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Research Paper

Simple measurements for prediction of drug release from polymer matrices – Solubility parameters and intrinsic viscosity

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ABSTRACT

Purpose: This study describes how protein release from polymer matrices correlate with simple measurements on the intrinsic viscosity of the polymer solutions used for casting the matrices and calculations of the solubility parameters of polymers and solvents used.
Method: Matrices of poly(DL-lactide-co-glycolide) (PLGA) were cast with bovine serum albumin (BSA) as a model drug using different solvents (acetone, dichloromethane, ethanol and water). The amount of released protein from the different matrices was correlated with the Hildebrand and Hansen solubility parameters of the solvents, and the intrinsic viscosity of the polymer solutions. Matrix microstructure was investigated by transmission and scanning electron microscopy (TEM and SEM). Polycaprolactone (PCL) matrices were used in a similar way to support the results for PLGA matrices.
Results: The maximum amount of BSA released and the release profile from PLGA matrices varied depending on the solvent used for casting. The maximum amount of released BSA decreased with higher intrinsic viscosity, and increased with solubility parameter difference between the solvent and polymer used. The solvent used also had an effect on the matrix microstructure as determined by TEM and SEM. Similar results were obtained for the PCL polymer systems.
Conclusions: The smaller the difference in the solubility parameter between the polymer and the solvent used for casting a polymer matrix, the lower will be the maximum protein release. This is because of the presence of smaller pore sizes in the cast matrix if a solvent with a solubility parameter close to the one of the polymer is used. Likewise, the intrinsic viscosity of the polymer solution increases as solubility parameter differences decrease, thus, simple measurements of intrinsic viscosity and solubility parameter difference, allow the prediction of protein release profiles.

1. Introduction

Conversion of biologically active proteins into useful medicines requires an extensive understanding of protein behaviour in the non-biological environments encountered during industrial scale processing of dosage forms, leading to only a few alternatives to administration by injection having been developed and successfully brought to the marketplace [1]. Polymeric delivery systems have been used for a variety of controlled release devices, decreasing required dosing frequency and thereby increasing patient compliance [2]. In some cases, controlled release may be the only viable treatment option, e.g. in case of drug delivery to the brain, in which each delivery carries a risk to the patient [3,4]. In such cases optimization of polymeric delivery may help to treat illnesses for which a drug candidate is known, but for which no delivery system

Abbreviations: ΔSP, solubility parameter difference; ACE, acetone; API, active pharmaceutical ingredient; DCM, dichloromethane; EtOH, ethanol; HaSP, Hansen solubility parameter; HiSP, Hildebrand solubility parameter; *M*, molecular weight; N_A, Avogadro constant; PCL, polycaprolactone; PLGA, poly(DL-lactide-co-glycolide); PTFE, polytetrafluoroethylene; $r_{Pearson}$, Pearson product–moment correlation coefficient (Pearson's *r*); SA, surface–air interface; SEM, scanning electron microscope; SM, surface–mould interface; SP, solubility parameter; TEM, transmission electron microscope; V_h, hydrodynamic volume.

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is currently available [5,6]. Desired release profiles are currently obtained by using different polymers, or altering their chemical structure to suit a given purpose. This approach is both costly, and relies somewhat on trial and error, rather than rational design. Here, we propose a simple method of obtaining desired release profiles from a given polymer. This method is based on measuring the conformation of the polymer by the intrinsic viscosity of the polymer solution, and calculation of the solvent's solubility parameters.

The volume of a dissolved polymer depends on the solvent in which it is placed. In solvents for which the polymer has a high affinity and is therefore readily dissolved (a "good" solvent), the polymer molecules will be extended and have a relatively large volume. In contrast, if the polymer is placed in a solvent for which it has low affinity, and is therefore not readily dissolved (a "poor" solvent), the polymer will coil up and have a relatively small volume [7,8]. Similarly, this phenomenon can be described as polymer–polymer interactions being favoured in a poor solvent, causing reduction in the polymer volume, while in a good solvent polymer–solvent interactions are favoured resulting in polymer extension and stretching. As the hydrodynamic volume of a polymer is proportional to the viscosity of the polymer solution, the intrinsic viscosity ($[\eta]$) of a polymer solution in a good solvent will be higher than for a solution made with a poor solvent [7–9]. The different solvents may be described by the use of solubility parameters (SP); the solvent being the better the closer its SP is to that of the solute. It follows from the above that SPs are correlated to $[\eta]$. SPs have indeed been used to predict $[\eta]$ in polymer solutions made with solvent blends [10–12].

As polymer molecules with larger volumes interact more with each other, than polymer molecules with smaller volumes, the size of the dissolved polymer may be expected to influence the microstructure, i.e. pore size, of the matrix that results when the solvent is removed (evaporated). As the pore size of the matrix affects the release rate of proteins [13,14], it follows that the release rate must also be influenced by the solvent used to dissolve the polymer. The effect of solvents on matrix morphology and drug release profile has been shown for spray-dried PLGA particles [15,16]. These studies found that the solvent used in the spray drying solution influenced both the morphology of the created particles, and their drug release profile.

This study investigates the following hypotheses:

(1) The $[\eta]$ of a polymer solution correlates with the SP difference (ΔSP) between the solvent and the polymer.
(2) The solvent used to dissolve a polymer, will affect the microstructure of a cast matrix which in turn will affect the release of protein from the matrix.
(3) The release profile of drug from the matrix can be predicted by measuring the $[\eta]$ of a polymer solution or calculating the ΔSP between the solvent and the polymer.

Poly(DL-lactide-co-glycolide) (lactide:glycolide: 50:50, PLGA) was used to test these hypotheses, while polycaprolactone (PCL) was used in support of our observations on the effect of the solvent on the matrix microstructure.

2. Materials and methods

2.1. Materials

Two polymers were used in this study: Poly(DL-lactide-co-glycolide) (PLGA) [CAS#: 26780-50-7, 50:50 Carboxylated End Group (nominal), $M_w \approx 57.6$ kDa, Lactel, AL, USA], and polycaprolactone (PCL) [CAS#: 24980-41-4, CAPA, $M_w \approx 50.0$ kDa, Solvay, OH, USA]. For drug release, bovine serum albumin (BSA) [CAS#: 9048-46-8, $-\geqslant$98%, lyophilized powder, Sigma–Aldrich, MO, USA], was employed. For matrices casting and dissolution, the organic solvents, dichloromethane (DCM) [Ph.Eur. analytical reagent, Merck, NJ, USA], acetone (ACE) [$\geqslant$99.8%, Ph.Eur. analytical reagent, Merck, NJ, USA], and ethanol (EtOH) [96%, Kemetyl A/S, Denmark] were employed. Epon embedding for the TEM investigations was performed using an Epon TAAB 812 Resin kit [VWR, PA, USA]. In the release studies, protein concentration was determined using a Thermo Scientific Pierce BCA Protein Assay Kit, [Thermo Scientific, IL, USA].

2.2. Intrinsic viscosity

Viscosity measurements of the polymer solutions were carried out using an Ubbelohde Semi-Micro dilution viscometer [No. 50, N212, Cannon instrument Company, USA] at 25 ± 0.2 °C. The viscosities were measured in dilute solutions. The time of flow (t) was measured at 8 different polymer concentrations (the highest concentration having a relative viscosity 3–4 times that of the solvent). The relative viscosity ($\eta_{rel} = t/t_0$) was calculated from the time of flow of the polymer solution (t) and that of the solvent (t_0). Specific viscosity was obtained from the relation $\eta_{sp} = \eta_{rel} - 1$ [17]. Subsequently, the reduced viscosity (η_{sp}/C) was calculated, where C is the polymer concentration in g/mL. The intrinsic viscosity ($[\eta]$) was obtained after extrapolation of η_{sp}/C as a function of C (Huggins plot), to a polymer concentration of zero.

2.3. Solubility parameters

For comparison, both the Hildebrand and Hansen solubility parameters (HiSP and HaSP respectively) were used in this study.

HiSP is derived from the heat of vaporization (ΔH_v) adjusted for thermal energy (RT) and related to molar volume (V_m)

$$\delta_{HiSP} = \sqrt{(\Delta H_v - RT)/V_m} \quad (1)$$

HaSP is derived from measurements of three different solvent energies: The intermolecular dispersion energy, E_D, the dipolar intermolecular energy, E_P, and the hydrogen bonding energy, E_H [18]. The summed square of which, divided by the molar volume, V_m, equals the square of the total solubility parameter, $\delta_T{}^2$ [18]

$$\delta_T^2 = \delta_{HaSP}^2 = \delta_D^2 + \delta_P^2 + \delta_H^2 \quad (2)$$

SPs of the pure solvents (δ_i) were gathered from the existing literature [19,20]. From these, the solubility parameters of the blends ($\bar{\delta}$) were calculated by averaging the solubility parameter values of the individual solvents by their volume fraction (ϕ_i)

$$\bar{\delta} = \sum_i \phi_i \delta_i \quad (3)$$

As SPs are not directly measurable for polymers, these were determined by their $[\eta]$ in different solvents; as described by Barton [20] and further developed by Segarceanu and Leca [10]:

$$\delta_{HiSP} = \sum(\delta_i[\eta]_i) / \sum[\eta]_i \quad (4)$$

$$\delta_{DP} = \sum(\delta_{Di}[\eta]_i) / \sum[\eta]_i \quad (5)$$

$$\delta_{PP} = \sum(\delta_{Pi}[\eta]_i) / \sum[\eta]_i \quad (6)$$

$$\delta_{HP} = \sum(\delta_{Hi}[\eta]_i) / \sum[\eta]_i \quad (7)$$

This method relies on the SPs of the polymer being identical to, or very like, the SPs of the solvent which best dissolve the polymer. The value returned is therefore also limited by the range of solvents used.