Incorporation and controlled release of dexamethasone, triamcinolone acetonide, simvastatin and montelukast from silicone elastomer dispersions to reduce capsular contracture

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Background: Capsular contracture (CC) is one of the most common clinical complications following breast augmentation or reconstruction surgery using implants. The foreign body reactions (FBR) due in parts to the hydrophobicity of the silicone elastomer and bacterial adherence to the implants are problematic and believed to be leading to the development of CC. A common strategy implemented to reduce FBR has been the addition of textures on the surface of the implants. While this approach has led to reduced incidence of fibrous capsule formation around implants, it has also led to an association with anaphylactic large cell lymphomas. Therefore, new strategies are needed to reduce rates of CC. Orally and intravenously administered agents such as dexamethasone (DEX), simvastatin (SIM), triamcinolone acetonide (TAA) or montelukast (MFA) have been reported as effective agents to reduce the formation of fibrous capsules. The incorporation and release of those drugs from the medical grade silicones used to manufacture breast implants have not been studied. Therefore, incorporation of these agents into either the silicone shell or gel components of the implants could offer an alternative pharmacological strategy to reduce the risks of CC and implant associated infection.

Methods: Silicone elastomer films (0.3 cm thick) containing 1, 2.5 and 5% w/w DEX, SIM, TAA and MFA were prepared from medical grade addition-cure silicone elastomer dispersions (MED 6600, NuSil). Briefly, silicone parts A and B (1:1) were mixed with drug (1 min, 3000 rpm), left overnight for solvent evaporation, and then post-cured (3 hr, 90°C). Circular discs of 1 cm diameter were cut from the resulting films. Discs were incubated at 37°C, 60 rpm in a 1:4 isopropanol (IPA):water media and samples were collected every 24 hr to measure the amount of drug released using previously developed HPLC methods. Solubility of the drugs in the silicone material was measured. Briefly, thin films (1 mm thick) were cut into pieces of 2 × 2 cm and subsequently immersed in drug saturated 1:4 IPA:water media at 37°C, 60 rpm. After 6 weeks of incubation, equilibrium was reached for all the candidates and the films were analysed for the content of drug. The samples were extracted with acetone for 24 h and drug concentrations assessed by HPLC.

Results: Cured 1, 2.5 and 5% w/w loaded thin films were successfully manufactured for DEX, TAA, and SIM but not for MFA; MFA appears to have reacted with the silicone during the curing and prevented the formation of cohesive films. A slow and controlled release of the loaded candidates was observed over time following a $t^{1/2}$ kinetic concurring with what has been reported about other silicone types in literature. The results also showed that the release was anomalous, hence showing that the drugs were not dissolved in the material at these ratios. Therefore, the solubility of the drugs in the silicone material was measured for DEX, TAA, SIM, and MFA, and were, respectively, 0.85 +/- 0.07, 0.71 +/- 0.04, 0.46 +/- 0.02, $1.8.10^{-3}$ +/- 8.10^{-4} % w/w.

Conclusions: Three drug candidates were successfully incorporated at different ratios into a medical grade silicone elastomer dispersion and a slow and controlled $t^{1/2}$ release kinetic was observed. Solubility of all the candidates in the silicone material was determined. These preliminary results are encouraging for further development of drug-releasing breast implants.