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A STUDY OF THE MOISTURE-UPTAKE KINETICS OF A HYGROSCOPIC PHARMACEUTICAL POWDER

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ABSTRACT

The moisture-uptake kinetics of a hygroscopic powder, sodium heparin contained in a cylindrical container, was determined using a novel moisture-uptake measuring device under a constant convective air flow. The amount of moisture uptake increased with the increase in the relative humidity of the air. The effect of powder-bed height on the total amount of moisture uptake was found to be significant only at the highest relative humidity (75%) evaluated in this study. However, the percent of weight increase of the powder as a result of moisture uptake decreases as the height of the powder bed increases. The results of this study are explained by the dynamic nature of the moisture-uptake process associated with the instrument.

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INTRODUCTION

Moisture plays an important role in pharmaceutical product development, particularly for solid dosage forms. For a drug which undergoes hydrolysis, its chemical instability in the presence of moisture has a major impact on the choice of formulation excipients, the selection of processing methods, and the design of the product package (1). The flow, mixing, and compaction properties of a powder are known to be a function of the moisture content of the powder (2). Therefore, the moisture level of a solid formulation should be optimally controlled so that both the desirable processing properties and maximum product stability are realized.

Pharmaceutically, the sorption of moisture by a solid substance is characterized by the equilibrium moisture content (EMC) of the substance at a specific relative humidity and temperature (3). In some studies, the amount of moisture uptake is measured as a function of the water vapor pressure at a constant temperature and the results are presented as adsorption isotherms (4). These adsorption isotherms can be further analyzed to obtain information about the surface interaction between the solid and the water vapor (5). While the equilibrium moisture content of a solid substance is an important formulation parameter, the rate at which this process occurs is also a critical factor which may have a direct impact on the humidity control of the processing environment, particularly for a water-sensitive drug. Devices with various degrees of sophistication have been developed to measure the moisture-uptake rate by solid substances in a powder or a compact form (6-9). However, most of the moisture-sorption kinetic studies have been performed by a static gravimetric method which involves exposing the sample to water vapor over a range of relative humidities in an enclosed chamber without air movement. In this study, a novel dynamic moisture-uptake measurement device was used to characterize the moisture-uptake kinetics of a hygroscopic pharmaceutical powder, sodium heparin under a constant convectional air flow. The effect of the powder-bed height on its moisture-uptake kinetics was also investigated.

MATERIALS AND METHODS

Materials:

Sodium heparin, USP, was obtained from Diosynth, Chicago, Illinois. Prior to the moisture uptake experiment, the sodium heparin powder was dried in a desiccator under vacuum overnight (80°C). Reagent-grade sodium bromide, sodium chloride, and potassium acetate were purchased from Sigma Chemical Co., St. Louis, Missouri.

Methods:

Dynamic Moisture-Uptake Measuring Device

The dynamic moisture-uptake measuring device used in this study is shown schematically in Figure 1. The device operated at ambient atmospheric pressure, with convective air flow entering from the bottom of the water-jacketed sample chamber and being distributed within the chamber in a laminar fashion. The flow rate (cc/min), temperature, and relative humidity (R.H.) of the air were controlled and monitored. The temperature was controlled within a range of ± 0.2°C and R.H. within a range of ± 2% or less. The powder was placed in a sample pan which was connected to an electronic balance (Mettler AE 1000) and suspended in the sample chamber. Saturated salt solutions maintained at a constant temperature were used to provide a constant R.H. Changes in the sample

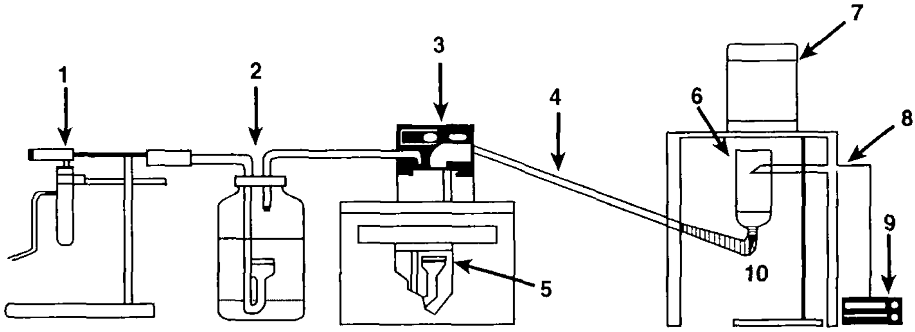

FIGURE 1

A schematic diagram of the dynamic moisture-uptake measuring device

1. Rotameter - Controls & Measures Air Flow
2. Saturated Salt Solution
3. Heating-Cooling Circulating Water Bath
4. Jacketed Condenser Tube
5. Saturated Salt Solution
6. Jacketed Sample Chamber
7. Digital Electronic Balance
8. Temperature/R.H. Probe
9. Temperature/R.H. Sensor With Chart Recorder
10. Heating Tape

weight as a result of moisture uptake were recorded by an electronic balance, and data were stored on a computer disk for ready retrieval. Temperature and R.H. in the sample chamber were monitored by a temperature/humidity probe which was positioned about 3 cm above the surface of the sample. Temperature and R.H. data were printed out by a strip-chart recorder as a permanent record.

Determination of Equilibrium Moisture Content (EMC)

The EMC of sodium heparin was determined at three different R.H. levels. Potassium acetate, sodium bromide, and sodium chloride were used to provide an R.H. of 22%, 57%, and 75%, respectively, at 25°C. An accurately weighed amount of sodium heparin powder (0.5 g) was placed on a fine mesh screen sample pan. The increase in the weight of the powder was monitored until no further weight increase was recorded. Dividing the weight increase (moisture gain) of the powder by the dried sample weight gave the EMC of sodium heparin at a specific R.H.

Determination of the Moisture-Uptake Profile

The effect of powder-bed height on the moisture-sorption kinetics of sodium heparin was investigated. Plastic cylinders of 3 cm in diameter and 1 cm, 3 cm, and 5 cm in height were used. The bottom of the cylinder was covered with a fine mesh screen. The cylinder was gravitationally packed with sodium heparin powder and the top of the cylinder was subsequently sealed by a lid. The cylinder was placed on the sample pan with the screen bottom downward, exposing the powder directly to the moist air flow inlet (air flow rate = 1,400 cc/min). The device was programmed to record the weight of the heparin powder sample every 10 minutes for three hours. Duplicate samples were used in this study.

RESULTS AND DISCUSSION

The equilibrium moisture content (EMC) of the sodium heparin powder at 22%, 57%, and 75% R.H. was found to be 5.6%, 15.9%, and 23.5%, respectively. The weight of the sodium heparin powder in the cylinder varied with the height of the cylinders, but the bulk density of the powder beds prepared in this study was not found to be significantly different (0.843 ± 0.029 g/cm^3). Therefore, it is assumed that porosity was the same for all powder samples evaluated in this study. Because of the difference in the initial sample weight, instead of using percent moisture uptake, the moisture weight-gain (in mgs) per sample was used to compare the moisture-uptake kinetics for the powder bed with different heights.

Figure 2 shows the moisture-uptake profiles for the 1-cm powder beds at three different relative humidities. The amount of moisture uptake was shown to be higher for samples exposed to a higher relative humidity for the three-hour time period. It is also noted that all three moisture-uptake curves exhibited an initial linear portion followed by a curvilinear segment. The moisture-uptake profiles for the 3-cm and 5-cm powder beds exhibited similar biphasic characteristics.

These biphasic moisture-uptake profiles can be further discussed with respect to the moisture-uptake process of the powder under convectional air flow. In such a process, water vapor was delivered to the surface of the powder bed by a convective air flow; thereby, moisture adsorption was not only limited to the very top layer of the powder bed but also took place concurrently in the powder bed as the air permeated the powder. As a result of the moisture uptake by the outer layer of the powder, the moisture content of the air decreased as the air permeated the powder bed. According to Campen et al. (9), the moisture uptake by a water-soluble solid occurred at a constant rate until a saturated solution was formed in the adsorbed film. Therefore, the residual moisture content of the air passing through this top layer of powder also remained constant, leading to a constant moisture uptake within the powder bed.

After a saturated solution was formed in the adsorbed film, the amount of moisture uptake by the top layer of powder decreased with time, resulting in an increase in the residual moisture of the air. This led to enhanced moisture uptake within the powder bed over time. The balancing effect of these two moisture-uptake processes may

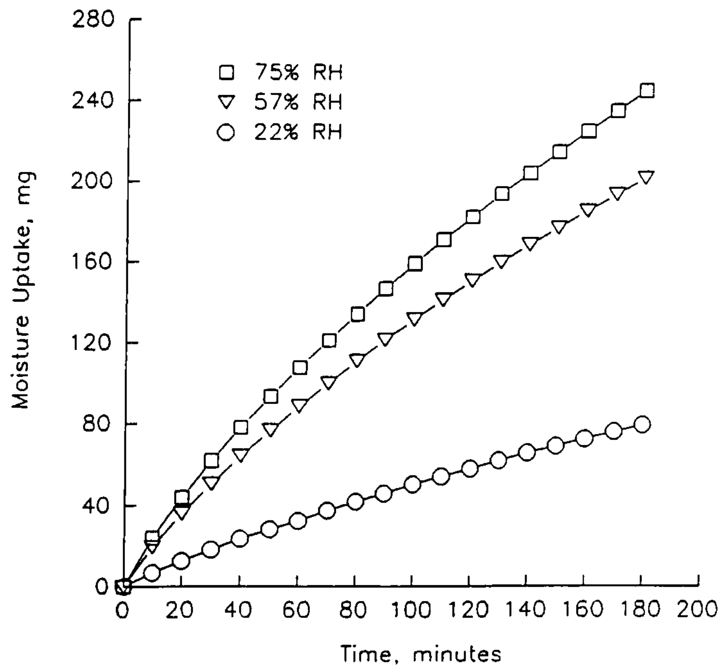

FIGURE 2.

The effect of relative humidity on the moisture-uptake curves for the 1-cm powder-bed samples

contribute to the constant initial moisture-uptake rate by the powder bed as shown in this study. When the EMC is established at the surface layer of the powder bed, the moisture-uptake front moves to the adjacent interior layer. As the moisture-uptake front shifts further into the powder bed, increasing resistance to the air flow may disrupt this balance and the total moisture-uptake rate declines with time.

Table 1 shows the amount of moisture uptake by sodium heparin powder as a function of time, relative humidity, and powder-bed height. The effect of relative humidity and powder-bed height on the moisture-uptake time profile was analyzed statistically using the repeated-measure ANOVA model (10). Data analysis was performed by the ANOVA

TABLE 1

The Amount of Moisture Uptake (mg) by the Sodium Heparin Powder Samples

Time (min)	Sample	Relative Humidity 22% Powder Bed Height 1 cm	22% 3 cm	22% 5 cm	57% 1 cm	57% 3 cm	57% 5 cm	75% 1 cm	75% 3 cm	75% 5 cm
10	1	7.1	6.5	6.8	19.8	20.2	21.5	25.2	29.4	29.3
	2	6.5	7.5	7.0	19.3	20.8	20.3	22.9	26.6	29.9
20	1	13.0	12.4	12.4	36.6	37.4	38.8	45.8	52.9	53.2
	2	12.4	14.0	13.3	35.3	37.1	37.7	42.3	48.2	53.5
30	1	18.7	19.1	17.9	51.4	52.7	54.1	63.9	73.9	73.0
	2	17.8	19.8	19.2	49.9	51.7	53.0	59.9	66.7	73.6
40	1	24.2	24.5	22.9	65.0	66.7	67.9	80.7	91.9	92.3
	2	23.1	25.1	24.6	63.3	65.2	67.3	75.7	83.7	92.3
50	1	28.9	29.5	27.7	77.7	79.7	80.6	96.0	109.3	109.0
	2	27.8	30.4	29.7	75.7	77.8	80.3	90.9	99.5	109.8
60	1	33.7	35.2	32.6	89.5	92.9	92.4	110.5	124.8	124.9
	2	32.6	35.3	34.6	87.7	89.5	92.7	105.2	113.8	125.1
70	1	38.2	39.0	37.1	100.8	103.7	103.2	124.1	140.3	140.7
	2	37.1	40.1	39.3	99.0	100.5	104.2	118.2	127.9	140.2
80	1	42.5	43.6	41.5	111.5	114.8	113.5	137.2	154.4	154.7
	2	41.5	44.6	43.7	110.0	110.9	115.2	131.0	141.8	155.1
90	1	46.6	48.6	45.7	121.9	125.5	122.9	149.9	168.5	168.9
	2	45.7	49.0	47.9	120.6	120.8	125.9	143.6	154.2	168.4
100	1	50.9	52.7	49.7	131.7	135.8	132.2	162.1	181.3	181.9
	2	49.9	53.2	52.1	130.8	130.6	136.2	155.6	167.0	181.7
110	1	54.8	56.2	53.5	141.2	145.4	140.9	173.9	194.1	194.5
	2	53.8	57.4	56.2	140.5	139.9	145.8	167.1	178.8	194.7
120	1	58.4	60.0	57.3	150.3	155.0	149.6	185.3	206.3	206.9
	2	57.7	61.2	60.1	150.1	149.0	155.5	178.2	190.4	206.9
130	1	62.3	64.3	60.9	159.2	164.3	158.3	197.2	218.3	219.5
	2	61.5	65.2	63.9	159.1	157.6	165.0	189.2	202.0	218.9
140	1	66.3	68.3	64.6	167.9	173.3	167.0	207.1	230.6	230.8
	2	65.1	68.9	67.5	167.9	166.2	174.1	199.6	213.0	230.5
150	1	69.4	71.7	68.1	176.2	182.2	175.4	217.7	241.1	242.1
	2	68.5	72.2	71.1	176.5	174.9	182.2	210.1	224.1	241.7
160	1	72.8	75.5	71.4	184.4	190.7	183.5	227.9	252.6	253.2
	2	72.1	75.8	74.6	185.0	183.1	190.8	220.4	234.2	252.7
170	1	76.4	78.4	74.8	192.5	198.9	191.1	238.0	262.9	264.2
	2	75.5	79.3	78.1	193.3	191.3	199.3	230.4	244.2	263.5
180	1	79.8	82.0	78.0	200.2	206.9	198.5	247.7	273.8	274.5
	2	78.8	82.5	81.4	201.4	199.3	207.2	240.2	254.4	274.3

procedures in SAS. The ANOVA results are shown in Table 2. The main effect of relative humidity was demonstrated to be significant at the α = 0.01 level, while both the powder-bed height main effect and the effect of interaction between these two variables are significant at the α = 0.05 level. Since the interaction is significant, a comparison of the effect of these two variables on the moisture-uptake profiles was performed by means of the Newman-Keuls multiple comparison test (at the α = 0.05 level) using all nine group means. The results indicate that powder samples showed a faster moisture-uptake time profile at a higher R.H. The powder-bed height did not affect the profile at an R.H. of 22% and 57%, whereas a thicker powder bed displayed a faster moisture-uptake profile at an R.H. of 75%.

Since there is more powder and more void space in a longer cylinder, a larger amount of moist air is likely to permeate and to be retained in the powder, leading to a greater total weight gain for the powder bed as a result of moisture uptake in this longer cylinder. Moreover, it is also true that the amount of residual moisture contained in the air permeating the powder bed is determined by the R.H. of the moist air entering the powder bed and the amount of moisture uptake by the outer layer of the powder bed. At the two low relative humidities, the residual moisture content of the air is relatively low; therefore, the increase in the amount of air permeating the powder bed in a longer cylinder does not generate a significantly higher overall moisture uptake. However, when the same situation is considered at R.H. 75%, the higher residual moisture content in the air may result in a significantly higher moisture uptake in the powder bed contained in a longer cylinder.

TABLE 2

The ANOVA Results for Moisture-Uptake Data

Source	df	SS	MS	F	Pr>F
Relative Humidity R_i	2	690532.79	345266.39	1396.03*	0.0001
Powder Height H_j	2	3825.38	1912.69	7.73*	0.0111
R x H Interaction $RH_{(ij)}$	4	4658.57	1164.64	4.71*	0.0251
Powder Sample $S_{(ij)k}$	9	2225.88	247.32	-	-
Restriction Error $\delta_{(ijk)}$	0	-	-	-	-
Sampling Time T_l	17	766882.32	45110.72	16421.14**	0.0001
R x T Interaction RT_{il}	34	126406.56	3717.84	1353.36**	0.0001
H x T Interaction HT_{jl}	34	351.65	10.34	3.76**	0.0001
R x H x T Interaction RHT_{ijl}	68	630.19	9.27	3.37**	0.0001
S x T Interaction $ST_{(ij)kl}$	153	420.31	2.75	-	-
Random Error $\epsilon_{(ijkl)}$	0	-	-	-	-

*F value obtained by using MS_S as the error term
**F value obtained by using MS_{ST} as the error term

The results of this study may be useful in understanding the consequence of handling a hygroscopic solid in an environment where moisture uptake by the soild may be possible. For example, when a small amount of powdered hygroscopic material is weighed in an analytical laboratory, moisture uptake by the powder may introduce relatively large errors to the sample weight as the total weight of the powder is usually small. However, when the same hygroscopic material is weighed during large-scale production, the amount of moisture uptake may have minimal or no effect on the final material weight because of the large quantity of material involved. In cases where a complete seal of the container is not achieved, temporary storage of a hygroscopic powdered material dispensed into containers with a smaller opening and slender shape may reduce the moisture uptake by the powder. Because the reduced surface area and increased height of the powder bed tend to limit the access of the powder to moisture uptake.

CONCLUSION

This study demonstrates the application of a novel dynamic moisture-uptake measuring device in determining the effect of relative humidity and powder-bed height on the moisture uptake of a hygroscopic powder. This moisture-uptake measuring device is capable of monitoring the moisture uptake of a sample under a steady air flow. The inital linear portion of the biphasic moisture-uptake profile resulted from the moisture absorption by the powder on the top layer of the powder bed as well as from the concurrent moisture uptake occurring within the powder bed. The significant effect of powder-bed height on the moisture uptake at an R.H. of 75% was attributed to the increasing amount of air permeating the powder bed in a longer cylinder.

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