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Prediction of drug solubility in amphiphilic di-block copolymer micelles: the role of polymer-drug compatibility

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The goal of the current study was to assess the value of predictive computational approaches for estimating drug solubility in hydrated micelles formed from di-block copolymers of polyethylene glycol (PEG) and random copolyesters of ε-caprolactone (CL) and trimethylene carbonate (TMC) using drug-polymer compatibility as assessed through the Flory-Huggins interaction parameter (χ). In order to accomplish this, the compatibility of several well-known model drugs (associated with the four biopharmaceutics classification system (BCS) classes) was assessed with both segments of the amphiphilic di-block copolymer PEG-b-P(CL-co-TMC). Compatibilities were estimated based on the Hansen modification of the Hildebrand approach using Molecular Modeling Pro software. Experimental solubilities for model drugs were determined using a shake-flask technique at various polymer concentrations. The solubilities of 8 compounds in 10% w/v micelle solutions were in relatively good agreement with the predicted drug-polymer compatibility. In addition, the approach allows for the selection of a suitable di-block copolymer for optimal solubilization of a specific drug. Furosemide was assessed as a model with results suggesting that it can be best entrapped in a di-block copolyester containing a relatively high CL content. The data suggests that prediction of drug solubilization of block copolymer-based micelles may be facilitated by assessing the compatibility of the drug for the component polymeric domains.

1. Introduction

During the last two decades, block copolymers have been extensively evaluated as drug solubilizers and carriers (Allen et al. 1999). Polymeric micelles prepared from amphiphilic block copolymers are one of the most actively studied systems in this regard (Kwon and Kataoka 1995; Jones and Leroux 1999; Adams and Lavasanifar 2003). Amphiphilic block copolymer molecules consist of hydrophobic and hydrophilic blocks that can assemble in aqueous solutions at a certain concentration, the critical micelle concentration (CMC), to form micelles. In the formed structures, the hydrophilic blocks constitute the outer shell (corona) while the hydrophobic blocks form the core (Fig. 1). Hence, the core is stabilized by the hydrophilic corona, which serves as an interface between the aqueous

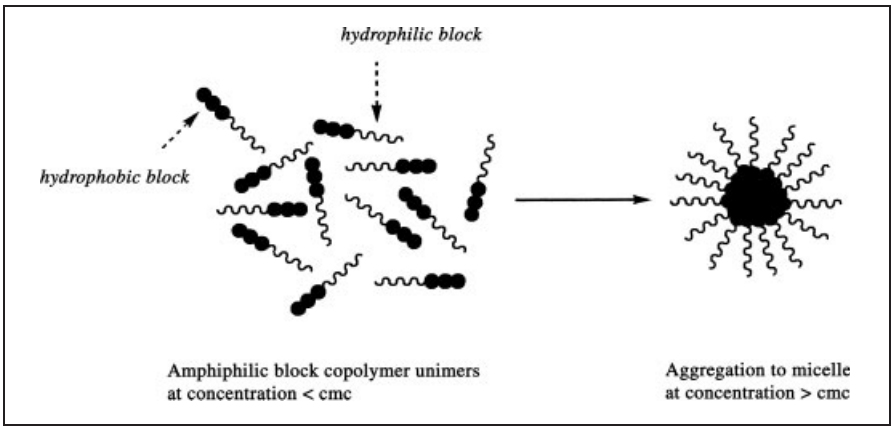
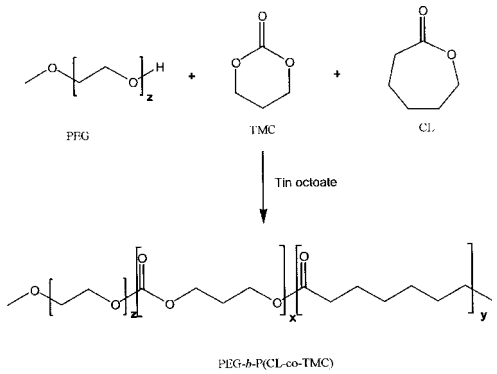


Fig. 1:
Self-assembling of amphiphilic di-block copolymers in water

Scheme Synthesis of PEG-b-P(CL-co-TMC) by ring opening polymerization



phase and the hydrophobic interior. One of the advantages of such a system is that the hydrophobic core can accommodate hydrophobic compounds that are poorly water-soluble thereby enhancing their solubility in water. Various studies have shown that these micelles can encapsulate hydrophobic drugs and release them *in vivo* (Torchilin 2001).

Recently, 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) have been developed (Arien et al. 2004) (Scheme). Of particular interest were di-block copolymers in which the PEG component had a molecular weight of 750 g/mol and the copolyester block was a (50/50) random copolymer of CL and TMC containing about 14 monomer units. The advantage of this di-block copolymer was its ability to self-assemble in presence of water to form micelles of ca. 20 nm. This di-block copolymer proved to be efficient in encapsulating hydrophobic drugs and further releasing them in a controlled way (Ould-Ouali et al. 2004).

The aim of this study was to generate a qualitatively method to assess the solubilization of hydrophobic drugs in polymers and more specifically in polymeric micelles formed by di-block copolymers in which PEG is the hydrophilic block and the random copolyester of CL with TMC, i.e. P(CL-co-TMC), is the hydrophobic segment. Such an approach may be helpful for the rapid screening of drug candidates with low water-solubility to assess their applicability to polymeric micelle solubilization. The prediction is based on the polymer-drug compatibility that was determined using a model based on the Hansen's approach to solubility (Hansen 1967, 2000).

2. Investigations, results and discussion

2.1. Thermodynamic approach

Solubilization of drugs into hydrated polymeric micelles is a complex process that involves a variety of molecular interactions and characteristics, e.g. hydrophobicity, molecular volume, crystallinity, flexibility, charge and interfacial tension (Allen et al. 1999). One of the key parameters would seem to be polymer-drug compatibility. An important way to assess the compatibility of the drug (= the entity being solubilized) and the polymer (= solvent) is to evaluate the Flory-Huggins interaction parameter (χ_{sp}) (Nagarayan et al. 1986; Gadelle et al. 1995). This approach has successfully been used to predict drug-polymer miscibility and solubility (Marsac et al. 2006; Greenhalgh et al. 1999; Hancock et al. 1997; Forster et al. 2001). In polymer-drug under discussion, this parameter assesses the specific interactions between polymer chains and drug molecules. The polymer is a thermodynamically good solvent for the drug if χ_{sp} is very low (ideally equal to zero), meaning favorable interactions with the drug thus leading to a good compatibility with it, therefore solubilization can occur. We used a thermodynamic approach based on the extended Hildebrand solubility model developed by Hansen to determine the interaction parameter χ_{sp} (Hansen 2000).

In the Hildebrand approach, the solubility parameter (δ) is defined as the square root of the cohesive energy density CED, i.e., the energy of vaporization ΔE_v per unit of molar volume (Eq. (1)) (Hildebrant and Scott 1950). The solubility parameter is used to calculate χ_{sp} using Eq. (2):

$$\delta = (\mathrm{CED})^{1/2} = (\Delta E_v/V)^{1/2} \quad (1)$$

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

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 forces of dispersion between atoms (δd), permanent dipole forces between molecules (δp), and propensity to form hydrogen bonds between molecules (δh). Therefore, one can define the solubility difference (Δ) between the polymer and the drug by Eq. (3). χ_{sp} is calculated using Eq. (4).

$$\Delta = [(\delta_s - \delta_p)^2_{\mathrm{dispersion}} + (\delta_s - \delta_p)^2_{\mathrm{polarity}} + (\delta_s - \delta_p)^2_{\mathrm{hydrogen}}]^{1/2} \quad (3)$$

$$\chi_{sp} = \Delta^2 \cdot V/R \cdot T \quad (4)$$

Thus, the polymer-drug compatibility can be assessed using Eq. (3). This compatibility is directly proportional to Δ^2 (i.e., the solubility difference between the polymer and the drug considered) but also to the size of the drug. 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 order to observe good solubility (Krevelen 1990). From this equation, it is obvious that large drug volume will tend to result in lower compatibility, all other factors being equal.

2.2. Calculations of solubility parameters, solubility differences and interaction parameters of various drugs with PEG and P(CL-co-TMC) (50/50)

Using Molecular Modeling Pro, we estimated the three components of the Hansen solubility parameter for various commercially available drugs belonging to different classes of the Biopharmaceutics Classification System (BCS) defined for orally administered medicines (Amidon et al. 1995; Dressman et al. 1998) (Table 1). This software utilizes a group contribution method based on Hansen theory of solubility to approximate δ values (Barton 1983). In this method, the cohesive energy of a molecule is considered to be an additive property and is the sum of contributions from individual groups contained in the molecule. Studies have revealed that solubility parameters estimated by this method are usually in agreement with experimental values especially in the absence of specific interactions (Cowie 1965; Marsac et al. 2006). Molar vol-

Table 1: Solubility parameters of selected model drugs at 298 K

Compound	BCS class	Molar volume (cm^3)	MW (g/mol)	δ polarity $(J/cm^3)^{1/2}$	δ dispersion $(J/cm^3)^{1/2}$	δ hydrogen $(J/cm^3)^{1/2}$
Amoxicillin	3	223.7	365.4	11.3	19.2	14.3
Antipyrine	1	151.9	188.2	9.2	18.7	6.8
Atenolol	3	217.8	266.3	14.2	21.6	11.9
Carbamazepine	2	166.6	236.3	5.2	23.6	8.3
Chloramphenicol	3	177.1	323.1	9.0	20.7	15.8
Cimetidine	3	180.3	252.3	9.1	21.1	9.2
Furosemide	4	196.7	330.7	10.3	22.0	12.7
Hydrocortisone	2	266.0	362.5	7.1	15.6	15.4
Indomethacin	2	222.4	375.8	6.5	20.9	8.8
Ketoconazole	2	345.8	532.4	7.5	22.9	9.3
Ketoprofen	2	187.9	254.3	6.8	20.0	8.0
Methyldopa	3	130.1	211.2	7.2	15.4	17.6
Metoprolol	1	241.5	684.8	12.0	18.8	10.1
Naproxen	1	170.6	230.3	3.5	18.7	9.6
Propranolol	1	218.0	295.8	13.0	20.9	9.6
Ranitidine	3	241.4	350.9	6.4	18.0	9.2
Risperidone	2	290.7	410.5	6.9	21.4	9.5
Theophylline	1	109.1	180.2	16.9	19.8	10.7
Verapamil	1	409.2	491.1	4.2	17.8	8.3

Table 2: Solubility parameters of PEG and P(CL-co-TMC) (50/50) at 298 K

Polymer	Molecular weight (g/mol)	δ polarity $(J/cm^3)^{1/2}$	δ dispersion $(J/cm^3)^{1/2}$	δ hydrogen $(J/cm^3)^{1/2}$
PEG	750	9.9	16.5	9.8
P(CL-co-TMC)	1545	1.4	22.6	7.6

umes were also calculated by means of Van Krevelen's theory (Krevelen 1990). Similarly, calculations of the different components of solubility parameters were done for the two constitutive blocks of the amphiphilic copolymer (Table 2). As would be expected, results indicate that the copolyester block, i.e. P(CL-co-TMC), is less polar and less susceptible to form hydrogen bonds than the hydrophilic block, i.e., PEG. Also, the dispersion forces are more prominent in the copolyester than in the PEG.

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 3). Few drugs have Δ values lower than 5 $(J/cm^3)^{1/2}$ with both the PEG and the copolyester blocks. Five drugs (antipyrine, ketoprofen, metoprolol, ranitidine and cimetidine) have low solubility difference (Δ) with PEG. Only two drugs (carbamazepine and naproxen) show low Δ with the copolyester block.

When calculating values of χ_{sp}, results ranged from about 0.9 to 6.5 in the case of the hydrophilic PEG block. Interaction parameters of these drugs with the hydrophobic copolyester block vary from about 1.1 (carbamazepine) to as high as 16.1 (atenolol). In order to have a very good compatibility, χ_{sp} should be as close as possible to zero.

2.3. Theoretical and experimental solubility of poorly water-soluble drugs in polymeric micelles of PEG-b-P(CL-co-TMC) (50/50)

In principle, solubilization of drugs in micelles can occur in the corona, the core and/or their interface. The location

Table 3: Evaluation of the compatibility between hydrophobic drugs with PEG and P(CL-co-TMC) (50/50) domains at 298 K

Compound	Δ (PEG)	Δ (CL/TMC)	χ_{sp} (PEG)	χ_{sp} (CL/TMC)	Solubility in water (mg/ml or mg/L)[a]
Amoxicillin	5.431	12.428	2.663	13.945	3.4 mg/mL
Antipyrine	3.785	8.757	0.878	4.701	> 100 mg/mL
Atenolol	6.994	13.540	4.300	16.115	13.5 mg/mL
Carbamazepine	8.646	3.991	5.026	1.071	0.018 mg/mL
Chloramphenicol	7.379	11.341	3.892	9.188	2.5 mg/mL
Cimetidine	4.707	8.006	1.612	4.664	5 mg/mL
Furosemide	6.230	10.275	3.081	8.381	0.006 mg/mL
Hydrocortisone	6.325	11.930	4.295	15.280	0.32 mg/mL
Indomethacin	5.650	5.508	2.865	2.723	0.937 mg/L
Ketoconazole	6.853	6.340	6.554	5.610	0.0866 mg/L
Ketoprofen	5.010	6.258	1.903	2.970	0.05 mg/mL
Methyldopa	8.327	9.771	3.641	5.013	1 mg/mL
Metoprolol	3.129	11.535	0.954	12.970	>100 mg/mL
Naproxen	6.770	4.860	3.156	1.626	0.016 mg/mL
Propranolol	5.386	11.893	2.552	12.445	0.07 mg/mL
Ranitidine	3.855	6.980	1.448	4.747	24.7 mg/mL
Risperidone	5.753	5.941	3.883	4.141	2.8 mg/L
Theophylline	7.791	16.053	2.673	11.347	4 mg/mL
Verapamil	6.036	5.601	6.016	5.181	4.47 mg/mL

[a] http://redpoll.pharmacy.ualberta.ca/drugbank/ (see section 3.4)

Table 4: Solubility of selected drugs in water and in 10% w/v solutions of PEG-b-P(CL-co-TMC) (50/50) at 298 K

Compound	χ_{sp} (PEG)	χ_{sp} (CL/TMC)	Solubility in water (mg/ml)[a]	Solubility in micelle (mg/ml)	Solubility in micelle (mole/ml)
Carbamazepine	5.026	1.071	0.01	1.37	0.580×10^{-5}
Cimetidine	1.612	4.664	1	10.47	4.150×10^{-5}
Furosemide	3.081	8.381	0.01	2.61	0.789×10^{-5}
Hydrocortisone	4.295	15.280	0.04	1.43	0.395×10^{-5}
Indomethacin	2.865	2.723	0.01	3.70	1.034×10^{-5}
Ketoconazole	6.554	5.610	0.01	1.85	0.347×10^{-5}
Ketoprofen	1.903	2.970	0.1	19.60	7.707×10^{-5}
Risperidone	3.883	4.141	0.06	2.16	0.526×10^{-5}

[a] Solubility determined as a function of this study (see section 3.4)

will likely depend on the compatibility of the considered drug with the core, the corona or both segments. Theoretical drug solubilization in di-block copolymers of PEG-b-P(CL-co-TMC) (50/50) was evaluated and is presented in Table 3. Poorly water-soluble drugs were selected for this study based on the potential value of the polymers as drug carriers. Eight drugs with low water-solubility (maximum 1 mg/mL) were selected (Table 4). Six of them belong to the BCS class 2 (low solubility and high gastrointestinal permeability), 1 to BCS class 3 (high solubility and low G.I. permeability) and 1 to the class 4 (low solubility and low G.I. permeability) (Amidon et al. 1995; Dressman et al. 1998). We predicted, based on calculated χ_{sp} values, that drug compatibilities with the hydrophobic copolyester core and the hydrophilic PEG corona would be as follows:

Copolyester core: Carbamazepine > indomethacin > ketoprofen > risperidone > cimetidine > ketoconazole > furosemide > hydrocortisone

PEG corona: Cimetidine > ketoprofen > indomethacin > furosemide > risperidone > hydrocortisone > carbamazepine > ketoconazole.

Assuming that a drug can be located in both regions of the micelles, i.e., core and corona, an overall compatibility can be predicted and thus allowing a qualitative prediction of solubility. As mentioned earlier, compatibility increases when χ_{sp} approaches zero. The overall compatibility (and presumably solubility) will be good when both χ_{sp} with PEG (χ_{sp} PEG) and P(CL-co-TMC) (χ_{sp} CL/TMC) is close to the point (0, 0). Based on this assumption we can predict the drug solubility in micelles by evaluating the distance between the point corresponding to the considered drug and the origin. Therefore the drug solubilities in micelles can be predicted as follows: Ketoprofen > cimetidine > indomethacin > risperidone > carbamazepine > furosemide > ketoconazole > hydrocortisone.

Three groups of drugs emerged from the plot. Ketoprofen, cimetidine and indomethacin are the closest to the origin and are expected to be well solubilized in both regions of the micelle and likely at the interface. Indeed, compared to all others drugs, they show better compatibility with both regions of the di-block copolymer. A second group is located at about the same distance to the origin and includes risperidone, carbamazepine and furosemide. The last group comprises ketoconazole and hydrocortisone.

Experimental solubilities were determined to check the validity of this qualitative prediction. An excess of drug was mixed with the di-block copolymers followed by water addition to prepare a 10% w/v aqueous solution of polymer (0.1 g in 1 mL of water). Experimental solubility data are listed in Table 4. Results indicate that micelles enhance solubility for all the drugs considered. Exceptional increase in solubility is observed for indomethacin, furosemide, ketoprofen, ketoconazole and carbamazepine with 370-, 261-, 196-, 185- and 137-fold increase, respectively. 38- and 36-fold enhancements are observed for hydrocortisone and risperidone while a 10-fold improvement is noted for cimetidine. Solubility values (in mg/mL) reach 10.5 mg/ml for cimetidine and about 20 mg/ml for ketoprofen in solutions containing 10% w/v of the di-block copolymer. Observed solubility data (presented in mole/ml for comparison) can be classed as follows: Ketoprofen > cimetidine > indomethacin > furosemide > carbamazepine > risperidone > hydrocortisone > ketoconazole.

Results show that the agreement, in rank order, between the predicted and measured solubility (in mol/ml) is reasonable. Indeed, the three most soluble drugs are correctly predicted. Within the second group, furosemide gives a better-than-expected result based on compatibility while risperidone and carbamazepine show comparable values. The two least soluble drugs are hydrocortisone and ketoconazole (with an inverted rank order as compared to the prediction) showing also comparable solubility values.

2.4. Solubilization of furosemide in PEG-b-P(CL-co-TMC) of various CL contents

The methodology developed helps to screen drugs with potentially high solubility in polymeric micelles of PEG-b-P(CL-co-TMC). An extension of the approach will be the design of the "ideal" polymeric micelle carrier for a specific drug. To investigate this possibility, di-block copolymers were designed and prepared where PEG (750 g/mol) was the amphiphilic block and the second block was a copolyester of CL and TMC containing various amounts of CL, i.e. 90, 70, 30, and 10% (mole). They all spontaneously self-assemble in water to form micelles of identical size, i.e., ca. 20 nm, at 25 °C (Table 5) (Latere Dwan'Isa et al. 2006). Their Hansen's solubility parameters were determined and found to depend on the CL content. According to the data generated, diminution of CL amount in the copolyester block results in a moderate reduction of the propensity to form hydrogen bonds but in a significant drop of permanent dipole forces. Dispersion forces also tend to decrease. In order to further validate our solubility prediction methodology, polymer-drug compatibility of these di-block copolymers with the poorly water-soluble drug, furosemide, was evaluated through the calculation of Δ and χ_{sp}. Results suggest a lower compatibility of furosemide when the amount of CL in the copolyester block is reduced. Indeed, calculations indicate that χ_{sp} increases with diminishing amount of CL meaning that more unfavorable interactions take place between the drug and the P(CL-co-TMC). Therefore, the solubility of furosemide in

Table 5: Solubility parameters of P(CL-co-TMC) copolyesters of various CL/TMC compositions and determination of their compatibility with furosemide at 298 K

CL/TMC molar ratio	Micelle size (nm)	δ polarity $(J/cm^3)^{1/2}$	δ dispersion $(J/cm^3)^{1/2}$	δ hydrogen $(J/cm^3)^{1/2}$	Δ (CL/TMC) + Furosemide	χsp (CL/TMC) + Furosemide
90/10	20.5	8.3	23.3	9.4	4.012	1.278
70/30	20.6	3.6	22.2	6.8	8.930	6.331
50/50	20.2	1.4	22.6	7.6	10.275	8.381
30/70	20.2	0	22.1	7.2	11.677	10.824
10/90	19.0	0	21.4	7.0	11.787	11.029

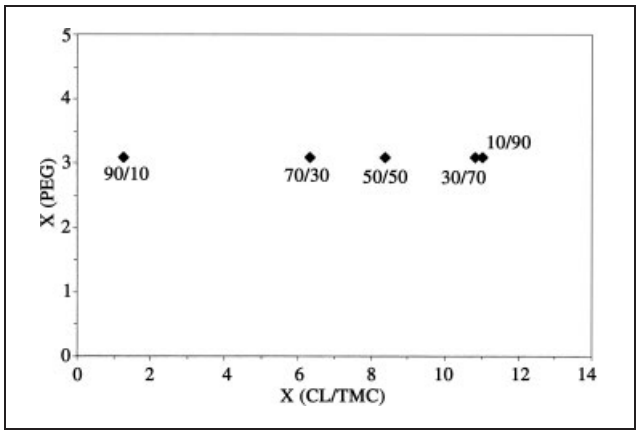


Fig. 2: Flory-Huggins parameter of furosemide with PEG and P(CL-co-TMC) as function of CL/TMC molar composition

micelles should be influenced even though the compatibility with PEG remains constant since this block has not been modified in this series of copolymers. Prediction of the furosemide solubility in micelles can be made by calculating the distance to the origin of the plot depicted in Fig. 2. Solubility dependence of furosemide in polymeric micelles should therefore diminish with decreasing amount of CL in the copolyester block as follows: 90% CL > 70% CL > 50% CL > 30% CL > 10% CL.

Experimental solubility data in 10% w/v di-block copolymers in water show that the CL to TMC molar ratio influences the drug solubilization (Table 6). Furosemide solubility is enhanced (when compared to aqueous solution) by 188 to about 320 times indicating that drug entrapment is possible in all cases. These experimental results confirm the prediction made, i.e., the solubility will decline when CL amount in the copolyester block is reduced. Solubility progressively decreases from as high as 3.17 mg/ml when the copolyester contains 90 mole % of CL to as low as 1.88 mg/ml, a 41% drop, when the amount of CL is 10 mole %.

Table 6: Solubility of furosemide in polymeric micelles of PEG-P(CL-co-TMC) as function of copolyester composition of P(CL-co-TMC) core

Entry	CL/TMC molar ratio	Solubility in micelles (mg/ml)	Solubility in micelles (mol/ml)	Solubility enhancement (times)[a]
1	90/10	3.17 ± 0.02	0.959×10^{-5}	317
2	70/30	3.05 ± 0.04	0.922×10^{-5}	305
3	50/50	2.61 ± 0.01	0.789×10^{-5}	261
4	30/70	2.50 ± 0.01	0.756×10^{-5}	250
5	10/90	1.88 ± 0.01	0.568×10^{-5}	188

[a] Compared to aqueous solution

2.5. Conclusions

This paper suggests a rapid and reasonably accurate method for qualitative prediction of solubilization of drugs in polymeric micelles made from PEG750-b-P(CL-co-TMC). The method uses a thermodynamic approach that assesses the polymer-drug compatibility through the Flory-Huggins interaction parameter χ. The method we used is based on determining the Hansen solubility parameters of the drugs and the different polymers of the di-block copolymer and then the solubility differences (Δ). This solubility difference can be used in the estimation of the Flory-Huggins parameter. We demonstrate that the drug-polymer compatibility, approximated by χ, is a key parameter in the process of drug encapsulation into the polymeric micelles considered. Experimental results indicate that the qualitative solubility prediction is in line with what is experimentally observed proving the validity of the approach developed. We show that in order to observe a significant solubility improvement, good compatibility of the drug with both the core and the corona parts of the micelle is helpful.

Some limitations of the method should be noted. Deviations from the prediction can occur because of secondary factors such as interfacial tension, drug rigidity and other effects. The methodology developed here does not take such items into consideration. Another practical weakness of the approach is the limited type of functional groups available in the software. For instance, nitrile groups are not taken into account in the calculations of solubility parameters by the software considered.

Having said this, we believe that this approach is a promising tool because it allows the rapid and accurate screening of numerous drugs and will help to select those with potential significant solubility enhancement. Moreover, it is possible to choose a specific drug and to screen between different polymers available for the most suitable to use for drug solubilization in polymeric micelles or even better to design the most efficient polymeric carrier based on polymer-drug compatibility.

3. Experimental

3.1. Materials

ε-Caprolactone (CAP) was purchased from Union Carbide (Danbury, CT, USA), and trimethylene carbonate (TMC) from Boehringer Ingelheim (Petersburg, VA, USA). Stannous octoate and toluene were from Aldrich (Milwaukee, WI, USA). Methoxy end-capped poly(ethylene glycol) (PEG) of molecular weigh 750 g/mol was purchased from Fluka (Milwaukee, WI, USA). Carbamazepine, cimetidine, furosemide, hydrocortisone, indomethacin and ketoprofen were purchased from Sigma-Aldrich. Johnson & Johnson Pharmaceutical Research & Development (a division of Janssen Pharmaceutica, Beerse, Belgium) produced risperidone and ketoconazole.

3.2. Di-block copolymer synthesis and characterization

Di-block copolymers were prepared and characterized as described elsewhere (Arien et al. 2004; Ould-Ouali et al. 2004). 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. Micelle formation was controlled for three polymer batches by adding water to the di-block copolymers (10% w/v). The mixture was stirred for 10 min. Micelle size was evaluated by dynamic light scattering at 25 °C without filtering the solution. The size of the micelles was determined with a Malvern Autosizer 4700 and found to be 20 ± 1 nm at 25 °C.

3.3. Determination of solubility parameters for drugs and the blocks of the copolymer

Molecular modeling was used to estimate Hansen solubility parameters of drugs and of a monomethoxy end-capped PEG and the random copolyesters of CL and TMC. Hansen solubility data were determined by the group contribution method incorporated in the Molecular Modeling Pro software suite (ChemSW Inc., Fairfield, CA).

3.4. Drug solubilization in 10% w/v di-block copolymer micelles

Solubility data for the compounds of interest were collected from the literature (Table 3). Based on the spread of values available, a separate set of solubility measurements for the eight selected compounds collected in Table 4 was performed using a shake-flask technique in water under conditions which copied the studies planned for the co-polymer as closely as possible. In some cases, these values deviated from literature values but were considered controls for the subsequent polymer studies. The maximum drug solubility in micelles was determined as follows: In a glass vial, 0.5 g of the copolymer and 0.1 to 0.15 g of the drug were weighed and then mixed at 50 °C for 10 min using a magnetic stirrer followed by addition of 5 mL of filtered water (0.1 μm Millipore). The solution (S) was stirred for 24 h at room temperature and then filtered through a 0.1 μm Millipore filter to remove non-solubilized drug. A linear calibration curve relating known drug concentrations and their UV absorbance (ranging from 0.08 to 0.9) was first determined using the spectrophotometer. Maximum drug solubility of the filtered solution (S) was measured with an ultraviolet (UV) visible spectrophotometer (Shimadzu UV-160, Japan) at the characteristic wavelength of the considered drug and then reported to the calibration curve. Solubility data are an average of at least three measurements.

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