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Influence of sterilization on the drug release behaviour of drug coated silicone

Abstract: Sterilization processes ensure sterility of drug delivery systems, but may negatively affect the properties of biomaterials and incorporated drugs by changing their physical, chemical, mechanical properties and drug release behaviour. Therefore, it is important to investigate their influence. In this study, the influence of ethylene oxide (EtO) sterilization on the drug loading and release behaviour of incorporated Diclofenac (DCF) in a Poly-L-lactide (PLLA) coating and Dexamethasone (DMS) in the silicone carrier is presented. Silicone samples containing DMS were coated with PLLA containing DCF varying in layer thickness (5, 10, and 20 μm). Half of the samples underwent EtO sterilization, the other half was not sterilized. All un-/sterilized sample surfaces were in view of the morphology and hydrophilicity examined. Furthermore, *in vitro* release studies of DMS and DCF were conducted. The sterilized sample surfaces showed no morphological and hydrophilicity changes. The DCF and DMS loadings were similar for the sterile and untreated samples. This also applied to the *in vitro* DMS release profiles apart from the end of the studies where slight differences were evident. The results indicate that both drugs loaded in the polymer coating and the silicone were not impaired by the sterilization process. Thus, EtO sterilization appears suitable for DMS containing silicone and DCF incorporated PLLA coatings as a dual drug delivery system.

Keywords: EtO-sterilization, Dexamethasone, Diclofenac, PLLA coating, silicone.

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1 Introduction

The sterilization of drug delivery systems for biomedical applications is a critical quality attribute and a key requirement for an adequate and safe performance. Contamination, such as bacteria, fungi, and viruses can lead to infection and result in severe complications prolonging or suspending healing [1]. However, the sterilization process affects the properties of biomaterials and incorporated drugs by changing their physical, chemical and mechanical properties [2, 3]. Thus, the efficacy and drug release behaviour of the drug can be significantly modified [4–7]. Therefore, it is always very important to assess the influence of sterilization in addition to the characterization of the drug delivery system.

In this study, the influence of ethylene oxide (EtO) sterilization on the release behaviour of incorporated Diclofenac (DCF) in a Poly-L-lactide (PLLA) coating and Dexamethasone (DMS) in the silicone carrier is presented.

DCF, as a non-steroidal anti-inflammatory drug, was incorporated into the PLLA coating to simulate a rapid initial release to prevent for example implantation-induced inflammation. DMS, as a well-established anti-inflammatory glucocorticoid, was incorporated in silicone for the long term release.

2 Materials and Methods

2.1 Materials

The silicone slides containing 5 wt% Dexamethasone (DMS) were provided by MED-EL (Innsbruck, Austria). Poly-L-lactide (PLLA, L210) was purchased from Evonik (Schwerte, Germany). The Diclofenac sodium salt (DCF) was purchased from Sigma Aldrich (Munich, Germany).

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Figure 1: Representative SEM images of polymer coated silicone samples before (a, c, e, g) and after EtO sterilization (b, d, f, h); (a,b) silicone, (c,d) silicone_5 μ m PLLA, (e, f) silicone_10 μ m PLLA Silicone, (g, h) silicone_20 μ m PLLA.

2.2 Methods

Silicone samples containing 5 wt% DMS ($\varnothing = 6$ mm) were coated with PLLA containing 20 wt% DCF varying in layer thickness (5, 10, and 20 μ m). Half of the samples underwent an EtO sterilization process, validated according to ISO 11135, the other half was not sterilized. Both sample variants (unsterile and sterile) were provided by MED-EL, Austria. All un-/sterilized sample surfaces were examined in a QUANTA FEG 250 (FEI Company, Germany) scanning electron microscope (SEM). A contact angle system (OCA20, Dataphysics Instruments GmbH, Germany) was used for analyzing surface modifications by contact angle measurements of ultra-pure water sessile drops ($n = 5$). The *in vitro* release studies of DMS and DCF were conducted in methanol under sink conditions at 37 °C ($n = 2$). The released amounts were quantified using High-performance liquid chromatography HPLC (Knauer, Germany).

3 Results

In these studies the influence of EtO sterilization on the surface morphology and hydrophilicity of the PLLA coated silicone samples were investigated. The uncoated silicone (as control group) and PLLA coated silicone surfaces before and after the EtO sterilization were examined via SEM. Several SEM images of investigated samples are presented in Figure 1. No significant changes were seen in the surface morphology between the untreated and sterilized silicone samples. Also the surface hydrophilicity showed no significant changes after sterilization (Table 1). All observed

contact angles for the un- and sterilized samples were not significantly different.

Besides the silicone surfaces, also the influence on the DCF and DMS loading and the DMS *in vitro* release profiles were investigated.

Table 1: Water contact angle $\Theta_W \pm$ standard deviation (SD) on several silicone surfaces for sessile drop method ($n = 5$).

Samples	unsterile $\pm$ SD [°]	sterile $\pm$ SD [°]
Silicone	103.6 $\pm$ 0.7	101.3 $\pm$ 3.5
Silicone_5 μ m PLLA	82.9 $\pm$ 5.4	81.0 $\pm$ 5.2
Silicone_10 μ m PLLA	80.0 $\pm$ 2.9	76.6 $\pm$ 5.4
Silicone_20 μ m PLLA	81.4 $\pm$ 1.2	79.5 $\pm$ 0.8

The DCF incorporated in the PLLA coating was already completely released within 1 h after addition of methanol as release medium at 37 °C. No differences were observed for all samples. No loss of DCF amount was detected for both sterile and untreated samples (data not shown). The DMS loading is shown in Table 2. Almost 100 % DMS were recovered from the silicone carrier without coating regardless of the sterilization process. For all coated samples a lower amount of DMS in the range of 80 - 87 wt% was recovered. However, no significant differences were observed before and after EtO sterilization.

Table 2: DMS loading (%) of un-/sterile PLLA coated silicone surfaces (n = 2).

Samples	unsterile [%]	sterile [%]
Silicone	96.8	98.6
Silicone_5 μ m PLLA	87.7	85.1
Silicone_10 μ m PLLA	87.8	80.8
Silicone_20 μ m PLLA	83.6	80.4

The DMS releasing profiles of all investigated silicone samples are shown in Figure 2.

The DMS release profiles for all PLLA coated silicone samples were similar regardless of the thickness of the coating (Fig. 2b-d). Only the DMS release profile of the uncoated sample was different (Fig 2a). However, the sterilization process does not seem to have any influence on the individual release profiles.

4 Discussion

Both surface morphology and hydrophilicity do not appear to be significantly affected by EtO sterilization. Both the SEM images and the contact angles of the silicone surface as well as the PLLA coated surfaces were very similar regardless of the coating thickness. The general differences in the contact angle between the pure silicone (103°) and the coated systems (approx. 80°) can be attributed to the coating itself. Since an accelerated *in vitro* release of DMS and DCF could be simulated by the addition of methanol, the DCF was released within a very short time frame. Here the completely incorporated amount could also be recovered independent on the sterilization. However, no release profiles could be generated and only the profiles of DMS were compared.

Moreover, with addition of the PLLA layer (5 - 20 μ m), less DMS was released which is most probably related to the coating process and independent of the sterilization. Due to the coating process, a certain amount of DMS is already released and thus the discrepancy between un- and coated silicone occurs. Without any PLLA coating almost 100 % of the calculated DMS amount was recovered.

5 Conclusion

In summary, the results of this study indicate that both drugs loaded in the polymer coating and the silicone were not impaired by the sterilization process. EtO sterilization

Figure 2: Cumulative *in vitro* release of un- and sterile DMS (5 wt%) incorporated into silicone with and without different thick PLLA coating containing 20 wt% DCF; **a** silicone, **b** silicone 5 μ m PLLA, **c** silicone 10 μ m PLLA and **d** silicone 20 μ m PLLA.

appears suitable for DMS containing silicone and DCF incorporated PLLA coatings as a dual drug delivery system.

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