

Evaluation of 2-Hydroxy Propyl β -Cyclodextrin in Release of Fluconazole from Cross-Linked Polymers

Maher Khattab, Robert Cochrane, Denis Carr, Mark Livingstone, Janet A Halliday
Controlled Therapeutics (Scotland) Ltd, 1 Redwood Place, Peel Park Campus, East Kilbride G74 5PB, Scotland, UK
maher.khattab@ctscotland.com

1. SUMMARY

Loading and release rates are controlled by the quantity of 2-hydroxy propyl β -cyclodextrin (HPBCD). A target dose of 100 mg of fluconazole resulted in 80 mg being loaded into cross-linked hydrogel polymer using 25 mg of HPBCD. Pessary appearance was improved using 50 mg of fluconazole with HPBCD.

2. INTRODUCTION

Many drugs are hydrophobic or sparingly soluble in water. HPBCD can improve drug solubility [1]. Controlled Therapeutics developed a hydrogel delivery system, which is approved for *in-vivo* drug delivery of certain active molecules. Pessaries prepared from that cross-linked hydrogel were examined using fluconazole.

The poster investigates the effect of HPBCD on loading and release of fluconazole from cross-linked hydrogel pessaries [2].

3. EXPERIMENTAL METHODS

Water-swallowable cross-linked polyurethane inserts (polyethylene glycol 8000: dicyclohexylmethane-4, 4-diisocyanate: hexanetriol, 1:2.8:1.2) of 0.8x10x30 mm were manufactured [3], purified twice with water then by 25% ethanol at 25°C, and dried in a coating pan for 24 hrs.

Purified polymers were loaded with fluconazole by incubating and mixing for 20 to 24 hrs in a solution containing the desired fluconazole and HPBCD doses for 24 hours at 25°C. Loading solution was either 25% ethanol (Table 1) or 50% ethanol (Table 2). Swollen loaded polymers were dried under vacuum.

The amount of fluconazole released from the hydrogel was studied by dissolution (USP paddle method). The following parameters were used: paddle speed 50rpm, temperature 37°C, media 500ml deionised degassed water, 20mm path length cells and wavelength of 261 nm.

4. RESULTS AND DISCUSSION

Using 25% ethanol as the loading solution, a quick release of fluconazole from polymers during the first few minutes was observed, followed by a controlled release, with and without HPBCD (Fig. 1). A trend existed of decreased initial drug release with increasing concentration of HPBCD. Thus HPBCD improves penetration of fluconazole into the hydrogel polymer, leaving less surface coating.

Release of 50 mg of fluconazole from polymers, using 50% ethanol as the loading solution (Fig. 2), shows similar results for the different batches, except for FU04021. FU04021 contained the highest amount of HPBCD (125 mg) and resulted in better controlled release than any of the other batches.

Release of 100 mg of fluconazole from batches with different concentrations of HPBCD (Fig. 3) shows that as the amount of HPBCD increases, the amount of fluconazole released decreases. It appears that the large amounts of HPBCD and fluconazole could not find space within the polymeric matrix to load. This explains the low amount of released fluconazole from batch FU04007 (250 mg of HPBCD).

Moreover, as the amount of HPBCD increases, burst release decreases and better controlled release is observed (comparing batches with 250 mg and 25 mg of HPBCD, Fig. 3). HPBCD enhances fluconazole solubility and thus drug is loaded deep into the polymeric matrix, which controls the release rate of fluconazole.

5. CONCLUSION

Loading 50 mg of fluconazole with HPBCD in cross-linked pessaries resulted in controlled release, with and without HPBCD, and with acceptable polymer shape and surface appearance.

Dissolution results of 100 mg target dose indicated that 95.7 mg of fluconazole can be loaded into pessaries using 25 mg of HPBCD. As HPBCD concentration increased, the achievable dose decreased.

Increased HPBCD lowered initial burst release and resulted in more controlled release. With no HPBCD, fluconazole loaded into pessaries but remained visible on the surface of the polymer. Thus, HPBCD aids in dissolving fluconazole, loading into polymers and controlling its release.

REFERENCES

1. Khattab et al., Solubility and Loading of Fluconazole in Cross-Linked Polymers, CRS 2006, Vienna, Austria
2. PCT/GB2005/004227
3. US 4,894,238.

Table 1. Target fluconazole & HPBCD per polymer. Loading solution is 25% ethanol.

Batch Number	Fluconazole	HPBCD
FU04014	50 mg	0 mg
FU04015	50 mg	12.5 mg
FU04016	50 mg	50 mg
FU04017	50 mg	125 mg

Table 2. Target fluconazole and HPBCD per polymer. Loading solution is 50% ethanol.

Batch Number	Fluconazole	HPBCD
FU04018	50 mg	0 mg
FU04019	50 mg	12.5 mg
FU04020	50 mg	50 mg
FU04021	50 mg	125 mg
FU04005	100 mg	25 mg
FU04006	100 mg	100 mg
FU04007	100 mg	250 mg

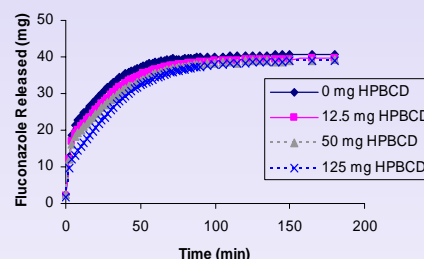


Fig. 1. Dissolution of 50 mg of fluconazole in water at 37°C from cross-linked pessaries loaded with various concentrations of HPBCD. Loading solution is 25% ethanol.

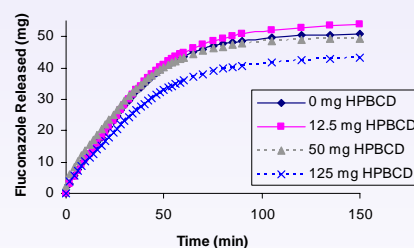


Fig. 2. Dissolution of 50 mg of fluconazole in water at 37°C from pessaries loaded with various concentrations of HPBCD. Loading solution is 50% ethanol.

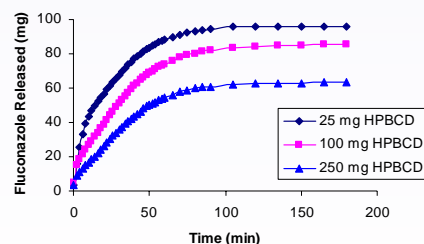


Fig. 3. Dissolution of 100 mg of fluconazole in water at 37°C from pessaries loaded with various concentrations of HPBCD over a period of 3 hours. Loading solution is 50% ethanol.