

LOADING AND RELEASE OF THE ANTIVIRAL DRUG, ITI-002, FROM POLYURETHANE HYDROGEL PESSARIES

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1. OBJECTIVES

The suitability of a polyurethane hydrogel pessary as a potential dosage form for the delivery of a novel antiviral drug, ITI-002 (Bukrinsky et al., 1996), to the vagina was investigated. The vagina is a rich source of blood vessels and it avoids first-pass metabolism.

The poster deals with the following issues:

- Entrapment of ITI-002 into the polymer
- Release rate of ITI-002 from the hydrogel pessaries *in vitro*

2. METHODOLOGY

Water-swallowable crosslinked polyurethane inserts (polyethylene glycol 8000 : dicyclohexylmethane-4,4-diisocyanate : hexanetriol, 1:2.8:1.2) of dimensions 1x10x30 mm were manufactured (Embrey and Graham, 1990), purified twice with water then by 25% ethanol at 25°C, and dried using the vacuum oven.

Purified polymers were loaded with ITI-002 by incubating and mixing, for 20 – 23 hrs, in a solution containing the desired dose per unit and sufficient water to completely swell the polymer, and then dried under vacuum.

Three batches were prepared: batches IT1 and IT3 (targeting 1 mg of drug per pessary at 25°C), and batch IT2 targeting 5 mg per pessary at 37°C (see Table 1).

The release profile was investigated using an automated dissolution apparatus (USP II) ($\lambda_{max}=298$ nm, 20mm cells, stirrer speed=50 rpm, pump speed=75 rpm). Dissolution was performed using 200mL of either degassed deionised water, phosphate buffer pH4, or phosphate buffer pH7 at 37°C for 6 hrs.

TABLE 1. ITI-002 batches

| Batch | IT1 | IT2 | IT3 |
|------------------------------|-----|-----|-----|
| Targeted dose (mg / pessary) | 1 | 5 | 1 |
| Loading Temperature (°C) | 25 | 37 | 25 |

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Fig. 1. Dissolution rate of ITI-002 from hydrogel pessaries in water at 37°C for 3 hrs 30 min (IT1, IT2 and IT3)

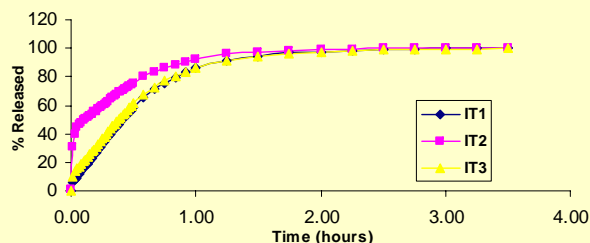


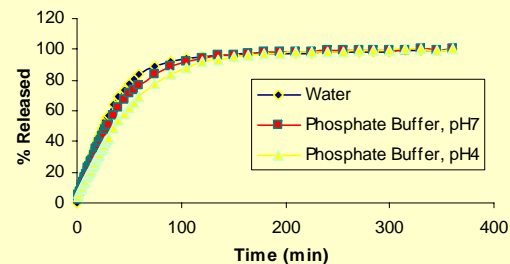
TABLE 2. Dissolution half-life of ITI-002 release from hydrogel pessaries of different batches in water at 37°C

| | IT1 | IT2 | IT3 |
|--|-----------------|-----------|--------|
| Half-life of ITI-002 from hydrogel pessaries | 25 min | 7 min | 23 min |
| Time to reach plateau | 2 hrs | 1hr 30min | 2hrs |
| % drug recovery at 6 hrs ^a | ND ^b | ND | 93.1% |

^a % drug recovery was calculated from the amount of drug recovered in the pessaries and the amount of drug in the excess solution.

^b ND: not determined

Fig. 2. Dissolution of ITI-002 from hydrogel pessaries in different media at 37°C for 3 hrs 30 min



3. RESULTS AND DISCUSSION

For comparison purposes, the data reported in Figs. 1 and 2 have been normalized for total content.

Fig. 1 compares the dissolution profiles of ITI-002 from hydrogel pessaries in water at 37°C for 3 hrs 30 min. Batches IT1 and IT3 behaved similarly and showed controlled release with time for the first 2 hours with 5.6% and 10.3% release, respectively, within the first minute (Fig.1) and half-lives of 25 and 23 min (Table 2). However, batch IT2, which incorporated the highest amount of ITI-002, showed the highest initial release of the drug within the first minute (30.9%), with 45% release after 3 minutes and a short half-life of only 7 min, which could imply that a high concentration of the antiviral drug, ITI-002, was on the surface of the pessary.

The profiles of the different ITI-002 batches in Tables 1 and 2 show that the more drug loaded, the faster the initial release. This could be due to full loading of the pessary with the drug and the active agent being deposited on the polymer surface. It can be extrapolated from batch IT2 in Fig. 1 that the maximum amount of drug that can be loaded into the pessary is 3 mg (i.e. 60% of 5 mg), which is the amount of drug that showed controlled release with 2mg on or close to the surface of the hydrogel.

The release of the antiviral drug from pessaries (batch IT1) was also studied in phosphate buffer at pH 4 & 7 at 37°C for 6 hours. Comparing the dissolution results of ITI-002 in water, phosphate buffer, pH7 & 4, Fig. 2 clearly shows that pH is not a factor in controlling the release of the drug from the pessaries.

4. CONCLUSION

- ITI-002 can be successfully loaded into polyurethane hydrogel pessaries.
- ITI-002 was released from hydrogel pessaries.
- Dissolution rate depends on the potency of the units.
- At a dose of 1 mg, release is controlled over 3 hours.
- At a dose of 5 mg, a burst effect is observed with 30% release within 1 min.
- Release rate appeared to be pH independent over range 4 to 7.

References

- Bukrinsky et al., US 5,774,040, 1996.
- Embrey and Graham, US 4,894,238, 1990.

