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HYDRATE RELATED DISSOLUTION CHARACTERISTICS OF NORFLOXACIN

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ABSTRACT

The effect of moisture and temperature on the physical and chemical stability of solid oral dosage forms of Norfloxacin was studied. The physical properties of the dosage form, i.e. breaking strength and disintegration time were not affected adversely. Dissolution characteristics of Norfloxacin tablets were found to be affected by humidity conditions. Tablets with poor dissolution characteristics were improved to satisfactory rates by exposure to 21-25°C/75% relative humidity. Exposure to lower humidities and higher temperatures adversely affected dissolution rates. Once favorable dissolution rates were attained, however, they remained unchanged in spite of dehydration of the tablets.

INTRODUCTION AND OBJECTIVES

Numerous researchers have investigated the relationship between the humidity of the atmosphere and the moisture contents of

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pharmaceuticals.[1-5] The relationship between the initial water content and changes in moisture content during storage to physicochemical properties such as breaking strength, disintegration time and dissolution rate have also been studied.[6-11]

Norfloxacin tablets were observed to exhibit erratic dissolution characteristics apparently related to moisture content. The objectives of the study were:

1. To determine the effect of moisture sorption and desorption on Norfloxacin tablets exposed to different temperatures and humidities by measuring such physical properties as breaking strength, disintegration time and dissolution rate.
2. To quantify by selected analytical techniques the level of the hydrate necessary to produce the most desirable tablet properties.

EXPERIMENTAL

The tablets were monolayered in open petri dishes and stored at the following conditions: 40°C/75% Relative Humidity (RH), 30°C/75% RH, Room Temperature[12] (RT)/75% RH, RT/53% RH and RT/Ambient (Amb.)RH. Saturated salt solutions were used to obtain the humidities. The temperature and relative humidities selected were considered typical conditions of storage.

The tablets, once hydrated at the above conditions, were then studied for dehydration behavior at 50°C/Amb. RH, RT/50% RH, RT/30% RH and RT/0% RH.

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Samples were withdrawn at predetermined invervals and disintegration times, breaking strength values and dissolution rates were determined. Disintegration tests were done with the USP apparatus in distilled water at 37°C without discs. Breaking strength was determined using a Schleuniger-2E tester.[13] Dissolution rates were determined in a 0.05M acetate buffer with USP dissolution apparatus II at 50 RPM. Three to six tablets were used for each point.

Tablets were also subjected to analyses by FTIR (Fourier Transform Infra Red absorbance ratio analyses) as a means of establishing the ratio of anhydrous to hydrated drug present. These absorbance ratios are independent of concentration and characteristic of the chemical being analyzed.[14]

Moisture contents during sorption and desorption were measured as the weight gained or lost by the same set of ten tablets and were calculated as % water in the tablets.

RESULTS AND DISCUSSION

Figure 1 shows the moisture levels of the tablets during sorption plotted against time. As expected, the rank order of moisture pickup during sorption is: 40°C/75% RH, 30°C/75% RH, RT/75% RH, RT/50% RH and RT/Amb.RH.

Figures 2 and 3 showing moisture loss during desorption plotted against time indicate that moisture losses at 50°C/Amb.RH of the tablets hydrated at 40°C/75% RH, 30°C/75% RH, RT/50% RH and RT/Amb. RH are roughly comparable. Moisture loss at RT/50% RH, RT/30% RH and RT/0% RH of tablets hydrated at RT/75% RH are in this rank order: RT/0%, RT/30% RH, RT/50% RH.

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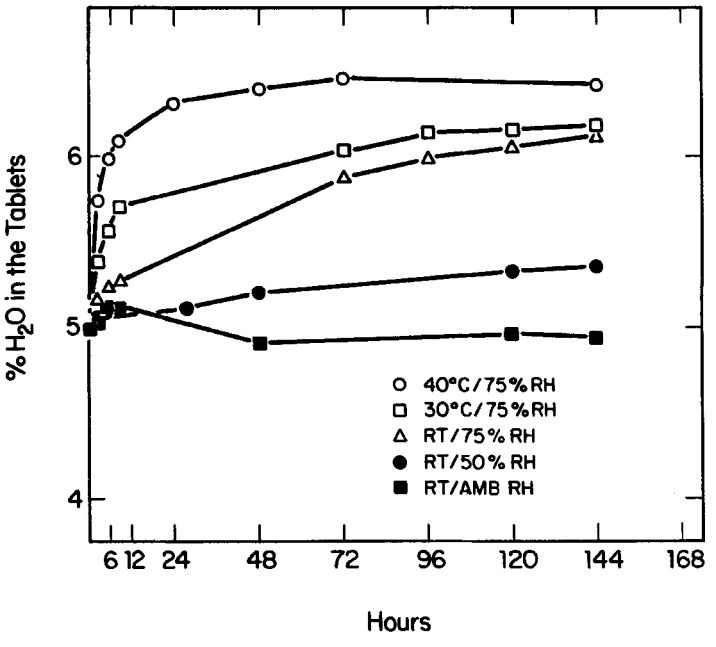

Fig.1 Moisture Pickup During Sorption vs.Time

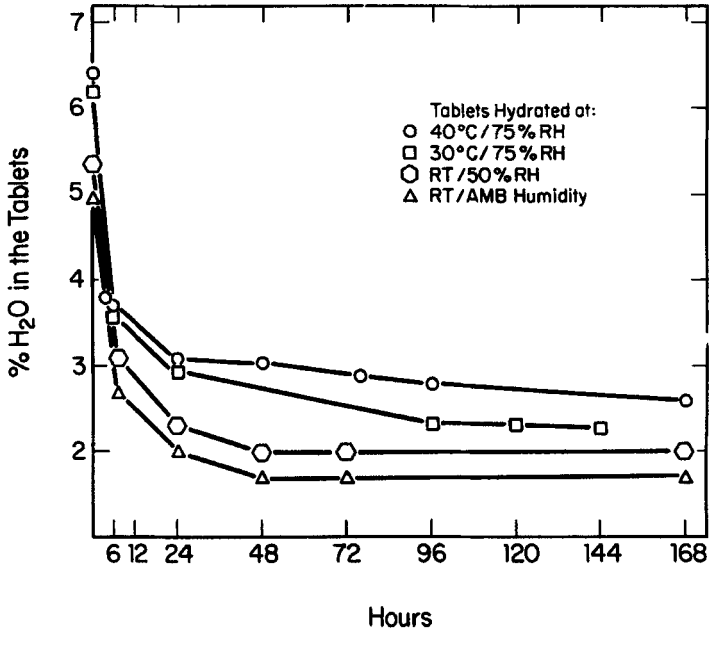

Fig.2 Moisture Loss During Desorption at 50°C / Ambient Humidity

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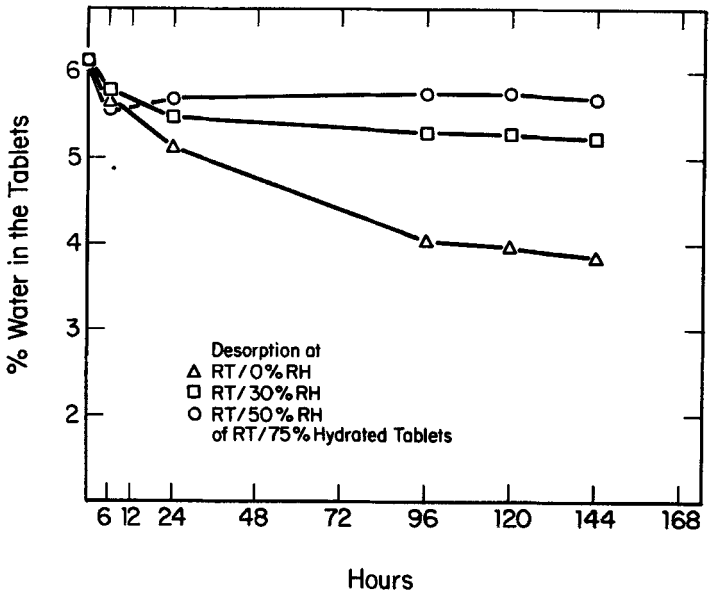

Fig. 3 Moisture Loss During Desorption vs. Time

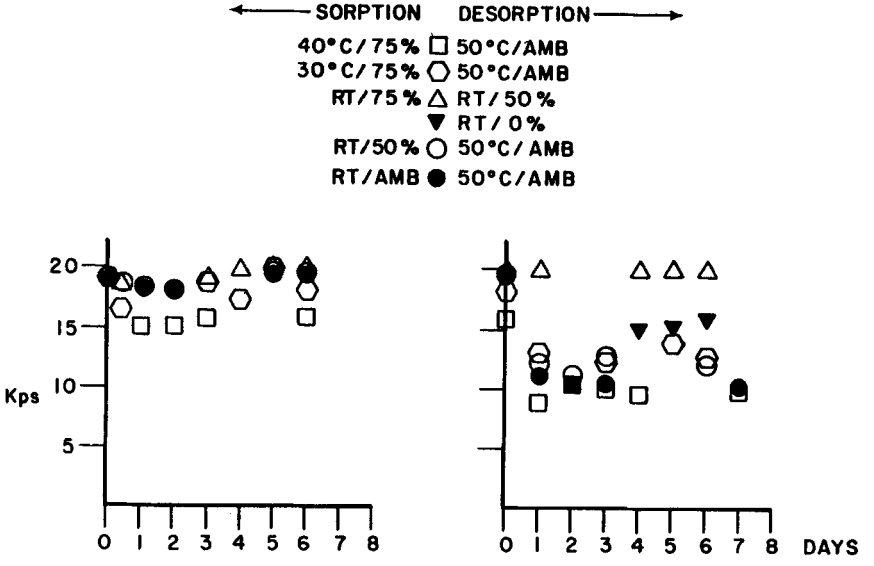

FIG. 4

BREAKING STRENGTH VS. TIME

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TABLE 1

Effect of Sorption of Water on the Breaking Strength of Tablets

Time (Hours)	Tablet Breaking Strength in Kp *				
	40°C/75% RH	30°C/75% RH	RT/75% RH	RT/50% RH	RT/AMB
0	18.2 (16.7-19.8)	18.6 (16.9-19.5)	18.6 (16.9-19.5)	18.6 (16.9-19.5)	18.6 (16.9-19.5)
2	15.6 (13.8-16.4)	17.43 (14.7-19.9)	18.7 (16.9-19.9)	18.28 (16.4-19.2)	18.03 (16.3-19.9)
5	14.8 (13.9-15.9)	17.3 (15.1-19.4)	18.2 (16.8-20.0)	19.38 (17.9-20.0)	18.13 (17.5-18.9)
8	14.3 (13.0-16.7)	16.58 (15.3-19.3)	18.8 (17.6-20.0)	18.95 (17.9-20.0)	18.10 (17.5-18.9)
24	15.1 (14.3-15.6)	--	--	18.6 •• (16.4-20.0)	18.43 •• (16.4-20.0)

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48	15.3 (14.2-16.5)	--	--	18.78 (17.8-20.0)	18.13 (16.5-20.0)
72	15.8 (14.9-16.5)	18.9 (16.8-19.9)	19.18 (17.5-20.0)	--	--
96	--	17.2 (16.1-17.9)	> 20	--	--
120	--	20.0 (19.2- >20.0)	> 20	≈20.0 (17.0-20.0)	19.48 (18.8-20.0)
144	15.8 (15.0-16.5)	18.25 (18.0-19.0)	> 20	≈ 20.0	≈ 20.0

* 4-6 Tablets were tested at each data point.

** 28 Hours.

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TABLE 2

Effect of Water Desorption at 50°C/Ambient Humidity on the Breaking Strength of Tablets Previously Exposed to Selected Humidity Conditions

Time (Hours)	Tablet Breaking Strength in Kp*			
	40°/75% RH	30°/75% RH	RT/50% RH	RT/Amb.Hum.
6	8.5 (6.8-9.1)	12.1 (10.8-14.4)	12.4 ** (11.8-13.4)	9.9 ** (9.0-10.2)
24	8.8 (7.8-9.5)	13.0 (11.0-14.7)	12.3 (11.0-13.7)	11.13 (10.5-11.8)
48	10.5 (9.7-11.2)	--	11.1 (9.5-12.0)	10.5 (9.9-11.2)

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72	10.01 (9.4-10.8) (76)	--	12.6 (11.0-14.8)	10.53 (9.8-12.0)
96	9.48 (8.7-10.6)	12.13 (11.1-13.8)	--	--
120	--	13.8 (11.6-15.9)	--	--
144	9.8 *** (8.8-11.0)	12.65 (10.9-13.5)	12.3 (11.4-12.9)	10.05 (9.1-10.9)

* 4-6 Tablets were tested at each data point.

** 8 Hours.

*** 168 Hours.

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TABLE 3

Effect of Water Desorption on the Breaking Strength of Tablets Previously Exposed to RT/75% RH

Time (Hours)	Tablet Breaking Strength in Kp*		
	RT/50% RH	RT/30% RH	RT/0% RH
6	18.4 (15.4-20.0)	≈ 20.0	≈ 20.0
24	> 20.0	> 20.0	≈ 20.0
48	--	--	--
72	--	--	--
96	> 20.0	> 20.0	15.13 (14.0-16.3)
120	> 20.0	≈ 20.0	15.4 (14.4-16.6)
144	> 20.0	≈ 20.0	16.01 (15.8-16.4)

* 4-6 Tablets were tested at each data point.

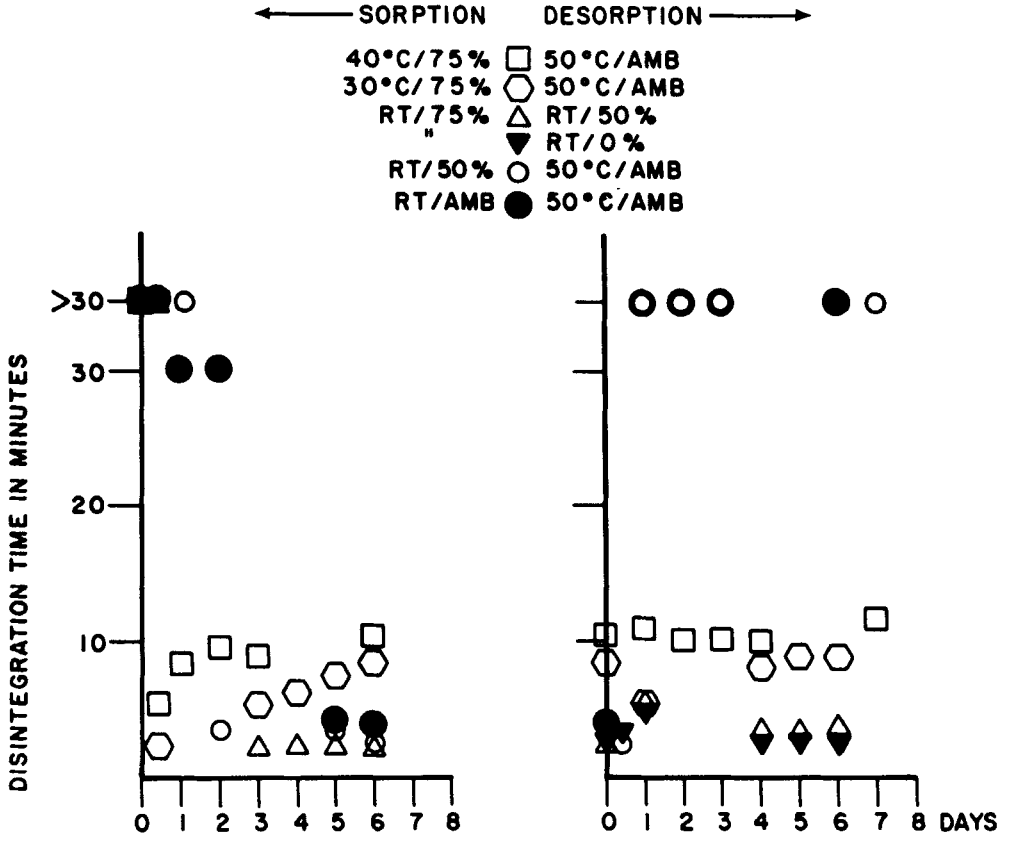

FIG. 5 DISINTEGRATION TIME VS. TIME

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Figure 4 and Tables 1, 2 & 3 show the effect of water sorption-desorption on the breaking strength of the tablets. While desorption at elevated temperatures causes some reduction in breaking strength of the tablets, the tablets appear less affected by desorption at room temperature and low humidities.

Figure 5 and Tables 4, 5 & 6 show the effect of sorption-desorption on disintegration times. Water absorption reduces the disintegration times to acceptable levels. Subsequent desorption at 50°C/Amb.RH of the tablets hydrated at RT/50% RH and RT/Amb.RH causes disintegration times to revert to original values. The fact that disintegration times at other desorption conditions were not affected adversely is attributed to formation of certain hydrates during sorption at RT. An extensive study of this phenomena has recently been completed,[15] confirming that different hydrates are formed during exposure to elevated humidities and that these hydrates can be differentiated by physicochemical analyses.

Figure 6 shows the effect of sorption and desorption on the FTIR ratio. Generally, hydration produces an FTIR ratio of about 0.4; however, at RT/50% RH and RT/Amb. RH, these values were about 0.6. Desorption at 50°C/Amb.RH causes the FTIR ratio to rise again. Desorption at RT/50% RH and RT/0% RH, however, did not produce an increase in the FTIR ratio.

Figures 7, 8 & 9 show the effect of sorption and desorption on the dissolution behavior of the tablets. Hydration at RT increases the amount of drug going into solution with RT/75% RH producing the highest values. Subsequent desorption at 50°C/Amb.RH had less an adverse effect on dissolution than on loss of water

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TABLE 4

Disintegration Time of Tablets*

after Exposure to Elevated Humidity Conditions

Time (Hours)	40°C/75% RH	30°C/75% RH	RT/75% RH	RT/50% RH	RT/AMB
0	> 30'	> 30'	> 30'	> 30'	> 30'
2	> 30'	> 30'	> 30'	> 30'	> 30'
5	3'-5'	2'10"-3'59"	> 30'	> 30'	> 30'
8	5'10"-6'0"	2'18"-2'58"	> 30'	> 30'	> 30'
24	8'26"-9'44"	--	--	> 30'**	3'47"-8'15"**

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48	9'33"-9'-59"	--	--	2'49"-4'36"	9'09"-10'29"
72	8'23"-10'50"	4'59"-6'33"	1'44"-2'40"	--	--
96	--	6'12"-6'54"	2'15"-2'43"	--	--
120	--	7'44"-8'12"	2'10"-3'30"	2'59"-3'42"	3'15"-4'10"
144	9'32"-12'40"	5'50"-9'15"	2'40"-3'30"	2'15"-3'12"	2'50"-3'05"

* 4-6 Tablets were tested at each data point.

** 28 Hours.

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TABLE 5

Effect of Water Desorption at 50°C Ambient Humidity on the Disintegration Time of Tablets* Previously Exposed to Selected Elevated Humidity Conditions

Time (Hours)	40°C/75% RH	30°C/75% RH	RT/50% RH	RT/Amb
6	8'57"-10'20"	5'30"-6'15"	2'35"-3'10"	2'15"-2'50"
24	9'22"-10'30"	5'28"-6'15"	> 30'	> 30'
48	8'35"-10'47"	--	> 30'	> 30'
72	9'47"-10'52"**	--	> 30'	> 30'
96	8'43"-10'06"	7'08"-8'32"	--	--
120	--	7'20"-9'32"	--	--
144	10'58"-14'33"	6'12"-6'58"	> 30'	> 30'

* 4-6 Tablets were tested at each data point

** 76 Hours.

(See Fig. 2). It is hypothesized that in this case the reduction in breaking strength observed may have masked the adverse effect on dissolution due to loss of water. This hypothesis is further supported by the observed increases in FTIR ratio. A surprising aspect of the study is that once the tablets are hydrated at RT/75% RH and attain acceptable dissolution levels, desorption at RT/50% RH, RT/30% RH and RT/0% did not affect their dissolution rates adversely in spite of loss in water content.

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TABLE 6

Effect of Water Desorption on the Disintegration Time* of Tablets Previously Exposed to RT/75% RH

Time (Hours)	RT/50% RH	RT/30% RH	RT 0%/RH
6	3'0"-3'38"	2'35"-3'20"	2'50"-4'40"
24	4'55"-6'0"	3'50"-4'40"	3'20"-5'35"
48	--	--	--
72	--	--	--
96	3'0"-4'09"	3'42"-4'26"	2'05"-3'20"
120	3'20"-3'45"	3'30"-5'0"	2'20"-3'10"
144	3'40"-4'30"	3'15"-6'15"	1'50"-2'40"

* 4-6 Tablets were tested at each data point.

CONCLUSIONS

1. At constant relative humidity conditions (75% RH), moisture levels in the tablets are directly proportional to temperature.
2. At constant temperature the moisture levels of the tablets are directly proportional to the relative humidity of storage.
3. When stored at 50°C/Amb. RH the moisture losses of the tablets hydrated at 40°C/75% RH, 30°C/75% RH, RT/50% RH and RT/Amb. RH are comparable.
4. The moisture levels reached by the tablets when stored at RT are inversely proportional to % relative humidity conditions, i.e. 0% RH, 30% RH and 50% RH.

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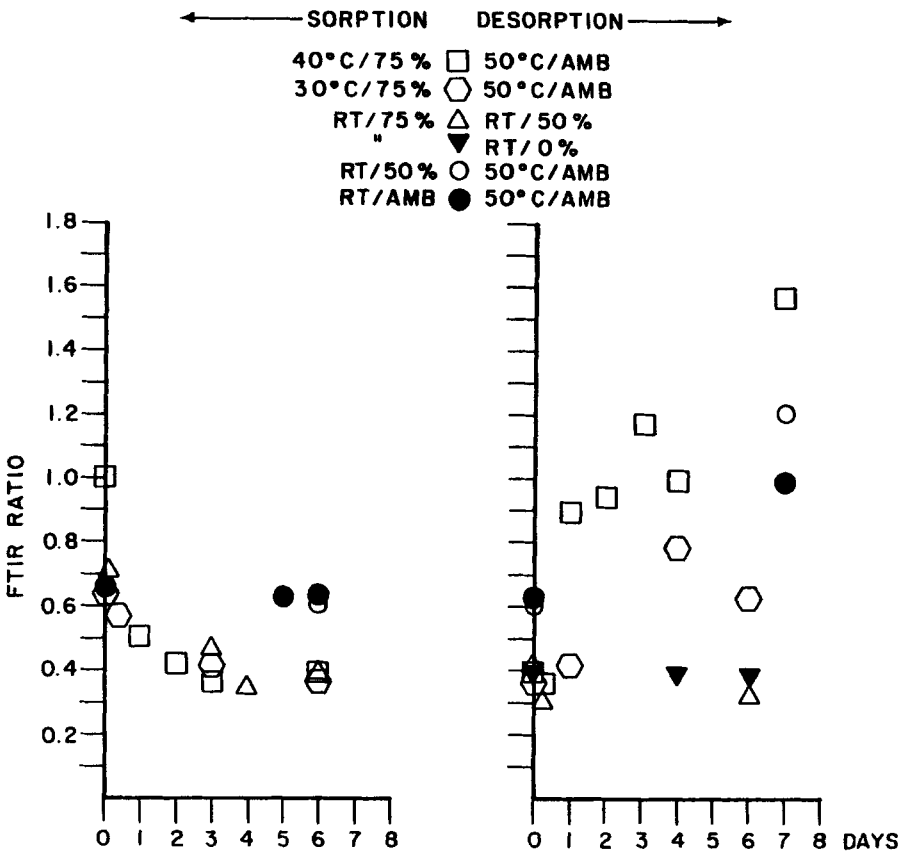

FIG. 6 FTIR RATIO VS. TIME

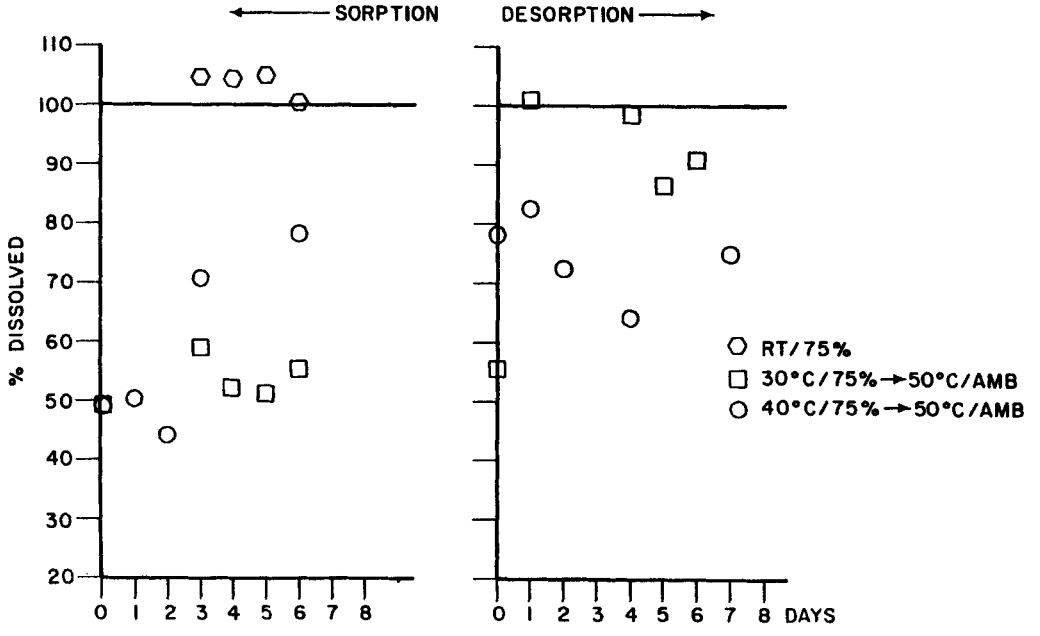

FIG. 7
% DISSOLVED VS. TIME

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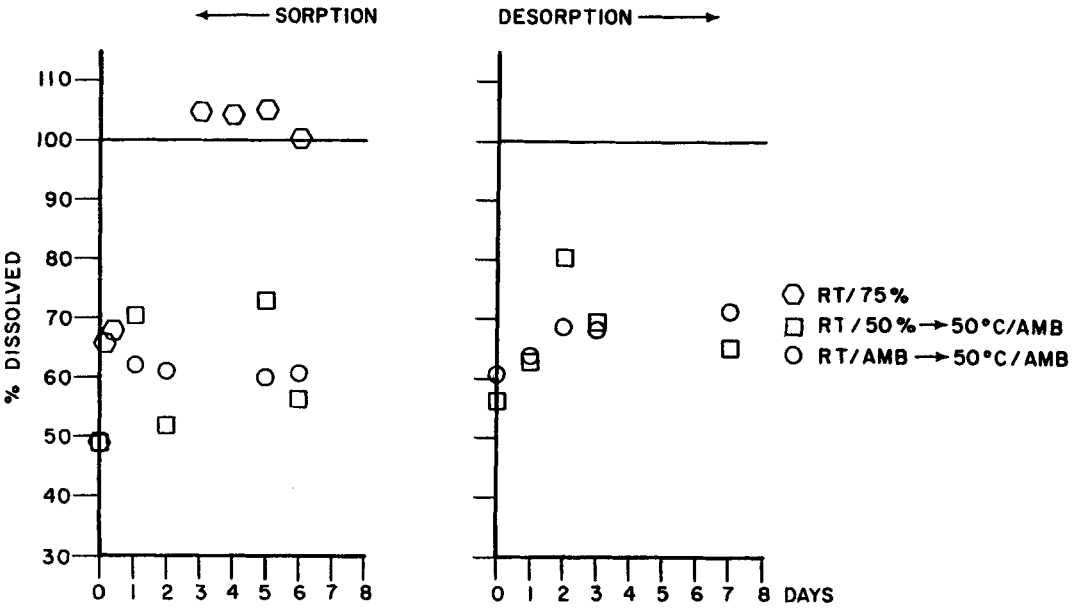

FIG. 8
% DISSOLVED VS. TIME

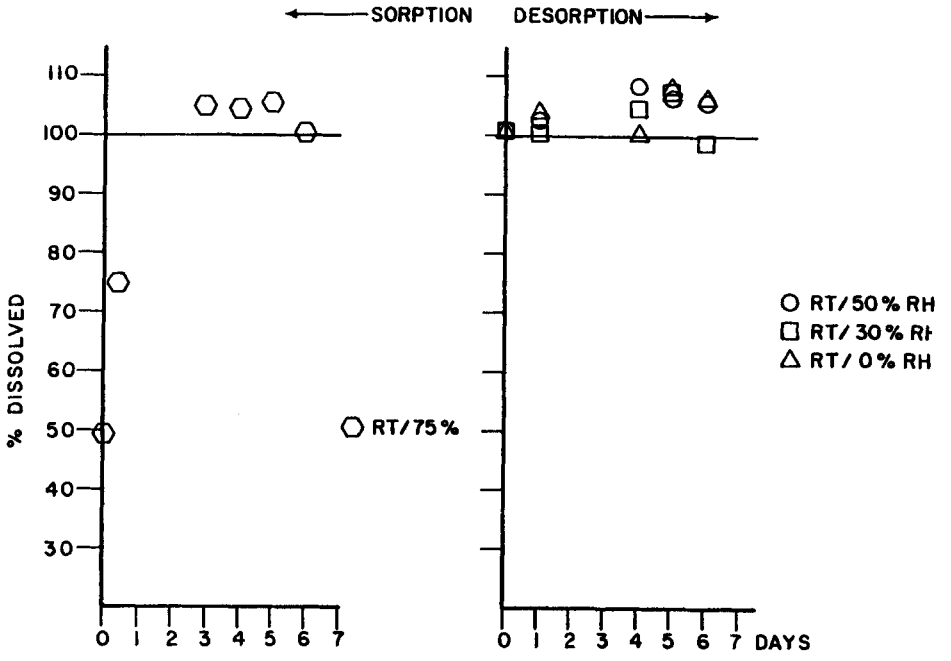

FIG. 9
% DISSOLVED VS. TIME

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5. An increase in breaking strength of the tablets, when stored at RT/75% RH and RT/50% RH, does not adversely affect the dissolution. Changes in breaking strength (increase or decrease) do not correlate with the disintegration time. Dissolution rates also do not seem to be correlatable to breaking strength, water content or FTIR ratio.
6. The most noticeable improvement in dissolution rates of tablets is attained by hydrating at RT/75% RH. Subsequent desorption at RT/30% RH or RT/0% did not adversely affect the dissolution rates in spite of an observed loss of water.
7. More recently, a study was completed evaluating interactions within the formulation.[16] This study showed that drug-excipient or excipient-excipient interactions were not responsible for the erratic dissolution characteristics observed, thus implying that the intrinsic rate of dissolution of the drug (more specifically hydrate form) limits the dissolution characteristics of the finished dosage form.

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