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STORAGE RELATED PHYSICO-CHEMICAL CHANGES IN ASPIRIN AND PHENYLBUTAZONE TABLETS COMPRESSED WITH DIFFERENT INITIAL MOISTURE CONTENT

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ABSTRACT

The storage conditions as well as the compressional conditions of the aged tablets were found to have significant effect on their physico-chemical properties. In this study the changes in tablet weight, thickness, hardness, disintegration, drug release and drug content were evaluated for aspirin and phenylbutazone (pbz) tablets made with microcrystalline cellulose (MCC) and lactose bases. Tablets were made with different initial moisture content and stored at 40°C/90% relative humidity (R.H.). Tablet thickness was found, in general, to increase with storage, this increase was more prominent with aspirin. The increase in thickness was always accompanied with a decrease in hardness. There was a marked increase in disintegration time

and decrease in dissolution rate of phenylbutazone tablets. This was more significant for the lactose based tablets, while, for aspirin tablets there was a negligible increase in both dissolution rate and the disintegration time. The present study indicated that incorporation of drugs in tablet bases has resulted in a different response towards storage.

INTRODUCTION

The effect of storage on some of the physical properties of tablets such as dissolution and disintegration time has been the subject of many reports (1-7). Tablet initial moisture content, among other compressional conditions was found to have significant effect on the behavioral changes during storage.

Several workers observed changes in hardness, disintegration and dissolution with changes in temperature and/or humidity (6-8). Changes in disintegration and drug release was not always consistent with changes in hardness (7-10). Studies have shown that method of tablet preparation (11), packaging, storage conditions and storage time (12) contribute to the behavioral changes observed upon storage of tablets.

The aim of this work is to study the effect of storage of two different formulations of aspirin and phenylbutazone tablets with different initial moisture content at $40^{o}C/90\%$ R.H. on their physico-chemical properties.

MATERIALS

Phenylbutazone (Winlab, Berkshire, U.K.), Aspirin and starch (Fluka AG, Bucks SG, Switzerland), Talc (E. Merk, Darmstadt, W. Germany) Mag. stearate (Riedel de Haen AG, Seelze, Hanover, W. Germany), Spray dried lactose and microcrystalline cellulose (Winlab, Berkshire, U.K.) were used as received except for aspirin which was pulverized and sifted through 60-mesh sieve.

METHODS

Two different bases were prepared according to Table 1. Before mixing with the drug, each base was divided into three portions and each portion was equilibrated at 30°C in one of three different relative humidity compartments. Immediately before compression, the moisture content in each base was determined using the dry weight method (Table 2). Mixing of the base with the drug was performed in a tumbling mixer for 20 minutes. Each blend was then compressed in a rotary tabletting machine (Korsh pH 108, W. Germany) at 30 K.N. of pressure. Tablet weight was in the range of 240-260 mg for formulations A and B, and 340-360 mg for formulations C and D. Tablets were then packed in groups in paper bags and stored in a humidity chamber at 40°C/90% R.H.

Samples were examined initially and after 2, 4, 7, 10 and 14 weeks for hardness (6 tablets) in a hardness tester (Erweka

Table 1

Tablet Formulations

Formulation / Ingredients.% w/w	A	B	C	D
Phenylbutazone	20	20	—	—
Aspirin	--	--	20	20
Spray dried lactose	72	—	72	—
Microcrystalline cellulose	--	72	--	72
Starch	4	4	4	4
Talc	2	2	2	2
Magnesium stearate	2	2	2	2

Table 2

Moisture Content of the Different Bases

Base	Exposure Relative Humidity (%)	Moisture Content after 3 days (% w/w)
Lactose	28	0.737
	68	1.228
	99	1.352
Cellulose	28	3.259
	68	5.560
	99	6.725

G.m.b.H., Type T.B. 24, W. Germany), thickness (4 tablets), weight variation (20 tablets), disintegration time (4 tablets) using a standard apparatus (Erweka G.m.b.H., Type ZT4, W. Germany), according to U.S.P. method and using distilled water. Drug release was determined for 2 tablets by measuring the amount of drug dissolved as function of time using USP dissolution apparatus (Erweka G.m.b.H. Type D.T. W. Germany). Phosphate buffer, pH 7.5 and acetate buffer, pH. 4.5 were used for the pbz and the aspirin tablets respectively. Samples were withdrawn from the dissolution medium every five minutes for upto one hour, replaced with fresh buffer and filtered through a 0.45 uM pore size filter. Pbz was assayed spectrophotometrically (13) and aspirin was assayed according to the USP XX method.

The aspirin and salicylic acid contents were followed spectrophotometrically by measuring the absorbance of the tablet extract in ethanol and 278 and in chloroform at 530 respectively. The pbz content was followed by HPLC (13).

DSC analysis was performed on crushed tablets using a thermal analyzer (Dupone 9900) and a differential scanning calorimeter (Dupond 912).

Evaluation of the effect of storage on the different parameters was based on comparison between the calculated means.

RESULTS AND DISCUSSION

Tablet weight, upon storage, was shown to remain constant for pbz and to slowly decrease in case of aspirin. It appears that the loss in weight was basically due to decomposition of aspirin and the subsequent evaporation of acetic acid and sublimation of salicylic acid. A situation which is more related to the storage conditions rather than the initial moisture content. This explanation was supported by the determination of aspirin and free salicylic acid content at each sampling time. On the other hand, pbz content in both lactose and cellulose tablets was found to decrease by storage specially for tablets with higher initial MC. High pressure liquid chromatographic analysis of pbz tablets (Fig. 1) showed that a degradation product was slowly forming and its peak is building by time. No attempts were made to identify it.

Measurement of thickness and hardness showed, for aspirin, a continuous decrease in hardness coincided with continuous increase in thickness for both cellulose and lactose tablets. In case of pbz the low moisture containing cellulose tablets showed a slight increase in thickness and decrease in hardness during the first two weeks of storage with no further changes thereafter. The pbz lactose tablets showed no change in thickness by storage, while, their hardness showed initial decrease followed by a continuous increase. The change was more prominent for the low mois-

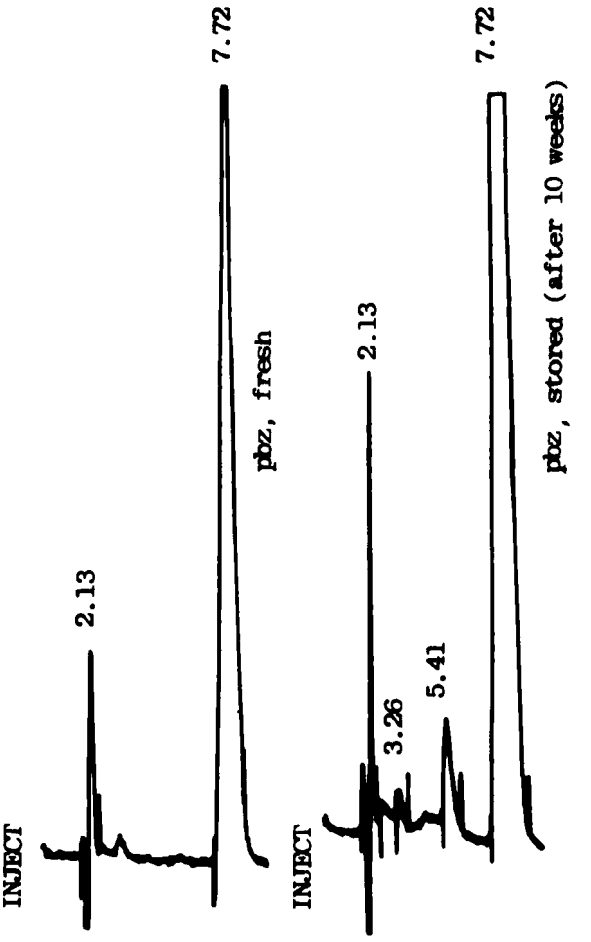

Fig. 1: HPLC trace for phenylbutazone and degradation product

ture containing tablets. This is probably due to initial moisture uptake followed by precipitation of lactose and strengthening of the interparticulate bonds.

In comparison with pbz tablets, the effect of storage on disintegration of aspirin tablets was negligible. Fig. 2 shows that, for lactose tablets with different initial MC, while the

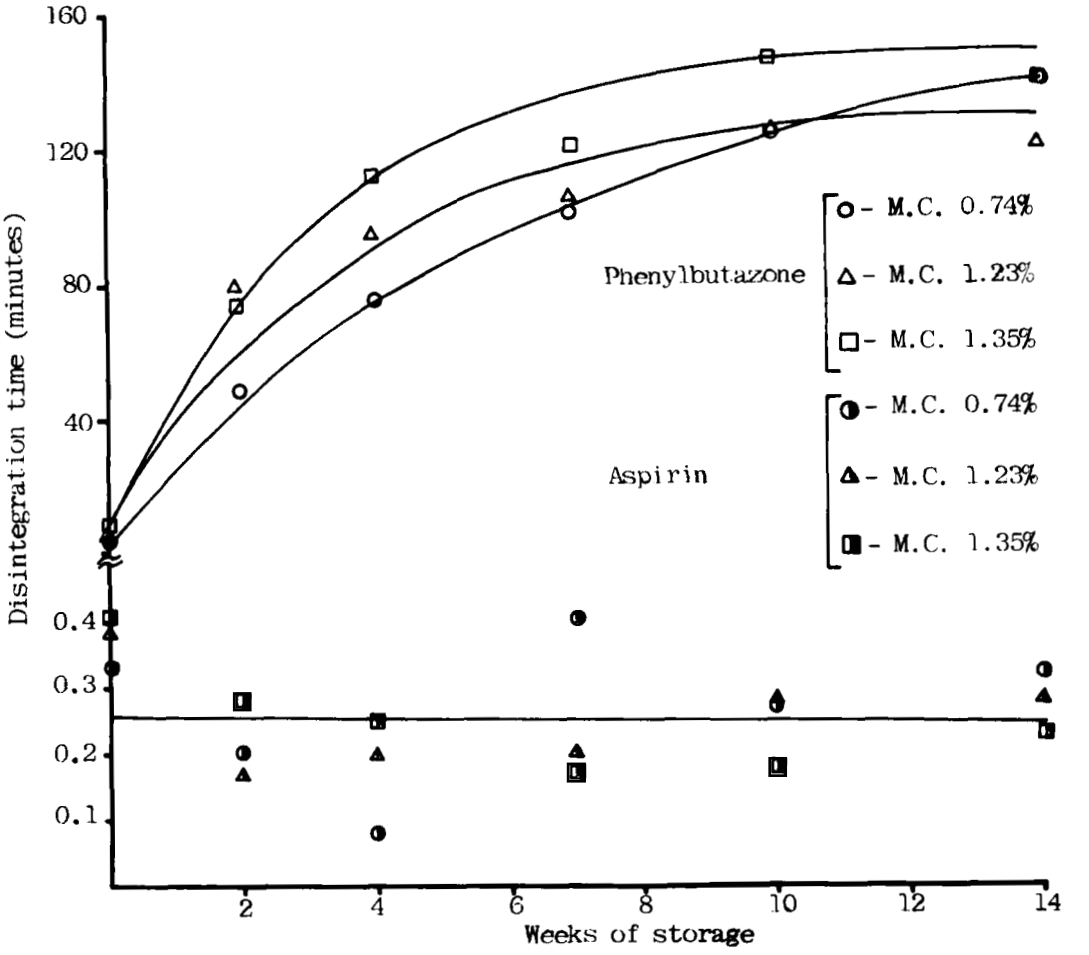

Fig. 2: Disintegration time of lactose based Aspirin and phenylbutazone tablets.

disintegration time of pbz tablets increased after 14 weeks of storage by a factor of 30–40, the aspirin tablets disintegration time slightly decreased during the first two weeks of storage and then remained almost constant. Similar changes in disintegration of cellulose tablets were observed with the increase in pbz disintegration time of only 1.5 - 3 folds.

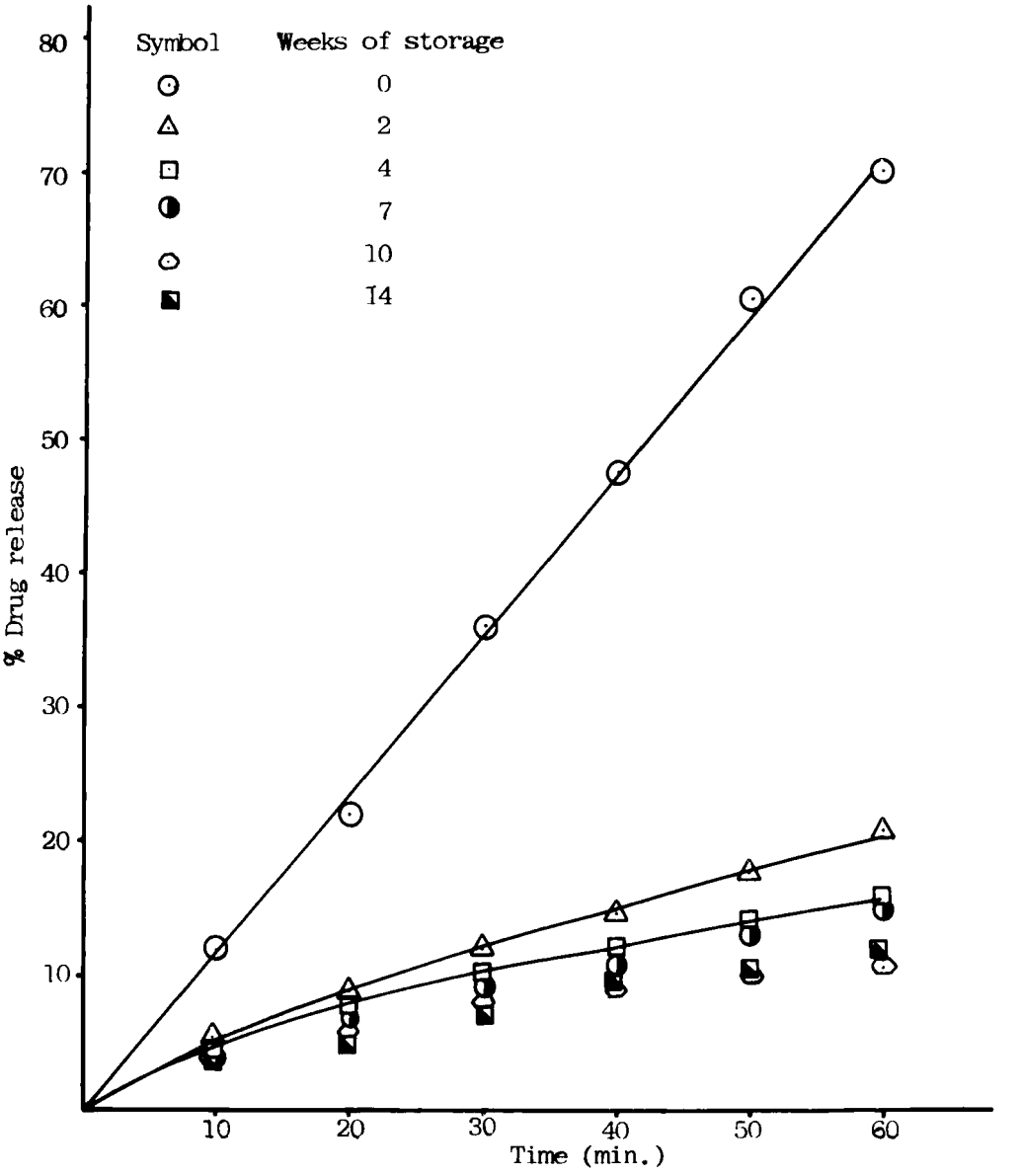

Fig. 3: Drug release from stored pbz/lactose tablet-M.C. 1.35%.

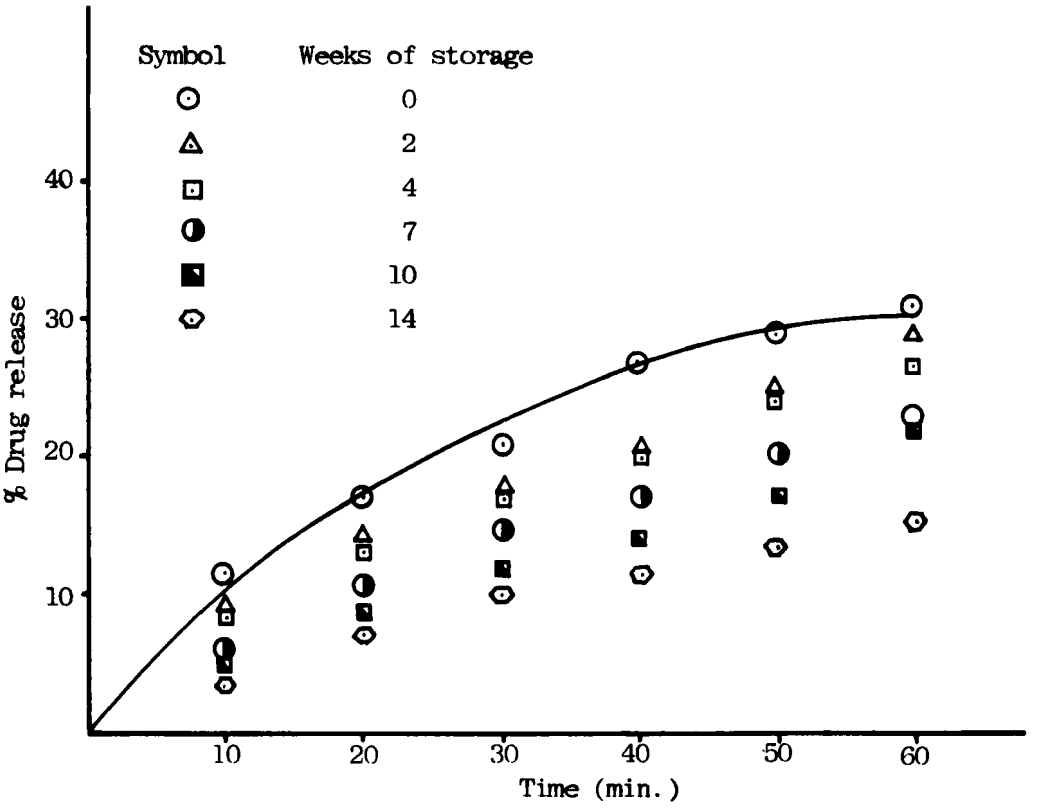

Fig. 4: Drug release from stored pbz/cellulose tablets-M.C, 1.35%.

Aspirin release from cellulose tablets was found to slightly increase by storage, while, from the lactose tablets, the change in its release was insignificant. This is probably due to the relatively slow disintegration of cellulose based tablets compared to the lactose based ones. The different initial moisture content did not alter the aspirin release behavior from the two bases. The release of pbz from the lactose based tablets showed marked decrease upon storage, while, the cellulose

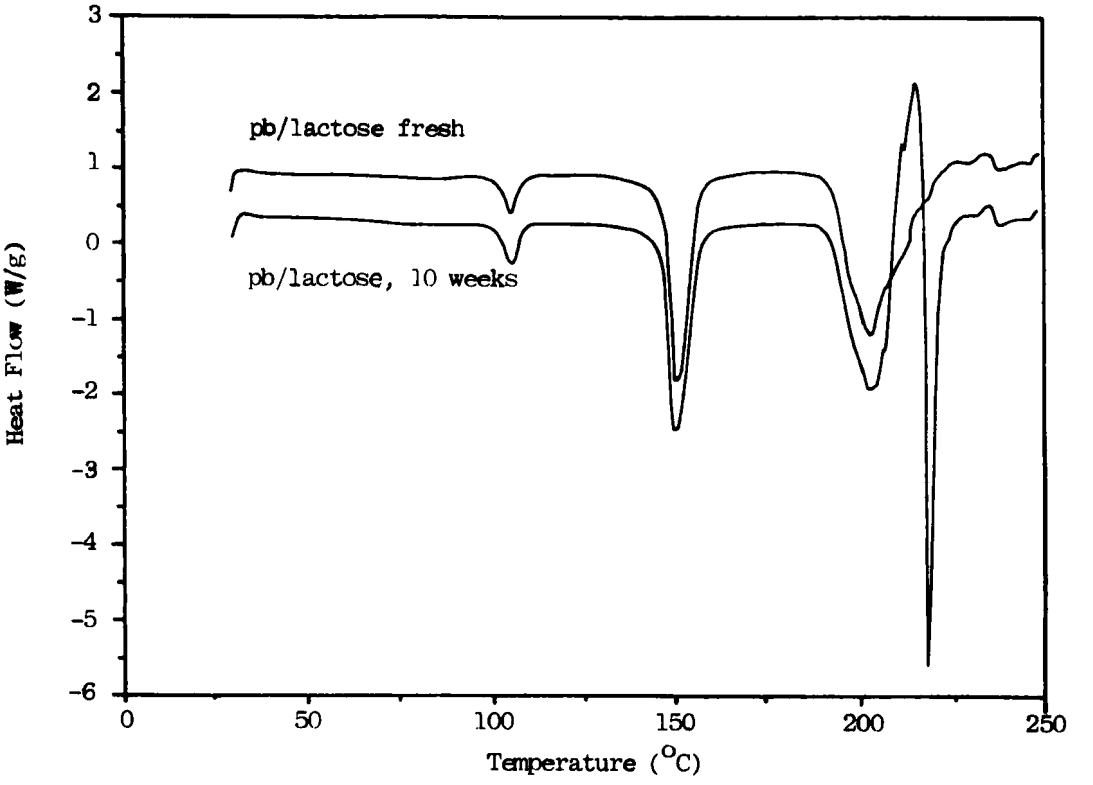

Fig. 5: D.S.C. thermogram for pbz/lactose samples before and 10 weeks after storage (heating rate 10°C/min., sample size 4-6 mg and under nitrogen flow).

based tablets showed decrease only for the high humidity containing ones. Figures 3 and 4 are representative examples of the changes pattern from the lactose and the cellulose tablets respectively.

Despite the apparent agreement between the disintegration and the drug release results, we believe that an interaction between lactose and pbz has contributed to the drastic decrease

in the release rate. This speculation was based on DSC analysis of the tablets as function of time (Fig. 5). An endothermic peak at 220°C developed and increased in intensity by storage. This low energy product with its relatively higher MP (MP of pbz and lactose are 107 and 200°C respectively) is expected to dissolve at a slower rate than the parent drug. A similar base-drug interaction was observed through DSC analysis (14).

In conclusion, the interfacing of tablet bases with different drugs may change the tablet base behavior during storage. Despite the reported preference of lactose over cellulose as a tablet base (7), such relation may not exist if pbz and possibly other drugs are incorporated in the formulation. Moisture content in the powder mix before compression may have dramatic effect on the tablet behavior during storage.

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