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EFFECTS OF TEMPERATURE, HUMIDITY, AND AGING ON THE DISINTEGRATION AND DISSOLUTION OF ACETAMINOPHEN TABLETS

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ABSTRACT

The effect of storage for 8 weeks at 40 °C in moderate and high humidity on acetaminophen tablets prepared by the wet granulation method using povidone or pregelatinized starch as a binder was studies. Storage at 52 % relative humidity produced an increase in hardness of acetaminophen tablets and storage at 94 % relative humidity caused a decrease in hardness. In all cases tablets granulated with pregelatinized starch were less susceptible to change caused by humidity than tablets granulated with povidone. The disintegration of tablets containing starch or povidone was slowed as the humidity was increased. Tablets stored at 40 °C and 94 % relative humidity showed a substantial slowing of dissolution, but there was little change of dissolution of tablets when aged at 40 °C / 52 % relative humidity. In comparing starch and povidone as binders, acetaminophen tablets prepared with pregelatinized starch were less effected by high humidity than tablets prepared with povidone.

INTRODUCTION

It is generally recognized that aging may create problems caused by chemical and physical changes in tablets. Recent studies have reported changes in characteristics of tablets upon

storage.[1-6] Such changes have been found to be responsible for altered bioavailability.[2,4] The purpose of this investigation was to study the effect of storage of acetaminophen tablets at 40 °C/ 52 % relative humidity (R.H.) and at 40 °C/ 94 %R.H. on hardness, disintegration, and dissolution. Other properties, such as weight, size, and loss on drying, were also examined.

METHODS

Preparation and Storage of Tablets: Two formulations containing 325 mg acetaminophen (Monsanto) per tablet were prepared by wet granulation method. Both formulations contained in each tablet: corn starch (DMV, Veghel) 16.2 mg, magnesium stearate (Monsanto) 3.4 mg, talc (Monsanto) 10.2 mg, and binder (6 mg povidone (Luviskol K30, BASF) in I, and 33.3 mg pregelatinized starch (Starch 1500, Staley and Co.) in II). The acetaminophen and half of the corn starch were mixed and granulated with 10 %w/w povidone aqueous solution, and oven-dried at 50 °C for 6 hours. Granules were passed through a 16-mesh screen and then mixed with the remainder of the corn starch, talc and magnesium stearate, and were compressed into tablets with a single punch tablet press[a] to a targeted hardness of 5-6 kg.

For the tablet containing pregelatinized starch as a binder, granulation was prepared in the same way except that the starch was added dry and then activated with distilled water to wet mass.

Immediately after compression the tablets were placed in open glass bottles and placed in controlled environmental chamber[b] at 40 °C and at 52 and 94 % relative humidity. Samples were removed weekly for a period of 8 weeks and tested.

Determination of Physical Characteristics: The weights (20 tablets), diameter and thickness (10 tablets), and moisture content for each condition and formulation were determined weekly. The hardness of 6 tablets was measured using a Stokes-Monsanto hardness tester. Disintegration was determined in distilled water at 37 ± 0.2°C using the USP apparatus. Dissolution(3 tablets) was determined using the USP apparatus 1[c] operating at 100 rpm and 900 ml of 0.1N hydrochloric acid at 37 °C in a 1-liter beaker.

RESULTS AND DISCUSSION

Tablets using either povidone or pregelatinized starch as a binder and stored at 40 °C/94 %R.H., their weights as well as moisture content gradually increased. However, dry atmosphere has slight effect on both moisture content and weight of tablets used. There was no significant change in thickness or diameter under storage condition. At 40 °C/52 %R.H. tablets containing povidone showed a rapid increase in hardness the first week from 5.8 to 7.2 kg afterwhich there was merely a slight increase. For tablets containing pregelatinized starch the hardness increased gradually from an initial value of 5.1 kg to 6.4 kg at 8 weeks. The systems

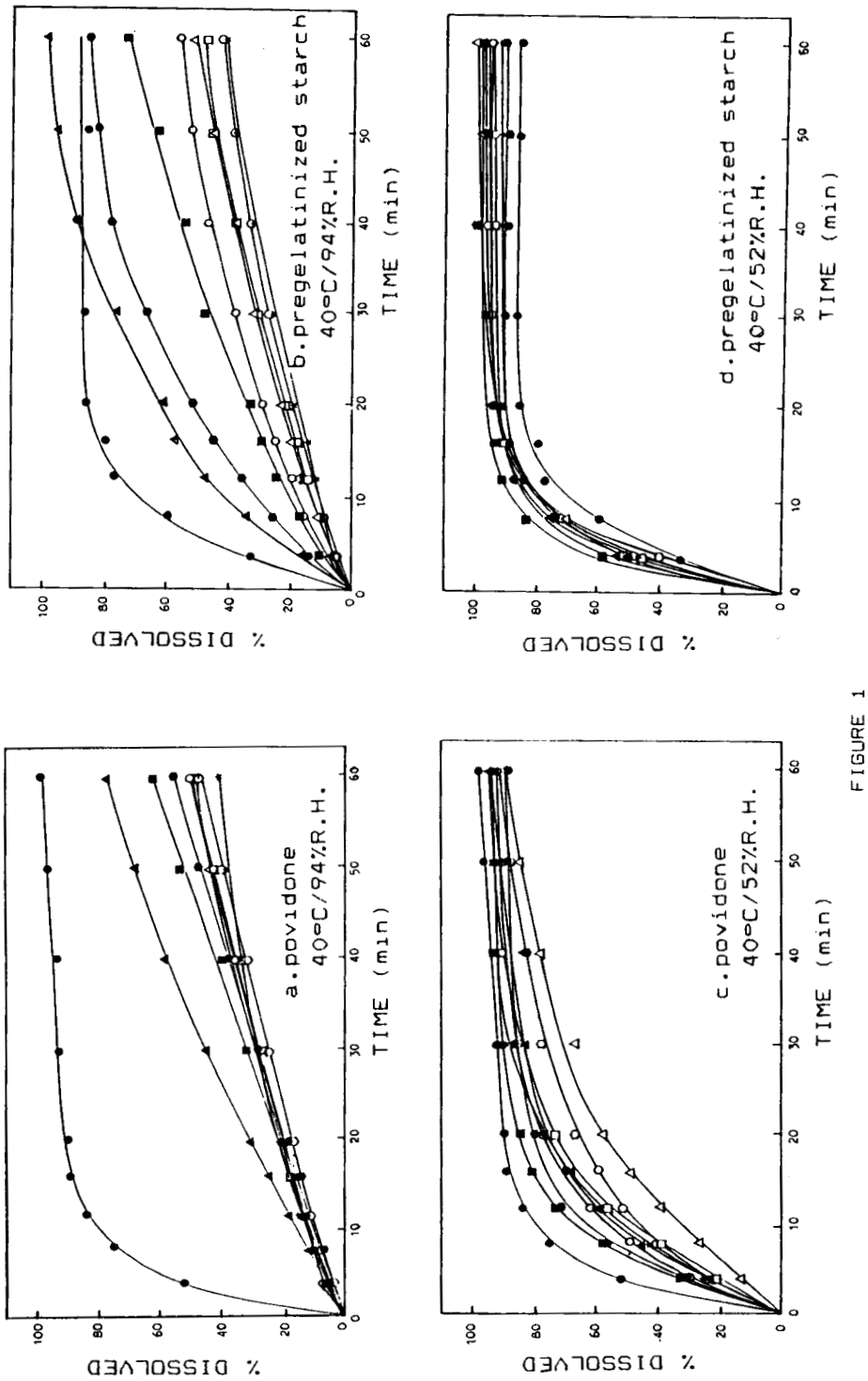

FIGURE 1

The influence of aging on the dissolution of acetaminophen tablets.
Key: ●, initial profile; ▲, 1 week; ■, 2 weeks; ⬢, 3 weeks;
○, 4 weeks; △, 5 weeks; □, 6 weeks; ⬡, 7 weeks; ★, 8 weeks.

stored at 40 °C/94 %R.H., however, opposite effect was observed: both systems revealed a reduction in hardness yet at different degrees. The system containing povidone showed an initial large reduction in the first week from 6.1 to 4.4 kg and then became levelled off. For those containing pregelatinized starch, the hardness was reduced slowly from an initial value of 5.4 to 4.1 kg in 8 weeks. The results above indicate that besides the active drug itself, the choice of binders used in the wet granulation procedure may be another parameter having considerable importance.

At both humidities the disintegration was greatly increased for both formulations. The disintegration time for tablets with povidone increased dramatically from an initial value of 2.3 min. to more than 1 hour after 1 week storage at 94 %R.H. In contrast that of the tablet containing pregelatinized starch increased slightly from 2.3 to 6.3 min. after 8 weeks at 52 %R.H. The increase in disintegration time of tablets stored in a warm and dry environment may be related to hardness increase induced by partial moisture loss that causes recrystallization resulting in solid bridges at points of contact. For tablets stored in a warm and humid environment, their disintegration time surprisingly increased to a larger extent despite the reduction in hardness. This may be due to the corn starch, which as it sorbed moisture would become less effective as a disintegrating agent. The extent of increase in disintegration time of tablets with pregelatinized starch was less than those containing povidone. This may be due to the dualistic action of a binder and a disintegrating agent.

To conveniently observe the changes of dissolution profiles during the storage period the profiles are plotted on the same scale in FIGURE 1(a - d). After 1 week of storage the dissolution from both formulations was drastically decreased with the greater decrease at 94 %R.H. Under storage the formulation containing povidone dissolved slower than those with pregelatinized starch.

From an examination of FIGURE 1a and 1b it may be concluded that storage at high temperature and humidity would have a strong influence on the dissolution of tablets using povidone or pregelatinized starch as a binder, but the influence would be less for the starch. As seen in FIGURE 1c and 1d at 40 °C and 52% R.H. dissolution from tablets containing povidone was only moderately affected whereas dissolution from tablets containing pregelatinized starch was practically unaffected.

ACKNOWLEDGEMENT

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FOOT NOTES

a. Fette Exacta I, West Germany.
b. Hotpack Corp., U.S.A.
c. Hanson Research, U.S.A.

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