

THE STABILITY OF CALCIUM GLUCOHEPTONATE SOLUTIONS

R. Suryanaryanan and A.G. Mitchell, Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, V6T 1W5, B.C., Canada.

Calcium glucoheptonate is official in the USP XX as Calcium Gluceptate and is described as the calcium salt of D-glycero-D-gulo-heptonic acid which is the α epimer of glucoheptonic acid. It is an extremely soluble compound and in excess of 250 percent w/v can be dissolved in water to give a highly viscous solution. Reports of recrystallization on storage have appeared from 1976 onwards and were attributed by Muller et al (1979) to the presence of seed crystals of an insoluble hydrate. They suggested that stable solutions could be prepared if the seed crystals were destroyed by heating. We have confirmed that stable solutions can be prepared by autoclaving but that the α hydrate crystallized rapidly from unheated solutions. The time for precipitation varied with the commercial source. The most stable solution was prepared from a salt described as calcium α - β glucoheptonate and the least stable was supplied as Calcium Gluceptate USP which precipitated within 2 hours, Table 1.

Table 1. Stability of calcium glucoheptonate solution 26.7% w/v and proportion of α epimer in various commercial samples

Source	Time for recrystallization (days)	Proportion of α epimer (percent)
Pfanstiehl α - β	stable	51.8
Givaudan	8	71.8
Italsintex	2	72.4
Pfanstiehl USP	<1	100

It therefore seemed likely that, in addition to the presence of seed crystals, stability may depend on the relative proportions of the α and β epimers. It is interesting that to comply with the USP specifications, calcium glucoheptonate should be the unstable α epimer, although no procedure is given in the monograph for the identification or assay of the α form. Hence methods have been developed to identify and to determine the proportions of the α and β epimers.

An aqueous solution of calcium glucoheptonate was converted into a mixture of glucoheptonic acids and their corresponding γ lactones by a passage through a cation exchange column. The solution was freeze-dried and the acid-lactone mixture was completely converted to the γ lactones using concentrated HCl.

Trimethylsilyl (TMS) derivatives of the lactones were formed by reaction with trimethylsilylimidazole in pyridine. Gas chromatography on a 3% OV-225 column using a flame ionization detector gave two peaks. A control experiment using the TMS derivative of a reference sample of the γ lactone of α -glucoheptonic acid gave a single peak having the same retention time as the second peak of the sample, thereby indicating that the second peak is due to the TMS derivative of this γ lactone. The two GC peaks gave similar mass spectral patterns and subjecting the reference material to the same GC-MS analysis, confirmed that peak 2 was the TMS derivative of the γ lactone of α -glucoheptonic acid. Since the GC peaks 1 and 2 have different retention times but the same molecular ion and similar fragmentation patterns, the chemical structures of the two compounds must be very similar and hence peak 1 is attributed to the TMS derivative of the γ lactone of β glucoheptonic acid. The relative proportions of the α and β epimers were calculated using the TMS derivative of sucrose as an internal standard. The correlation between the stability results and the proportions of the α and β epimers in various commercial samples of calcium glucoheptonate shown in Table 1, supports our hypothesis that precipitation depends on the proportion of the α epimer. Muller, R. et al (1979) Ann. Pharm. Franc. 37:301-308.