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An investigation of phenobarbitone–sucrose glass systems

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Summary

An investigation of the stability and dissolution behaviour of phenobarbitone–sucrose glasses has been made. An increased dissolution rate of phenobarbitone can be achieved and the glass is sufficiently stable to withstand powdering. However, the dissolution rate of a powdered glass is the same as that of the corresponding physical mixture because the dissolution medium, water, causes the glass to devitrify. Atmospheric moisture also reduces the stability of the glass, therefore it is probably not suitable for use in formulation.

Introduction

A range of measures have been devised for improving the dissolution rate of sparingly water-soluble drugs. A reduction in the particle size by formation of solid dispersions was demonstrated by Sekiguchi and Obi (1961) and developed by Chiou and Riegelman (1971), using readily water-soluble carriers. Chiou and Riegelman (1969) also looked at the formation of a glass solution when they prepared griseofulvin in citric acid in the metastable, high energy, vitreous state (Clark and Hawley, 1966). Chiou and Riegelman obtained improved dissolution rates of griseofulvin, but were uncertain whether this was due to the high dissolution rate of the glassy citric acid or to other factors. Several potential factors have been pointed out (Chiou and Riegelman, 1971; Hajratwala, 1974) including an increased drug solubility, a solubi-

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lizing effect of the carrier, the prevention of aggregation of fine crystallites and an increased wettability of the dispersion.

A number of reports have appeared where citric acid has been used as a glass-forming carrier. Summers and Enever (1974, 1976, 1977) investigated the behaviour of primidone–citric acid systems and showed an increased dissolution rate of the glassy system. Summers (1978) used citric acid with pentobarbitone, hexobarbitone and heptabarbitone and confirmed that glasses, with a glass transition temperature higher than expected, were formed. He did, however, find that the glasses tended to devitrify on grinding and, therefore, had a reduced potential in dosage form design. Timko and Lordi (1979) have also reported the formation of stable glass systems of citric acid with benzoic acid and phenobarbitone.

Allen et al. (1977) investigated glass dispersions using dextrose, galactose and sucrose as carriers for a range of corticosteroids. The results indicated a marked increase in the dissolution rates of the steroids when compared to the plain powder.

There appears to be potential for increasing the dissolution rate using glassy systems providing they can be made sufficiently stable to withstand pharmaceutical processing. One approach to improving stability may be to use two glass-forming materials to effect a mutual stabilization. The work presented here investigated this possibility using phenobarbitone and sucrose as examples of glass-forming materials.

Materials and Methods

Phenobarbitone (May and Baker) and sucrose (BDH Analar) were used as received.

DTA thermograms were obtained using a Stanton Redcroft Model 671B analyzer and T_1-T_2 pen recorder. The samples, approximately 10 mg, were in open aluminium crucibles. Alumina was used as reference and heating was at 10°C min in static air.

Physical mixtures of phenobarbitone and sucrose were prepared by thoroughly mixing the appropriate quantities in a pestle and mortar to ensure adequate distribution. After obtaining the thermogram, the crucible containing the liquid melt was removed from the apparatus and immediately placed on a cold metal surface to form a glass. The same conditions were used to obtain thermograms of these glass systems.

Larger scale production of glasses was achieved by melting phenobarbitone and sucrose together in a ceramic crucible, using minimal heat (about 180°C) and quenching by pouring onto a metal surface. The glass was chipped off and powdered for use, using a pestle and mortar.

Dissolution studies were carried out using BP rotating basket apparatus. To adhesive tape fastened around the outside of the basket sticky side out, was attached either DTA aluminium crucibles containing a glass produced in situ, or a powdered system (50–100 mg). The basket was rotated at 55 rpm in 1 litre of water at 37°C and pH 7. Assay of phenobarbitone was performed by adding a drop of 2 N ammonium hydroxide to a 5 ml sample and measuring absorbance at 240 nm using a Unicam SP500.

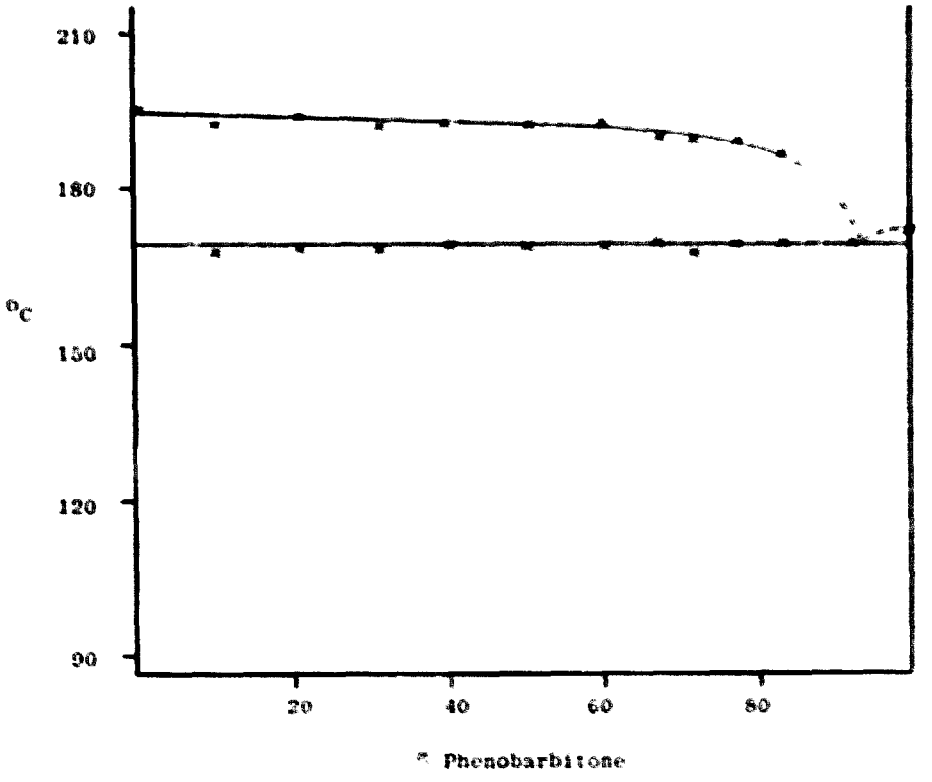

Fig. 1. Phase diagram of phenobarbitone–sucrose system prepared using physical mixtures.

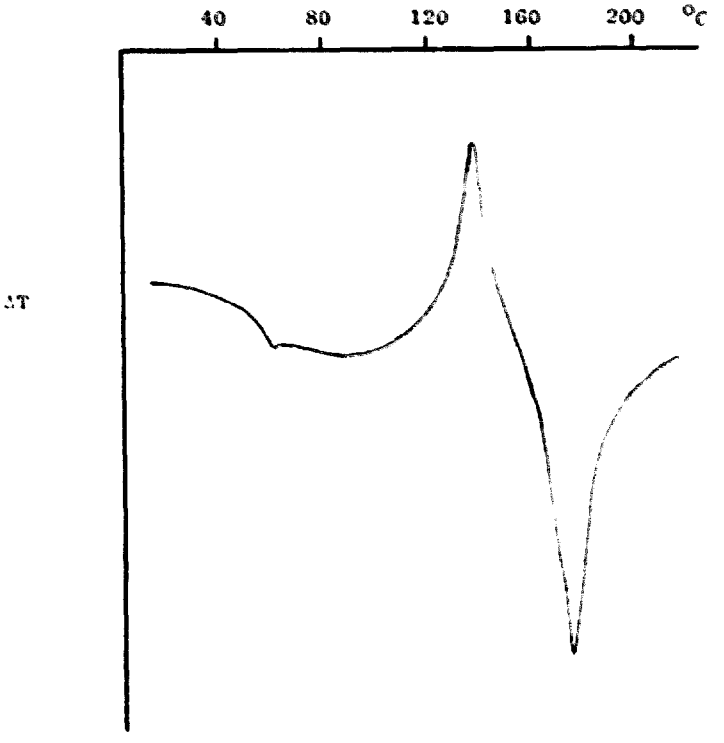

Fig. 2. DTA thermogram of the vitreous system containing 50% phenobarbitone.

Results and Discussion

The phase diagram for physical mixtures (Fig. 1) was constructed using the extrapolated onset temperature (T_{onset}) of the first endotherm and the peak temperature (T_{peak}) for the second endotherm. A simple eutectic system is shown to exist with a eutectic temperature of 168°C. The eutectic composition has not been determined exactly, but is about 90% phenobarbitone.

Rapid cooling of the fused system, produced by a DTA run, gave clear brittle glassy materials. Their thermograms showed an exotherm preceding the endotherm (Fig. 2) and, when a sub-ambient starting temperature was used, a low temperature glass transition. The exotherm was taken to indicate the crystallization of the glass. This was confirmed by observation of the crystalline appearance of samples at temperatures between the exotherm and endotherm. An extrapolated onset temperature was determined for the exotherm with a view to producing a phase diagram.

Construction of a phase diagram for the vitreous systems at first proved difficult due to an apparent lack of reproducibility of the exotherm T_{onset}. It was subse-

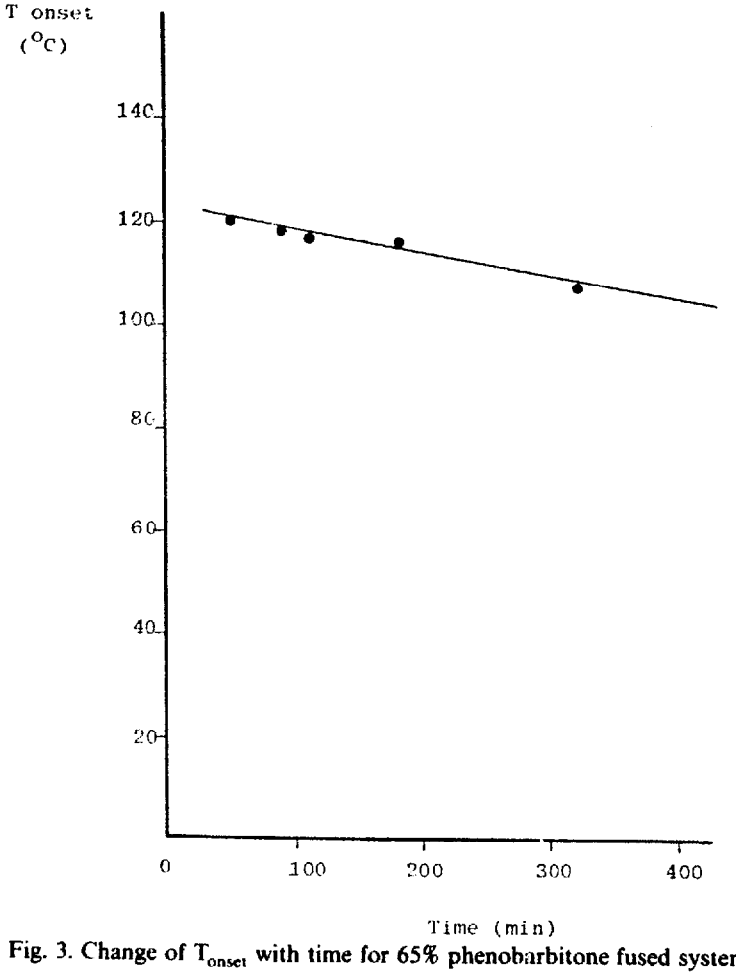

Fig. 3. Change of T_{onset} with time for 65% phenobarbitone fused system.

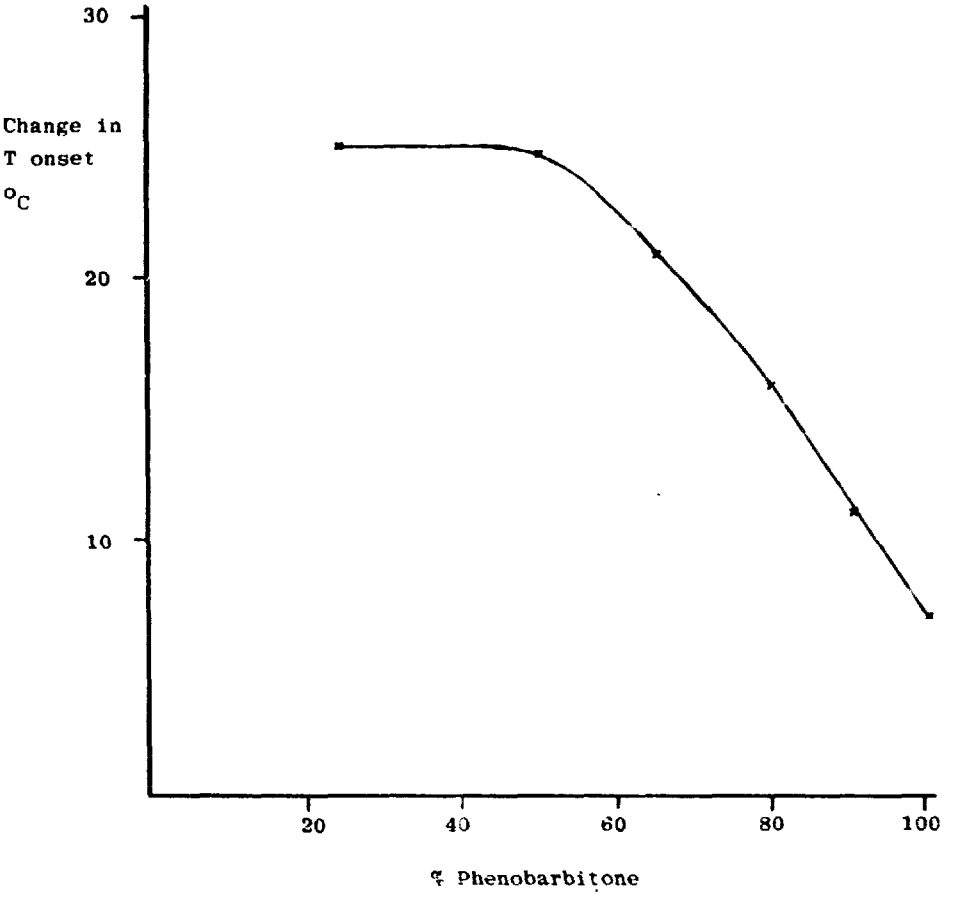

Fig. 4. Relationship between reduction of exotherm T_{onset} and phenobarbitone concentration after 400 min storage.

quently found that the T_{onset} decreased with storage time (Fig. 3) and that the extent of this decrease increased with sucrose content. Fig. 4 shows the latter relationship for 400 min samples. There is little variation in exotherm T_{onset} with composition when using values obtained at a fixed time after preparation (Fig. 5). Thus it would appear that the mixing of these two glass-forming materials does not significantly alter the temperature stability of the resultant glass. It was found that bulk prepared glasses, when powdered, showed the same thermograms as the corresponding in situ-prepared glass. Thus there does appear to be a greater physical stability of these phenobarbitone–sucrose glasses than Summers (1978) found with pure barbiturates.

Two techniques have been used for dissolution studies. The first used in situ glasses retained in the DTA aluminium crucibles in which they were prepared. Whilst there will be some changes in the exposed surface area, it was hoped that dissolution on these systems would give an indication of the intrinsic dissolution rate of the glass systems. The results, shown in Fig. 6, indicate that the dissolution rate is proportional to sucrose concentration. The second dissolution method used powdered glasses and compared them with physically mixed powders of the same composition.

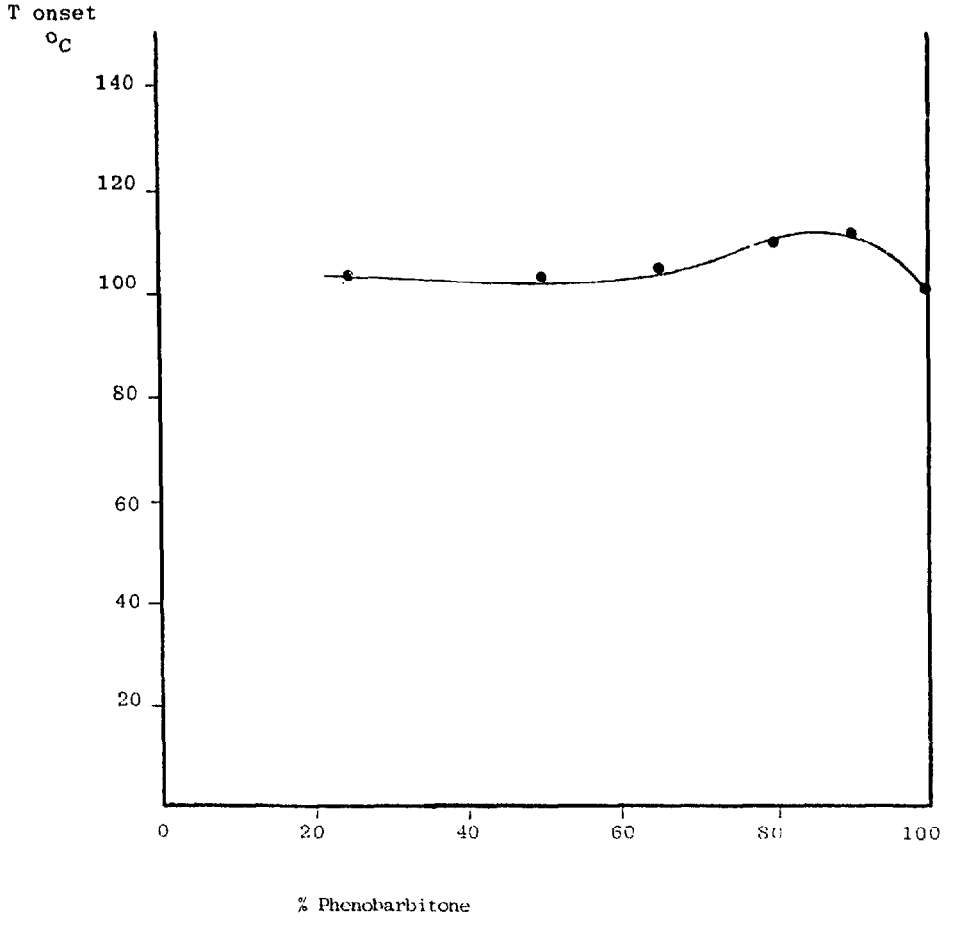

Fig. 5. Relationship between exotherm T_{onset} and phenobarbitone concentration after 400 min storage.

Fig. 7 shows that no significant differences were found between the dissolution profiles of the systems studied.

Thus there appears to be a conflict between the results obtained by the two methods. However, it was observed that the in situ glass samples became opaque during dissolution experiments. Thermograms of the residues, after drying, showed no glass transition and no exotherm. Interpreting the exotherm as indicating the crystallization of the glass, these thermograms confirm that no glass remained after the dissolution experiments. A possible explanation for this finding was that the dissolution medium water was causing devitrification. The effect of both water and atmospheric moisture was, therefore, investigated.

A technique was evolved whereby a drop of water was added to a glass in a DTA crucible. After a predetermined time, the bulk of the water was removed using a paper tissue, then the sample was further dried in an oven at 50°C for 5 min. This process did not give complete drying with the result that the glass crystallization exotherm was frequently superimposed on an endotherm due to water evaporation. Table 1 records the duration of existence of these glasses, as indicated by the

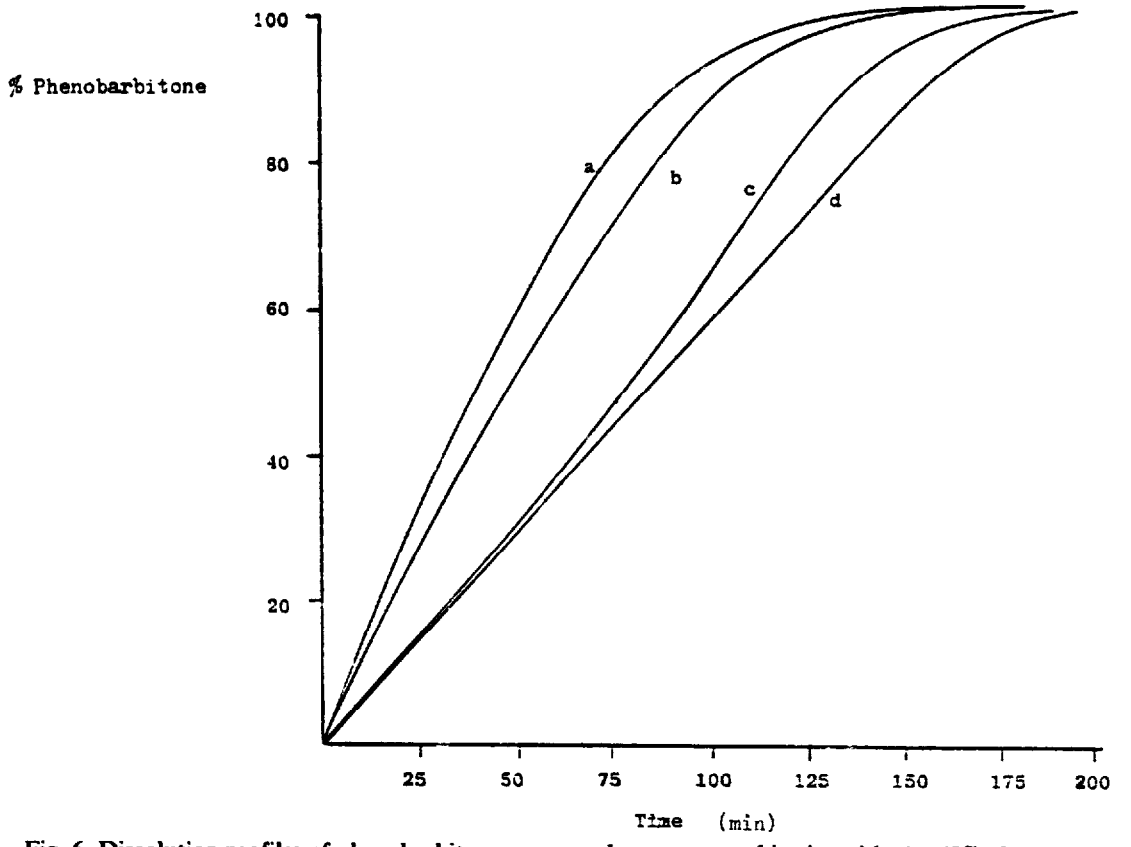

Fig. 6. Dissolution profiles of phenobarbitone–sucrose glasses prepared in situ with: (a) 40% phenobarbitone; (b) 65% phenobarbitone; (c) 80% phenobarbitone; and (d) 100% phenobarbitone.

presence of the exotherm. It demonstrates that water can cause devitrification and that the rate of the process is dependent on sucrose concentration.

Some glasses were also stored under various humidity conditions. Storage in a dessicator resulted in a sample having a thermogram identical to a freshly prepared glass. As the relative humidity of storage increased, so the T_{onset} of the exotherm decreased. These changes paralleled the decrease in T_{onset} with storage time observed during phase diagram construction.

It has been shown, therefore, that both water and atmospheric moisture, have the effect of destabilizing phenobarbitone–sucrose glass systems. This finding can also explain the dissolution results. The DTA exotherm peak height observed during stability studies underwent gradual reduction with time. Thus it may be deduced that the process is not instantaneous. Unfortunately, because of the overlapping endotherm due to water evaporation, this process could not be accurately quantified. Sucrose dissolves rapidly when in contact with water allowing the phenobarbitone to crystallize. Because sucrose is the water-soluble component in the glasses, the higher its concentration the faster will be the process. Likewise at a given sucrose concentration, the rate of devitrification will depend on the area of contact between sucrose and water. These deductions can be used to explain the different rates of devitrification observed during this work.

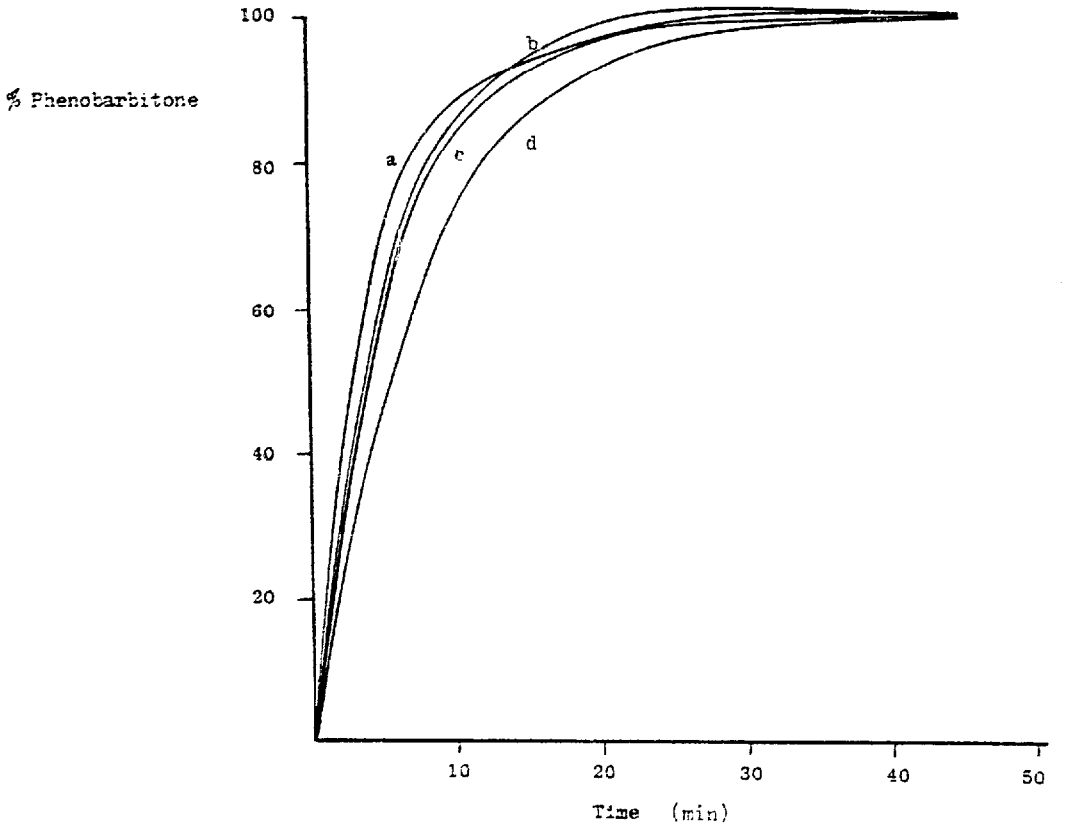

Fig. 7. Dissolution profiles of phenobarbitone–sucrose powder systems: (a) 100% phenobarbitone; (b) 65% phenobarbitone powder mixture; (c) 65% phenobarbitone powdered glass; and (d) 100% phenobarbitone powdered glass.

With the in situ-prepared glasses, a relatively small surface area is exposed to water and so devitrification is relatively slow and becomes dependent on the rate of penetration of the water. Thus the observed differences between the dissolution rates of the in situ-prepared glasses reflects, to some extent, real differences in dissolution rate. However, with the powdered glasses, the large exposed surface area results in a

TABLE I

THE STABILITY OF PHENOBARBITONE–SUCROSE GLASS SYSTEMS WHEN EXPOSED TO WATER. THE PRESENCE OF A DTA EXOTHERM WAS TAKEN TO INDICATE THAT A GLASS WAS PRESENT

Composition (% phenobarbitone)	Last time glass present (min)	First time devitrified (min)
40	12.5	15
65	23.5	25
85	60	77
100	270	–

rapid devitrification. As a result the observed dissolution profiles match those of non-glass-containing powder mixtures. Powdered glasses exposed to atmospheric moisture will acquire a film of moisture on the surface which will also cause devitrification but at a slower rate owing to the small amount of water present.

This work has shown that the glasses produced have a faster dissolution rate than phenobarbitone and can be powdered. However, the instability of the glasses to atmospheric moisture means that they are probably not suitable for use in formulation. Likewise, the powdered form of the glass, if incorporated into a dosage form, would not offer any advantageous dissolution rate.

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