**Table S3** Coded levels, real values of each factor, and Critical Quality Attributes (CQA)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Levels | | | | |
| Coded Values | | | | |
| -1.681 | -1 | 0 | +1 | +1.681 |
| Independent variables (CMAs and CPP) | Real values | | | | |
| Phospholipon® 90 H (X1, mg) | 315.91 | 350 | 400 | 450 | 484.089 |
| Tween® 80 (X2, mg) | 15.91 | 50 | 100 | 150 | 184.089 |
| Probe Sonication Time (X3, min) | 0.954 | 3 | 6 | 9 | 11.045 |
| Dependent variables (CQAs) | Goal | | | | |
| Vesicle Size (Y1, nm) | To minimize | | | | |
| Entrapment Efficiency (Y2, %) | To maximize | | | | |
| Flexibility (Y3, mL/s) | To maximize | | | | |

CQAs: critical quality attributes; CMAs: critical material attributes and CPP: critical process parameter