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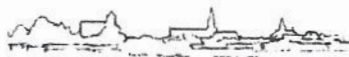


Fig. 1 Schematic view of an ethmoid sinus with an implanted sinus spacer (left) and enlarged image of the drug reservoir (right) [1].

## Purpose

The drug-eluting balloon-like MicroFlow Spacer has recently been introduced to be used with steroids for the treatment of chronic paranasal sinusitis. The spacer is FDA approved to be used with saline. The use with triamcinolone acetonide is currently considered off label [1,2]. After implantation into the involved sinus the device is filled with triamcinolone acetonide injectable suspension and allows the substance to elute from an expandable reservoir, containing multiple laser-cut-openings over a sustained period of time (up to 14-28 days). The scope of this study was to investigate the in-vitro release properties of a MicroFlow Spacer. The reciprocating holder apparatus (USP7) was utilized for this purpose. To understand the mechanisms that facilitate drug elution from the balloon, additional release experiments were performed with the suspension in a dialysis bag.

## Methods

Drug release was evaluated in a small volume USP apparatus 7 (400-DS Agilent Technologies), the reciprocating holder, equipped with 10 mL dissolution cells (Fig. 2). In all experiments the test temperature was 37 °C. Automated sampling and media replacement was performed via a port at the bottom of the dissolution cell. To ensure sink conditions in the outer compartment the release medium was completely replaced with sampling. Analytical quantification was performed using HPLC-UV-Vis (Column: RP-18 4.6x150 mm, 5 µm, Mobile phase: 65/35 Methanol/H<sub>2</sub>O (V/V), Flow rate: 1 mL/min, Detection wavelength 238 nm). After each study the residual drug content in either dialysis bag or balloon was determined.

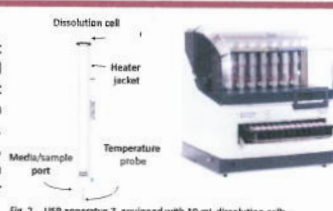


Fig. 2 USP apparatus 7, equipped with 10 mL dissolution cells.

## Dialysis bag

For the experiments with the dialysis bag TriamHexal® injectable suspension (Hexal AG), containing 40 mg/mL triamcinolone acetonide was injected into a dialysis tube with defined length that was then sealed with a nylon strand and attached to a reciprocating holder (Fig. 3). Two different membranes (both from Spectrum Laboratories, Inc.) were used.

- Spectra/Por® 7 (regenerated cellulose) with a MWCO of 25 kDa and a flat width of 8 mm
- Spectra/Por® CE (cellulose ester) with a MWCO of 300 kDa and a flat width of 10 ± 1 mm

Experiments were performed in phosphate buffered saline pH 7.4 (PBS) with different concentrations of sodium dodecyl sulfate (SDS), added injection volumes and dipping speeds were varied.



Fig. 3 Dialysis bag (left) and mesh basket holder (right).

## Drug-eluting balloon

The MicroFlow Spacer (Fig. 4) consists of a catheter shaft with an expandable reservoir (Fig. 5) which is mounted on the distal shaft portion of the device. The spacer is implanted into the involved sinus and filled with a therapeutic agent via the Luer Hub connector through the proximal shaft portion causing the reservoir to expand in situ (a one way valve prevents backflow). Thereafter the catheter is trimmed to the desired implanted length. A Relieva Stratus™ MicroFlow Spacer for the frontal sinus (product code BC1417RS, Lot # 120203C, Acclarent, Inc.) was used for the in-vitro study. A clinically relevant dose of 310 µL of TriamHexal 40 was infused with an 1 mL syringe. Since the capacity of the device does not hold the entire dose a small amount of the suspension is pressed through the laser-cut-openings of the reservoir upon injection. Subsequently, the proximal shaft of the device (Fig. 4, indicated by arrow bar) was cut away. To prevent the suspension to leak from the distal end of the shaft and to assure that only suspension that is located in the reservoir is assessed during the dissolution study the distal end was sealed with an instant adhesive. The adhesive was allowed to dry for at least half an hour. To prevent dehydration of the suspension in the reservoir in the intervening period, the balloon was placed in an Eppendorf vial containing a defined amount of suspension throughout the preparation process. To avoid sedimentation of the suspension the vial was gently shaken while the adhesive was allowed to dry. After half an hour the balloon was removed from the vial, wiped clean and placed in a mesh basket holder (Fig. 3). Dissolution studies were performed in PBS containing 0.3 % SDS and the dipping speed was set at 20 dpm.



Fig. 4 Relieva Stratus™ MicroFlow Spacer [1].

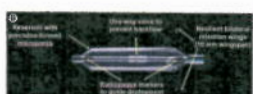


Fig. 5 Distal shaft portion with reservoir [2].

## Results

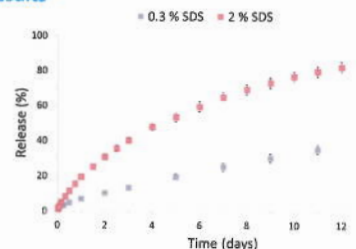


Fig. 6 Drug release from the dialysis bag (Spectra/Por® CE) in PBS with different concentrations of surfactant, dipping speed 20 dpm, injection volume 310 µL, mean ± SD, n = 3.

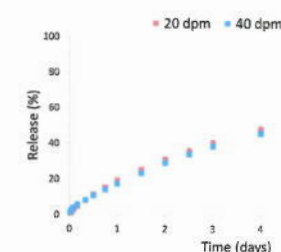


Fig. 7 Drug release from the dialysis bag (Spectra/Por® CE) in PBS + 2 % SDS at different dipping speeds, injection volume 310 µL, mean ± SD, n = 3.

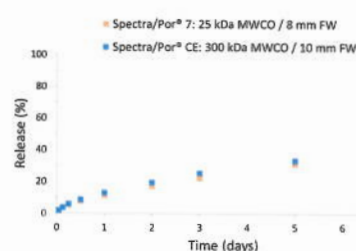


Fig. 8 Drug release from two different dialysis bags (Spectra/Por® CE and Spectra/Por® 7) with distinct MWCO and flat widths (FW) in PBS with 0.3 % SDS, dipping speed 20 dpm, injection volume 100 µL, mean ± SD, n = 3.

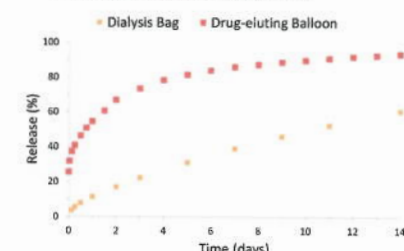


Fig. 9 Drug release from the balloon and dialysis bag (Spectra/Por® CE) in PBS with 0.3 % SDS, dipping speed 20 dpm, injection volume 76.8 µL (balloon) and 100 µL (dialysis bag), dialysis bag: mean ± SD, n = 3; balloon: n = 1.

Figures 6-8 show the release profiles from experiments with the dialysis bag under different test conditions. Overall, drug release was sustained and increased with increasing concentration of surfactant (Fig. 6). Dissolution studies with the plain suspension in the Paddle apparatus under sink condition without coning (adequate surfatation) showed comparatively fast dissolution in PBS within 30 minutes, dissolution was significantly slower when coning was observed (data not shown). Drug release from the dialysis bag was independent of the applied dipping speed (Fig. 7) which can be explained by poor hydrodynamic conditions inside the dialysis bag (drug particles accumulated at the bottom of the dialysis bag). Figure 8 shows that small variations in the membrane flat width and the pore size (which is related to the molecular weight cut off (MWCO) of the membrane) did not affect drug release. Drug release from the spacer is shown in Figure 9. To allow direct comparison, the normalized release profiles obtained from experiments with the dialysis bag and the spacer are plotted in the same graph. Under the present test conditions drug release from the spacer was somewhat faster when compared with the dialysis bag. The release rate is initially high and decreases with time (with a steep gradient over the first part of the curve).

## Discussion

Experiments with the suspension in a dialysis bag indicate that drug release is controlled by poor hydrodynamics and low solubility inside the dialysis bag, i.e. that slow dissolution of the suspension inside the dialysis bag is the rate limiting step. Only dissolved particles are being released from the dialysis bag. In comparison, the balloon has multiple laser-cut-openings also allowing elution of undissolved particles. In a first experiment with the balloon drug release was initially higher when compared with the dialysis bag. It is possible that in the early stage undissolved drug particles are washed out through the balloon openings facilitated by pressure or gravity. However, hydrodynamics inside the balloon are poor and sedimentation of undissolved particles could also be observed in the balloon experiment. It is therefore likely that the initial burst is followed by diffusive washout of undissolved drug remaining in the reservoir, thereby providing sustained release over an extended period of time. We believe that drug release in this later phase is influenced by similar parameters as observed for the suspension in a dialysis-bag. However, for a representative characterization of the in vitro release properties additional release experiments with the balloon are required. Also, it should be taken into account that for adequate assessment of drug elution in the initial phase the preparation of the balloon in-vitro might play a critical role.

## Acknowledgment:

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## References:

- [1] Kuhn FA. Presentation at AAO-HNSF 112th annual meeting and OTO exposition, Chicago, USA, 2008.
- [2] Catalano PJ et al. J Otolaryngol Head Neck Surg. 2011, 63(3):279-84.