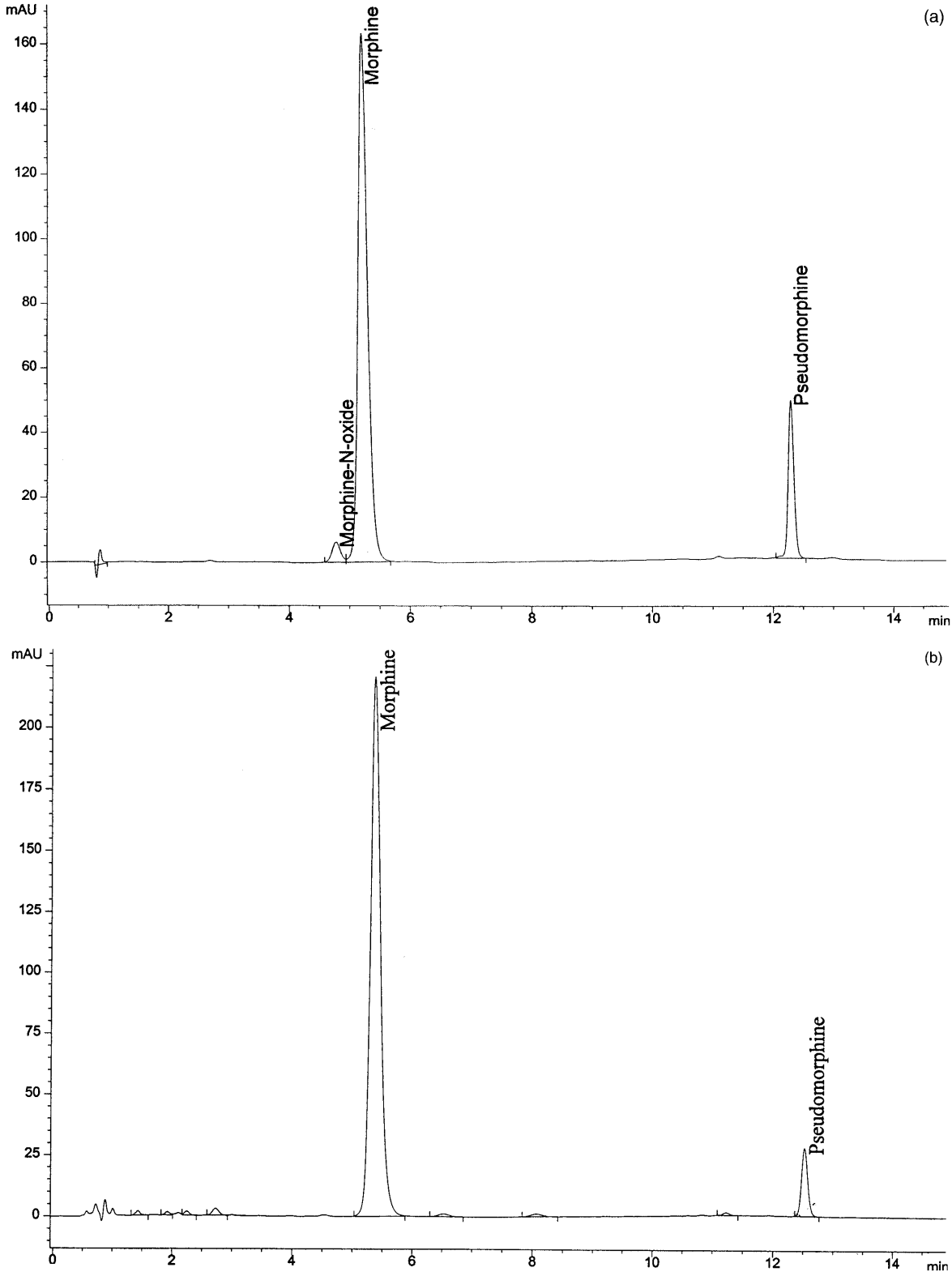

Fig. 1. The chromatograms of (a) a standard with morphine-*N*-oxide 22 ng/μl, morphine hydrochloride 700 ng/μl, and pseudomorphine 22 ng/μl and (b) a sample stored 36 days at 70°C and 75% relative humidity.

Table 1
The range, recovery, precision and limits of detection (LOD) and quantification (LOQ) of the HPLC method and the correlation coefficient of the calibration curve

	Range (μg/ml)	Concentration (μg/ml)	Accuracy (%)			Calibration curve Correlation coefficient	LOD (μg/ml)	LOQ (μg/ml)
			Recovery (95%–confidence intervals)	Method prescision (RSD)	System prescicion (RSD)			
Morphine	700–1100	700	97.5–102.0	0.91	0.10	>0.999	31	700
		800	99.5–104.3	0.95	0.10			
		900	99.0–104.4	1.08	0.10			
		1000	99.3–102.7	0.69	0.10			
		1100	97.8–101.8	0.81	0.10			
Pseudomorphine	2–22	2	106.5–126.9	4.09	12.20	0.998	0.13	2
		7	92.0–102.0	2.02	1.70			
		12	94.9–105.5	2.14	2.80			
		17	93.5–106.9	2.69	1.80			
		22	95.0–104.8	1.97	0.70			
Morphine-*N*-oxide	2–22					>0.999	0.21	2

4.2.2. Morphine oxidation

The data needed to calculate an oxidation rate had to be collected within six months. It was thus necessary to store the ampoules at temperatures ranging from 60 to 80°C. Temperatures above 80°C were not used because elevation of the storage temperature may change the rate determining reaction (Connors et al., 1986). The elevation of the storage temperature in connection with accelerated stability studies should therefore be limited to lower storage temperatures than 80°C.

The concentration of morphine in the ampoules from the accelerated stability studies was calculated as a percentage of the initial concentration. The concentration varied between 97 and 103% in the entire storage time at all temperatures examined (Fig. 4). Morphine degradation is partly compensated for by water diffusion out of the plastic ampoules. In Fig. 5 the remaining amount of morphine in percent of the initial concentration is visualised.

The oxidation rate can not be determined on the basis of this stability study. Despite one month of storage at 80°C, only 13% degradation was obtained. Connors et al. (1986) recommend at least 10–20% degradation in order to differentiate between 0 and 1 order kinetics.

Fig. 6 shows the formation of pseudomorphine. The formation of pseudomorphine is initiated after a lag phase which decreases at increasing temperatures. The lag phase is assumed to be depended on the degradation of sodium

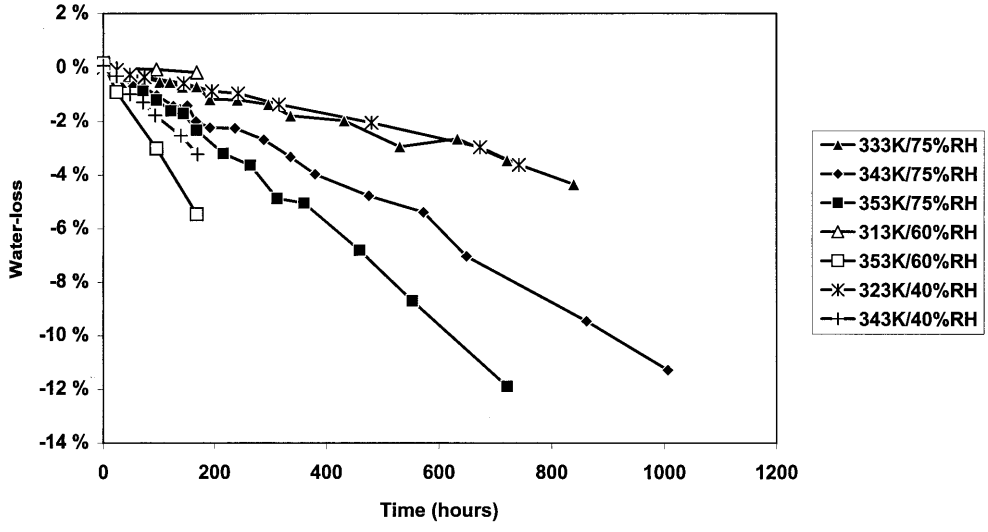

Fig. 2. The water-loss of the samples from the accelerated studies.

Table 2
Lack-of-fit analysis of the results from the accelerated studies[a]

	SS_{TOTAL}	SS_{REG}	SS_{PE}	SS_{LOF}	$n-m$	$m-2$	F_0	$F_{0,25,m-2,n-m}$
Water diffusion	9.00	2.81	5.43	2.39	58	3	8.50	1.41
Water diffusion without 80°C	6.93	3.84	2.50	0.60	44	2	5.23	1.44
Morphine oxidation	13.28	8.50	4.37	0.40	29	1	2.65	1.38

[a] The hypothesis tested are: H_0: the model fits the data; H_1: The model does not fits the data; The H_0 hypothesis can be rejected at a 75% significance level if $F_0 > F_{0.25,m-2,n-m}$; SS_{TOTAL} = total sum of squares; SS_{REG} = sum of squares of regression; SS_{PE} = sum of squares of the pure error; SS_{LOF} = sum of squares of the lack-of-fit; n = number of expermental conditions; m = number of parallells; F_0 = F-value.

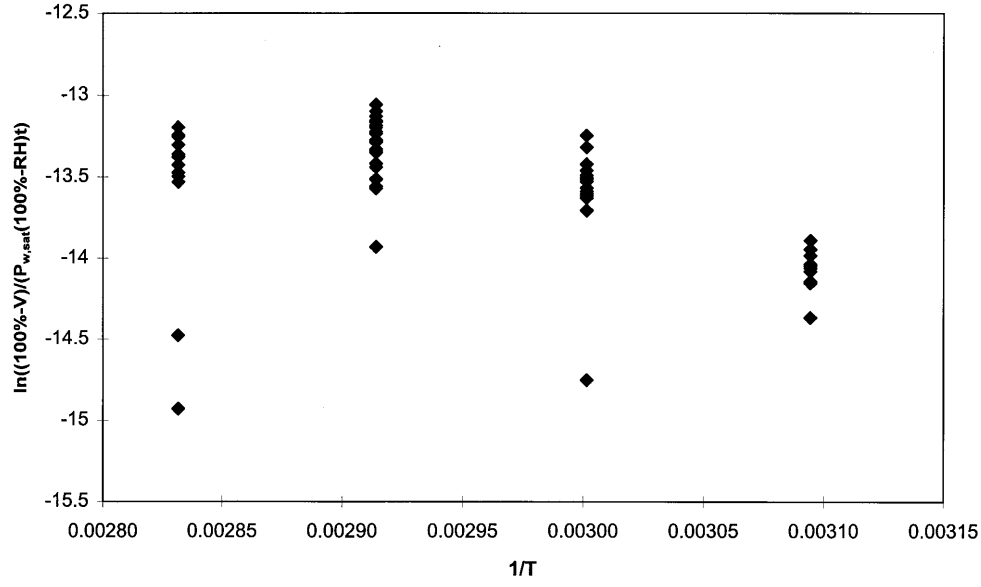

Fig. 3. The plot of the results from the accelerated studies adjusted to Eq. (10).

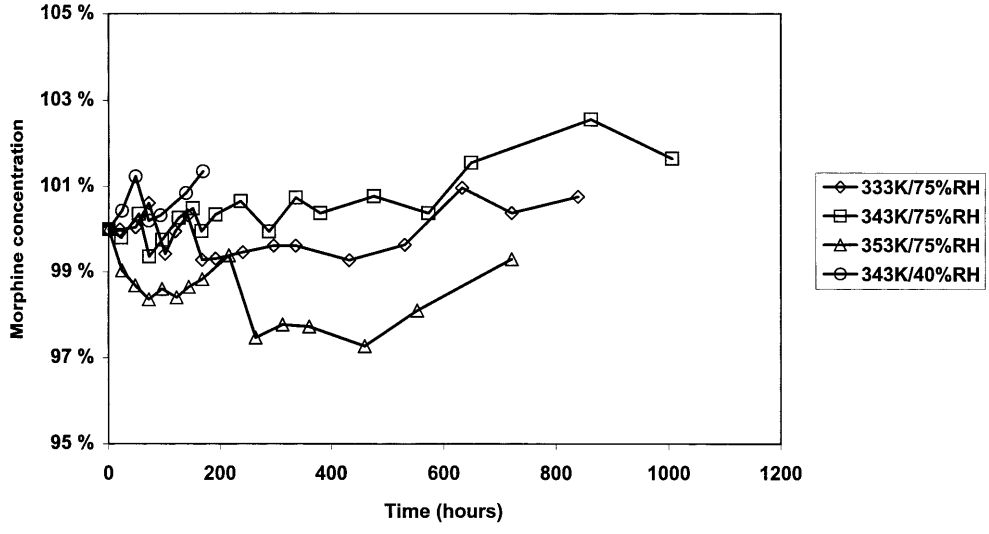

Fig. 4. The concentration of morphine in the samples from the accelerated studies.

metabisulphite. There are differences in the shapes of the curves from the three studies. Whereas the curves representing 60 and 70°C approach 0 order, the curve representing 80°C has a sigmoid shape. The concentration of pseudomorphine seems to approach a maximum level at 80°C. At 60 and 70°C the concentration of pseudomorphine increases continuously and passes the maximum level at 80°C. This indicates that there might be a different reaction at 80°C, which can be related to the oxidation rate of morphine. The differences in formation of pseudomorphine at the three temperatures is assumed not to have any influence on the duration of the lag phases.

Eq. (6) was fitted to the experimental results by linear regression. A lack-of-fit test (Table 2) was used to evaluate the correlation between the models and the results. Since $F_0 > F_{25\%,1,29} = 1.38$ the models can be rejected at a 75% significance level. The lack-of-fit test is sensitive if there are few degrees of freedom for the sum of squares of lack of fit. This may result in rejection of models even though they fit the measured results adequately. The plot of Eq. (6) (Fig. 7) shows a trend in the

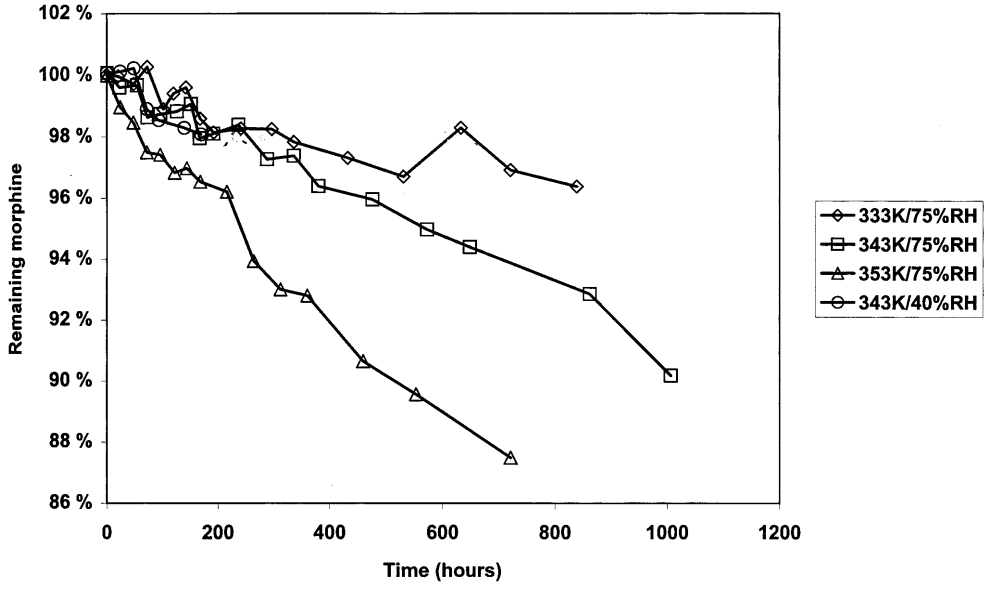

Fig. 5. The remaining amount of morphine in percent of the initial amount in the samples from the accelerated studies.

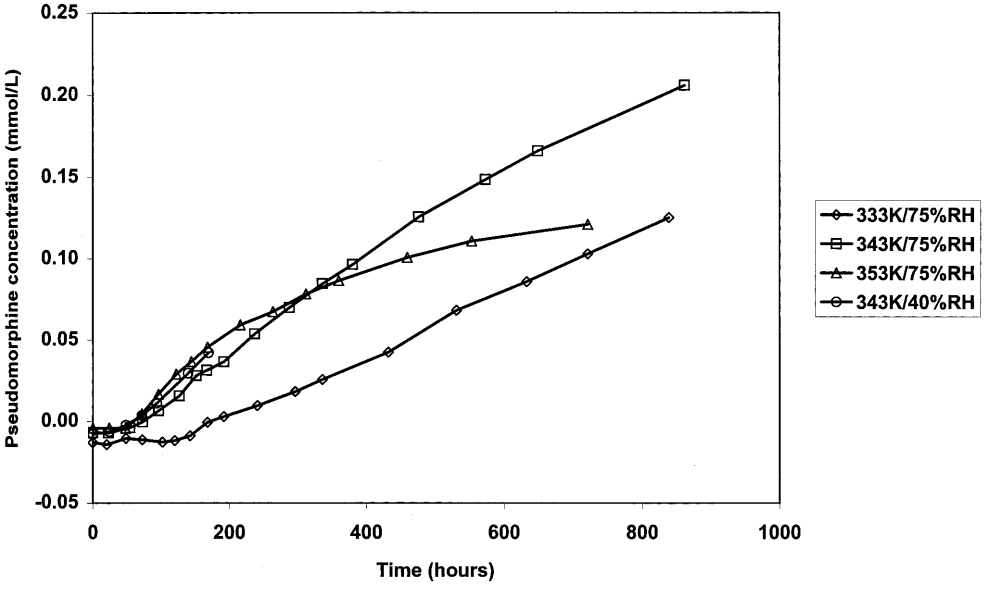

Fig. 6. The concentration of pseudomorphine in the samples from the accelerated studies.

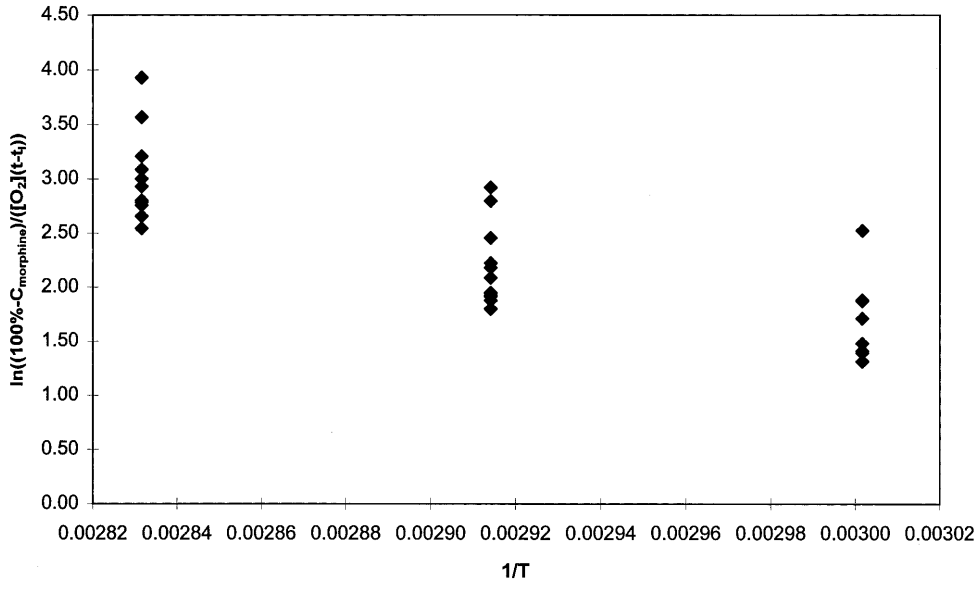

Fig. 7. The plot of the results from the accelerated studies adjusted to Eq. (6).

Table 3
The concentration of morphine in the samples from the earlier long-time study ($[morphine]_{measured}$) at 25°C and ambient humidity and the extrapolated results for the concentration of morphine ($[morphine]_{extrapolated}$), the percentage of remaining morphine ($C_{morphine}$) and remaining water (V) at 25°C and 35% relative humidity

Time (months)	Morphine (mg/ml)		$C_{morphine}$ (%)	V (%)
	Measured	Extrapolated		
6	9.7	10.2	98.8	96.9
12	10.0	10.3	95.3	92.5
18	10.0	10.4	92.3	88.7
24	10.1	10.5	89.2	84.9
36	10.8	10.8	83.2	77.4
48		11.1	77.2	69.9

data. A possible explanation is that an unknown component is not taken care of in the model. This can for example be an alteration in the rate determining mechanism at different temperatures.

4.2.3. Extrapolation

Extrapolation presupposes that the same rate determining reaction is valid at both the accelerated and the extrapolated conditions. However, increasing deviation from the experimental conditions increases the risk for a change in the reaction pattern. In spite of this, an estimate for the shelf life is often required.

In this study theoretical models have been derived for prediction of shelf life. We have based the extrapolation on Eq. (6), Eq. (10) and Eq. (11) and displayed the results in Table 3. The extrapolation of diffusion of water through the ampoules was based on all examined conditions, even though one would expect a change in the polymer materials at high temperatures. In Table 3 the calculated values are compared with the results from a previously long time study at 25°C and ambient relative humidity (Headquarters Defence Command Norway/Pharmaceutical Laboratory, 1997). All extrapolated results correspond with

the measured results with less than 5% deviation. This strengthens the validity of the derived models for prediction of the shelf-life. Although there pertains uncertainty to the models, they seem useful for prediction of the shelf-life of medicaments stored for military or civil preparedness. These medicaments are often stored longer than the formal shelf-life approved by the civilian authorities. Because of the uncertainty of the models the medicaments have to be analysed according to regular quality control programs.

The models describing oxidation and water loss were derived on general basis. They may therefore be used for other drugs degraded by oxidation and stored in plastic ampoules. If they are not stabilised with an antioxidant, the lag phase can be excluded ($t_l = 0$).

The shelf life is not limited by the concentration of morphine, but merely by the diffusion of water out of the ampoules. The increase in the measured morphine concentration caused by water loss is partly compensated for by a parallel oxidation of morphine. Thus if the limit for diffusion of water through the ampoules is set to 10%, the shelf life calculated according to Eq. (10) is limited to about 15 months at 25°C and 35% relative humidity.

Appendix A

A.1. Oxidation of morphine

The diffusion rate F of oxygen through the polymer wall and into the solution is assumed to be Ficksian:

$$F = k_{\text{oxygen,diff}}\ ([O_2]_{\text{sat}} - [O_2]), \tag{A1}$$

where $k_{\text{oxygen,diff}}$ is the rate constant, $[O_2]_{\text{sat}}$ is the concentration of oxygen in a saturated solution and $[O_2]$ is the actual concentration.

The two oxidation reactions in the solution are:

$$\text{morphine} + O_2 \rightarrow \text{products}$$

$$\text{metabisulphite} + O_2 \rightarrow \text{products}$$

which gives the following equations:

$$-\frac{dC_{\text{morphine}}}{dt} = k_{\text{morphine}}[O_2]C_{\text{morphine}} \tag{A2}$$

$$-\frac{dC_{\text{sulphite}}}{dt} = k_{\text{sulphite}}[O_2]C_{\text{sulphite}} \tag{A3}$$

where k_{morphine} and k_{sulphite} are the rate constants for the oxidation of morphine and sodium metabisulphite and C_{morphine} and C_{sulphite} are the amounts of remaining morphine and sodium metabisulphite.

The concentration of oxygen is controlled by the diffusion through the plastic wall and the oxidation of morphine and sodium metabisulphite:

$$\frac{d[O_2]}{dt} = k_{\text{oxygen,diff}}([O_2]_{\text{sat}} - [O_2]) - k_{\text{morphine}}[O_2]C_{\text{morphine}} - k_{\text{sulphite}}[O_2]C_{\text{sulphite}} \tag{A4}$$

Assume that after a lag-time t_1 that all sodium metabisulphite is oxidised a steady state in oxygen concentration is reached. This gives for $t > t_1$:

$$\frac{d[O_2]}{dt} = k_{\text{oxygen,diff}}([O_2]_{\text{sat}} - [O_2]) - k_{\text{morphine}}[O_2]C_{\text{morphine}} = 0 \tag{A5}$$

and transformed:

$$[O_2] = \frac{[O_2]_{\text{sat}}}{k_{\text{morphine}}/k_{\text{oxygen,diff}} + 1}. \tag{A6}$$

Inserting Eq. (A6) into Eq. (A3) gives:

$$-\frac{dC_{\text{morphine}}}{dt} = \frac{[O_2]_{\text{sat}}C_{\text{morphine}}}{1/k_{\text{oxygen,diff}} + 1/k_{\text{morphine}}}. \tag{A7}$$

Assume that sodium metabisulphite prevents oxidation of morphine until all sodium metabisulphite is oxidised. Integration of Eq. (A7) from t_1 to t and $C_{\text{morphine},0} = 100\%$ to C_{morphine} gives:

$$t_l - t = \alpha(C_{\text{morphine}} - 100\%) + \beta \ln C_{\text{morphine}} \tag{A8}$$

where

$$\alpha = \frac{1}{k_{\text{oxygen,diff}}[O_2]_{\text{sat}}},$$

and

$$\beta = \frac{1}{k_{\text{morphine}}[O_2]_{\text{sat}}}.$$

Eq. (A8) is a zero or first order equation depending on the magnitudes of α and β. The magnitudes of α and β reflect the two possible rate determining mechanisms of morphine oxidation in plastic ampoules. If $\alpha \gg \beta$, the diffusion of oxygen through the polymer wall is rate determining and the degradation appears as zero order. If $\beta \gg \alpha$, the oxidation of morphine is rate determining and the degradation appears as first order.

A.2. Diffusion of water

The diffusion of water out of the ampoules is described by Ficks law:

$$-\frac{dV}{dt} = k_{\text{diff}}\Delta P_w, \tag{A9}$$

where V is the volume of the ampoule, k_{diff} is the diffusion rate constant and ΔP_w is the concentration gradient of water at across the ampoule wall.

The vapour pressure is a function of the relative humidity RH:

$$P_w = P_{w,\text{sat}}RH, \tag{A10}$$

where $P_{w,\text{sat}}$ is the saturated vapour pressure.

Inserting Eq. (A10) into Eq. (A9) and assuming that the ampoules are saturated with water vapour inside gives:

$$-\frac{dV}{dt} = k_{\text{diff}}P_{w,\text{sat}}(100\% - RH). \tag{A11}$$

Integration of Eq. (A11) from $V_0 = 100\%$ to V and $t_0 = 0$ to t gives:

$$\frac{100\% - V}{P_{w,\text{sat}}(100\% - RH)t} = k_{\text{diff}}. \tag{A12}$$

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