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


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**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, Fig. 1) 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 prevention technology (MPT) products. Despite having previously been incorporated into SE devices, LNG’s propensity to react with addition cure SEs involves the platinum-catalysed reaction between two types of silicone polymer – one containing silane groups (Si–H) and the other containing vinylsilane groups (Si–C=H) (Fig. 2). These systems are preferred for medical and drug delivery applications, since they do not produce reaction by-products. However, certain systems are preferred for medical and drug delivery applications, thereby minimise covalent bonding of LNG to the SE. With raw materials controls, process controls, and reproducible assay values of greater than 90%, this formulation is now ready to proceed to Phase I clinical testing.

**Figure 1.** Chemical structure of LNG. The ethinyl group (top right) and the enone group (bottom left) have the potential to react with addition cure SE cure reaction (Fig. 2). To test this hypothesis, the DAP+LNG SE (hence the temperature, time and particle size dependency). The data demonstrate that by carefully controlling (i) LNG particle size distribution (A), (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. LNG materials with different particle size characteristics (e.g. non-micronised vs. micronised) had a very significant impact on % LNG recovery from DDU-4320 (Fig. 5A). The best LNG recovery values (>90%) were achieved with large particle size (non-micronised) LNG, low SE cure temperatures and short SE cure times.

Part A, (NM) Part B, (NM)

Part A (NM) Part B (NM)

Part A (M) Part B (M)

Part A & B (M)

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