and not the dispersion and adhesion energy interactions between components. The Flory–Huggins solubility parameter, χ, can be calculated using the Hildebrand solubility parameters:

$$\chi = \frac{V_{\text{drug}}(\delta_{\text{drug}} - \delta_{\text{poly}})^2}{RT}$$

where the Hildebrand solubility parameters, δ_{poly} and δ_{poly}, are square roots of the cohesive energy densities of the drug molecule and hydrophobic repeating group of the copolymer, respectively; V_{drug} is the molar volume of the drug molecule; R is the ideal gas constant; and T is the temperature. The Hildebrand solubility parameters may be calculated using group contribution methods, wherein the overall solubility parameter is the sum of contributions from Van der Waals dispersion forces, δ_d; dipole–dipole interactions, δ_p; and hydrogen bonding, δ_h.

$$\delta_{\text{total}} = [\delta_d^2 + \delta_p^2 + \delta_h^2]^{1/2}$$

$$\delta_d = \frac{\sum F_{\text{di}}}{V} \quad \delta_p = \frac{\sqrt{\sum F_{\text{pi}}^2}}{V} \quad \delta_h = \frac{\sqrt{\sum E_{\text{hi}}}}{V}$$

The molar attraction constants of dispersion, F_{di}; dipole–dipole interactions, F_{pi}; hydrogen bonding, E_{hi}; and the molar volume, V; for the drug and the hydrophobic block may be determined from group contribution tables provided by Hoftyzer-Van Krevelen and Fedor (Krevelen, 1990).

Liu et al. (2003) recently applied classic Flory–Huggins solution theory to predict the solubility of the hydrophobic drug ellipticine in several block copolymers (Table 13.1). Solution theory predicted the solubility of ellipticine in block copolymers to be PBLA > PCL > PDLA > PGA. Liu et al. found PEO-*b*-PCL to encapsulate up to 21% w/w ellipticine, whereas PDLA encapsulated a maximum of 0.1% w/w.

Factors Affecting Micellization and Solubilization

Temperature and Concentration Effects on Micellization

Before discussing the temperature and concentration effects, some terms need to be defined. First, a solvent is considered a *selective solvent* if it is a thermodynamically good solvent for one type of block but a nonsolvent for the other type of block. Next, the CMC of copolymers can be defined as the concentration below which only single chains are present but above which both single chains and micellar aggregates coexist. Then *critical micelle temperature* (CMT) is the temperature below which only single chains are present, while above the CMT both single chains and micelles coexist. Therefore, by monitoring an appropriate property of the system of interest, an inflection point, which corresponds to the CMC or CMT, can usually be found on the concentration or temperature curve.

TABLE 13.1
Solubility Parameters and Heat of Mixing of Ellipticine in Various Polymers

Polymer	δ_{total} (MPa$^{1/2}$)	$\delta_{\text{ellipticine}} - \delta_{\text{polymer}}$	ΔH_{mix}(MJ/m^3)
Poly(benzyl l-aspartate) (PBLA)	25	0.8	2.2
Poly(ε-caprolactone) (PCL)	20.2	5.9	10.8
Poly(dl-lactic acid) (PDLA)	23.3	2.8	14.3
Poly(glycolic acid) (PGA)	28	−1.9	21.7
Ellipticine	26.1	–	–

Source: Liu, J. et al., *J. Pharm. Sci*., 93, 132–143, 2003.