DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 9(8), 1399-1416 (1983)

USE OF SORPTION ISOTHERMS TO STUDY THE EFFECT OF MOISTURE ON THE HARDNESS OF AGED COMPACTS

Nicholas Lordi, and Prafull Shiromani*[x]

Department of Pharmaceutics
School of Pharmacy, Rutgers University
New Brunswick, New Jersey 08854

ABSTRACT

Hardness changes in aged compacts of the salts of sodium, potassium and ammonium were studied at various humidities. The anionic and cationic effects on tablet hardening were determined from sorption isotherms of the salts. The sorption isotherms were obtained by inverse gas chromatography. The isosteric heats of adsorption were calculated from isotherms measured at temperatures from 40-60°C. The heat of sorption was highest for the chloride salt, intermediate for the bromide salt, and the least for the iodide salt. Potassium chloride attained the highest hardness increase while the iodide salt experienced the least hardness increase. The cationic effect was also rationalized from the heat of sorption data.

INTRODUCTION

Physical aging of compressed tablets causes complex changes of hardness over a relatively short period. The crushing strength of sodium chloride compacts prepared from dried samples doubled 1 hour after compaction[1]. No significant changes in crushing strength were observed when compacts were stored for longer periods at low humidities. The effect of moisture on tablet hardness has recently been studied[2]. Significant hardness increase was measured for sodium, potassium and ammonium chloride tablets stored at low humidities.

---

*Present address: Merck Sharp & Dohme, West Point, Pa. 19486

[x] To whom inquiries should be directed.

0363-9045/83/0908-1399$3.50/0

Tablets stored at 76% relative humidity showed no increase or slight decrease in hardness.

Sorption isotherms relate to the energy level of a component present in both the solid and gaseous phases of material. Such isotherms can be accurately obtained by inverse phase gas chromatography. This technique involves the characterization of the interaction between the column packing and an injected probe. Conventional chromatography, on the other hand, involves the analysis of a mixture by the components of the mixture reacting differently with respect to a previously characterized stationery phase. The theories relating adsorption isotherms to elution peaks have been described[3]. Recently, an inverse phase gas chromatographic procedure has been used to give fast, reliable results in the study of water sorption on collagen[4], acrylonitrile in acrylonitrile-styrene copolymer[5], decane and hexanol in polystyrene and poly (methyl methacrylate)[6], sucrose and glucose[7] and lactose and aspirin[8].

Therefore, the importance of aging and humidity on the strength of tablets has been recognized but is still incomplete in many aspects and needs more clarification.

EXPERIMENTAL

Materials

Single lots of the salts (Fisher Chemicals) were selected for this investigation.

Preparation and Treatment of Compacts

Batches of compacts were prepared from 30/40 mesh salts previously dried at 65°C for 24 hours. Tablets were compressed using a 127 cm. diameter die and punch assembly on a single punch machine (Manesty Machines Ltd.). Compacts of a suitable weight, thickness and hardness were produced and stored in open petri dishes at different relative humidities, in 5 liter closed desiccators. The hardness of the compacts was determined at the time of making and at regular intervals thereafter. The construction and evaluation of the hardness tester used in this work has been described before[9].

Inverse Phase Gas Chromatography

A gas chromatograph (Hewlett-Packard Co.) with a thermal conductivity detector was used for inverse chromatography. Helium was used as the carrier gas. To insure uniform column temperatures, 1.5 inch aluminum inserts were placed between the column and the ignition part and the column and the detector cells. To minimize the void volume the inserts were packed with glass wool. A schematic of the system is shown in Figure 1.

Each salt (50-60 mesh) was packed into a 3 foot by 0.25 inch (outer diameter) aluminum chromatographic column. A vacuum pump and a mechanical vibrator were used to insure a proper, even packing. Columns were conditioned by allowing the carrier gas to flow through for a minimum of 24 hours at the required temperature prior to analysis. An uncorrected flow rate of 20 cc/min. was used.

Inlet pressures were measured on a pressure gauge. Outlet pressure was taken to be 1 atmosphere. The compressibility factor, j, was calculated for each set of conditions, using the inlet and outlet pressures. The j factor is used to convert for the apparent flow rate. The isotherms were obtained at 40^o, 50^o, 60^o and 70^o. The injection sizes ranged from 0.05 to 0.5 μl for the chloride salt, 0.1 to 2.0 μl for the bromide salt and 0.5 to 10.0 μl for the iodide salt.

Figure 2 shows a typical chromatogram. The area was determined by weighing the chromatogram and then converting the weight to the area units. A sample calculation is given in Appendix I.

RESULTS AND DISCUSSION

The amount of moisture picked up by the salts below their critical deliquescent point is so small that it cannot be registered on a microbalance, which has a sensitivity of 0.1%. However, the inverse gas chromatographic procedure allowed estimation of the affinity of the salts for moisture at low humidities.

Typical chromatograms for the adsorption of water on the surface of potassium chloride (I), bromide (II) and iodide (III) are shown in Figure 3. The water-substrate interaction ranged from relatively weak on potassium chloride to very weak with potassium iodide as evidenced by the symmetrical peaks for potassium chloride and broad leading edges for potassium chloride and broad leading edges for potassium iodide. The corresponding adsorption isotherms,

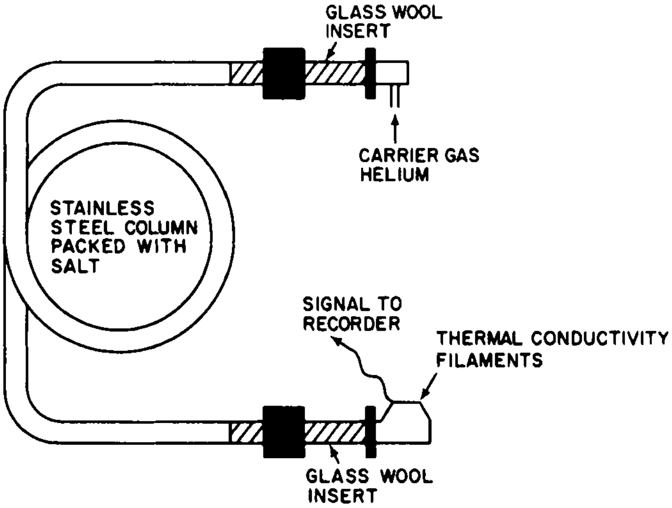

FIGURE 1

Schematic of the G-C System

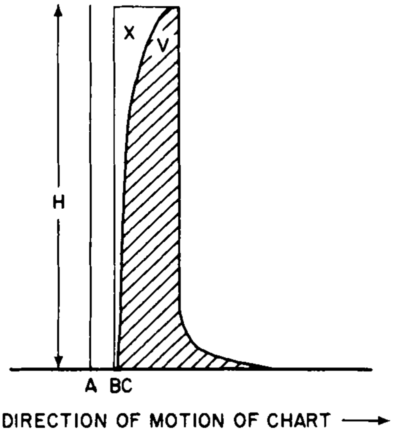

FIGURE 2

A Typical Gas Chromatogram of Water/Salt

Key:
A = Point of Injection
B = Point of Emergency of Unadsorbed Peak (Air)
C = Point of Emergence of Probe Peak
S = Area (y) (shaded)
S_p = Area (x)
H = Pen Deflection (peak height)

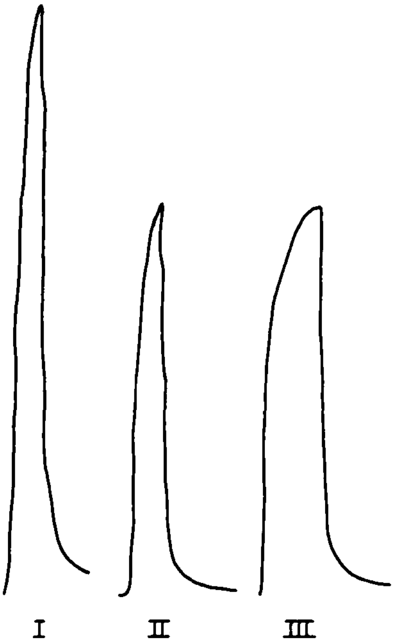

FIGURE 3

Typical Chromatogram of Sorption of Water on Salts

Key: I - Potassium Chloride

II - Potassium Bromide

III - Potassium Iodide

Chromatographic Conditions:

Column Temperature:	40°C
Detector Temperature:	150°C
Injector Temperature:	150°C
Carrier Gas Flow Rate:	20 cc/min.
Chart Speed:	0.635 cm/min.
Injector Size:	0.5 microliter

calculated according to the model in the appendix at 40°C, are shown in Figures 4 and 5. The isotherms are anti-Langmuirian.

The anionic effect on the sorption phenomenon was studied by determining the retention of water by the potassium salts at a pressure of 0.035 atmospheres. The retention of water by the iodide salt was about 150 percent greater than

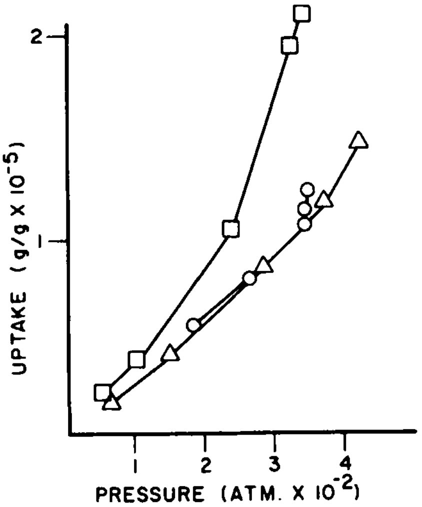

FIGURE 4

Sorption Isotherms of Water on Salts at 40°C

Key: ○ - Sodium Chloride

△ - Potassium Chloride

□ - Ammonium Chloride

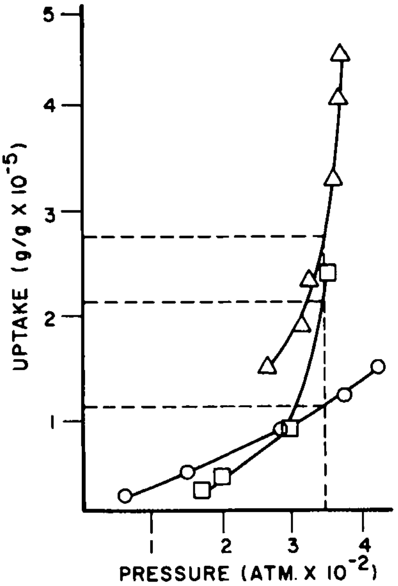

FIGURE 5

Sorption Isotherms of Water on Salts at 40°C

Key: ○ - Potassium Chloride

□ - Potassium Bromide

△ - Potassium Iodide

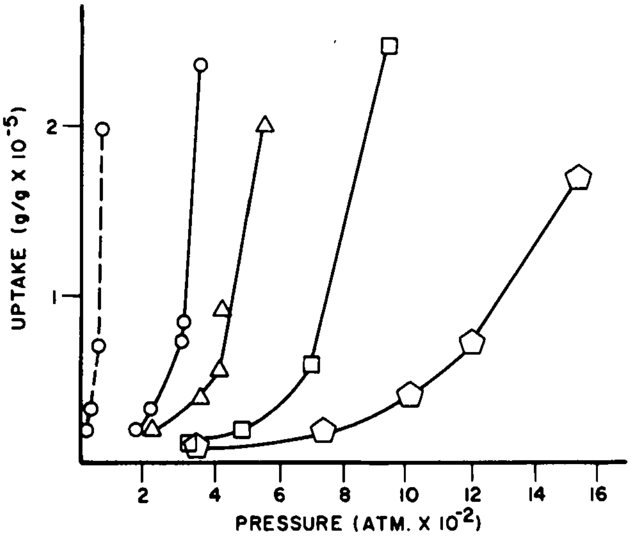

FIGURE 6

Sorption Isotherms of Water on Potassium Bromide

Key: ○- -○ - 25°C
○ - 40°C
△ - 50°C
□ - 60°C
⬠ - 70°C

that for the chloride salt and about 50% above that for the bromide salt. This effect may be directly related to the relative aqueous solubilities of these salts: where KI > KBr > KCl. The cationic influence also follows the same trend with more water being retained by the salt with the greater aqueous solubility, at a constant pressure. However, this influence is not as pronounced as that exerted by the group of salts with the same anion. This is probably due to the fact that the relative solubilities of the salts with the same cation do not differ from each other appreciably.

The isosteric heats of adsorption were calculated from isotherms measured at temperatures from 40°-70° for sodium chloride and the potassium salts. The isotherms characterizing potassium bromide are shown in Figure 6 and the corresponding sorption data is presented in Table 1. These isotherms show a

TABLE 1

Sorption Data for Potassium Bromide

Temp.	Mp (g)	a ($g/g \times 10^{-5}$)	p (atm)	Aw (p/po)
40°C	0.0001	0.185	0.0167	0.2292
	0.0002	0.32	0.0202	0.2781
	0.0005	0.72	0.0306	0.4207
	0.001	0.82	0.0301	0.4140
	0.002	2.38	0.0359	0.4940
50°C	0.0001	0.198	0.0215	0.1764
	0.0002	0.38	0.0366	0.3009
	0.0005	0.55	0.0420	0.3451
	0.001	0.91	0.0427	0.3512
	0.002	2.13	0.0568	0.4671
60°C	0.0001	0.10	0.0330	0.1679
	0.0002	0.19	0.0498	0.2534
	0.0005	0.59	0.0715	0.3638
	0.001	0.55	0.0756	0.3843
	0.002	2.52	0.0949	0.4825
70°C	0.0001	0.11	0.0348	0.1131
	0.0002	0.18	0.0754	0.2453
	0.0005	0.38	0.1019	0.3314
	0.001	0.72	0.1224	0.3982
	0.002	1.72	0.1543	0.5017

decrease in the amount sorbed with an increase in temperature at constant pressure, which indicates that the reaction is exothermic.

The isosteric heat of adsorption can be calculated from the chromatographic data using the Clausius-Clapeyron equation, which is:

$$\left[\frac{\partial \ln p}{\partial (1/T)}\right]_a = \left[\frac{\Delta H(ads)}{R}\right]_a$$

where p is the partial pressure of the probe in the gas phase. The subscript a indicates quantities measured at a given value of a, the amount of probe sorbed on the adsorbant. A plot of log p as a function of 1/T for potassium bromide is shown in Figure 7. Straight lines were obtained in each case and the relationship validated by the values of the correlation coefficients which were about 0.99 in all instances. The isosteric heats of adsorption, obtained from the slope and calculated by linear regression analysis of the data, are plotted as function of the moisture uptake in Figure 8. The heat of sorption is a measure of the strength of the bond between the water molecules and the sorbent molecules. For the potassium salts, the heats of sorption seem to remain constant over the range studied, indicating similar site activity. The magnitude of these heats are small, thereby indicating physical adsorption rather than chemisorption. Potassium chloride has the highest heat of sorption while potassium iodide has the lowest heat of sorption, which would suggest that the water substrate interaction is strongest for potassium chloride and weakest for the iodide salt. This conclusion concurs with the shapes of the respective chromatograms, as discussed earlier.

The heat of sorption of sodium chloride decreases with increasing moisture uptake. This may be related to the temperature coefficient of solubility, i.e., the solubility of sodium chloride does not change greatly with an increase in temperature.

In order to determine the amount of moisture taken up by the salts at different humidities at 25°C, the temperature at which the hardness measurements were made, sorption isotherms at 25°C were obtained as follows. Each higher temperature isotherm was divided into two linear regions, the respective slopes of which were determined by linear regression analysis. A plot of these slopes as a function of the reciprocal of the absolute temperature yielded a straight line. Extrapolation of these lines to 25°C gave the corresponding slopes at this temperature. Hence, the initial and secondary linear regions at the 25°C isotherm could be constructed and is shown as the broken line in Figure 6. The amount of moisture taken up by the salts at different partial pressures of water in the carrier gas and hence at different humidities, at 25°C, may then be deduced from this isotherm.

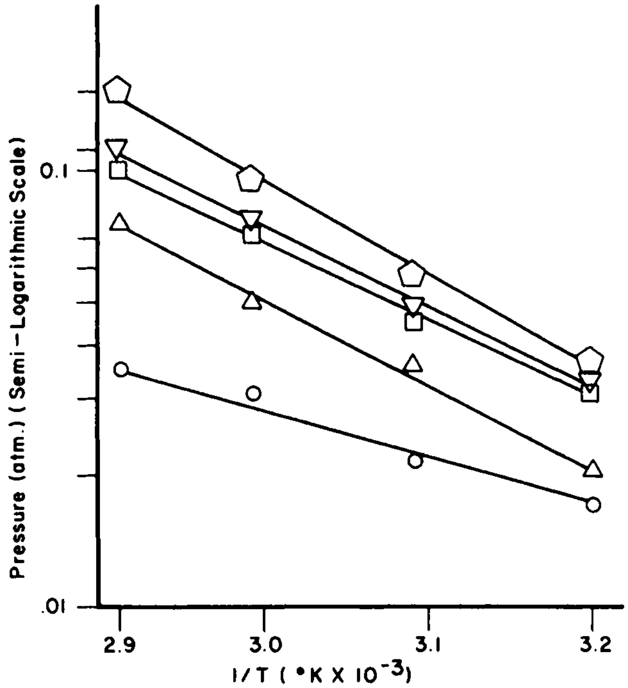

FIGURE 7

Clausius-Clapeyron Plots of the Sorption of Water on Potassium Bromide

Key:
○ - 0.1 microliter
△ - 0.2 microliter
□ - 0.5 microliter
▽ - 1.0 microliter
⬠ - 2.0 microliter

HARDNESS OF AGED COMPACTS AT DIFFERENT HUMIDITIES

As the humidity increases but remains below the critical deliquescent point, the hardness of the salt increases. The critical deliquescent point is the relative humidity of air in equilibrium with the saturated solution of the salt since it is at this relative humidity that the substance should commence to deliquesce. At a particular humidity, hardness should probably change until the compact attains its equilibrium moisture compact. Thereafter, the hardness would remain constant. This may also indicate that all sites for water-substrate interaction are saturated.

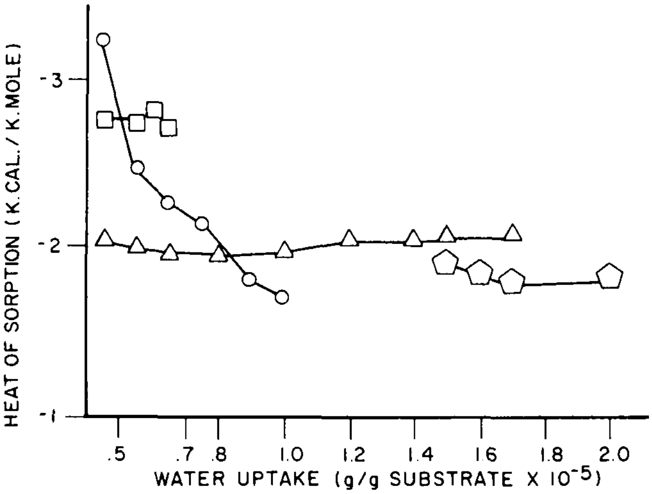

FIGURE 8

Isosteric Heat of Sorption as a Function of Water Uptake for the Salts

Key:
○ - Sodium Chloride
□ - Potassium Chloride
△ - Potassium Bromide
⬠ - Potassium Iodide

Therefore, moisture picked up by storage at humidities below the critical deliquescent point helps heal any fractures or flaws present in the internal surface of the compact. Thus, points of contact are brought closer to each other and bond formation is facilitated with a resultant increase in compact hardness.

With an increase in moisture uptake, brought about by storage at humidities near or above the critical deliquescent point, some interparticulate bonds are probably dissolved. Accordingly, the points of contact are separated from each other resulting in a decreased magnitude of the molecular forces of attraction. This is manifested in a considerable reduction in compact strength.

THE IONIC EFFECTS ON HARDNESS

1. The Anionic Effect

Figure 9 shows the relative hardness change measured after 30 days for the potassium salts at various humidities. The maximum hardness change for

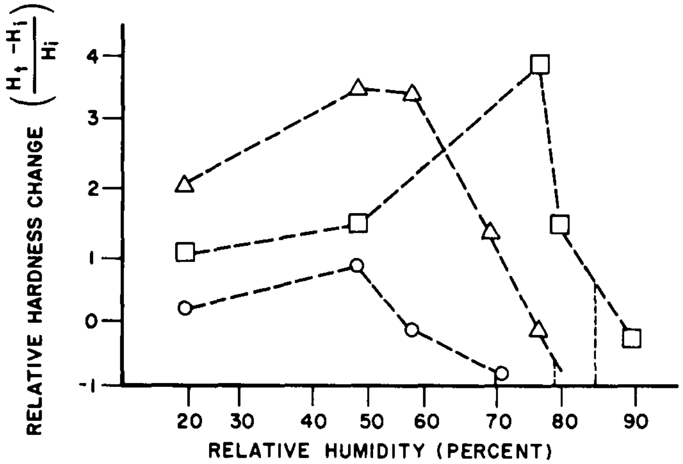

FIGURE 9

A Comparison of the Relative Hardness Change of Compacts Stored for 30 Days at Various Relative Humidities

Critical Deliquescent Points are Shown as Vertical Lines

(H_t - hardness at time t

H_i - initial hardness)

Key: ○ - Potassium Iodide

□ - Potassium Chloride

△ - Potassium Bromide

potassium chloride was slightly higher than that for potassium bromide and both were much higher than that for potassium iodide. With increasing moisture content, the salts showed increasing hardness up to a maximum; which may be attributed to the healing effect of surface moisture whereby surface cracks or flaws are dissolved.

The percent moisture picked up by these salts at various humidities and their heat of sorption are presented in Table 2.

The heat of sorption is highest for potassium chloride, lowest for potassium iodide, indicating that the water-substrate interaction is strongest for potassium chloride and weakest for potassium iodide. This agrees with the highest hardness increase attained by the potassium chloride compacts and the lowest by potassium iodide. The heat of sorption of potassium bromide is slightly less than that for potassium chloride and this is reflected in the slightly decreased

TABLE 2

Percent Moisture Uptake and Heat of Sorption of Salts

	Percent Moisture Uptake At			
Salt	47% RH	Maximum Hardness	Critical Deliquescent Point	ΔH K.Cal./K.Mole
NaCL	0.00238	0.00385	0.00381	
KC1	0.00201	0.00326	0.00359	-2.75
KBr	0.00967	0.00967	0.0166	-2.00
KI	0.0258	0.0258	0.038	-1.80

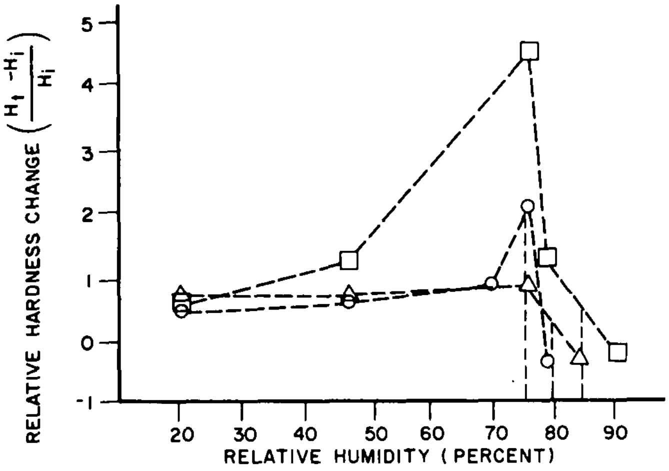

FIGURE 10

A Comparison of the Relative Hardness Change of Compacts Stored for 15 Days at Various Relative Humidities

Critical Deliquescent Points are Shown as Vertical Lines

(H_t - hardness at time t

H_i - initial hardness)

Key:
△ - Ammonium Chloride
○ - Sodium Chloride
□ - Potassium Chloride

maximum hardness change for potassium bromide when compared to that for the chloride compacts. At humidities below their critical deliquescent region, the hardness increase for the bromide compacts is more than that for the chloride compacts. This may be attributed to the larger amount of moisture picked up by the bromide salt.

The critical deliquescent point for potassium iodide is low and the amount of moisture picked up is high. The moisture begins to condense and in so doing, disrupts the binding forces. Consequently, the hardness increase of the iodide salts is not too pronounced.

2. The Cationic Effect

Figure 10 shows the relative hardness change measured after 15 days for the chloride salts of sodium, potassium and ammonium. The maximum hardness

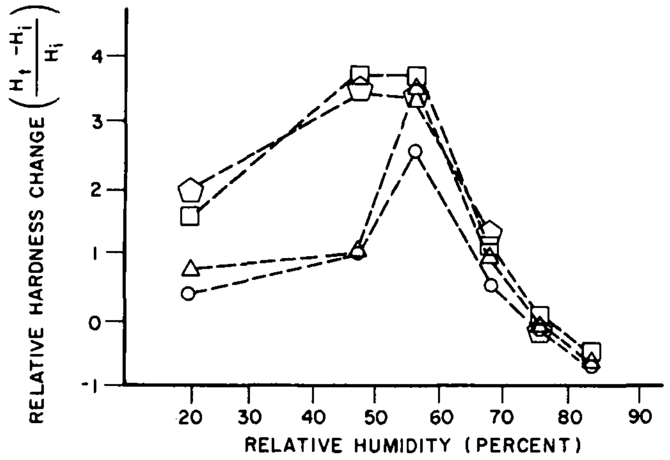

FIGURE 11

A Comparison of the Relative Hardness Change of Potassium Bromide Compacts Stored at Various Relative Humidities for Different time Periods

(H_t - hardness at time t

H_i - initial hardness)

Key:

○ - 3 days

△ - 7 days

□ - 15 days

⬠ - 30 days

change for potassium chloride was much higher than that for sodium chloride and both were higher than that for ammonium chloride.

The percent moisture picked up by sodium chloride is presented in Table 2. The amount of moisture picked up by sodium and potassium chlorides is almost the same as that which could be expected on the basis of their similar hygroscopicity. However, the heat of sorption for potassium chloride is independent of moisture uptake whereas that for sodium chloride shows a precipitous decline with increasing moisture uptake. This indicates that the water-substrate interaction for sodium chloride decreases in magnitude with increasing amounts of moisture uptake. This result could explain the differences observed in their respective strength as a function of humidity.

The maximum strength of ammonium chloride compacts at its critical deliquescent point is not too different from that observed at lower humidities. Pauling[10] states that the small ionic character of the N-H bond of crystalline and liquid ammonia gives it only small hydrogen-bond-forming power which is suggestive of a weak water-substrate interaction. Lordi and Bhatia[2] in their comparative studies of the above chloride salts found that the strength of ammonium chloride did not change appreciably with time at 20% relative humidity and that these compacts were weaker than those of the other chloride salts.

Figure 11 shows a set of curves for potassium bromide at different times. At shorter time intervals, maximum hardness was obtained at 56% relative humidity whereas at longer time period, similar hardness values were obtained at 47% and 56% relative humidities.

APPENDIX

SAMPLE CALCULATION

Chromatographic Conditions

Column:	Sodium Chloride
Column Temperature	60^oC
Detector Temperature:	150^oC
Injector Temperature:	150^oC
Carrier Gas Flow Rate:	20.7 cc/minute
Mass of Sodium Chloride in Column:	20.78 grams = m
Chart Speed:	1.27 cm/minute = q
Inlet Pressure:	1.0748 kg/cm^2
Outlet Pressure:	1.0332 kg/cm^2
R. Universal Gas Constant:	82.07 $(cm^3atm) / (mole\ ^oK)$
Injection Size:	0.5 microliter = 0.5 mg = m_p

SAMPLE CALCULATION

AREA UNDER THE CURVE:	5.3955 cm^2 = S
AREA NOT UNDER THE CURVE:	2.265 cm^2 = Sp
PEAK HEIGHT:	10.7025 cm = h

$$a = \frac{m_p s_p}{mS} = \frac{0.0005 \times 2.265}{20.78 \times 5.3955}$$

$$= 1.0103 \times 10^{-5} \ \frac{\text{g H}_2\text{O}}{\text{g Salt}}$$

$$W = (\text{uncorrected flow rate}) \quad \left(\frac{\text{Column Temperature}}{\text{Room Temperature}}\right) \quad (j)$$

$$j = \left(\frac{3}{2}\right) \frac{\left(\frac{Pi}{Po}\right)^2 - 1}{\left(\frac{Pi}{Po}\right)^3 - 1}$$

Where Pi = inlet presssure

Po = outlet pressure

$$j = \left(\frac{3}{2}\right) \frac{\left(\frac{1.0748}{1.0322}\right)^2 - 1}{\left(\frac{1.0748}{1.0332}\right)^3 - 1} = 0.98$$

$$W = (20.7 \text{ cc/minute}) \quad \left(\frac{333^\circ\text{K}}{298^\circ\text{K}}\right) \quad (0.98) = 22.7 \text{ cc/minute}$$

$$p = \frac{m_p q h R T}{S W m}$$

$$= \frac{(0.0005 \text{ g}) \ (1.27 \text{ cm/min.}) \ (10.7025 \text{ cm}) \ (82.07 \text{ cm}^3 \text{ atm/mole}^\circ\text{K}) \ (333^\circ\text{K})}{(5.3955 \text{ cm}^2) \ (22.7 \text{ cc/min.}) \ (18 \text{ grams/mole of water})}$$

$$= 0.08425 \text{ Atmospheres}$$

REFERENCES

1. J. E. Rees and E. Shotton, J. Pharm. Pharmacol., 22, Suppl., 17S (1970).
2. R. P. Bhatia and N. J. Lordi, J. Pharm. Sci., 68, 896 (1979).
3. A. V. Kiselev and Y. I. Yashin, in "Gas-Adsorption Chromatography," Plenum Press, N.Y., 1969, p. 104.
4. U. J. Coelho, J. Milty, and S. G. Gilbert, Macromolecules, 12, 284 (1979).
5. A. Ox, M.S. Thesis, Rutgers University, New Brunswick, N.J., (1979).
6. D. G. Gray and J. E. Guilett, Macromolecules, 5 (3), 316 (1972).
7. D. S. Smith, M.S. Thesis, Rutgers University, New Brunswick, N.J., 1980.
8. I. Jagnandan, "The Use of Inverse Gas Chromatography in Accelerated Stability Testing for Products Affected by Temperature and Humidity," Ph.D. Thesis, Rutgers University, New Brunswick, N.J., (1981).

9. R. P. Bhatia, "The Conductivity of Direct Compression Materials and Its Relation to Hardness in Aged Compacts," Ph.D. Thesis, Rutgers University, New Brunswick, N.J., (1976).

10. L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, 3rd Edition, 1960, page 475.