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EFFECT OF MOISTURE ON THE PHYSICAL AND CHEMICAL STABILITY OF GRANULATIONS AND TABLETS OF THE ANGIOTENSIN CONVERTING ENZYME INHIBITOR, ENALAPRIL MALEATE

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Granulations and tablets of enalapril maleate in a lactose matrix were stored in open petri dishes at a range of relative humidities and respective moisture uptakes measured. Extrapolation of the moisture uptake rates measured at the exaggerated humidities yielded a critical humidity, i.e. humidity where the moisture uptake rate is zero and, therefore, least detrimental to the product.

Enalapril maleate was reasonably stable at the storage conditions. The hardness of the tablets decreased at all humidities except when stored with silica-gel. The disintegration times were unaffected except at very high humidities. The dissolution profiles of the tablets remained unchanged.

INTRODUCTION

The effect of residual moisture in tablets on such physical properties as breaking strength (hardness), disintegration times, and the dissolution rates thereof has been studied extensively[1,2]. Some investigators[3] found that exposure of some tablets to low humidities increased breaking strength and disintegration times, while

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exposure to high humidities produced opposite effects. These changes were attributed to the dissolution or the formation of solid bridges within the tablet structure. Interestingly, other workers[4] observed similar changes in dissolution rates but little effect on breaking strength in their studies of moisture levels versus tablet properties. The conclusions from much of this effort were that changes in breaking strength could not adequately predict possible dissolution rate changes.

Enalapril maleate tablets formulated of a predominantly lactose matrix were found to be sensitive to certain conditions of elevated humidity. Effects on the tablets similar to those described above, i.e. changes in breaking strength not correlated with adverse effects on rates of drug dissolution, were observed.

These observations provided the impetus for the efforts described herein. Principally, the objective was to define optimum conditions for storing tablets in bulk as well as final market packages. This was to be achieved by determining the 'hygroscopic' properties of the composition of matter, particularly since the literature[5] indicates that characterization of the equilibrium moisture content (EMC), as well as the rate at which it is achieved, is imperative in formulations of drugs that show the potential for degradation in the presence of water.

EXPERIMENTAL

The tablets were prepared by wet granulation and were composed principally of lactose. Corn starch is included as a disintegrant and binder and magnesium stearate as a lubricant. The

granulations and tablets made from them were stored in open petri dishes at relative humidities (RH) ranging from 5% to 93% at room temperature (RT) and 30°C, respectively. A series of saturated salt solutions were employed to obtain the range of humidities[6].

Granulation moisture uptake was measured by a loss on drying (% LOD) method, using a Moisture Computer[1]. These LOD values were converted to moisture contents (dry basis). For the tablets, the moisture uptake was measured as the weight gained by the same set of twenty tablets. Weight gains were recorded after various intervals of storage. The hardness and disintegration times were also measured. Hardness was measured on the Schleuniger tester[2], and disintegration times were determined in distilled water at 37°C, without the use of discs, in the USP apparatus. Dissolution was measured with USP apparatus II.

Tablets in two potencies, 10 mg and 40 mg, were evaluated.

RESULTS AND DISCUSSION

Moisture uptake rates were determined by a least squares linear regression analysis on the initial portion of the moisture uptake versus time plots. One such plot for the 10 mg granulation at RT is presented in Figure 1, after converting LOD values to moisture contents. All correlation coefficients were significant. To facilitate comparison between the granulations and the tablets, the moisture uptake by the tablet was converted to a percent basis. This data is presented in Table 1. That the variables in each case are indeed correlated the population correlation coefficient, ρ, was subjected to a test of hypothesis, viz. $\rho = 0$ or $\rho \neq 0$ using students's t distribution[7]. The computation rejected the null hypothesis.

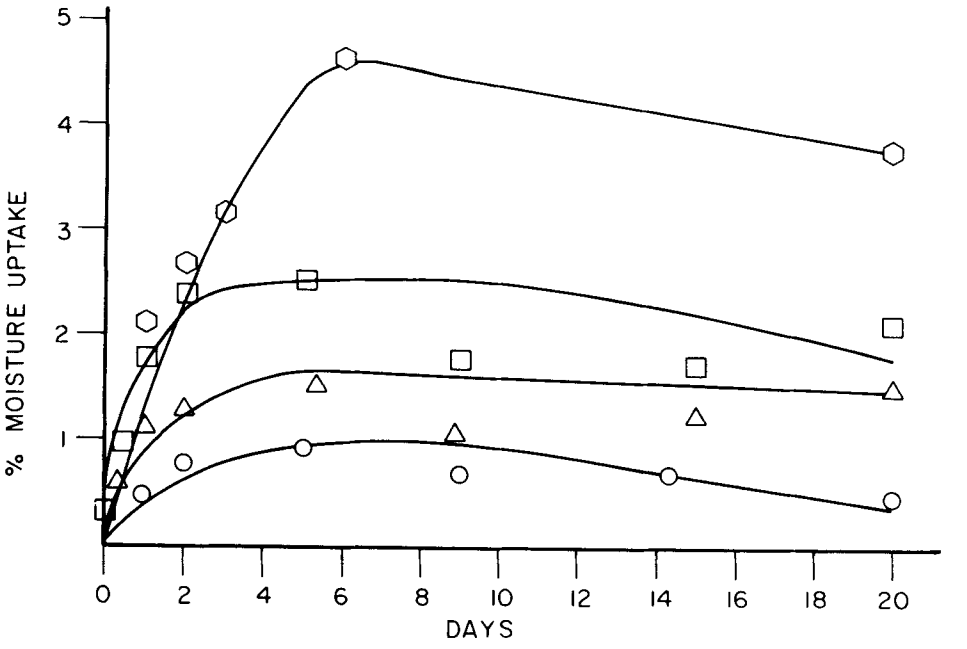

FIGURE 1

Moisture Uptake Versus Time for 10 mg Granulation at RT

Key:
- ○ - 33% RH
- △ - 53.5% RH
- □ - 74.8% RH
- ⬡ - 92.9% RH

TABLE 1

The Rate of Moisture Uptake (%/Hour) for the 10 mg and 40 mg Granulations and Tablets of Enalapril Maleate

Relative Humidity	Granulations				Tablets			
	10 mg		40 mg		10 mg		40 mg	
%	RT	30°C	RT	30°C	RT	30°C	RT	30°C
92.9	0.029	0.049	0.071	0.094	0.03	0.028	0.046	0.051
80.1	0.026	0.023	0.045	0.0722	—	—	—	—
74.8	0.017	0.005	0.049	--	0.013	0.016	0.023	0.039
64.8	0.017	—	0.034	0.038	0.0086	0.0062	0.018	0.014
53.5	0.010	0.003	0.033	0.024	0.0034	0.0064	0.011	0.008
43.9	—	—	—	0.014	—	—	—	—

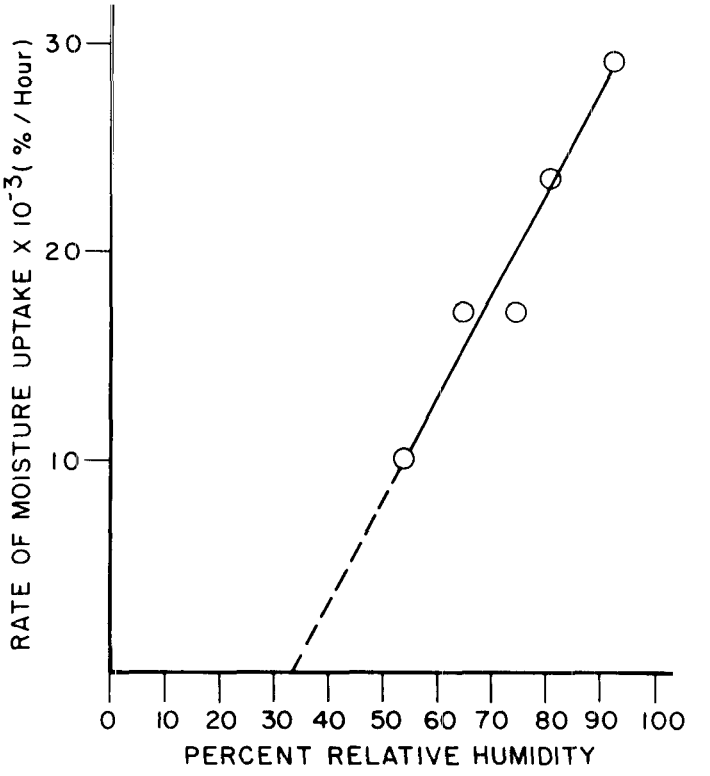

FIGURE 2

Moisture Uptake Rate Versus Percent Relative Humidity

for 10 mg Granulation at RT

The following conclusions were reached on these data: (1) The rates of moisture uptake were higher for the granulations than for the corresponding tablets. This may be attributed to the larger surface area of the granules compared to that for an equivalent weight of the tablet. (2) The rates were greater for the 40 mg formulation than for the 10 mg. formulation. This is because the higher potency formulation is not a direct multiple of the lower potency and, therefore, the proportions of the ingredients are different. There is

TABLE 2

The Critical Relative Humidities for the 10 mg and 40 mg Granulations and Tablets of Enalapril Maleate

	Granulations				Tablets			
	10 mg		40 mg		10 mg		40 mg	
Critical RH %	RT	30°C	RT	30°C	RT	30°C	RT	30°C
	33	56	24	37	36	36	33	36.5

also a four-fold increase in the concentration of the active drug component for approximately the same weight of the tablet. Figure 2, a plot of RH and moisture uptake rate, for the 10 mg granulation at RT, reveals a straight line with a positive slope. Similar plots were obtained for the other systems. Correlation coefficients were significant in all instances. This line extrapolated to intersect with the horizontal axis estimates the RH of a saturated solution of the tablet formulation, i.e. when the moisture uptake rate is zero. The particular formulation, therefore, should be handled in an environment below this critical RH. The critical humidities are presented in Table 2. The actual moisture uptake rate at these humidities was almost zero. The critical humidities for the 5 mg and 20 mg potencies were obtained by non-linear approximation, using the corresponding values of the 10 mg and 40 mg potencies. These data are presented in Table 3.

TABLE 3

The Critical Relative Humidities for the 5 mg and 20 mg Granulations and Tablets of Enalapril Maleate

	Granulations				Tablets			
	5 mg		20 mg		5 mg		20 mg	
Critical RH %	RT	30°C	RT	30°C	RT	30°C	RT	30°C
	32.6	54.7	26	40	32.6	36.5	33.5	35.9

TABLE 4

Chemical Analysis of Tablets and Granulations of Enalapril Maleate After Three Weeks, at 33% RH

10 mg Granulation	Enalapril	DKP +	Diacid +
RT	9.68 mg/199 mg*	None	0.42%
30°C	9.48 mg/199 mg*	0.53%	1.65%
10 mg Tablets			
(Initial	9.88 mg	None	0.20%)
RT	10.05 mg	None	0.20%
30°C	9.98 mg	None	0.37%
Dissolution			
RT	108, 108, 105, 108, 105, 105% of Claim		
30°C	98, 100, 94, 98, 94, 98% of Claim		
40 mg Granulation			
RT	39.4 mg/230 mg*	0.22%	0.30%
30°C	41.4 mg/230 mg*	0.33%	0.45%
40 mg Tablets			
(Initial	39.5 mg	0.15%	0.32%)
RT	40.0 mg	0.17%	0.31%
30°C	40.3 mg	0.38%	0.45%
Dissolution			
RT	104, 103, 102% of Claim		
30°C	103, 102, 102% of Claim		

*Weight equivalent to that of corresponding tablet.

+As percent of intact drug.

The granulations and the tablets stored at the critical humidities for about a month were chemically analyzed.

Enalapril maleate is reasonably stable at the conditions under test. The drug degrades slightly to form a diketopiperazine (DKP) by dehydration and the diacid by hydrolysis. These degradates increase with temperature. Their concentrations do not appreciably change at RT after three weeks. The dissolution characteristics of the tablets remained unaffected at the conditions tested. The data are presented in Table 4.

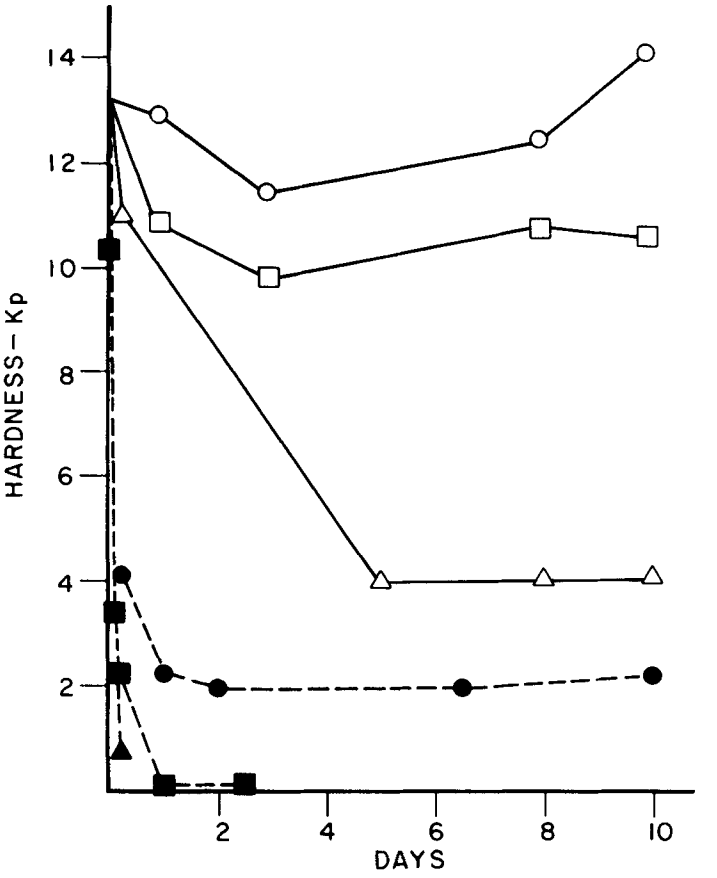

FIGURE 3

Hardness Versus Time for 10 mg Tablets at R.T.

Key:

○ - 5% RH

□ - 33% RH

△ - 53.5% RH

● - 64.8% RH

■ - 74.8% RH

▲ - 93% RH

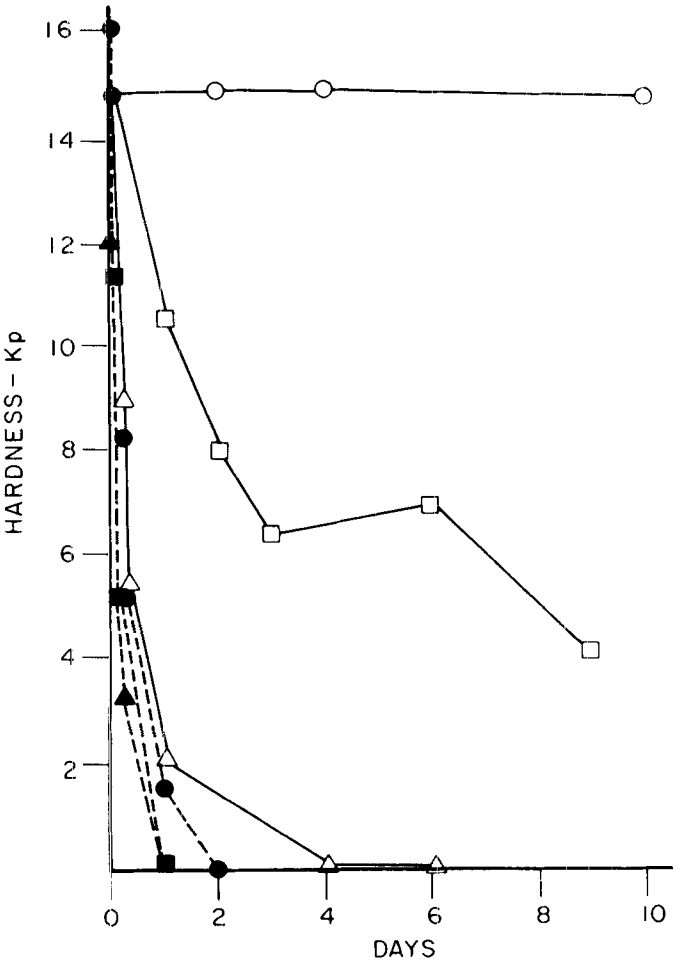

FIGURE 4

Hardness Versus Time for 40 mg Tablets at R.T.

Key:
○ - 5% RH
□ - 33% RH
△ - 53.5% RH
● - 64.8% RH
■ - 74.8% RH
▲ - 93% RH

Figures 3 and 4 depict hardness changes in the tablets with time and exposure to humidity. The hardness of the tablets decreased at all humidities except when stored with silica-gel. The magnitude of decrease was more pronounced at the higher humidities. The extent of the decrease was higher for the 40 mg tablets in accordance with their higher moisture uptake rates. It has been shown[8] that free moisture exists in solids in at least two states; a 'pendular' state where liquid bridges occur between individual particles and a 'capillary' state where all the pores of the solid are filled with liquid which forms concave mensci at the pore ends. The significant decrease in hardness could be explained, therefore, by the presence of 'capillary' water, through which interparticulate bonds are removed by dissolution, and the points of solid contact are separated from each other, thereby minimizing the magnitude of molecular forces of cohesion. Khan and Rhodes[9] have attributed reduction in strength of tablets to absorption of moisture by the disintegrant, thus causing swelling and bond disruption.

As an extension to this study, tablets stored for 31 and 32 hours at 74 and 93%RHs, respectively, were transferred to a 5% RH condition for 17 hours. About half the amount of moisture gained was lost on transfer to low humidity. The hardness, however, increased from 0 Kp to 22.5 Kp, possibly due to crystallization of the dissolved material in the void spaces forming solid bridges. The disintegration time nevertheless was not affected.

In general, the disintegration times were unaffected, except at 92.9% RH for the 10 mg tablets and 74.8% RH for the 40 mg tablets. At these conditions, the disintegration times increased substantially. At

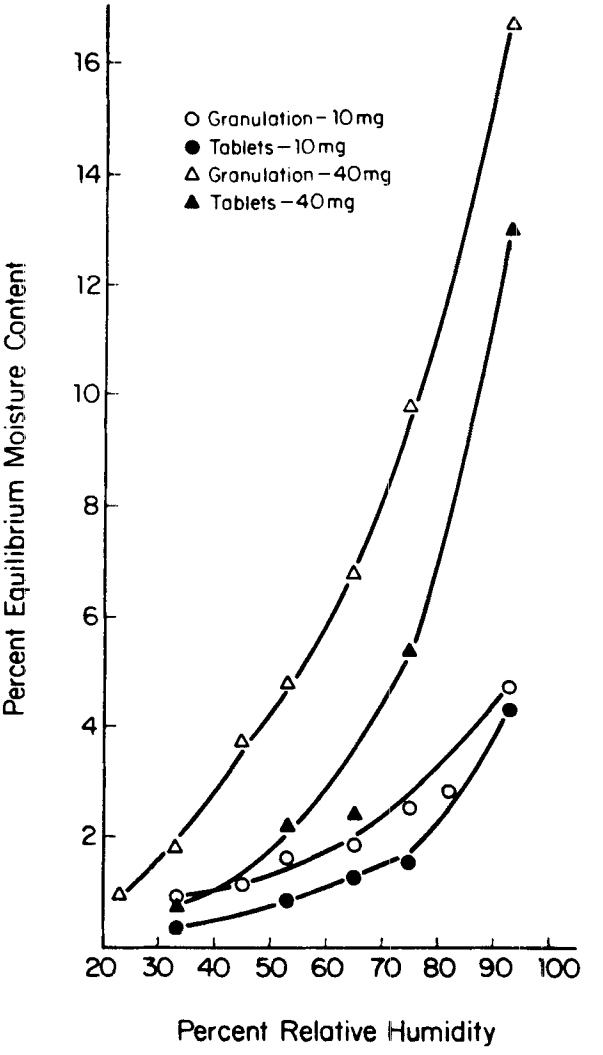

Figure 5
Equilibrium Moisture Content vs. Relative Humidity for 10 mg and 40 mg Formulations

these respective humidities, the EMCs of these two potencies were very similar. The increase in disintegration time may be explained as follows[8]: Tablets containing a disintegrant break up readily in water because of the sudden and immediate application of stress. However, when a tablet containing such a disintegrant is exposed to water vapor, stress is built up slowly, and the tablet structure absorbs some of the strain. Since the disintegrant within the tablet has lost some of its absorptive ability, disintegration times tend to increase. For the 40 mg tablet, the disintegration time decreased at 92.9% RH. The hardness and disintegration behavior was similar at room temperature and 30°C.

The EMCs were determined for both formulations. Equilibrium is established when the vapor pressure exerted by the moisture in the solid equals the partial pressure of the water vapor in the air. Figure 5 illustrates the EMC curves, i.e. the variation in the EMC of a material which changes in humidity, at RT. These curves have a two-fold utility: firstly to design optimum drying conditions for a wet granulated material, (for instance, the EMC at 30°C/33% RH for the 10 mg and 40 mg granulations are 0.695% and 1.419%, respectively; thus, it would be futile to dry the granulations to below these moisture levels), secondly, in the prudent selection of the types of package protection required for the product. The values of the EMCs obtained in this study were confirmed by measuring proton magnetic resonance relaxation time by pulsed NMR[3] of water contained in tablets equilibrated at different humidity conditions. The data for the 10 mg tablets at RT are presented in Table 5. This technique may be used to differentiate between bound and free moisture quantitatively.

TABLE 5

EMCs (percent) for 10 mg Tablets at RT Confirmed by Pulsed NMR

	Relative Humidity %			
	53	64.8	74.8	93
EMC by Pulsed NMR	0.86	1.13	1.6	3.88
EMC by Weight Gain	0.72	1.08	1.99	4.62

CONCLUSIONS

1. The bulk granulations and the tablets should be stored at room temperature at or below their critical RHs.
2. The presence of desiccant in the market package is essential.

Foot Notes

1. Moisture Computer Model 500M, Moisture Systems Corporation, Hopkinton, MA
2. Schleuniger Model 2E-106, Dr. K. Schleuniger and Co., CH-4501, Solothurn, Switzerland
3. PC/20 Series Nuclear Magnetic Resonance Analyzer, I.B.M. Instruments, Inc., Danbury, CT

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