

An Evaluation of the Stability of a Polymeric Controlled Release Hydrogel Formulation in Relation to ICH Guidelines

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1. Summary

A stability study was carried out on novel clindamycin phosphate controlled release (CR) hydrogel polymer inserts. The inserts also contained citric acid and butylated hydroxyanisole. Nine impurity / degradation peaks were found and required further investigation.

2. Introduction

Controlled Therapeutics is developing a clindamycin phosphate vaginal hydrogel insert (CVI) for the delivery of clindamycin phosphate. It is intended that incorporation of clindamycin phosphate into a hydrogel polymer system will result in an efficient and efficacious intravaginal treatment of bacterial vaginosis in women. Clindamycin phosphate (C-P) is a semi synthetic lincosamide antibiotic produced from the less active lincomycin. Citric acid is present in the loading solution to give optimal loading of clindamycin phosphate into the polymer. Upon manufacture of the insert, in total there were six peaks that were at or above the ICH identification threshold for drug products. Of these, three were attributed to the method used to manufacture the bulk drug. As described earlier, the active is a semi synthetic, part fermentation product and contains many impurities. The remaining peaks were attributed to the hydrogel polymer and excipients used to manufacture the CVI. When these inserts were placed on stability, eight new peaks were found at or above the identification level after storage at 40°C for three months. Of these, four were attributed to the stability of C-P in the CR product. There was a need to establish the cause of these peaks. In particular a peak at 1.36 relative retention time (RRT) to C-P was found to be a major impurity / degradation product on real time stability at 25°C and 40°C. This paper will focus upon it and will demonstrate issues relating to developing novel CR formulations, for the delivery of actives, which can be used in clinical studies.

3. Experimental Methods

A stability indicating HPLC method for clindamycin phosphate was developed and adapted from the European Pharmacopoeia method. Column – 250 x 4.6mm (id) octylsilica 5-10µm. Detection – 210nm. Flow rate – 1ml min⁻¹. Column temperature – 30°C. Mobile phase – 18% acetonitrile, 82% of a 13.6g/l solution of potassium dihydrogen orthophosphate adjusted to pH 2.5 with orthophosphoric acid.

A stability investigation was carried out on the samples shown in table 1. Desiccation was being considered as an option to enhance stability. Accelerated stability at 60°C for one week was found to mimic real time stability at 25°C and 40°C. This technique provided a means of screening a number of CR formulations in a short period of time.

4. Results and Discussion

A typical chromatogram of the citric acid loaded polymer can be seen in figure 1. It can be seen that in addition to the main band peak (ca. 14.5 minutes), there were nine other impurity / degradation peaks present at or above the reporting / identification level.

A typical chromatogram for the potency / impurity testing, after three months at 40°C, of citric acid loaded polymer can be seen in figure 2. It can be seen that in addition to the main band peak (ca. 14.5 minutes) there is now a total of 18 impurity / degradation peaks (at or above the reporting / identification level), some of which are present in significant amounts.

The four peaks attributed to the stability of the novel CR inserts had RRT to C-P of 1.10, 1.15, 1.36 and 1.47. The sources of these peaks were examined by chromatographically evaluating the samples in table 1.

For the citric acid solution there were no peaks beyond the solvent front. Bulk drug samples did not show any major degradation peaks after one week at 60°C. However, when the citric acid loaded polymer was analysed after one week at 60°C there was found to be a major degradation peak at 1.36RRT, and the other key degradation peaks were evident. This is shown in figure 3.

The peak at 1.36RRT was found to increase further on stability when there was desiccant present. This is shown in figure 4.

The accelerated study produced chromatographic profiles for samples stored at 60°C for 1 week that were similar to those obtained on real time stability for 3 months.

It was thought that the peak at 1.36RRT might be due to the presence of citric acid. Therefore a batch loaded with clindamycin phosphate using only water in the loading solution was tested. The peak at 1.36RRT was not detected in either the non-desiccated (figure 5) or desiccated (figure 6) water loaded batch. Importantly the three other product related degradation peaks were not observed.

To further confirm the citric acid as being the cause of this major degradation peak, analysis was performed on mixtures containing bulk drug (C-P), citric acid and PEG 8000, and bulk drug (C-P), citric acid, PEG 8000 and desiccant. PEG 8000, the main component in the hydrogel polymer, was added as this would produce a mixture that had a composition which is closest to the finished product.

Table 1

Sample	Solution Prepared
1	Bulk Drug
2	Bulk Drug (1 week at 60°C)
3	Citric acid
4	Citric acid loaded polymer
5	Citric acid loaded polymer (1 week at 60°C)
6	Citric acid loaded polymer (1 week at 60°C) desiccated
7	H ₂ O loaded polymer
8	H ₂ O loaded polymer (1 week at 60°C)
9	H ₂ O loaded polymer (1 week at 60°C) desiccated
10	Bulk drug, citric acid, PEG 8000 (1 week at 60°C)
11	Bulk drug, citric acid, PEG 8000, desiccant (1 week at 60°C)

Figure 1 Citric acid loaded polymer (Initial testing)

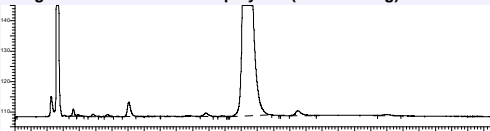


Figure 2 Citric acid loaded polymer (3 months at 40°C)

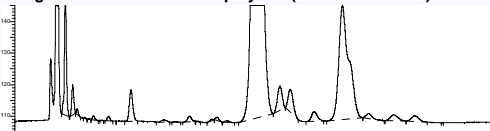
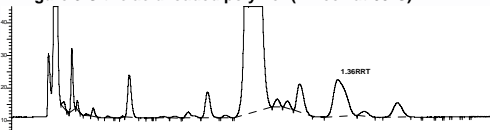


Figure 3 Citric acid loaded polymer (1 week at 60°C)



4. Results and Discussion Continued

These experiments found that the peak at 1.36RRT is present in these mixtures and is further accelerated when there is desiccant present. This degradation pathway did not take place when similar samples, where citric acid was absent, were examined and produced chromatograms that were similar to figures 5 and 6.

Figure 4 Citric acid loaded polymer (1 week at 60°C desiccated)

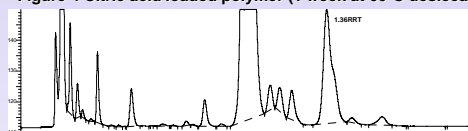


Figure 5 Water loaded batch (1 week at 60°C)

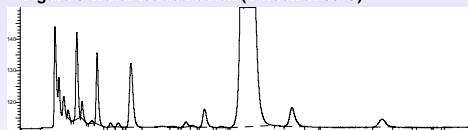
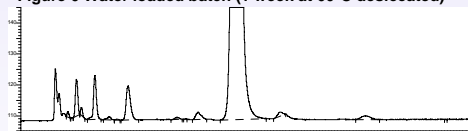


Figure 6 Water loaded batch (1 week at 60°C desiccated)



5. Conclusion

The major degradation product (1.36RRT) seen in the finished product testing for clindamycin phosphate loaded hydrogel polymer is due to the presence of citric acid and is further accelerated by the presence of desiccant. The removal of citric acid from the loading solution used would prevent this degradation. A method has been established that would allow fast screening of a number of C-P hydrogel CR formulations using different excipients that would indicate in a short period of time potential stability issues that might arise. Sources of peaks from polymeric CR formulations require to be attributed before stability studies can be properly conducted and product released for clinic.

References

1. ICH Harmonised Tripartite Guideline – Impurities in New Drug Products Q3B(R)
2. European Pharmacopoeia 4th Edition