DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(8), 1067-1081 (1991)

THE EFFECT OF MOISTURE ON THE PHYSICAL CHARACTERISTICS OF RANITIDINE HYDROCHLORIDE TABLETS PREPARED BY DIFFERENT BINDERS AND TECHNIQUES

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ABSTRACT

The effect of moisture on the physical properties of ranitidine hydrochloride tablets prepared by direct-compression and by wet-granulation method using PVP or EC as binders was studied. Tablets adsorped moisture at 50 and 75 % RH (relative humidity) but lost moisture at 30% RH. Except storage at 75% RH, however, tablet volumes did not change significantly

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during the test period. Moisture sorption caused a decrease in strength of tablets except low humidity (30% RH). Also, the disintegration time of tablets showed a decrease at all conditions except 30% RH. Furthermore, generally dissolution profiles of tablets prepared by direct-compression and by ethyl cellulose remained unchanged. Changes in the binder type in the tablet formulations changed the water uptake properties and also the physical properties of tablets. Directly-compressed tablets were much susceptible to change caused by humidity than tablets prepared by wet-granulation.

INTRODUCTION

Ranitidine hydrochloride is widely used in the treatment of peptic ulcers and related disorders. However, current literature does not contain any reference that deal with the physical stability of rantidine tablets. Previously, the effect of moisture on the physical characteristics of ranitidine hydrochloride in powder and granule forms was reported (1).

On the other hand, earlier studies on the effect of moisture on tablet properties indicated wide response differences among the formulation and tabletting methods (2-4).

The present study was undertaken to investigate the effect of moisture sorption and desorption on the physical properties of ranitidine tablets. The changes in tablet characteristics upon aging in correlation to tabletting methods and binder type were also assessed.

Table 1

Tablet Formulations

Ingredient	Formulation (mg)		
	F-I	F-II	F-III
Ranitidine hydrochloride	150	150	150
Avicel PH 101	75	75	75
Anhydrous Lactose	25	25	25
Corn starch	48	48	48
Polivinyl pyrrolidone*	--	q.s.	--
Ethyl cellulose**	--	--	q.s.
Magnesium stearate:Talc (1:9)	2.9	16.8	16.8

* Alcoholic solution of PVP (%5)
** Alcoholic solution of EC (%5)

EXPERIMENTAL

Materials

Ranitidine hydrochloride (Deva, Turkey) anhydrous lactose (Sheffield Chem. USA), Avicel PH101 (FMC, USA), polyvinylpyrrolidone (PVP K-30, BASF, FRG), ethyl cellulose (EC) (Prodotti-fromi, Italy).

Methods

Tablets were prepared by direct compression and wet-granulation methods. Formulations were given in Table 1.

For wet-granulation, after mixing the powders, the granulating solution was added while mixing and ovendried. The dry granulation was screened and mixed with magnesium stearate-talc mixtures.

Tablets were compressed on a rotary tablet machine (Manesty D-33, UK) using 10.4 mm diameter flat faced punches.

Tablets were stored on open petri dishes at 30, 50, 75 and 90% RH chambers and also RT/Ambient (Amb) RH.

The samples were removed at regular intervals and evaluated over 120 days for their moisture content, diameter and thickness, crushing strength, disintegration time and dissolution characteristics.

Moisture contents during the test were determined as the weight gained and lost and were expressed as per cent water in the tablets. The crushing strength of tablets were determined (Erweka TBH-28, FRG) and the mean value of 6 tablets were reported. Disintegration time of tablets was measured by the USP XXI method. Dissolution test was performed according to basket method of USP XXI. The drug content was determined by spectrophotometrically (Varian Techtron 634).

RESULTS and DISCUSSION

Moisture Content

Moisture adsorption levels of ranitidine hydrochloride tablets were given in Table 2. At 90% RH,

Table 2

Moisture Levels (%)* of Ranitidine hydrochloride Tablets after Storage different Relative Humidities

Time (days)	Formulation											
	F-I				F-II				F-III			
	30%	50%	75%	90%	30%	50%	75%	90%	30%	50%	75%	90%
1	-0.196	0.112	0.950	10.52	-0.027	0.585	2.070	9.45	-0.227	0.322	1.542	5.61
2	-0.229	0.159	1.284	18.83	-0.040	0.694	2.460	17.89	-0.226	0.392	1.907	12.00
5	-0.270	0.189	1.275	-	-0.018	0.703	3.070	-	-0.283	0.412	2.306	-
8	-0.178	0.181	1.237	-	-0.069	0.686	3.690	-	-0.247	0.402	2.248	-
14	-0.218	0.163	1.223	-	-0.105	0.641	3.930	-	-0.277	0.372	2.290	-
30	-0.221	0.166	1.299	-	-0.142	0.649	4.450	-	-0.280	0.375	2.318	-
45	-0.224	0.164	1.304	-	-0.151	0.657	4.440	-	-0.299	0.361	2.346	-
60	-0.230	0.169	1.309	-	-0.148	0.648	4.450	-	-0.305	0.339	2.341	-
90	-0.225	0.167	1.301	-	-0.144	0.651	4.450	-	-0.310	0.347	2.345	-
120	-0.228	0.166	1.296	-	-0.146	0.656	4.441	-	-0.312	0.350	2.350	-

* The mean of 2 values.

during the first 24 hrs, all the tablets rapidly water adsorbed and softened. As seen in the table, at 50 and 75% RH, tablets prepared by direct compression adsorbed less water than tablets made by wet-granulation. In contrast, all tablets lost the water at 30% RH, however the less water desorption was observed in the tablets prepared with PVP. In general, except storage at 90% RH, direct-compressed tablets showed the lowest water sorption. Among the studied binders, tablets made with

PVP adsorbed more moisture than those made with EC. This effect was attributed to the hygroscopic nature of PVP.

The amount of moisture adsorbed depended upon the type of binder used in ranitidine tablets. This data confirms the earlier report (5).

Tablet Volume

Except exposure to 75% RH, tablet volumes did not alter during the storage period (Table 3). At 75% RH, an extensive volume expansion was observed at all formulations. In particular, tablets prepared with direct compression indicated the highest increase in volume as seen in the table. On the other hand the directcompressed tablets indicated the lowest moisture uptake but the highest volume increase. This may be due to the effect of binders in wet-granulation methods.

Crushing Strength

As seen in Fig.1, the crushing strength of tablets decreased when they were stored at 75% RH. However, the extent of the decrease was higher for wet-granulated tablets in accordance with their higher moisture uptake. It has been shown that free moisture exists in solids in 2 states; a "pendular" state where liquid bridges occur between indivindual particles and a "capillary" state where all the pores of the solid are filled with liquid. The significant decrease in strength could be explained by presence of capillary water, though which interparticulate bonds are removed by dissolution (6). Therefore, reduction in strength of ranitidine hydrochloride tablets can be attributed to

Table 3

Effect of Moisture on Tablet Volumes (mm^3) (n=10)

Time (days)	% RH								
	F-I			F-II			F-III		
	30	50	75	30	50	75	30	50	75
0	332.7	330.4	343.1	319.5	319.7	328.0	315.7	316.3	317.7
1	329.8	329.5	342.0	319.5	321.5	334.7	316.9	317.7	323.0
2	331.3	330.4	356.7	319.5	323.3	334.7	316.9	317.1	324.5
5	331.9	333.6	385.7	321.5	326.2	341.3	319.2	320.7	332.6
8	330.6	332.7	380.8	319.5	322.6	339.2	316.3	317.1	329.1
14	332.1	332.1	399.0	320.1	322.6	342.2	317.1	318.0	332.0
30	329.8	331.9	400.3	320.3	321.2	349.0	315.7	318.0	333.5
45	330.6	332.7	402.1	320.9	322.0	358.1	315.7	319.5	337.8
60	332.1	332.1	408.3	319.5	323.5	365.2	316.5	318.6	339.9
90	331.3	331.3	409.4	318.8	321.8	349.2	315.9	317.1	336.5
120	332.1	332.1	406.2	320.3	322.0	355.9	315.9	317.7	335.6

the capillary effect of moisture. Furthermore, the decrease in strength may also be due to the significant increase in moisture content of the compacts which would separate the crystals from each other and thereby minimize the effect of the inherent forces and cohesion as noted by Lordi and Shiromani (7).

Table 4 summarized the crushing strength of tablets stored at 50% RH. At this condition, a

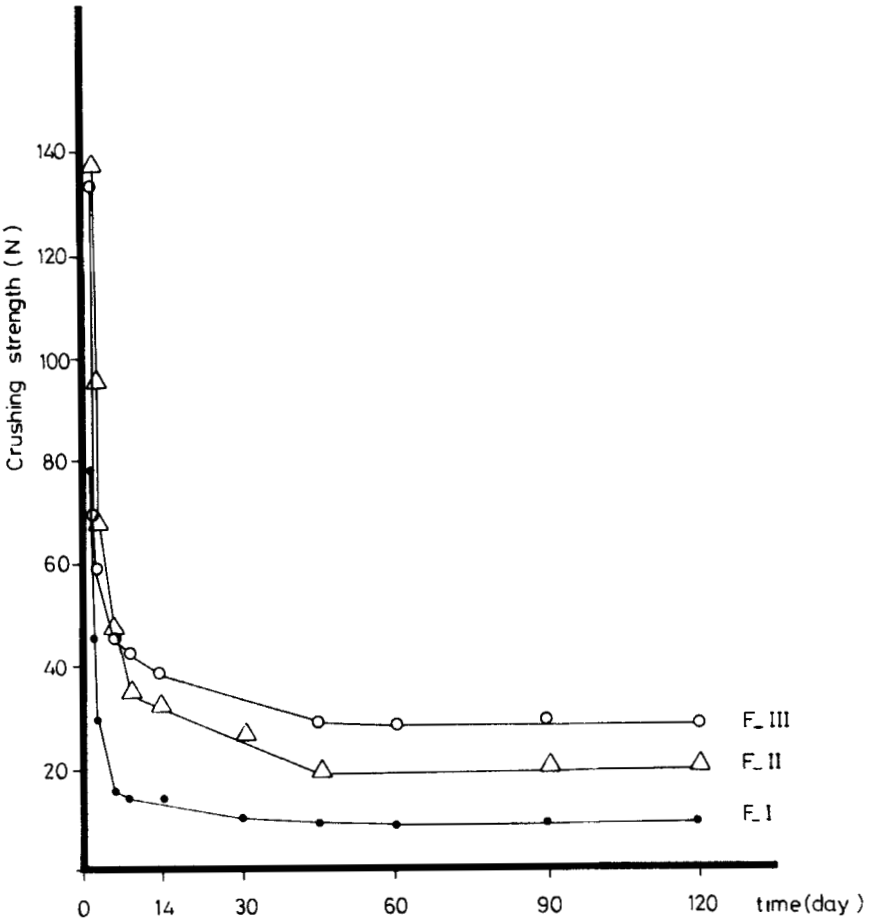

Figure 1

Changes in Crushing Strength of Ranitidine hydrochloride Tablets at 75 % RH
Key: F-I (•), F-II (▵); F-III (0)

considerable reduction was observed with direct-compressed tablet whereas a slight decrease was seen in tablets made with EC. However the strength of tablets made with PVP did not change.

Except direct-compressed tablets, there is no significant change in tablet strength after storage at 30% RH (Table 4).

Table 4

Effect of Moisture on the Crushing Stength (N ± SD) of Tablets

Time (days)	% RH								
	F-I			F-II			F-III		
	30	50	Amb	30	50	Amb	30	50	Amb
0	91.16 (6.958)	91.16 (6.958)	91.16 (6.958)	138.33 (7.637)	138.33 (7.637)	138.33 (7.637)	134.16 (9.242)	134.16 (8.465)	134.16 (9.242)
1	79.75 (9.504)	74.83 (9.827)	-	127.25 (4.072)	118.87 (5.807)	-	116.25 (7.500)	112.00 (3.559)	-
2	72.50 (8.779)	62.25 (7.071)	-	138.66 (3.535)	115.62 (3.145)	-	118.00 (9.848)	106.62 (5.121)	-
8	71.75 (2.516)	85.70 (11.750)	-	137.83 (8.838)	128.70 (10.986)	-	131.50 (4.272)	113.20 (2.252)	-
14	82.00 (5.338)	81.75 (2.901)	-	135.87 (5.452)	123.25 (7.836)	-	130.25 (1.842)	116.12 (6.383)	-
30	86.00 (6.940)	71.90 (6.618)	65.30 (3.013)	137.80 (4.500)	124.50 (7.234)	125.70 (5.345)	139.00 (7.675)	118.10 (3.629)	115.50 (3.162)
45	84.45 (4.140)	71.33 (1.414)	-	122.87 (6.450)	129.75 (10.214)	-	125.25 (3.426)	103.75 (2.986)	-
60	89.75 (9.899)	69.87 (10.150)	40.00 (7.549)	130.60 (8.655)	143.20 (7.000)	150.00 (0.547)	139.90 (7.127)	118.00 (6.041)	136.70 (3.774)
90	84.50 (7.751)	57.87 (4.949)	35.40 (5.338)	136.70 (4.893)	135.90 (10.655)	126.00 (6.574)	133.60 (8.294)	117.00 (8.796)	105.80 (1.181)
120	82.83* (3.013)	55.97** (3.618)	15.40* (4.098)	135.54* (6.641)	138.10* (3.865)	61.80** (3.053)	134.42* (3.824)	118.75* (6.694)	57.80** (4.220)

* $p<0.001$
** $p>0.001$

Moreover, at RT/Amb RH, the extent of reduction in strength of tablets was the same for all the formulations. Generally, direct-compressed tablets were much susceptible to moisture.

Disintegration Time

Table 5 represents the disintegration time of tablets exposed to 75% RH. At this condition, the most remarkable decrease was found with direct-compressed tablets but no change was observed in tablets prepared with EC. The same results were also obtained at RT/Amb RH (Table 5).

At 50% RH, moisture sorption shortened the disintegration time of tablets prepared by direct-compression and by PVP, but no change was seen in tablets made by EC. The extent of decrease in disintegration time of tablets prepared with PVP was less than direct compressed formulations. These changes were attributed to the dissolution of solid bridges within the tablet structure.

In general, moisture sorption during the storage did not affect the disintegration time of tablets prepared by EC. When compared two binders, tablets granulated with PVP were much susceptible to change caused by moisture than tablets granulated with EC. This data indicated in accordance with earlier report (3).

When exposing to low humidity (30% RH), no noticeable change depending on moisture loss of tablets was found (Table 5).

Table 5

Effect of Moisture on the Disintegration time (min ± SD) of Tablets (n=5)

Time (days)	% RH											
	F-I				F-II				F-III			
	30	50	75	Amb	30	50	75	Amb	30	50	75	Amb
0	5.38 (0.175)	5.38 (0.175)	5.38 (0.175)	5.38 (0.175)	13.26 (0.950)	13.93 (0.404)	13.26 (0.950)	13.26 (0.950)	12.26 (0.205)	12.21 (0.288)	12.13 (0.205)	12.13 (0.205)
1	4.45 (0.975)	4.03 (0.879)	2.70* (0.638)	-	12.33 (0.775)	13.40 (0.983)	11.20 (0.867)	-	12.26 (1.155)	13.91 (1.282)	11.76 (0.375)	-
2	5.36 (0.758)	3.57 (0.629)	3.36 (0.485)	-	12.61 (0.573)	12.25 (0.050)	11.65 (0.996)	-	13.07 (0.332)	13.78 (1.320)	11.80 (0.435)	-
8	4.53 (0.680)	4.15 (1.409)	3.06 (1.001)	-	12.46 (0.144)	13.02 (0.390)	11.47 (0.153)	-	12.64 (0.314)	11.98 (0.815)	11.31 (0.076)	-
14	4.99 (0.820)	3.96 (0.401)	2.50 (1.169)	-	12.83 (0.464)	13.48 (0.455)	11.65 (0.482)	-	12.96 (0.693)	13.13 (0.884)	11.20 (0.150)	-
30	5.40 (0.744)	4.70 (0.648)	1.95 (0.444)	3.50 (0.410)	12.65 (1.284)	12.40 (0.431)	11.11 (0.390)	12.44 (0.825)	12.41 (0.768)	12.33 (0.426)	12.14 (0.193)	14.07 (0.444)
45	5.02 (0.372)	3.95 (0.261)	0.61 (0.115)	-	13.06 (0.684)	12.68 (0.640)	11.26 (0.691)	-	11.87 (0.261)	12.74 (1.236)	11.96 (1.652)	-
60	5.30 (0.641)	4.67 (1.010)	0.53 (0.327)	3.85 (0.900)	12.75 (0.971)	12.78 (0.794)	11.08 (0.849)	12.58 (0.660)	12.35 (0.649)	11.82 (0.823)	11.66 (0.777)	14.98 (0.653)
90	4.33 (0.483)	3.66 (0.978)	0.61 (0.369)	3.88 (0.595)	12.25 (0.453)	12.95 (1.162)	10.79 (0.782)	12.33 (0.545)	11.53 (1.420)	13.70 (0.512)	13.29 (0.308)	11.78 (0.707)
120	5.18* (0.270)	3.06* (0.679)	1.63** (0.652)	2.31* (0.718)	12.64* (1.044)	12.11* (1.775)	11.37* (1.090)	11.81* (1.121)	12.07* (1.200)	12.42* (0.920)	15.32* (0.780)	11.88* (1.118)

* $p<0.001$
** $p>0.001$

Table 6

Effect of Moisture on the Dissolution Parameters [k(min⁻), t_{50}(min)] of Ranitidine hydrochloride tablets

[% RH]	Time (days)	Formulations								
		F-I			F-II			F-III		
		k	k*	t_{50}	k	r	t_{50}	k	r	t_{50}
-	0	0.0483	-0.962	14.34	0.0552	-0.988	12.55	0.0414	-0.998	16.73
75	90	0.0299	-0.887	23.17	0.0667	-0.980	10.38	0.0483	-0.972	14.34
	120	0.0529	-0.924	13.10	0.0391	-0.980	17.72	0.0854	-0.970	8.11
50	90	0.0345	-0.893	20.08	0.0575	-0.985	12.05	0.0483	-0.930	14.34
	120	0.0460	-0.907	15.06	0.0414	-0.980	16.73	0.0437	-0.940	15.85
30	90	0.0598	-0.983	11.58	0.0368	-0.922	18.83	0.0414	-0.904	16.73
	120	0.0414	-0.861	16.73	0.0299	-0.995	23.18	0.0437	-0.992	15.85
Amb RH	90	0.0391	-0.909	17.72	0.0483	-0.983	14.34	0.0460	-0.951	15.06
	120	0.0437	-0.916	15.58	0.0322	-0.991	21.52	0.0529	-0.972	13.10

* Correlation Coefficients

Dissolution Studies

Table 6 indicates the effect of moisture on the dissolution parameters of ranitidine hydrochloride tablets. After 120 days, a remarkable decrease was observed in the dissolution rate of drug from tablets made by PVP. This may be due to the high binding effect of PVP. On the other hand, except exposed to 75% RH drug release from tablets prepared with EC did not

Table 7

Drug Content (%) of Ranitidine hydrochloride Tablets during the Storage (n=3)

Time (days)	% RH											
	F-I				F-II				F-III			
	30	50	75	Amb	30	50	75	Amb	30	50	75	Amb
0	97.96* (2.13)	97.96 (2.13)	97.96 (2.13)	97.96 (2.13)	95.54 (1.07)	95.54 (1.07)	95.54 (1.07)	95.54 (1.07)	95.21 (7.23)	95.21 (7.23)	95.21 (7.23)	95.21 (7.23)
30	95.57 (4.86)	95.22 (5.69)	94.32 (2.53)	96.00 (4.38)	97.01 (6.76)	97.56 (1.47)	94.55 (0.57)	94.36 (5.05)	96.54 (3.85)	95.59 (3.64)	94.64 (2.26)	92.76 (6.97)
60	95.36 (1.13)	96.40 (5.20)	93.58 (4.40)	91.13 (7.55)	93.38 (2.88)	94.42 (2.74)	95.73 (1.65)	96.34 (3.56)	94.04 (3.95)	92.59 (1.80)	93.09 (1.31)	106.30 (0.84)
90	96.41 (2.67)	93.71 (3.88)	95.42 (3.79)	93.48 (5.51)	94.33 (5.70)	93.56 (4.28)	93.00 (0.26)	93.48 (0.57)	95.76 (5.55)	93.40 (3.91)	94.37 (1.37)	95.11 (6.43)
120	93.44 (3.69)	96.71 (1.74)	96.34 (1.73)	92.16 (3.21)	96.67 (5.20)	95.44 (2.32)	93.41 (3.64)	93.24 (2.21)	97.93 (2.72)	96.43 (2.75)	94.66 (1.13)	94.18 (2.53)

* ± SD was given in the brankets.

alter. However, at 75% RH, drug release increased within the storage period.

Furthermore, as seen in Table 7 ranitidine hydrochloride is reasonably stable at the tested conditions.

As a conclusion, tabletting technique and binder type have an importance on the physical stability of ranitidine hydrochloride tablets.

ACKNOWLEDGEMENTS

The authors wish to thank F.Aktan and M.Nevzat Pharm.Comp. for the supply of compressing facilities.

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