DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(9-11), 1933-1946 (1987)

AGING OF TABLETS PREPARED BY DIRECT COMPRESSION OF BASES WITH DIFFERENT MOISTURE CONTENT

A.M. Molokhia, H.I. Al-Shora and A.A. Hammad,
College of Pharmacy, King Saud University,
Riyadh, Saudi Arabia.

ABSTRACT

Properties of aged tablets prepared by the wet granulation method were found to be affected by the moisture content of the granules. In this study, the storage-induced changes in hardness, disintegration and drug release were evaluated for tablets made by direct compression of three different bases with different initial moisture content. Tablets with high initial moisture content were found to increase in hardness upon storage. The magnititude of such increase is dependant upon the physical properties of the base and the absolute moisture content. The increase in hardness may increase the disintegration time and decrease drug release. Tablets with low initial moisture content were minimally affected by storage. The gain of moisture by some of these tablets led to enhancement in disintegration and drug release. Among the tablets studied lactose based tablets with different initial moisture content were found to be the most resistant to changes upon storage.

INTRODUCTION

Previous studies on the effect of aging on tablet hardness, disintegration and drug release[1-10] indicated wide response differences among different formulations and tabletting methods. The changes in tablet behavior upon aging in correlation to granule moisture content were assessed[7-10] in tablets made by wet granulation method. Tablets made from granules with high initial moisture content, upon storage, showed increase in hardness induced by partial moisture loss[7]. While tablets made from granules with low moisture content gained moisture from high humidity exposures and increased in hardness as a consequence of the partial loss of the gained moisture, after storage[8]. Such increase in hardness which was not related to initial tablet hardness showed minimum effect on tablet disintegration with no appreciable effect on the in-vitro dissolution of the drug[7,8]. The binder type and concentration as well as the physical properties of the drug and the base were shown to have an effect on the magnitude of hardness increase[9,10].

In this study the evaluation of the effect of moisture content on aging of tablets is extended for tablets made from powdered bases rather than wet granules. Tablets made by direct compression of three different bases with different initial moisture content were stored at 40°C/90% relative humidity (R.H.). The changes in hardness, disintegration and drug release were followed for up to ten weeks.

MATERIALS

Pure grades of lactose, talc, benzoic acid (E. Merck, Darmstadt, W. Germany); cellulose, magnesium stearate (BDH Chemicals Ltd., Poole, England); mannitol

(Hopkins and Williams Ltd., Chadwell Health, Essex, Engalnd) and starch (Fluka AG, Buchs SG, Switzerland) were used as received. All other chemicals were of analytical grade.

METHODS

Table 1 shows the three different tablet formulations studied. The powder blend of each formulation was mixed in a tumbling mixer (Erweka G.m.b.H., UG. Frankfurt, W. Germany) for twenty minutes then divided into three portions. The moisture content of each portion was varied by placing the powders in three desiccators with relative humidity adjusted by salt solutions at 12.5, 68 and 99%. The desiccators were kept in a 30°C oven. After three days, the powders were removed and the moisture content of each was determined either by the Karl Fischer Reagent, USP or the loss on drying method, USP. Immediately before compression, the mag-

TABLE 1

Formulations Used In This Study

Formulation / Ingredients(%)	A	B	C
Lactose	66.5	----	----
Mannitol	----	66.5	----
Cellulose	----	----	66.5
Starch	4	4	4
Talc	2	2	2
Magnesium stearate*	3.5	3.5	3.5
Benzoic acid	24	24	24

* Mixed immediately before compression.

nesium stearate was mixed with each formulation in the tumbling mixer for five minutes. The tablets were then compressed by means of a single punch machine (Erweka G.m.b.H., Type EKD, Frankfurt, W. Germany). Tablet weight in the range of 503-527 mg was obtained. Because of the difficulties met in compressing tablets with high moisture content, a zero-time common hardness value was impossible to obtain for all formulations. Tablets were then packed in groups in paper bags and stored in a humidity chamber maintained at 40°C/90% R.H.

In addition to the zero-time sample, individual packs were taken at different time intervals for ten weeks and examined for hardness (6 tablets), disintegration (4 tablets) and drug release (3 tablets). Hardness was measured in Kilograms in a hardness tester (Erweka G.m.b.H., Type TB 24, Frankfurt, W. Germany). Disintegration time was measured (Erweka G.m.b.H., Type ZT 4, W. Germany) according to the USP method in a medium made of phosphate buffer .05M, pH 6.0. Drug release was determined by measuring the amount of benzoic acid dissolved as a function of time using a USP dissolution apparatus (Erweka G.m.b.H., Type DT, Frankfurt, W. Germany) and the same medium used in the disintegration experiements. Samples were withdrawn from the dissolution medium every ten minutes for one hour, filtered through a 0.45 μm pore size filter and assayed for dissolved benzoic acid by measuring UV absorption at 222 nm.

RESULTS AND DISCUSSION

Table 2 presents the results of the moisture content of each base as determined immediately before compression. The Karl Fischer method was used for the cellulose and mannitol based tablets. However, because

TABLE 2

Moisture Content Of Different Formulations

Formulation	Humidity exposure % R.H.	Moisture content MC %
A	12.5	0.15
	68	0.97
	99	3.21
B	12.5	0.23
	68	1.69
	99	6.85
C	12.5	0.99
	68	2.91
	99	13.14

of the presence of one molecule of water of crystallization in the lactose molecule, the loss on drying method was used for the lactose based tablets. Previous measurements[8] have shown good correlation between these two methods.

Figure 1 gives the plots of the lactose tablet hardness versus the number of weeks of storage in the humidity chamber. As indicated in the experimental section, the differences in hardness at zero time are not related to moisture gain or loss. We assessed the effect of aging on hardness by following the pattern of changes rather than following the absolute hardness figures. As can be seen, a gradual increase in hardness was observed for the high moisture containing tablets with minimum or no change in the low moisture containing

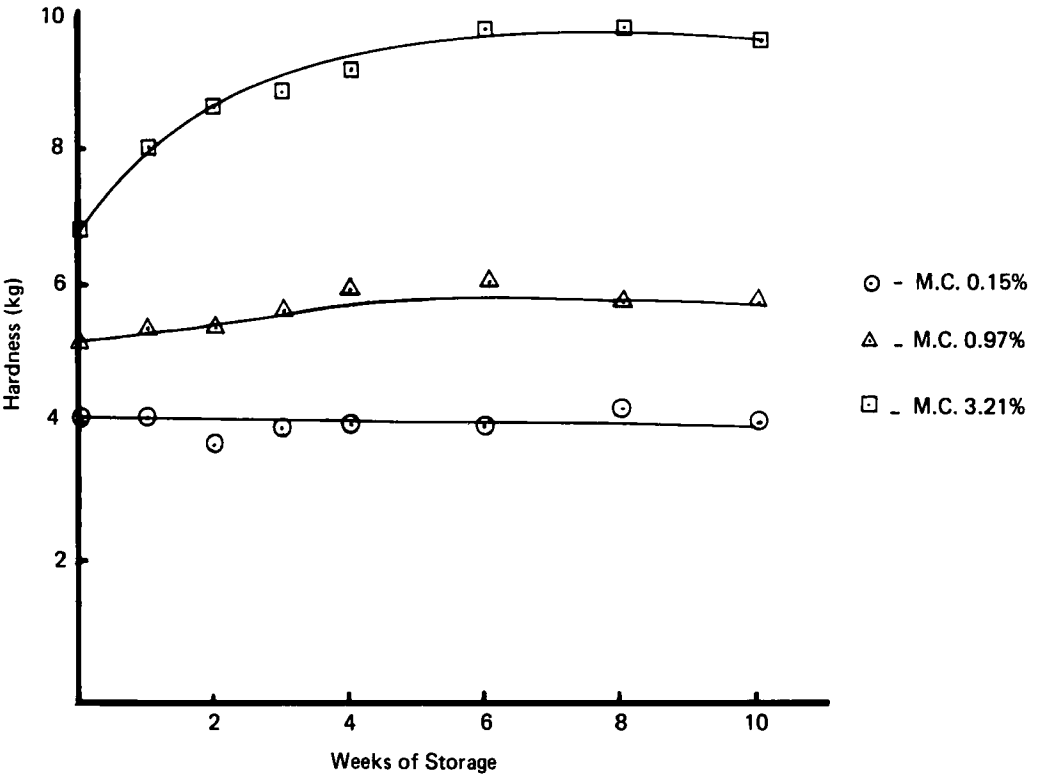

FIGURE 1

Effect Of Aging On The Hardness Of Lactose Based Tablets.

ones. A maximum value of hardness was reached after about four weeks. The increase in tablet hardness may be explained by the partial moisture loss accompanied by deposition of soluble excipients in spaces between particles resulting in strengthening of the interparticulate bonds. This effect of aging on hardness of lactose based tablets did not correlate with the changes observed in disintegration time (Fig. 2) or in drug release (Fig. 3-5). Figure 2 shows that while the disintegration of the low moisture containing tablets has enhanced upon storage, the high moisture containing

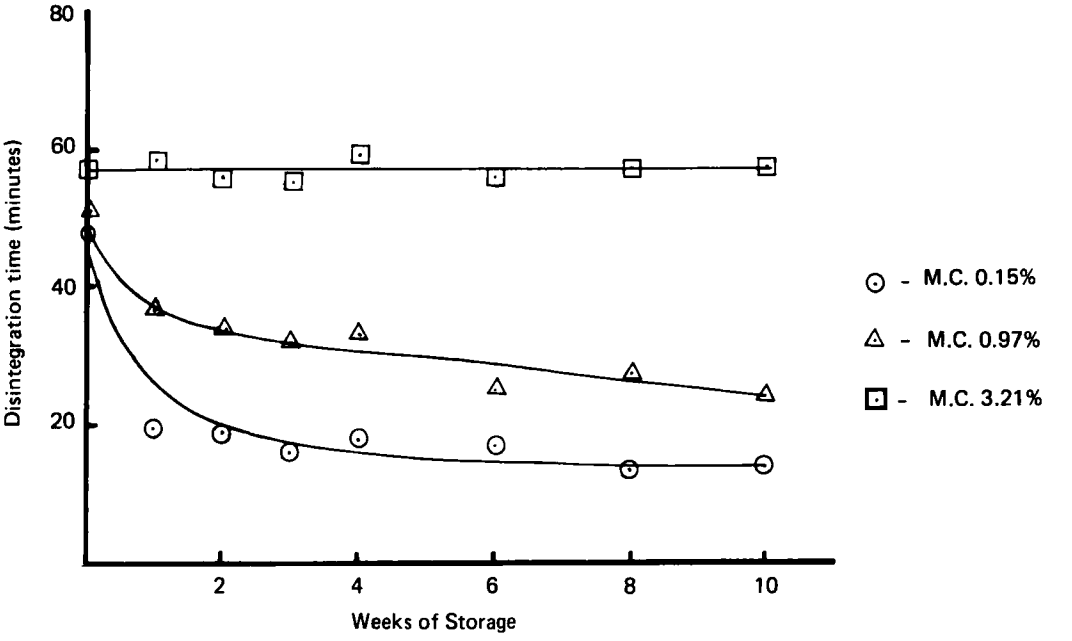

FIGURE 2

Effect Of Aging On The Disintegration Time Of Lactose Based Tablets.

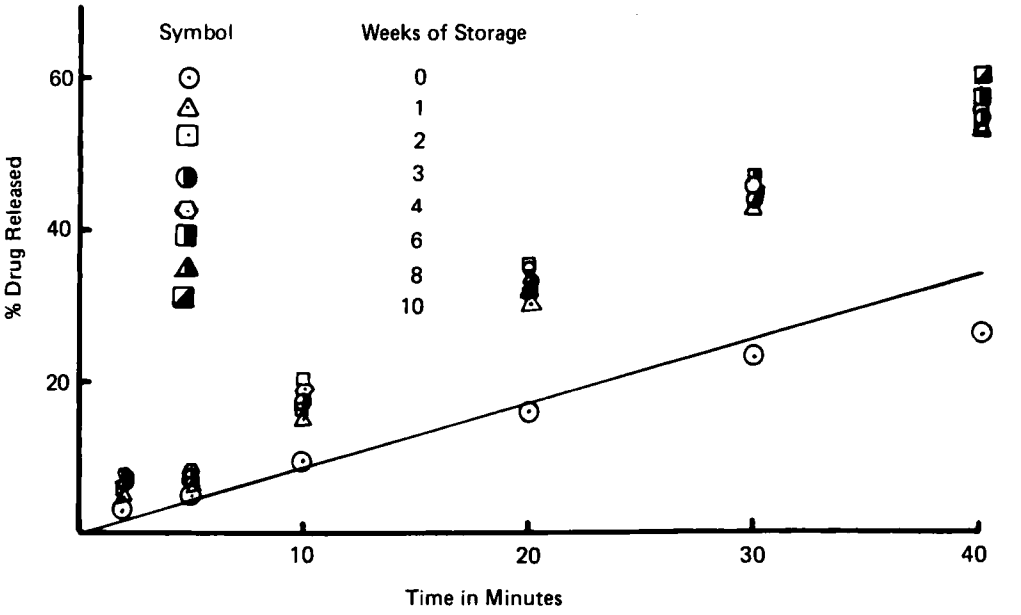

FIGURE 3

Drug Release From Stored Lactose Based Tablets-M.C. 0.15%.

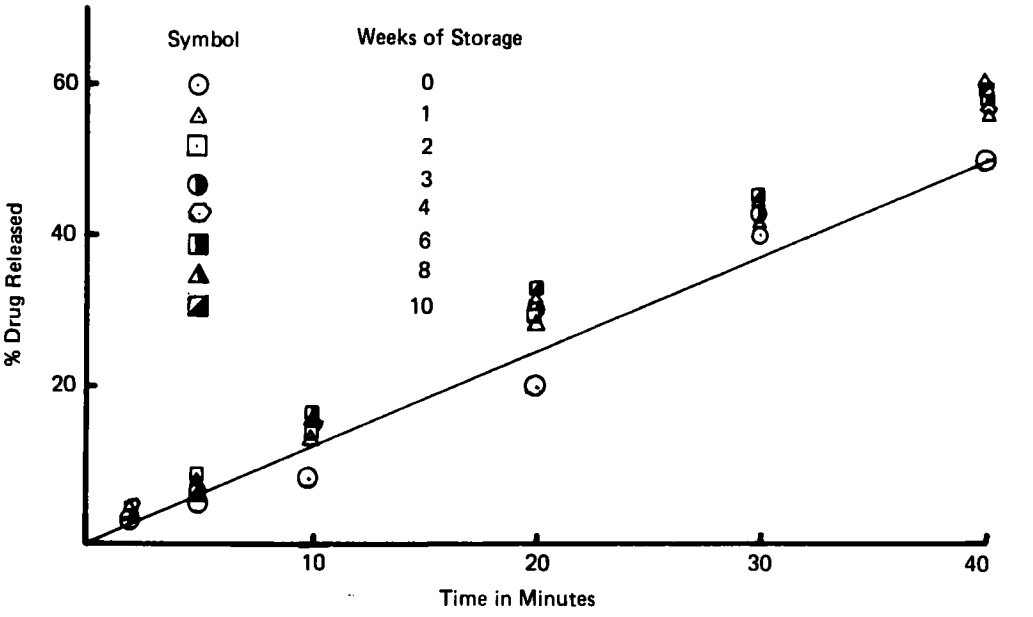

FIGURE 4

Drug Release From Stored Lactose Based Tablets-M.C. 0.97%.

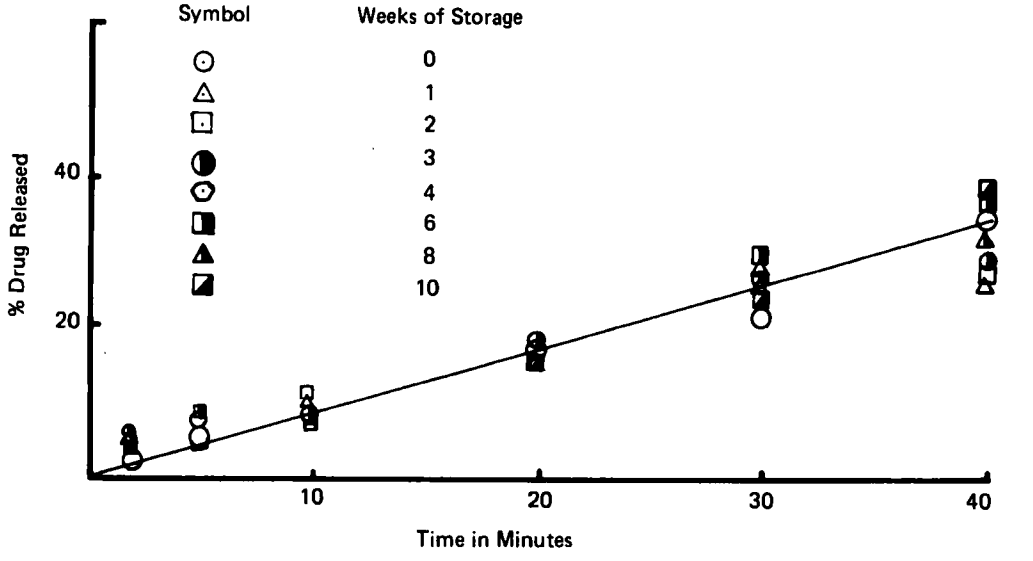

FIGURE 5

Drug Release From Stored Lactose Based Tablets-M.C. 3.21%.

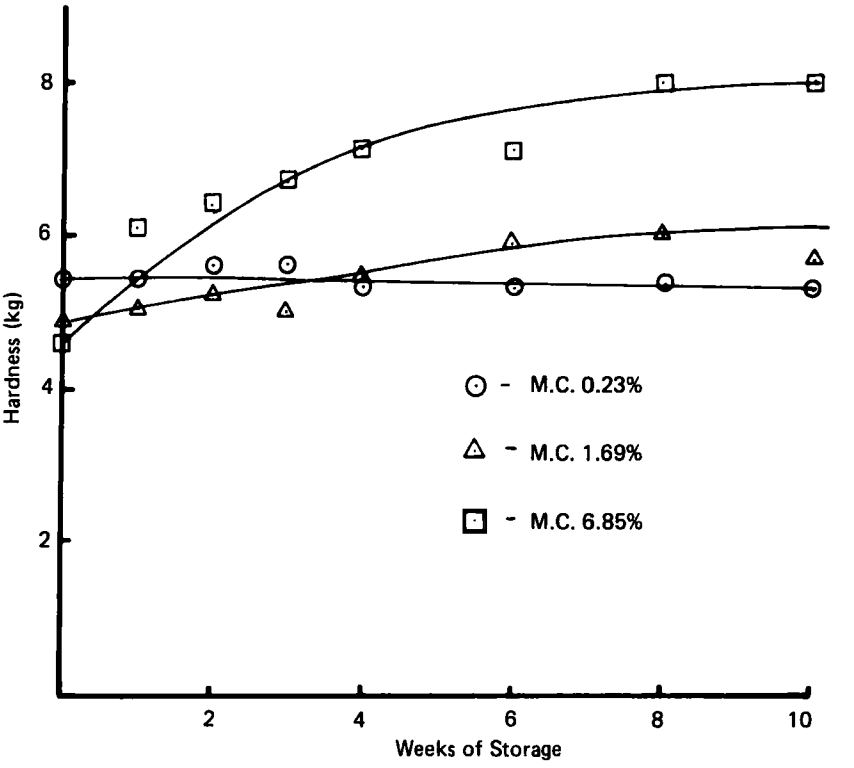

FIGURE 6

Effect Of Aging On Hardness Of Mannitol Based Tablets.

ones were not affected. This is probably due to moisture absorption expected to take place. Measurement of tablet weight after storage indicated slight increase in weight for tablets with low initial moisture content. Figures 3-5 are representative diagrams for the drug release results obtained in this study. Figures 3 and 4 show enhancement in drug release upon storage of tablets with low moisture content. This enhancement effect took place within the first week of storage and the drug release rate remained almost constant after that. This change in behavior which is in agreement with that ob-

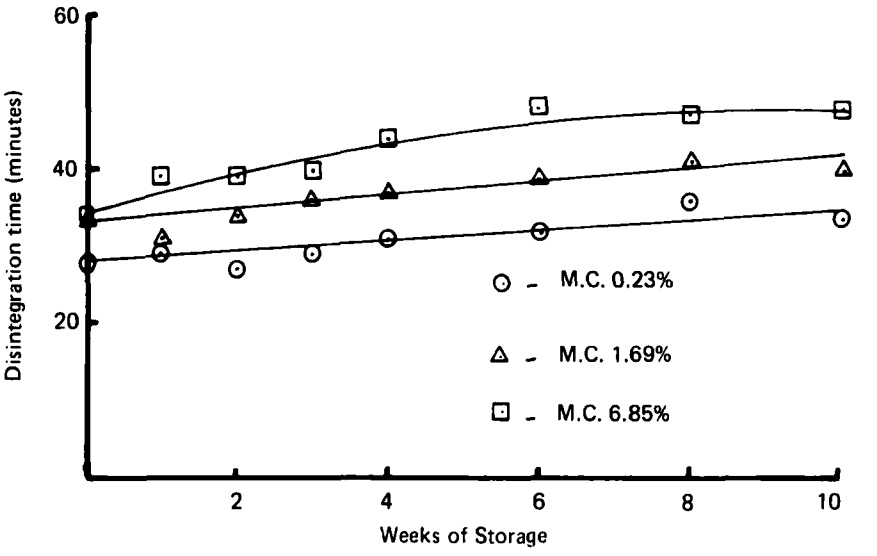

FIGURE 7

Effect Of Aging On Disintegration Of Mannitol Based Tablets.

served for disintegration is again probably due to moisture absorption. Figure 5 shows clustering of the amounts released after storage for different time intervals with no clear trend for change in the dissolution pattern.

Figure 6 shows the effect of aging on hardness of mannitol based tablets. The results which are comparable to those obtained with the lactose based tablets indicate an increase in hardness for the high moisture containing tablets. The drug release results showed no aging effect for the different moisture containing mannitol based tablets. However, the disintegration time (Fig. 7) was found to slightly increase upon storage in particular for the high moisture containing tablets. This difference in behavior between the lactose and the mannitol based tablets seems to be related to

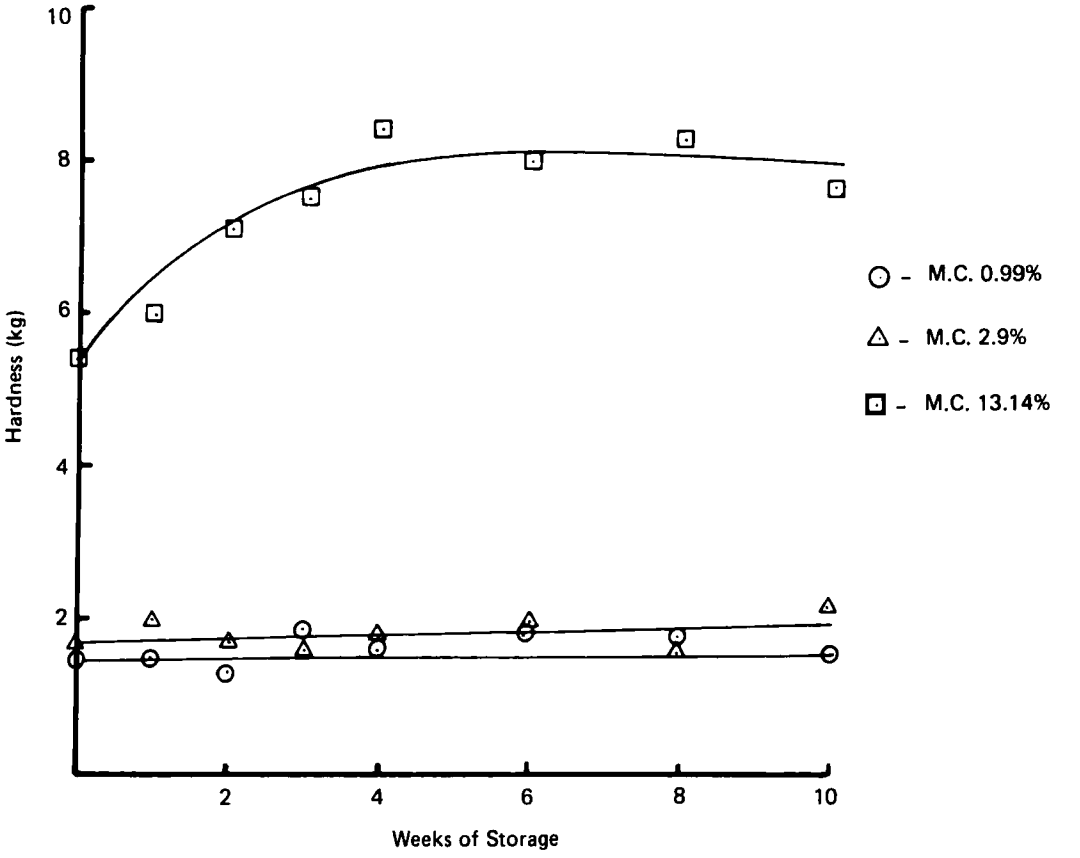

FIGURE 8

Effect Of Aging On Hardness Of Cellulose Based Tablets.

the higher initial moisture content in the mannitol tablets (Table 2). The partial water loss accompanied by stronger interparticulate bonds is believed to be the cause of increased hardness and delayed disintegration.

Figure 8 presents the effect of aging on hardness of cellulose based tablets with different initial moisture content. As expected, the high moisture containing tablets showed an increase in hardness which reached a maximum value after about four weeks. No change in

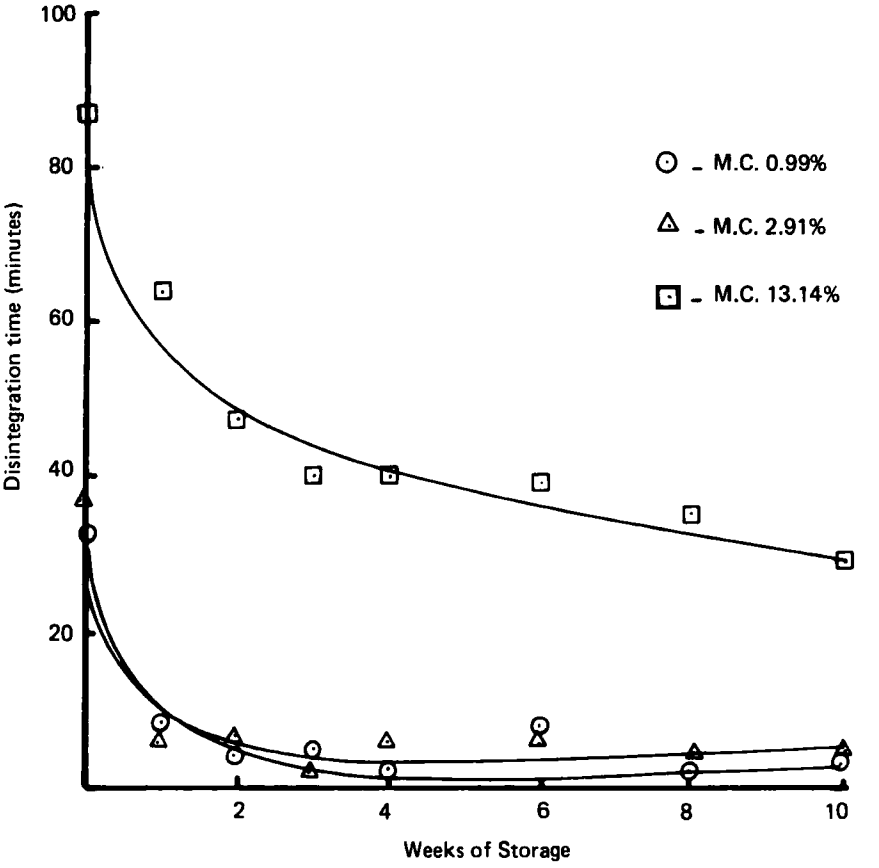

FIGURE 9

Effect Of Aging On Disintegration Of Cellulose Based Tablets.

hardness was observed for the low moisture containing tablets. On the other hand, the disintegration and drug release were enhanced upon storage. Figure 9 shows the disintegration time for the cellulose based tablets after aging for different time intervals. As can be seen, the high moisture containing tablets showed a continuous decrease in disintegration time throughout the experiment. However, the disintegration time of the low moisture containing tablets showed a decrease only

during the first week of storage and remained almost constant thereafter. A parallel storage effect on drug release was observed. The rate of drug release continuously increased by storage of the high moisture containing tablets but increased only during the first week for the remaining tablets. The discrepancies between the changes in drug release and disintegration on one hand and changes in hardness on the other hand, upon aging cellulose based tablets, may be explained by intrinsic changes in the cellulose particles attributed to storage in the humidity chamber.

CONCLUSION

Despite the considerable literature available on the effect of storage on tablet hardness, disintegration and dissolution, yet more studies are essential to understand the role of the variables that exist during tablet compression. The tablet base(s), the binder(s), the moisture content and the method of compression are among the important variables to be considered. To elucidate our understanding of the role of moisture content on aging of directly compressible tablets three commonly used tablet bases were studied. The data suggest that: (a) a high initial moisture content is likely to induce increase in hardness upon storage, the magnitude of such increase is dependant upon the physical properties of the base and the absolute moisture content; (b) the increase in hardness may increase the disintegration time and decrease drug release depending upon the particular base used, the mechanism(s) by which such changes are induced is (are) not fully understood and (c) minimum changes take place upon aging of tablets made from low moisture containing blends unless further gain of moisture takes place.

Under the conditions of this study, one may arrange the bases with regard to resistance to storage in a declining order as lactose > mannitol > cellulose. Further studies are necessary to correlate bioavailability changes of stored tablets to variables that exist during compression.

ACKNOWLEDGEMENTS

The authors are grateful to the generous support provided by the Research Centre of the College of Pharmacy, King Saud University and to Mr. K. Abbas for manuscript typing.

REFERENCES

1. A.M. Molokhia, M.A. Moustafa and M.W. Gouda, Drug Develop. Ind. Pharm., 8, 283 (1982).
2. A.M. Molokhia, Int. J. Pharm., 22, 127 (1984).
3. J.M. Lausier, C.W. Chiang, H.A. Zompa and C.T. Rhodes, J. Pharm. Sci., 66, 1636 (1977).
4. S.T. Horhota, J. Burgio, L. Lonski and C.T. Rhodes, J. Pharm. Sci., 65, 1746 (1976).
5. R.P. Bhatia and N.G. Lordi, J. Pharm. Sci., 68, 896 (1979).
6. S.A. Sangekar, M. Sarli and R.P. Sheth, J. Pharm. Sci., 61, 939 (1972).
7. Z.T. Chowhan and L. Palagyi, J. Pharm. Sci., 67, 1385 (1978).
8. Z.T. Chowhan, Drug Develop. Ind. Pharm., 5, 41 (1979).
9. Z.T. Chowhan, J. Pharm. Sci., 69, 1 (1980).
10. Z.T. Chowhan, J. Pharm. Pharmacol., 32, 10 (1980).