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Physical transformation of niclosamide solvates in pharmaceutical suspensions determined by DSC and TG analysis

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This study reports the preparation of four niclosamide solvates and the determination of the stability of the crystal forms in different suspension vehicles by DSC and TG analysis. Thermal analysis showed that the niclosamide solvates were extremely unstable in a PVP-vehicle and rapidly changed to monohydrated crystals. A suspension in propylene glycol was more stable and TG analysis showed that crystal transformation was less rapid. In this vehicle, the crystals transformed to the anhydrate, rather than the monohydrate, since the vehicle was non-aqueous. The TEG-hemisolvate was the most stable in suspension and offered the best possibility of commercial exploitation.

1. Introduction

Niclosamide is an anthelmintic drug that is used for the treatment of worm infestations in humans and animals (Reynolds 1993). It is mainly marketed as suspension for animal use. A major problem with the formulation of niclosamide suspensions is the conversion of the anhydrous crystal form to the monohydrous form causing caking of the suspension (Van Tonder et al. 1998). In this study, the effect of suspension medium and temperature on the physicochemical stability of the pseudopolymorphs was investigated by differential scanning calorimetric (DSC) and thermogravimetric (TG) analysis. The appearance of new peaks, disappearance of peaks, changes in enthalpy as a function of time and temperature, and changes in the onset of melting and desolvation peaks were investigated and correlated with the stability of the solvates.

In this study DSC and TG analysis were employed to determine the physical stability of the 1 : 1 dimethyl formamide (DMF), 1 : 1 dimethyl sulfoxide (DMSO), 1 : 1 methanol (MeOH), and 1 : 2 tetraethylene glycol (TEG) niclosamide solvates, in pharmaceutically important suspension vehicles.

2. Investigations, results and discussion

2.1 Characterization of the solvates

The preparation of the pseudopolymorphs of niclosamide needed only a general crystallization method. XRPD, DSC and TGA results were used to characterize the crystal forms. The XRPD patterns, Fig. 1, confirmed the difference in the crystal structures of the pseudopolymorphs. The DSC thermograms and the TG weight loss, Figs. 2 and 3, were distinctive for each pseudopolymorph and different from that of the anhydrate and monohydrate. DSC thermograms showed two endotherms; desolvation and melting respectively, that were characteristic for each crystal form. Beside the characterization of the weight loss, the TGA also confirmed the stoichiometric ratio of the niclosamide to solvent of crystallization as being 1 : 1 solvent to niclosamide for the DMF, DMSO and MeOH solvates and 1 : 2 for TEG solvate.

2.2. Stability in the xanthan gum suspension vehicle

In the xanthan gum vehicle, all the suspensions turned hard and they were not resuspendable. Since resuspendability is a critical requirement for suspension use and stability, this vehicle was not considered for further study.

2.3. Stability of the DMF-solvate

The transformation of the solvate to the anhydrate or monohydrate while suspended in the PVP or propylene glycol vehicle was followed by measuring changes in DSC and TGA thermograms, compared to that of the original solvate. For example in Figs. 4, 5, and 6 the changes in the weight-loss, heat of melting, and heat of desolvation of the DMF-solvate in the PVP-suspension is shown respectively. In Table 1 a summary of the linearity data obtained for the various solvates when plotted according to equation 1 is given and in Fig. 7 examples of the pseudo-first order plots are shown. In all cases the linear regression revealed R^2 values ≥ 0.900. From the data listed in Table 1 the rate constants (k_{obs}) for transformation (desolvation) were taken as the slopes of the lines. The log of k_{obs}, determined at a number of different temperatures, were plotted against 1/T to estimate the activation energy, E_a. Examples of the Arrhenius plots are shown in Fig. 8.

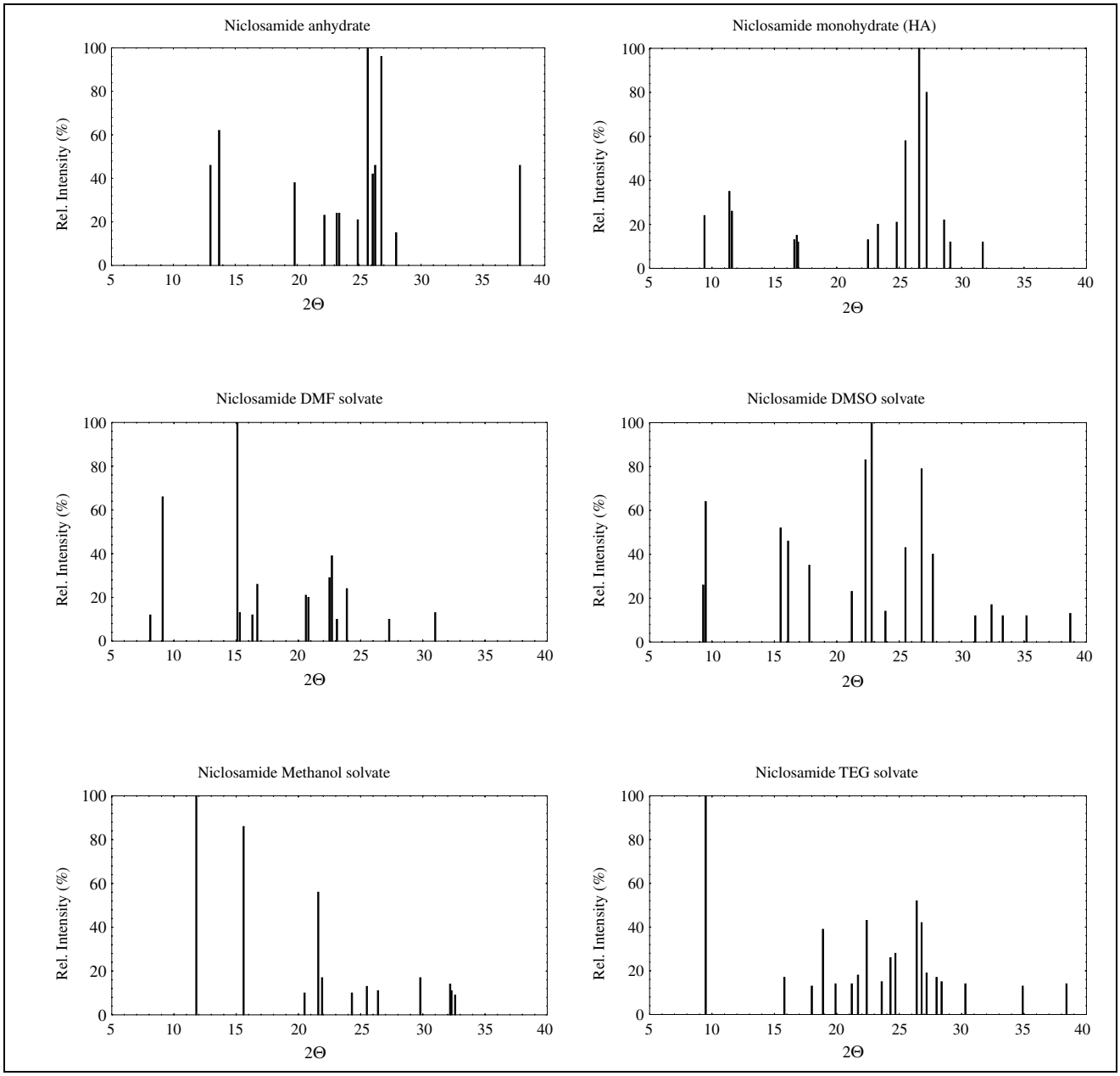

Fig. 1: XRPD patterns of the niclosamide crystal forms

In Table 2, k_{obs}, $t_{1/2}$, and $t_{0.9}$ (point where 90% of the original concentration is left) and E_a values are listed for the DMF-solvate suspensions. Desolvation, as measured by a change in the weight-loss with time, Fig. 4, in the PVP suspension depended on temperature and was fastest at 50 °C, $k_{obs} = 0.030\ h^{-1}$, and slowest at 30 °C, $k_{obs} = 0.025\ h^{-1}$. This related to half-lives ranging from only 23 to 27 h at these temperatures. From a quality assurance point of view, 90% of the DMF-solvate was only present for less than 5 h, even at 30 °C. This was because in the PVP-suspension the energy necessary for desolvation was only 6.8 kJ/mol. DSC results, Figs. 5 and 6 suggest that more than 95% of the conversion process was completed in less than 50 h and that the product formed was either the anhydrate and/or a monohydrated form of niclosamide as described by Van Tonder et al. (1998). The dip between 20–50 h in the heat of melting or heat of desolvation against time graphs, Figs. 5 and 6, could be attributed to the presence of an unknown transition phase. In this study, it was not possible to isolate this phase

The heat of melting of the anhydrate or monohydrates ranges from 100–105 J/g (Van Tonder 1996) but in this study after desolvation the heat of melting never reached this value although the melting temperatures stayed in the range 225–230 °C, close to the reported melting point of 229 °C. This decrease in the ultimate heat of melting could only be explained if an interaction between the suspension vehicle and the drug particles. PVP is known for forming complexes with drugs and these products usually lead to the formation of a less crystalline phase with a lower heat of melting (De Villiers et al. 1998).

In Fig. 9 the changes in the weight-loss of the DMF-solvate in the propylene glycol suspension are shown. The weight-loss process for this solvate in this vehicle was significantly different from that in the PVP-vehicle, Fig. 4. Table 2 lists the relevant k_{obs}, $t_{1/2}$, $t_{0.9}$ and E_a values. Desolvation, as measured by a change in the weight-loss with time, in the propylene glycol suspension also depended on temperature and was again fastest at 50 °C, $k_{obs} = 0.034\ h^{-1}$, and slowest at 30 °C, $k_{obs} = 0.007\ h^{-1}$.

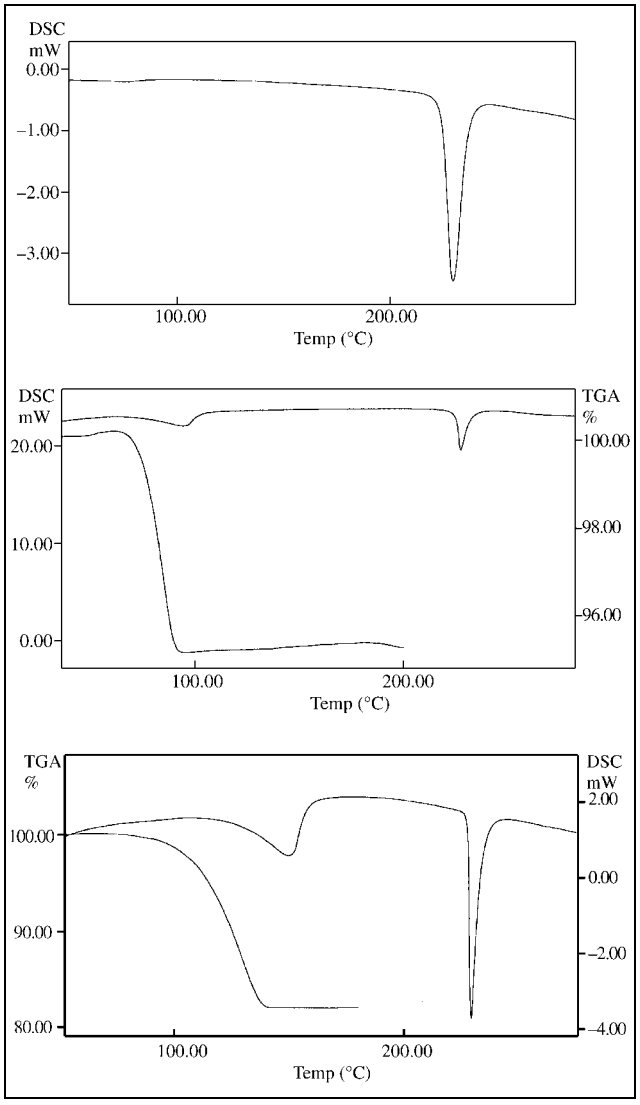

Fig. 2: DSC and TG thermograms of niclosamide anhydrate (top), monohydrate (middle) and DMF-solvate (bottom)

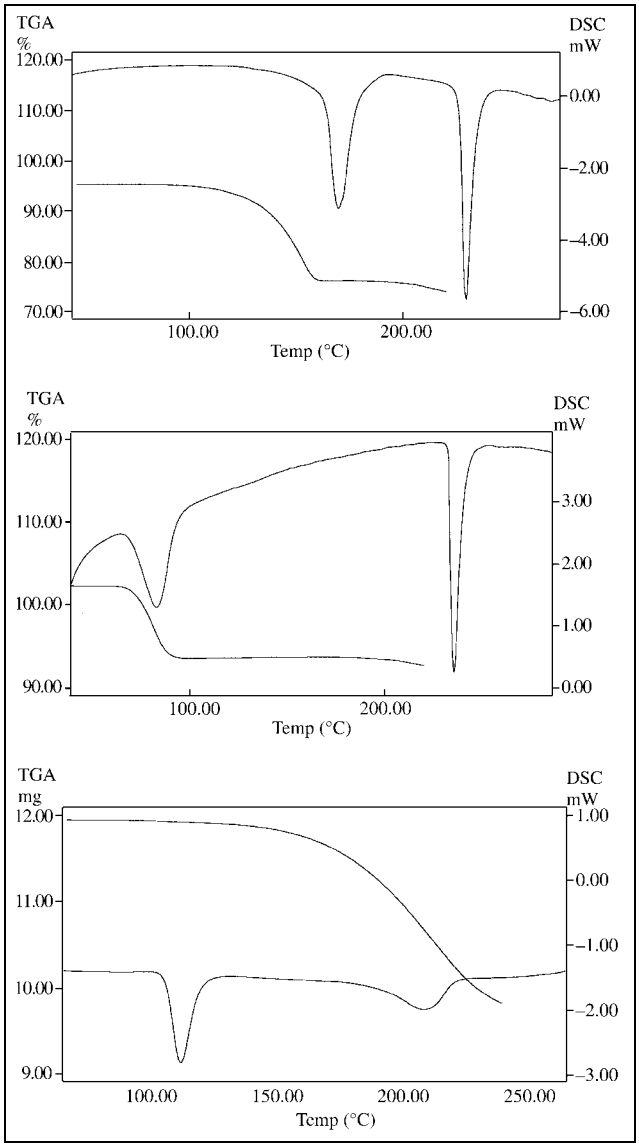

Fig. 3: DSC and TG thermograms of niclosamide DMSO-solvate (top), MeOH-solvate (middle) and TEG-solvate (bottom)

In this suspension, an increase in temperature had a much more adverse effect of the desolvation rate compared to the PVP-vehicle. However, the better stability in propylene glycol suspension at 30 °C could be related to the higher energy necessary for desolvation, 64.0 kJ/mol, compared to that of the PVP-suspension. DSC results also showed that the conversion process was much more gradual and took longer at 30 and 40 °C, compared to 50 °C. The fact that the heat of desolvation approached zero suggested that the product formed was the anhydrate and not the monohydrated form. This was most probably true since the propylene glycol suspension did not contain any water. In this vehicle, the dip in the heat of melting or heat of desolvation versus time graphs between 20–50 h for the suspensions stored at 40 and 50 °C was also less abrupt and more gradual, again suggesting the formation of the anhydrate.

2.4. Stability of the DMSO-solvate

Table 3 lists the relevant k_{obs}, $t_{1/2}$, $t_{0.9}$ and E_a values for suspensions of the DMSO-solvate in the PVP and propylene glycol suspension vehicles. Desolvation, change in the weight-loss with time, in the PVP suspension depended on temperature and was fastest at 50 °C, $k_{obs} = 0.028\ h^{-1}$, and slowest at 30 °C, $k_{obs} = 0.026\ h^{-1}$. This related to half-lives ranging from only 25 to 27 h at these temperatures. From a quality assurance point of view, 90% of the DMSO-solvate was only present for less than 5 h, even at 30 °C. This was because in the PVP-suspension the energy necessary for desolvation was extremely low, 3.8 kJ/mol. There was not much differ-

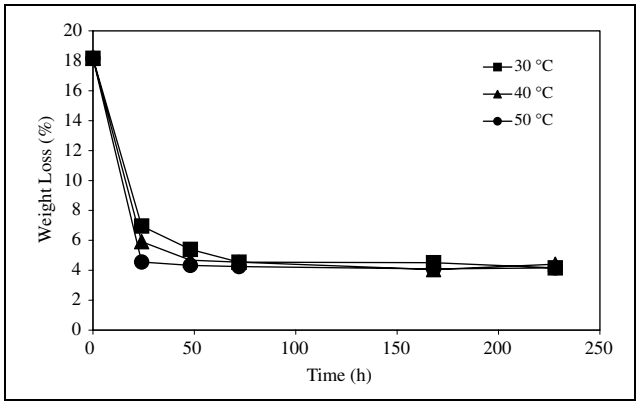

Fig. 4: TGA weight-loss as a function of time for the DMF-solvate in the PVP-suspension vehicle

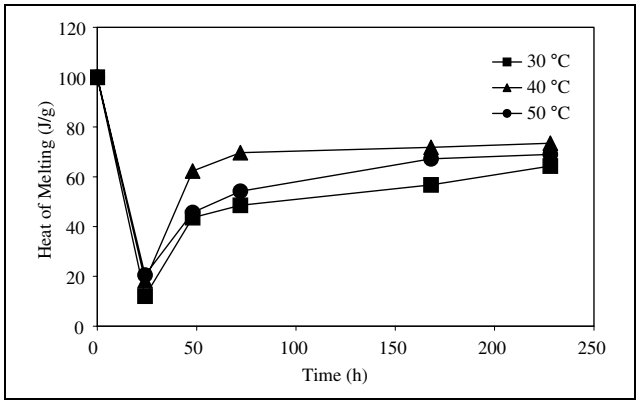

Fig. 5: Change in the heat of melting as a function of time for the DMF-solvate in the PVP-suspension vehicle

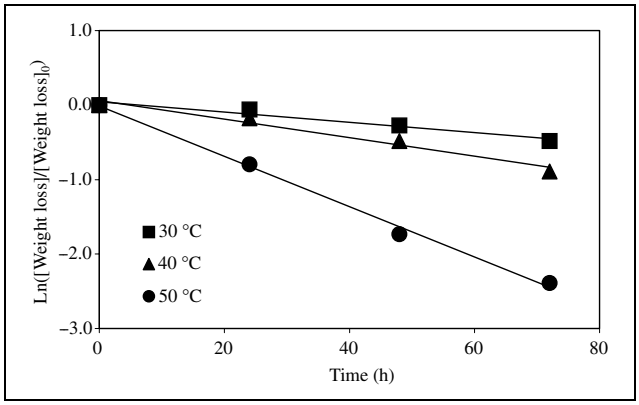

Fig. 7: Linear fits for ln([Weight Loss]/[Weight Loss]$_0$) against time data of the DMF-solvate in the propylene glycol suspension vehicle

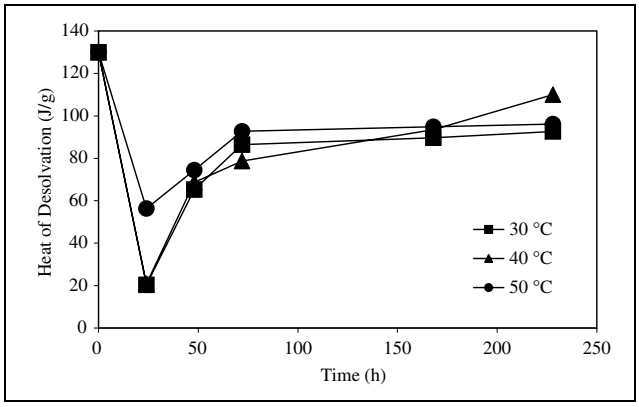

Fig. 6: Change in the heat of desolvation as a function of time for the DMF-solvate in the PVP-suspension vehicle

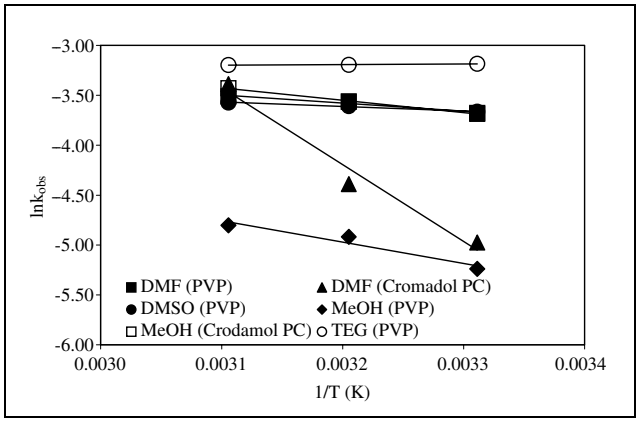

Fig. 8: Arrhenius plots for the desolvation of the different solvates stored at 30, 40 and 50 °C while suspended in PVP or propylene glycol suspension vehicles

ence in k_{obs} at the different temperatures. An increase from 30 to 50 °C only increased the desolvation rate by 0.0025 h^{-1}. As was seen for the DMF-solvate the heat of melting and desolvation rapidly decreased for 0–50 h then increased where after it stayed constant as. The ultimate heat of melting and desolvation corresponded with that obtained for the niclosamide monohydrate, suggesting that the DMSO-solvate most probably also changed from the solvate through the anhydrate to the monohydrated form of niclosamide.

The DMSO-solvate was very stable in the propylene glycol suspension because no weight loss and no changes in the heat of desolvation was measured. However, a gradual decrease in the heat of melting was measured. This could be due to a decrease in the crystallinity of the niclosamide upon heating in a polymer solution because it is known that during DSC analysis at high temperatures >150 °C polymers often cause shifting, shrinking, or even disappearance of the melting endotherms of drugs (Malan et al. 1997).

2.5. Stability of the MeOH-solvate

Table 4 lists the relevant k_{obs}, $t_{1/2}$, $t_{0.9}$ and E_a values for suspensions of the MeOH-solvate in the PVP and propylene glycol suspension vehicles. Desolvation, as measured by a change in the weight-loss with time, in the

Table 1: Linear regression data for pseudo-first order fits of ln([Weight Loss]/[Weight Loss]$_0$) against time data for the different niclosamide solvates in PVP and propylene glycol suspension vehicles

Solvate	Temperature (°C)	PVP			Propylene glycol		
		Slope	Y-intercept	R^2	Slope	Y-intercept	R^2
DMF	30	−0.0253	−0.1173	0.948	−0.0069	0.0451	0.976
	40	−0.0283	−0.1478	0.936	−0.0124	0.0596	0.984
	50	−0.0299	−0.2226	0.900	−0.0338	−0.0131	0.997
DMSO	30	−0.0256	−0.0630	0.985	No solvent loss was observed		
	40	−0.0271	−0.0604	0.987	No solvent loss was observed		
	50	−0.0281	−0.0517	0.991	No solvent loss was observed		
MeOH	30	−0.0053	−0.0368	0.973	−0.0251	−0.1853	0.900
	40	−0.0073	−0.0622	0.961	−0.0284	−0.1889	0.901
	50	−0.0082	−0.0852	0.942	−0.0324	−0.2088	0.907
TEG	30	−0.0414	−0.1708	0.959	No solvent loss was observed		
	40	−0.0410	−0.2267	0.929	No solvent loss was observed		
	50	−0.0409	−0.2556	0.912	No solvent loss was observed		

Table 2: Rate constants (k_{obs}), half-life ($t_{1/2}$), and activation energy necessary for the desolvation (E_a) of the DMF-solvate in the PVP and propylene glycol suspension vehicles

Vehicle	Temperature (°C)	k_{obs} (h^{-1})	$t_{1/2}$ (h)	$t_{0.9}$ (h)	E_a (kJ/mol)
PVP	30	0.0253	27.4	4.2	6.8
	40	0.0283	24.5	3.7	
	50	0.0299	23.2	3.5	
Propylene glycol	30	0.0069	100.4	15.2	64.0
	40	0.0124	55.9	8.5	
	50	0.0338	20.5	3.1	

PVP suspension depended on temperature and was fastest at 50 °C, $k_{obs} = 0.0082\ hour^{-1}$, and slowest at 30 °C, $k_{obs} = 0.0053\ hour^{-1}$. This related to half-lives ranging from 130 to 85 hours at these temperatures. From a quality assurance point of view, 90% of the MeOH-solvate was present for less than 20 h, even at 30 °C. This was because in the PVP-suspension the energy necessary for desolvation was only 17.7 kJ/mole compared to the 72.5 kJ/mol necessary in the absence of the vehicle.

DSC results suggested that more than 95% of the conversion process was completed in less than 50 h and that the product formed was either the anhydrate and/or a monohydrated form of niclosamide as described by Van Tonder (1996). The presence of a transition phase attributed to the break (dip) in the heat of melting or heat of desolvation graphs was again observed between 20–50 h. However, this dip was not observed at 30 °C suggesting that at this temperature and with the slow rate of change the MeOH-solvate changed directly to the monohydrate. Once again, a decrease in the ultimate heat of melting could only be explained if an interaction between the PVP in the suspension vehicle and the drug particles occurred.

Desolvation, as measured by a change in the weight-loss with time, in the propylene glycol suspension also depended on temperature and was again fastest at 50 °C, $k_{obs} = 0.032\ h^{-1}$, and slowest at 30 °C, $k_{obs} = 0.025\ h^{-1}$. This related to half-lives ranging from only 21 to 28 h at these temperatures. In this suspension an increase in temperature did not cause a significant increase in the desolvation rate (Table 4). From a quality assurance point of view, 90% of the MeOH-solvate was only present for about 4 h, even at 30 °C, which means that this solvate suspension was not viable.

In contrast to the other solvates, the MeOH-solvate was more stable in the PVP-suspension than in propylene glycol suspension. The poor stability profile of the propylene

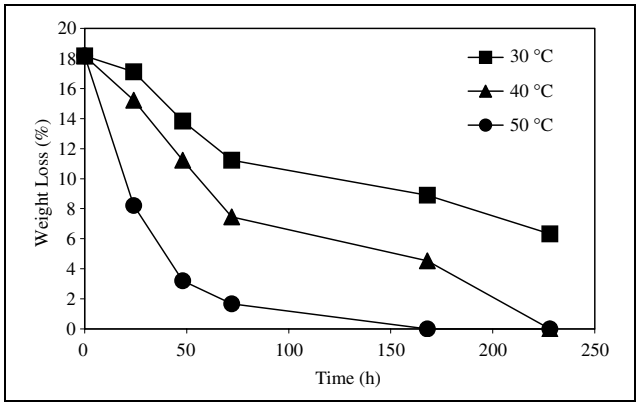

Fig. 9: TGA weight-loss as a function of time for the DMF-solvate in the propylene glycol suspension vehicle

Table 3: Rate constants (k_{obs}), half-life ($t_{1/2}$), and activation energy necessary for the desolvation (E_a) of the DMSO-solvate in the PVP suspension vehicle

Vehicle	Temperature (°C)	k_{obs} (h^{-1})	$t_{1/2}$ (h)	$t_{0.9}$ (h)	E_a (kJ/mol)
PVP	30	0.0256	27.1	4.1	3.8
	40	0.0271	25.6	3.9	
	50	0.0281	24.7	3.7	

Table 4: Rate constants (k_{obs}), half-life ($t_{1/2}$), and activation energy necessary for desolvation (E_a) for the MeOH-solvate in the PVP and propylene glycol suspension vehicles

Vehicle	Temperature (°C)	k_{obs} (h^{-1})	$t_{1/2}$ (h)	$t_{0.9}$ (h)	E_a (kJ/mol)
PVP	30	0.0053	130.8	19.8	17.7
	40	0.0073	94.9	14.4	
	50	0.0082	84.5	12.8	
Propylene glycol	30	0.0251	27.4	4.2	10.3
	40	0.0284	24.4	3.7	
	50	0.0324	21.4	3.2	

glycol-suspension compared to the PVP-suspension could be related to the smaller energy necessary for desolvation 10.3 kJ/mol compared to that of the PVP-suspension, 17.7 kJ/mol. DSC results suggested in this vehicle that the conversion process was much more gradual at 30 and 40 °C, and 50 °C. The fact that the heat of desolvation approached zero again suggested that the product formed was the anhydrate and not the monohydrated form.

2.6. Stability of the TEG-solvate

Table 5 lists the relevant k_{obs}, $t_{1/2}$, $t_{0.9}$ and E_a values for suspensions of the TEG-solvate in the PVP and propylene glycol suspension vehicles. Desolvation, as measured by a change in the weight-loss with time, in the PVP suspension was independent of temperature, $k_{obs} = 0.041 \pm 0.0003\ h^{-1}$. This related to a half-life around 17 h at the temperatures tested. From a quality assurance point of view, 90% of the TEG-solvate was only present for less than 3 h, even at 30 °C. This was because in the PVP-suspension the energy necessary for desolvation was extremely low, 0.4 kJ/mol. All this contributed to the TEG-solvate rapidly being desolvated in the PVP-suspension and changed to the monohydrate as seen in Fig. 10. The TEG-solvate was stable in the propylene glycol suspension. No weight loss was observed, and no changes in the heat of melting and heat of desolvation were measured.

In conclusion, Thermal analysis showed that the niclosamide solvates were extremely unstable in the PVP-vehicle and rapidly changed to the monohydrated crystals. Overall, the propylene glycol suspension was more stable and crystal transformation was less rapid. In most cases when crystal changes did occur in this vehicle, the crys-

Table 5: Rate constants (k_{obs}), half-life ($t_{1/2}$), and activation energy necessary for desolvation (E_a) for the TEG-solvate in the PVP suspension vehicle

Vehicle	Temperature (°C)	k_{obs} (h^{-1})	$t_{1/2}$ (h)	$t_{0.9}$ (h)	E_a (kJ/mol)
PVP	30	0.0414	16.7	2.5	0.4
	40	0.0410	16.9	2.6	
	50	0.0409	16.9	2.6	

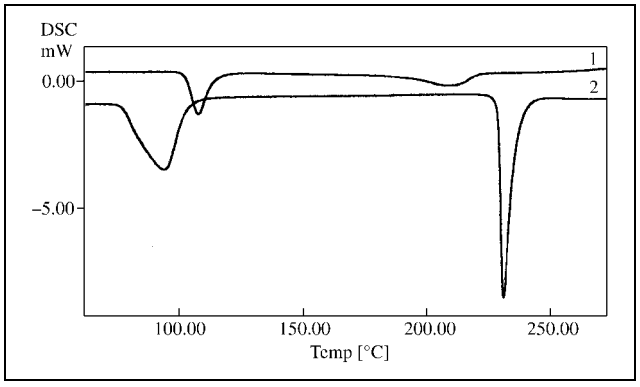

Fig. 10: DSC thermograms of the TEG-hemisolvate (1) transformed into monohydrate H_A (2)

tals transformed to the anhydrate, rather than the monohydrate, since the vehicle was non-aqueous. Both the DMSO and TEG-solvates stayed practically unchanged in the propylene glycol suspension because no crystal transformation was observed within the time, and at the temperatures, the suspensions were tested. Based on the thermal analysis results these two solvates, and in particular the TEG-hemisolvate in the propylene glycol suspension, offers the best possibility for commercial exploitation.

3. Experimental

3.1. Materials

Niclosamide were obtained from Sigma Chemical Company (St. Louis, USA). The following analytical grade solvents were obtained from Saarchem (Krugersdorp, South Africa), namely dimethyl sulfoxide, *N*,*N*′-dimethylformamide, and tetraethylene glycol. Methanol (BDH, Poole, England), and ethanol (Merck, Darmstadt, Germany) were also used.

3.2. Preparation of solvates

The solvates were prepared as described by Caira et al. (1998) and Van Tonder et al. (1998) by crystallization from saturated solutions in dry methanol, *N*,*N*′-dimethyl formamide, dimethyl sulfoxide and tetraethylene glycol. Solutions were covered and left at room temperature to crystallize. Crystals were stored in the solutions to prevent desolvation or hydration. Before use the solutions were filtered and the crystals dried on absorbing filter paper.

3.3. Thermal analysis

DSC traces were recorded with a Shimadzu DSC-50 instrument (Shimadzu, Kyoto, Japan) or a DSC 2920 modulated DSC (TA Instruments, New Castle, DE, USA). Indium (melting point 156.6 °C) and tin (melting point 231.9 °C) were used to calibrate the instruments. A mass, not exceeding 3.0 mg, was measured into aluminum pans with or without a small pin-hole in the lid. DSC-curves were obtained under a nitrogen purge of 20 ml per min at a heating rate of 10 K per min. Heating rates of 5 K to 20 K were used to examine changes in melting points and dehydration peaks. Melting temperatures were determined as extrapolated onset temperatures, defined as the point of transition, being the point of intersection between the base line and the DSC endothermal melting effect, which gives the most reproducible value, experimentally independent of the operator (Craig 1995).
TGA-traces were obtained with either a Shimadzu TGA-50 (Shimadzu, Kyoto, Japan) or Hi-Res Modulated TGA 2950 (TA Instruments, New Castle, DE, USA). TGA-traces were recorded at heating rates of 2 to 10 K per min under a nitrogen purge of 50 ml per min. Samples with masses between 1 mg and 10 mg were analyzed using a platinum pan. Mass loss (%) was calculated from TG curves, based on the mass of the original sample.

3.4. X-ray powder diffraction analysis (XRPD)

To identify the crystallized solvates, XRPD-profiles of the solvates were obtained at room temperature with a Philips PM9901/00 diffractometer. The measurement conditions were: target, CuKα; filter, Ni; voltage, 40 kV; current, 20 mA; slit, 0.1 mm; scanning speed, 2°/min. Crystals of the different crystal forms were ground into a fine powder with average particle size of ± 60 µm. Care was taken to avoid crystal changes during sample preparation. Approximately 200 mg samples were loaded into aluminum sample holders, taking care not to introduce a preferential orientation of the crystals.

3.5. Preparation of suspensions

Prior to making the suspensions, the pseudopolymorphs were allowed to dry on filter paper to remove the excess solvent taking care that the pseudopolymorphs did not desolvate or were exposed to water which would facilitate change to one of the monohydrated forms (Van Tonder et al. 1998; Caira et al. 1998). Three suspension vehicles were used. The first vehicle was an aqueous vehicle containing 0.1% xanthan gum (High molecular weight polysaccharide gum, Spectrum Chemical Company, Gardena, CA, USA). Before suspension formulation the solvate crystals was screened through an 85-mesh sieve to ensure the particle size of the different suspensions being the same. One gram of the crystals, accurately weighed, was then suspended in 15 ml of the suspension vehicle with mild stirring. The suspension was then accurately filled up to 20 ml with the vehicle, producing a 5% w/v suspension of the solvate in the 0.1% xanthan vehicle. The second vehicle were a combination of PVP, xanthan gum, potassium sorbate, and sodium benzoate containing 1 g PVP K25 (BASF, Germany), 0.1 g sodium benzoate (Saarchem, South Africa), 0.02 g potassium sorbate (Saarchem, South Africa) and 0.05 g xanthan gum in 50 ml with distilled water. Similar to the preparation of the xanthan gum suspension, 5% w/v suspensions of the solvates were prepared in this vehicle. The method of preparing the third, propylene glycol (Crodamol PC, Croda Chemicals, South Africa) suspension involved the inclusion of 1 g of the sieved crystal forms into 20 ml of continuously stirred propylene glycol.

3.6. Stability testing and kinetics of crystal form transformation

The suspensions were stored at 30 °C, 40 °C and 50 °C. Samples were taken after 24, 48, 72, 168 and 228 h and analyzed by TG and DSC. The melting point, heat of melting and desolvation temperature were plotted against time. Kinetic analysis of the data was used to compare the suspensions and to evaluate the different suspension vehicles and crystal forms. Preliminary fitting of data to known solid-state transformation kinetic equations revealed that the desolvation of the solvates followed pseudo-first order kinetics as shown by linear plots of ln([Weight Loss]/[Weight Loss]$_0$) versus time and the rate constant, k_{obs}, could be found from eq. (1) (Byrn 1999).

$$\ln([\text{Weight Loss}]/[\text{Weight Loss}]_0) = -k_{obs}.t \quad (1)$$

There are two concentration terms in eq. (1) and these appear as a ratio. This means that it is not necessary to express the concentrations in mol/l. Therefore the % weight-loss as a function as time was used directly. From k_{obs} values the half-lives ($t_{1/2}$) were calculated using the following equation.

$$t_{1/2} = \ln 2/k_{obs} \quad (2)$$

The temperature dependence of the rate constants was estimated from the Arrhenius relationship

$$\ln k_{obs} = \ln A - E_a/RT \quad (3)$$

where A is the pre-exponential factor, R is the gas constant (8.314 J/K/mol), T is the absolute temperature, and E_a is the activation energy in energy units per mol. If k_{obs} is determined at a number of different temperatures, a graph of log k_{obs} against 1/T should give a straight line of gradient −E/2.303R. Weight-loss was only followed at the temperature of desolvation of the specific solvate. In cases where the solvate changed to a monohydrate, this change was confirmed by comparing the DSC results.

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