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IN VITRO MODELLING OF IN VIVO DISCOLORATION OF THE DAPIVIRINE-LEVONORGESTREL RING USING A RANGE OF SIMULATED VAGINAL AND MENSTRUAL FLUIDS

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Background

Surface discoloration has been observed in clinical trials of various silicone elastomer vaginal rings (VRs) including IPM’s 25 mg dapivirine and 90-day dapivirine + levonorgestrel (DPV+LNG) formulation (Fig. 1).

To investigate the potential causes of this discoloration, four different silicone VR formulations were exposed to various simulated vaginal fluids (SVF) and simulated menstrual fluids (SMF) for up to 60 days in vitro. A range of dyes (Table 1) representing personal care and household cleaning products, as well as hydrogen peroxide and copper intrauterine devices (IUDs) were included in the test compositions.

Objectives

1. Expose four silicone vaginal ring formulations (placebo; 25 mg dapivirine; 200 mg dapivirine; 200/320 mg DPV+LNG) to a range of simulated vaginal fluid and simulated menstrual fluid solutions for up to 60 days.
2. Assess the extent of surface and internal discoloration

Methods

SVF media containing either 20 µM H₂O₂, 20 µM H₂O + copper IUD, methyl red (MR), toluidine blue (TB), or crystal violet (CV) were prepared, with SVF-only and ultrapure water as experimental controls.

SMF-based media (SMF-only, SMF + 20 µM H₂O₂ or SMF + 20 µM H₂O + copper IUD) were prepared using a 1:1 mixture of horse blood and SVF containing 0.5% w/v xanthan gum.

Single rings from each formulation were placed in 100 mL of each media. Flasks were incubated (37°C/60 rpm) for 30 and 60 days with media replenished weekly. At scheduled timepoints, rings were removed, rinsed, dried and photographed alongside controls. Cross-sections of VRs were examined for interior staining using a Keyence digital microscope.

Results & Discussion

After 60 days, the surfaces of SMF-treated rings appeared yellow compared to controls (Fig. 4), with colour intensity correlating with duration of exposure. After 14 days, rings exposed to IUDs showed black/dark surface markings consistent with direct IUD contact (Fig. 5). Non-uniform red-brown staining – later demonstrated to be blood debris – was also observed on the surface of rings exposed to SMF-only and SMF + H₂O₂ (Fig. 6). No significant staining was observed beneath the surface of the ring.

After 30 and 60 days, rings soaked in SVF-only, SVF + H₂O₂, SVF + H₂O₂ + IUD media showed no surface discoloration. Rings soaked in SVF + dye media showed uniform surface staining (Fig. 2).

Rings exposed to methyl red and toluidine blue showed significant colour integration throughout the ring. Rings exposed to crystal violet showed minimal colour integration (Fig. 3).

Staining patterns were similar to those observed with dapivirine rings (Fig. 1A–C) exposed to highly coloured personal care and household cleaning products during clinical trial use.

Conclusions

Exposure of rings to SMF caused yellow surface discoloration and dark markings. Staining was identified as blood debris from the SMF and was consistent with the appearance observed in post clinical use VRs (Fig. 1D–F). Discolorations were not associated with any specific safety risks for the user but may impact acceptability.