

Supplementary Materials

Table S1. Analysis of variance performed to compare the drug loading values of F1a-MH, F1b-MH and F1c-MH formulations.

ANALYSIS OF VARIANCE

| Source | Type III SS | df | Mean Squares | F-ratio | p value |
|----------|-------------|----|--------------|---------|---------|
| VAR\$(1) | 6.585 | 2 | 3.293 | 68.354 | 0.000 |
| Error | 0.434 | 9 | 0.048 | | |

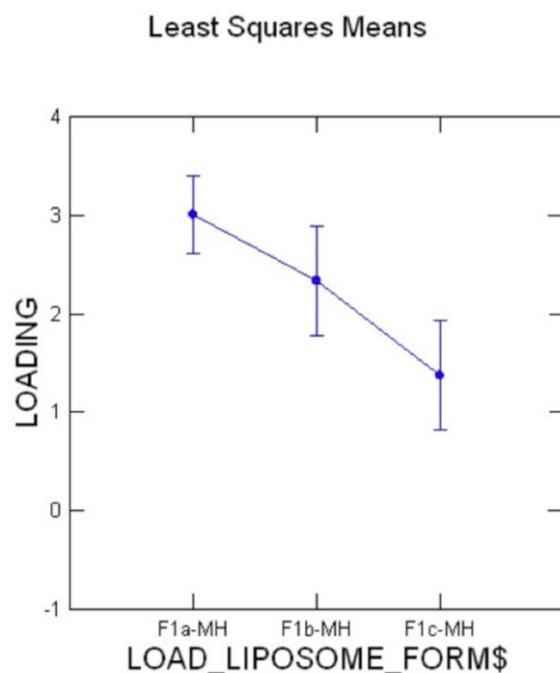


Figure S1. Drug loading values of the three MH-loaded liposomal formulations, in a graphical representation.

Table S2. Post-hoc analyses results deriving from the Tukey's (A), Bonferroni (B) and Fisher's (C) tests, applied to the ANOVA performed on the drug loading data.

| A Tukey's Honestly-Significant-Difference Test | | | | | |
|--|----------|-------------|-------------|------------|-------------------------|
| | | VAR\$(1)(i) | VAR\$(1)(j) | Difference | p-Value |
| | | | | | 95% Confidence Interval |
| | | | | | Lower Upper |
| F1a metf | F1b metf | 0,671 | 0,005 | 0,238 | 1,105 |
| F1a metf | F1c metf | 1,796 | 0,000 | 1,362 | 2,229 |
| F1b metf | F1c metf | 1,124 | 0,000 | 0,691 | 1,558 |

| B Bonferroni Test | | | | | |
|-------------------|----------|-------------|-------------|------------|-------------------------|
| | | VAR\$(1)(i) | VAR\$(1)(j) | Difference | p-Value |
| | | | | | 95% Confidence Interval |
| | | | | | Lower Upper |
| F1a metf | F1b metf | 0,671 | 0,006 | 0,216 | 1,126 |
| F1a metf | F1c metf | 1,796 | 0,000 | 1,340 | 2,251 |
| F1b metf | F1c metf | 1,124 | 0,000 | 0,669 | 1,580 |

| C Fisher's Least-Significant-Difference Test | | | | | |
|--|----------|-------------|-------------|------------|-------------------------|
| | | VAR\$(1)(i) | VAR\$(1)(j) | Difference | p-Value |
| | | | | | 95% Confidence Interval |
| | | | | | Lower Upper |
| F1a metf | F1b metf | 0,671 | 0,002 | 0,320 | 1,022 |
| F1a metf | F1c metf | 1,796 | 0,000 | 1,445 | 2,147 |
| F1b metf | F1c metf | 1,124 | 0,000 | 0,773 | 1,476 |

Table S3. Analysis of variance comparing the mean hydrodynamic diameter of unloaded and MH-loaded F1 formulations.

ANALYSIS OF VARIANCE

| Source | Type III SS | df | Mean Squares | F-ratio | p value |
|-----------------|-------------|----|--------------|---------|---------|
| LIPOSOME_FORM\$ | 1172,595 | 3 | 390,865 | 4,765 | 0,021 |
| Error | 984,339 | 12 | 82,028 | | |

Table S4. Post-hoc analyses results deriving from the Tukey's (A), Bonferroni (B) and Fisher's (C) tests, applied to the ANOVA performed on the mean size data of unloaded and MH-loaded F1 liposomes.

| A Tukey's Honestly-Significant-Difference Test | | LIPOSOME_FORM\$(-LIPOSOME_FORM\$(-Difference | p-Value | 95% Confidence Interval | |
|--|--------|--|---------|-------------------------|--------|
| i) | j) | | | Lower | Upper |
| F1 | F1a-MH | 4,817 | 0,842 | -12,540 | 22,174 |
| F1 | F1b-MH | 6,733 | 0,767 | -13,804 | 27,270 |
| F1 | F1c-MH | -17,300 | 0,110 | -37,837 | 3,237 |
| F1a-MH | F1b-MH | 1,917 | 0,990 | -17,097 | 20,930 |
| F1a-MH | F1c-MH | -22,117 | 0,021 | -41,130 | -3,103 |
| F1b-MH | F1c-MH | -24,033 | 0,031 | -45,988 | -2,078 |

| B Bonferroni Test | | LIPOSOME_FORM\$(-LIPOSOME_FORM\$(-Difference | p-Value | 95% Confidence Interval | |
|-------------------|--------|--|---------|-------------------------|--------|
| i) | j) | | | Lower | Upper |
| F1 | F1a-MH | 4,817 | 1,000 | -13,615 | 23,248 |
| F1 | F1b-MH | 6,733 | 1,000 | -15,075 | 28,542 |
| F1 | F1c-MH | -17,300 | 0,167 | -39,108 | 4,508 |
| F1a-MH | F1b-MH | 1,917 | 1,000 | -18,274 | 22,107 |
| F1a-MH | F1c-MH | -22,117 | 0,029 | -42,307 | -1,926 |
| F1b-MH | F1c-MH | -24,033 | 0,042 | -47,347 | -0,719 |

| C Fisher's Least-Significant-Difference Test | | LIPOSOME_FORM\$(-LIPOSOME_FORM\$(-Difference | p-Value | 95% Confidence Interval | |
|--|--------|--|---------|-------------------------|--------|
| i) | j) | | | Lower | Upper |
| F1 | F1a-MH | 4,817 | 0,426 | -7,921 | 17,555 |
| F1 | F1b-MH | 6,733 | 0,350 | -8,338 | 21,805 |
| F1 | F1c-MH | -17,300 | 0,028 | -32,372 | -2,228 |
| F1a-MH | F1b-MH | 1,917 | 0,770 | -12,037 | 15,870 |
| F1a-MH | F1c-MH | -22,117 | 0,005 | -36,070 | -8,163 |
| F1b-MH | F1c-MH | -24,033 | 0,007 | -40,146 | -7,921 |

Figure S2. Mean size values of unloaded and MH-loaded F1 liposomes.

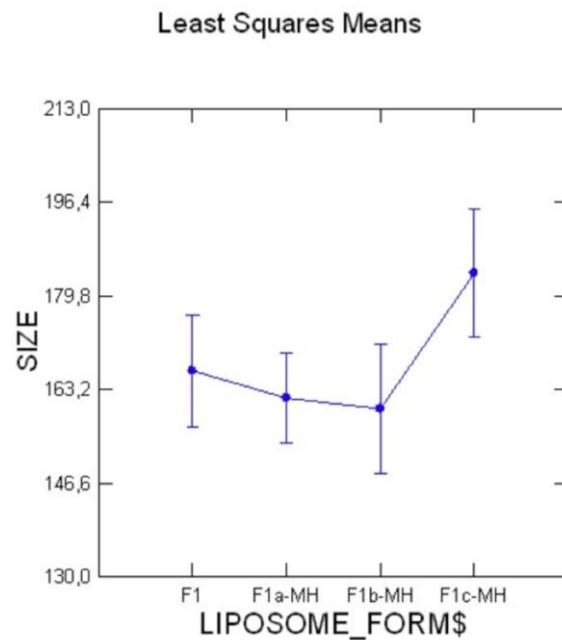


Table S5. Analysis of variance performed to compare the mean zeta potential values of unloaded and MH-loaded F1 formulations.

ANALYSIS OF VARIANCE

| Source | Type III SS | df | Mean Squares | F-ratio | p value |
|---------------|-------------|----|--------------|---------|---------|
| LIPOSOME_FZ\$ | 26,583 | 3 | 8,861 | 2,817 | 0,094 |
| Error | 31,460 | 10 | 3,146 | | |

Table S6. Post-hoc analyses results deriving from the Tukey's (A), Bonferroni (B) and Fisher's (C) tests, applied to the ANOVA performed on the mean zeta potential values of unloaded and MH-loaded F1 liposomes.

| A Tukey's Honestly-Significant-Difference Test | | | | | |
|--|------------------|------------------|------------|---------|-------------------------|
| | LIPOSOME_FZ\$(i) | LIPOSOME_FZ\$(j) | Difference | p-Value | 95% Confidence Interval |
| | | | | | Lower |
| F1 | F1a-MH | | 0,994 | 0,867 | -2,968 4,957 |
| F1 | F1b-MH | | -2,672 | 0,229 | -6,635 1,291 |
| F1 | F1c-MH | | -1,839 | 0,516 | -5,802 2,124 |
| F1a-MH | F1b-MH | | -3,667 | 0,114 | -8,097 0,764 |
| F1a-MH | F1c-MH | | -2,833 | 0,266 | -7,264 1,597 |
| F1b-MH | F1c-MH | | 0,833 | 0,937 | -3,597 5,264 |

| B Bonferroni Test | | | | | |
|-------------------|------------------|------------------|------------|---------|-------------------------|
| | LIPOSOME_FZ\$(i) | LIPOSOME_FZ\$(j) | Difference | p-Value | 95% Confidence Interval |
| | | | | | Lower |
| F1 | F1a-MH | | 0,994 | 1,000 | -3,250 5,239 |
| F1 | F1b-MH | | -2,672 | 0,396 | -6,917 1,572 |
| F1 | F1c-MH | | -1,839 | 1,000 | -6,083 2,406 |
| F1a-MH | F1b-MH | | -3,667 | 0,179 | -8,412 1,079 |
| F1a-MH | F1c-MH | | -2,833 | 0,473 | -7,579 1,912 |
| F1b-MH | F1c-MH | | 0,833 | 1,000 | -3,912 5,579 |

| C Fisher's Least-Significant-Difference Test | | | | | |
|--|------------------|------------------|------------|---------|-------------------------|
| | LIPOSOME_FZ\$(i) | LIPOSOME_FZ\$(j) | Difference | p-Value | 95% Confidence Interval |
| | | | | | Lower |
| F1 | F1a-MH | | 0,994 | 0,460 | -1,892 3,881 |
| F1 | F1b-MH | | -2,672 | 0,066 | -5,558 0,214 |
| F1 | F1c-MH | | -1,839 | 0,186 | -4,725 1,047 |
| F1a-MH | F1b-MH | | -3,667 | 0,030 | -6,894 -0,440 |
| F1a-MH | F1c-MH | | -2,833 | 0,079 | -6,060 0,394 |
| F1b-MH | F1c-MH | | 0,833 | 0,578 | -2,394 4,060 |

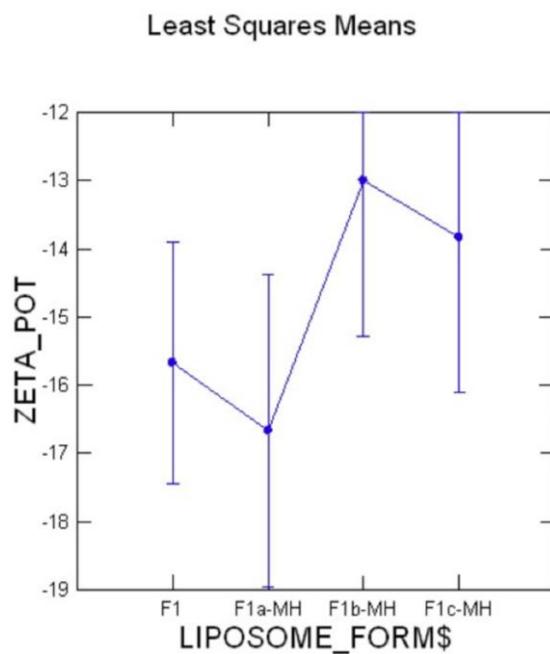


Figure S3. Mean zeta potential values of unloaded and MH-loaded F1 liposomes.