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Kinetic parameters for thermal decomposition of supramolecular polymers derived from flunixin-meglumine adducts

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Abstract Meglumine, (2*R*,3*R*,4*R*,5*S*)-6-methylaminohexane-1,2,3,4,5-pentol, is a carbohydrate derived from sorbitol in which the hydroxyl group in position one is replaced by a methylamine group. It forms binary adducts with substances having carboxyl groups, which have in common the presence of hydrogen bonding as the main force in the stabilization of these species. During melting, adducts of meglumine with flunixin (2-[[2-methyl-3-(trifluoromethyl)phenyl]amino]pyridine-3-carboxylic acid) polymerize or self-assemble in amorphous supramolecular structures with molecular weights around 2.0×10^5 kDa. DSC curves, in a first heating, show isomorphic transitions where the last one at 137 °C for the flunixin-meglumine adduct originated the supramolecular amorphous polymers with glass transition around 49.5 °C. The kinetic parameters for the thermal decomposition step of the polymers were determined by the Capela-Ribeiro non-linear isoconversional method. From data for the TG curves in nitrogen atmosphere and heating rates of 5, 10, 15, and 20 °C $\min^{-1}$, the E_α and B_α terms could be determined and, consequently, the pre-exponential factor, A_α, as well as the kinetic model, $g(\alpha)$.

Keywords Supramolecular polymers · Flunixin-meglumine · Adducts · Non-isothermal kinetics · Thermal decomposition

Introduction

Meglumine, (2*R*,3*R*,4*R*,5*S*)-6-methylaminohexane-1,2,3,4,5-pentol, also known as *N*-methylglucamine, is a carbohydrate derived from sorbitol in which the hydroxyl group from position one is replaced by a methylamine group, as shown in Fig. 1.

The increased applicability of meglumine lies in its ability to form adducts with carboxylic acids and markedly increases their solubility in aqueous solution, due to the large number of hydroxyl groups.

This property has been extensively exploited by the pharmaceutical industry in the improvement of existing drugs, where the pharmacologically active substance is more soluble in water when taken in the form of an adduct with meglumine, without affecting the original activity of the drug in combination. The most successful example of this approach involves the non-steroidal anti-inflammatory drugs (NSAIDs), which have terminal carboxylic acid groups [1–3].

The first study on adducts derived from the reaction between a carboxylic acid and meglumine did not elucidate the structure, since the major interest has always limited to increasing the solubility of NSAIDs in aqueous media. Some understanding about the structure of this class of binary species came only with the work of Cao et al. and Telang et al. [4, 5].

A more meaningful understanding of the structure of these adducts was obtained by X-ray diffraction (XRD) of a single crystal of the species generated by the reaction between flunixin, 2-[[2-methyl-3-(trifluoromethyl)phenyl]amino]pyridine-3-carboxylic acid, and meglumine, anionic and cationic components, respectively [4]. The adduct is primarily stabilized by hydrogen bonds between hydroxyl groups of the meglumine cation and the carboxylate of the flunixin anion (Fig. 2).

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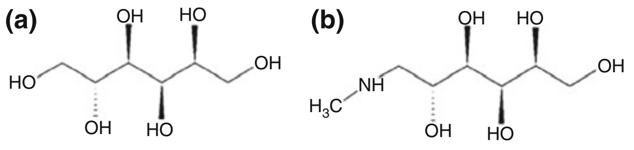

Fig. 1 Molecular structures for **a** sorbitol and **b** meglumine

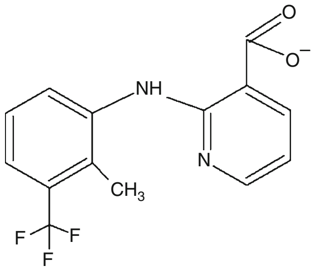

Fig. 2 Molecular structure for flunixin anion

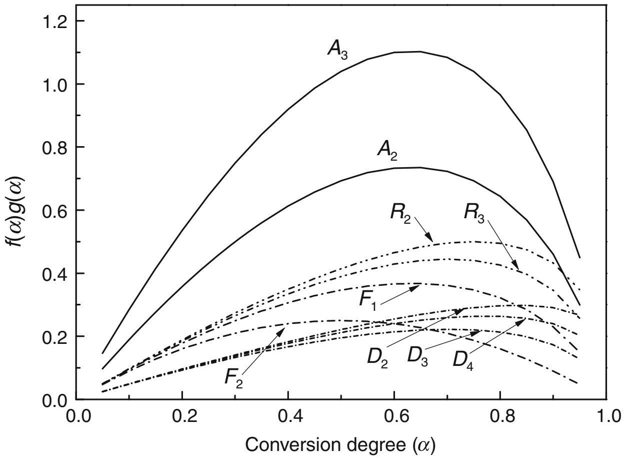

Fig. 3 Theoretical master plots of $f(\alpha)g(\alpha)$ against α for kinetic models in Table 1

Telang [5] investigated by differential scanning calorimetry (DSC) the formation of a thermally induced solid adduct involving indomethacin acid and meglumine. By FTIR, it was determined that the formation of new species occurs by proton transfer from the carboxyl group of indomethacin to the methylamine group of meglumine.

The aim of the present study was to prepare the flunixin-meglumine supramolecular polymer, to observe the thermal behavior through the TG-DTA and DSC techniques and to obtain the kinetic parameters for the thermal decomposition reaction.

Kinetic parameters—non-linear isoconversional method

The kinetic parameters for the thermal decomposition step of the compound were estimated by the Capela-Ribeiro non-linear isoconversional method, using fourth-order rotational approximation of the temperature integral [6]. For a given conversion α and a set of n experiments carried out at different heating rates β_i $(i = 1,\ldots,n)$, the parameters activation energy, E, and the B term could be determined from Eq. 1 for the least sum of squares for the plot of heating rate β for each α as a function of $z_i = 10^3/RT_i$ $(i = 1,\ldots,n)$:

$$S(E,B) = \sum_{i=1}^{n} \left(\beta_i \frac{\exp(B - Ez_i)}{z_i} \frac{E^3 z_i^3 + 14E^2 z_i^2 + 46Ez_i + 24}{E^4 z_i^4 + 16E^3 z_i^3 + 72E^2 z_i^2 + 96Ez_i + 24}\right)^2, \tag{1}$$

$$B = \ln\left(\frac{10^3 A}{Rg(\alpha)}\right), \tag{2}$$

where A is the pre-exponential factor, R is the gas constant, and $g(\alpha)$ represent the reaction mechanism.

In order to estimate the reaction model, $g(\alpha)$, an expression based on both differential and integral forms of the kinetic equation can be used:

$$f(a)g(a) = \frac{10^3 E}{R}\frac{\mathrm{d}a}{\mathrm{d}T}\exp\left(\frac{10^3 E}{RT}\right) I\left(\frac{10^3 E}{RT}\right), \tag{3}$$

where $I(10^3E/RT)$ is the integral of Arrhenius [6].

For each heating rate, the values on both sides of Eq. 3 depend only on α. Therefore, a method for estimation of $g(\alpha)$ could be constructed by comparing the values on the right-hand side of Eq. 3 against α and the theoretical master plots of $f(\alpha)g(\alpha)$ against α (Fig. 3) assuming several kinetic models from Table 1.

From the results of Eq. 3, the kinetic exponent n was estimated from the least sum of squares, Eq. 4:

$$\sum_{i=1}^{n}\left[f(\alpha)g(\alpha) - \frac{10^3 E\mathrm{d}\alpha}{R\ \mathrm{d}T}\exp\left(\frac{10^3 E}{RT}\right) I\left(\frac{10^3 E}{RT}\right)\right]^2. \tag{4}$$

The pre-exponential values, A, could be estimated by replacing the term B in Eq. 2:

$$\ln A = \ln g(\alpha) + B - \ln\left(\frac{10^3}{R}\right). \tag{5}$$

Experimental

Infrared absorption spectra were obtained from 4,000 to 400 cm^{-1}, with 4 cm^{-1} spectral resolution and 64 scans. KBr pellets were analyzed in a Nicolet FTIR Impact-400 spectrometer.

DSC curves were obtained from 5 mg of the samples in a TA Instruments DSC 2910, from 40 to 160 °C under nitrogen atmosphere (50 mL min^{-1}), heating rate of 2.5, 5, and 10 °C min^{-1}, in sealed aluminum pans.

Table 1 Most common expression for the $f(\alpha)$ and $g(\alpha)$ functions

Symbol	Reaction model	$g(\alpha) = k(t - \tau) = kt$	$f(\alpha) = (1/k)(\mathrm{d}\alpha/\mathrm{d}t)$
R_n	Geometric models $n = 2$: Contacting area $n = 3$: Contracting volume	$1 - (1 - \alpha)^{1-n}$	$n(1 - \alpha)^{1-1/n}$
F_n or $RO(n)$	n Order	$\frac{1-(1-\alpha)^{1-n}}{1-n}$	$(1 - \alpha)^n$
A_n	Avrami-Erofeev or JMAEK	$[\ln (1 - \alpha)]^{1/n}$	$n(1 - \alpha)[-\ln (1 - \alpha)]^{1-1/n}$
D_2	Two-dimensional diffusion	$((1-\alpha)\ln(1-\alpha)) + \alpha$	$-\frac{1}{\ln(1-\alpha)}$
D_3	Three-dimensional diffusion (Jander)	$(1 - (1 - \alpha)^{1/3})^2$	$\frac{3(1-\alpha)^{2/3}}{2\left[1-(1-\alpha)^{1/3}\right]}$
D_4	Three-dimensional diffusion (Ginstling–Brounshtein)	$-\frac{2}{3}\alpha - (1-\alpha)^{2/3}$	$\frac{3(1-\alpha)^{1/3}}{2\left[1-(1-\alpha)^{1/3}\right]}$

Thermal degradation was followed using a TA Instruments 2960 SDT, in the 30–550 °C temperature range in open alumina reference and sample pans under dynamic nitrogen atmosphere (flow rate: 50 mL min^{-1}) and a heating rate of 5, 10, 15, and 20 °C min^{-1}.

Results and discussion

The DSC curves for flunixin-meglumine (Fig. 4a–c) in a nitrogen atmosphere and heating rate of 2.5, 5, and 10 °C min^{-1} showed two endothermic peaks for first-order transitions. The first, at approximately 109 °C, and the second, at 137 °C, could be attributed to the melting of two polymorphous present in the sample, forms II and I, respectively.

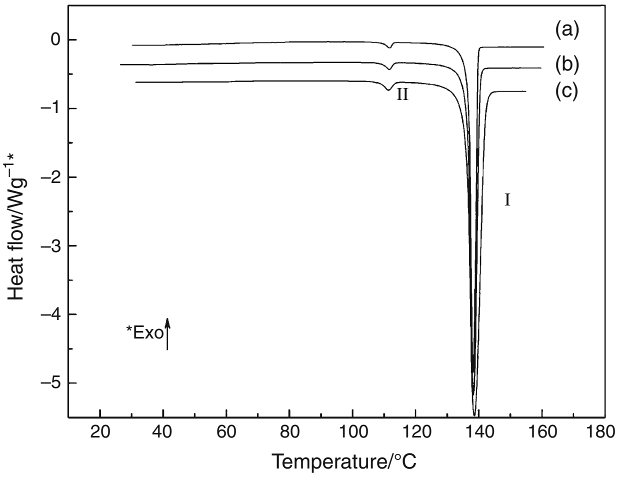

Fig. 4 DSC curves for the flunixin-meglumine adduct (*a*) 2.5, (*b*) 5, and (*c*) 10 °C min^{-1}, sample mass: ~5.00 mg, N_2 atmosphere (50 mL min^{-1}), aluminum pan

On the basis of the “heat of fusion rule” of Burger and Ramberger [7], two crystalline phases can be monotropically related since the form having a higher melting point [$T_{\mathrm{melting}}(\mathrm{I}) > T_{\mathrm{melting}}(\mathrm{II})$] also shows higher enthalpy of transition [$\Delta H_{\mathrm{melting}}(\mathrm{I}) > \Delta H_{\mathrm{melting}}(\mathrm{II})$] in the normal pressure conditions. Thus, from the T_{melting} and $\Delta H_{\mathrm{melting}}$ values shown in Table 2, the monotropic transition from form II for the flunixin-meglumine adduct in these experimental conditions could be suggested.

The transition II → I is thermodynamically favorable. However, no peak for the crystalline phase transition was observed in the DSC, which may be due to a kinetic hindrance in the conversion of II → I in the solid state.

The DSC curves (Fig. 5a, b) show the first-heating up to 160 °C (a), above the melting point of form I, and the second one (b) in a nitrogen atmosphere. For the second heating, only the change of baseline characteristic for glass transition at 49.5 °C, followed by an enthalpic relaxation peak, could be observed.

The experimental evidence suggested that during melting, the flunixin-meglumine adduct polymerizes or self-organizes, which is retained after cooling the sample, resulting in the formation of a supramolecular polymer. This is defined as an arrangement of monomeric units, which do not necessarily have a repetition of chemical fragments, held together by secondary interactions. The kinds of interactions that are involved in the formation and stabilization of supramolecular polymers are reversible and highly directional, ensuring that supramolecular polymers are always formed under conditions of thermodynamic equilibrium. An example of this kind of interaction is the hydrogen bond.

The static light-scattering technique allowed the determination, in aqueous medium, of the molecular weight of the supramolecular polymer formed by flunixin-meglumine.

Table 2 Values obtained from the melting peaks for crystalline forms I and II of flunixin-meglumine adducts at different heating rates

Heating rate/°C min^{-1}	Melting "onset" temperature/°C		Peak temperature/°C		Enthalpy of transition ΔH/J g^{-1}	
	I	II	I	II	I	II
2.5	136.7	109.1	138.2	111.6	118.0	2.3
5	136.7	109.3	138.3	111.8	125.6	2.5
10	137.0	109.5	139.0	111.8	128.0	2.5

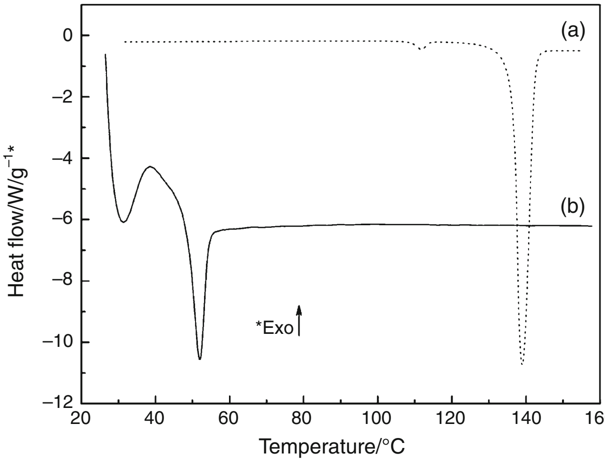

Fig. 5 DSC curves for flunixin-meglumine adduct (*a*) first heating; (*b*) second heating. Sample mass = 5.02 mg, heating rate 10 °C min^{-1}, nitrogen atmosphere (50 mL min^{-1})

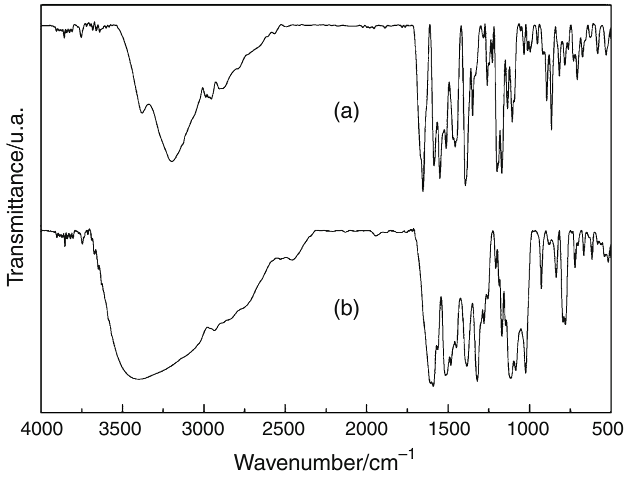

Fig. 6 FTIR spectra for (*a*) flunixin-meglumine adduct and (*b*) supramolecular polymer obtained after heating to 160 °C

The weight-average molecular weight ($\overline{M}_{\mathrm{w}}$) found was high and equal to $2.91 \times 10^5 \pm 8.77 \times 10^4$ kDa.

One can observe the widening and the overlapping of the bands in the FTIR spectra for polymer (a) compared with that for the flunixin-meglumine adduct (b) (Fig. 6a, b). The FTIR spectra do not indicate that covalent bonds occur during the formation of the polymer. This observation is consistent with the nature of supramolecular polymers, since these species are not products of chemical reactions of addition or condensation, but the self-organization of the monomeric units through the action of weak interactions (secondary interactions) [8].

The TG and DTA curves for the flunixin-meglumine adduct, obtained with a heating rate of 10 °C min^{-1} and nitrogen atmosphere, are shown in Fig. 7.

The DTA curves showed the phase transitions II and I, an isomorphic transition, without mass loss in the TG curves, followed by the thermal decomposition above 210 °C ($T_{\mathrm{onset}} = 249$ °C) in two main steps, with an endothermic peak in the DTA curves. The residue of thermal decomposition at 500 °C is around 3–4%, probably consisting of ash.

From the first step of thermal decomposition in the TG curves, at the heating rates of 5, 10, 15, and 20 °C min^{-1}, the conversion degree α as a function of temperature could be determined (Fig. 8).

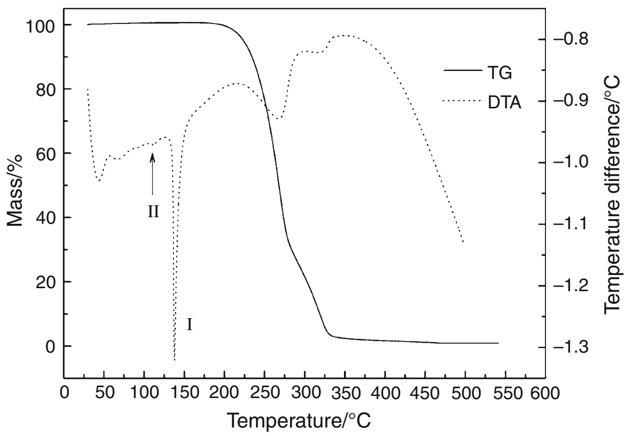

Fig. 7 TG and DTA curves for flunixin-meglumine adduct. Sample mass = 5.00 mg, heating rate 10 °C min^{-1}, nitrogen atmosphere (50 mL min^{-1})

For a given conversion α and a set of experiments carried out at different heating rate, β, Fig. 8, the parameters E and B could be estimated from the least sum of squares $S(E, B)$, as defined in Eq. 1, Table 3.

Continuing, from experimental curves $\alpha - T$, the term $\mathrm{d}\alpha/\mathrm{d}T$ could be determined by numerical integration. Thus, the data $\mathrm{d}\alpha/\mathrm{d}T$ plus activation energy from Table 3 could be substituted in the right side of Eq. 3 to obtain the

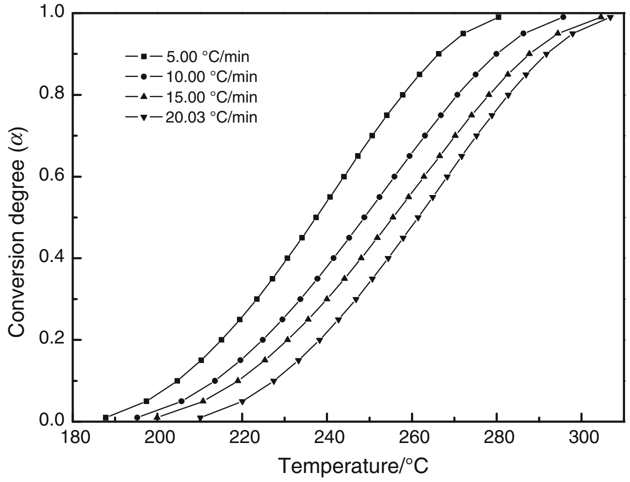

Fig. 8 Conversion degree against temperature for thermal decomposition of the polymer formed from the flunixin-meglumine adduct

Table 3 Parameters of activation energy and B term obtained from evaluation of the TG data using Eq. 1 and the pre-exponential factor calculated from Eq. 5

Conversion degree "α"	Pyrolysis of the supramolecular polymer		
	E/kJ mol^{-1}	B	ln A/min^{-1}
0.05	143.1	40.51	33.08
0.1	137.8	38.54	31.83
0.15	136.2	37.7	31.42
0.2	134.5	36.89	30.94
0.25	132.6	36.12	30.41
0.3	132.3	35.76	30.27
0.35	131	35.19	29.89
0.4	129.8	34.65	29.52
0.45	128.4	34.09	29.12
0.5	127.6	33.69	28.87
0.55	127.2	33.37	28.69
0.6	126.5	32.99	28.45
0.65	125.6	32.59	28.18
0.7	125	32.25	27.98
0.75	124.2	31.86	27.73
0.8	123.8	31.55	27.56
0.85	122.9	31.14	27.32
0.9	121.2	30.48	26.86
0.95	119.1	29.69	26.33
Media values	128.9 ± 6.1	34.16 ± 2.89	29.18 ± 1.81

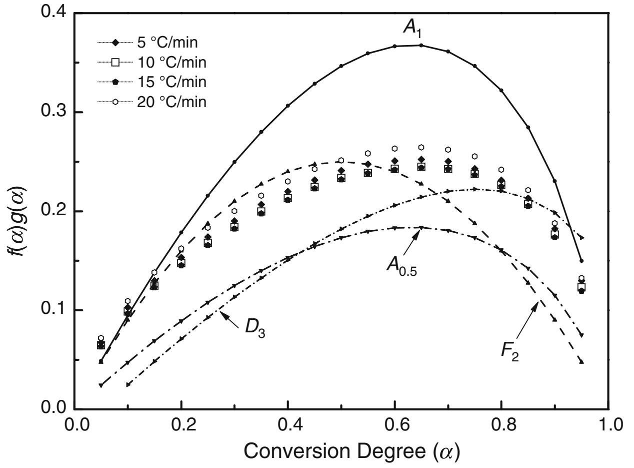

Fig. 9 Theoretical and experimental master plots of $f(\alpha)g(\alpha)$ against α calculated from Eq. 3

Table 4 Kinetic exponent calculated from Eq. 4

Compound	Heating rate/ °C min^{-1}	Kinetic exponent, n ± SD	Adj. R^2
Flunixin-meglumine supramolecular polymer	5	0.72 ± 0.01	0.89766
	10	0.70 ± 0.01	0.90697
	15	0.70 ± 0.01	0.91959
	20.03	0.75 ± 0.02	0.8919
	Average value	0.72 ± 0.03	

experimental $f(\alpha)g(\alpha)$ for each heating rate against α (Fig. 9) and then compared with the model from Fig. 3 and Table 1.

Figure 9 shows that the experimental $f(\alpha)g(\alpha)$ curves are more significantly situated between the theoretical curves from models A_1 and $A_{0.5}$. Thus, it can be suggested that the function for the kinetic model follows $g(\alpha) = ([-\ln(1-\alpha))]^{1/n}$ where $0.5 < n < 1$. The estimate for the kinetic exponent n can be obtained from Eq. 4 and is shown in the Table 4.

The mean value found for n was 0.72. From the definition of n in the derivation of the Avrami equation, this value is suggestive of a diffusion controlled growth mechanism as defined by Hulbert [9] considering that nucleation can be deceleratory ($0 < \eta < 1$, η = number of steps involved in the formation of nuclei) [10–12]. The lower values of n ($n < 1$) may be attributed to a one-dimensional (rod-shaped parallel molecules) diffusion controlled nuclei growth during the decomposition process of the supramolecular polymer.

Now that n (Table 4) and E, B (Table 3) are known, the pre-exponential factor ln A can be calculated from Eq. 5, and the results are shown in Table 3.

Conclusions

The flunixin-meglumine adduct gave rise to an amorphous supramolecular polymer during melting. The polymer associated with hydrogen bonds showed a high molecular weight of 2.0×10^5 kDa and a vitreous transition around 49.5 °C.

The kinetic triplet for thermal decomposition of the supramolecular polymer could be evaluated through the Capela-Ribeiro method. The mean value for R^2 obtained, 0.90403, indicated that the $g(\alpha) = ([-\ln(1-\alpha))]^{1/n}$, where $n = 0.7$ was the better approximation considering the known kinetic models. However, the R^2 may indicate a more complex mechanism for the thermal decomposition of the supramolecular polymer.

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