

SYNTHESIS OF LINEAR WATER-SWELLABLE POLYURETHANE POLYMERS FOR DRUG DELIVERY SYSTEMS

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1. Introduction

Water-swollable crosslinked polyurethanes are excellent polymer matrices for controlled drug release systems,^{1,2,3,4} especially when water-soluble low-molecular-weight active agents are used. The relatively low swelling behaviour of crosslinked poly(ethylene glycol) based polyurethanes has been one of the limitations for their use with high-molecular-weight active agents, as well as, the restricted processability due to the crosslinked nature of the polymer. Development of a more versatile polymer matrix could open up the traditional routes of delivery, e.g. vaginal or buccal delivery, for new pharmaceutically active agents. In this work, the effects of molar ratios, length and type of diol and PEG on the properties of linear poly(ethylene glycol) based polyurethanes were studied.

2. Synthesis of Poly(ethylene glycol) based polyurethanes

Different types of linear polyurethanes (Tables 1, 2 and 3) were synthesised by reacting poly(ethylene glycol) (PEG), diol and dicyclohexylmethane-4,4-diisocyanate (DMDI) at different molar ratios.⁵ In the polyurethane synthesis, various molecular weight PEGs (PEG4000, PEG8000, PEG12000 or PEG35000) were used as a hydrophilic structure unit with 1,6-hexanediol (HD), 1,10-decanediol (DD), 1,12-dodecanediol (DDD) or 1,16-hexadecanediol (HDD) as a hydrophobic structure unit. Generally these hydrogels were made by melting the dried PEG together with the diol at 85°C. Molten mixture was dried under vacuum at 95°C to remove excess moisture. Catalyst, ferric chloride, was mixed with a small amount of molten mixture and added to the reaction vessel together with the PEG-diol mixture before DMDI addition. Reaction mixture was agitated for 150 s at 427 rpm before the polymer was poured into billet moulds and reacted for 10 hours at 95°C. After cooling to ambient temperature, polymer was demoulded and polymer slabs were sliced. These pessaries were purified before model drugs were loaded and dissolution studies performed.⁶ Crosslinked PEG based polyurethanes were polymerised as described elsewhere.^{1,2}

3. Results

Polymer properties were tailored and the swelling of hydrogels were controlled by changing the molar ratios of PEG, diol and DMDI, and by changing the type and length of diol and PEG. Increasing the molecular weight of PEG increases the swelling of polyurethanes (Table 1).

The effect of different diols on the swelling of pessaries can be seen in Table 2. Increasing the length of diol, which decreased the hydrophilicity of polymer, decreased the swelling of pessaries.

Table 3 shows that by changing the molar ratio between PEG and diol from 0.1:1.0 to 0.9:1.0 the swelling properties of hydrogel pessaries were dramatically increased. When the above-mentioned variables were combined, the swelling of hydrogel pessaries varied in a range from 200 to 1050% or more.

The swelling behaviour, which depends on the polymer structure, of the various polymers can be utilised to give different drug release rates.^{4,6} The dissolution profiles of model drugs with the linear hydrogel polymers were compared with the crosslinked polymer by Lee et al.⁶

Table 1. The effect of PEG molecular weight on the pessary swelling percentage.

| PEG (g/mol) | 4 000 | 8 000 | 12 000 |
|-------------------------|-------|-------|--------|
| PEG (Molar Ratio) | 0.7 | 0.7 | 0.7 |
| DD (Molar Ratio) | 1.0 | 1.0 | 1.0 |
| DMDI (Molar Ratio) | 1.7 | 1.7 | 1.7 |
| Percentage Swelling (%) | 400 | 750 | 1 000 |
| Crystallinity (%) | 36.3 | 49.3 | 46.5 |

Table 2. The effect of different diol on the pessary swelling percentage.

| Diol | HD | DD | DDD | HDD |
|-------------------------|------|------|------|------|
| PEG 8 000 (molar ratio) | 0.7 | 0.7 | 0.7 | 0.7 |
| Diol (molar ratio) | 1.0 | 1.0 | 1.0 | 1.0 |
| DMDI (molar ratio) | 1.7 | 1.7 | 1.7 | 1.7 |
| Percentage Swelling (%) | 900 | 750 | 650 | 500 |
| Crystallinity (%) | 52.8 | 49.3 | 38.2 | 45.8 |

Table 3. The effect of molar ratio on the pessary swelling percentage.

| PEG 8 000 (Molar Ratio) | 0.9 | 0.7 | 0.1 |
|-------------------------|------|------|------|
| DD (Molar Ratio) | 1.0 | 1.0 | 1.0 |
| DMDI (Molar Ratio) | 1.9 | 1.7 | 1.1 |
| Percentage Swelling (%) | 1050 | 750 | 200 |
| Crystallinity (%) | 48.6 | 49.3 | 33.1 |

4. Conclusion

The swelling percentage, which also affects drug release profiles, of linear water-swollable polyurethane polymers can be tailored over a wide range by adjusting the molar ratio, the type and length of diol and PEG (Figure 1 and 2). The advantages over the crosslinked polymer are that the linear polymer behaves as a hydrogel in aqueous environment, but is thermoplastic, solvent soluble and can be processed using conventional polymer processing methods. These linear polymers offer new properties to existing hydrogels and can be utilized in the design of future drug delivery systems.

References

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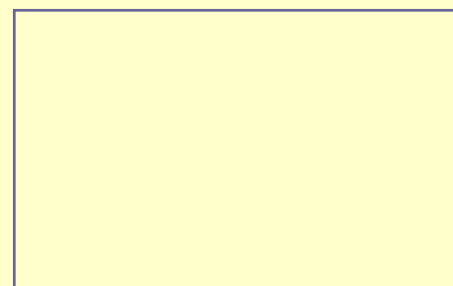


Figure 1. The effect of PEG and diol on swelling.

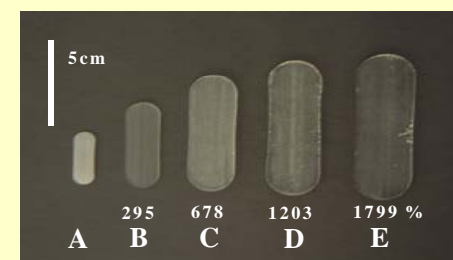


Figure 2. Dry (A) and swollen pessaries made of PEG8000:DD:DMDI 0.1:1:1.1 (B), 0.7:1:1.7 (C), 0.9:1:1.9 (D) and PEG8000:DDD:DMDI 1.5:1:2.5 (E) molar ratios.