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PREPARATION, PROPERTIES AND AGEING OF TABLETS PREPARED FROM THE CHLORPROPAMIDE–UREA SOLID DISPERSION

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SUMMARY

Tablets have been prepared from the solid dispersion of 30% chlorpropamide and 70% urea. Granulation was accomplished using two formulations at 100°C. The melt acted as binder and hard tablets were produced whose dissolution properties were superior to those of traditional wet granulated products. Initial dissolution rates of 11.5 and 7.5 mg min^{-1} were obtained from tablets containing the solid dispersion of chlorpropamide and compressed at 150 MNm^{-2} whereas a rate of only 3.2 mg min^{-1} was obtained from the wet granulated product similarly compressed. During dry storage the melt-granulated tablets became harder due to crystallization of the melt. Disintegration times generally decreased and dissolution rates decreased during the intitial two months of storage at 25°C and 35°C but, thereafter increased. Subsequently, the melt-formulated tablets were more sensitive to moisture during storage than the wet-granulated tablets.

INTRODUCTION

It is well recognized that solid dispersions of poorly water-soluble drugs and inert water-soluble carriers enhance in vitro drug dissolution rates (Chiou and Riegelman, 1971). However, the use of the melt method for preparation may lead to the formation of solids which are unpulverizable (Riegelman and Chiou, 1976), soft and sticky (Chiou and Niazi, 1971), are metastable (Chiou and Riegelman, 1969) or glassy (Summers and Enever, 1976). Since ageing may also alter the dissolution rates from solid dispersed systems (Ford and Rubinstein, 1979) few reports on the formulation of solid dispersed systems have been reported. El-Banna et al. (1977) prepared tablets by the direct compression of the resolidified melts of paracetamol–mannitol, amylobarbitone–urea and caffeine–nicotinamide, using magnesium stearate as the lubricant. The paracetamol–mannitol system required starch as a disintegrant. Patents describing the formulation of the griseo-

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fulvin–PEG6000 solid dispersion with cross-linked polyvinylpyrrolidone have been issued (Kornblum and Stoopak, 1977; Sandoz, 1975).

Formulation of these systems was comparatively simple since the dispersions themselves were readily pulverizable and formed crystalline solids. Ford and Rubinstein (1980) have, however, developed a technique, using the molten melt, to prepare granules from the solid dispersion of indomethacin and polyethylene glycol 6000 (PEG 6000), despite its tacky nature. In effect the melt of indomethacin–polyethylene glycol 6000 was used as the binding agent.

Ford and Rubinstein (1977a) established the phase diagram of the chlorpropamide–urea solid dispersion and a eutectic composition was found to contain 89% (w/w) chlorpropamide with a eutectic temperature of 95°C. Melts in the range 50–100% chlorpropamide existed as glass solids, although after preparation tacky, semi-solids were often formed. Dissolution studies on the system (Ford and Rubinstein, 1977b) showed that dissolution rates over 900 times greater than that of the pure drug were obtained from melts containing 30% (w/w) chlorpropamide. The formulation of a free-flowing granulate of chlorpropamide and urea has already been briefly described (Wells et al., 1975) but no details of the ageing and stability of the formulated system were reported. This paper describes the preparation of tablets containing the solid dispersion of chlorpropamide and urea and compares the ageing and stability of such tablets with those of tablets prepared by conventional wet granulation techniques.

MATERIALS AND METHODS

Chlorpropamide (Berk Pharmaceuticals), urea, calcium hydrogen phosphate anhydrate and magnesium stearate (BDH Chemicals), microfine cellulose (Elcema G250, Degussa), sodium starch glycolate (Explotab, K and K Greef, Fine Chemicals) and polyvinylpyrrolidone (PVP-K30, GAF) were dried at 60°C for 12 h, and sieved <250 μm before use.

Melt granulation

Traditional aqueous wet granulation could not be used for solid disperions of chlorpropamide–urea since exposure of the solid dispersion to water would destroy the

TABLE 1

FORMULAE OF TABLETS

	mg/tablet		
	Formula A	Formula B	Formula C
Chlorpropamide	90	90	90
Urea	210	210	–
Anhydrous calcium hydrogen phosphate	50	50	260
Sodium starch glycolate	20	100	20
Microfine cellulose	50	–	50
10% PVP solution	–	–	q.s. (≡23 mg P.V.P.)

structure of the dispersed system. The addition of other materials may also modify the ageing of the dispersion, so a melt granulation technique was devised such that: (a) the drug-carrier in the molten state would act as a binder; and (b) the other solid materials could be used to absorb the melt to produce a large surface area for dissolution and at the same time promote rapid crystallization of chlorpropamide–urea. It was originally intended to perform granulation at 135°C (as with Wells et al., 1975). However, the chlorpropamide–urea system was unstable at this temperature (Ford et al., 1979). Consequently, granulation was performed at 100°C.

Approximately 200 g quantities, weighed and fully mixed in the proportions indicated in Table 1 by formula A or B were placed in a 1 litre, wide-necked round-bottom flask. The flask was rotated at 40 rpm for 15 min horizontally about the flask neck in a water bath maintained at 100°C. During this period the in situ formation of granules occurred. The flask was rotated without heat for a further period of 30 min to cool the granules. They were passed through a 1000-μm sieve and stored for 12 h at 45°C, so as to allow crystallization of the melt onto the unfused urea and other tablet components. Subsequently the granules were sieved, <500 μm, and dry-mixed with 1% magnesium stearate as lubricant prior to tablet compression.

Traditional wet granulation

For comparative purposes formula A was modified to allow wet granulation to be carried out using aqueous PVP solution as formula C in Table 1. The ingredients were dry-mixed and wetted with the 10% aqueous PVP solution and wet-massed through a 1000-μm sieve before drying for 12 h at 45°C. The mass was then dry-sieved, <500 μm, to produce granules which were lubricated with 1% magnesium stearate before compression.

Compaction

Granules were compressed on a Manesty F3 tablet machine, using 11.1 mm diameter, flat-faced punches. Compaction pressures corresponding to 150, 100 and 50 MNm^{-2} were used for each granulation.

Tablet properties

The heights and diameters of 10 tablets were determined using a screw micrometer (More and Wright, Sheffield). The same tablets were used throughout the study.

Tablet diametrical crushing strengths were determined using a Schleuniger hardness tester. Means and standard deviations of 10 tablets were evaluated. A Manesty tablet disintegration test unit was used to determine the disintegration times of tablets. The BP 1973 disintegration times were determined at 37°C in distilled water and values are the average of two determinations. Dissolution rates were measured using the USP dissolution apparatus. The basket was positioned 2 cm from the bottom of the flask and rotated at 100 rpm. Dissolution rates of individual tablets were determined at 37°C in 1000 ml freshly distilled water. 2 ml aliquots were withdrawn and, suitably diluted, assayed at 232 nm for chlorpropamide content (Ford and Rubinstein, 1977b).

Storage tests

Tablets were stored in tightly closed glass bottles at 25, 35 and 55°C. Further quantities were stored in open necked bottles at 25°C in a closed container containing a saturated solution of ammonium chloride and potassium nitrate which gave a relative humidity of 71% (abbreviated to 25°RH) (Handbook of Chemistry and Physics, 1962–1963). The tests under tablet properties were carried out at the time of preparation and after 1, 2, 4, 8 and 12 months storage.

Stability studies were performed on the tablets stored for 12 months. Individual tablets were weighed and allowed to disintegrate in about 60 ml ethanol. After disintegration the insoluble solids were filtered and washed and the filtrate made up to volume (100 ml) with further ethanol.

Chlorpropamide content was determined using the thin-layer chromatography–reflectance densitometry methods of Ford et al. (1979). The stability of tablets was estimated using the formula:

$$\frac{\text{Clorpropamide assay value (mg)} \times \text{theoretical tablet weight (mg)} \times 100\%}{\text{Actual tablet weight (mg)} \times 90}$$

where 90 = theoretical tablet chlorpropamide content (mg).

RESULTS AND DISCUSSION

Table 2 summarizes the properties of unaged tablets. Crushing strengths and disintegration times increased with increasing compaction pressure. Tablets prepared using

TABLE 2

SUMMARY OF THE PROPERTIES OF CHLORPROPAMIDE TABLETS, PREPARED BY MELT- AND WET-GRANULATION, AT THE TIME OF PREPARATION

Formulation	Compaction pressure (MNm^{-2})	Crushing * strength (Strong-cobb units)	Disintegration ** times (min)	$T_{50\%}$ *** (min)
A	150	21.3 ± 1.1	3.74	5.3
(melt	100	10.4 ± 0.8	1.98	2.4
granulation)	50	6.6 ± 1.6	0.78	2.9
B	150	24.8 ± 4.5	7.44	8.6
(melt	100	19.2 ± 1.3	4.87	6.1
granulation)	50	10.9 ± 0.5	4.08	5.6
C	150	23.7 ± 4.9	11.40	15.3
(wet	100	12.6 ± 2.6	6.87	11.1
granulation)	50	<1.0	2.59	15.7

* Mean ± standard deviation of 10 tablets.

** Mean of 2 × 5 tablets.

*** Mean of 3 tablets.

the melt technique (formulations A and B) were considerably harder than the wet-granulated product, probably due to the strong intergranular bridges formed by the melt after compaction. Tablets prepared from formula A gave the lowest disintegration times. The wet granulated product C gave the longest disintegration times for tablets compressed at 100 and 150 MNm^{-2}, whereas for tablets compressed at 50 MNm^{-2} product B gave the longest times.

Dissolution times, measured at $t_{50\%}$ are given in Table 2. Calculated initial dissolution rates from tablets compressed at 150 MNm^{-2} were 11.5, 7.5 and 3.2 mg min^{-1} for batch A, B and C, respectively. Similar results have been shown by Wells et al. (1975) for tablets prepared from chlorpropamide–urea solid dispersions. Although higher dissolution rates were obtained from the solid dispersed chlorpropamide tablets, these are not as large as those obtained from the unformulated dispersions, where dissolution rates over 900 times greater than those of the pure drug were obtained (Ford and Rubinstein, 1977).

Tablets from formulations A and C showed the same pressure-dependent dissolution changes; tablets compressed at 50 MNm^{-2} gave the lowest dissolution rates whereas tablets compressed at 100 and 150 MNm^{-2} showed similar profiles. Conversely the dissolution profiles of tablets prepared from formula B were similar in tablets compressed at 50 and 100 MNm^{-2}, but lowest from tablets compacted at 150 MNm^{-2}.

During storage brown mottling became apparent in tablets containing the solid dispersed drug and stored at 55°C and after 1 year's storage these tablets were also waxy. Storage of the traditionally prepared tablets did not result in any similar changes. The drug contents of tablets after one year's storage are shown in Table 3. The wet-granulated tablets were stable and showed a marginal drug loss during storage. The melt-granulated tablets were stable at 25°C, but decomposition occurred at 35°C and 55°C, especially in batch A tablets stored at 55°C. Thermal degradation of chlorpropamide in the presence of urea has been reported (Ford et al., 1979) but in these studies no degradation of chlorpropamide occurred except during storage.

Changes in crushing strengths during storage depended on the storage conditions. Generally the melt-granulated tablets exhibited crushing strength increases during the initial two-month storage period whereas the wet-granulated product showed fluctuations in hardness. Storage at 25°C (Table 4) resulted in an approximate 80% increase for formulation A, and a 60% increase for formulation B. Storage at 35° resulted in more rapid and slightly larger increases for both formulations A and B. Decreases in strengths

TABLE 3

THE STABILITY OF CHLORPROPAMIDE TABLETS, PREPARED BY MELT- OR WET-GRANULATION, COMPRESSED AT 150 MNm^{-2}, AFTER ONE YEAR'S STORAGE

Granulation	% Chlorpropamide remaining under storage conditions:		
	25°C	35°C	55°C
Melt A	97.3	90.3	34.0
Melt B	102.5	94.3	91.2
Wet C	103.5	100.2	99.7

TABLE 4

THE EFFECT OF AGE ON THE CRUSHING STRENGTHS (STRONG-COBB UNITS ± S.D.) OF TABLETS PREPARED BY MELT- OR WET-GRANULATION AND COMPRESSED AT 100 NMm^{-2}

Granulation method	Storage conditions	Age (months)					
		0	1	2	4	8	12
Melt A	35°C	10.4 ± 0.8	19.4 ± 1.0	20.4 ± 3.4	15.9 ± 2.9	17.0 ± 1.4	15.5 ± 1.3
	25°RH	10.4 ± 0.8	5.8 ± 0.5	1.6 ± 0.4	<1.0	<1.0	<1.0
Melt B	25°C	19.2 ± 1.3	24.8 ± 1.0	>28	>28	>28	>28
	25°RH	19.2 ± 1.3	9.7 ± 0.5	4.6 ± 0.2	<1.0	<1.0	<1.0
Wet C	25°C	12.6 ± 2.6	13.2 ± 3.8	11.7 ± 3.5	13.4 ± 3.1	12.0 ± 3.4	9.6 ± 2.9
	25°RH	12.6 ± 2.6	6.6 ± 1.5	6.7 ± 1.5	5.8 ± 1.4	6.8 ± 2.6	9.4 ± 2.8

occurred during the final 4-month storage of tablets A and B at both 25° and 35°C. The traditional product C showed no general trends in crushing strengths during storage at 25° and 35°C.

The increases in crushing strength in the melt-formulated products were probably due to crystallization of the chlorpropamide–urea eutectic, which in these tablets acted as the binding agent. Chowhan and Palgyi (1978) showed that tablets increased in hardness by the recrystallization of either a soluble drug or carrier in the void spaces of tablets, because of moisture loss after expulsion of the solution of the excipient or drug in the void space during compression. It is probable that crystallization of the melt occurred during storage and resulted in increased hardness.

A different pattern of ageing was observed during storage in the presence of moisture (Table 4). All tablets displayed crushing strength decreases during storage. Tablets prepared by solid dispersion methods decreased in strengths to less than 1 s.c.u. within 4 months' storage. The tremendous decreases in strength of tablets of batches A and B may be explained by their containing large proportions of urea which is hygroscopic, and sodium starch glycolate which has been shown to absorb over 50% of its weight in water in 25 h at 37°C and 100% RH (Khan and Rhodes, 1975). The strengths of traditionally prepared tablets C decreased to about 50% of their original hardness during the initial 4 months' storage. Horhota et al. (1976) showed a decrease in hardness of tablets (containing dibasic calcium phosphate dihydrate and sodium starch glycolate) also to

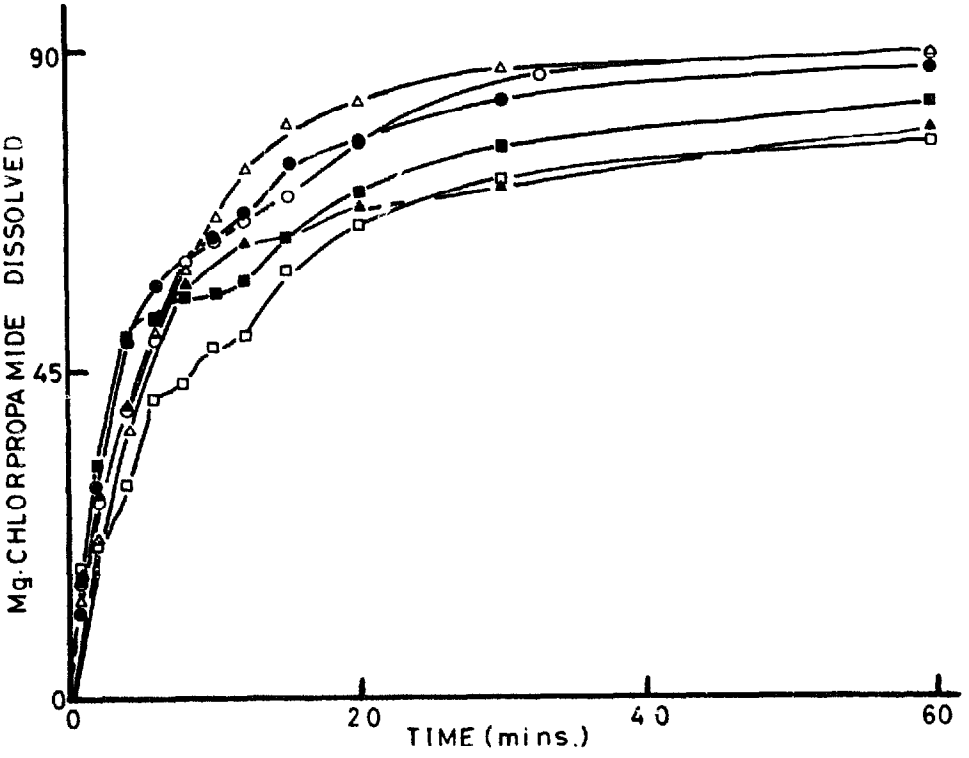

Fig. 1. The effect of storage at 25°C on the dissolution profiles of formula A chlorpropamide tablets, compressed at 150 MNm^{-2}. Age of tablets: △, unaged; ▲, 1 month; □, 2 months; ■, 4 months; ○, 8 months; and ●, 12 months.

TABLE 5

THE EFFECT OF AGE ON THE DISINTEGRATION TIMES (min) OF TABLETS PREPARED BY MELT OR WET GRANULATION COMPRESSED AT 100MNm^{-2}

Granulation method	Storage conditions	Age (months)					
		0	1	2	4	8	12
Melt A	25°C	1.98	1.56	1.67	1.85	1.60	1.76
	25°RH	1.98	0.20	0.21	0.16	0.11	0.11
Melt B	35°C	4.08	1.66	1.70	1.46	1.50	1.45
	25°RH	4.87	1.26	1.01	0.65	0.43	0.32
Wet C	25°C	6.87	7.15	6.99	6.73	5.73	6.39
	25°RH	6.87	10.78	16.94	59.78	75.40	67.81

about half their original value withing 30 days of storage at 23°C and 75% RH.

Table 5 shows the changes that occurred in disintegration time, as represented by tablets compressed at 100 MNm^{-2}. Decreases in disintegration times occurred for tablets containing solid dispersed chlorpropamide during storage at 25 and 35°C, which was more marked for batch B tablets. No marked changes in disintegration times appeared for

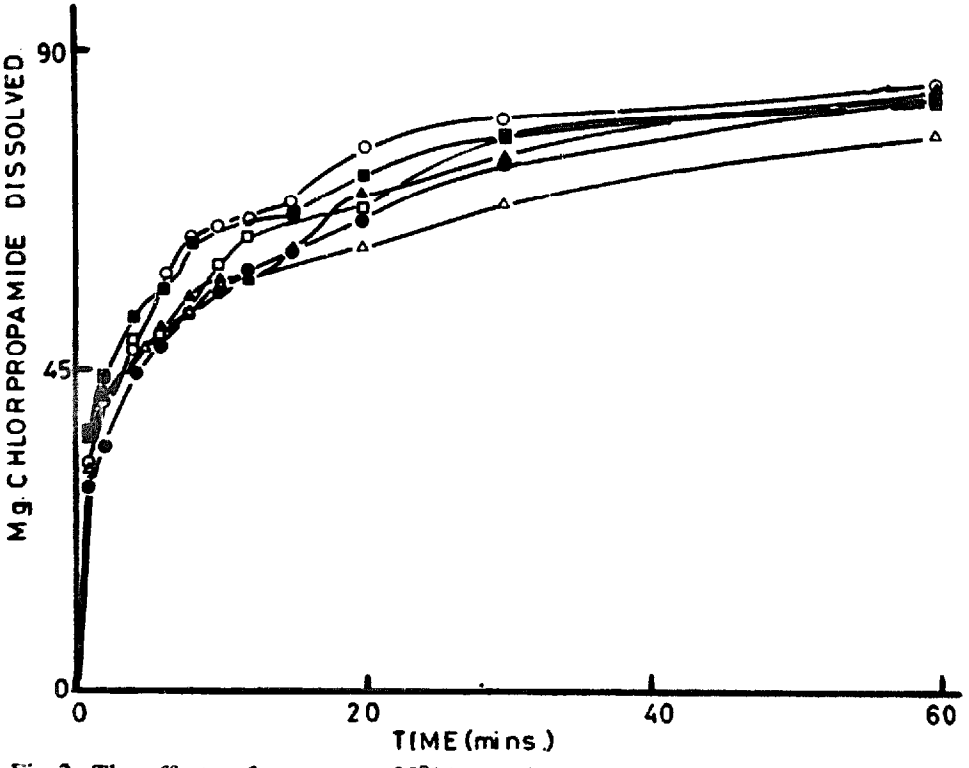

Fig. 2. The effects of storage at 25°RH on the dissolution profiles of formula A chlorpropamide tablets, compressed at 50 MNm^{-2}. Age of tablets: △, unaged; ▲, 1 month; □, 2 months; ■, 4 months; ○, 8 months; and ●, 12 months.

TABLE 6

THE EFFECT OF STORAGE ON CHLORPROPAMIDE DISSOLVED (D_{30min}) AFTER 30 MINUTES (mg) DURING DISSOLUTION OF TABLETS COMPRESSED AT 100 MNm^{-2}

Granulation method	Storage conditions	D_{30min} values					
		Tablet age (months)					
		0	1	2	4	8	12
Melt A	25°C	87	80	72	80	84	84
	25°RH	87	80	82	73	78	80
Melt B	35°C	82	84	88	90	86	90
	25°RH	82	88	82	79	86	81
Wet C	25°C	72	66	71	69	68	67
	25°RH	72	63	43	37	29	23

the similarly stored traditional tablets. Storage of tablets under humid conditions (25 RH) resulted in disintegration time decreases to relatively consistent values for melt-granulated tablets (Table 5), whereas increases occurred for the wet-granulated product. Since the binding agent in the melt-formulated tablets was chlorpropamide and urea,

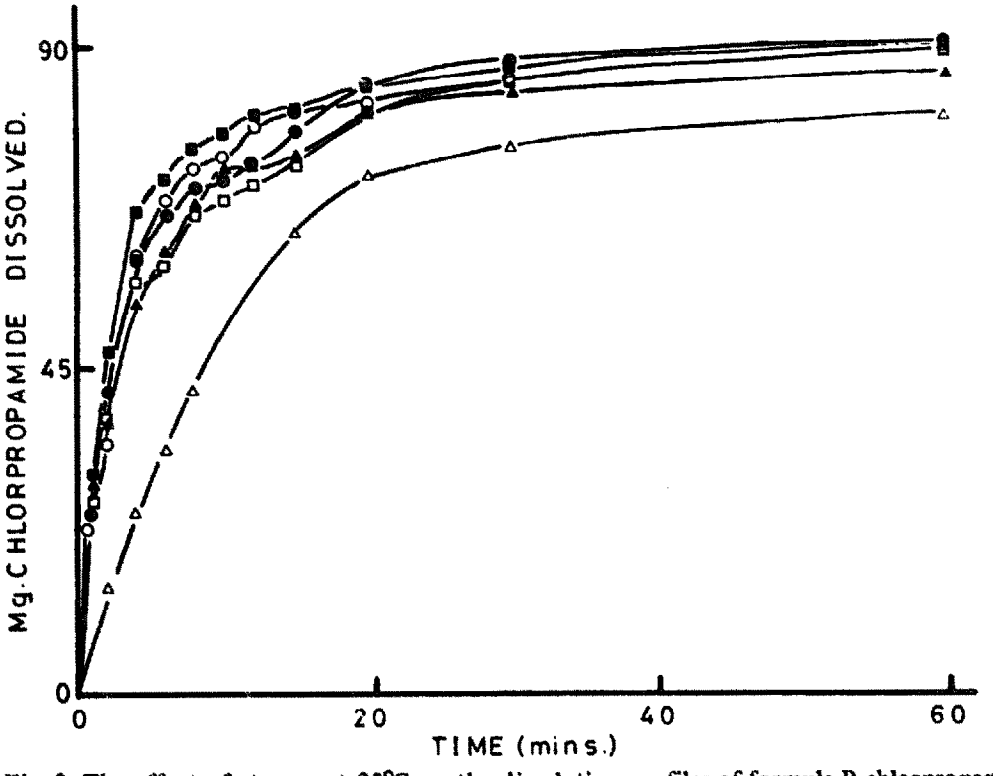

Fig. 3. The effect of storage at 35°C on the dissolution profiles of formula B chlorpropamide tablets, compressed at 150 MNm^{-2}. Age of tablets: △, unaged; ▲, 1 month; □, 2 months; ■, 4 months; ○, 8 months; and ●, 12 months.

adsorption of water would lead to dissolution of the cementing agent and the tablet structure would therefore crumble resulting in rapid breakdown of the tablet on exposure to water. Khan and Rhodes (1975) have shown that under humid conditions the disintegration times of tablets containing calcium phosphate dibasic dihydrate and sodium starch glycolate increased with time, since the disintegrant lost its absorption and swelling ability and swelling was the most important mechanism by which sodium starch glycolate exerted its disintegration mechanism. Although this factor is overshadowed in the melt-granulated tablets by solution of urea during storage it is probably the most important factor in the increase in disintegration times shown by the wet-granulated product.

The effect of storage on dissolution profiles provided difficult changes to interpret. The smoothness of the dissolution curves of melt-granulated tablets at their time of preparation was lost and erratic chlorpropamide release occurred (Figs. 1–3). Under dry storage conditions the initial release of chlorpropamide, especially in batch B tablets generally increased. This phenomenon is related to the decrease in disintegration times during storage (Table 5). Although generally considered as artifacts, similar observations (Ford, 1980) in poorly formulated chlorpropamide and indomethacin tablets suggested that such problems were associated with failure of the disintegrated tablets to deaggregate. Crystallization of the eutectic at local centres in the tablet during storage may have occurred, effectively cementing aggregates together and slowing dissolution.

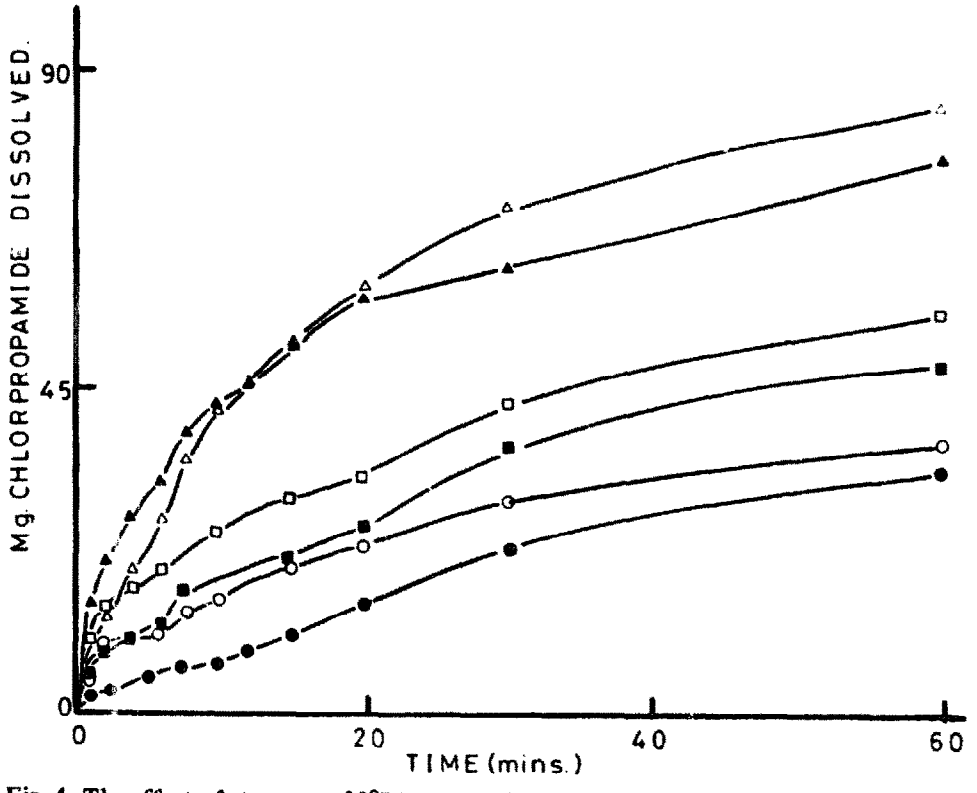

Fig. 4. The effect of storage at 25°RH on the dissolution profiles of formula C chlorpropamide tablets, compressed at 100 MNm^{-2}. Age of tablets: △, unaged; ▲, 1 month; □, 2 months; ■, 4 months; ○, 8 months; and ●, 12 months.

The final stages of the dissolution profiles (>20 min) varied tremendously but by studying the amount of drug dissolved after 30 min (D_{30min}) trends in ageing could be identified (Table 6). D_{30min} values decreased and subsequently increased from batch A tablets compressed at 150 and 100 MNm^{-2} after storage at 25 and 35°C (Fig. 1), whilst they increased to an approximately consistent value in tablets compressed at 50 MNm^{-2} and similarly stored. Generally D_{30min} values of batch A tablets stored at 25°RH decreased although an initial increase occurred for batch A tablets compressed at 50 MNm^{-2} (Fig. 2). D_{30min} values of batch B tablets generally increased on storage at 25, 35°C and 25°RH for tablets at all 3 compaction pressures (Fig. 3).

Dissolution rates of the wet-granulated product C, generally decreased during storage at 25 and 35°C. Storage at 25°RH resulted in larger decreases in dissolution rates (Fig. 4, Table 6), findings that are similar to those of Horhota et al. (1976) and reflect the great increases in disintegration times of tablets of batch C, brought about by the loss of effectiveness of sodium starch glycolate due to moisture absorption (Khan and Rhodes, 1975).

This paper has outlined the formulation and ageing of tablets prepared from chlorpropamide–urea solid dispersions. The unaged tablets displayed superior dissolution rates than the wet-granulated products of similar composition. However, during storage the solid dispersed tablets showed considerable changes in crushing strengths, disintegration times and dissolution rates. Ford and Rubinstein (1977b) showed that unformulated dispersions containing 30% chlorpropamide in urea did not age during storage at room temperature. It would appear that ageing in formulated solid dispersions may limit their usefulness as prospective dosage forms.

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