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A STATISTICAL MODEL FOR THE OPTIMIZATION OF DSC PERFORMANCE IN THE EVALUATION OF DRUGS FOR PREFORMULATION STUDIES

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Differential scanning calorimetry (DSC) is a thermal analytical tool for preformulation studies. Extrapolated melting temperature (T_P) and heat of fusion (ΔH_f) can be used as parameters for optimizing the DSC performance. Two model pharmaceuticals acetaminophen and nicotinamide are used in this study. Using a factorial design for the experimental model and matrix analysis the results, the effect of sample mass, heating rate and the nitrogen flow rate were evaluated on the ΔH_f values and T_P values. Two levels for each of the procedural variables were used as a balanced experimental design with two sample sizes, two heating rates and two nitrogen flow rates. It was found that the change in the heating rate caused significant changes in the ΔH_f values but not the T_p values for acetaminophen. However, no significant effect was found for the T_p value but ΔH_f value was affected to a certain extent for nicotinamide.

Keywords: *DSC, extrapolated melting temperature, factorial design, heat of fusion, matrix analysis*

Introduction

DSC can be used to characterize pharmaceuticals for preformulation studies and for evaluation of pharmaceuticals by characterizing the melting behavior, crystallization, polymorphism and solid state transitions. However the effect of procedural variables should be taken into consideration in doing such studies and standardize the process. The heat of fusion (ΔH_f) values and the extrapolated melting temperature (T_p) are used as the parameters for thermal characterization of two model USP drugs acetaminophen (typical melting range 168–172°C and heat of fusion of 28 kJ mol^{-1}) [1, 2] and nicotinamide (typical melting range 129–131°C and heat of fusion of 25.4 kJ mol^{-1}) [3, 4]. Heating rates, nitrogen flow rate and sample size were considered as the procedural variables. These are the primary variables in evaluating an inorganic compound by DSC. In studying organic compounds e.g. vegetable oils, volatile oils other related procedural variables may be included in the model like pan with pin holes and hermetically sealed pans. The effect of these procedural variables on heat of fusion (ΔH_f) values and extrapolated melting temperature (T_p) were studied to optimize the DSC performance and the (ΔH_f) and (T_p) values thus obtained were compared with the literature values. There are various theoretical models to evaluate the effect of the evaluation parameters in DSC studies. Here a factorial design is being used to analyze the data. The objective of this study is to optimize the DSC performance [5] and thus develop a DSC performance protocol to characterize these pharmaceuticals.

Experimental

Materials

Acetaminophen (Lot Number SN 0803 Spectrum Chemical, Gardena, CA), MW 151.1646, molecular formula $C_8H_9NO_2$ and nicotinamide (Lot No. N7558 Sigma Aldrich Chemicals, St. Luis, MO), MW 122.1262, molecular formula $C_6H_6N_2O$ were used as two model drugs for this study.

Methods

A TA DSC 2010 unit from TA instruments® using Thermal Advantage® and Universal Analysis® software, open aluminum crucible pans (40 μL) without pinholes, indium (reference material) nitrogen purge gas flow (Aga Gas), electronic balance from Denver Instrument XE-100.

A 2^3 factorial design experimental model was set up with three procedural variables each having two levels; sample size, heating rate and nitrogen flow rate to optimize the DSC performance. Statistical Analysis Software was used to evaluate data. The advantage of a factorial design in modeling an experimental set-up is that fewer runs are required than with

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Table 1 DSC results for acetaminophen

Random no.	Sample mass/ mg	N_2 flow rate/ mL min^{-1}	Heating rate/ °C min^{-1}	T_m/°C	T_p/°C	Heat of fusion/ J g^{-1}
5	3.2	50	10	168.95	170.4	173.7
6	3.85	100	10	168.9	170.56	175.5
8	5.9	50	10	168.90	170.56	176.2
4	7.05	100	10	169.36	172.9	109.5
3	3.1	50	20	169.42	171.76	192.2
1	4.3	100	20	169.45	171.86	186.5
7	5.65	50	20	169.22	171.91	196.6
2	9.3	100	20	169.58	173.15	184.7

T_m – melting point onset, T_p – extrapolated peak temperature

one-at-a-time experiment, they have increased precision, they have possibility of estimating interaction effect and have wider inductive basis. Two levels of each of the variables were taken. For sample size two levels of sample mass 1–5 and 6–10 mg were used; for heating rate the two levels are 10 and 20°C min while that for nitrogen flow rate are 50 and 100 mL min^{-1}. The sequence of the run is determined with the help of a random number table. A total of eight run is performed on each of acetaminophen and nicotinamide. Calibration of both temperature and enthalpy of the DSC was done for each ramp settings of 10 and 20°C min^{-1} with standard indium. The melting point onset temperature (T_m), extrapolated peak temperature (T_P) and the heat of fusion (ΔH_f) are estimated using the TA Universal Analysis software®. Statistical Analysis was performed on T_m, T_P and ΔH_f.

Results and discussion

In Table 1 the sample pan weight standard deviation is 0.1414 while standard deviation for the heat of fusion is 27.45 J g^{-1}. A matrix design [6–8] is used to estimate the effect of the procedural variables on the heat of fusion values. It was found from Fig. 1 that increased heating rate from 10–20°C min^{-1} caused an increase in the heat of fusion from 173.7–192.2 J g^{-1} for small sample size with N_2 flow rate of 50 mL min^{-1}. Changes in flow rate and sample mass did not change the heat of fusion values appreciably. The small value of ΔH_f of 109.5 J g^{-1} at random no. 4 may be attributed a possible interaction of acetaminophen with nitrogen. The extrapolated peak temperature did not vary appreciably [9, 10].

From Fig. 2 the changes in enthalpy values (ΔH_f) of acetaminophen due to change in heating rate from 10 to 20°C min^{-1} was observed. The enthalpy value changed appreciably from 173.7 to 192.92 J g^{-1} while the extrapolated peak temperature (T_p) changed appreciably from 170.4 to 171.76°C. Fig. 3 shows the matrix design for the DSC data.

From Table 2 employing the matrix design it was found that for nicotinamide the increase in heating rate from 10 to 20°C min^{-1} did not change the heat of fusion values appreciably as evident from Fig. 4. Also the T_p values did not change significantly with a change in the procedural variables. For the experiment on nicotinamide the sample pan weight standard deviation=0.757, standard deviation conducted on the heat of fusion = 9.5 J g^{-1}, while standard deviation for T_P = 0.746.

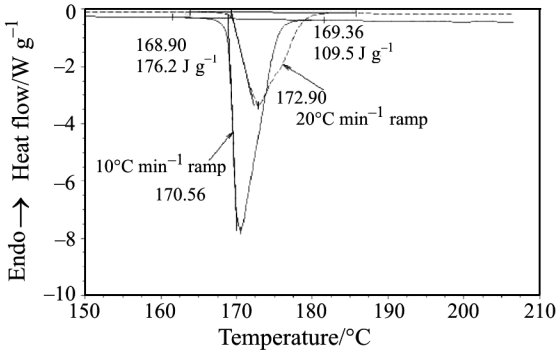

Fig. 1 Changes in ΔH_f and T_p of acetaminophen at N_2 flow rate of 50 mL min^{-1} due to the change in heating rate

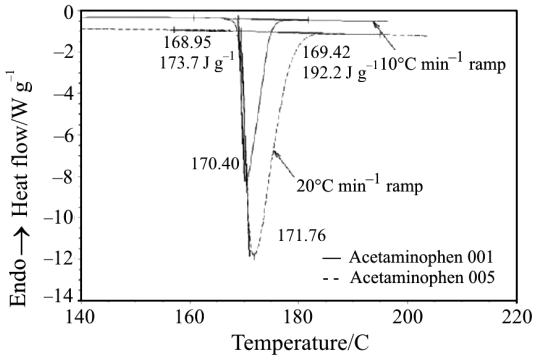

Fig. 2 Graph overlay to show the difference in ΔH_f and T_p values for acetaminophen due to heating rate

Table 2 DSC results for nicotinamide

Random no.	Sample mass/ mg	N_2 flow rate/ mL min^{-1}	Heating rate/ °C min^{-1}	T_m/°C	T_p/°C	Heat of fusion/ kJ mol^{-1}
8	4.37	100	10	128.17	130.22	203.55
4	8.43	100	10	128.39	130.95	188.55
1	5.59	100	20	128.57	131.27	208.40
6	3.43	100	20	128.67	131.27	188.30
3	8.45	50	20	128.70	132.43	204.20
5	4.72	50	10	128.30	130.93	195.90
2	7.21	50	10	128.02	130.4	213.80
7	3.46	50	20	128.81	132.00	118.60

Table 3 Summary of results

Sample	Parameter	Average differences due to variable parameter		
		Sample mass	Flow rate	Ramp
Acetaminophen	T_p	0.985°C	1°C	1.065°C
	ΔH_f	–8.3%	–0.16%	17.6%
Nicotinamide	T_p	0.1575°C	0.5°C	1.12°C
	ΔH_f	–1.7%	7.59%	10.14%

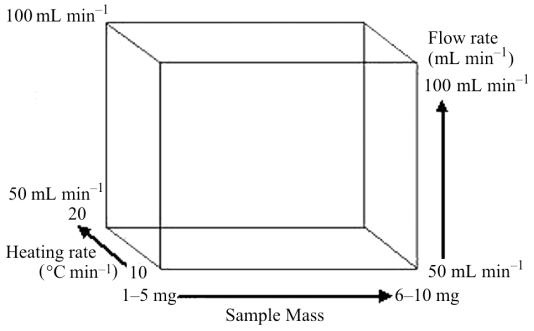

Fig. 3 Matrix design for the DSC data

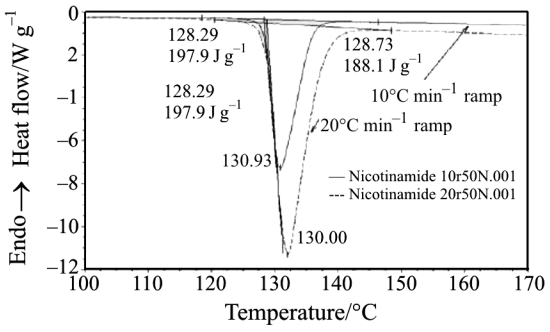

Fig. 4 Graph overlay to show the effect in ΔH_f and T_p values for nicotinamide due to the heating rate

From Fig. 5 it is clear that the extrapolated peak temperature (T_p) did not change appreciably. It changed from 132°C for 50 mL min^{-1} flow rate to 131.27°C for 100 mL min^{-1} nitrogen flow rate. However the change in heat of fusion values (ΔH_f) was from 118.6 to 188.3 J g^{-1}.

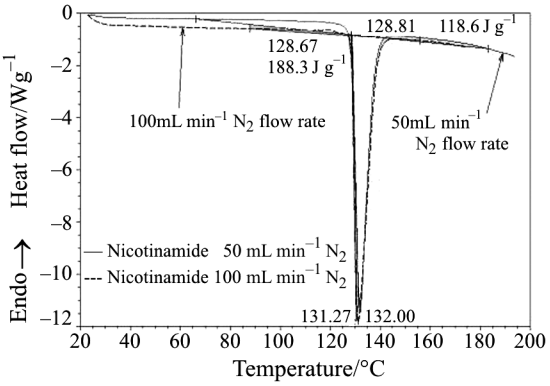

Fig. 5 Graph overlay to show the effect in ΔH_f and T_p values for nicotinamide due to nitrogen flow rate

Conclusions

From the matrix analysis, the ramp was found to cause a high variation of 17.6% in the ΔH_f values for acetaminophen. The contributions from the other variables on T_p and ΔH_f values were not found to be significant. For nicotinamide none of the variables affected the T_p values but ΔH_f values were to a certain extent affected by heating rate and nitrogen flow rate. Further work intends to the development of a data library of drug having stable baseline in solid–liquid transitions and drugs that sublimes and melt.

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