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

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

Karl Malcolm 1, Diarmaid Murphy 1, Clare McCoy 1, Peter Boyd 1, Sandeep Kumar 1, Susan Fetherston 1, Andrew Brimer 2, Jonathon Holt 2, Wendy Blanda 2, Brid Devlin 2, Jeremy Nuttall 2, Chris Gilmour 2, Tiffany Derrick 2

1 Queen’s University Belfast, UK, 2 International Partnership for Microbicides (IPM), USA.

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), 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 silicone elastomers.

Effect of addition of LNG to different parts of the SE system on % LNG recovery. M=micronised; NM=non-micronised. Mean ± SD.

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 silicone elastomers.

Figure 2. Simplified representation of the curing chemistry for addition-cure, platinum-catalysed silicone elastomers.

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 (i.e. the temperature, time and particle size dependency). Both the ethinyl and enone functional groups in LNG (Fig. 2) have potential to undergo hydrosilylation 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.

Figure 3. Percentage recovery of LNG from addition-cure silicone elastomer vaginal rings as a function of SE type, cure time and cure temperature. Mean values ± SD.

Figure 4. Effect of addition of LNG to different parts of the SE system on % LNG recovery. M=micronised; NM=non-micronised. Mean ± SD.

Figure 5. Influence of LNG particle size distribution (A) and cure time and temp. (B) on LNG recovery in DDU-4320 rings and slabs. For A, cure time = 90 s, cure temp. = 100°C. For B, non-micronised LNG was used. (>90%) were achieved with large particle size (non-micronised) LNG, low SE cure temperatures and short SE cure times.

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.

Figure 6. Schematic representation of the curing chemistry for addition-cure, platinum-catalysed silicone elastomers.