Research Article

COMPATIBILITY AND THERMAL STABILITY STUDIES BETWEEN OMEPRAZOLE AND AMBROXOL HYDROCHLORIDE

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ABSTRACT

The objective of this research was to explore the compatibility and thermal stability of omeprazole/ambroxol hydrochloride in solid-state mixtures by differential scanning calorimetry (DSC) with different heating rates. The kinetic parameters and critical temperature of thermal explosion were calculated and analyzed by Kissinger methods. Results show that the thermal decomposition of omeprazole/ambroxol hydrochloride has low-temperature and high-temperature decomposition stages. The peak decomposition temperature and the critical temperature of thermal explosion for the mixture are 25.7 °C and 12.4 °C lower than that of omeprazole, respectively. In a word, omeprazole/ambroxol hydrochloride has poor compatibility. Omeprazole becomes less thermal stable in the presence of ambroxol hydrochloride.

Keywords: compatibility, omeprazole, ambroxol hydrochloride, DSC

INTRODUCTION

A combination of at least two drugs or excipients has seen a widely application in clinical practice partly due to the complexity of a disease¹⁻². However, drug-drug interactions are common between recommended drugs for different conditions³. Interactions arising from the incompatibility during the combination may lead to unsuspected change in the stability, chemical properties, efficacy and safety of the final mixture.

Therefore, compatibility study of drug–drug is a key element in pre-formulation analysis⁴⁻⁵. Differential scanning calorimetry (DSC) has been proved to be a simple, effective and screening method in compatibility evaluation of drug–excipient mixtures. DSC analysis offer valuable information about the properties of materials such as stability, kinetic analysis and phase

transitions⁶⁻⁷.

Omeprazole is a drug belonging to the benzimidazole family. The pH value of omeprazole solution with the maximum stability can be around 11⁸. Omeprazole is commonly used for diagnosis and treatment of diseases like gastro-oesophageal reflux and reflux esophagitis⁹⁻¹¹. The pH value of ambroxol hydrochloride solution is 5.0, and the solution is often administered concomitantly for the treatment of respiratory infections¹². Recently, several studies have found that chemical reactions and incompatibility were suspected between omeprazole and ambroxol hydrochloride injection by simple observation¹³⁻¹⁴. However, more efforts need to be done in order to further understand the observations.

Give above, the aim of the present work was to evaluate the possible interactions between omeprazole and ambroxol hydrochloride by DSC. To our knowledge, data were not available in physiochemical interaction study for the mixture before our investigation.

MATERIALS AND METHODS

Omeprazole was commercially purchased from the Aladdin Reagent Co. Ltd. Shanghai, China and its chemical purity was 98%. Ambroxol hydrochloride was purchased from Nanjing Chemlin Chemical Industry Co., Ltd, Nanjing, China.

Experiments

A SETARM DSC 131 differential scanning calorimeter (SETARAM Instrumentation, Caluire, France) with a stainless-steel crucible was used for thermal analysis of omeprazole, ambroxol hydrochloride and their binary mixtures (BMs). BMs were prepared by grinding in an agate mortar with pestle at a mass ratio of 1:1 before DSC testing. The 1:1 (m/m) ratio was chosen to maximize the probability of observing any interaction¹⁵. Approximately 1.2mg sample mass was weighed for individual components and the premixed mixture. DSC test of each sample was under a flowing atmosphere of nitrogen at a rate of 50 mL/min and heating rates of 5, 10, 15 °C/min.

RESULTS AND DISCUSSION

Thermal Behaviors

The selected DSC curves of omeprazole, ambroxol hydrochloride and their binary mixture at a heating rate of 10°C/min are shown in Figure 1. Thermal behaviours of pure omeprazole, ambroxol hydrochloride and binary mixtures are compared in the DSC curves.

It can easily be found from Fig. 1 that the DSC curve of omeprazole consists of two endothermic peaks and one exothermic peak. The two endothermic peaks, at 126.4 °C and 162.9 °C, are related to the phase change and melting process of omeprazole, respectively. The exothermic event with a peak temperature of 175.9 °C occurs instantly after the endothermic process, and the event is associated with the decomposition of the material. Similar to omeprazole, the DSC curve of ambroxol hydrochloride showed that one exothermic event ($T_{peak}=265.7$ °C) exists followed by an endothermic one ($T_{peak}=241.7$ °C).

In the DSC curve of omeprazole/ambroxol hydrochloride mixture, one endothermic and two exothermic events can be observed. The melting peak temperature of the mixture is 141.8 °C, primarily due to the phase change of omeprazole from solid to liquid, and the temperature is 21.1 °C lower than that of pure omeprazole. The exothermic peaks of omeprazole/ambroxol hydrochloride at 150.2 °C and 302.4 °C are caused by the decomposition of omeprazole and ambroxol hydrochloride, respectively.

The first peak temperature of the mixture was used to calculate the temperature shift corresponding to individuals. The temperature shift between omeprazole/ambroxol hydrochloride and omeprazole is 25.7 °C, suggesting a strong evidence of some incompatibility phenomena¹⁶. Therefore, ambroxol hydrochloride can accelerate the thermal decomposition of omeprazole. Notably, the melting endothermic peak of ambroxol hydrochloride disappears in the omeprazole/ambroxol hydrochloride mixture, which may also indicate possible incompatibility between the two excipients¹⁷.

Thermal Kinetic Analysis

Kissinger method has been widely applied as a fast method for thermal behavior and kinetic parameters analysis of pharmaceutical products assessment¹⁸⁻¹⁹. In 1957, Kissinger²⁰ developed a model-free non-isothermal method, where there is no need to use apparent activation energy (E) for each conversion value in order to evaluate kinetic parameters. This method is described as following equation (1):

$$\ln\left(\frac{\beta_i}{T_{pi}^2}\right) = \ln\left(\frac{RA_k}{E_k}\right) - \frac{E_k}{R} \frac{1}{T_{pi}} \quad (1)$$

Where, β is the heating rate in °C/min. T_p is the peak

temperature of decomposition reaction at β in K. The E (kJ/mol) and pre-exponential factor (A) can be obtained from the slope $-\frac{E}{R}$ and intercept $\ln\left(\frac{RA}{E}\right)$, respectively. R is the universal gas constant (8.314 J·mol⁻¹·K⁻¹)

Based on E and A , two vital parameters T_{p0} and T_b concerning safe storage and process operations can be extrapolated out according to the following equations.

$$T_{pi} = T_{p0} + a\beta + b\beta_i^2, \quad i = 1, 2, 3 \quad (2)$$

$$T_b = \frac{E - \sqrt{E^2 - 4RET_{p0}}}{2R} \quad (3)$$

Where, T_{p0} is the value of T_p corresponding to $\beta \rightarrow 0$. A , b and c are coefficients. T_b , related to safe storage and process operations of tested ingredient, is the critical temperature of thermal explosion in °C.

The DSC curves of omeprazole, ambroxol hydrochloride and their binary mixture at three different heating rates of 5, 10 and 15°C/min are shown in Figure 2. DSC data of omeprazole/ambroxol hydrochloride mixtures at different

heating rates are listed in Table 1. Thermal kinetic parameters were calculated and presented in Table 2.

As can be observed in Figure 2 and Tables 1-2, the following observations can be concluded. The activation energy value for low-temperature decomposition event of omeprazole/ambroxol hydrochloride is 9.04 kJ/mol higher than that of omeprazole. For high-temperature decomposition process of the mixture, the value is close to that of ambroxol hydrochloride. The T_{p0} value of the omeprazole/ambroxol hydrochloride is 11 °C lower than that of omeprazole, indicating that the mixture is less thermal stable in the presence of ambroxol hydrochloride. The critical temperature of thermal explosion of the mixture is 12.4 °C lower than that of omeprazole, suggesting that the binary mixture is more hazardous than omeprazole at low temperatures.

Table 1: DSC data of omeprazole/ambroxol hydrochloride mixtures at different heating rates

Sample	Mass mg	Heating rate °C/min	T_p °C
Omeprazole	1.16	5	160.2
	1.17	10	175.9
	1.18	15	183.3
Ambroxol hydrochloride	1.17	5	253.0
	1.19	10	265.7
	1.17	15	271.8
Omeprazole/ambroxol hydrochloride	1.16	5	139.2
			289.1
	1.19	10	150.2
			302.4
	1.17	15	158.2
			310.8

Table 2: Thermodynamic parameters of omeprazole/ambroxol hydrochloride mixtures

Sample	E kJ/mol	$\ln A$ s^{-1}	r %	T_{p0} °C	T_b °C
Omeprazole	73.38	24.98	99.76	136.2	138.4
Ambroxol hydrochloride	133.15	35.45	99.82	233.7	237.2
Omeprazole/ambroxol hydrochloride	82.42	33.57	99.99	125.2	126.8
	133.64	33.55	99.88	270.9	275.6

Figure 1: DSC curve of omeprazole, ambroxol hydrochloride and omeprazole/ambroxol hydrochloride at a heating rate of 10°C/min

(a)

Figure 2: DSC curve of omeprazole (a), ambroxol hydrochloride (b) and omeprazole/ambroxol hydrochloride (c) at different heating rates

CONCLUSION

The compatibility and thermal stability for omeprazole/ambroxol hydrochloride was analyzed by DSC. Based on the DSC results, the following conclusions can be concluded.

(1) Thermal decomposition process of omeprazole/ambroxol hydrochloride consists of two stages. The first stage is related to the rapid decomposition process of omeprazole, while the second stage is caused by ambroxol hydrochloride.

(2) The first exothermic decomposition peak temperature of the mixture is 25.7 °C lower than that of omeprazole at the heating rate of 10 °C/min, indicating some incompatibility between omeprazole and ambroxol hydrochloride.

(3) The omeprazole/ambroxol hydrochloride is more hazardous than omeprazole at low temperatures because the omeprazole/ambroxol hydrochloride is more hazardous than omeprazole at low temperatures because the critical temperature of thermal explosion for the mixture is 12.4 °C lower than that of omeprazole

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