A STUDY OF 5-HYDROXYMETHYLFURFURAL LEVELS IN LAEVULOSE INJECTIONS AFTER AUTOCLAVING AND DURING STORAGE

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Laevulose Injection is manufactured for use as an intravenous infusion and one of the major problems is the formation of the degradation product 5-hydroxymethylfurfural (5HMF) due to exposure to high temperature during sterilisation (Stenlake 1975). 5HMF has been implicated as a contributory factor in infusion thrombophlebitis (Wing 1971). The level of 5HMF and related substances is currently controlled in the British Pharmacopoeia where an absorbance limit $A^{284}_{1\,cm} \not> 0.250$ is specified. In this study, the spectrophotometric method has been used to examine the level of 5HMF in Laevulose Injection under various conditions of sterilisation and storage in order to establish adequate criteria for the shelf-life of this product.

Preliminary studies revealed that immediately after autoclaving at 115–118°C for 30 minutes, batches of Laevulose Injection 5% w/v displayed 5HMF levels in the range $A^{284}_{1\,cm}$ 0.080 to 0.231. After two years nominal shelf-life, the 5HMF levels in these batches had approximately doubled, and some of the batches exceeded the BP limit. A series of experiments were designed to examine this problem. Batches of Laevulose Injection 5% (500ml) were sterilised in an Express Portable autoclave using sterilisation cycles which varied from 24–50 minutes, temperatures being monitored by a recording thermocouple. The effect of storage temperature, which in hospital wards was 24–26°C, was examined by storing parts of each batch at ambient laboratory temperature (19–22°C), at 25°C and at 4–6°C. The level of 5HMF was assessed by measuring the $A^{284}_{1\,cm}$ in duplicate bottles from each batch at each temperature, initially and at 28 day intervals. The relative standard deviation of the spectrophotometric assay, with respect to initial 5HMF values in 6 identical bottles of Laevulose Injection 5% after sterilisation for 24 minutes was 1.50%. In samples of the injection before autoclaving, the absorbance at 284nm was zero.

5HMF Levels (as $A^{284}_{1\,cm}$) in Laevulose Injection 5% w/v After Autoclaving at 115–118°C and Storage at 25°C.

Storage Time (days)	Sterilisation Time Cycle (mins)			
	24	33	45	50
0	0.156	0.157	0.172	0.197
35	0.188	0.198	0.224	0.243
56	0.193	0.202	0.229	0.245
84	0.203	0.212	0.240	0.255
112	0.206	0.218	0.244	0.260
140	0.218	0.228	0.255	0.271
210	0.243	0.253	0.282	0.297

The results of this study confirm the progressive rise in 5HMF levels. The data at ambient temperature differs little from that at 25°C but the rate of 5HMF production at 6°C is substantially lower. Variation in the autoclave cycle time directly affects the initial 5HMF level. If the injections are stored at 6°C this initial variability is of less concern since the level does not rise sufficiently to exceed the BP limit after 2 years. Storage in a refrigerator is however a costly procedure for such large volume injections. At ambient temperature the shelf-life of a batch autoclaved at 115°C for 33 minutes would be < 1 year while at 25°C it would be < 8 months before the BP limit was exceeded. In practice it is necessary to reduce to a maximum of 1 year the shelf-life of this injection. To reduce the effect of autoclave cycle variation it would be reasonable to apply a limit on the initial 5HMF level so that batches where $A^{284}_{1\,cm} > 0.100$ are rejected.

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