QUALITATIVE PREDICTION OF SOLUBILIZATION OF HIGHLY HYDROPHOBIC DRUGS IN BLOCK COPOLYMER MICELLES

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Summary

Micelles obtained from block copolymers of polyethylene glycol and random copolyesters of ε-caprolactone and trimethylene carbonate (50/50) can be used as carriers for hydrophobic drugs. We show in this study that the drug loading into the micelles depends strongly on the compatibility of both blocks with the drug considered. Using modeling, we developed a methodology that opens the way to qualitatively predict the drug solubility in polymeric micelles based on polymer–drug interaction parameters.

Introduction

During the last two decades, block copolymers have been extensively evaluated as drug carriers [1]. Indeed, micelles can be formed in aqueous solutions of amphiphilic di- or tri-block copolymers that associate in water in such a way that the hydrophobic blocks form the core of the micelle and the hydrophilic blocks come into contact with the aqueous environment as a corona. Various studies have shown that these micelles can encapsulate hydrophobic drugs and release them in vivo [2].

In recent years, researchers at Johnson & Johnson have developed a new family of biocompatible and biodegradable di-block copolymers containing polyethylene glycol (PEG) and a random copolyester of ε-caprolactone (CL) and trimethylene carbonate (TMC) [3]. The net advantage of this new family of liquid diblock copolymers is their ability to self-emulsify in the presence of water to form micelles of ca. 20 nm. This family of polymers proved to be efficient in encapsulating hydrophobic drugs and further releasing them in a controlled way [4].

This paper aims at presenting a qualitatively predictive approach to the solubilization of some common hydrophobic drugs (risperidone, ketoconazole, indomethacin and hydrocortisone) in polymers and more specifically in polymeric micelles formed by di-block copolymers in which PEG is the first block and the random copolyester of CL with TMC, i.e., P(CL-co-TMC), is the hydrophobic segment. The prediction is based on the polymer–drug compatibily that was determined using a model based on the Hansen's approach to solubility [5].

Experimental methods

Di-block copolymers were prepared and characterized as presented elsewhere [3,4]. The molecular weight of PEG is 750 g/mol while the P(CL-co-TMC) is about 1500 g/mol and is a 50/50 mixture of both monomers. Drugs were first mixed with the copolymers at room temperature for 24 h and then water was added. The freshly prepared solutions were stirred for 24 h at room temperature. Solubility data are an average of at least three measurements carried out at room temperature. Molecular modeling was used to estimate solubility parameters. Hansen solubility data were determined by the group contribution method with Molecular Modeling Pro software (ChemSW).

Results and discussion

Solubilization of drugs into polymeric micelles is a complex mechanism that involves different parameters, e.g., hydrophobicity, molecular volume, crystallinity, flexibility, charge and the interfacial tension against water [1]. However, one of the key parameter is certainly the polymer–drug compatibility.

An excellent way to assess the compatibility of the drug (=solubilizate) and the polymer (=solvent) is to evaluate the Flory–Huggins solubility parameter (χ_{sp}) [6]. The polymer is a thermodynamically good solvent if χ_{sp} is low (typically close to zero), meaning that when the compatibility is significant, solubilization occurs. We use a thermodynamic approach based on the extended Hildebrand solubility model developed by Hansen to determine the interaction parameter χ_{sp} [5].

In the Hildebrand approach, the solubility parameter (δ), which is defined as the root square of the cohesive energy (i.e., the energy of vaporization per volume unit), is used to calculate χ_{sp} using Eq. (1):

$$\chi_{sp} = (\delta_s - \delta_p)^2 \times V/R \times T \quad (1)$$

where s and p refer to solubilizate and polymer, V is the molar volume of the solubilizate (=drug), R the gas constant and T the temperature in Kelvin. Hansen modified the Hildebrand approach and divided δ into three components that take into account force of dispersion (δ_d), polarity (δ_p), and hydrogen bonds (δ_h). Therefore, the solubility difference (Δ) between the solubilizate and the drug is defined by Eq. (2). Therefore, χ_{sp} is calculated using Eq. (3).

$$\Delta = [(\delta_s - \delta_p)^2_{\text{dispersion}} + (\delta_s - \delta_p)^2_{\text{polarity}} \quad + (\delta_s - \delta_p)^2_{\text{hydrogen}}]^{1/2} \tag{2}$$

$$\chi_{sp} = \Delta^2 \times VR \times T \tag{3}$$

With Molecular Modeling Pro, we estimated the three components of the Hansen solubility parameter for the drugs and the block polymers (Table 1). This software utilizes a group contribution method to approximate δ values. Solubility differences (Δ) between the drugs and both segments of the di-block copolymer and the respective χ_{sp} are then calculated at 298 K (Table 2). In general, the lower the value of Δ, the better is the solubilization. Typically, Δ must be lower than 5 $(J/cm^3)^{1/2}$. In the case of the drugs studied, Δ values are systematically higher than 5 suggesting limited solubility. As a general observation, values of χ_{sp} range from 3 to 16. In order to have a good solubility, χ_{sp} should be as close as possible to zero. It is clear from Table 2 that solubility of these drugs in both blocks should be quite low to almost impossible because of the poor (or bad) compatibility.

Table 1
Hansen solubility parameters of drugs and block of PEG750 and P(CL-co-TMC) (50/50) at 298 K determined by Molecular Modeling Pro software

Compound	MW (g/mol)	Molar volume (cm^3)	δ $(J/cm^3)^{1/2}$	δ_d $(J/cm^3)^{1/2}$	δ_p $(J/cm^3)^{1/2}$	δ_h $(J/cm^3)^{1/2}$
Risperidone	410.49	316	24.4	21.4	6.9	9.5
Indomethacin	357.79	275	23.6	20.9	6.5	8.8
Ketoconazole	532.43	410	25.8	22.9	7.5	9.3
Hydrocortisone	362.47	279	23.0	15.6	7.1	15.4
P(CL-co-TMC)	1545	–	23.9	22.6	1.4	7.6
PEG	750	–	21.6	16.5	9.9	9.8

Table 2
Evaluation of the compatibility between hydrophobic drugs with PEG and P(CL-co-TMC) (50/50) at 298 K

Compound	Δ (CL/TMC)	Δ (PEG)	χ_{sp} (CL/TMC)	χ_{sp} (PEG)	Solubility (mole/ml)
Risperidone	5.941	5.753	4.501	4.221	0.527×10^{-5}
Indomethacin	5.508	5.650	3.367	3.543	1.034×10^{-5}
Ketoconazole	6.340	6.853	6.651	7.771	0.347×10^{-5}
Hydrocortisone	11.930	6.325	16.026	4.505	0.395×10^{-5}

Based on χ_{sp} parameter, we tried to predict qualitatively the solubility of the drugs in the copolymers and subsequently in the micelles. Indeed, we assumed that solubilization in the micelles can occur in either the core or the corona or in both regions.

We predicted based on χ_{sp} values that the compatibility with the core, i.e., the P(CL-co-TMC) block, will be as follows: indomethacin> risperidone>ketoconazole>hydrocortisone.

In the same manner, the compatibility with the PEG-corona is: indomethacin>risperidone $\geq$ hydrocortisone>ketoconazole. Assuming that solubilization of a drug can occur in both regions of the micelles, i.e., core and corona, we can predict the overall compatibility and thus the solubility. Therefore, the solubility in micelles can be ranked as follows: indomethacin>risperidone>hydrocortisone $\approx$ ketoconazole. At this point, since we cannot quantitatively predict the solubility extent, we believe that ketoconazole and hydrocortisone should show similar values. Indeed, hydrocortisone has a better compatibility than ketoconazole towards PEG and is highly incompatible with the polyester core, but the reverse is observed when it comes to ketoconazole and the P(CL-co-TMC) core.

Experiments were carried out to check the validity of the qualitative prediction. Excess of drug was mixed with the di-block copolymers then water was added to prepare a 10% w/v solution of polymer in water. Solubility data measured are listed in Table 2. Results show that indomethacin

is the most soluble of all the drugs considered followed by risperidone and then hydrocortisone and ketoconazole with close values (ca. 0.4 mole/ml). These results are in line with the prediction made based on the polymer–drug compatibility.

Conclusions

This study demonstrates that qualitative prediction of solubilization of hydrophobic drugs in micelles is possible using a thermodynamic model that assesses the polymer–drug compatibility through the Hildebrand interaction parameter χ. The approach we used is based on the Hansen solubility parameter of the drugs and the different polymers of the di-block copolymer. Results indicate that the prediction is in line with what is experimentally observed proving the validity of the approach. This methodology is a promising tool because it allows the screening of drugs in development in pharmaceutical labs and thus represents a gain of time and money. On the other hand, it is possible to choose a specific drug and screen between different polymers for the most suitable to use for drug solubilization (or dispersion) in a polymer.

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