Evaluation of the Release Behavior of the Dexamethasone Embedded in Polycarbonate Polyurethane Membranes: An In Vitro Study

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Purpose: To evaluate the release behavior of dexamethasone embedded in a polycarbonate polyurethane membrane.

Materials and Methods: Both water-soluble and water-insoluble dexamethasone were tested, and the release behavior of five water-insoluble dexamethasone films of different thickness (78 to 211 μm) was also evaluated. The amount of Dexamethasone used was 10% of the total weight of the polyurethane film mass. Each film was placed in a centrifuge tube containing 25 ml of 0.1-M neutral phosphate buffer, and the tubes were placed in a shaking incubator to quantify the amount of drug released into the buffer, absorption spectroscopy (A max = 242 nm) was employed.

Results: In the test involving water-soluble dexamethasone, 60% of the drug was released during the first two hours of the study. Films containing water-insoluble Dexamethasone, on the other hand, released 40%, 60% and 75% of the dexamethasone in one, three and seven days, respectively. Both types of film maintained low-dose drug release for 28 days. When release behavior was compared between water-insoluble films of different thickness, thicker film showed less initial burst and more sustained release.

Conclusion: Dexamethasone release behavior varies according to drug solubility and membrane thickness, and may thus be conrolled.

Index words: Drugs, side effects
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proaches. Techniques to provide sustained local drug delivery have focused on polymers as matrices for drug incorporation and elusion. The purpose of our in-vitro study was to evaluate the release behavior of dexamethasone embedded in polycarbonate polyurethane membranes.

Materials and Methods

Dexamethasone/Polyurethane Film Design and Manufacture

The film solution was made using phosphate-based water-soluble and acetate-based water-insoluble dexamethasone (Sigma, St Louis, Minn., U.S.A.), and polycarbonate polyurethane (Cardiotech, Woburn, Mass., U.S.A.). 0.132 g of dexamethasone was added to 5 ml of dimethylacetamide (DMAc), and when the Dexamethasone had completely dissolved, 6 ml of 22% polyurethane was added to the mixture. To ensure complete admixture, a magnetic stirrer was used for 24 hours until the solution became transparent. Dexamethasone accounted for approximately 10% of the polyurethane mass.

The film was made using a specially designed, four-way thickness gauge roller known as a doctor’s blade (patent pending). This device ensured that the liquid solution conformed to the thickness required for the study. The film was then dried for three days in an oven, and then for three more days in a vacuum oven. Once dried, a round punch 1cm in diameter was employed to make the samples. Each of five water-soluble and five water-insoluble films were used in this study. The thickness of two types was, respectively, 78±9 μm, and 89±9 μm; the difference was not statistically significant (p=0.257). To evaluate Dexamethasone release behavior, water-insoluble films of five different thicknesses (78 to 211 μm) were made. For surface analysis, scanning electron microscope (SEM) was used to compare the morphology of the two types of film.

Release Test

Four round films were inserted into separate centrifuge tubes (Falcon Labware) containing 25 ml of 0.1-M neutral phosphate buffer, and the tubes were placed in a shaking incubator. Absorption spectroscopy (A max = 242 nm) was employed to quantify the amount of dexamethasone released into the buffer, which was changed after each measurement. The procedure was repeated at two, four, and eight hours, and then daily for 28 days.

Results

The study showed that for the two types of film, the results were significantly different. The water-soluble Dexamethasone/DMAc/polyurethane solution became transparent after 24 hours of magnetic stirring, and the water-soluble film released 60% of the drug within the first two hours, with low-dosage drug release continuing for 28 days [Fig. 1]. SEM surface analysis of the film demonstrated a fibrous pattern [Fig. 2].

The water-insoluble Dexamethasone/DMAc/polyurethane solution, on the other hand, became transparent within five minutes of magnetic stirring, and the water-insoluble film released 40, 60 and 75% of the drug in one, three and seven days respectively [Fig. 1]. Low dosage drug release also continued for 28 days. SEM surface analysis of the water-insoluble film indicated a smooth surface [Fig. 3]. Comparison of dexamethasone release behavior between the water-insoluble films of different thickness showed that thicker film showed less initial burst and more sustained release [Fig. 4].

Discussion

In the field of vascular intervention, metallic stents show poor long-term patency due to smooth muscle cell proliferation or neointimal hyperplasia around the stent, resulting in restenosis [1]. To prevent this, systemic administration of numerous drugs has been tried [2-4],

![Fig. 1. The change of water-soluble Dexamethasone (DM phosphate) and water-insoluble Dexamethasone (DM acetate) release rate over time. 60% of the drug is released from water-soluble Dexamethasone film during the first 2 hours. 40% of the drug is released from water-insoluble Dexamethasone film during the first 24 hours.](image-url)
but adverse side effects have sometimes arisen. In an attempt to achieve and sustain high tissue levels of the drug, and decrease or avoid these potential side effects, new approaches to more effective site-specific drug delivery are being directed toward local delivery system rather than systemic drug administration. Glucocorticoids have a potent anti-proliferative effect and have been shown to inhibit smooth cell proliferation in-vitro (6-8, 12).

Several studies have indicated that dexamethasone reduces restenosis in the field of vascular intervention. Stone et al. (13) randomly administered 125 mg methyl-prednisolone intramuscularly to 52 patients the night before and in the morning of the day of repeat percutaneous transluminal coronary angioplasty (PTCA). The restenosis rate was 36% in the steroid group and 40% in the control group, and while this difference was not statistically significant, it was interpreted as suggesting a trend in favor of steroid treatment to reduce restenosis.

In a study using sustained release from biodegradable nanoparticles, Voisard (9) found that a significant amount of dexamethasone was present in the treated segment for up to 14 days after a single infusion, through none of the drug was detected in plasma after the first three hours. There was a 31% reduction in the intima-media ratio in animals treated with local dexamethasone nanoparticles compared with the control group. Strecker et al. (5) percutaneously implanted Strecker stents coated with a biodegradable membrane containing into the femoral artery of 14 dogs, finding that in comparison with non-coated stents, they reduced neointimal hyperplasia (5).

In local drug delivery studies by Lincoff et al. (10) and Muller et al. (11), poly-L-lactic acid (PLLA) and silicone were used, respectively, showing respective rate of 0.8 mg/day over 6 days, and 5 mg/day for the first 3 days and 0.3 mg/day thereafter. Lincoff et al., using stents coated with Dexamethasone in high-molecular-weight PLLA, found no decrease in neointimal hyperplasia, concluding that the stent used for elution appeared to be a well-tolerated and effective means of providing sustained, site-specific drug delivery to porcine coronary artery wall for at least 28 days. Muller et al. used dexamethasone-impregnated silicone polymers (20% by weight), and the intimal hyperplastic response was not reduced (11). According to previously published literature, drug concentration and duration within tissue were the most important criteria when evaluating a drug’s anti-inflammatory and anti-proliferative effects.

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**Fig. 2.** SEM Photograph of water-soluble Dexamethasone film (× 1,000). The surface of the matrix shows fiber pattern.

**Fig. 3.** SEM Photograph of water-insoluble Dexamethasone film (× 1,000). The surface of the matrix is smooth compare to that of water-soluble Dexamethasone film.

**Fig. 4.** Comparison of the Dexamethasone release behavior among the water-insoluble films of different thickness. The figures of the graphs represent the thickness of the films (µm). Thicker film showed less initial burst and more sustained release.
DMAc is an ideal solvent for polyurethane because it contains an amide group, which dissolves solutes that have a urethane linkage. It is also a good solvent for the water-insoluble dexamethasone, but a poor one for the water-soluble dexamethasone, as evidenced by the time required for the solute to dissolve. In our study, the water-soluble dexamethasone-dimethyacetamide solution, we believe, affected the shape of the polyurethane surface. During the drying procedure, the polyurethane chains formed tighter bonds, separated from the water-soluble dexamethasone which, unprotected by the polymer chains, was rapidly released from the film, as the large initial burst indicated. DMAc is a good solvent for both water-insoluble dexamethasone and polyurethane. There was little separation of the drug from the polymer chains during the drying procedure, as the homogeneous polymer surface indicated, and for this film, drug release was therefore much slower.

We also found that the initial drug release was slower in thick film than in thin, and believe this is because the drug on the surface can be released easily from the polymer matrix and that the thicker film has a lower surface/volume ratio, and thus less surface effect. Film thickness, however, cannot be infinitely increased, as this would increases the diameter of the stent delivery catheter.

In this study, we showed that the delivery rate of dexamethasone could be affected greatly by different chemical structures of the drug, as well as the film thickness of the drug-carrying matrix. In addition, polyurethane film was found to be a good matrix for sustained local delivery of dexamethasone. We believe that water-insoluble dexamethasone can more effectively present hyperplasia, as drug delivery is more sustainable. An animal study in which water-insoluble Dexamethasone is used is currently underway.

References

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