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HYGROSCOPICITY AND MOISTURE ADSORPTION KINETICS OF PHARMACEUTICAL SOLIDS: A REVIEW

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INTRODUCTION

Moisture adsorption has been found to play an important role in physical and chemical stability, solid dosage forms, excipients, and polymers for sustained release formulations. For a drug known to undergo hydrolysis in the presence of moisture, it is important to study moisture adsorption kinetics including the rate of moisture uptake, equilibrium moisture content (EMC), and hygroscopicity. In terms of solid dosage forms and excipients, moisture adsorption phenomena will give useful information for selecting excipients such as disintegrating agents, direct compression carriers and binders, as well as humidity control during production and storage. The amount of moisture adsorbed by drugs and excipients at a certain temperature and relative humidity will influence flow, compression characteristics, and the hardness of granules and tablets. In addition, moisture transmission through polymers and free films may be useful for characterization of the possible effects on the dissolution and the transport of drugs from the dosage forms.

HYGROSCOPICITY

There is no accepted definition for hygroscopicity; the reason for this is that there are both thermodynamic and kinetic components in the term[1]. Hygroscopicity of substances can be obtained by determining the critical relative humidity (CRH), which can be defined as the relative humidity in equilibrium with a saturated solution of the salt[2]. For example, CRH of drug "A" equaling 30% R.H. means that, if drug "A" is stored below or at 30% R.H., no moisture adsorption will occur. If, however, drug "A" is stored at over 30% R.H., it will start to adsorb moisture and therefore be hygroscopic. Edgar and Swan[3] studied hygroscopic behavior of fertilizer salts and related compounds. They concluded that the rate of moisture adsorbed will depend on five factors: (a) the pressure gradient between the vapor pressure of water in the atmosphere and over the sorbed moisture layer of drug substance, (b) temperature, (c) surface area of solid drug exposed to the water vapor, (d) the velocity of movement of moist air, and (e) a reaction constant characteristic of the solid. Mikulinskii and Rubinshstein[4] studied moisture uptake kinetics of magnesium sulfate. They concluded that the kinetics of moisture uptake depend on two steps: (a) surface adsorption, occurring at a rate proportional to the difference between the partial pressures of water vapor in the atmosphere and that of the saturated salt solution, and (b) water diffusion into the crystal, at a rate dependent on the product of the diffusion coefficient and water concentration gradient. Griffin et al[5] introduced three basic terms for hygroscopicity of humectants: (a) equilibrium hygroscopicity, (b) dynamic hygroscopicity (rate at which substance gains or loses water while approaching equilibrium), (c) volatility (tendency of substance to evaporate water). In addition, they suggested that the thickness layer of the drug substance also influences water uptake. Czetsch-Lindenwald[6] studied moisture uptake of pharmaceutical powders at various relative humidities. He classified degree of hygroscopicity into 3 classes: (a) softening substances, (b) substances retaining moisture, and (c) antistatica. Modrezejewski et al[7] proposed the term called " hygroscopic point " which was defined as the relative humidity in

the atmosphere at which the powder can uptake ≈ 1% of moisture within 24 hours. The hygroscopic point was calculated using the Lagrange's equation as follows:

$$f(HP') = ((HP'-RH_2)(HP'-RH_3)/(RH_1-RH_2)(RH_1-RH_3))(MC_1)+ ((HP'-RH_1)(HP'-RH_3)/(RH_2-RH_1)(RH_2-RH_3))(MC_2)+ ((HP'-RH_1)(HP'-RH_2)/(RH_3-RH_1)(RH_3-RH_2))(MC_3) \quad (1)$$

where HP' is the hygroscopic point of substance; RH_1,RH_2 and RH_3 are the three different relative humidities studied ; MC_1,MC_2 and MC_3 are the moisture contents of substance stored for 24 hours at RH_1, RH_2 and RH_3, respectively.

He found that the hygroscopic point, as well as the CRH, is characteristic of each substance and can be used to determine at what limit of the relative humidity the material begins to uptake moisture. Recently, Callahan et al[8] classified degree of hygroscopicity into 4 classes:

Class 1 Non-hygroscopic: essentially no moisture increases occur at relative humidities below 90%. Furthermore, the increase in moisture content after storage for one week above 90% R.H. is less than 20%.

Class 2 Slightly-hygroscopic: essentially no moisture increases occur at relative humidities below 80%. The increase in moisture content after storage for one week above 80% R.H. is less than 40%.

Class 3 Moderately-hygroscopic: moisture content does not increase more than 5% after storage at relative humidities below 60%. The increase in moisture content after storage for one week above 80% R.H. is less than 50%

Class 4 Very-hygroscopic: moisture content increase may occur at relative humidities as low as 40 to 50%. The increase in moisture content after storage for one week above 90% R.H. may exceed 30%.

SATURATED SALT SOLUTIONS FOR MAINTAINING RELATIVE HUMIDITIES

For maintaining specified relative humidities in closed chambers, saturated salt solutions are widely used. The important fact is that, as long as there is a solid in equilibrium with a saturated solution, the water vapor pressure over the system will remain constant. This makes such salt solutions useful since they produce an atmosphere of controlled humidity.

Nyqvist[9] studied the relative humidities given by a series of saturated salt solutions at various temperatures between 0 and 50°C, examples are shown in Table1. Some solutions, such as LiCl, $MgBr_2$, CrO_3, NaCl, and Li_2SO_4, give relative humidities that are constant throughout the temperature interval. Others, such as NaI, $Mg(NO_3)_2$, NaBr, and KNO_3, show a strong temperature dependence. The saturated salt solutions were found to maintain the relative humidities within the limits in the desiccators for a period of up to five years.

THERMODYNAMICS AND KINETICS OF MOISTURE ADSORPTION

At a given temperature and pressure, the driving force or the net integral free energy change, $\overline{\Delta G}$, associated with the adsorption of moisture on the solid surface is given by:[10]

$$\overline{\Delta G} = \overline{\Delta G}_1 n_1 + \overline{\Delta G}_2 n_2 \qquad (2)$$

where $\overline{\Delta G}_1$ and $\overline{\Delta G}_2$ are the partial molal free energy changes of the adsorbate and adsorbent, respectively; n_1 and n_2 are the number of moles of adsorbate and adsorbent, respectively.

The adsorption of moisture takes place because the solid seeks to satisfy its excess surface energy by interacting with molecules in the vapor

TABLE 1
Relative Humidities of Various Saturated Salt Solutions

Salt	Temperature (°C)			
	25	35	45	50
LiCl	11.3(0.104)	11.2(0.105)	11.2(0.117)	11.1(0.152)
CH_3COOK	21.6(0.095)	21.6(0.202)	21.5(0.197)	21.5(0.292)
$MgBr_2$	30.7(0.224)	30.2(0.245)	29.8(0.215)	29.7(0.237)
CrO_3	40.0(0.198)	44.8(0.152)	45.2(0.191)	45.4(0.188)
NaI	38.2(0.142)	37.4(0.174)	31.0(0.131)	29.2(0.129)
$Mg(NO_3)_2$	52.8(0.219)	50.0(0.101)	47.1(0.114)	45.5(0.137)
NaBr	57.5(0.177)	54.0(0.153)	52.0(0.113)	50.9(0.111)
NaCl	75.3(0.062)	74.8(0.126)	74.7(0.124)	74.7(0.107)
Li_2SO_4	87.8(0.209)	87.5(0.185)	88.0(0.213)	88.3(0.211)
KNO_3	93.7(0.299)	90.8(0.385)	87.0(0.368)	84.8(0.378)
K_2SO_4	97.3(0.401)	96.7(0.498)	96.2(0.588)	95.8(0.637)

From Ref.#9, Results are mean values with s.e.m. (n=10)

state[11-12]. The equilibrium adsorption isotherm provides the information necessary to determine both the differential and integral free energy changes. Markowitz et al[13] proposed a thermodynamic approach to hygroscopicity. The term hygroscopic potential (HP) is given by a negative value of partial molal free energy changes of the adsorbate (water) between the pure state and the adsorbed state:

$$HP = -\overline{\Delta G}_1 = \mu^o - \mu_1 = RT\ln P^*/P' \qquad (3)$$

where μ^o and μ_1 are the chemical potentials of water in the pure state and the adsorbed state, respectively; P^* is the vapor pressure of pure water at temperature T; P' is the vapor pressure over the sorbed moisture layer; R is the gas constant.

It is often not feasible to determine the partial molal free energies and the activities of solutes from measurements of the vapor pressure. For an adsorbent which is non volatile, an alternative method to determine the partial free energy change is given by the Gibbs-Duhem equation:[14]

$$\overline{\Delta G}_2 = -X_1/X_2 \, (dX_1/dX_2) \, \overline{\Delta G}_1 \qquad (4)$$

where X_1 and X_2 are the mole fractions of adsorbate and adsorbent ; respectively. By using the expressions for either adsorbate or adsorbent molal free energy, equation (4) becomes:

$$-X_1/X_2 = d(\ln a_2)/d(\ln a_1) \qquad (5)$$

where a_1 and a_2 are activities of adsorbate and adsorbent, respectively.

The calculation of the activities for water and sucrose using equation(5) is shown in Table 2. The total integral free energy change of the system can be obtained by putting equation (3) and (4) into equation (2).

ENTHALPY CHANGES

For hydrophobic substances, the adsorption of moisture occurs on the surface of the particles and no dissolution of drug into the sorbed moisture layer is involved. The net integral enthalpy change associated with the adsorption process (ΔH), is given by:[15]

TABLE 2

The Activities of Water and Sucrose in Water-Sucrose Solutions at 0°C Obtained from the Vapor Pressure of Water and the Gibbs-Duhem Relation

Molality of Sucrose	Mole fractions		Vapor pressure of water, mm Hg.	a_{water}	$a_{sucrose}$
	Sucrose	Water			
0	0	1.000	4.579	1.000	0
0.2	0.0036	0.996	4.562	0.996	0.0036
0.5	0.0089	0.991	4.536	0.990	0.0089
1.0	0.0177	0.982	4.489	0.980	0.0190
3.5	0.0590	0.941	4.195	0.916	0.1460
4.5	0.0750	0.925	4.064	0.888	0.2380
5.0	0.0820	0.918	3.994	0.872	0.2920
6.0	0.0980	0.902	3.867	0.845	0.4030

(From: Reference # 10, p. 293, 1979. Reproduced with permission of the copyright owner.)

$$\Delta H = \Delta H_{ads} + n_1.H_v \quad (6)$$

where ΔH_{ads} is the heat of adsorption; H_v is the molar heat of vaporization of the liquid; n_1 is the number of moles of moisture adsorbed . ΔH can also be expressed by:[15]

$$\Delta H = \Delta H_d - \Delta H_w \quad (7)$$

where ΔH_d is the heat of immersion of the dry solid; ΔH_w is the heat of immersion of the wet solid.

ΔH_d can be obtained by measuring the heat of immersion of the clean dry solid in water, whereas ΔH_w can be obtained by measuring the heat of immersion of solids with varying moisture contents; hence, the values of ΔH at different humidities can be calculated from equation (7). From equation (6), by plotting ΔH versus n_1, the differential heat of adsorption (ΔH_{ads}) will be obtained.

ENTROPY CHANGES

The entropy change is the change in the degree of disorder of the system. If ΔH is unchanged the more disordered the system becomes, the more tendency the spontaneous reaction will occur. The entropy changes for the adsorption process are given by:[15-16]

A) Integral entropy change

$$\Delta S = (\Delta H - \overline{\Delta G})/T \quad (8)$$

B) Differential entropy change

$$\Delta S_{ads} = (\Delta H_{ads} - \overline{\Delta G}_1)/T \quad (9)$$

where ΔS_{ads} is the entropy of adsorption at temperature T; ΔH_{ads} and $\overline{\Delta G}_1$ are as previously described.

MOISTURE ADSORPTION KINETICS

Kuvshinnikov et al[17] studied the kinetics of the hygroscopicity of water soluble salts and minerals. The term "hygroscopicity coefficient" was defined as logarithm of the initial slope of the kinetic curve of moisture uptake. They described the kinetics of the adsorption curve by the relation:

$$W_t = W_\infty(1 - e^{-\partial t}) \quad (10)$$

where W_∞ and W_t are equilibrium moisture content and moisture content at time t, respectively; ∂ is the rate of moisture uptake.

Veillard et al[18] proposed the equation for moisture permeation through polymer packages. This equation may be applied for the permeation of air, perfume ingredients and other volatile agents through plastic bottles, packaging films, and polymer-coated tablets and capsules. According to Fick's law, the passage of vapor diffusion through a polymer film is expressed as:

$$dm/dt = DA\P(P_o - P_i)/l \quad (11)$$

where dm/dt is the weight of moisture permeated per unit time; D is the diffusion coefficient through a polymer film of thickness l; A is the

surface area; ¶ is a proportionality constant; P_o and P_i are the pressures gradient outside and inside the container.

These authors assumed that the weight of moisture passing through the container in a time unit is equal to the increase in moisture content of the solid inside and also there is a linear relationship between moisture vapor pressure and the moisture content of the solid as well. Then the following equation was obtained:

$$\ln(X_\infty - X) = \ln(X_\infty) - \pi t \quad (12)$$

where π is the rate of moisture permeation; X_∞ and X are the amounts of moisture adsorbed at equilibrium and at time t, respectively.

Yamamoto et al[19-22] found that the moisture transmission through a package can be expressed by:

$$W = K(P_a - P')t \quad (13)$$

where W is the sample weight gain per unit area of effective surface area at time t; K is the moisture transmission factor of container; $P_a - P'$ is the pressure gradient between the atmosphere and over the sorbed moisture layer of substance.

Carstensen[1] modified equation (13) to lead to the following expression:

$$W_t - W_o = \partial t \quad (14)$$

where W_t and W_o are the total and initial weights of sample at time t and

time O, respectively; ∂ is the rate of moisture uptake (initial rate in this case), which can be expressed by:

$$\partial = kA(P_a - P') \quad (15)$$

Equation (15) then leads to:

$$\partial = kAP^*(RH_a - RH')/100 \quad (16)$$

where P^* is the vapor pressure of pure water at the temperature of study; RH_a and RH' are the relative humidities of the atmosphere and over the sorbed moisture layer, respectively; k is a proportionality constant; A is the surface area.

At the rate of moisture uptake (∂) = O, $RH_a = RH'$. If ∂ is plotted versus RH_a, the intercept at ∂ = O is equal to RH' (critical relative humidity). At this relative humidity or below, no moisture adsorption occurs. Berlin et al[23] found that temperature influences the equilibrium moisture uptake of dried milk. At an initial sorption curve, the high values of isosteric heat of adsorption were obtained due to protein water binding.This was followed by low energy values which were less than the heat of liquefaction of water itself. These authors explained that in the latter process the energies were attributed to mobility of sorbed moisture molecules, solubilization and crystallization of lactose in dried milk. Recently, Umprayn and Mendes[24-26] studied the moisture adsorption of cefaclor (a relatively soluble drug) at temperatures between 25 and 50°C. The photomicrograph of drug kept at 25°C and 90.2% R.H. for 54 weeks, as compared to standard, indicated no change on the surface appearance as illustrated in Figure 1 and the adsorption curves were successfully described by:

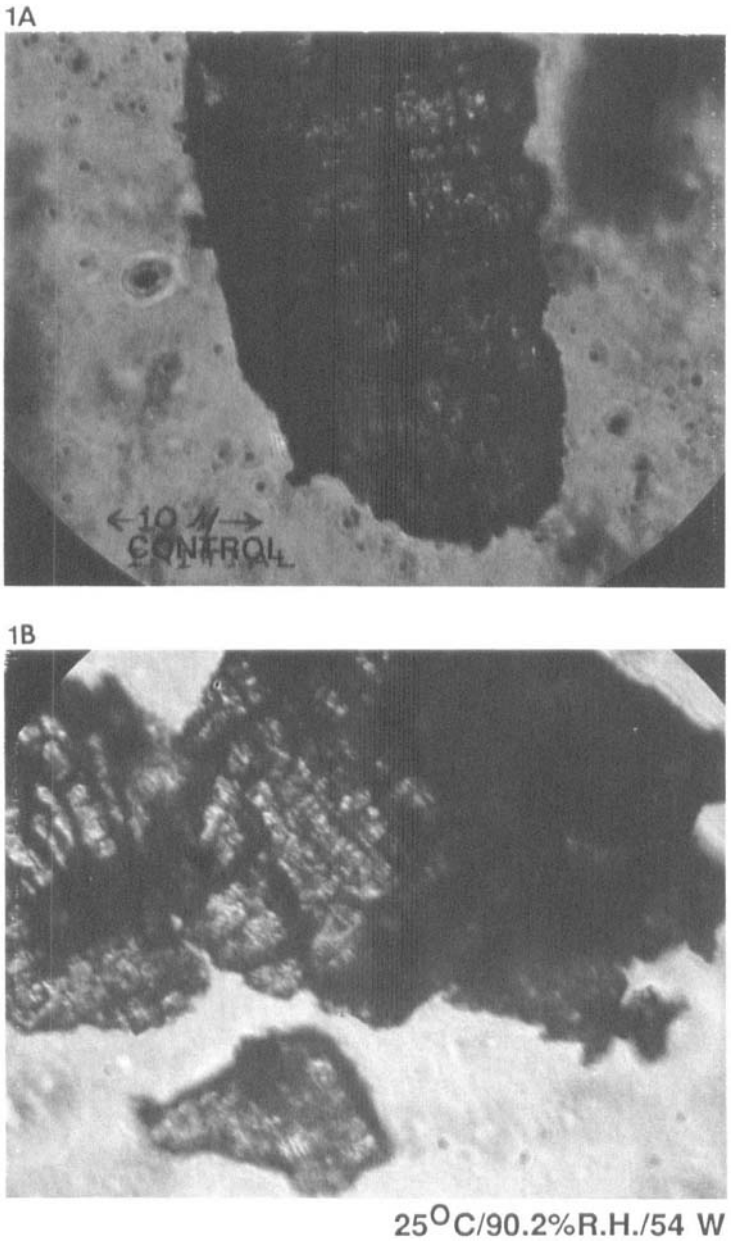


FIGURE 1

Comparision photomicrographs of cefaclor before (1A) and after storage at 25°C and 90.2% R.H. for 54 weeks (1B). No change on the surface appearance has been observed (600x)

$$W_t - W_o = \partial t^{1/2} \quad (17)$$

where W_t, W_o, ∂ and t are as previously described.

The plots of $W_t - W_o$ versus $t^{1/2}$ for cefaclor are shown in Figure 2. The effect of temperature on the rate of moisture uptake of cefaclor at various relative humidities are shown in Figure 3. It was found that increase in temperature resulted in increasing the rate of moisture uptake and also the amount of moisture adsorbed at equilibrium. Figure 4, shows the effect of temperature and humidity on the change in crystal morphology of cefaclor. Fusion on the crystal surface occurs at 35-45°C and 70% R.H. At 55°C/50% R.H. the crystal deformed. A glass-like structure was formed at 55°C/70% R.H. The effect of the sorbed moisture on the change in crystal morphology of cefazolin sodium (a water soluble drug) at 25°C was also described by these authors and the results are illustrated in Figure 5. It may be seen that, at relative humidities ≥ 55%, drug particles were fused and dissolved in the sorbed moisture layer.

El-Sabaawi and Pei[27] proposed the desorption model and the correlation between pore structure and equilibrium moisture content (EMC) of insoluble porous substances. Carstensen et al[28] extended the use of the El-Sabaawi relationship to insoluble substances with log normally distributed pore spaces and to poorly soluble substances, as defined in the USP. The following equation was obtained:

$$P/P^* = e^{-4¥X/RTd} \quad (18)$$

where P and P^* are the vapor pressures of liquid in the pores and pure water at a given temperature (T); ¥ is the interfacial tension between solid and liquid in the pores; d is the capillary pore

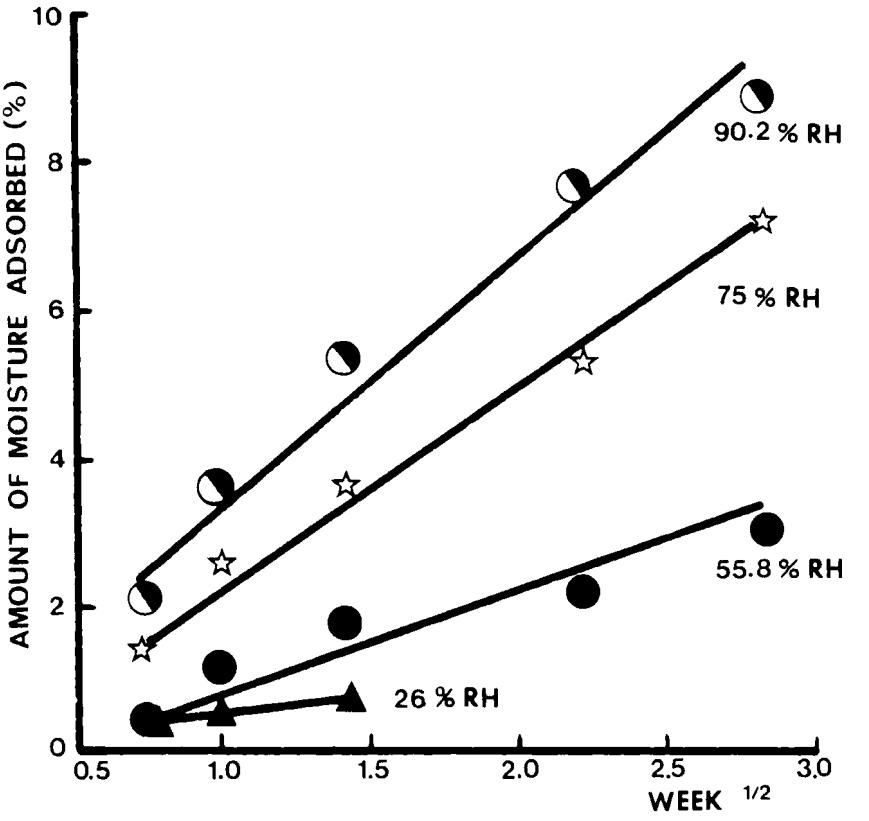


FIGURE 2

Moisture adsorption of cefaclor as a function of $t^{1/2}$ at various relative humidities and 25°C

diameter; X is the amount of moisture adsorbed; R is the gas constant.

The limitations of equation (18) are: (a) no swelling or pore size distortion may occur during moisture uptake, (b) solubility of the drug must be low so that no significant volume changes can result from the dissolution.

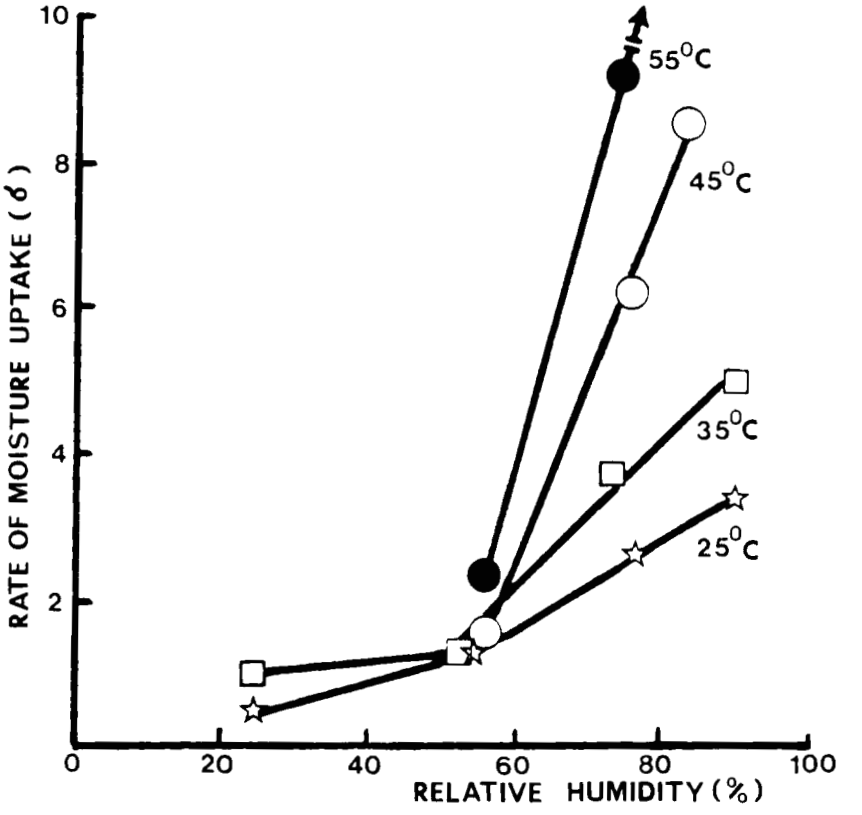


FIGURE 3

Effect of temperature on the rate of moisture uptake of cefaclor

The thermodynamics and kinetics of moisture sorption for compressed circular disks of water soluble substances were described by Campen et al[29-31]. The model is based on heat transport control as shown in Figure 6.

A) Drug particles start to pick up moisture from the atmosphere.

B) After the drug adsorbs moisture, the sorbed moisture layer is formed with the vapor pressure over the sorbed moisture layer equal to P'

C) The drug starts to dissolve into the sorbed moisture layer. The dissolution of drug in the sorbed moisture layer will lead to a decrease in the vapor pressure P'.

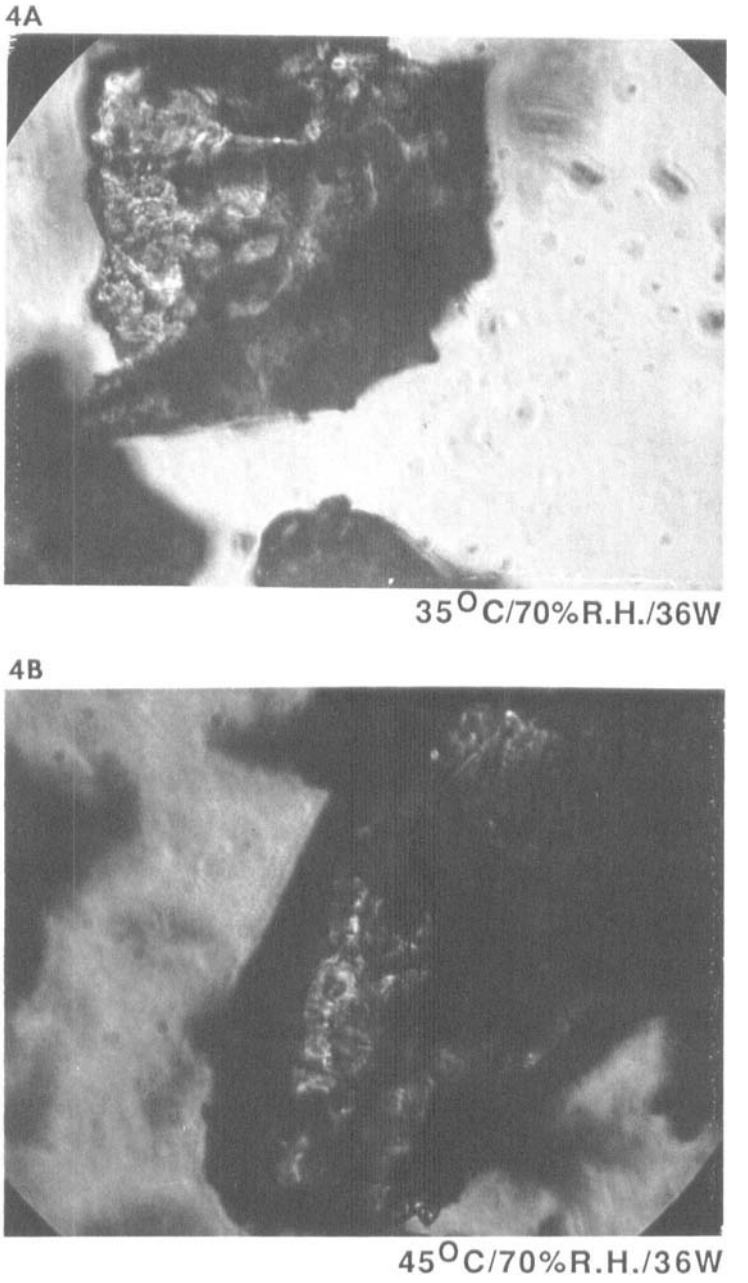
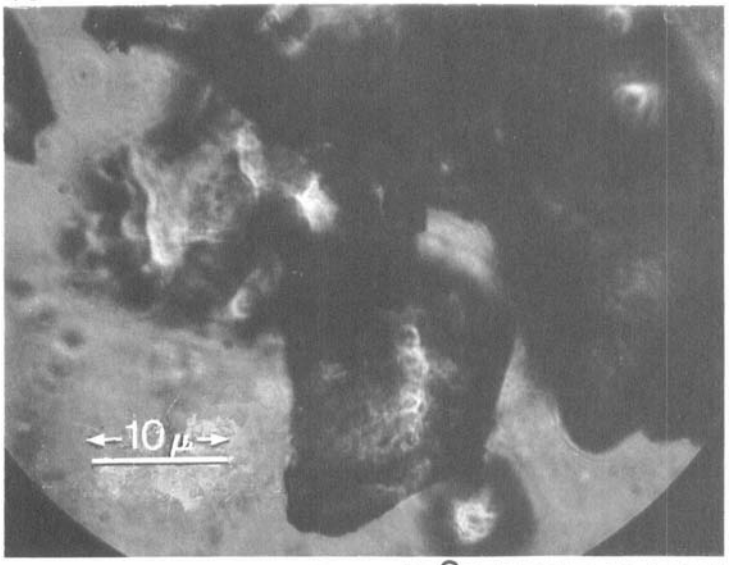


FIGURE 4

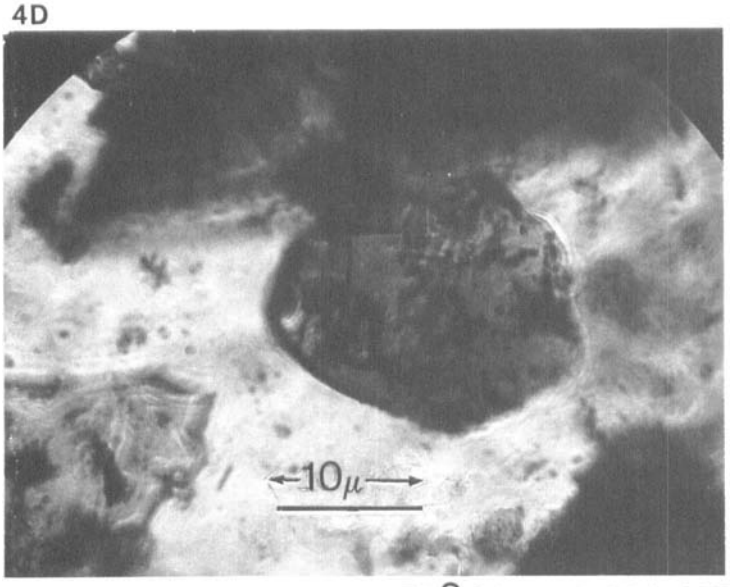
Photomicrographs of cefaclor at various relative humidities and temperatures (600x)(Key: A-Slight fusion on the surface is obtained; B-Similar to A, but more fusion occurs; C-The crystal deformed; D-The glass-like structure formed)

4C



55°C/50%R.H./10W

4D



55°C/70%R.H./10W

FIGURE 4 CONTINUED

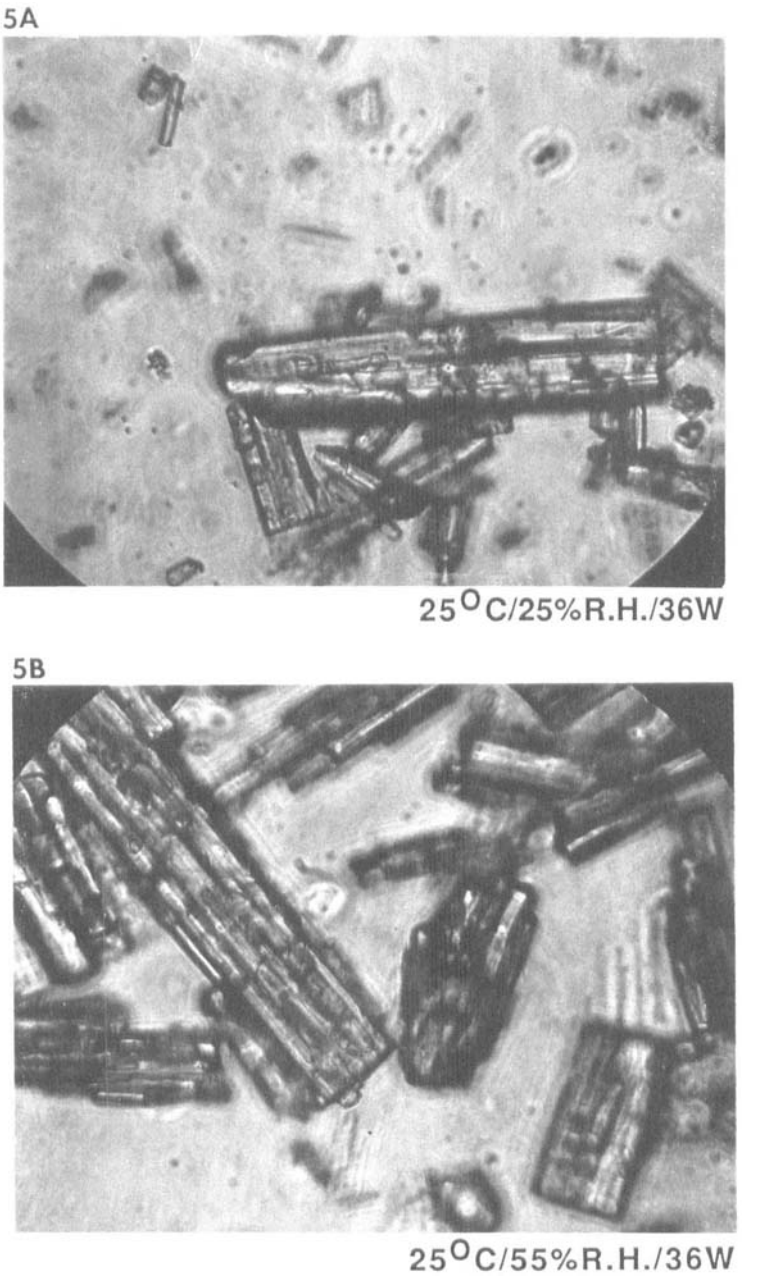
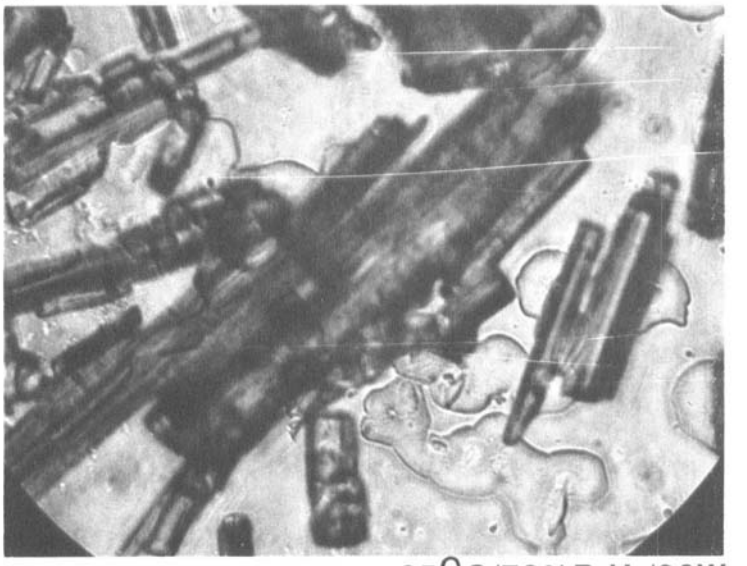


FIGURE 5

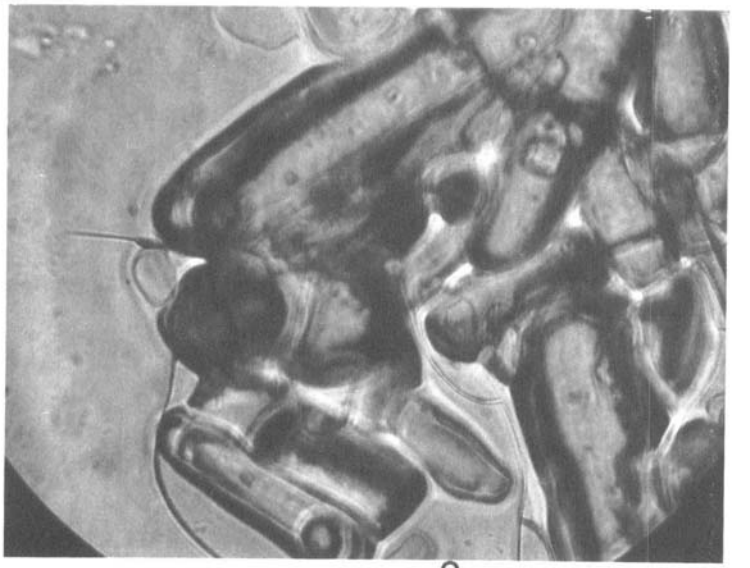
Comparision of the photomicrographs of cefazolin sodium at various relative humidities and 25°C for 36 weeks (600x) (Key: A - No change on the crystal morphology; B - Crystal surface fused and dissolved, aggregations have been observed; C - The same as in B but more degree of aggregation; D-Drug dissolved in the sorbed moisture layer).

5C



25°C/70%R.H./36W

5D



25°C/90%R.H./36W

FIGURE 5 CONTINUED

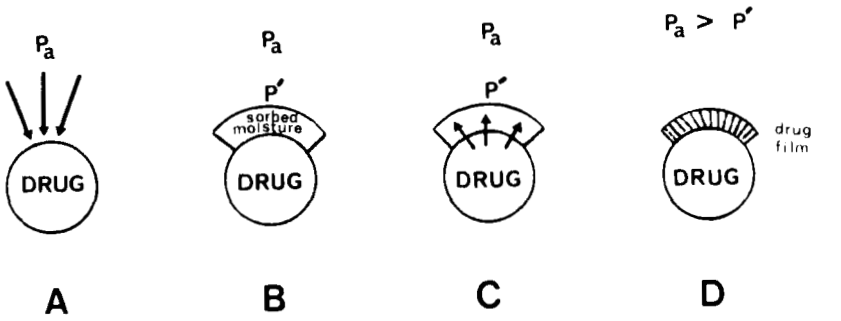


FIGURE 6

Moisture sorption model for water soluble solids based on heat transport control (Key: P_a = vapor pressure in the atmosphere; $P^{/}$ = vapor pressure over the sorbed moisture layer)

D) The decrease in $P^{'}$ is effectively offset by the increase in temperature of the film (and the solid) caused by the heat released on condensation of the water vapor. The moisture sorption will occur spontaneously and the thickness of the condensate film will grow as long as $P_a > P^{'}$. The solid will continue to dissolve and saturate the film, maintaining the vapor pressure over the sorbed moisture layer ($P^{'}$). To reach equilibrium with atmospheric pressure (P_a), total dissolution and some degree of solution dilution must occur.

These authors also described steady-state and non steady-state heat transport controlled condensation, mass transport, and mass-heat transport models. For the steady-state heat transport model of a hollow sphere the following equation was obtained:

$$\partial_h = (C+F)\ln(RH_a/RH^{'}) \qquad (19)$$

where ∂_h is the moisture sorption rate associated with heat transport control; C and F are the values from conduction and radiation terms; RH_a and RH' are the relative humidities in the atmosphere and over the sorbed moisture layer, respectively.

MOISTURE TRANSMISSION THROUGH POLYMERS FOR SUSTAINED RELEASE AND FREE FILMS FOR TABLET COATING

Moisture transmission through polymers and free films was found to be useful for characterization of the possible effects on the dissolution and transport of drugs from the dosage forms. The process of moisture transmission through films or polymers has been described by many authors[32-40]. Fick's law[41] can be used to determine the rate of moisture transmission across film membranes or polymers. The diffusion coefficient will be involved in the process and the rate of moisture transmission will depend on film thickness. Thus, the permeability constant can be defined by[32]:

$$P = W.l/(A\Delta P).t \qquad (20)$$

where P is the permeability coefficient of the polymer or film of thickness l; W is the weight of moisture transmitted at time t; A is the surface area; ΔP is the pressure gradient across the film.

Equation (20) then leads to:

$$\ln(\pi) = \ln(P) - \ln(l) \qquad (21)$$

where π is the rate of moisture transmission; P is the permeability coefficient of the polymer or film of thickness l.

The rate of moisture transmission is given by:

$$\pi = W/(A\Delta P)t \quad (22)$$

where π is the rate of moisture transmission; W, A , t and ΔP are as previously described.

In the above, π is defined as the weight of moisture transmitted per unit time through a film of unit area when the film is subjected to a vapor pressure gradient of unity. The value of π can be calculated as the slope of the line resulting from the plot of moisture transmitted (W) versus time. The variables A and ΔP are held constant. From equation (21), the permeability coefficient should be independent of the films thickness which exhibit Fickian diffusion. Banker et al[34]found that for lipophilic films, such as n-butylmethacrylate the weight of moisture transmitted approximates to that predicted by Fick's law. However, for hydrophilic films and mixed hydrophilic-lipophilic systems such as hydroxypropylester of cellulose and methylhydroxypropyl cellulose: ethyl cellulose, respectively, diffusion does not follow Fick's law. As the thickness of the films was increased, the permeability coefficient also increased. The reason for this increase may be due to swelling of the amorphous regions of the hydrophilic film during the moisture transmisstion process. Also, the polar functional groups of the film indicate the possible existence of van der Waals' forces and hydrogen bonds. This bonding, together with the swelling accompanying the sorption, facilitates water transmission. Higuchi et al[42] found that the more polar films are, the greater the rate of moisture transmission.

MOISTURE ADSORPTION ISOTHERMS

As was mentioned previously, the weight of moisture adsorbed on a unit weight of an adsorbent is given by:

$$W = f(A,T,\Delta P,E) \quad (23)$$

where W is the weight of moisture adsorbed; A is the surface area; T is the temperature; ΔP is the pressure gradient; E is the interaction potential between the water vapor and the adsorbent.

Since the amount adsorbed is measured at a constant temperature, the surface area and the interaction potential will have specific values for a given adsorbent. Hence, if W is plotted versus relative humidity or water vapor pressure the curve obtained is called the "adsorption isotherm".
Brunauer et al[43-45] found that the adsorption isotherms can be divided into five types as given in Figure 7.

TYPE 1: These occur in chemisorption and are limited to a few monolayers of adsorbate. The asymtotic will approached when the adsorbate molecules occupy all of the available sorption sites. In some cases, physical adsorption also exhibits type 1 if the microporous surfaces are present. At higher pressures, the pores are filled , thus leading to the plateau.

TYPE 2 : These occur in physical adsorption on nonporous or microporous adsorbent that allow a multilayer of adsorbate to be bound to the surface. An inflection point indicates the first monolayer formation.

TYPE 3 : These occur when the heat of adsorption is less than the adsorbate's heat of liquefaction. Thus, additional adsorption is facilitated because the adsorbate's interaction with the monolayer is greater than its interaction with the adsorbent surface.

TYPE 4 : These occur on porous surfaces with pores from 15-1000 Å in radius. An inflection point of type 4 indicates adsorption of the first monolayer.

TYPE 5 : Result from small adsorbate-adsorbent interaction potentials and capillary condensation. They are also associated with pores in the same size range as those of type 4.

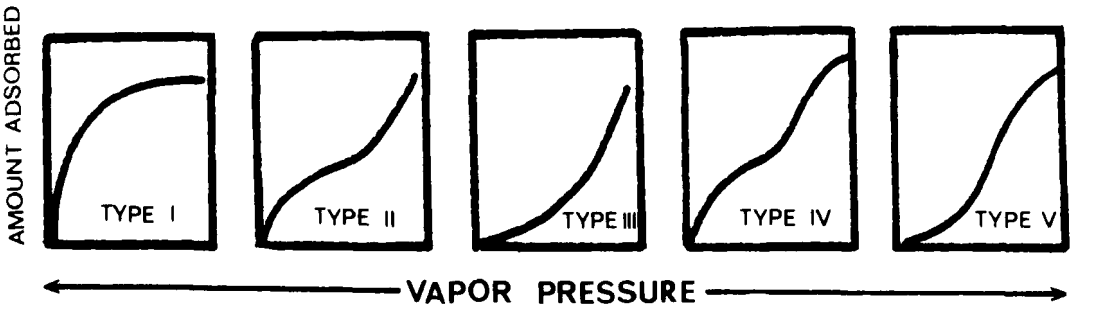


FIGURE 7
Various types of adsorption isotherms

THE BET EQUATION AND SURFACE AREA ANALYSIS

The BET equation is widely used to analyze the moisture adsorption of solid drugs. The linear form of BET equation[44-45] is given as:

$$(P/P_o)/V(1 - P/P_o) = 1/C.V_m + (C - 1)(P/P_o)/C.V_m \quad (24)$$

where P and P_o are the water vapor pressures for the experiment and in an atmosphere saturated with water vapor, respectively; V and V_m are the STP volume of water adsorbed at pressure P and at the monolayer coverage, respectively; C is the BET constant.

When $(P/P_o)/V(1 - P/P_o)$ is plotted versus P/P_o, a straight line will be obtained, with the values of the intercept and slope, the volume of adsorbed moisture at the monolayer will be calculated. From the known molecular area of water (12.5 $Å^2$), the surface area of substance will be obtained. The parameter C is related to the average energy of adsorption as follow:

$$C = e^{-(E/RT)} = e^{-(E_1 - E_2/RT)} \quad (25)$$

where E_1 and E_2 are the energy of adsorption of the first layer and the energy of liquefaction of the adsorbate, respectively.

Wurster et al[46] studied moisture adsorption-desorption properties of corn starch USP and gelatinized starch 1500. The BET equation was used to determine monolayer coverage (V_m) for both excipients.

BET adsorption isotherms provide a tool for better understanding of surface phenomena. The isotherms may provide a criterion for the proper selection of additives, vehicles, and coating materials to be used in the production of different types of dosage forms. They are also important in determining the degree of hydrophilicity of polymer films at different vapor pressures[47]. Sloan and Labuza[48] studied moisture adsorption isotherms of some pure crystalline food systems (such as lactose) and a non crystalline system. The isotherms are shown in Figure 8. The non crystalline system can adsorb much more water due to the space between randomly spaced molecules, while the tightly packed molecules in the pure crystalline lactose system adsorb only on the outside crystal surfaces. However, at high relative humidity, both systems dissolve and approach the same moisture content. Increasing the vapor pressure of water in the surrounding air can cause a phase transition of products to occur such as in sucrose (Mackower and Dye)[49], and lactose (Berlin)[50-52] and (Buma)[53]. Both substances will undergo a transition from the amorphous state to the crystalline state. Typical isotherm obtained shows a discontinuity as in Figure 9.

FREUNDLICH ADSORPTION ISOTHERM

If the weight of the moisture adsorbed on a solid follows the Freundlich adsorption isotherm then:

$$X = KP^{1/n} \qquad (26)$$

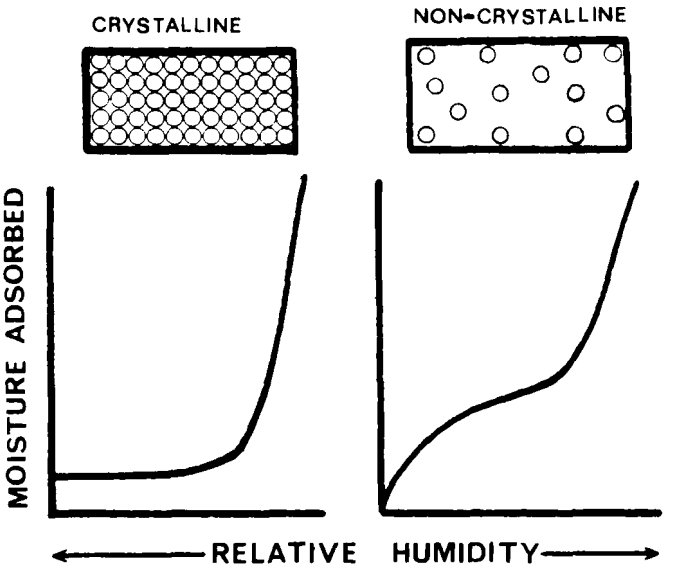


FIGURE 8

Moisture adsorption isotherms of some pure and non-crystalline systems

where X is the moles of moisture adsorbed per mole of drug; K and 1/n are the Freundlich parameters; P is the water vapor pressure.

The equation is handled more conveniently when written in the logarithmic form

$$\log X = \log K + 1/n \log P \quad (27)$$

The moisture adsorption of cefaclor[24] was found to follow the Freundlich adsorption isotherm as shown in Figure 10. Freundlich adsorption isotherm may be useful in predicting the equilibrium moisture adsorption of a particular solid at a given temperature and relative humidity.

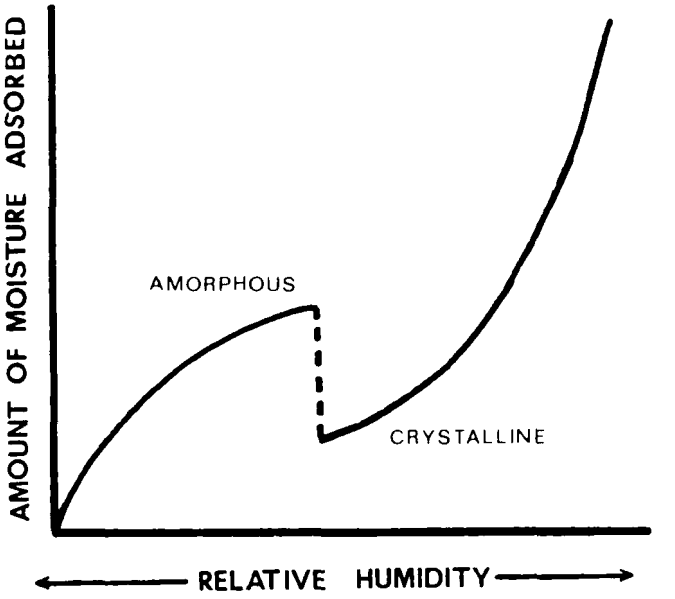


FIGURE 9

Moisture adsorption isotherm of some pure food systems while undergoing a transition from amorphous to crystalline state

MOISTURE ADSORPTION STUDIED FOR SOLID DOSAGE FORMS AND EXCIPIENTS

Lee et al[54] studied adsorption isotherms of various drugs in tablet matrices, such as ascorbic acid in lactose and mannitol-starch , aspirin in cellulose and amylose. They also studied the moisture uptake of the dosage units in closed containers to evaluate the packaging methods.

Moisture adsorption was found to be a very useful tool in determining the efficiency of disintegrating agents [11, 55-66]. Equivalent tablets with the same percentage of various disintegrating agents were made and stored in various relative humidities between 30 and 90%. The amount of moisture adsorbed (W_∞-W_0) and the volume expansion (V_∞-V_0) at equilibrium were calculated.

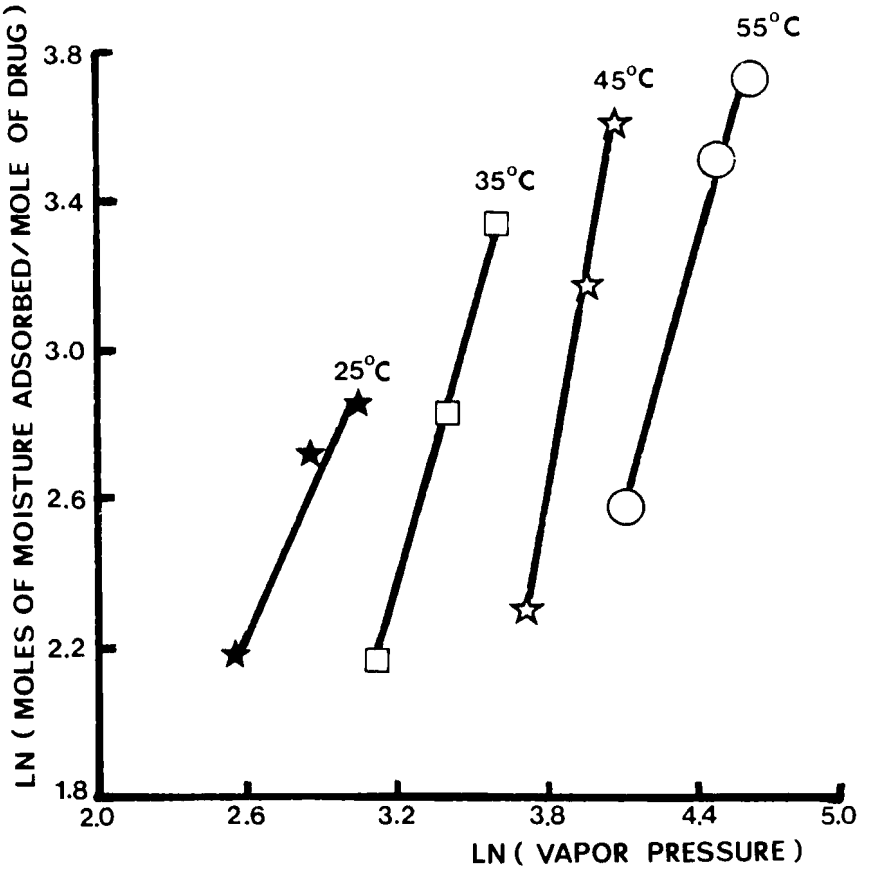


FIGURE 10

Freundlich adsorption isotherm of cefaclor at various temperatures and vapor pressures

The ratio between the value of $((V_\infty - V_0)/(W_\infty - W_0))$ at selected level of humidity can be used to compare the efficiency of disintegrating agents[64]. In a recent study, Mitrevej et al[11] evaluated swelling properties of various tablet disintegrants including Ac-Di-Sol®, CLD®, Explotab®, and Primogel®. By exposing powders to different relative humidities between 5 and 95%, water adsorption and desorption isotherms were constructed. In addition, the

swelling was measured by microscopy, swelling and desorption ratios were calculated and compared for each disintegrant studied. Caramella et al [65] proposed the employment of the COULTER Counter for particle swelling measurements of various disintegrating agents. The swelling index was calculated from the ratio between the average mean volume diameter of particles in an aqueous medium and in an inert medium. This method is useful for materials which swell to a limited extent and are difficult to evaluate by optical microscopy.However, some limitations of this method are also present, especially for materials containing highly hydrophilic ionizable moieties such as Amberlite IRP 88®. Gissinger and Stamm[66] evaluated major disintegrants by using tablets of pure excipient compressed at approximately the same compression force. Vertical expansion during water uptake was measured. The results are shown in Table 3.

The penetration of water into the compact mass can be used to determine adhesive tension. Liquid penetration into the capillary structure of bulk solids is high when the adhesive tension is high. The rate of liquid penetration into a compact mass may also be regarded as a rate limiting step in the process of disintegrating, disaggregation and dissolution. Adhesive tension is related to the contact angle by the following equation:[67]

$$T' = \beta\cos\phi \qquad (28)$$

where T' is the adhesive tension of solid; ß is the surface tension of liquid; ø is the solid-liquid contact angle.

The distance of liquid penetration into a bed of powder or a compacted bulk solid can be calculated by using the Washburn's equation:[68]

$$L^2 = \beta\cos\phi rt/2n \qquad (29)$$

TABLE 3

Swelling Properties of Various Pure Disintegrants

Disintegrant		Contact Angle (^{o})	Swelling after 1 min (%)	Time for Maximun Swelling	Maximun Swelling (%)
Starch/ Starch Deriva- tives.	Primogel LV	0	114	5 Minutes	201
	Primogel Std.	0	53	5 Minutes	110
	Maize Starch Std.	0	82	3 Minutes	103
	Explotab	0	60	5 Minutes	93
	Waxy Maize Starch	0	88	1 Minute	88
	STARX 1500	0	4	15 Minutes	13
Cellulose Derivatives	L-HPC	50	26	15 Minutes	313
	Ac-Di-Sol	0	48	10 Minutes	210
	NYMCEL ZSB 16	51	34	14 Minutes	98
	ELCEMA G250	52	90	1 Minute	92
	ELCEMA P 100	43	62	1 Minute	62
	ELCEMA F 150	40	57	1 Minute	58
	AVICEL PH 101	17	39	1 Minute	43
	AVICEL PH 102	21	30	1 Minute	33
Mis- cellaneous	POLYPLASDONE XL	34	29	9 Minutes	112
	VEEGUM F	26	24	13 Minutes	111
	ESMA SPRENG	104	56	1 Minute	57
	AMBERLITE IRP 88	35	17	15 Minutes	57

(Vertical Expansion During Moisture Uptake of Tablets of Pure Excipient Compressed at100 Mpa. From Reference # 57 with permission of the copyright owner)

where L is the distance of liquid penetration at time t; r is the radius of capillary; n is the viscosity of liquid.

Moisture desorption is the reverse of moisture adsorption for physical or van der Waals type adsorption. Physically adsorbed water vapor may be desorbed from the solid by increasing the temperature or by reducing the pressure. In some cases during the desorption process a hysteresis loop will be present. There are two types of hysteresis loops[69] as given in Figures 11 and 12.

A) Open hysteresis loop presumably due to materials having "ink bottle" pores (narrow neck pores).

B) Closed hysteresis loop presumably due to materials having capillary pores size.

Sadek and Olsen[47] studied water adsorption isotherms of hydrophilic polymers such as methyl cellulose, polyvinylpyrrolidone, gelatin, and polymethylmethacrylate. Open hysteresis loops were obtained during desorption from adsorption-desorption studies. They concluded that the available sorption site in a polymer film depends on the size of the molecules that are used as a solvent in casting the polymer film. The hysteresis loop area would increase as the available pore size increases. This finding was useful in controlling the degree of film porosity of polymeric materials. Nurnberg[70-71] reviewed the hygroscopicity of 22 pharmaceutical products including their limits of hygroscopicity, critical hygroscopicity and moisture adsorption isotherms. He also correlated the relationship between hygroscopicity and hydrolysis of pharmaceutical esters, vitamins and hormones. Harb et al[72] studied the equilibrium moisture content of several powders such as KBr, K (citrate), NH_4Cl, NH_4Br, tartaric acid, light MgO, $CaCO_3$, bentonite, gelatin and talc. Lachman et al[73] reviewed the effect of moisture on the stability of medicated

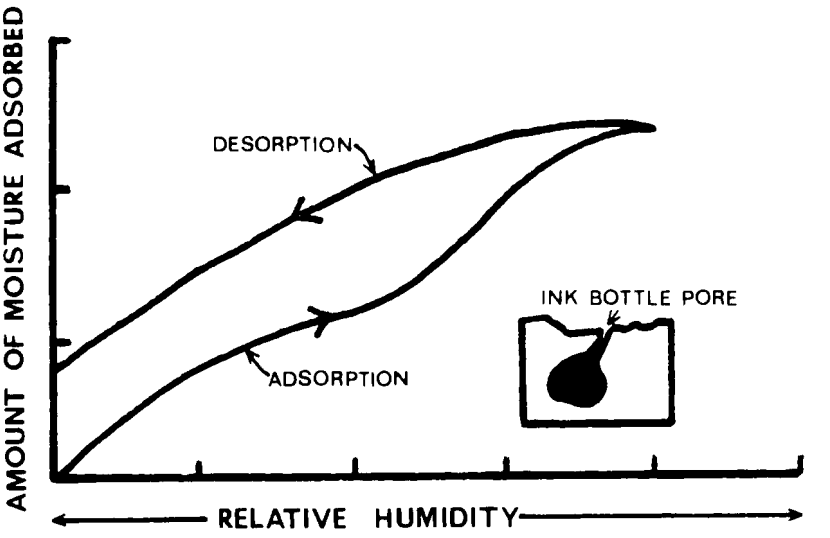


FIGURE 11

Open hysteresis loop of moisture adsorption-desorption isotherms

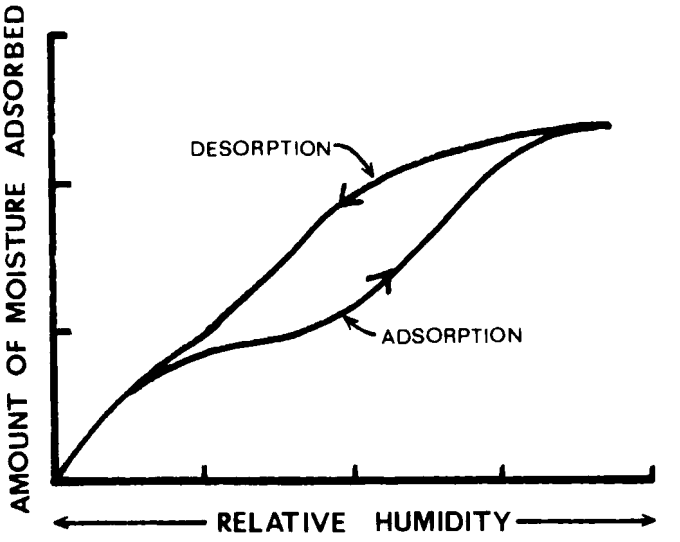


FIGURE 12

Closed hysteresis loop of moisture adsorption-desorption isotherms

candies. Ito et al[74] studied adsorption of water vapor by hard gelatin capsules and by several excipients such as microcrystalline cellulose, corn and potato starch. Campen et al[75] reviewed the kinetics of moisture adsorption and also proposed the method of determining the initial rate of moisture uptake and CRH of highly hygroscopic halides of choline salt. Nicklasson et al[76] correlated the rates of moisture adsorption of resorcylamide salts and related compounds to the intrinsic rates of dissolution in water. They found that the ability to adsorb moisture increases as the dissolution rate increases. Recently, Callahan et al[8] determined the equilibrium moisture content for pharmaceutical excipients as shown in Table 4.

MOISTURE AND STABILITY

The decomposition of pure drug components and solid dosage forms depends not only on temperature but also on the surrounding atmosphere, which may contain moisture. Moisture plays a very important role in solid state decomposition of pure drugs and solid dosage forms. Since, under usual storage conditions there is always moisture adsorbed on the surface of solid drugs and dosage forms, this layer is a factor in drug decomposition. The effect of the sorbed moisture on physical stability of cefazolin sodium at 35°C is given in Figure 13.

In the presence of the sorbed moisture layer:

a) The drug may dissolve and the decomposition kinetic will depend on the saturated solubility of the drug in this layer(various decomposition kinetic models which involve sorbed moisture were proposed by many authors[77,79,81-83,94-95]).

b) The active drug may chemically bond with moisture, and the resulting pseudomorph of the active drug may present a bioavailability problem.

c) The sorbed moisture layer may dissolve oxygen and lead to oxidation of the active drug.

TABLE 4
Initial and Equilibrium Moisture Content of some Common Pharmaceutical Excipients

Excipient	Initial Moisture Content	Equilibrium Moisture Content at 25°C (R.H.)			
		33%	52%	75%	93%
Dicalcium Phosphate, Anh. USP.	< 0.1	< 0.1	< 0.1	< 0.1	0.5
Lactose, USP., Monohydrate	0.2	0.2	0.2	0.2	0.2
Lactose, USP., Spray Dried	0.2	0.5	1.0	1.0	1.5
Lactose, USP., Anhydrous	0.2	0.2	0.2	1.0	3.0
Ethylcellulose N.F.	0.7	0.9	1.3	2.7	5.0
Magnesium Stearate N.F.	3.0	3.1	3.2	3.5	6.9
Microcrystalline Cellulose N.F.	3.6	3.7	5.4	8.1	13.2
Cellulose Acetate Phthalate N.F.	2.2	3.7	6.0	8.7	11.9
Sucrose, USP.	< 0.1	0.3	1.6	0.4	38.7
Dextrose, USP.	8.3	8.4	9.7	10.0	31.2
Polyethylene Glycol 3350 N.F.	0.3	< 0.3	0.6	2.0	48.3
Hydroxypropyl Cellulose	3.1	3.0	5.4	11.0	21.3
Hydroxypropyl Methylcellulose, USP.	2.1	3.5	5.9	10.5	25.7
Pregelatinized Starch N.F.	7.0	7.8	10.4	14.7	22.7
Corn Starch, USP.	7.1	8.0	11.6	14.4	21.5
Sodium Starch Glycolate N.F.	1.2	6.2	9.5	17.3	41.4
Povidone, USP.	4.5	12.2	17.6	27.8	44.8
Sorbitol, USP.	0.7	1.4	1.8	28.4	50.8
Sodium Caboxymethylcellulose, USP.	8.5	15.1	19.5	25.8	46.2

(From Reference #8 with permission of the copyright ower)

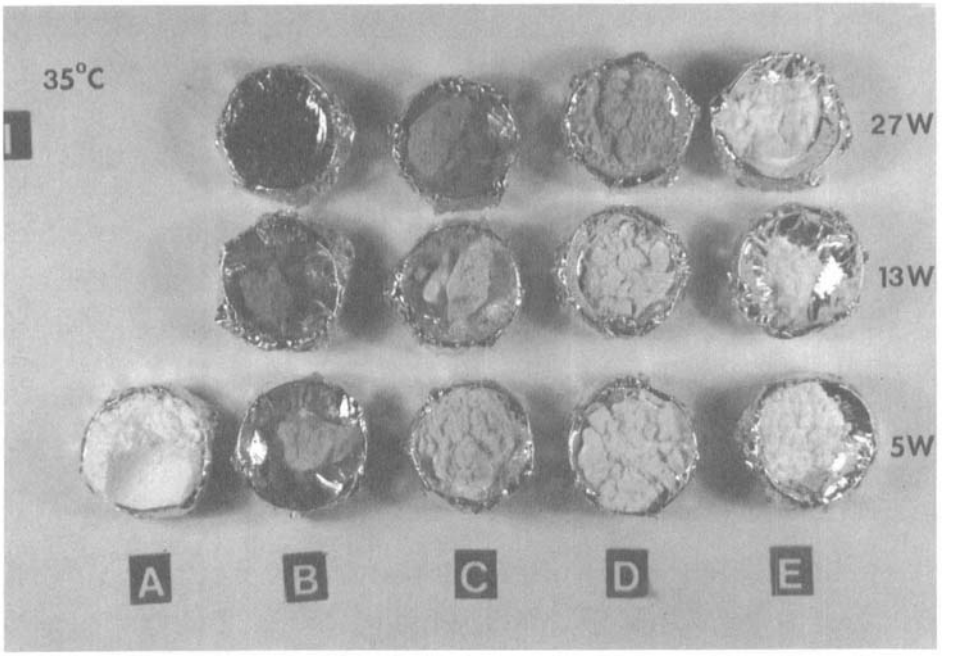


FIGURE 13

Physical changes in cefazolin sodium kept at various relative humidities and 35°C for 5,13 and 27 weeks (Key: A = Control; B = 85% R.H.; C = 70% R.H.; D = 55% R.H.; E = 25% R.H.)

d) The excipients in the solid dosage form may affect the stability of the active drugs by undergoing direct solid state reaction or by reacting as a surface catalyst. In addition, acidity and basicity properties of the excipients may also alter the pH of the sorbed moisture layer and may lead to the decomposition of the active drugs.

The effect of relative humidity on the stability of pharmaceutical products has been reviewed extensively, for examples, aspirin[77-83]; urea and linoleic acid[84]; hydrochlorothiazides[85]; ascorbic acid[86-87]; acetamino -phen[88]; nystatin[89]; steptomycin[90]; noradrenaline[91]; sodium p-amino salicylate[92-95]; ß-Lactam antibiotics[96-97]; nitrazepam[98];

meclofenoxate HCl[99]; vitamin D_2[100]; thiamine HCl[101]; cycloserin[102-103]; ketophenylbutazone[104]; vitamin A palmitate and acetate[105].

An exellent review by Tingstad and Dudzinski[106] discussed the stability of drug substances in solid pharmaceutical dosage systems as affected by moisture content. Theoretical models for various situations were proposed and their practical implications were considered.

SUMMARY

Hygroscopicity, thermodynamics, kinetics and the application of moisture adsorption for pharmaceutical solids have been described. Better understanding of the effect of moisture and the moisture adsorption phenomena will give useful informations that may be employed to develop a successful formulation.

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