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CORRELATION STUDIES BETWEEN THERMAL AND DISSOLUTION RATE CONSTANTS OF CIMETIDINE DRUG AND TABLETS

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Abstract

This work developed a methodology that can potentially be applied to the quality control of cimetidine drug substance and its tablets. The *kT* obtained at different temperatures (200, 190, 180, 170 and 160°C) were determined by isothermal thermogravimetric method using the classical Arrhenius equations. The dissolution profiles were obtained using USP 24 (Method 711) and rate constants (*kD*) were determined by Kitazawa equations. An evaluation was made to check if there was statistically significant correlation between the two variables *kT* and *kD*. Isothermal TG data were used to determine the reaction order and degradation reaction rate constants. The results showed that in all temperatures thermal order (*kT*) was: *C*<*A*<*B* tablets, while dissolution order (*kD*) was: *C*<*A*<*B* tablets. In conclusion, correlation between *kT*/*kD* seems to be a suitable method for detecting possible interactions between cimetidine and excipients in development or manufacturing changes, particularly for immediate release dosage forms and therefore could be especially useful on quality control.

Keywords: cimetidine, dissolution rate constants, thermal analysis

Introduction

Stability studies are routinely conducted by the pharmaceutical industry in order to evaluate chemical and physical degradation of products. Individual samples are taken at predetermined times and analysed in order to verify a decrease in the active drug content, increase in the degradation product content, or dissolution behaviour changes [2, 3].

It is well-known that the bioavailability of drugs is influenced by their dissolution characteristics [1–3]. Numerous methods to modify the dissolution characteristics of solid dosage forms have been investigated in order to improve their bioavailability [4–6]. The degree of crystallinity is one of the important factors governing the dissolution rate, and consequently, the bioavailability of drugs [6]. In the case of drugs with water solubility, amorphous preparations are sometimes used in the field of pharmaceutical sciences to improve the bioavailability [5–7]. Many authors report that interactions between drugs and polymers used as excipients can be responsible for the formation of an amorphous solid [11–17].

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Changes in the physicomechanical properties of a formulation are usually due to chemical interactions between the drug and excipients [13, 14]. These interactions can influence the degree of crystallinity and consequently its stability and rate dissolution profile [9]. The chemical, physical and mechanical properties of excipients have been thoroughly investigated by numerous authors, as well as their effects upon the thermal stability of the drug substance [13–15]. From the kinetic point of view, thermal stability of drug substances can be inferred from isothermic thermogravimetry studies conducted at different temperatures [17]. Lastly, the stability of the active components of commercial pharmaceutical forms stored at room temperature is crucial in defining the products' shelf-life (the length of time over which a drug's activity is preserved) [13–18].

The aim of this study was to verify if there is any significant correlation between dissolution and thermal degradation rate constants. A correlation between these two parameters can be of interest in predicting stability of formulations and possible drug-excipient interactions.

Experimental

Materials

The excipients Microcel MC101®, Explocel®, Aerosil®, PVPK30® and magnesium stearate, as well as cimetidine drug substance and tablet A, were obtained from Laboratory of Pharmaceutical Technology of the Federal University of Paraíba (LTF-UFPB). Tablets *B* and *C* were acquired in a local drugstore.

Cimetidine tablet *A* was prepared with the following composition: cimetidine 74.10%, Microcel MC101® 17.69%, PVPK30® 4.67%, Explocel® 2.07%, Aerosil® 0.40% and magnesium stearate 1.11%. Cimetidine tablet *B* had the following excipients: Microcel MC101®, povidone, carboxymethyl starch, ethylcellulose, diethyl phthalate, Opaspray®, FDC 2 (Aluminium Lake), Yellow cosmetic dye. The excipients present in cimetidine tablet *C* were: corn starch, Microcel MC101®, povidone, magnesium stearate, croscarmellose sodium, amorphous silica.

Thermal analysis

Isothermal TG curves for cimetidine drug substance and tablets *A*, *B* and *C* were obtained in a Shimadzu thermobalance, model TGA-50H, under a flow of air at 10 mL min^{-1}, at 200, 190, 180, 170 and 160°C over 4 h. The TG was calibrated for mass and temperature using anhydrous calcium oxalate. A 1–5 mg sample of the powder was spread out on an aluminium pan. Both isothermal and non-isothermal tests were carried out.

The rate constants were calculated using the Arrhenius' equation (1) and reaction order was similarly determined. For each temperature condition, a rate constant, (k), was calculated. By plotting $\ln k$ *vs.* $1/T$ using the Arrhenius relationship, it is possible to extrapolate back to ambient temperature and hence determine the rate constant at that temperature.

$$k = A\exp\left(-\frac{E}{RT}\right) \quad (1)$$

where k is the specific rate constant at temperature T (K), A is the Arrhenius frequency or pre-exponential factor, E is the activation energy and R is the gas constant. It is generally assumed that k is derived from first-order kinetics at isothermal temperatures. However many solids decay by non-first-order reactions and the thermal data need careful mathematical manipulation before accurate and reliable interpretations can be made.

Dissolution

The dissolution testing for cimetidine drug substance, tablets *A*, *B* and *C* was conducted according to the procedure described in the United States Pharmacopeia method (USP 24). Dissolution profile was obtained by sampling at 2, 4, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32, 36 and 40 min. Quantitation was performed by U.V. at 218 nm by measuring the absorbance of filtered portions of the solution under test in comparison with a reference solution having a known concentration of cimetidine standard.

The dissolution rate constants were calculated by the Kitazawa (2) [7, 8] equation and its kinetic parameter was similarly determined.

$$\ln W^{\infty}/(W^{\infty} - W) = kt \quad (2)$$

where W^{∞} is the amount of drug released in solution at infinite time, W is the amount of dissolved drug, k is the dissolution constant and t is the time in question.

Results and discussion

TG dynamic curves of cimetidine drug substance and tablets *A*, *B* and *C*, presented three stages of thermal decomposition for all samples, showing similar thermogravimetric profiles with small differences in the third stage of tablet B.

TG isothermal data in Fig. 1 was used to determine reaction orders and rate constants for the thermal decomposition reaction. The results are presented in Table 1 and show that cimetidine drug substance has a greater rate constant at all temperatures compared to tablets *A*, *B* and *C*.

The values for the thermal rate constants showed that formulations *A*, *B* and *C* presented greater stability in relation to cimetidine drug substance (Table 1). Our results demonstrate that TG isothermal data can be used to determine stability data amongst similar drug formulations, as well as reveal differences between them.

Figure 2 shows dissolution profiles of the 3 tablets. The dissolution of a capsule containing 200 mg of cimetidine drug substance served as a control. Dissolution rate constant data (Table 1) showed different kinetic dissolution behaviour amongst tablets *A*, *B* and *C* and cimetidine drug substance. The use of a kinetic method can demonstrate the difference between them.

Cimetidine drug substance released 50.6% within 2 min. Tablet *B* showed the fastest and most complete dissolution, with 105.1% release within 8 min (T_{max}). Tablets *A* and *C* released approximately 100% of cimetidine at times 8 and 14 min, respectively.

Table 1 Thermal and dissolution rate constants correlation (*kT/kD*) for cimetidine drug substances and tablets *A*, *B* and *C*

Kinetic parameters	Samples			
	Cimetidine drug	Tablet *A*	Tablet *B*	Tablet *C*
$kT200°C/s^{-1}$	$9.86 \cdot 10^{-0.5}$	$4.43 \cdot 10^{-0.5}$	$4.33 \cdot 10^{-0.5}$	$8.18 \cdot 10^{-0.5}$
$kT190°C/s^{-1}$	$3.62 \cdot 10^{-0.5}$	$2.34 \cdot 10^{-0.5}$	$2.19 \cdot 10^{-0.5}$	$2.31 \cdot 10^{-0.5}$
$kT180°C/s^{-1}$	$1.69 \cdot 10^{-0.5}$	$1.00 \cdot 10^{-0.5}$	$9.53 \cdot 10^{-0.6}$	$1.72 \cdot 10^{-0.5}$
$kT170°C/s^{-1}$	$1.23 \cdot 10^{-0.5}$	$6.05 \cdot 10^{-0.6}$	$3.76 \cdot 10^{-0.6}$	$6.01 \cdot 10^{-0.6}$
$kT160°C/s^{-1}$	$2.83 \cdot 10^{-0.6}$	$2.37 \cdot 10^{-0.6}$	$1.86 \cdot 10^{-0.6}$	$3.39 \cdot 10^{-0.6}$
kD_{max}/mg s^{-1}	$4.67 \cdot 10^{-0.3}$	$3.04 \cdot 10^{-0.3}$	$3.45 \cdot 10^{-0.3}$	$1.89 \cdot 10^{-0.3}$
T_{max}/min	4.00	6.00	8.00	12.00
*T*90%/min	4.45[(a)*]	6.09[(c)]	6.06[(e)]	8.54[(g)]
*T*50%/min	2.44	3.38	3.32	4.73
*T*10%/min	0.42[(b)]	0.67[(d)]	0.58[(f)]	0.92[(h)]

*(a–b) $y = -0.07939+0.05031x$; (c–d) $y = -0.01149+0.06779x$; (e–f) $y = -0.10398+0.06853x$ and (g–h) $y = -0.03021+0.09517x$
(r) – $kT200°C/kD_{max}$: 0.9729; $kT190°C/kD_{max}$: 0.5562; $kT180°C/kD_{max}$: 0.9797; $kT170°C/kD_{max}$: 0.6923 and $kT160°C/kD_{max}$: 0.9970

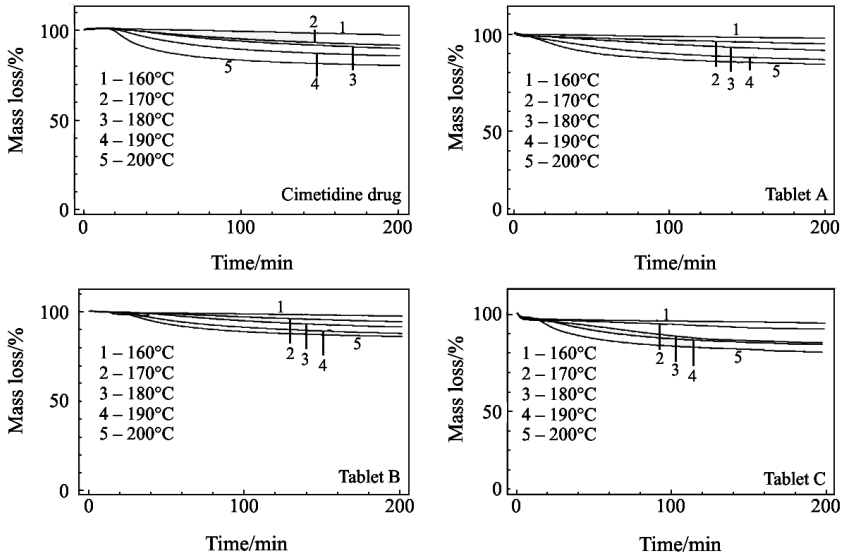

Fig. 1 Isothermal TG curves of the cimetidine drug substance and its tablet *A*

It can be seen that tablet *B* exhibited a dissolution profile similarly to cimetidine drug substance. The dissolution of drug, however, was slightly better than that of tablet *B*. Tablet *C* showed the poorest release profile of all formulations. This pattern ob-

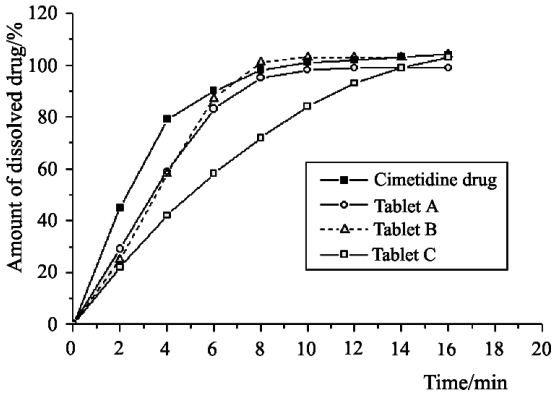

Fig. 2 Dissolution profiles of the cimetidine drug substance and its tablets

served for tablet *C* might be related with a possible interaction between excipients and drug substance in this particular formulation.

The other tablets do not show evidence of any significant chemical interaction, as indicated by the relatively small changes in dissolution behaviour. Cimetidine drug is a water soluble compound easy to formulate into suitable tablets when incorporated into tablet formulations at high percentages. The change in the molecular orientation under heated conditions in an aqueous environment can result in modified crystal forms. This effect might reflect as different and decreasing dissolution response. Indeed, often polymorphic forms are distinguished by way of solubility (or dissolution rates) [9].

The comparison of all the given results shows that the kD_{max} of cimetidine (Table 1), in tablets was always lower than that of the drug substance.

An evaluation was made to check if there was statistically significant correlation between the two variables *kT* and *kD*. The results showed correlation ($p<0.05$) between rate constants of thermal decomposition reaction (*kT*) and dissolution (*kD*). The results evidenced (Table 1) that in all temperatures thermal order (*kT*) was: *C*<*A*<*B* tablets, following the same dissolution order (*kD*): *C*<*A*<*B* tablets.

Conclusions

Correlation between *kT*/*kD* is a suitable method for detecting possible interactions between cimetidine drug substance and its excipients in development or after manufacturing changes particularly for immediate release dosage forms and therefore could be especially useful in a quality control environment.

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