SYNTHESIS OF NOVEL POLY(ETHYLENE GLYCOL) BASED POLYURETHANES FOR DRUG DELIVERY SYSTEMS

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1. Introduction

Poly(ethylene glycol) based crosslinked polyurethane (PU) hydrogels have been used successfully in different drug delivery applications.[1,2,3] These types of water-swellable polymers have been loaded with many different types of pharmaceutically active agents and the ability of releasing the active agents over a prolonged period of time has opened up their commercial use. However, crosslinked polyurethane hydrogels have some limitations in their use as a polymer matrix for drug delivery systems. Only water-soluble active agents can be used and the molecular weight of the active agent is limited with the degree of polymer swelling. A wider range of swelling and more variety of polymer processing methods are desired properties for PEG based polyurethanes. In this study, we investigated the effects of molar ratios of monomers, length and type of diol and PEG on the properties of linear poly(ethylene glycol) based polyurethane.

2. Synthesis of Poly(ethylene glycol) based polyurethanes

Linear PEG based polyurethanes[4] were polymerised by using various molecular weight hydroxyl-terminated PEGs (PEG 4000, PEG 8000, PEG 12000 or PEG 35000), different type of diols (1,6-hexanediol, 1,10-decanediol [DD], 1,12-dodecanediol [DDD] or 1,16-hexadecanediol) and dicyclohexylmethane-4,4-diisocyanate [DMDI] with different molar ratios of PEG:diol:diisocyanate (0.1:1:1.1 to 1.5:1:2.5). Generally these polymers were made by melting the dried PEG together with the diol at 85°C. The molten mixture was dried under vacuum at 95°C to remove excess moisture. The catalyst, ferric chloride, was mixed with a small amount of molten mixture and fed 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 loading model drugs and conducting dissolution studies. Crosslinked PEG based polyurethanes were polymerised as described elsewhere[1].

3. Results

Changing the molar ratios between PEG, diol and DMDI, could control the swelling over a wide range (Table 1).

The molecular weight of PEG and the type of the diol had clear effects on the swelling of hydrogel pessaries as seen in Figures 1 and 2. By increasing the molecular weight of PEG from 4 000 g/mol to 12 000 g/mol the swelling of pessaries increased almost linearly from 400 % to 1 000 % and by increasing the amount of CH_2 in diol the swelling of pessaries decreased almost linearly from 900 % to 500 %.

In vitro dissolution studies (Figure 3) of hydrogel pessaries showed that the dissolution profile of model drugs can be tailored by changing the structure and swelling of hydrogel polymer. High-swelling polymers may enhance the possibility of loading larger molecules and achieving higher doses than current crosslinked polymer.

Table 1. The effect of molar ratios.

PEG 8 000 (Molar Ratio)	0.9	0.7	0.1
DD (Molar Ratio)	1	1	1
DMDI (Molar Ratio)	1.9	1.7	1.1
Percentage Swelling (%)	1050	750	200
WSE (%)	2.3	1.4	2.3
Tm (°C)	62.4	62.4	54.9
Crystallinity (%)	48.6	49.3	33.1

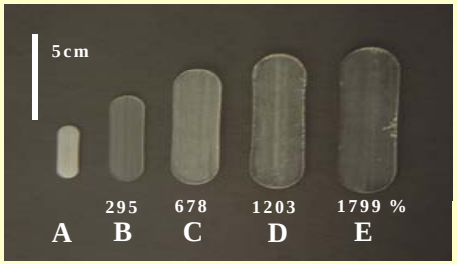

Figure 2. Dry (A) and swollen pessaries made of PEG8000:DD:DMDI 0.1:1:1.1 (B), 0.7:1:1.7 (C), 0.9:1:1.9 (D) and PEG8000:DDD:DMDI 1.5:1:2.5 (E) molar ratios.

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

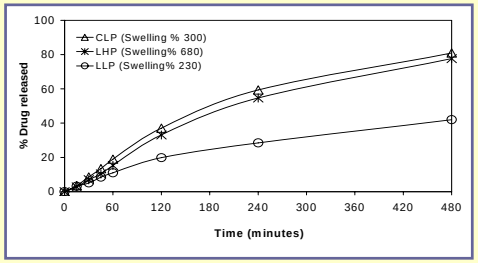

Figure 3. Dissolution profile of 200 μg misoprostol from crosslinked (CLP), linear high swelling (LHP) and linear low swelling (LLP) polymer pessaries.

4. Conclusion

The swelling properties of novel linear poly(ethylene glycol) based polyurethanes can be tailored to a wide range by changing the molar ratios of monomers and by independently changing the type and length of diol and PEG. Linear polymers behaved like crosslinked polymer in aqueous environments, but were thermoplastic and solvent soluble. Thus, a wide range of conventional polymer processing methods can be used in the manufacture of drug release devices. These linear polymers bring more variety to existing crosslinked PU hydrogels and the new properties can be utilized in the design of future drug delivery systems.

References

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