Evaluation of the release kinetics of hydrophilic and lipophilic compounds from lipid-polymer hybrid nanoparticles:
Supplementary material

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1 Load efficiency after purification, proposed mathematical determination

It is important to clarify that this is an approximation and not a model, as it has not been proven or tested yet. Future works may undertake the validation of this approximation. With that noted, we propose a mathematical expression to approximate the loading efficiency, which quantifies the amount of drug encapsulated within the LPHNPs after purification. This approach could be useful for calculating the efficiency of the purification method and obtaining a more accurate estimate of the actual quantity of compound loaded in the nanoparticles. The following assumptions were made to develop this approximation:

1. To simplify, after synthesis, the initial mass of the compound may either remain encapsulated or become free. Therefore, we define the mass of encapsulated compound \( q_{ce} \) in the polymeric nanoparticles as the initial mass of compound used in synthesis \( q_{ci} \) minus the mass of non-encapsulated compound \( q_{cn} \).

\[
q_{ce} = q_{ci} - q_{cn}
\]  

2. We assume that eventually, 100% of the encapsulated compound will be released. Therefore, at infinite time, the amount of released compound \( q_{cl} \) will equal the total amount of encapsulated compound after purification \( q_{cp} \).

\[
q_{cp} = \lim_{t \to \infty} q_{cl}(t)
\]

3. Assuming that a quantity of nanoparticles is lost during purification, some compound would also be lost, so this amount of lost compound \( q_{cπ} \) should be subtracted from the amount of encapsulated compound.

\[
q_{cp} = q_{ci} - q_{cn} - q_{cπ}
\]

With these assumptions in place, encapsulation efficiency \( ξ \) can be defined as the ratio of encapsulated compound to the initial amount of compound. This concept can be expressed in terms of both encapsulated and non-encapsulated compound.
\[\xi = \frac{q_{ce}}{q_{ci}}\]  
(4)

\[\xi = \frac{q_{ci} - q_{cn}}{q_{ci}} = 1 - \frac{q_{cn}}{q_{ci}} = 1 - \frac{q_{cn}}{q_{ce} + q_{cn}}\]  
(5)

We can define the yield \(\epsilon\) as the fraction of purified encapsulated compound \(q_{ep}\) with respect to the amount of encapsulated compound, also, considering assumption 3, could be rewritten in terms of the compound lost during purification \(q_{c\pi}\)

\[\epsilon = \frac{q_{ep}}{q_{ce}}\]  
(6)

\[q_{c\pi} = q_{ci} - q_{cn} - q_{ep} = q_{ce} - q_{ep}\]  
(7)

\[\epsilon = \frac{q_{ce} - q_{c\pi}}{q_{ce}} = 1 - \frac{q_{c\pi}}{q_{ce}}\]  
(8)

By rearranging equation (8) and substituting it into equation (5), we obtain an expression that relates both efficiencies, which are the only data obtained experimentally

\[\frac{q_{c\pi}}{q_{ce}} = 1 - \epsilon\]  
(9)

\[q_{c\pi} = (1 - \epsilon)(q_{ce})\]  
(10)

\[q_{ce} = \frac{q_{c\pi}}{1 - \epsilon}\]  
(11)

\[\xi = 1 - \frac{q_{cn}}{\frac{q_{c\pi}}{1 - \epsilon} + q_{cn}}\]  
(12)

Furthermore, we derive an expression that mathematically describes the amount of compound lost during purification in terms of the loading efficiency and yield.

\[1 - \xi = \frac{q_{cn}}{\frac{q_{c\pi}}{1 - \epsilon} + q_{cn}}\]  
(13)

\[q_{cn} = (1 - \xi)(\frac{q_{c\pi}}{1 - \epsilon} + q_{cn}) = (1 - \xi)\frac{q_{c\pi}}{1 - \epsilon} + q_{cn}(1 - \xi)\]  
(14)

\[q_{cn} - q_{cn}(1 - \xi) = (1 - \xi)\frac{q_{c\pi}}{1 - \epsilon}\]  
(15)

\[q_{cn}[1 - (1 - \xi)] = q_{cn}\xi = (1 - \xi)\frac{q_{c\pi}}{1 - \epsilon}\]  
(16)

\[q_{c\pi} = q_{cn}\xi(1 - \epsilon)\]  
(17)

Now, we define a new term \(R_c\) as the fraction of compound mass to polymer mass \(q_p\)

\[R_c = \frac{q_{ci}}{q_{p}}\]  
(18)

\[q_{ci} = R_c q_p\]  
(19)

By substituting equations (17) and (19) into equation (3)

\[q_{ep} = R_c q_p - q_{cn} - q_{cn}\xi(1 - \epsilon)\frac{1 - \epsilon}{1 - \xi} = R_c q_p - q_{cn}[1 + \xi(1 - \epsilon)]\]  
(20)
If we rearrange 5 and substitute (19) into it, then we obtain an expression that defines $q_{cn}$ in terms of the mass of the polymer and encapsulation efficiency

$$\frac{q_{cn}}{q_{ci}} = (1 - \xi) \quad (21)$$

$$q_{cn} = q_{ci}(1 - \xi) = R_c q_p (1 - \xi) \quad (22)$$

By substituting 22 into 20, and regrouping the terms, we obtain a general equation to calculate the mass inside the LPHNPs after purification

$$q_{ep} = R_C \cdot q_p - R_C \cdot q_p (1 - \xi) [1 + \xi \left( \frac{1 - \epsilon}{1 - \xi} \right)] \quad (23)$$

$$q_{ep} = R_C \cdot q_p [1 - (1 - \xi)(1 + \frac{1 - \epsilon}{1 - \xi} \cdot \xi)] \quad (24)$$

$$q_{ep} = R_C \cdot q_p [1 - [(1 - \xi) + \xi (1 - \epsilon)]] \quad (25)$$

$$q_{ep} = R_C \cdot q_p [1 - (1 - \xi + \xi - \xi \epsilon)] \quad (26)$$

$$q_{ep} = R_C \cdot q_p \cdot \xi \cdot \epsilon \quad (27)$$

If we divide that quantity by the initial mass $q_{ci}$, we can obtain an approximation of the loading efficiency after purification $E_f$ of the LPHNPs with this specific synthesis method

$$E_f = \frac{q_{ep}}{q_{ci}} \quad (28)$$

## 2 Antioxidant activity of gelatine aerogels and LPHNPs embedded in gelatine

Figure S1: Antioxidant activity of gelatin aerogels and lipid/polymer hybrid nanoparticles (LPHNPs) embedded in gelatin aerogels, determined by inhibition of DPPH• radical.
3 Determination of the DPPH• inhibition technique sensibility

Figure S2: Preliminary calibration curve of DPPH• radical inhibition by the antioxidant activity of gallic acid (GA), made to determine the method’s sensitivity to low concentrations.

Figure S3: Preliminary calibration curve of DPPH• radical inhibition by the antioxidant activity of quercetin (QCT), made to determine the method’s sensitivity to low concentrations.
Figure S4: Behavior of gelatin aerogels subjected to different ethanol concentrations (25%, 50%, 75%, and 90%) after 2 hours. The image illustrates that in higher ethanol concentrations (75% and 90%) the aerogels shrunk while those in lower concentrations swelled as in aqueous conditions (25% and 50%).
Figure S5: Release profile (from 0 to 40 min) of quercetin (QCT) from gelatin aerogels (Gel/QCT) and from LPHNPs embedded in gelatin aerogels (Gel/LPHNPs/QCT) in different ethanol conditions (25%, 50%, 75%, and 90%). The optimal concentration for QCT release is 50%, as it allows the highest quantity of compound release in a sustained form. The lowest concentration of ethanol (25%) allows some release of QCT from aerogels but shows poor release from Gel/LPHNPs. The highest concentrations (75% and 90%) result in poor release from both Gel and Gel/LPHNPs.