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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.

Solvents–polymer pairs that did not dissolve the polymer were given an intrinsic viscosity of zero.

2.4. Polymer matrix formation

The polymer matrices were cast by evaporating solvent from 10% w/v polymer solutions in polytetrafluoroethylene (PTFE) moulds. The PTFE moulds were custom made and cylindrical in shape with an inner diameter of 23 mm (Fig. 1). Before casting, the polymer solutions were left for approximately 24 h to ensure complete dissolution.

1 mL of the polymer solution was added to each mould. Glass petri-dishes were used to cover the moulds in order to allow for a slow and reproducible solvent evaporation rate. The covered moulds were left at room temperature for 48 h, after which their weight was monitored until constant, indicating complete or almost complete evaporation of the solvent.

The thickness of the resulting matrices varied according to the polymer and the solvent used, and ranged from 24.2 ± 0.3 μm (PLGA cast in acetone) to 11.5 ± 0.5 μm (PCL cast in dichloromethane). For release studies 10% w/w lightly ground BSA was added to the polymer solution.

The SM surface was in direct contact with the casting mould, while the SA surface was exposed to the gas phase.

2.5. Transmission electron microscopy (TEM)

Dry matrices of PLGA were stained with osmium tetroxide, washed with ultrapure water and embedded in Epon. Following complete Epon polymerization, the matrices were sectioned perpendicular to the mould surface using a diamond knife, and studied by TEM [FEI Tecnai G2 20 TWIN]. Not all staining solution could be removed, leaving black areas in the denser parts of the matrices.

2.6. Scanning electron microscopy (SEM)

The surface (SA-interface) microstructures of PCL matrices were observed using a scanning electron microscope (SEM) with an acceleration voltage of 25 kV [JSM-5200, JEOL, Tokyo, Japan]. The polymer matrices were fixed on a metal stub with carbon tape, and coated with a 5 nm gold layer prior to imaging.

2.7. In vitro protein release

A Franz diffusion cell with a 14 mm-diameter orifice was used for the release studies. The cell consisted of a receptor chamber (4 mL, heated to 37 °C using a water jacket), a sampling and a medium replacement port. A 10 mM phosphate buffer (pH 7.4) was used as receptor phase. The receptor phase was stirred using a magnetic stirrer throughout the release study, with 2 mL release medium collected at predetermined time points. Each release study and protein concentration measurement was performed in triplicate.

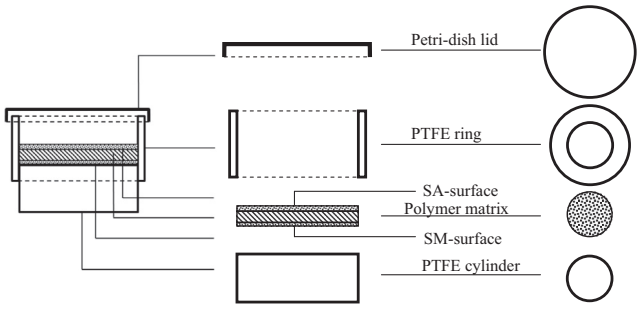

Fig. 1. Schematic of the polytetrafluoroethylene (PTFE) moulds used for casting of polymer matrices, viewed assembled (left), disassembled (middle), and from the top (right). SA denotes surface–air interface; SM denotes surface–mould interface.

2.8. Statistical analysis

The Pearson product–moment correlation coefficient (Pearson's r) was calculated using Graphpad Prism version 6.04, current as of January 17th, 2014. Pearson's r was used as a measure of the linear correlation between BSA release and the ΔSP of a solvent and polymer on the one hand and $[\eta]$ of the solution on the other hand. Calculations were based on a 99% confidence interval, and a two-tailed test. Graphpad Prism version 6.04 was also used for calculating the data fits for SP/$[\eta]$ data sets.

3. Results

3.1. Intrinsic viscosity and solubility parameters

3.1.1. PLGA matrices

The intrinsic viscosities of PLGA in various solvents and solvent blends were obtained (Table 1), and plotted against their respective SPs (Fig. 2). Higher $[\eta]$ values were observed for PLGA when dissolved in solvents with SPs closer to that of PLGA itself.

The highest $[\eta]$ was observed for PLGA in pure DCM. While PLGA was not totally soluble in H_2O (results not shown), blends of ACE and H_2O (98.2/1.75% v/v and 97/3% v/v ACE/H_2O) gave solutions with higher $[\eta]$ than that of pure ACE. Increasing the H_2O fraction, above 3% v/v, led to a lowering of $[\eta]$, and eventually to the polymer becoming insoluble in the blend.

3.1.2. PCL matrices

The intrinsic viscosities of PCL in different solvents were determined (Table 1), and plotted against their respective solubility parameters (Fig. 3).

Of the pure solvents examined with PCL, the highest $[\eta]$ was observed in DCM, while PCL was not soluble in ACE, EtOH or H_2O (Fig. 3). PCL remained insoluble in 98.25/1.75% v/v ACE/H_2O blends, even though the total SP of the blend was similar to that of DCM. Blends of 50/50% v/v DCM/ACE dissolved PCL, despite having a greater ΔSP to PCL than the 98.25/1.75% v/v ACE/H_2O blend. 95/5% v/v DCM/EtOH blends gave in the highest $[\eta]$ obtained. Further increase in the fraction of EtOH in the blend (up to 15% v/v) resulted in lower $[\eta]$, but higher than for the solution in pure DCM.

Similar to the results for PLGA, the measured intrinsic viscosities correlated well with the calculated HiSP and HaSP differences between the solvent and PCL (Fig. 3).

3.2. Imaging of the matrix microstructure

3.2.1. Transmission electron microscopy (TEM) of PLGA matrices

PLGA matrices were cast from pure DCM, pure ACE or a 95/5% v/v ACE/H_2O blend, representing a good, intermediate and poor solvent respectively (Fig. 2). These were then encased in Epon resin, sectioned perpendicular to the SM interface and imaged by TEM.

While the SM and SA interfaces were similar for matrices cast in pure DCM, the SM interface was denser in matrices cast in either pure ACE or the 95/5% v/v ACE/H_2O blend (Fig. 4).

Both interfaces of the matrix cast in DCM, and the SA interfaces of matrices cast in pure ACE or the 95/5% v/v ACE/H_2O blend all contained pores, evident as circular dark-grey holes in the cut matrices (Figs. 4 and 5). The pores increased in size the further they were from the denser (darker) inner core of the matrices. Matrices

Table 1
Solubility parameters and intrinsic viscosity of PLGA and PCL in various solvents.

Solvent/blend/polymer	Hildebrand solubility parameter ($MPa^{1/2}$)	Hansen solubility parameter ($MPa^{1/2}$)				Intrinsic viscosity (dL/g)
	δ_{HiSP}	δ_{HaSP}	δ_D	δ_P	δ_H	
Poly(DL-lactide-co-glycolide) (PLGA)						
PLGA (calculated)	20.20	20.43	16.38	9.13	7.12	n/a
100% v/v acetone (ACE)	19.70	20.00	15.50	10.40	7.00	0.2510
50/50% v/v dichloromethane/acetone (DCM/ACE)	19.95	20.18	16.85	8.35	6.55	0.3033
100% v/v dichloromethane (DCM)	20.20	20.30	18.20	6.30	6.10	0.4099
98.25/1.75% v/v acetone/water (ACE/H_2O)	20.20	20.49	15.50	10.50	7.62	0.3528
97/3% v/v acetone/water (ACE/H_2O)	20.55	20.83	15.50	10.57	8.06	0.3082
95/5% v/v acetone/water (ACE/H_2O)	21.12	21.39	15.51	10.68	8.77	0.0962
90/10% v/v acetone/water (ACE/H_2O)	22.53	22.78	15.51	10.96	10.53	Insoluble
Polycaprolactone (PCL)						
PCL (calculated)	20.57	20.70	17.88	6.71	7.05	n/a
100% v/v acetone (ACE)	19.70	20.00	15.50	10.40	7.00	Insoluble
50/50% v/v dichloromethane/acetone (DCM/ACE)	19.95	20.18	16.85	8.35	6.55	0.5435
100% v/v dichloromethane (DCM)	20.20	20.30	18.20	6.30	6.10	0.8592
98.25/1.75% v/v acetone/water (ACE/H_2O)	20.20	20.49	15.50	10.50	7.62	Insoluble
100% v/v ethanol (EtOH)	26.00	26.50	15.80	8.80	19.40	Insoluble
95/5% v/v dichloromethane/ethanol (DCM/EtOH)	20.50	20.61	18.08	6.43	6.77	1.1939
90/10% v/v dichloromethane/ethanol (DCM/EtOH)	20.80	20.92	17.96	6.55	7.43	1.0251
85/15% v/v dichloromethane/ethanol (DCM/EtOH)	21.10	21.23	17.84	6.68	8.10	0.9672

The Hildebrand and Hansen solubility parameters for each solvent were obtained from [19,20], whereas the solubility parameters of solvent blends, PLGA and PCL were calculated.

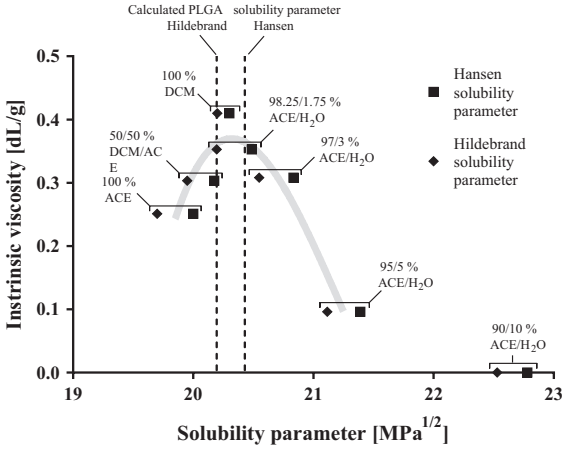

Fig. 2. Intrinsic viscosities and solubility parameters of PLGA in various solvents. ACE: acetone, DCM: dichloromethane, H_2O: water. Solvents in which the polymer is insoluble were given an intrinsic viscosity of zero. The calculated Hildebrand and Hansen solubility parameters of PLGA are indicated by broken lines. The shaded line indicates best cubic fit ($R \leqslant 0.95$). The 90/10% ACE/H_2O blend was excluded from the fit.

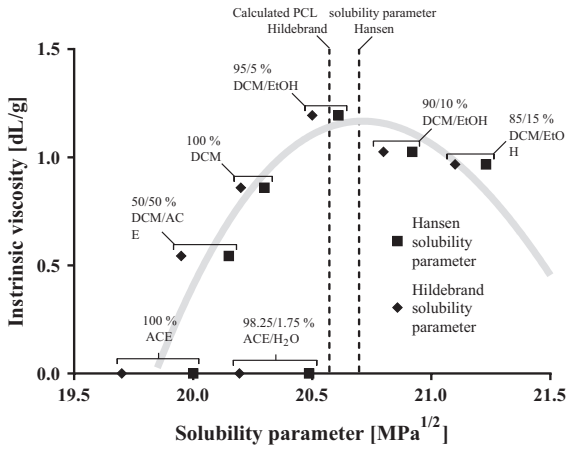

Fig. 3. Intrinsic viscosities and solubility parameters of PCL in various solvents. ACE: acetone, DCM: dichloromethane, EtOH: ethanol, H_2O: water. Solvents in which the polymer is insoluble were given an intrinsic viscosity of zero. The calculated Hildebrand and Hansen solubility parameters of PLGA are indicated by broken lines. The shaded line indicates best cubic fit ($R \leqslant 0.95$). The 98.25/1.75% ACE/H_2O blend was excluded from the fit.

cast in DCM had pores of intermediate size clustering close together on its SA interface. The same tendency was observed for matrices cast in ACE however, the pores were bigger, creating a less dense SA interface. Matrices cast in the 95/5% v/v ACE/H_2O blend had the least dense SA interface, consisting of several small pores (Fig. 4F). Also, while both the matrices cast from either pure DCM or ACE had a dense black core, the cores of the matrices cast from the 95/5% v/v ACE/H_2O blend were much brighter, indicating that the water used to wash the staining solution from the matrices had penetrated deeper into these samples (Fig. 4C).

3.2.2. Scanning electron microscopy (SEM) imaging of PCL matrices

While SEM imaging of PLGA matrices was not successful, as these matrices rapidly deteriorated when irradiated by the electron beam (deterioration observed at acceleration voltages of 5, 10 and 25 kV; lower voltages yielding insufficient contrast), PCL matrices did not deteriorate and imaging was successful. PCL matrices were cast from 95/5% v/v DCM/EtOH, 100% v/v DCM, and 50/50% v/v DCM/EtOH representing good, intermediate and poor solvents respectively (Fig. 3). The matrix cast in 95/5% v/v DCM/EtOH had several, but relatively small pores, whereas the one cast in 100% v/v DCM had fewer but larger pores, and the one cast from 50/50% v/v DCM/ACE contained numerous intermediate pores (Fig. 5).

3.3. BSA release from PLGA matrices

BSA release was measured from matrices cast from solvents of different ΔSP to the polymer. These were, in order of increasing ΔSP (Fig. 2): Pure DCM, 98.25/1.75% v/v ACE/H_2O, pure ACE, 95/5% v/v ACE/H_2O and 90/10% v/v ACE/H_2O. These showed a cumulative release of 0%, 12.9%, 21.7%, and 58.3%, respectively, over the

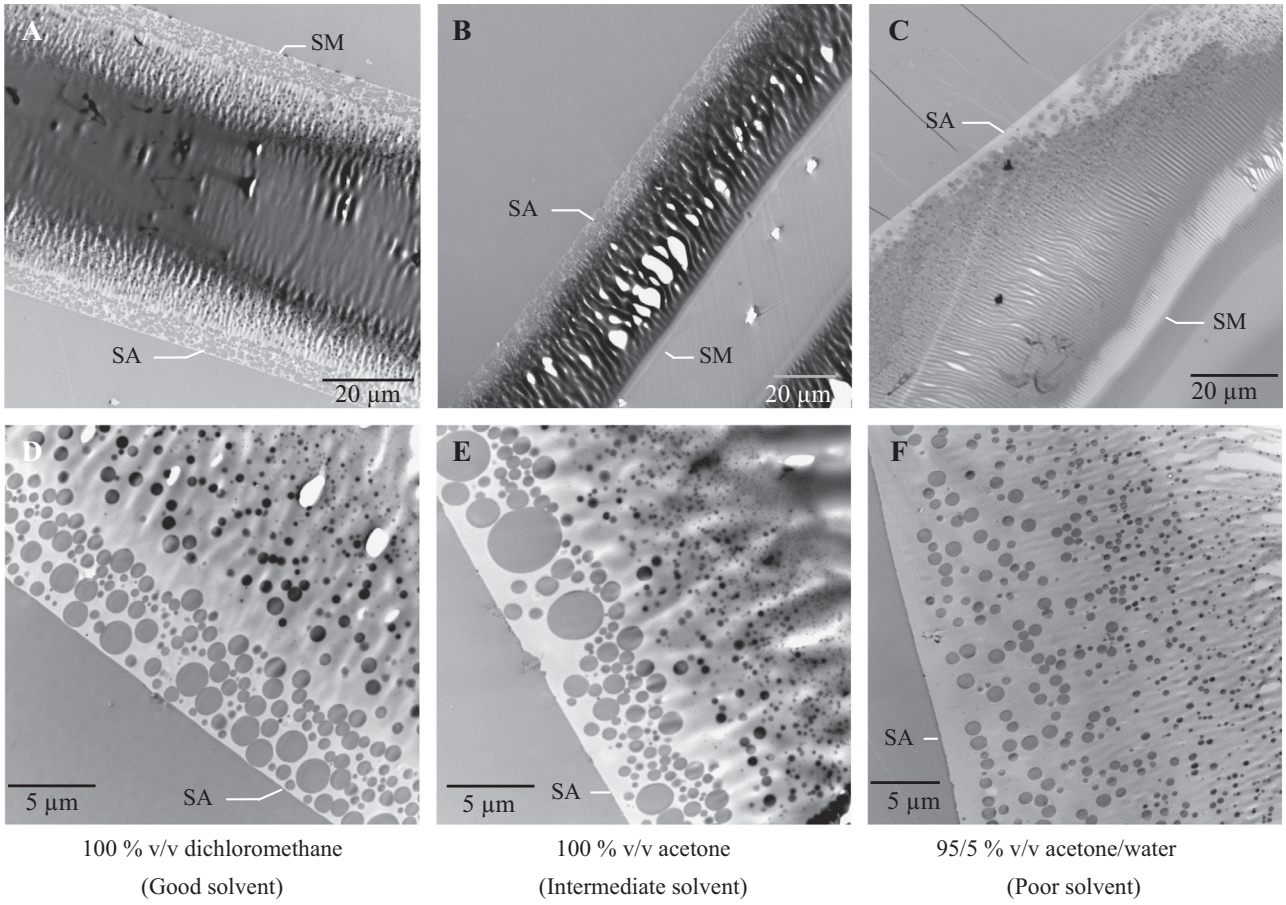

Fig. 4. TEM images of PLGA matrices embedded in Epon and sectioned perpendicular to the mould surface. Top: Matrices were cast from (A and D) dichloromethane, (B and E) acetone (C and F) 95/5% v/v acetone/water. Scalebars, top: 20 µm, bottom: 5 µm.

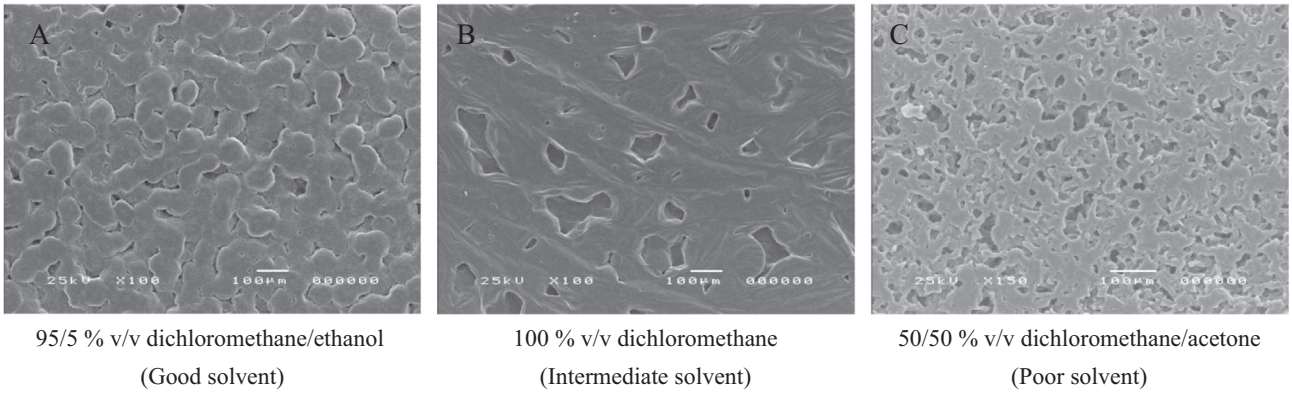

Fig. 5. SEM imaging of PCL matrices cast from (A) 95/5% v/v dichloromethane/ethanol, (B) 100% v/v dichloromethane and (C) 50/50% v/v dichloromethane/acetone. Scalebar: 100 µm.

5 day measuring period (Fig. 6). PLGA was insoluble in the 90/10% v/v ACE/H_2O, and did not form a matrix; this sample was therefore given a release of 100% (Fig. 6).

Cumulative BSA release within 5 days was found to correlate directly with ΔSP ($r(3)_{Pearson, HiSP} = 0.98$, $p = 0.0043$, $r(3)_{Pearson, HaSP} = 0.98$, $p = 0.0046$) and inversely with the $[\eta]$ of the solution used for casting ($r(3)_{Pearson} = -0.97$, $p = 0.0050$; Fig. 7.

4. Discussion

4.1. Intrinsic viscosity and solubility parameters

For both polymers, the $[\eta]$ increased with smaller ΔSPs between the solvent and the polymer. This can be explained by the hydrodynamic volume of the polymer being higher in solvents with

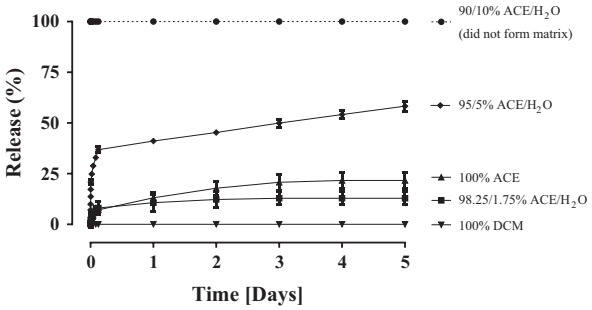

Fig. 6. Cumulative release of BSA from PLGA matrices cast from different solvents ($n = 3$). BSA loading (10% w/w), mean values are plotted with error bars representing standard deviation.

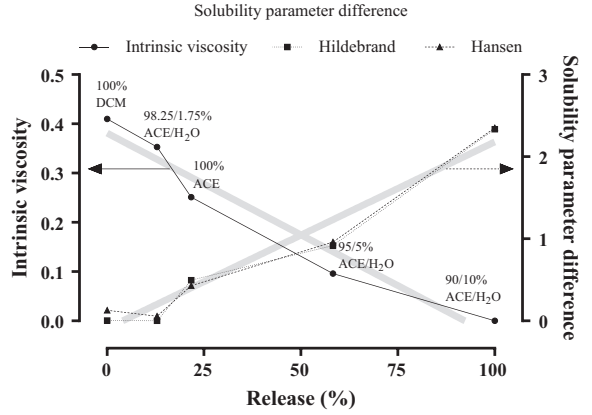

Fig. 7. Correlation between intrinsic viscosity/solubility parameter difference and released BSA. The shaded lines indicate the best fit of the data to a straight line ($R^2 \leqslant 0.95$).

smaller ΔSPs. PCL dissolved in blends of a poor solvent (ACE or EtOH) and a good solvent (DCM), which in some ratios gave higher $[\eta]$ than the good solvent alone. Likewise, increasing the fraction of H_2O in PLGA solutions in ACE/H_2O was found to first increase the $[\eta]$ of the solutions, and then decrease it (Fig. 2). The blend of 98.2/1.75% v/v ACE/H_2O had almost the same HiSP, and HaSP difference to PLGA as DCM, but resulted in PLGA solutions with a lower $[\eta]$ than those of DCM. This may be explained by the 98.2/1.75% v/v ACE/H_2O blend having strong dipole–dipole and hydrogen bonding interaction values (10.50 $MPa^{1/2}$ and 7.62 $MPa^{1/2}$ respectively, Table 1), whereas DCM had higher dispersion force values (18.20 $MPa^{1/2}$, Table 1), giving a comparable total SP value, but different individual HaSP values (δ_D, δ_P, δ_H). As the amount of H_2O in the blend increases, the hydrogen bonding parameter of the blend also increases. The SP of the blend thereby becomes more like that of PLGA up to 1.75% v/v H_2O, after which the blend becomes less like the polymer, causing a decrease in $[\eta]$.

Likewise, solutions of PCL in 85/15% v/v DCM/EtOH blends yielded higher $[\eta]$ than solutions in pure DCM, despite the pure solvent having a smaller ΔSP. While HiSP and HaSP of both the 85/15% v/v DCM/EtOH blend and DCM are equally close to that of PCL, the blend has individual HaSP values closer to those of PCL ($\Delta\delta_{D,PCL:blend} = 0.04$ $MPa^{1/2}$ versus $\Delta\delta_{D,PCL:DCM} = 0.32$ $MPa^{1/2}$, and $\Delta\delta_{P,PCL:blend} = 0.03$ $MPa^{1/2}$ versus $\Delta\delta_{D,PCL:DCM} = 0.41$ $MPa^{1/2}$; Table 1). Additionally, PCL remained insoluble in 98.25/1.75% v/v ACE/H_2O blends (ACE and H_2O both being poor solvents), even though the total SP of the blend was similar to that of DCM, indicating that the polymer must be soluble in at least one of the solvents in the blend for it to be an effective solvent.

In blends of solvents with large differences in vapour pressure, the most volatile component may evaporate faster, thereby changing the solvent power of the blend, and subsequently the matrix structure. In this case, the observed microstructural differences would, arguably, have been unrelated to the solvent power of the blend. In an effort to counteract this effect, the evaporation rate of solvents was slowed by covering the drying film with a Petridish lid, thereby creating a saturated vapour above the polymer film solution. For some blends (e.g. of ACE/H_2O), the differences in vapour pressure may have been too large to be counteracted. For example, the three solvents employed here, EtOH (10 kPa at 29.2 °C [21]) and DCM (10 kPa at −12.5 °C [21]) had the biggest vapour pressure difference, while DCM and ACE (10 kPa at 1.3 °C [21]) had the lowest. However, as the DCM fraction of the DCM/EtOH blend was much larger than the EtOH fraction, the risk of significant change in solvent blend composition during evaporation is deemed to be low.

The results show that both HiSP and HaSP correlate with polymer confirmation. However, care must be taken to compare not only the total SP but also the individual HaSP values (δ_D, δ_P, δ_H).

4.2. Imaging of the matrix microstructure

There were considerable differences in the microstructure of PLGA matrices, depending on the solvent used for casting the matrix. Matrices cast from a good solvent (pure DCM) had microscopically similar SM and SA sides, which had several circular pores of moderate size (Fig. 4). Matrices cast in an intermediate (pure ACE) or poor solvent (95/5% v/v ACE/H_2O) had SA sides similar to that the matrices cast in the good solvent and dense SM sides (Fig. 4A–C). Likewise, the SA sides of the matrices cast in either a good or intermediate solvent had a higher number of pores than the matrices cast from a poor solvent (Fig. 4D–F). This indicates that the polymer is more evenly distributed in the better solvents, giving the appearance of a darker, denser structure.

The low number of pores of the PCL matrix cast from a good solvent suggests the polymer is extended and more homogeneously distributed in the matrix, while the higher number of pores of the matrix cast from a poor solvent is consistent with polymer chains being unable to properly extend, and therefore exists as aggregated network in the solvent. These properties have previously been described [7,8] and are consistent with the finding that a relationship exists between the ΔSP of solvent and polymer (and an inverse relationship between $[\eta]$) and the microstructure of the resulting matrix.

4.3. BSA release from PLGA matrices

Protein release from PLGA matrices was found to correlate directly with solvent–polymer ΔSP, and inversely with the $[\eta]$ of the solutions used to cast the matrices (Fig. 7). This is in agreement with our results showing that $[\eta]$ increases as the ΔSP between the polymer and solvent decreases (Figs. 1 and 2). Even though the 98.25/1.75% v/v ACE/H_2O blend had a ΔSP similar to that of DCM (Fig. 2), matrices cast in the 98.25/1.75% v/v ACE/H_2O blend released protein in much higher amounts than from the matrix cast from DCM. This indicates that the correlation between ΔSP and protein release is weaker at small ΔSPs. At small ΔSPs, the $[\eta]$ may therefore be a better tool for predicting protein release than the ΔSP.

As the changes in $[\eta]$ reflect changes in the conformation of the dissolved polymer (i.e. $[\eta]$ increases with the hydrodynamic volume (V_h) of the polymer, as described by $V_h = [\eta]M/(2.5N_A)$ in which M is the polymer molecular weight and N_A is the Avogadro constant), the observed differences in released protein are likely caused by differences in the microstructure of the cast matrix. This is supported by the TEM and SEM images of the matrices, which

show that matrices cast from better solvents, are denser than those cast in poorer solvents, as stated above.

While the HiSP values may be used for rough estimation for protein release, at smaller ΔSPs attention must be taken to the individual HaSP values. As both HiSP and HaSP values can be calculated, few experiments are needed for their employment. However, at even smaller ΔSPs still, the [η] becomes a better predictive tool than either HiSP or HaSP. While this study has described relatively simple calculations, more accurate methods exist for calculating the HaSP values, using the Euclidian geometry to determine the distance between two solvents [11]. While a full description of these is outside the scope of the present work, this method may further improve the predictions on the relationship between the SP at maximum [η] and the SP of a given solvent.

5. Conclusion

In this study, a correlation between the intrinsic viscosity ([η]) of a polymer solution, the solubility parameter difference (ΔSP) between the polymer and the solvent, and the amount of protein released from a matrix cast from the polymer solution, was described.

The study found that the [η] of a polymer solution correlates with the ΔSP between the solvent and the polymer. This is caused by the polymer having a larger volume in solvents with SPs closer to those of the polymer: The larger the polymer volume, the higher the [η]. The higher the [η] of the solution (the lower the solvent's ΔSPs to those of the polymer), the denser the matrix. Protein release from the cast matrix correlated directly with the ΔSP between the polymer and solvent, and inversely with the [η] of the polymer solution. This is most likely due to changes in the matrix microstructure, caused by extension/contraction of the polymer molecules in solution.

The calculations and measurements described in this study may help to provide a method for predicting protein release from a polymer matrix. Thereby, rational choices may be made when developing new polymer based drug delivery systems, rather than relying on trial and error for achieving a certain release profile. However, care must be taken to compare not only the total SP but also the individual HaSP values when performing such predictions.

Conflict of interest

There is no conflict of interest at stake.

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