Evaluation of the Factors Contributing to Levonorgestrel Binding in Addition Cure Silicone Elastomer Vaginal Rings


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With the dapivirine (DPV)-releasing silicone elastomer (SE) vaginal ring (VR) now in Phase III clinical studies, there is now considerable interest in developing next-generation rings that could additionally provide contraception. Levonorgestrel (LNG) is a second generation synthetic progestin used as an active ingredient in various hormonal contraceptives, including oral pills, intrauterine devices, and contraceptive implants. It is also the lead progestin candidate for use in future multipurpose oral pills, intrauterine devices, and contraceptive implants. It is an active ingredient in various hormonal contraceptives, including oral pills, intrauterine devices, and contraceptive implants. It is also the lead progestin candidate for use in future multipurpose contraceptive implants. Once incorporated into SE devices, LNG’s propensity to react with addition cure silicone elastomers (SEs) has been widely investigated. LNG is a second generation synthetic progestin used as an active ingredient in various hormonal contraceptives, including oral pills, intrauterine devices, and contraceptive implants. It is also the lead progestin candidate for use in future multipurpose contraceptive implants. Once incorporated into SE devices, LNG’s propensity to react with addition cure silicone elastomers (SEs) has been widely investigated. LNG is a second generation synthetic progestin used as an active ingredient in various hormonal contraceptives, including oral pills, intrauterine devices, and contraceptive implants. It is also the lead progestin candidate for use in future multipurpose contraceptive implants. Once incorporated into SE devices, LNG’s propensity to react with addition cure silicone elastomers (SEs) has been widely investigated. LNG is a second generation synthetic progestin used as an active ingredient in various hormonal contraceptives, including oral pills, intrauterine devices, and contraceptive implants. It is also the lead progestin candidate for use in future multipurpose contraceptive implants. Once incorporated into SE devices, LNG’s propensity to react with addition cure silicone elastomers (SEs) has been widely investigated.

SEs are available with different cure chemistries. Addition-cure SEs involve the platinum-catalysed reaction between two types of silicone polymer – one containing silane groups (Si–H) and the other containing vinylsilane groups (Si–C=CH). These systems are preferred for medical and drug delivery applications, since they do not produce reaction by-products. However, certain silanes are known to inhibit the addition-cure reaction. A problem with LNG-loaded SE VRS was first noted with combination DPV (200mg) + LNG (32mg) matrix-type rings manufactured (160°C, 90s cure time) using micronised LNG and MED-4870, a high-temperature addition-cure SE supplied by Nusil. Specifically, the rings showed zero in vitro release of the LNG component. Furthermore, attempts to solvate-extract LNG from the rings immediately after manufacture revealed that no LNG was recoverable, irrespective of the cure time and cure temp. (Figs. 3C & 3D, black squares). Partial recovery was possible with non-micronised LNG (white squares); however, % LNG recovery significantly decreased with increasing cure time (Fig. 3D) and cure temp (Fig. 3C). We concluded that LNG was reacting with the SE system to an extent determined by its solubility in the SE (once the temperature, time and particle size dependency). The ethyl and vinyl functional groups in LNG (Fig. 2) have potential to undergo hydrolysis reactions, similar to the SE cure reaction (Fig. 2). To test this hypothesis, the DAP+LNG matrix rings were manufactured using Nusil DDU-4320 SE with a lower cure temp. This time, rings containing micronised LNG offered partial recovery of LNG, albeit only at lower cure temps. The data demonstrate that by carefully controlling (i) LNG particle size, (ii) SE cure temperature, and (iii) SE cure time, it is possible to lower LNG solubility in the SE during ring manufacture, and thereby minimise covalent bonding of LNG to the SE. With raw material controls, process controls, and reproducible assay values of greater than 90%, this formulation is now ready to proceed to Phase I clinical testing.

EVALUATION OF THE FACTORS CONTRIBUTING TO LEVONORGESTREL BINDING IN ADDITION CURE SILICONE ELASTOMER VAGINAL RINGS

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