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Research Article

DISSOLUTION RATE ENHANCEMENT OF KETOPROFEN BY SURFACE SOLID DISPERSION WITH COLLOIDAL SILICON DIOXIDE

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ABSTRACT

Surface solid dispersion with insoluble carriers is considered a recently developed technique, widely applied for the enhancement of solubility and dissolution of poorly water soluble drugs. The objective of this research article is to study the effect of surface solid dispersion of ketoprofen with colloidal silicon dioxide (Aerosil 200) on the dissolution rate. Surface solid dispersion (Adsorbate) containing increased amount of the carrier (1:1 and 1:2) were prepared by surface deposition of ketoprofen from alcoholic solution on the surface of aerosil 200. The prepared adsorbates were characterized by DTA, X-ray and the dissolution profiles were compared by model independent methods. The model independent parameters showed that, the dissolution profiles of adsorbates were greatly higher than that of untreated drug or physical mixtures. The increase in the dissolution rate of the adsorbate compared with untreated drug is due to the conversion of the drug form the crystalline state to the highly energetic amorphous state as proved by DTA and X-ray. The surface solid dispersion proved to be efficient method for improving the dissolution of low water soluble drug which results in dramatic increase in the dissolution rate, rapid absorption, enhanced biological activity and reduced side effects.

Keywords: Ketoprofen, Dissolution, Enhancement Surface Solid Dispersion, Aerosil 200.

INTRODUCTION

Solubility enhancement of poorly water soluble drugs leads to dramatic increase in the dissolution rate, rapid absorption and decreased side effects. Solubility improvement of drugs is always aiming to make the solid drug available to the human body at certain rate and extent. So far, enhancement the solubility of poorly water soluble drugs is considered to be the corner stone for improvement of drug efficacy and bioavailability. The most common methods for improving the solubility include solid dispersion¹⁻³, inclusion complexation with cyclodextrin⁴⁻⁷, microemulsion and micellar solubilization^{8,9}, nanosuspension formation¹⁰⁻¹², surface adsorption on inert carriers¹³ and liquisolid technique^{14,15}. One of the most recent approaches for this challenge is the physical adsorption (surface solid dispersion) of slightly soluble active substances on the surfaces of inert carriers. Aerosil 200, colloidal silicon dioxide, is an ideal example of the inert carriers (adsorbent) which is commonly used in pharmaceutical industries. The carrier is highly pure, amorphous, hydrophilic and anhydrous, with large surface area and controlled particle size. These characters are associated with a wide range of pharmaceutical applications. The carrier is commonly used as a thickening and thixotropic

filler (viscosity control) for semisolid dosage forms. In tablet manufacture, aerosil 200 is used as lubricant, glidant and as component of the tablet coat^{9,16-18}.

Ketoprofen, a propionic acid derivative, is a potent non-steroidal anti-inflammatory drug, widely used as analgesic and in treatment of inflammatory conditions. The very poor water solubility of the drug limits the therapeutic application and bioavailability. Oral administration of ketoprofen causes severe complication to the GIT due to the acidic nature of the drug. Therefore, increasing the solubility and dissolution of the drug will decrease the side effects on the stomach due to rapid absorption and shortening the contact with the stomach wall^{19,20}.

This research article is aiming to increase the solubility and dissolution of ketoprofen through physical adsorption of the drug on the surface of aerosil 200. The adsorption process will lead to decrease in the degree of crystallinity of the active ingredients and formation of the high energetic more soluble amorphous form. Also, the large surface area of the adsorbent helps in increasing the dissolution of adsorbed materials and more concentrations of the drug will be available for absorption from the administration site. Additionally, increasing the solubility of acidic drugs especially NSADs leads to low gastric residence time after oral administration,

rapid absorption and this is very useful in the reduction of side effects to the stomach.

MATERIALS AND METHODS

Materials

Ketoprofen was a kind gift from Alexandria Pharmaceutical Co., Alexandria, Egypt. Aerosil 200 was supplied by CID pharmaceutical Co., Egypt. All other chemicals and reagents used were of analytical grade.

Methods:

Preparation of Surface Solid Dispersion:

Accurately weighed amount of ketoprofen was dissolved in least amount of ethyl alcohol. The required amount of aerosil 200 (adsorbent) was then added to the alcoholic solution of drug and stirred until homogenous suspension is formed. Different weight ratios of ketoprofen and aerosil 200 were used to prepare the adsorbate, namely 1:1 and 1:2. The obtained slurries of aerosil 200 in alcoholic solution of the drug were placed in glass dish and left overnight at room temperature for evaporation of solvent. Complete evaporation of solvent was carried out by placing the dishes in hot oven at 40 °C. The dried samples were then powdered and stored in desiccators till further use²¹. The physical mixture of the drug and carrier were prepared by simple mixing of dry powders in the mortar.

X-Ray Diffraction Pattern:

Powder X-ray diffractograms of pure materials and all binary systems (physical mixture and adsorbate) were performed by using Philips Analytical XRD (PW 3710). The samples were irradiated with monochromatized Cu Ka radiation and analyzed between 2θ angles of 10 and 80°. The voltage, current, and time per step used were 30 Kv, 20 mA, and 0.5 s, respectively.

Differential Thermal Analysis (DTA):

The thermal analysis of the samples is performed by the Differential Thermal Analyses (DTA) measurements using the Shimadzu thermal analysis apparatus (DTG-60/60H). About 10 mg of each sample is placed in a quartz basket suspended from the arm of the balance by means of a quartz wire. The sample temperature is adjusted using a Heraeus temperature controller (Type TRK) which is a component of the DTA apparatus. The samples were heated under non-isothermal conditions at different heating rates (5-35 °C/min⁻¹) from 40-150 °C under nitrogen atmosphere. The activation energy (E_a) and kinetic parameters of degradation of pure drug and adsorbate (1:1) were determined according to the method of Augis and Bennett²² applying the following equation.

$$\ln\left(\frac{\alpha}{T_m}\right) = -\frac{E_a}{R}\left(\frac{1}{T_m}\right) + \ln K_0$$

Where; α: is the heating rate, T_m: is the temperature of the melting peak, E_a: is the activation energy, K₀: is the frequency factor and R: is the universal gas constant and.

In vitro Dissolution Study:

The USP paddle method was used for in vitro dissolution studies. 100 mg of pure drug or the equivalent weight of physical mixture or adsorbate were added to the dissolution medium which consists of 500 ml of saline phosphate buffer (pH 7.4). The dissolution medium was continuously stirred at

50 rpm and kept at 37 ± 0.5 °C. At predetermined time intervals, 5 ml samples were taken, filtered using 0.45 mm filter and replaced with 5 ml of fresh buffer. Drug concentrations were calculated by measuring absorbance at the specified wave length (292 nm) by Uv-visible spectroscopy.

Dissolution Parameters:

To compare between the dissolution profile of pure drug and dissolution profiles of adsorbates (1:1 and 1:2) different model independent tests such as dissolution efficiency, relative dissolution rate, similarity and dissimilarity tests have been performed^{23,24}.

Dissolution Efficiency (%):

Dissolution efficiency (DE %) represents the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100 % dissolution in the same time and calculated according to the following equation^{25,26}.

$$D.E. (\%) = \frac{\int_0^t Y dt}{Y_{100} \times t} 100$$

Where: Y is drug percent dissolved at time t.

Relative Dissolution Rate:

Cumulative amount dissolved of test formula divided by the amount dissolved of pure drug at certain time point.

Mean Dissolution Time (MDT):

The mean dissolution time was calculated to understand the effect of different carrier concentration on the dissolution enhancement of ketoprofen. The mean dissolution time can be calculated from the following equation^{27,28}.

$$MDT_{in\ vitro} = \frac{\sum_{j=0}^n T_m \Delta M}{\sum_{j=1}^n \Delta M}$$

Similarity Factor (f₂) and Dissimilarity Factor (f₁):

A model-independent approaches proposed by Moore and Flanner²⁹ and approved by FDA were used for comparison of the dissolution profiles of various materials. The similarity factor (F₂) was defined by the following equations³⁰:

$$F_2 = 50 \log_{10} \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^{-0.5} \right] \times 100 \right\}$$

Where: F₂ similarity factor, n is the number of time points, R_t is the dissolution value of the reference formulation at time t and T_t is the dissolution value of the test formula at time t. FDA has set a public standard of f₂ value between 50-100 to indicate similarity between two dissolution profiles. A similarity factor of 50 or more, the profiles are considered similar but similarity factor of less the 50 the profiles are considered not similar.

The dissimilarity factor, i.e. difference factor, (F₁) is described by the following equation³¹:

$$F_1 = \frac{\sum_{t=1}^n (R_t - T_t)}{\sum_{t=1}^n R_t} \times 100$$

The profiles are considered similar, if f₁ values are close to zero (<15). While, high values of F₁ (>15) indicates difference (dissimilarity) in dissolution profiles³².

RESULTS AND DISCUSSION

X-ray Diffraction:

The X-ray diffraction (XRD) pattern of powders of pure drug (ketoprofen), adsorbate (1:1), physical mixture (1:1) and pure aerosil 200 are shown in Figure 1. The diffraction pattern (a) of pure ketoprofen is characterized by the presence of the

intense characteristic peaks, in the range of 5-50 2θ , indicating the highly crystalline nature of the drug. In contrast, the pattern (d) of the carrier is characterized by the absence of characteristic any peaks which showing the amorphous nature of aerosil 200. The intensity in the case of adsorbate (b) and physical mixture (c) becomes weaker when compared with the intensity of pure drug (a). In addition, the diffraction patterns of physical mixture and adsorbate where $2\theta > 30^\circ$ are almost faded away. In case of adsorbate, this observation may be attributed to decrease in degree of crystallization and increase in the amorphous nature of due to adsorption of the drug on the surface of aerosil 200. The decrease in the peak intensity in case of physical mixture (c) may be due to the dilution of the drug with the amorphous carrier^{21,33,34}.

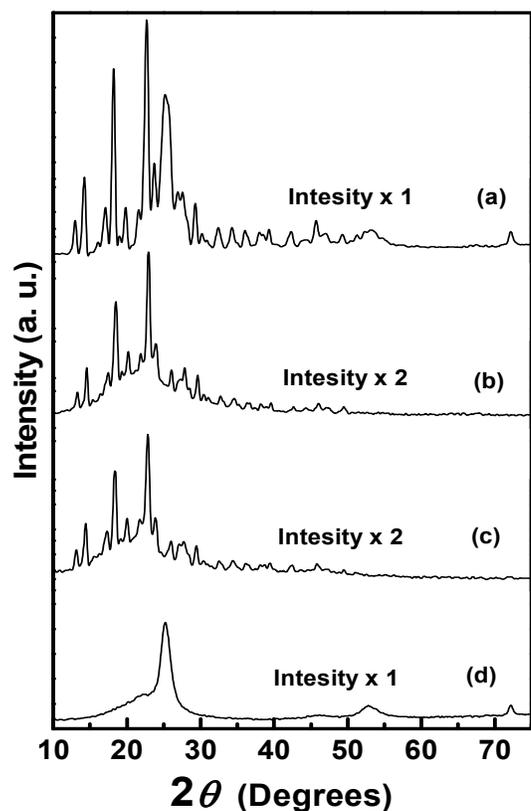


Figure 1): X-ray diffraction pattern of (a) pure drug, (b) adsorbate (1:1), (c) physical mixture (1:1) and (d) pure aerosil 200.

Differential Thermal Analysis

Figure 2 show the DTA traces of pure ketoprofen (a), adsorbate (b), physical mixture (c), and pure aerosil 200 (d) at a heating rate of 15 °C/min. The DTA curves of a, b, and c are characterized by one endothermic peak representing the melting process. The melting peak positions are at 98.71, 93 and 98.40 °C for a, b, and c, respectively. The sharp endothermic peak of the drug become shorter in the thermogram of the physical mixture which may be due to reduced purity of drug after mixing with aerosil 200³⁵. The drug in the form of adsorbate has lower melting point (about 93 °C) compared with that of pure drug (98.71 °C). The decrease in melting temperature in case of adsorbate may be attributed to decrease in crystallinity of the drug due to the

adsorption of ketoprofen on the surface of aerosil 200. There is no difference in the melting temperature between pure drug and physical mixture (curves a and c). The DTA trace of d (carrier alone) has no any thermal event indicating the inert nature of this material. These results indicate the absence of any chemical interaction between ketoprofen and aerosil 200³³.

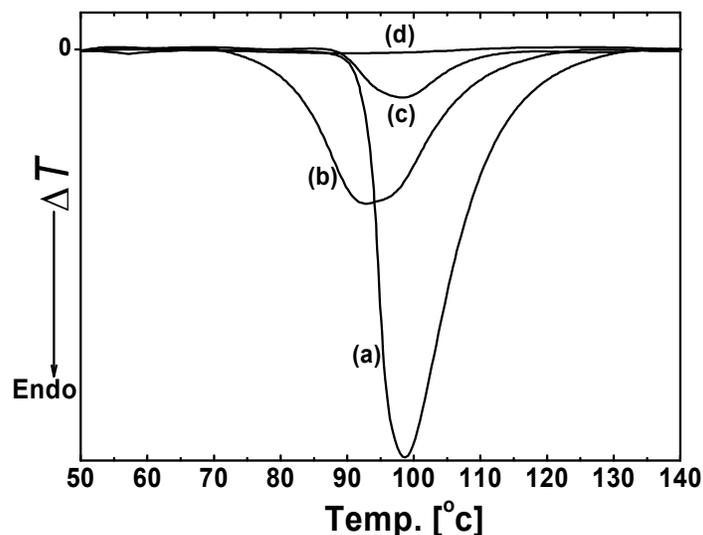


Figure 2: DTA curves of: (a) pure drug, (b) Adsorbate (1:1), (c) Physical mixture (1:1) and (d) pure Aerosil 200.

Figures 3 and 4 show the dependence of melting peak temperature (T_m) on the heating rate (α) for the sample pure drug and adsorbate (1:1). It can be noticed that T_m of ketoprofen, either the pure drug or the adsorbate form, shifts toward higher temperature as the heating rate increases.

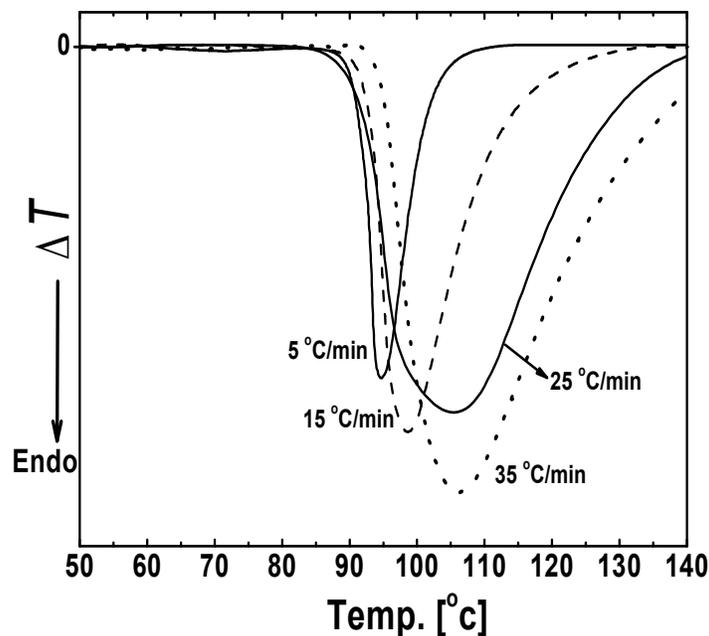


Figure 3: DTA curves for ketoprofen alone at different heating rates

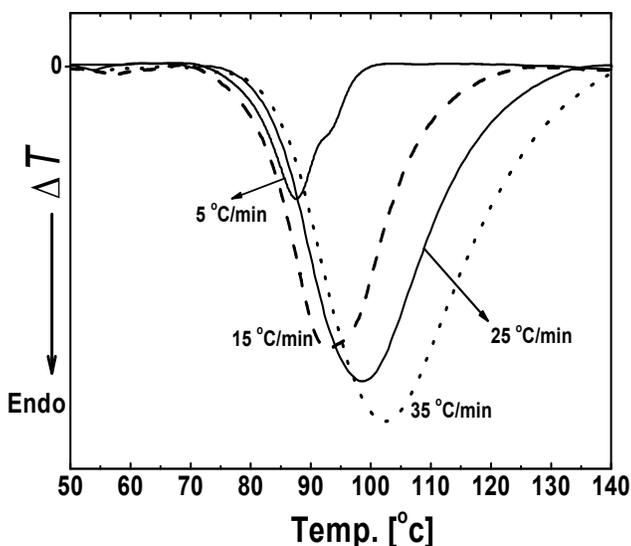


Figure 4: DTA curves for adsorbate (1:1) at different heating rates.

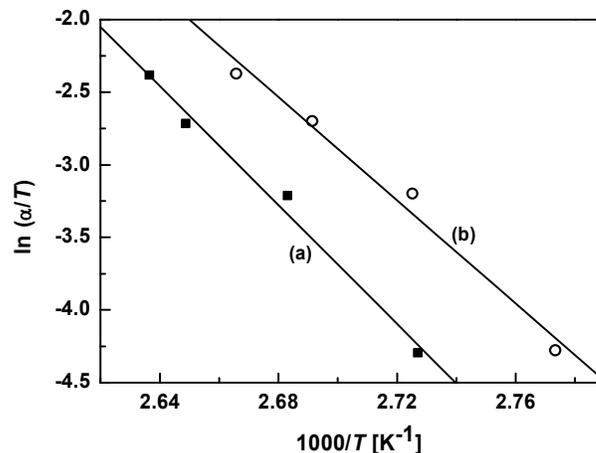


Figure 5: Plots of $\ln(\alpha/T)$ versus $(1000/T)$ for pure drug (a) and adsorbate (b).

The activation energy (E_a) and Arrhenius frequency factor (k_o) for ketoprofen alone or for ketoprofen adsorbed on aerosil 200 were extracted from plotting $\ln \alpha/T$ versus $1/T_m$ as shown in figure 5. The values of E_a , determined from the slopes of the straight lines, were found to be equal 170.11 and 147.64 kJ/mol for drug alone and the adsorbate form respectively. The frequency factor k_o , as melting parameter, was calculated from the intercept of the straight fitting lines and it is found to be $4.2 \times 10^{20} \text{ s}^{-1}$ for pure drug and $3.8 \times 10^{19} \text{ s}^{-1}$ for adsorbate. The obtained values of E_a and k_o indicate that the drug alone has higher melting activation energy and consequently is more thermally stable than drug adsorbed on aerosil 200³⁶.

In vitro Drug Dissolution:

Dissolution profiles of pure ketoprofen, physical mixture and adsorbate are shown in figure 6. The cumulative amount dissolved were about 100% in case of adsorbate (1:1) and (1:2) after 60 minutes. While the amount dissolved from pure drug or physical mixtures were not more than 40% after 120 minutes. The faster dissolution rate in case of adsorbate may be due decreased in drug crystallinity and formation of the highly energetic amorphous state as indicated by X-ray and DTA. There is no difference between the dissolution profiles in case of adsorbate containing higher ratio of aerosil 1200 (1:2) or that containing lower ratio (1:1). This means that, (1:1) ratio is enough to convert all the crystalline drug into the amorphous form and further increase in the carrier has no or limited effect on increasing drug dissolution rate³⁷.

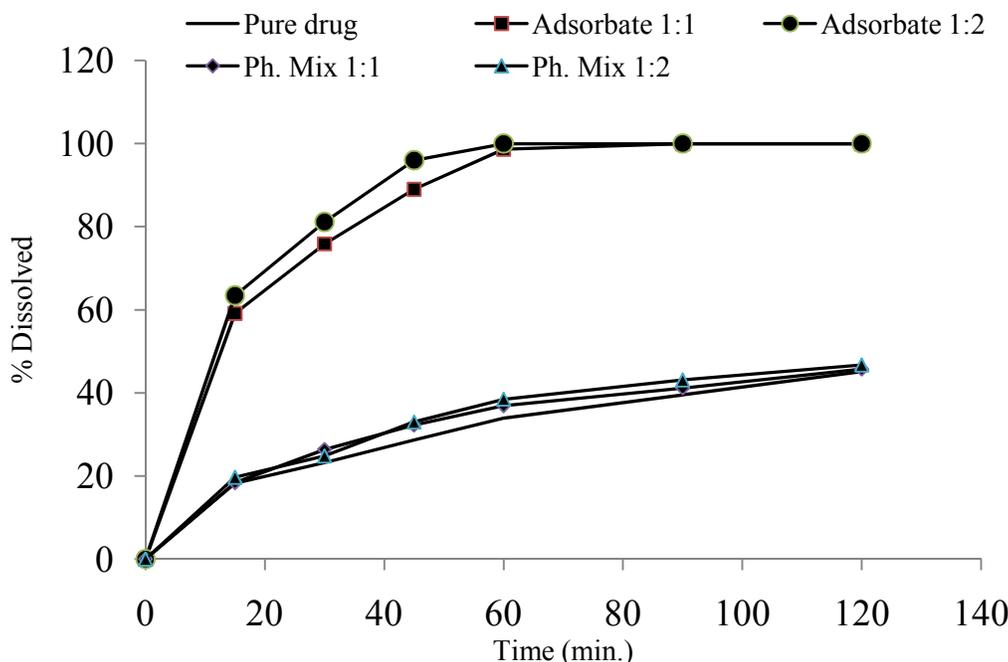


Figure 6: Dissolution profiles of pure ketoprofen, physical mixture and adsorbate.

Comparison of Dissolution Data:

The dissolution parameters including dissolution efficiency (DE), relative dissolution rate (RDR), mean dissolution time (MDT), percent dissolved (PD), similarity factor (F2) and difference factor (F1) were calculated and listed in table 1 to compare between dissolution profiles of pure drug, physical mixtures and the adsorbate forms. High dissolution efficiency of 59.64 and 64.2 were found for adsorbates (1:1) and (1:2) respectively, while lower DE were observed pure drug and

physical mixtures, 18.58 and 20.48 respectively. The RDR of adsorbates were 3.27 and 3.5 compared with RDR of 1, 1.014 and 1.08 for pure drug and physical mixtures. The adsorption of ketoprofen on aerosil 200 resulted in decrease of the in vitro mean dissolution time from 38.51 to 19.18. These findings indicate that, the actual amount of drug dissolved in case of adsorbate is much higher than that of pure drug and thus better and rapid amount can absorbed form adsorbate compared with untreated drug.

Table 1: Dissolution parameters of pure drug, physical mixtures and adsorbates

Drug Form	Dissolution Parameters					
	DE %	RDR	PD ₆₀	MDT	F2	F1
Pure drug	18.58	1	33.97	38.51	-	-
Physical mixture (1:1)	20.48	1.14	36.93	34.46	76	10
Physical mixture (1:2)	20.36	1.08	38.52	33.91	76	11
Adsorbate (1:1)	59.86	3.27	38.52	19.18	14	221
Adsorbate (1:2)	64.2	3.5	100	16.11	12	244

The values of similarity factor (F2) of adsorbates are less than 50 and these of dissimilarity (difference) factor (F1) are larger than 15. This means that the dissolution profiles of adsorbate are very higher than the dissolution rate of pure drug and improvement of dissolution rate have been occurred as consequent to surface adsorption onto aerosil 200^{38,39}.

CONCLUSION

Surface adsorption on inert carriers such as aerosil 200 was very successful tool for enhancement the dissolution rate of ketoprofen. The difference in dissolution rate between samples containing low and high amount of aerosil 200 of was very low. Comparison between the dissolution profiles showed that, surface adsorption highly improved the dissolution of ketoprofen. DTA and x-ray proved the conversion of the crystalline ketoprofen into the high energetic amorphous form. The adsorbate form of the drug has lower activation energy than the pure drug which reflects the thermal instability of adsorbed drug.

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