DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(9-11), 1827-1845 (1987)

THE EFFECT OF MOISTURE SORPTION AND DESORPTION ON FUROSEMIDE TABLET PROPERTIES

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ABSTRACT

The effect of moisture sorption and desorption on the physical characteristics of furosemide tablet was studied at moderately elevated temperatures and different relative humidity conditions over 20 days. The rate of moisture sorption and desorption was founud to follow first order kinetics within first hours. Except ambient conditions (RT/Amb.RH), moisture sorption caused a decrease in hardness values of furosemide tablets. Also the disintegration times of hydrated tablets showed a remarkeable decrease. Changes in hardness and disintegration time were dependent on the amount of water sorbed into the tablets. These significant changes occured during the first days of the test and then became invariant. The variations in hardness and disintegration times of tablets were irreversible as demonstrated by desorption experiments.

Furthermore, except storage at high temperature and high relative humidity dissolution parameters of tablets were less affected by moisture sorption and desorption.

INTRODUCTION

Recently, the relationship between moisture content and physical properties of tablets have received considerable attention(1-8). It is known that decrease in therapeutic activity without a change in chemical potency may occur as a result of physical changes in tablet forms.

On the otherhand, furosemide is widely used for the treatment of edematous states. However, in some cases, the treatment has been reported to be ineffective and this seems to have been due to low blood levels(9-11). Although various studies have been reported on formulation factors affecting drug release of furosemide tablets(12-14), the effects of aging and relative humidity have not been studied.

The present study was undertaken to investigate the effect of moisture sorption and desorption, at different temperatures and humidities, on the physical properties of furosemide tablets such as hardness, disintegration time and dissolution rate.

EXPERIMENTAL

Materials

Furosemide (Hoechst AG., Frankfurt, FRG), anhydrous lactose (Sheffield Chem. N.J., USA) magnesium

stearate (E.Merck, Darmstadt, FRG). Starch, gelatin and talc were pharmaceutical grade.

Methods

Tablets were prepared by wet-granulation technique as previously described(11). The following formulation was used; furosemide 40 mg, lactose 100 mg, corn starch 50 mg, gelatin solution (5% w/w) 30 % v/w, talc 8.1 mg, magnesium stearate 5.4 mg per tablet.

The tablets were placed in open petri dishes, first were hydrated and then dehydrated. For moisture sorption, tablets were stored at 40°/75% relative humidity (RH), 30°/75%RH, room temperature (RT)/75%RH and RT/Ambient (Amb.)RH. For desorption, the same tablets were placed at 50°/Amb.RH, RT/50%RH and RT/30%RH. Saturated salt solutions were used for obtaining the humidities.

The samples were removed at four days intervals and evaluated over 20 days for their moisture content, hardness, disintegration time and dissolution characteristics.

Moisture contents during sorption and desorption were determined as the weight gained or lost and were expressed as per cent water in the tablets. A Monsanto hardness tester (Monsanto Chem. Co. USA) was used to estimate tablet hardness. The mean of 6 tablets was given. Disintegration time of tablets was measured by the USP XXI method. Dissolution test was performed according to paddle method of USP XXI. Porosity of

furosemide tablet was calculated from the weight, volume and density of the material with an air pycnometer (Gerhard, FRG, air pycnometer).

No significant chemical decomposition was found in tablets over 20 days period.

RESULTS AND DISCUSSION

Moisture Content

Moisture sorption was found to be very rapid at high relative humedities within four days and equilibrium was also attained in this period. At RT/Amb.RH, however moisture sorption continued beyond 4 days (Table I).

It was observed that sorption followed first-order kinetics. The water sorption as a function of time can be described by the following equation(7).

$$\log\left(\frac{m_\infty - m_t}{m_\infty - m_o} \cdot 100\right) = -\frac{t}{2.303\tau}$$

Where m_o, m_t and m_∞ are the amounts of water sorbed at zero time, time t and equilibrium respectively and τ is a constant.

As it is seen in Fig. 1, the changes in water content with storage time at various sorption conditions were plotted according to above equation in semiloga-

Table 1

Moisture Pick-up Values (%) of Furosemide Tablets During Sorption

Conditions	4.days	8.days	12.days	16.days	20.days
40°/75%RH	1.53	1.06	0.76	0.86	0.78
30°/75%RH	1.05	1.46	1.46	1.25	0.89
RT/75%RH	1.71	1.61	1.56	1.61	1.96
RT/Amb.RH	0.38	0.61	0.63	0.82	0.60

rithmic manner andstraight lines were obtained. The slopes of these lines were interpreted as the water sorption rate constants.

With the comparison at these results, it was seen that the acceleration of moisture sorption at 40° was greater than ambient room temperature within the first hours. But, the total changes in moisture content were independent of temperature within the period used. These findings are in accordance with previous report(6). Tablets showed an initially rapid moisture uptake which leveled off after 4 days and continued picking up moisture.

After the equilibrium period as it was demonstrated in Table 1, moisture sorption was not related to temperature. At constant relative humidity (75%RH) at 40°, 30° and room temperature moisture pick up values of tablets changed between 0.78-1.96 per cent. Thus

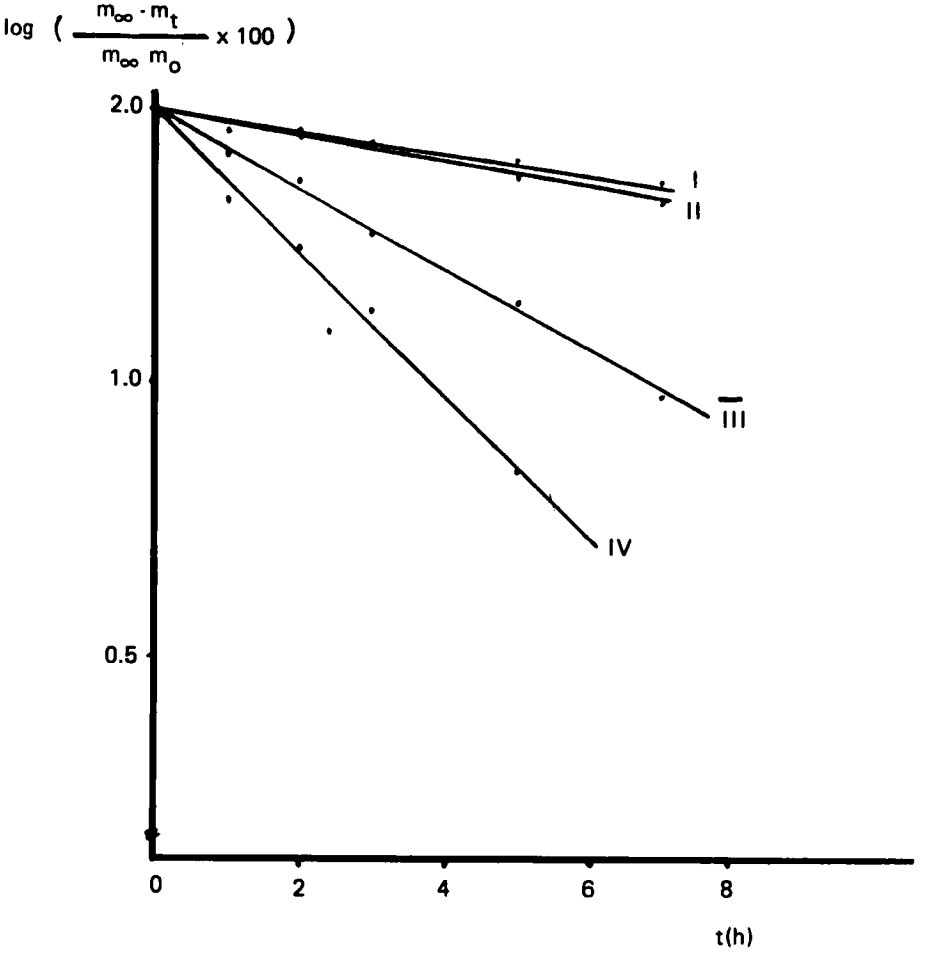

FIGURE 1

Change in Water Content as a Function of Storage Time for Furosemide Tablets
Key; RT/Amb.RH (I); RT/75%RH (II), 30°/75%RH (III); 40°/75%RH (IV)

significant changes in moisture pick up values of tablets were not observed at different temperatures as previously reported(6).

During the sorption period whatever the temperature was, the moisture pick up values were found proportional to the relative humidity. At room temperature in 75%RH and Amb.RH, the moisture pick up values were 1.96 and 0.6 per cent respectively.

The water desorption of tablets within the first hours was shown in Fig. 2. Water desorption was also followed first order kinetics. Furthermore, in all cases water desorption was faster than the moisture sorption process.

Table 2 summarized the change at water content of the tablets during desorption period. As seen in this table, moisture loss of tablets was independent on the relative humidity regardless of temperature variations. So at 50^{o}/Amb.RH significant difference between the moisture loss values of the tablets hydrated at 40^{o}/75% RH, 30^{o}/75%RH and RT/75%RH was not observed. The values were in between 2.5 - 3.0 per cent. As expected, the highest moisture loss was observed with the tablets stored at lower relative humidity (RT/30^{o}RH).

Hardness

Table 3 outlined the hardness changes of furosemide tablets during the moisture sorption period. Within 4 days, before the equilibrium, changes in hardness values were directly related to the amount of

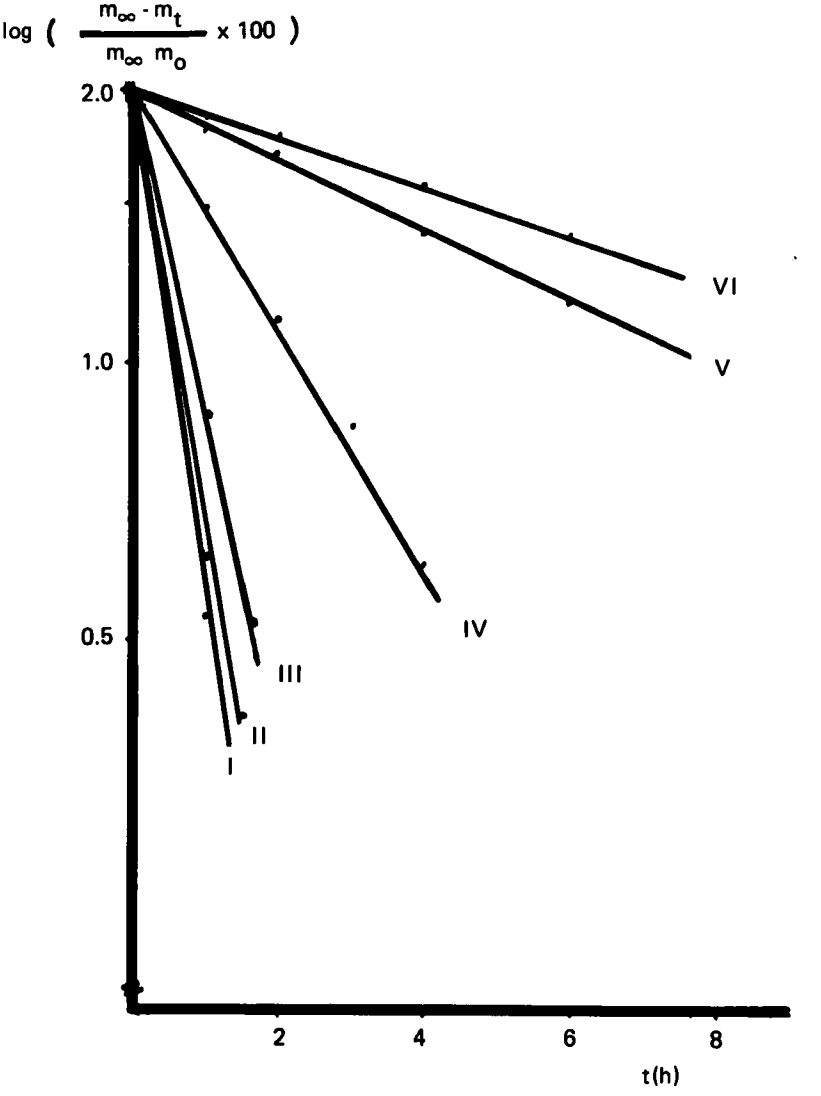

FIGURE 2

Change in Water Content as a Function of Storage Time for Tablets Stored at 50°/Amb.RH and RT/50%RH, RT/30%RH Key: RT/Amb.RH (I), RT/75%RH (II), 30°/RT/Amb.RH (III), 40°/75%RH (IV), RT/50%RH (V), RT/30%RH (VI)

Table 2

Moisture Loss Values (%) of Furosemide Tablets During Desorption (50^{o}/Amb.RH, RT/50%RH, RT/30%RH)

Conditions	4.days	8.days	12.days	16.days	20.days
**40^{o}/75%RH	2.94	2.96	2.79	2.96	3.02
**30^{o}/75%RH	2.64	2.57	2.48	2.54	2.71
**RT/75%RH	2.95	2.44	3.03	3.11	3.09
**RT/Amb.RH	1.82	1.70	1.80	1.29	1.96
*RT/50%RH	0.79	0.82	0.85	0.93	0.93
*RT/30%RH	3.44	3.58	3.70	3.64	3.72

* Previously exposed to RT/75%RH

** Previously exposed to these conditions.

Table 3

Effect of Moisture Sorption on the Hardness { Mean (kg) $\pm$ SD} of Furosemide Tablets

Conditions	0-time	4.days	8.days	12.days	16.days	20.days
40^{o}/75%RH	4.52 (0.9877)	3.70 (0.2738)	3.66 (0.2581)	3.45 (0.3708)	2.5 (0.3535)	2.40 (0.4541)
30^{o}/75%RH	4.52 (0.9877)	3.70 (0.9002)	3.37 (0.4107)	3.35 (0.1881)	2.60 (0.2236)	3.05 (0.1118)
RT/75%RH	4.52 (0.9877)	2.30 (0.4472)	2.10 (0.5477)	2.20 (0.5700)	2.20 (0.5701)	2.20 (0.4472)
RT/Amb.RH	3.95 (0.4472)	3.70 (0.2738)	3.20 (0.2738)	3.20 (0.2738)	3.65 (0.6510)	3.80 (0.4808)

sorbed water. After this period, with the exception of the ambient condition (RT/Amb.RH) a general decrease was observed in hardness values. At elevated temperatures in constant relative humidity tablet hardness significantly decreased ($p<0.001$).

As seen in Table 3, almost fifty per cent reduction in tablet hardness values was observed at 40°/75% RH, 30°/75%RH and RT/75%RH. These results are in accordance with previous papers(5-8).

On the other hand, there was no change in hardness values of the tablets stored at RT/Amb.RH. As a result, hardness of furosemide tablets was dramatically affected by water sorption.

Furthermore, as seen in Table 4, desorption at 50°/Amb.RH also affected the hardness of tablets. The decrease in hardness was between 0.25-0.60 kg at these conditions. When the tablets were stored at 50°/Amb.RH after hydration at ambient condition (RT/Amb.RH), desorption of water did not lead any detectable change in the tablet hardness. It can be said that decrease in hardness values of tablets during water sorption were not found to be reversible at water desorption.

On the otherhand, when the tablets first hydrated at RT/75%RH and then stored at RT/50%RH, their hardness values exhibited a significant increase ($p<0.001$) but dehydration at RT/30%RH showed no difference compared to the initial values (Table 4). For furosemide tablets, desorption conditions had an importance in desorption period.

Table 4

Effect of Water Desorption (50°/Amb.RH, RT/50%RH and RT/30%RH) on the Hardness {Mean (kg) ± SD} of Furosemide Tablets

Conditions	0-time	4.days	8.days	12.days	16.days	20.days
** 40°/75%RH	2.4 (0.4541)	1.4 (0.4183)	2.0 (0.3535)	1.5 (0.4472)	1.95 (0.2090)	1.8 (0.7582)
** 30°/75%RH	3.05 (0.1118)	2.5 (0.6123)	2.45 (0.3708)	2.85 (0.2236)	2.65 (0.2230)	2.75 (0.2500)
** RT/75%RH	1.41 (0.3077)	0.92 (0.2041)	0.83 (0.2041)	0.75 (0.2236)	0.70 (0.1581)	0.75 (0.1581)
** RT/Amb.RH	3.95 (0.4442)	3.75 (0.2500)	3.45 (0.2738)	3.31 (0.2393)	3.90 (0.65L9)	4.20 (0.7582)
* RT/50%RH	2.2 (0.4472)	3.16 (0.6645)	3.8 (0.7582)	3.4 (0.2236)	3.2 (0.4472)	3.35 (0.2236)
* RT/30%RH	2.2 (0.4472)	2.15 (0.2236)	2.8 (0.2738)	2.55 (0.2738)	1.6 (0.4133)	2. 5 (0.3354)

* Previously exposed to RT/75%RH
** Previously exposed to these conditions.

When the rate of hardness changes were compared at moisture sorption and desorption periods, it can be said that the rate of hardness change was faster in sorption period than in desorption.

Disintegration Time

As it is observed at Table 5, moisture sorption has an important effect on the disintegration time of

Table 5

Effect of Moisture Sorption on the Disintegration Time (seconds) of Furosemide Tablets

Conditions	0-time	4.days	8.days	12.days	16.days	20.days
40°/75%RH	115.0	34.8	23.5	26.5	20.0	20.0
30°/75%RH	108.3	46.6	40.0	30.0	29.6	25.0
RT/75%RH	108.3	55.8	35.0	33.0	35.0	39.0
RT/Amb.RH	115.0	86.8	90.0	90.0	62.4	76.0

furosemide tablets. At constant relative humidity (75% RH) as the temperature increased, disintegration time of tablets substantially decreased. At 40°/75%RH disintegration time of furosemide tablets changed from 115 s to 20 s. Disintegration time of the tablets also reduced at RH/Amb.RH.

At all conditions, water sorption resulted a decrease in the disintegration times of tablets. Our data are in accordance with previous reports(5,8). Generally the decrease in the disintegration time of tablets was very rapid during the first 4 days.

Table 6 shows the effect of moisture desorption on the disintegration time of tablets. Almost no change was found in the disintegration time of the tablets which were hydrated at 40°/75%RH, 30°/75%RH and RT/75% RH and afterwards maintained at 50°/Amb.RH for desorption. However, at the other desorption conditions, disintegration time of the tablets slightly increased.

Table 6

Effect of Water Desorption (50°/Amb.RH, RT/50%RH and RT/30%RH) on the Disintegration Time (second) of Furosemide Tablets

Conditions	0-time	4.days	8.days	12.days	16.days	20.days
** 40°/75%RH	20.0	27.0	25.0	23.0	16.0	15.0
** 30°/75%RH	55.0	76.0	75.0	72.4	50.5	83.5
** RT/75%RH	39.0	40.0	43.3	55.0	35.0	38.3
** RT/Amb.RH	108.3	109.0	95.0	94.8	96.0	130.0
* RT/50%RH	39.0	30.0	38.2	35.7	40.2	56.6
* RT/30%RH	39.0	46.9	45.0	48.0	46.2	48.4

* Previously exposed to RT/75%RH
** Previously exposed to these conditions

It was noted that in furosemide tablets, the decrease in disintegration time caused by water sorption could not be reversed by desorption of the moisture.

Dissolution Studies

Table 7 indicates the effect of moisture sorption on the dissolution parameters of furosemide tablets. Except 40°/75%RH a significant change in the dissolu-

Table 7

Effect of moisture Sorption on the Dissolution Parameters
{ $k(min^{-})$, $t_{50}(min)$} of Furosemide Tablets

Conditions	0-time		4.days		8.days		12.days		16.days		20.days	
	k	t_{50}	k	t_{50}	k	t_{50}	k	t_{50}	k	t_{50}	k	t_{50}
40°/75%RH	0.1468	4.72	0.1345	5.15	0.1514	4.57	0.1147	6.04	0.0930	7.45	0.0551	12.50
30°/75%RH	0.3011	2.30	0.2438	2.84	0.2206	3.14	0.2404	2.88	0.1913	3.62	0.1925	3.60
RT/75%RH	0.3011	2.30	0.3132	2.21	0.2731	2.53	0.1886	3.67	0.2786	2.48	0.2772	2.50
RT/Amb.RH	0.1468	4.72	0.2591	2.67	0.1337	5.18	0.2236	3.09	0.2783	2.49	0.2582	2.68

tion parameter was not observed during the water sorption. When the different thermal conditions were compared, except to 40°/75%RH no significant difference was also found. However, after the tablets have been hydrated at 40°/75%RH for 20 days, dissolution properties of tablets changed and t_{50} value altered from 4.72 min to 12.50 min.

Table 8 demonstrates the effect of moisture desorption on the dissolution characteristics of tablets. Desorption at 50°/Amb.RH of the tablets produced an adverse effect on their dissolution characteristics. Except desorption at 40°/75%RH, a slight decrease in drug release was found in the tablets thermally dehydrated. However no difference was found after desorption of the tablets at a low humidity conditions.

Porosity

Table 9 shows the effect of moisture sorption and desorption on tablet porosity. It appeared that after sorption, tablet porosity increased from 15 to 30-50 per cent. However, after desorption low porosity values were observed.

After the water sorption, the disintegration time increased with increasing porosity as expected. However, the increase in tablet porosity during moisture sorption were found to be reversible at moisture desorption. On the other hand at this period no relation between the disintegration time and porosity was seen.

Table 8

Effect of Water Desorption on the Dissolution Parameters {k(min), t_{50}(min)} of Furosemide Tablets

Conditions	0-time		4.days		8.days		12.days		16.days		20.days	
	k	t_{50}	k	t_{50}	k	t_{50}	k	t_{50}	k	t_{50}	k	t_{50}
**40°/75%RH	0.0551	12.50	0.1006	6.88	0.1104	6.20	0.1036	6.68	0.1144	6.05	0.1144	6.05
**30°/75%RH	0.1925	3.60	0.1503	4.61	0.1578	4.39	0.1480	4.68	0.1209	5.73	0.1601	4.32
**RT/75%RH	0.2786	2.48	0.2882	2.40	0.2600	2.66	0.2733	2.53	0.2905	2.38	0.2193	3.16
**RT/Amb.RH	0.4020	1.72	0.2612	2.65	0.1757	3.94	0.2579	2.68	0.2854	2.42	0.2987	2.32
*RT/50%RH	0.2751	2.51	0.2657	2.60	0.2697	2.56	0.2686	2.58	0.2615	2.65	0.2675	2.59
*RT/30%RH	0.2751	2.51	0.2366	2.92	0.2605	2.66	0.2655	2.61	0.2310	3.00	0.2295	3.01

*, ** for abbreviations see Table 3.

TABLE 9

Porosity (%) of Tablets After Moisture Sorption and Desorption

	Sorption	Desorption
Initial	15.04	-
40°/75%RH	18.53	7.17
30°/75%RH	19.55	15.81
RT/75%RH	52.90	11.00
RT/Amb.RH	34.94	20.70
RT/50%RH	-	26.60
RT/30%RH	-	19.96

As a conclusion, moisture sorption in furosemide tablets is a very rapid first-order rate process producing substantial changes in the physical properties of tablets. After equilibrium at constant temperature, the moisture levels of furosemide tablets are proportional to the relative humidity of the storage conditions. At different temperatures moisture sorption caused a remarkable decrease in hardness values of furosemide tablets. Furthermore, a complex change in hardness values was observed after moisture desorption. By water sorption the disintegration time of tablets indicated on extreme decrease. However, the changes in the physical properties of furosemide tablets were found to be irreversible when the water was removed by desorption.

These significant changes in most of the measured parameters occured during the first days of the tests, became almost invariant afterwards.

Except storage at high temperature and high relative humidity, dissolution parameters of the tablets are less affected by moisture sorption and desorption.

ACKNOWLEDGEMENTS

The autors thank İ.Sel and Fako Pharmaceutical Company for the supply of compressing facilities.

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