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Research paper

Artificial neural network based particle size prediction of polymeric nanoparticles

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ABSTRACT

Particle size of nanoparticles and the respective polydispersity are key factors influencing their biopharmaceutical behavior in a large variety of therapeutic applications. Predicting these attributes would skip many preliminary studies usually required to optimize formulations. The aim was to build a mathematical model capable of predicting the particle size of polymeric nanoparticles produced by a pharmaceutical polymer of choice. Polymer properties controlling the particle size were identified as molecular weight, hydrophobicity and surface activity, and were quantified by measuring polymer viscosity, contact angle and interfacial tension, respectively. A model was built using artificial neural network including these properties as input with particle size and polydispersity index as output. The established model successfully predicted particle size of nanoparticles covering a range of 70–400 nm prepared from other polymers. The percentage bias for particle prediction was 2%, 4% and 6%, for the training, validation and testing data, respectively. Polymer surface activity was found to have the highest impact on the particle size followed by viscosity and finally hydrophobicity. Results of this study successfully highlighted polymer properties affecting particle size and confirmed the usefulness of artificial neural networks in predicting the particle size and polydispersity of polymeric nanoparticles.

1. Introduction

Nanoparticles (NPs) have proven their efficient use as drug delivery carriers in a wide range of therapeutic applications [1,2]. This is based on unique properties allowing for the enhancement of drug penetration across biological barriers [3,4] and drug targeting towards malignant [5,6] and inflamed tissues [7]. Approaches such as passive targeting with modified surface properties by using different surfactants or stealth NPs by polyethylene glycol decoration involve significant changes to surface properties. Similarly, active targeting can be accomplished by decorating the surface of nanoparticles with targeting moieties and ligands [8]. Most of these phenomena have been found to be size-dependent, for example; enhanced oral drug absorption [9], selective targeting towards tumors [10] or inflamed tissues [11]. Therefore, controlling the particle size of NPs and its distribution is of crucial importance. Size distribution is usually defined by the polydispersity index (PDI), which specifies the uniformity and stability of NPs and should be within 0.01 to 0.5 [12]. Until now, when a certain particle size with a narrow size distribution is aimed for, this has been done by empirical approaches and trial and error. Accordingly, developing a mathematical model that can predict the particle size and PDI of polymeric NPs obtained from various types of polymers would be very beneficial, as it will save time and money by preserving polymers, chemicals and materials normally consumed during the optimization phase.

The main statistical and modelling tools used for optimizing and predicting characteristics of NPs are response surface methodology (RSM) [13,14] and artificial neural network (ANN) [15–18]. Both approaches were already compared to each other with the results demonstrating the superiority of ANN to RSM in data fitting and prediction capabilities [19–22]. This was attributed to the limitation of RSM to quadratic functions only unlike ANN, which can handle a broader range of functions and find relationships between independent and dependent variables with no prior specific mathematical equation or function [19]. ANN learns by example, where a data set is used for building the model termed training data and

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List of Abbreviations

ANN	artificial neural network	PLA	poly(lactic acid)
EC	ethyl cellulose	PLGA	poly(lactic-co-glycolic acid)
IFT	interfacial tension	PVA	poly(vinyl alcohol)
MW	molecular weight	PVAc	poly(vinyl acetate)
NPs	nanoparticles	RMSE	root mean square error
PCL	poly(ε-caprolactone)	RSM	response surface methodology
PDI	polydispersity index	θ_c	contact Angle

then the efficiency of established model is checked against new data termed testing data.

Previous studies using ANN focused mainly on investigating the process parameters affecting particle size and examined a limited number of polymers without relating polymer properties to the obtained particle size [16–18]. In these cases, the developed models were used to characterize and optimize the factors affecting the NPs preparation process. However, thorough evaluation of the prediction power of these models was not the primary focus in these studies, as the test data were relatively small and confined to the training range of the model.

Here, ANN was utilized to develop a mathematical model capable of predicting the particle size and PDI of polymeric nanoparticles manufactured from a larger choice of pharmaceutical polymers with various properties. In order to achieve this goal, polymer properties affecting particle size and PDI were precisely identified, quantified and then used as an input for the model. Afterwards, the model was tested comprehensively against data located inside and outside the borders used to train it. Furthermore, the evaluation of the established model involved completely new polymers, which were not included in the training data.

2. Materials and methods

2.1. Materials

Ethyl cellulose (EC) with an ethoxy content of 48–49.5% but different molecular weights (MWs) and consequently viscosity grades (Ethocel® standard 4, 7, 10 and 45 premium) was a kind donation from Colorcon (Dartford, England). Acid terminated poly(lactic acid) (PLA) (Purasorb PDL 02 A) was a gift from Purac Biomaterials (Gorinchem, The Netherlands). Poly(vinyl acetate) (PVAc) (Vinnapas B17 special) was kindly granted by Wacker Chemie AG (Burghausen, Germany). Ammonio Methacrylate Copolymer, Type B (Eudragit® RS PO) was a kind sample from Evonik (Darmstadt, Germany). Poly(vinyl alcohol) (PVA) (Poval® 40–88) was a gift from Kuraray (Frankfurt, Germany). Acid terminated poly(DL-lactide-co-glycolide) (PLGA) 50:50 of different MWs and viscosities (Resomer® RG 502 H MW 7000–17,000, Resomer® RG 503 H MW 24,000–38,000 and Resomer® RG 504 H MW 38,000–54,000) and ester terminated PLGA 50:50 (Resomer® RG 505 MW 54,000–69,000) were purchased from Evonik (Darmstadt, Germany). Poly (ε-caprolactone) (PCL) (Mn 10,000 and Mn 45,000) were purchased from Sigma-Aldrich (Steinheim, Germany). All other chemicals were of analytical grade or equivalent purity (For further details on the characteristics of EC and PLGA polymer types see supplementary materials Tables 1 and 2).

2.2. Preparation of polymeric nanoparticles

Polymeric nanoparticles were prepared using the emulsification solvent evaporation method [23] replacing dichloromethane with ethyl acetate. Briefly, 100 mg of the respective polymer was dissolved in ethyl acetate to form the organic phase, while the aqueous phase was composed of PVA in different concentrations (0.05–1.5%). The aqueous phase was added to the organic phase and the mixture was ultrasonicated using a probe ultrasonicator (Sonoplus HD 2200, Bandelin, Berlin, Germany) at an amplitude of 50% for 3 min. Preliminary experiments revealed that varying the emulsification energy input did not significantly affect neither the particle size nor PDI (Data not shown). After emulsification, the organic solvent was evaporated using a rotary evaporator (Rotavapor RE 120, Büchi, Flawil Switzerland) under reduced pressure to form the polymeric NPs. The volume of the aqueous phase was kept constant at 10 ml while the volume of ethyl acetate, in which the polymer was dissolved, was changed (2–9 ml) altering the solvent to water ratio (S:W) to elucidate its effect on the particle size.

2.3. Particle size and PDI of polymeric nanoparticles

The particle size and PDI of the nanoparticles were determined by dynamic light scattering technique (Nanopartica SZ-100, Horiba, Kyoto, Japan) at a fixed angle of 90° at 25 °C using 1.5 ml polymethyl methacrylate cuvettes. The samples were diluted with distilled water before measuring to avoid multiple scattering.

2.4. Determination of polymer solutions viscosity

Viscosity of polymer solutions in ethyl acetate was measured using a rotation viscometer (Haake Rheostress 1, Thermo Fisher Scientific, Karlsruhe, Germany). 100 mg of the respective polymer was dissolved in 5.5 ml of ethyl acetate (1.81% w/v) and its viscosity was measured at shear rate of 100 s^{-1} at 20 °C.

2.5. Determination of polymer contact angle

The static contact angle (θ_c) of different polymers was measured by the drop shape analysis technique (DSA100, Krüss, Germany). Firstly, polymer films were fabricated using the solvent casting method [24]. The polymer was dissolved in ethyl acetate to simulate the NPs preparation procedure and then the solution was cast on a glass slide and placed in a hood overnight at room temperature to evaporate the organic solvent. To ensure complete drying, the glass slides were further dried under vacuum at 25 °C overnight (VDL23, Binder, Germany). Secondly, the θ_c between the obtained dried polymer films and water was determined using sessile drop method at room temperature. A constant volume of water (8 µl) was deposited on the surface of the polymer film and the contact angle value was calculated from the recorded droplet image using sessile drop fitting method.

2.6. Interfacial tension measurements

Interfacial tension (IFT) between water and either pure or polymer-containing ethyl acetate was also determined using drop shape analysis technique (DSA100, Krüss, Germany) applying pendant drop method. A water drop was formed through a needle of diameter 1.8 mm in the organic phase, which was placed in an