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# The effect of polymeric wall on the permeability of drug-loaded nanocapsules

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**Abstract**

The aim of this work was to establish a quantitative correlation between the drug permeability and the polymer concentration in the nanocapsules. Indomethacin ethyl ester-loaded nanoemulsion and nanocapsules containing poly(epsilon-caprolactone) at different concentrations (0, 2, 4, 6, 8 and 10 mg/mL) presented drug loading between 0.981 and 1.005 mg/mL, pH values from 5.0 to 5.4, particle sizes between 232 and 261 nm, polydispersity lower than 0.24 and zeta potentials from −8.54 mV to −11.86 mV. An alkaline hydrolysis of indomethacin ethyl ester carried out at the particle/water interface was used to simulate a sink condition of release. The number of particles in each suspension was estimated. The calculated values ranged from $5.84\times10^{12}$ to $6.60\times10^{12}$ particles $cm^{-3}$, showing similar concentration of particles in the formulations. The diffusion was proposed as the main mechanism of the indomethacin ester release after fitting the data to the Higuchi model. Applying the Fick's first law, the calculated indomethacin ester fluxes ($J$) decreased from $2.20\times10^{-7}$ to $1.43\times10^{-7}$ mg $cm^{-2}$ $min^{-1}$. Then, the drug relative permeability decreased according to the increase in the polymer concentration fitting a power law.


*Keywords:* Diffusion; Nanocapsules; Permeability; Turbidimetry; Nanoparticles; Drug

## 1. Introduction

Polymeric nanoparticles have been extensively studied as drug carriers because they have the ability to control the release of a variety of drugs [1–4], to increase the drug stability [5–7] and to reduce their toxicity [8–10]. The general term nanoparticles is used to design nanospheres or nanocapsules, which compositions differ by the presence of oil in the latter [11]. The main theoretical models for nanocapsules and nanospheres are, respectively, vesicles of oil surrounded by a polymeric wall and a polymer matrix [12]. Another nanosized system usually employed as drug carrier is the nanoemulsion, which formulation is obtained by spontaneous emulsification [13]. The release of drugs from nanoparticles depends on drug desorption, drug diffusion and/or polymer erosion, which mechanisms are related to the form of drug encapsulation and the kinetic of polymer degradation [14,15]. To determine the drug release profiles from nanocarriers, in general, is necessary to separate the drug from the nanostructure using ultracentrifugation, ultrafiltration/centrifugation or dialysis techniques. However, those methods are limited to the determination of the drug partition coefficient between the nanoparticles and the continuous phase, besides an experimental sink condition is not achieved [16]. In order to circumvent those drawbacks, we proposed the use of an interfacial reaction, in which no drug-nanocarrier separation is needed, to compare the release behaviors of nanocapsules, nanospheres and nanoemulsion [17,18]. The results showed that nanocapsules, nanoemulsion and nanospheres present similar kinetic behaviors when the drug is adsorbed on the nanocarriers [18]. However, when the drug is entrapped within the nanocarriers, the presence of the polymer increased the half-life of the burst phase, whereas the presence of the oil increased the half-life of the sustained phase.

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The vesicular model for nanocapsules is widely proposed in the literature since experimental data suggest that the polymeric wall is an important factor for drug release kinetics. Nanocapsules and microcapsules of liquid perfluorocarbons have been prepared using different ratios of polymer and liquid core [19]. The wall thickness-to-particle radius ratio of the capsules could be easily varied by modifying the polymer-to-perfluorocarbon ratio in the organic phase prior to the emulsification. A model for the particle/water interface of nanocapsules has been proposed using fluorescent dyes chemically bound to the polymer [20]. The results demonstrated that the interface is composed by the oil, the surfactant, the polymer and water. Different studies based on transmission electron microscopy (TEM) [21] or small angle neutron scattering [22] have been used to determine the thickness of the polymeric wall of nanocapsules. TEM images of nanocapsules prepared with poly(epsilon-caprolactone) and Miglyol® 812, observed in close contact, presented deformed nanoparticles due to the liquid core. Magnifying this image, and considering that the sodium phosphotungstic acid, used as contrast agent, has not penetrated in the nanocapsules or between the adjacent walls of the two nanocapsules, the polymeric wall thickness was estimated as 1.5 to 2.0 nm [21]. However, using small angle neutron scattering to investigate nanocapsules prepared with other polyester, the poly(lactide), and triglycerides as core presented a wall thickness of 9.8 nm [22]. Regarding the drug release behaviors, the polymeric wall of nanocapsules influenced on the triamcinolone profile compared to the drug-loaded nanoemulsion profile [23]. More recently, the release profiles of 4-nitroanisol entrapped within poly(lactide) nanocapsules prepared with two different amounts of polymer presented a linear correlation with the square root of the time fitting the Higuchi model [24]. The calculated diffusion coefficients were higher for nanocapsules prepared with the lower amount of polymer. The authors suggested that the thickness of the polymeric wall rises with the increase in the polymer concentration leading to a slower diffusion of the 4-nitroanisol. In the same sense, the increase in the poly(epsilon-caprolactone) concentration in nanocapsules containing Miglyol® 810, as core, showed higher half-lives of the indomethacin ethyl ester sustained release [25].

Although some studies have been developed in order to investigate the relations between structure and morphology of nanocapsules and drug release profiles [24,26,27], there is a lack of information regarding the quantitative influence of the nanocapsule polymeric wall on the control of the drug permeability. Taking all these considerations into account, this work aimed to establish a quantitative correlation between the drug permeability and the polymer concentration in the nanocapsule suspensions. The hypothesis considers that the polymeric wall acts as a diffusional barrier to the drug diffusion from the core of nanocapsule to the particle/water interface. To evaluate this hypothesis, different formulations containing increasing amounts of poly(epsilon-caprolactone) were prepared and characterized. Indomethacin ethyl ester was chosen as model due to the possibility to simulate a sink condition to determine the release profiles by its interfacial alkaline hydrolysis.

## 2. Theory

When drugs are encapsulated, different forms of association can result depending on the physico-chemical properties of the drug and the carrier. In the case of the drug encapsulation within the carrier (device or matrix), the drug is ideally completely dissolved or it is homogeneously dispersed as discrete solid drug particles [28]. The latter condition occurs when the drug concentration is higher than the drug solubility in the matrix ($C_0 \gg C_s$). Regarding the release kinetics in that case, the Higuchi model [29] considers a concentration gradient between the concentration downstream and the concentration upstream of the interface. When a linear approximation of the drug release is observed a pseudo-steady state can be assumed. The Fick's first law of diffusion (Eq. (1)) describes the release of dispersed drugs from a matrix.

$$J = -D\frac{\Delta C}{\Delta l} \tag{1}$$

where $J$ is the flux along the $l$-direction, $D$ is the diffusion coefficient of the molecule in the particle and $\Delta C/\Delta l$ is the concentration gradient. The flux ($J$) can be easily determined from the slope of the linear region of the plot of the cumulative amount of the released drug $M_t$ as a function of time $t$ (Eq. (2)).

$$M_t = M_0 - SJ \cdot t \tag{2}$$

where $S$ is the surface area and $M_0$ is the total amount of drug entrapped in the device.

When $C_0 \gg C_s$, the drug diffusion coefficient ($D$), under sink condition of release, can be determined by using Eq. (3), derived from the Fick's first law.

$$M_t = M_0 - S\sqrt{(2DC_0C_s \cdot t)} \tag{3}$$

In addition, considering the nanocapsule as an oil core surrounded by a polymeric wall, the system corresponds to two compartments separated by a membrane, which controls the diffusion of the drug molecules from the inner compartment, the reservoir core, to the outer phase. When the entrapped drug concentration is higher than its solubility in the device, the drug dissolved in the inner phase (the reservoir) is maintained at a constant level. In this situation, and in a perfect sink condition of release, Eq. (2) can be rewritten (Eq. (4)).

$$M_t = M_0 - \frac{4\pi DkC_s r_0 r_i}{r_0 - r_i}t \tag{4}$$

where $k$ is the partition coefficient of the drug between the membrane and the outer phase, $r_0$ is the particle radius and $r_i$ is the core radius.

When the membrane thickness ($r_0 - r_i$) is unknown or other parameters must be calculated (like $D$ or $k$), the permeability coefficient ($P$) can be used (Eq. (5)).

$$P = \frac{Dk}{r_0 - r_i} \tag{5}$$

Therefore, substituting $P$ into Eq. (4) gives Eq. (6).

$$M_t = M_0 - (4\pi \cdot P \cdot C_s \cdot r_0 \cdot r_i)t \tag{6}$$