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Correlation studies between dissolution and thermal rate constants of Rabeprazole sodium drug and their tablets

Sanjiv Arora*[1], Deepak K. Aneja[1], Mahesh Kumar[1] and Om Prakash[2]

[1]Department of Chemistry, Kurukshetra University, Kurukshetra, India
[2]Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, India

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ABSTRACT

The thermal profile of rabeprazole sodium drug and tablets A, B and C were studied by isothermal thermogravimetry (TG) at different temperatures i.e. 120, 140, 160, 180 and 200 ^{0}C over 200 minutes under nitrogen atmosphere. The thermal data was used to calculate order of reaction and rate constant (k_T). The dissolution profile was studied according to Indian Pharmacopeia and dissolution rate constant (k_D) was calculated using Kitazawa equation. The rate constant k_T and k_D were correlated and were found to be complying a linear function, with correlation coefficient value close to 1 and follow the same order i.e. tablet A > tablet C > tablet B > rabeprazole drug.

Keywords: Rabeprazole Sodium; Isothermal Thermogravimetry (TG); Dissolution and Thermal Rate Constant.

INTRODUCTION

Rabeprazole sodium drug is a sodium salt of 2-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methylsulfinyl)-1*H*-benzo[d]imidazole (Fig. 1), belongs to a class of proton pump inhibitors (PPIs). It suppress gastric acid secretion by specifically inhibiting the H^+/K^+- ATPase enzyme system at the secretory surface of the gastric parietal cell [1]. Of all PPIs tested, rabeprazole was the most potent acid inhibitor [2]. Rabeprazole is converted to several degradation products when exposed to acidic or neutral environments. Rabeprazole degrades at faster rate as compared to other PPIs [3]. Rabeprazole undergoes pre-systemic and mainly non-enzymatic metabolism that contribute to absolute bioavailability of about 52% of the drug after oral administration of a 20 mg dose [4]. Therefore, a formulation that stabilizes rabeprazole needs to be developed. It has been observed that if a drug is chemically degraded, its therapeutic efficacy begins to turn down. Furthermore, drug degradation can go together with not only a loss in potency, but also

formation of harmful and toxic byproducts [5-6]. Therefore, maintaining drug stability is significant to successful product development.

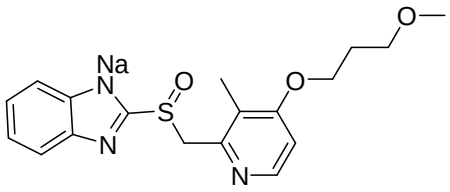

Fig. 1. Structure of rabeprazole sodium drug

Excipients are known to facilitate the administration and release of active components as well as to protect them from the environment. Excipients are considered pharmaceutical inert, but physical and chemical interactions are possible with an active component [7].

Thermal stability of drug substances can be inferred from isothermal thermogravimetric studies conducted at different temperature. Dissolution test has become known in the pharmaceutical industry as a very important tool to characterize drug product performance. It provides measurements of the bioavailability of a drug as well as can demonstrate bioequivalence from batch to batch. Besides, dissolution is a requirement for regulatory approval for product marketing and is a vital component of the overall quality control program [8].

As from the literature survey [9-10], it has been revealed that the correlation studies between thermal and dissolution rate constant is a suitable method for detecting possible interaction between drugs and excipients in development and manufacturing processes, particularly for immediate release dosage forms and also as a parameter in the studies of pharmaceutical equivalence. We have recently reported the correlation between thermal and rate constant of cefpodooxime proxetil drug and tablets [11]. Therefore, in continuation of our previous work, we hereby studied if there is any correlation between dissolution and thermal rate constant of rabeprazole sodium drug and their tablets.

MATERIALS AND METHODS

Materials:

The rabeprazole sodium drug and enteric coated tablets with different excipients were selected in the present study. Rabeprazole sodium drug and tablets A, B and C containing 20 mg rabeprazole sodium drug along with different excipients were analyzed. Excipients present in the tablet A were D-mannitol, magnesium oxide (MgO), low substituted hydroxypropyl cellulose (L-HPC), hydroxypropyl cellulose (HPC) and magnesium stearate. Tablet B contained cross carmillose sodium, magnesium stearate, polyvinylpyrrolidone (PVP K-30), mannitol, microcrystalline cellulose powder (MCCP) and sodium bicarbonate. Rabeprazole drug, tablet A and B were donated by Cure Quick Pharmaceuticals, Karnal, India. Tablet C was acquired from local drug store. All samples were stored in closed plastic containers until they were needed for analysis.

Methods:

Thermal analysis:

Isothermal thermogravimetric (TG) analysis of rabeprazole sodium drug and tablets A, B and C was carried out using Perkin Elmer Diamond TG/DTA thermogravimetric analyzer instrument. Runs were carried out at 120, 140, 160, 180 and 200 ^{0}C over 200 minutes under high purity nitrogen (99.999%) at a flow rate of 20 ml min^{-1}. Before starting each run, nitrogen was used to wash out the furnace for 30 minutes to create an inert atmosphere so as to avoid unwanted oxidation. The TG/DTA analyzer was calibrated before recording thermograms. Dried alumina powder was used as a reference material and powdered samples were placed in aluminium sample holder for taking thermograms. In order to ensure the uniformity of temperature of the sample and good reproducibility, small amount (3–6 mg) were taken. To verify obtained mass loss curve, two runs of same sample were run under same experimental conditions for each sample.

Data processing and calculations:

Isothermal TG curves data were taken from TG Analyzer by using Pyris software and data was processed in MS Excel software to calculate thermal rate constant (k_T) at different temperatures for all samples.

Dissolution:

The dissolution testing for rabeprazole sodium drug, tablets A, B and C was conducted according to the procedure described in the Indian pharmacopeia 2007 (IP-2007, 1647-1648p). Dissolution profile was obtained by sampling at 10, 20, 30, 40, 50 and 60 min. Quantification was obtained by U. V. at 291nm by measuring the absorbance of the filtered portion of solution under test in comparison with a reference solution having a known concentration of rabeprazole sodium standard.

RESULTS AND DISCUSSION

Thermal studies:

Isothermal TG curves of Rabeprazole drug and tablets A, B and C at 120, 140, 160, 180 and 200 ^{0}C over 200 minutes under nitrogen atmosphere are shown in Fig. 2-5. All the isothermal TG curves are showing similar behaviors. The mass loss of samples increases with increase in isothermal temperature condition. Isothermal TG data can be used to study the thermal stability of drug and tablets. A plot between log mass *vs* time from TG data is found to be linear which demonstrate that thermal decomposition process is of first order for all the samples. TG data was used to calculate the rate constant using integrated rate equation for first order of reaction.

Table 1. Rate constant of Rabeprazole drug and tablets

Temperature (^{0}C)	K (sec^{-1})			
	Drug	Tablet A	Tablet B	Tablet C
120	6.9×10^{-6}	0.92×10^{-6}	0.92×10^{-6}	2.07×10^{-6}
140	9.2×10^{-6}	1.15×10^{-6}	2.30×10^{-6}	2.30×10^{-6}
160	23.0×10^{-6}	2.07×10^{-6}	4.61×10^{-6}	$2..30\times10^{-6}$
180	69.1×10^{-6}	2.30×10^{-6}	6.91×10^{-6}	2.30×10^{-6}
200	69.1×10^{-6}	4.6×10^{-6}	6.91×10^{-6}	4.60×10^{-6}

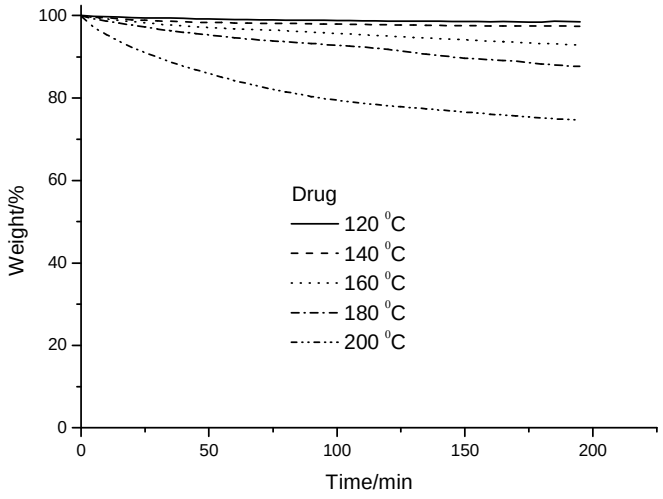

Fig. 2 Isothermal TG curves of the rabeprazole drug at different temperatures

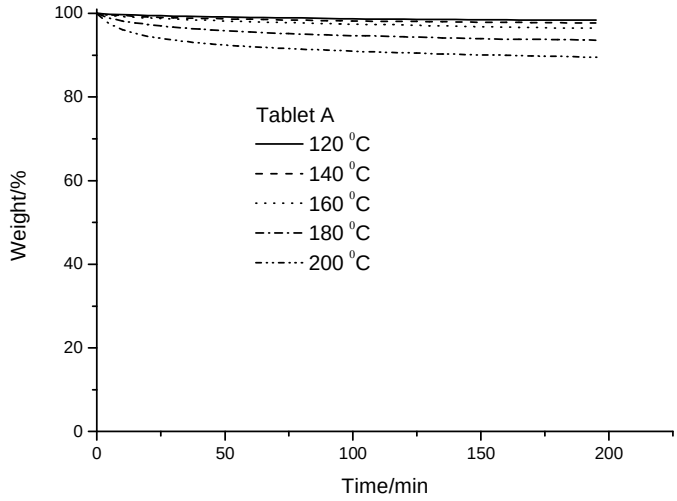

Fig. 3 Isothermal TG curves of tablet A at different temperatures

From the literature study, it has been revealed that lower value of rate constant, higher will be the thermal stability. Rate constant values for raberprazole drug and tablets are summarized in Table 1. The rate constant value for tablet A, B and C is lower than rabeprazole drug at every isothermal condition which lead to conclusion that tablets are more thermally stable than pure drug which may be due to greater interaction between drug and excipients. Among the tablets rate constant value for tablet A is least and highest for B at every temperature condition. It means tablet A is thermally the most stable and B the least. Overall thermal stability order on the bases of rate constant is: tablet A > tablet C > tablet B > Drug. Also this order is in good agreement

with all isothermal TG curves of drug and tablets at every isothermal condition as shown in Fig. 6 (shown only at one temperature for illustration).

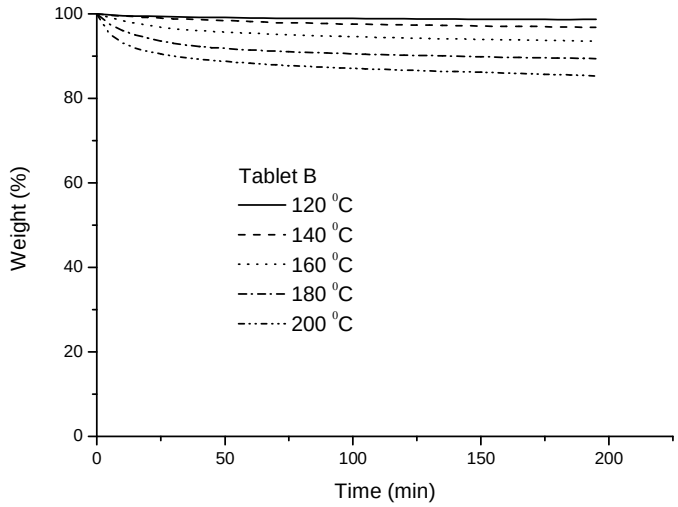

Fig. 4 Isothermal TG curves of tablet B at different temperatures

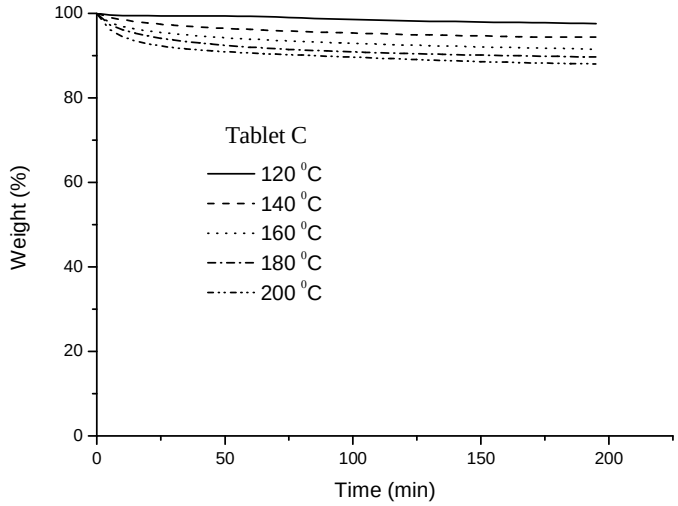

Fig. 5 Isothermal TG curves of tablet C at different temperatures

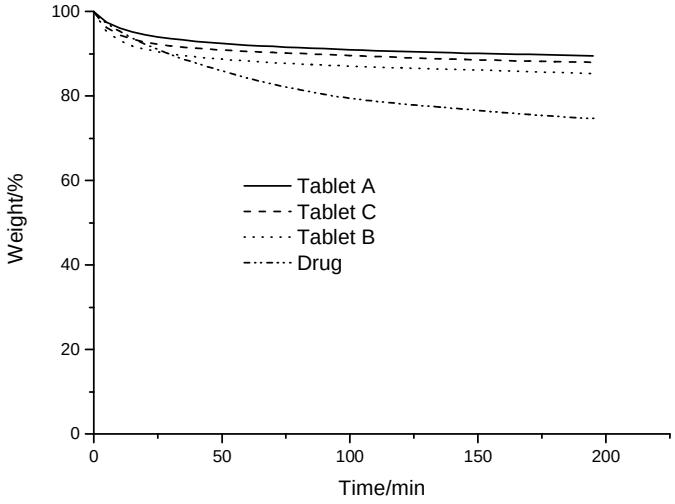

Fig. 6 Isothermal TG curves of rebeprazole drug and tablets A, B and C at 200 °C temperature

Dissolution studies:

Dissolution profiles of drug and tablets are shown in Fig 7. It can be seen that tablet A, B and C exhibit better dissolution profile than drug. The best release profile of tablets may be due to the some attractive forces between components of tablets and media which are stronger than drug excepient interaction. As a result attractive forces which exist in a tablet breaks down and hence tablets shows better disintegration and dissolution. Drug show the poorest release profile which may be due some repulsive forces between drug and media prepared for dissolution study. Here, tablet A is showing better dissolution than the tablets B and C.

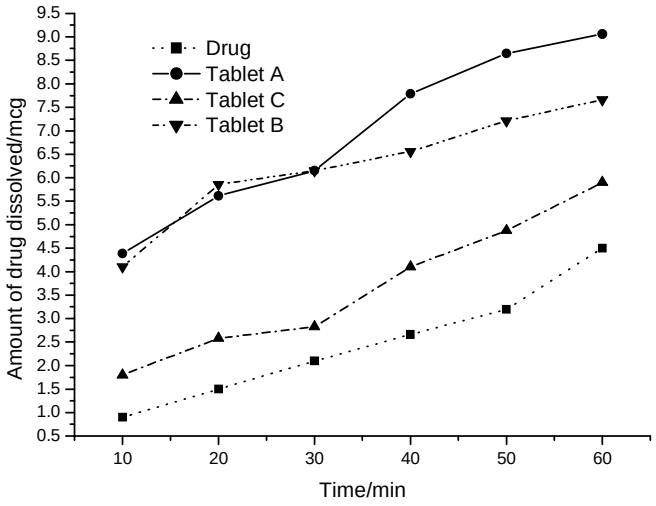

Fig. 7 Dissolution profile of Reberprazole drug and its tablet A, B and C

Dissolution Kinetics

The dissolution rate constant (k_D) was determined from dissolution data by the Kitazawa equation:

$$\ln W^{\infty} / (W^{\infty} - W_t) = k_D t \quad \ldots(1)$$

Where, W^{∞} is the amount of drug released in solution at infinite time, W_t is the amount of dissolved drug at time t and k_D is the dissolution rate constant. The k_D values of all samples are shown in the Table 2. The dissolution rate constant obtained from Kitazawa equation is in following order: tablet A > tablet C > tablet B > drug.

Table 2. Dissolution rate constant obtained from Kitazawa equation

Dissolution rate constant	Drug	Tablet A	Tablet B	Tablet C
k_D (mcg min^{-1})	1.5×10^{-2}	1.09×10^{-1}	7.5×10^{-2}	8.6×10^{-2}

Correlation study:

A correlation between these two parameters k_T and k_D can be of great importance in predicting drug excipient interactions**.** So, statistically significant correlation between the two variables k_T and k_D was evaluated (Fig. 8). It is observed from the figure 8 that there is good correlation between thermal rate constants (k_T) and dissolution rate constants (k_D), obeying a linear function, with correlation coefficient value close to 1. Therefore, correlation between variables k_T/k_D seems to be a suitable method for detecting possible interactions between rebeprazole drug and its excipients in development and could be useful in a quality control.

The kinetic thermal and dissolution order are in good agreement and follows order: tablet A > tablet C > tablet B > drug. Here, tablets are thermally more stable than drug and also shows better release profile. And among tablets, tablet A is thermally the most stable and showing best dissolution.

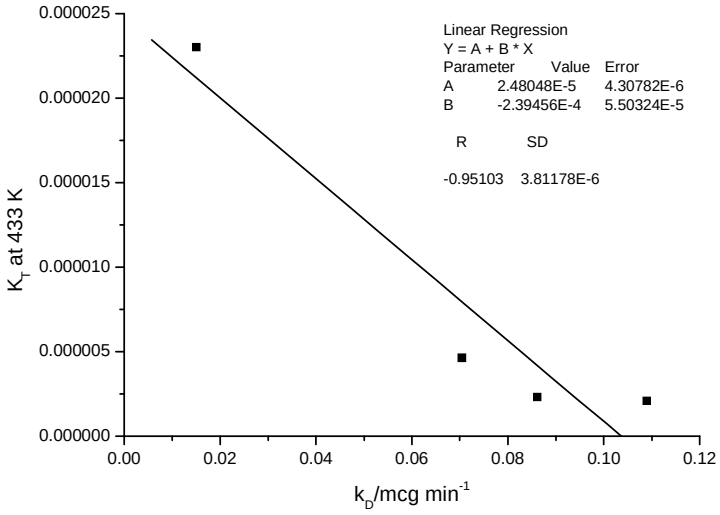

Fig. 8 Correlation between k_T at 433 k and K_D

CONCLUSION

The thermal and dissolution kinetic data showed evidence of difference between the tablets formulations. The thermal and dissolution rate constants are correlated which are helpful in study of drug excipient interaction and could be useful in a quality control. The thermal and dissolution rate constant follow the same order i.e. tablet A > tablet C > tablet B > rabeprazole drug.

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