Rheological Properties of Serum with Nanoparticles

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ABSTRACT

One promising method of increasing effect of cytotoxin for cancer treatment is to encapsulate the medicine into tailor made nanoparticles prior to injection into the circulatory system. The encapsulation of cytotoxin limits exit of the drug out of the blood vessel to healthy cells. However, the blood vessels around many tumors are leaky, and here the nanoparticles can escape the vessels and accumulate in the cancerous tissue. Such targeted drug delivery strategies may potentially allow for safer and more efficient treatments of cancer. Since one of the most limiting factors of today's cancer cure is the number of cytotoxin treatments a body may be able to tolerate, this would have significant impact on many patient's ability to heal.

When adding nanoparticles to the circulatory system it is necessary to understand all perspectives that may affect the blood behavior. In the experiments presented here blood serum with various concentrations and sizes of nanoparticles have been investigated. The key objective has been to determine if the flow properties of the serum changes with particle fraction, size and material within the realistic concentrations.

INTRODUCTION

The development of nanoparticle-based drug formulations opens new opportunities to address and treat challenging diseases such as cancer and infectious diseases. Encapsulation of drugs into nanoparticles (NPs) ranging from 50 to 300 nm can potentially solve several issues associated with conventional therapeutic agents, including their poor water solubility, nonspecific distribution, systemic toxicity, and low therapeutic efficacy (Shi et al 2017, Lammers et al 2010). Over the past several decades, remarkable progress has been made in the development and application of engineered NPs to treat diseases more effectively, and several products of drug-loaded NPs have already reached the market.

A large range of materials, chemistries and formulation technologies are currently being investigated for making NP-based medicines. Due to their versatility and stability, synthetic polymer NPs are frequently used as drug delivery vehicles offering unique customization of many key properties like hydrophobicity and molecular weight. They can increase stability of drugs, they possess controlled release properties and they allow for high drug loading and encapsulation efficiency (Soppimath et al 2001). One very interesting polymer, poly(alkyl cyanoacrylate) (PACA) has for a decade been utilized at SINTEF for nanoencapsulation of various drugs and dyes for both treatment and diagnosis using SINTEF-proprietary emulsion-based encapsulation technology ([Patent], WO 2014/191502-family). These PACA nanoparticles are currently being used in *in*

vitro and preclinical studies towards cancer and infectious diseases with very promising clinical effects (Snipstad et al 2017, Sulheim et al 2016, Sulheim et al 2017).

Upon treatment, NPs are injected into the blood stream where they circulate for several hours before accumulating in diseased tissues. Hence, their potential effect on the rheological properties of blood is a relevant parameter to investigate. Here we have studied the rheological behaviour of serum after addition of polymeric NPs using two different materials and three different NP sizes.

Because of the nanoparticles sizes ranging from 50 to 300 nm, Brownian motion should disperse the particles perfectly in the circulatory system. The smallest blood veins are around 5 μm. Hence, their presence should not create any blockage in the vein unless the concentration is extremely large.

Ideally, addition of the drug material should not affect the viscosity profile. However, addition of such small particles are known to create a region with shear thickening and shear thinning in the fluid at selected shear rates (see for example Barnes et. al. 1989). Hence this study was set up to verify if the particle addition could leave the blood viscosity un-altered.

FLUIDS

The tests were conducted on a model system. The biological serum was a fetal bovine serum (FBS) of non-USA origin, sterile-filtered, and suitable for cell culture.

To optimize the selection on the nanoparticle sizes for medical treatment, synthetic particles with known diameter were used. These nanoparticles were latex beads, made of polystyrene in sizes of 60 nm (LB60), 100 nm (LB100), and 200 nm (LB200). Additional experiments were conducted with particles resembling more closely to the medical particles. These particles consisted of Poly(ethylbutyl cyanoacrylate) and had a size of 100nm (PEBCA100). The particles were prepared by SINTEF as described earlier (Snipstad et al. 2017).

All tests were conducted with NP concentrations of 0.1% and 0.2% (w/v). The concentrations were chosen based on clinical relevance.

EXPERIMENTAL

Measurements were conducted using an Anton Paar MCR 302 rheometer with a cone and plate measuring configuration (CP50). The rheometer is equipped with a Peltier element to keep the temperature constantly at 37 °C. The flow curves were measured in a shear rate range of 0-1400 1/s. The amplitude sweep tests were conducted with different frequencies between 10 Hz and 50 Hz in a shear strain range of 0.01 % - 100%.

RESULTS

The flow curves from the experiments in the rheometer are shown in Figure 1. Within the accuracy of the measurements, all the plotted curves show a similar viscosity. The addition of particles in this experimental campaign did not alter the serum viscosity in any systematic way. Hence all the flow curves show a Newtonian viscous behaviour.

Oscillating rheometry testing was attempted, but did not provide any useful results. This is anticipated to be a result of the very low viscosity and the mass of the applied equipment.

CONCLUSIONS

The performed work shows that the applied particles in tested concentrations do not affect the viscosity of the blood serum. Based on this the circulatory system should not be affected by a medical treatment including injection of such particles.

Elasticity of the measured fluids could not be measured in the applied setup.

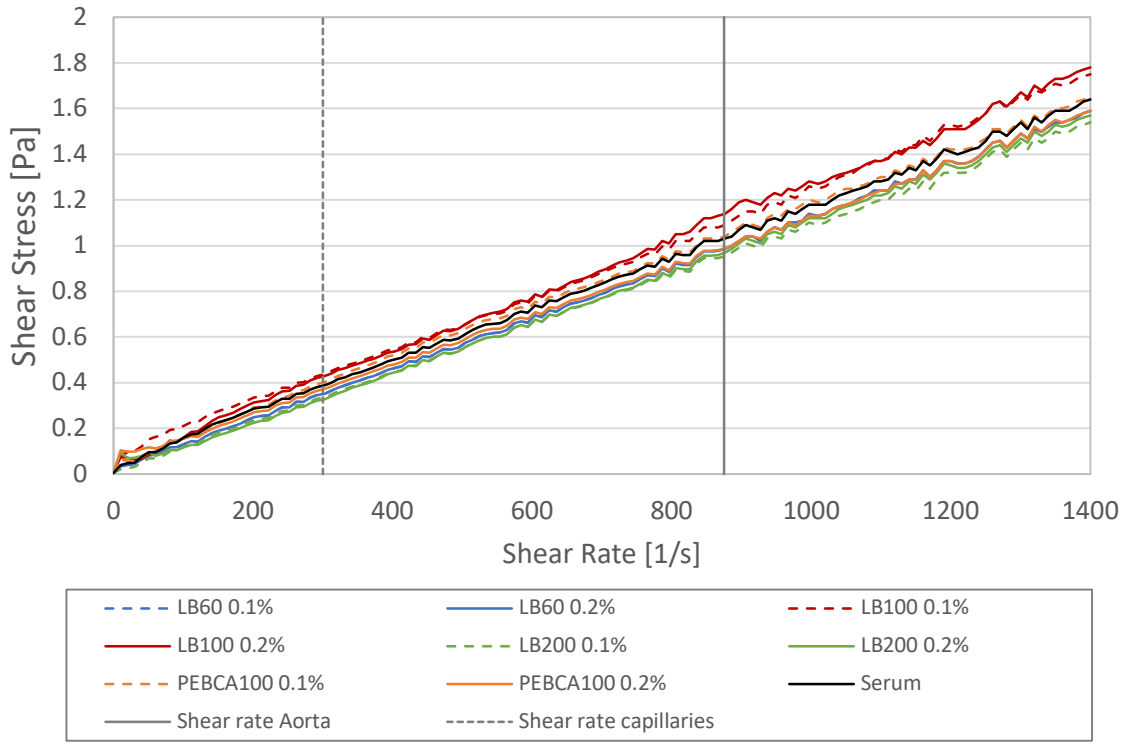

Figure 1. Flow curves of LB60, LB100, LB200, and PEBCA100, measured at 37 °C in a shear rate range of 0-1400 1/s.

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