

Controlled Release of Fluconazole from Linear Polyurethane Hydrogel Polymers with Different Percentage Swellings

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Summary

A linear polyurethane hydrogel polymer developed at Controlled Therapeutics was diffusion loaded with fluconazole (an antifungal drug) as a model drug molecule. The hydrophobicity and block structure of the polymer influenced the release of fluconazole from the linear polymer, as well as its loading capabilities.

1. Introduction

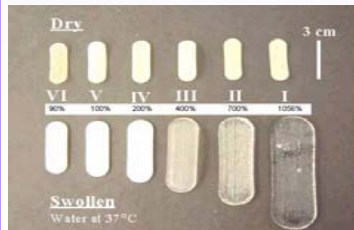
Controlled Therapeutics is currently developing thermoplastic polyurethane polymers for application as a delivery system, for *in-vivo* delivery of active molecules. The polymers manufactured are amphiphilic polymers which are composed of hydrophilic and hydrophobic components. Changing the molar composition of these polymers will result in a change in the nature of these polymers and the balance between these two compositions.

The controlled release of fluconazole (Fu) was examined by means of dissolution. It was found that the hydrophobic nature of the various linear polymers influenced the release of fluconazole.

2. Experimental Methods

Linear PEG based polyurethanes were polymerised from various molecular weight hydroxyl-terminated PEGs (PEG 4000 and PEG 8000), different types of diols (1,10-decanediol (DD) and 1,12-dodecanediol (DDD) and dicyclohexylmethane-4, 4-diisocyanate (DMDI) with different molar ratios of PEG: diol: diisocyanate. Generally, these polymers were made by melting the dried PEG together with the diol and the molten mixture was dried under vacuum to remove excess moisture. The reaction was catalysed by ferric chloride in the presence of DMDI. Reaction mixture was poured into billet moulds and cured and after cooling to ambient temperature, sliced into flat pessary shapes of dimension 30mm x 10mm x 1.0mm. Fluconazole was incorporated into the sliced polymer matrix by means of a solution diffusion technique. This involved swelling the polymer slices in a solution of the drug. The release of drug was examined from swollen units before drying and from units dried to the finished state. This enabled the effect of the swelling process on the release profile to be identified and show the effect of polymer composition only on drug release.

The amount of fluconazole released from the polymer was studied by means of dissolution based on the USP paddle method. This technique employed an automated UV dissolution system in which a Distek dissolution paddle system 2100C was connected to a Unicam UV 500 spectrophotometer via an Icalis peristaltic pump. The system was operated using Dsolve® software. The following parameters were used: paddle speed 50rpm, temperature 37°C, media 250ml or 500ml deionised degassed water, 20mm pathlength UV cells, wavelength 217nm or 261nm was used depending on the potency of the formulation analysed.



Picture 1. Dry and swollen units (in water) of six batches of polymer with different percentage swellings.

3. Results and Discussion

In advance of the determination of the fluconazole release from the different linear polymers, a validation package was established to demonstrate fitness for purpose of the methods. Linear polymer batches loaded with 10mg and 50mg of fluconazole per unit were analysed. Each batch had a different swelling in water (% swelling in brackets). Picture 1. This is due to the different stoichiometric compositions of the hydrogel polymers.

There is a relationship between the hydrophobic content of the polymers manufactured and drug release profile. Figure 1. The plot of amount released for different batches of 50mg fluconazole in linear polymer showed that the total amount of drug loaded into the different polymers had decreased, with decreasing swelling percentage of linear polymers. Figure 2. This effect observed for the loaded amount was due to the difference in the capacity of the polymers to absorb fluconazole. This appears to be directly related to swelling. It means that the higher the hydrophobic regions in the polymer, the lower the swelling. For example, the highest swelling polymer contained 92% w/w PEG in comparison to the lowest swelling polymer which contained 45% w/w PEG. Also, the capacity of polymer for absorption of fluconazole was lower. Therefore, a lower amount of fluconazole was loaded and released. It can be concluded that each polymer had a different capacity to absorb fluconazole.

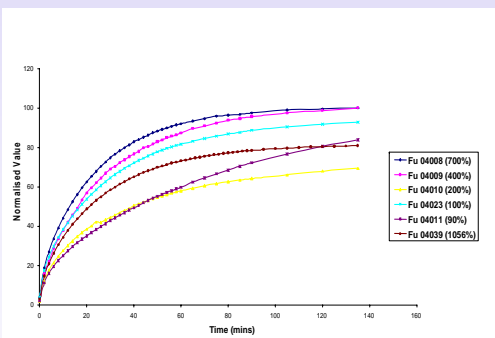


Figure 1. Comparison of the release of 10mg fluconazole from different batches of linear polymers with different swellings in the in-process swollen state.

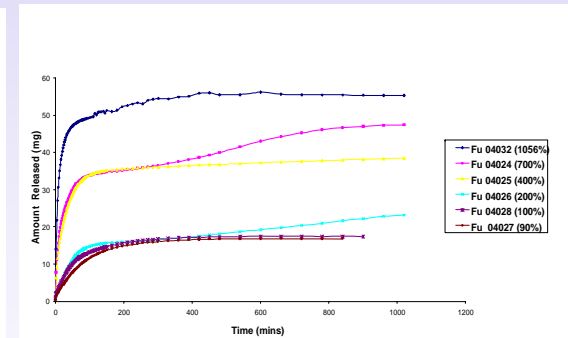


Figure 2. Comparison of the release of fluconazole from different batches of linear polymer with different percentage swelling in the dried state. 50mg target.

4. Conclusion

Each of the linear polymers had a different absorption capacity for fluconazole. This difference was due to the variation in the internal structure and composition of each polymer used. The linear polymers with lower swelling had higher hydrophobic content. This affected the amount of fluconazole that could be loaded for each batch. At low concentrations of fluconazole (10mg) for the various batches, the release from the swollen units indicates that the polymer composition impacts control on the fluconazole release profile. For the 50mg fluconazole loaded batches, it was observed that the polymer with the highest absorption capacity resulted in the largest amount of fluconazole loaded and released.

References

Patent No. Halliday J.A. et al. WO2004029125

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