Solubility and Loading of Fluconazole in 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

Fluconazole (FU) solubility increased from 5 mg/ml in water to 100 mg/ml using 2-hydroxy propyl β-cyclodextrin (HPBCD) (100 mg) or sulfobutyl ether-β-cyclodextrin (SBECD) (50 mg) in a solution of 1 g of 50% ethanol.

Drug loaded into cross-linked polymers increased as ethanol percentage in the loading solution increased.

2. INTRODUCTION

Many potential drugs are water insoluble or sparingly soluble in water, thus limiting their use in various drug formulations, such as hydrogel polymeric systems, aqueous gel formulations, drop solutions or solutions for injection.

Loading hydrophobic drugs into hydrogels is problematic, because water is the main loading medium. Even if hydrophobic drugs are loaded into hydrogels, they are not easily released.

The poster investigates the solubility of fluconazole in solvents with and without HPBCD or SBECD. Loading and release of fluconazole in cross-linked polymers was also studied using different loading media [1].

3. EXPERIMENTAL METHODS

Solubility of fluconazole was determined by adding drug to water or water, ethanol and cyclodextrins. Solubility was assessed visually at room temperature. Soluble samples were incubated at 4°C, 25°C and 37°C overnight and their solubility was re-examined.

Water-swellable crosslinked polyurethane pessaries (polyethylene glycol 8000: dicyclohexylmethane-4, 4-diisocyanate: hexanetriol, 1:2.8:1.2) of 0.8x10x30 mm were manufactured [2] and purified according to in-house procedures.

50 mg of fluconazole and 50 mg of HPBCD were loaded into pessaries overnight by means of solution diffusion and dried under vacuum overnight. Loading temperature was 25ºC. Loading solution varied between water, 25% ethanol and 50% ethanol. Fluconazole release from the hydrogels was studied by dissolution (USP paddle method), using the following parameters: paddle speed 50rpm, temperature 37ºC, media 500ml deionised degassed water, 20mm path length cells and 261nm.

4. RESULTS AND DISCUSSION

5 mg of fluconazole is soluble in 1 g of water; higher amounts are not (Table 1).

Table 2 shows the solubility of 50 mg of fluconazole in 1 g of 50% ethanol/water (w/w), containing 0 to 100 mg of HPBCD or SBECD. As HPBCD content increased, solubility at 4°C also increased. Incubating overnight at 25°C and 37°C resulted in soluble solutions.

Solubility of FU at 4°C improved using SBECD as compared to HPBCD.

100 mg of fluconazole was also soluble in a solution of 1g of 50% ethanol, containing 100 mg of HPBCD, at 25°C and 37°C.

Loading was assessed by the amount of drug released using dissolution testing. As the amount of ethanol in the loading solution increases, fluconazole solubility increases and loaded drug increases (Fig. 1 and Table 3). Fig. 2 is the normalised % release, which shows less burst release with 50% ethanol loading solution. Table 3 shows actual fluconazole potency after 3.5 hour dissolution.

Table 1. Fluconazole solubility in water at room temperature

Floucoazole conc	Solubility
5 mg/ml	Soluble
15 mg/ml	Insoluble
25 mg/ml	Insoluble
50 mg/ml	Insoluble

Table 3. Target HPBCD and fluconazole content and actual fluconazole content after 3.5 hour dissolution in water at 37°C

Batch Number	Loading Solution	Target HPBCD	Target FU	Actual FU Content
FU04022	Water	50 mg	50 mg	20.6 mg
FU04016	25%ethanol	50 mg	50 mg	39.7 mg
FU04020	50%ethanol	50 mg	50 mg	49.6 mg

Table 2. Solubility of fluconazole with HPBCD or SBECD in 50% ethanol. Concentration is mg/1 g of 50% ethanol. (ND: Not determined)

FU Conc	HPBCD or SBECD Conc	Solubility after overnight incubation, using HPBCD, at			Solubility after overnight incubation, using SBECD, at		
		4°C	25°C	37°C	4°C	25°C	37°C
50	0	Insoluble	Soluble	Soluble	Soluble	Soluble	Soluble
50	5	Insoluble	Soluble	Soluble	Soluble	Soluble	Soluble
50	12.5	Insoluble	Soluble	Soluble	Soluble	Soluble	Soluble
50	25	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
50	50	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
50	100	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
100	100	Insoluble	Soluble	Soluble	ND	ND	ND

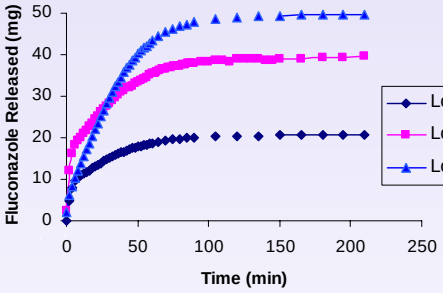

Fig. 1. Release of 50 mg of fluconazole in water at 37°C from pessaries loaded with 50 mg of HPBCD using different loading solutions

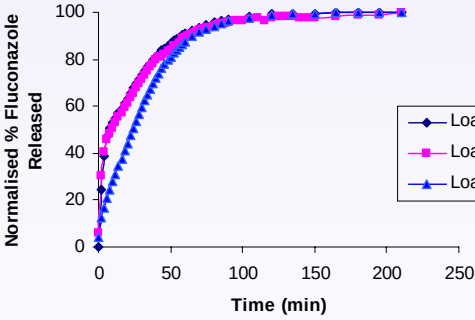

Fig. 2. Normalised % release of 50 mg of fluconazole in water at 37°C from cross-linked pessaries loaded 50 mg of HPBCD

5. CONCLUSION

Three factors aided the solubility of fluconazole: ethanol, cyclodextrin derivatives (HPBCD and SBECD) and temperature, where SBECD is superior to HPBCD.

Fluconazole solubility in the loading solution is a major factor in controlling the loading of drug into cross-linked polymers. As the amount of ethanol in the loading solution increases, loaded fluconazole also increases.

REFERENCES

1.PCT/GB2005/004227
2.US 4,894,238