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Adsorption of ketotifen onto some pharmaceutical excipients

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Abstract

The adsorption of a drug onto solid dosage form excipients may influence its dissolution characteristics, analytical testing and bioavailability. This is particularly important for drugs which are normally used in low doses such as ketotifen fumarate. Ketotifen fumarate, an orally active prophylactic agent used for the management of bronchial asthma and allergic disorders, was found to adsorb onto microcrystalline cellulose, croscarmellose sodium and pregelatinized starch. Croscarmellose exhibited the highest affinity followed by micorocrystalline cellulose and then pregelatinized starch. The Freundlich adsorption isotherm was found to best describe the adsorption data indicating that adsorption is a continuous function of the initial drug concentration. The extent of adsorption of ketotifen onto croscarmellose showed dependency on the pH of the media. In addition, a correlation between adsorption of the drug and its solubility at different pH values was observed. The low and negative values of the heat of adsorption (ΔH) of ketotifen obtained in case of croscarmellose sodium and the pH dependency in case of its adsorption onto microcrystalline cellulose suggest that the predominant mechanism of ketotifen adsorption is physical and exothermic in nature. © 1997 Elsevier Science B.V.

Keywords: Ketotifen; Adsorption; Excipients

1. Introduction

Drug excipient interactions are one of the most important factors that should be considered in any preformulation study. These interactions can affect the stability (Loewe et al., 1983), dissolution (Kellawey and Najib, 1983; Aboutaleb et al., 1986; Aly and Udeala, 1987) and possibly the bioavailability of the drug (Calis et al., 1986; El-Gamal et al., 1986; Aly and Megwa, 1987).

Adsorption is one of the most important mechanisms of interaction between drugs and excipients. It is essentially the preferential partitioning of the drug to the solid-liquid interface as opposed to the bulk. This partitioning occurs because most of drugs have hydrophilic and/or

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hydrophobic regions within their structures. Thus, when they are dissolved they tend to adsorb at interfaces orientating themselves so that their regions are associated with the proper phase. This orientation leads to a reduction in excess surface free energy of the molecules and as a result a reduction in the surface or interfacial tension. The forces involved in this type of interaction can be either physical or chemical in nature or a combination of both. Physical interaction occurs to some extent in all systems and is primarily due to weak van der Waals' attraction forces. In some systems, however, stronger electrostatic attractions can be involved. Chemical interaction is more specific and is primarily attributed to covalent bond formation and occurs only when a chemical interaction between the drug and excipient is possible.

Ketotifen is an orally active prophylactic agent used for the management of bronchial asthma and allergic disorders. (Grant et al., 1990). It is a weakly basic drug and such drugs are known for their potential to adsorb onto many pharmaceutical excipients (Hollenbeck, 1988; Hollenbeck et al., 1983). In addition, it is a potent drug used in low doses (1 mg twice daily) and has a poor bioavailability, only about 50% of the given dose is bioavailable due to the 'first pass effect' (Grant et al., 1990). Therefore, any adsorption that might occur may possibly lead to significant reduction of its pharmacological effect.

This work was therefore undertaken to study the possible adsorption of ketotifen onto some commonly employed pharmaceutical excipients such as pregelatinized starch, croscarmellose sodium and microcrystalline cellulose. It also investigates the effect of drug concentration, temperature and pH on the kinetics of the adsorption process.

2. Materials and methods

2.1. Materials

Ketotifen hydrogen fumarate was supplied by the United Pharmaceutical Manufacturing (Jordan). Microcrystalline cellulose (Avicel), croscarmellose sodium (Acdisol) and pregelatinized starch were kindly donated by Hikma Pharmaceuticals (Jordan). Single lots of each excipient were used throughout this work. Hydrochloric acid, sodium hydroxide, monopotassium phosphate and sodium phosphate were supplied by Sigma (St. Louis, MO, USA). All water used was freshly distilled and deionized. All materials were used as supplied.

2.2. Equipment

A Julabo mechanical shaker water bath was used for equilibrating the solutions. Solutions were centrifuged using a Kubota refrigerated centrifuge (KN-70). Sartorious disposable millipore filter units (Germany) were used. A Hanna pH meter, model H-8417 (Italy) was used for pH measurements. The assay of the clear supernatants was carried out using a Shimadzu UV-VIS spectrophotometer model UV 1201 (Japan).

2.3. Methods

2.3.1. Mass adsorption isotherms

Accurate weight of the used excipients of about 0.2 g each were taken and dispersed each in a 10-ml solution of ketotifen (10 μg/ml). All samples were hand shaken for 30 s to ensure good dispersion. They were then shaken at 100 rpm in a shaking water bath maintained at 37°C for 3 h, a period which was previously determined to be sufficient to attain equilibrium. The samples were then centrifuged for 15 min at 3000 rpm and 37°C. The supernatants were then filtered through 0.45 μm millipore filters. Drug content in each sample was assayed spectrophotometrically at 300 nm using suitable blanks consisting of the proper excipient dispersed in 10 ml water.

Similar solutions of ketotifen were prepared without the addition of the excipients and treated as above and used as controls for the determination of the initial drug concentration. The initial and equilibrium concentrations of ketotifen were calculated by reference to a suitable calibration curve of the drug. The amount of drug adsorbed was then calculated by subtracting the equilibrium concentration from the initial concentration then

multiplying by the total volume of the sample. The percentage of drug adsorbed was calculated by dividing the amount of drug adsorbed by the initial drug amount and multiplying by 100%.

2.3.2. Effect of drug concentration and temperature on adsorption

Accurate weights of Acdisol of about 0.2 g each were taken and dispersed in several 10 ml solutions of ketotifen of different concentrations in phosphate buffer of pH 6.8. Samples were then equilibrated at different temperatures, centrifuged, filtered, assayed and the amount of drug adsorbed was determined as described above.

2.4. Effect of pH on adsorption

Accurate weights of Avicel of about 0.2 g each were taken and dispersed each in 25 ml water. A volume of 5 ml ketotifen aqueous solution (500 μg/ml) was added to each dispersion. The pH value of each sample was adjusted using either 0.1 N HCl or 0.1 N KOH, to span the pH range 2–11. The volume was then made to 50 ml with water, achieving a final drug concentration of 50 μg/ml. The total added ionic strength was maintained constant at (0.01) using 1 N KCl solution. Samples were then equilibrated at 37°C, centrifuged, filtered, assayed and the amount of drug adsorbed at each pH value was determined as described previously.

2.4.1. Equilibrium solubility

The solubility of ketotifen was studied over the pH range 2–11 using phosphate buffer and either 0.1 N HCl or 0.1 N KOH, at 25°C. An excess of ketotifen powder was added to 10 ml of each buffer solution and shaken at 100 rpm for 3 h, a period which was previously determined to be sufficient to attain equilibrium. Each sample was then centrifuged, filtered and the content of ketotifen was assayed as described previously.

3. Results and discussion

3.1. Mass adsorption isotherms

The percentage of ketotifen adsorbed onto different excipients from water is shown in Table 1. The results in Table 1 show that the percentage of drug adsorbed is highest in case of Acdisol followed by Avicel and pregelatinized starch. This is attributed to the difference in the physicochemical nature of each excipient. Acdisol has the smallest particle size distribution (not more than 2% retained on a # 200 (75 μm) mesh and not more than 10% retained on a # 325 (45 μm) mesh) and thus has the highest specific surface area, followed by Avicel (typical mean particle size is 20–200 μm) then starch (greater than 90% through a # 100 mesh (149 μm) and less than 0.5% retained on a # 40 mesh (420 μm). This indicates that a larger number of active sites for interaction with the drug, per a given weight, is available in the case of II compared to the other two excipients.

3.2. The effect of drug concentration on adsorption

Mass adsorption isotherms were constructed by plotting the amount (μg) of drug adsorbed (x) per g of the excipient (m) against the equilibrium concentration (C_{eq}) in the presence of different initial drug concentrations for the adsorption of ketotifen onto Acdisol the isotherm obtained is shown in Fig. 1. The isotherm shows an increase in the adsorption of ketotifen as the concentration increases. This is because more drug molecules will be available for adsorption at higher concentrations than at lower ones.

Table 1
The percentage of ketotifen adsorbed onto different excipients at 37°C from water

Excipient	Percentage ketotifen adsorbed
Pregelatinized starch	27.6
Avicel PH 102	35.8
Acdisol	95.65

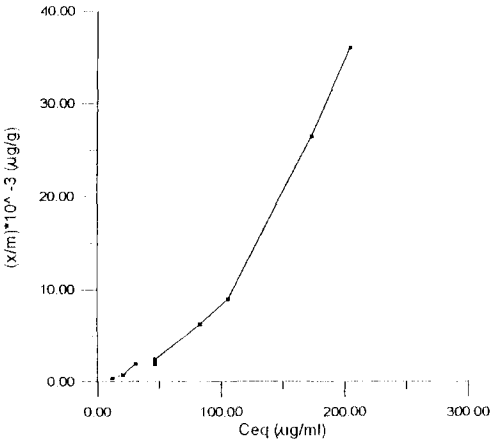

Fig. 1. Adsorption isotherm of ketotifen onto Acdisol in phosphate buffer.

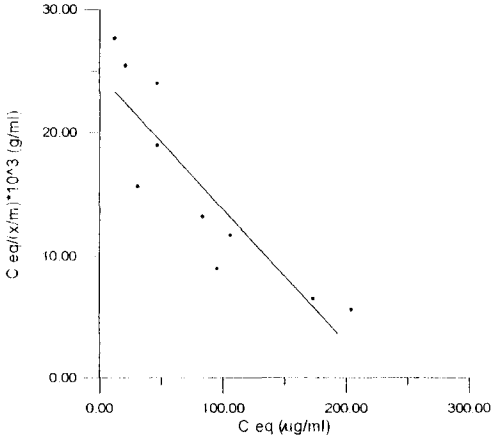

Fig. 2. Langmuir plot for the adsorption of ketotifen onto Acdisol.

In order to determine the type of adsorption isotherm that best describes the adsorption data, the data were first fitted to the following form of Langmuir adsorption isotherm:

$$\frac{C_{eq}}{x/m} = \frac{1}{k_1 k_2} + \frac{C_{eq}}{k_2} \quad (1)$$

where x is the amount of solute adsorbed by a weight m of adsorbent. C_{eq} is the solution equilibrium concentration, and k_1 and k_2 are constants. k_1 is the limiting adsorptive capacity, k_2 is used as a measure of the relative affinity of the adsorbate for the adsorbent (Martin et al., 1983). Therefore, a plot of $C_{eq}/(x/m)$ against C_{eq} was constructed and is shown in Fig. 2. The low regression coefficent value ($r = 0.8827$) of the plot indicated the poor applicability of the Langmuir isotherm to the obtained data

The applicability of the Freundlich adsorption isotherm to the obtained data was therefore investigated. A plot of $\log(x/m)$ against $\log C_{eq}$ was constructed according to Eq. (2), and is shown in Fig. 3.

$$\log x/m = \log k + n \log C_{eq} \quad (2)$$

where k and n are constants, k gives an approximate measure of the relative adsorbent capacity for a given drug, while n gives a general idea about the affinity of the adsorbate for the adsorbent (Martin et al., 1983).

A higher linearity was observed in the Freundlich plot ($r = 0.9883$) than in the Langmuir plot ($r = 0.8827$), indicating the greater adherence of the obtained data to the Freundlich equation. This suggests that adsorption is a continuous function of the initial drug concentration and therefore the formation of a monolayer is precluded. The values of the two constants k and n are 0.327 and 0.621, respectively.

The Freundlich adsorption isotherms of ketotifen on Acdisol at different temperatures are presented in Fig. 4. Linear relationships were

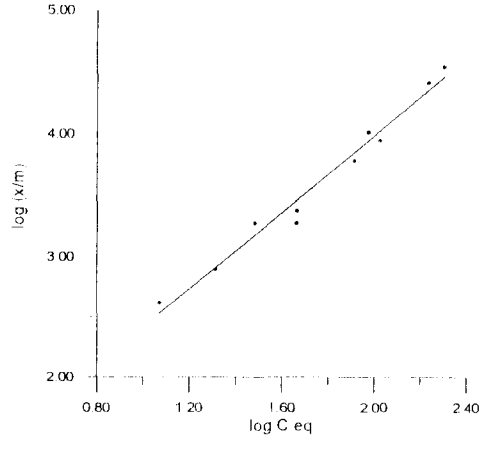

Fig. 3. Freundlich plot for the adsorption of ketotifen onto Acdisol.

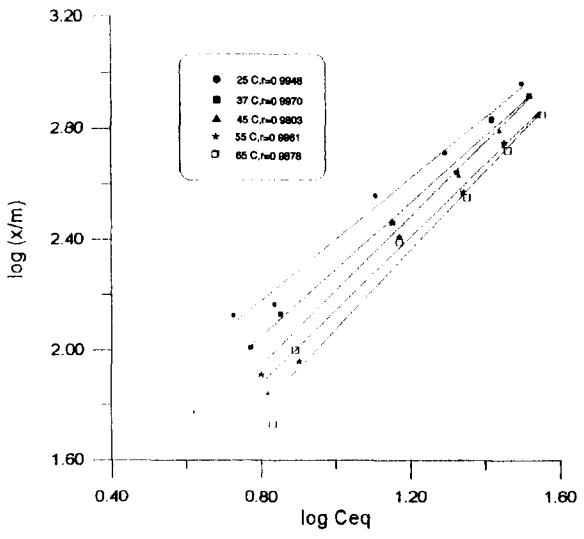

Fig. 4. Freundlich plot for the adsorption of ketotifen onto Acdisol.

obtained ($r > 0.9803$) in all cases, confirming the applicability to the Freundlich equation and the formation of multilayers. It appears that the slope of each isotherm decreases as the temperature increases. This indicates a decrease in adsorption of ketotifen onto Acdisol with an increase in temperature. This is to be expected, since an increase in temperature would result in an increase in entropy of the system and hence reduces the tendency of the molecules to adsorb. Increasing the temperature would also decrease the solid-liquid interfacial tension and hence would further decrease the tendency of the drug to adsorb at the solid-liquid interface

Fig. 5 shows the effect of temperature on adsorption of ketotifen onto Acdisol at pH 6.8, constructed by plotting log A against $1/T$, according to the following equation:

$$\log A = \text{constant} - \Delta H/(2.303RT) \quad (3)$$

where A is the percent drug adsorbed at equilibrium, T is the absolute temperature, R is the gas constant (8.314 J/mol·k) and ΔH is the heat of adsorption of ketotifen onto Acdisol. The slope, intercept, regression coefficient and the heat of adsorption (ΔH) of each plot were calculated and are listed in Table 2.

In all cases linear plots were obtained. A decrease in adsorption with an increase in temperature is noticed, indicating that the adsorption process is exothermic in nature. This is because the molecules of ketotifen tend to adsorb at the solid surface of the insoluble excipient in order to become energetically more stable. An increase in temperature shifts the adsorption reaction backwards and decreases the amount adsorbed per gram of the excipient. Moreover, in order for adsorption to occur, the bonds between ketotifen and water should be first broken. The increase in temperature causes an increase in the solubility of ketotifen, thus, the affinity of water to ketotifen increases and therefore, bonds between ketotifen and water become stronger and more difficult to break. This will result in a reduction in the extent of adsorption. The heat of adsorption in all cases was low suggesting that the adsorption process is physical in nature. It shows also that ΔH is decreasing with increasing the concentration of ketotifen.

The effect of drug concentration on ΔH is further illustrated in Fig. 6. The entropy of drug molecules (ΔS) is expected to decrease with increasing the drug concentration because the media becomes more crowded and the molecules have

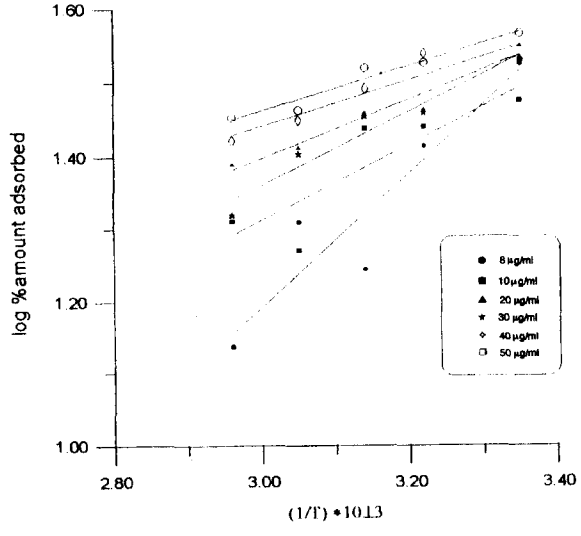

Fig. 5. The effect of temperature on the adsorption of ketotifen onto Acdisol.

Table 2
The slope, intercept, regression coefficient (r) values and the heat of adsorption (ΔH) of different ketotifen solutions in phosphate buffer (pH 6.8) onto Acdisol

Concentration (μg/ml)	Slope	Intercept	Regression coefficient	ΔH^* (kJ·mol^{-1})
8	919.643	−1.563	0.9242	−17.60
10	518.235	−0.241	0.8631	−9.92
20	416.124	0.193	0.9682	−7.96
30	399.384	0.193	0.9888	−7.64
40	328.596	0.455	0.9482	−6.29
50	301.539	0.558	0.9745	−5.77

* ΔH values were calculated from the slope of each plot according to Eq. (3).

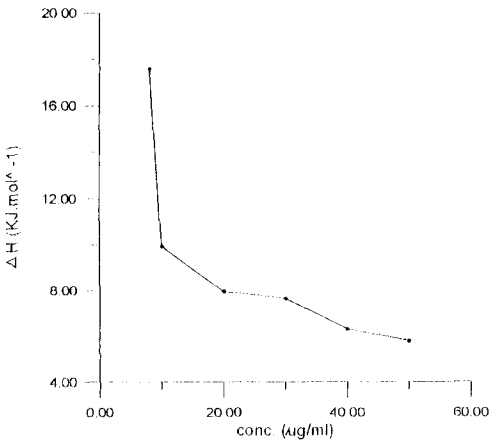

Fig. 6. The effect of ketotifen concentration on the heat of adsorption (ΔH) onto Acdisol.

less space to move in. Generally, for thermodynamic stability, systems tend to maximize their entropy and minimize their free energy (Martin et al., 1983). Ketotifen molecules will, therefore, favor the adsorption at the solid-liquid interface. As ΔH is directly proportional to ΔS. The decrease in entropy associated with increasing the drug concentration, will lead to a decrease in ΔH values.

Fig. 7 illustrates the effect of pH on the adsorption of ketotifen (50 μg/ml) at constant ionic strength onto Avicel. The percentage fraction of ketotifen adsorbed increases as the pH of solution increases. This is attributed to the reduction of the solubility of the drug with the increase in pH as indicated from pH-solubility profile (Fig. 8), thus favoring drug partitioning to the excipient-liquid

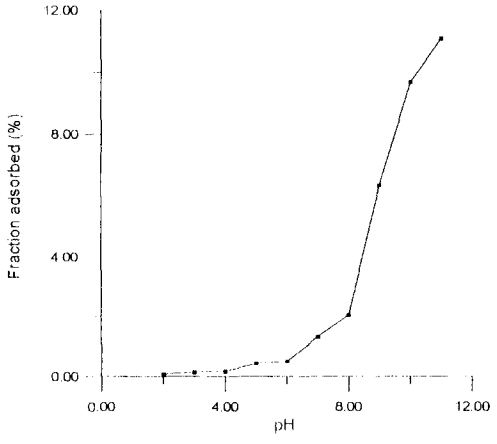

Fig. 7. The effect of pH on the adsorption of ketotifen (50 μg/ml) on Avicel.

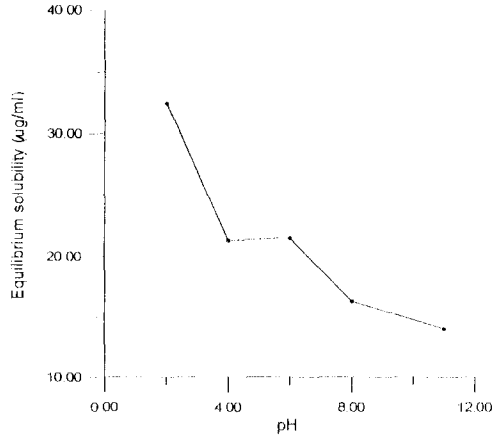

Fig. 8. pH Solubility profile of ketotifen in phosphate buffer at 25°C.

interface as opposed to the bulk solution. At low pH values, the degree of ionization of ketotifen and hence its solubility increases, thus increasing the solvent affinity to the solute and consequently reducing the extent of adsorption.

The effect of pH on adsorption can be also attributed to the possible alteration of the surface charge at the adsorbent and adsorbate surfaces. This alteration results from the selective adsorption of hydronium ions at low pH, thus, rendering the molecules positively charged. This would decrease the attractive forces between the drug and excipient, thus, reducing the extent of adsorption.

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