Lodz University of Technology
Faculty of Process and Environmental Engineering
Department of Chemical Engineering

Anna Katarzyna Rył

Wpływ sił ścinających występujących podczas przepływu w naczyniach kapilarnych na mechanizm żelowania polimerowych nośników leków

Influence of shear forces occurring during the flow in capillaries on the gelation mechanism of polymeric drug carriers

PhD dissertation abstract

Supervisor: Piotr Owczarz, PhD, DSc, Assoc. Prof.

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Abstract

Due to the increasing number of traffic accidents, the development of civilization and oncological diseases, recently there has been a growing demand for modern methods of treatment and regeneration that would shorten the convalescence time and simultaneously would be minimally invasive for the patient. One of the solutions proposed by the researchers are polymer drug carriers obtained by thermoinduced sol-gel phase transition, during which polymer aggregates form a spatial scaffold inside which drugs are trapped. Potential applications of hydrogels include injectable cell scaffolds, shear-sensitive drug release systems, and matrices manufactured using 3D printing techniques. Such systems, when properly designed, can be injected directly into the lesion, and the and the formation of the lattice occurs *in vivo*. Even though thermosensitive systems are often tested in many respects, their application potential in the form of minimally invasive injection is determined exclusively by the Lower Critical Solution Temperature. Simultaneously, no studies have determined the possibility of injection of these systems, as well as no studies have discussed the influence of the flow through the injection needle or 3D printer nozzle on the gelation time. The available studies conducted with synthetic polymers, emulsions, and protein systems indicate that exposure to the shear field of colloidal systems may lead to reversible or irreversible structural changes.

The research aims to determine the effect of the shear field occurring in the capillaries used during the injection application of colloidal polysaccharide systems on the mechanism and kinetics of thermoinduced sol-gel phase transition leading to the formation of spatial polymer networks constituting an intelligent form of drug carriers.

The dissertation presents the results of studies carried out with the use of colloidal systems obtained from chitosan solutions in hydrochloric acid with the addition of disodium β-glycerophosphate salt and aqueous hydroxypropyl cellulose (HPC) solutions with concentrations ensuring gelation under physiological conditions, i.e. temperature 37 °C and pH in the range 6.8-7.2. Selected polymers are common research materials due to their biomedical application potential resulting from their biocompatibility and availability.

To determine the influence of the aggregation regime on the isothermal and non-isothermal kinetics of the sol-gel phase transition, studies using the turbidimetric and rheometric techniques combined with the small-angle light scattering (SALS) analysis were carried out. The impact of the injection application on the gelation conditions was determined based on the rheometric and turbidimetric tests preceded by shear directly in the measuring system of the rheometer or by injecting the sol through needles of different sizes 14G – 25G using an infusion

pump. The flow conditions, with particular emphasis on the shear rate range, were determined based on the theory of non-Newtonian fluids flow in the conduits, and then experimentally validated using a texture analyzer. Simultaneously, instrumental injectability tests were performed to determine the possibility of injection application of the tested systems. The evaluation of the influence of the shear field observed during the injection on the macro- and microscopic scale on the structural properties of the tested systems was performed by multi-interval thixotropic tests combined with the light scattering analysis.

Based on the analysis of the conducted research, it was found that aggregation in the perikinetic regime (limited by diffusion) is a slower process than aggregation under the influence of a velocity gradient (orthokinetics) due to the synergistic effect of molecular, diffusion, and thermal changes. In the extreme case (HPC), no gelation limited by stochastic Brownian motion was observed despite the occurrence of the shear-induced phase transition. The analysis of the results of research on the influence of the deformation direction in rheometric measurements showed that the application of unidirectional rotational shear leads to a significant acceleration of the rapid gelation stage; in the case of a sufficiently low value of the shear rate, it even leads to a spontaneous phase transition. According to the proposed mechanism, the observed acceleration of the sol-gel phase transition occurs due to the loosening and simultaneous disentangling of the polymer coils, and thus easier access to functional groups involved in the lattice formation and faster generation of intermolecular interactions.

The research on the impact of the injection application on the gelation kinetics showed that the use of low (in relation to injection) shear rates accelerated the phase transition of all tested polymer systems due to the ordering of aggregates and easier access to the so-called junction zones. After exceeding the critical value of the shear rate (characteristic for each system), colloidal aggregates are fragmented, leading to an increase in their number with a simultaneous reduction in their size. Depending on the type of interactions between the aggregation nuclei, this phenomenon may accelerate (chitosan) or delay (HPC) the gelation process. The proposed author's methodology for determining the characteristic time of the phase transition, considering the kinetics of the polymer network formation, unequivocally confirmed the acceleration of aggregation caused by the velocity gradient (convection) compared to aggregation limited solely by stochastic Brownian motion (diffusion).

The proposed research methodology allows determining the potential of the polymer material as a minimally-invasive drug carrier, according to which an attempt to use a hydroxypropyl cellulose sol is associated with difficult or even impossible manual injection, and additionally leads to undesirable spilling of the sol before its gelation in the body. Contrary,

chitosan sol was possible to inject even with the use of small diameter needles (23G - 25G), and additionally, the flow through the capillary caused a significant reduction of the sol-gel phase transition time.

Finally, based on the discussion of the obtained results of tests carried out in a wide range of shear rates from $\dot{\gamma}$ = 200 s^{-1} to $\dot{\gamma}$ = 57,000 s^{-1}, the dual nature of the observed phenomena, caused both by changes in the spatial conformation of polymer molecules and the accumulation of energy inside the system resulting from shear, was demonstrated. An extremely important factor in the formation of the three-dimensional polymer lattice in the presence of a shear field is the primary mechanism of the sol-gel phase transition, in particular the intermolecular interactions between the aggregation nuclei and their sensitivity to mechanical stimuli.