

PRE-TERM LABOUR DRUGS IN A HYDROGEL PESSARY DRUG DELIVERY SYSTEM

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1. INTRODUCTION

The aim of tocolytics is to prolong or delay labour. Current treatment includes using β -antagonist drugs such as terbutaline sulphate or salbutamol sulphate following parenteral delivery or ritodrine hydrochloride following both oral and parenteral delivery. This study investigates the feasibility and suitability of delivering these drugs via sustained-release cross-linked hydrogel pessaries, intended for the vaginal route.

2. METHODOLOGY

A cross-linked polyurethane hydrogel polymer made of poly(ethylene glycol) 8000 (PEG8000), hexanetriol (HXT) and dicyclohexylmethane-4,4-diisocyanate (DMDI) in a molar ratio of 1.0:1.2:2.8 were prepared as described by Embrey and Graham (1983). The polymer billets of dimension 10 x 30mm were sliced to thickness 1.0, 1.5 and 2.0mm respectively and purified (using 2 washes in water; 1 wash with 25% w/w ethanol-water solution). The pessaries were subsequently dried in a vacuum oven at room temperature until their loss on drying (LOD), analysed using thermogravimetric analysis (TGA) was below 0.5%.

The dosage of drug per unit pessary was based on the tocolytic therapeutic concentration. Terbutaline sulphate (TER), salbutamol sulphate (SAL) and ritodrine hydrochloride (RIT) doses were selected to be 10mg, 15mg and 70mg respectively. Loading solution for each drug was prepared by dissolving drugs in purified water. Dried purified pessaries of each thickness were loaded by placing them in a pre-determined quantity of loading solution required for maximum swelling. This was calculated based on pessary swelling % and mean water uptake in purified water at 25°C. The mixtures were incubated for 16 to 26 hours at 25°C. After incubation, the drug loaded swollen pessaries were dried in a vacuum oven at room temperature for 24 to 72 hours until the pessaries were thoroughly dried.

The dissolution profile of each drug from pessaries of various thicknesses was determined using an automated dissolution apparatus (USP XIII Apparatus 2) operated at 50 rpm paddle speed and maintained at 37°C. Terbutaline sulphate, salbutamol sulphate and ritodrine hydrochloride release were analysed at wavelengths 274, 276 and 276nm respectively using UV spectroscopy.

3. RESULTS AND DISCUSSION

Terbutaline sulphate, salbutamol sulphate and ritodrine hydrochloride can be loaded into cross-linked polyurethane hydrogel pessaries. In the preparation of the loading solutions, these drugs dissolved well in purified water. No drug particles precipitated or sedimented out of the loading solution before or after incubation. Loaded swollen pessaries were clear, transparent and retained the original appearance of blank swollen pessaries. The drug loading solution in each batch was totally absorbed by pessaries after incubation.

The drying time required for each pessary batch varied. In general, thinner pessaries dried faster than thicker pessaries. After drying, even though loaded pessaries retained the original shape and size as blank purified pessaries, they were uniformly opaque and slightly yellow. Visual observations showed that there were no patchy discolourations or drug particles on the surfaces.

Effect of drug type on dissolution from pessaries of various thicknesses is shown in Figures 1 and 2.

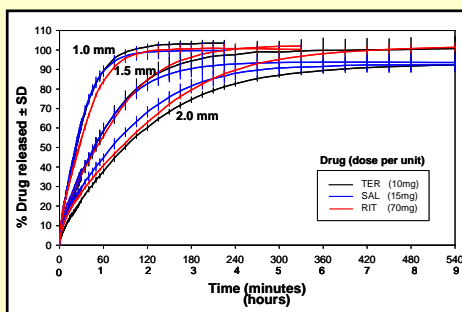


Figure 1. Mean dissolution profile (n=6) for 1.0, 1.5 & 2.0mm thick pessaries loaded with various pre-term drugs.

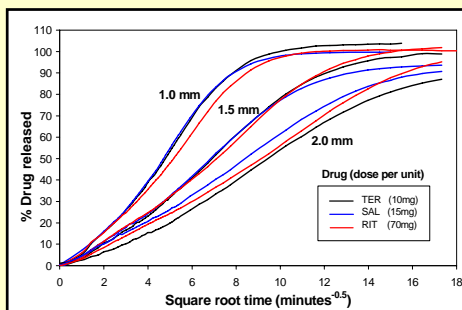


Figure 2. Graph % drug release (Q) versus square root time ($t^{1/2}$) for the mean (n=6) dissolution profiles of 1.0, 1.5 & 2.0mm pessaries loaded with various pre-term drugs.

Dissolution profiles of each pessary thickness for the three drugs from the polymer appeared to be similar and overlapping (Figure 1), even though the drug dosage is different. For all drugs, as pessary thickness increased, drug dissolution from pessaries decreased.

All formulations in each drug series exhibited Higuchian release (Labastie et al., 1992) according to equation $Q = k t^{1/2}$ which correlates the percentage of drug dissolved (Q), square root time ($t^{1/2}$) and the slope of the graph (k). The relationship between Q and $t^{1/2}$ for all drug loaded pessaries are linear (Figure 2), indicating Higuchian (Fickian) drug release. Rate of drug release k for each dissolution profile, determined from the slope of graph Q versus $t^{1/2}$ is shown in Table 1. For all drugs, as pessary thickness increase, rate of drug release k decreased.

Drug Pessary thickness (mm)	Rate of drug release k (minutes ^{-1/2})		
	1.0	1.5	2.0
TER	13.49	8.68	6.22
SAL	13.87	8.48	6.54
RIT	12.14	7.98	6.11

Table 1. Rate of drug release (k) from pre-term drug loaded pessaries

The gradual swelling process in the aqueous environment is postulated to be the rate limiting step which controls drug release from these hydrogel pessaries. Following hydrogel swelling, the water soluble pre-term drug present in the polymer matrix dissolves and diffuses rapidly into the aqueous bulk environment. Sink conditions during dissolution ensured that ~100% drug release was achieved at the end of the 10 hours dissolution run.

4. CONCLUSION

Drugs such as terbutaline sulphate, salbutamol sulphate and ritodrine hydrochloride can be loaded successfully into a hydrogel pessary vaginal drug delivery system. Drug release from this cross-linked polyurethane polymer is affected by drug type and pessary thickness and can be employed in the design of a sustained-release formulation for the treatment of pre-term labour. Sustained release of these types of drugs are of interest in the treatment of endometriosis.

References

- Embrey, M.P. and Graham, N.B. (1983) GB 2047093 B.
- Labastie, M. et al. *J. Pharm. Biomed. Analysis.* 10 (10-12) (1992) 1105-1108.