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Role of Colloidal Silicon Dioxide in Eudragit *In-situ* Forming Gel

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Abstract

Colloidal silicon dioxide (Aerosil) is fumed silica that has been used as gelling agents, thickening agents and filling agents. The objectives of this study were to characterize the effect of hydrophilic (aerosil 200) and hydrophobic (aerosil R972) colloidal silicon dioxide on physical properties of eudragit gels which *N*-methyl-pyrrolidone was employed as dispersing medium. The samples were investigated in terms of viscosity, rheology and syringeability. The results indicated that the aerosil 200 and aerosil R972 amount influenced the viscosity, rheology and syringeability of the prepared gels. Viscosity and syringeability of the systems were increased with an increased amount of both aerosils. However, the viscosity and syringeability of the prepared gels containing aerosil 200 were increased higher than that of systems containing aerosil R972. The rheological behaviors of all systems consisting aerosil 200 and R972 were non-Newtonian flow. These studies demonstrated that aerosil 200 and R972 could improve the physical properties of eudragit gels dispersed in *N*-methyl-pyrrolidone.

Introduction

Colloidal silicon dioxide (aerosil) has been utilized in many applications for several manufacturing products. This material has been employed as pharmaceutical excipient such as glidant, absorbent, filler etc.[1] which can be divided into two main groups as hydrophilic and hydrophobic colloidal silicon dioxides. Siloxane and silanol groups are located on the surface of silicon dioxide particles that show the hydrophilic behaviour [2]. Aerosil 200 and aerosil R972 are hydrophilic and hydrophobic colloidal silicon dioxide, respectively. Aerosil 200 hydrogels exhibited the thixotropic type for rheological behavior [3]. *N*-methyl-pyrrolidone (NMP) is a polar solvent and also a water-miscible organic solvent. It is widely used in the petrochemical industry, and in the manufacturing of various compounds, including pigments, cosmetics, insecticides, herbicides, and fungicides. The solubility parameter of NMP is similar to those of ethanol and dimethyl sulfoxide [4]. Eudragit RS (ERS) is a copolymer of ethyl acrylate and methyl methacrylate [5]. The mixture of this polymer in NMP can form as *in situ* forming gel therefore it exhibits the property to be used as drug delivery system. The network formation from colloidal silicon dioxide in this system has not been reported previously. Therefore this research work was to investigate the role of both hydrophilic and hydrophobic types of colloidal silicon dioxide on the physical properties of this system.

Materials and Methods

Materials

Two different types (hydrophilic and hydrophobic) of colloidal silicon dioxide (Aerosil 200 and Aerosil R972) (Wacker-Chemie GmBH, Germany) were used. *N*-methyl-pyrrolidone (NMP) as the solvent in this study was purchased from Fluks, New Jersey, USA. Eudragit RS PO (ERS) was purchased from Evonik Degussa Co., Ltd., Germany.

Preparation and evaluations of systems

Aerosil 200 and aerosil R972 (2.5 -5.5 %w/w) were suspended in *N*-methyl-pyrrolidone (NMP) and kept for full dispersion at room temperature overnight before use. To study the effect of aerosil on the properties of eudragit systems, aerosil (2.5%-5.5%w/w) was incorporated into the prepared system consisting 35 %w/w ERS in *N*-methyl-pyrrolidone. The viscosity of the sample was measured (n=3) with a Brookfield DV-III Ultra programmable rheometer using spindle CPE 40 or 52. The spindle was rotated in the sample for 15 second prior to a reading the viscosity value at temperature of 25 °C and 37 °C. The flow curves of the systems were determined using Brookfield DV-III Ultra programmable rheometer with spindle CPE 40 or 52. Samples were applied to the lower plate. A flow curve of the samples was obtained by plotting between shear rate and shear stress for various revolution rates. The samples were measured at 25 °C and 37 °C (n=3). Syringeability is an important factor to consider for the ease of injection. Syringeability of the sample was evaluated using a texture analyzer (TAXT2, Stable Micro systems, UK) in compression mode. The sample was filled into 1 mL syringe (Nipro disposable syringe) equipped with 18G needles. The upper probe of the texture analyzer was moved then downwards at a rate 1 mm/s and a depth 20 mm. The resistance to expression of the syringe contents was determined from the area under the force-time curve (n=3).

Results and discussion

The shear rate-viscosity of systems containing aerosil 200 and R972 in NMP and ERS systems were measured at 25° C and 37 °C. The viscosity of systems containing aerosil 200 and R972 in NMP and the ERS systems decreased with increasing shear rate, therefore they presented as pseudoplastic flow as shown in Fig 1 and 2.

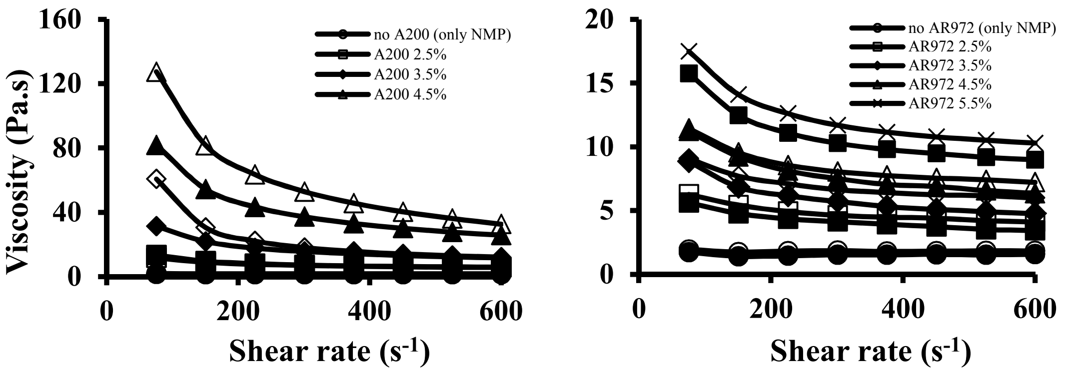

Fig. 1 Viscosity of systems containing aerosil 200 (A200)(left) and aerosil R972 (AR972)(right) (2.5-5.5 %w/w) in NMP at 25° (opened symbols) and 37 °C (closed symbols) as function of shear rate.

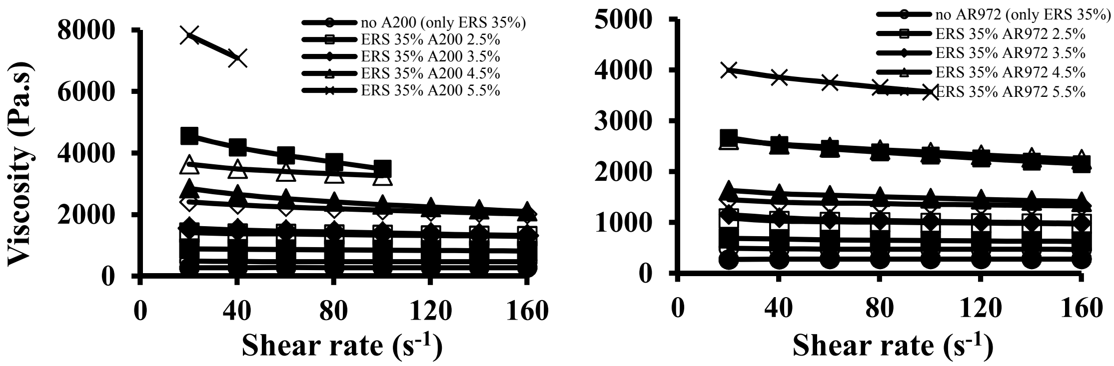

Fig. 2 Viscosity of systems containing aerosil 200 (A200)(left) and aerosil R972 (AR972) (right) (2.5-5.5 %w/w) in ERS (35%) and the gel based (ERS 35%w/w) at 25° (opened symbols) and 37 °C (closed symbols) as function of shear rate.

NMP and ERS gel which were used as control showed the constant viscosity when shear rate was increased indicating as Newtonian flow. However, the viscosity of systems containing aerosil 200 was apparently higher than that containing aerosil R972. The viscosity of all systems was lowered as the temperature was higher. The flow of the NMP and ERS systems comprising aerosil 200 were non-Newtonian characteristic whereas the flow of only NMP and the ERS gels were Newtonian as shown in Fig 3 and 4. The flow of the NMP and ERS systems containing aerosil R972 were non-Newtonian characteristic (data not shown). The flow curves of systems containing aerosil 200 and R972 in NMP and eudragit systems shifted from low shear stress to higher shear stress when the amount of aerosil was increased. In contrast, the flow curve shifted from high shear stress to lower shear stress when temperature was increased from 25 °C to 37 °C. The results suggested that the gel structures at low shear stress were less compact. Thus the added aerosil affected the strength of gel structure. The gel structure of the systems with hydrophilic colloidal silicon dioxide (aerosil 200) was higher than that containing hydrophobic colloidal silicon dioxide (aerosil R972). The silanol groups on the surface of aerosil 200 particles could interact via hydrogen bond with each other to form connecting bridges [6]. A thickening effect was occurred when there was a mismatch between the chemical nature of the particle surface and that of the liquid. The particle surfaces were rendered polar (silanol group), and the dispersion medium was non-polar, a tendency for the polar surfaces would associate to form connecting bridge. Whereas, silanol groups on the surface of aerosil R972 were chemically modified with dimethyldichlorosilane. Thus, the non polar surfaces of aerosil R972 might have a tendency to form connecting bridges in polar dispersing media, but the failure in gel formation was found in rather high polar dispersing media such as PG. Both non-polar (dimethyldichloro) and polar (residual silanol) components on aerosil R972 surface can exhibit either polar or nonpolar characteristics. Depending on the extent of mismatch between particle surface and liquid, the nonpolar dimethyldichloro groups would tend to cluster together in highly polar dispersing media. On the other hand, the polar silanol would tend to associate in nonpolar dispersing media [7].

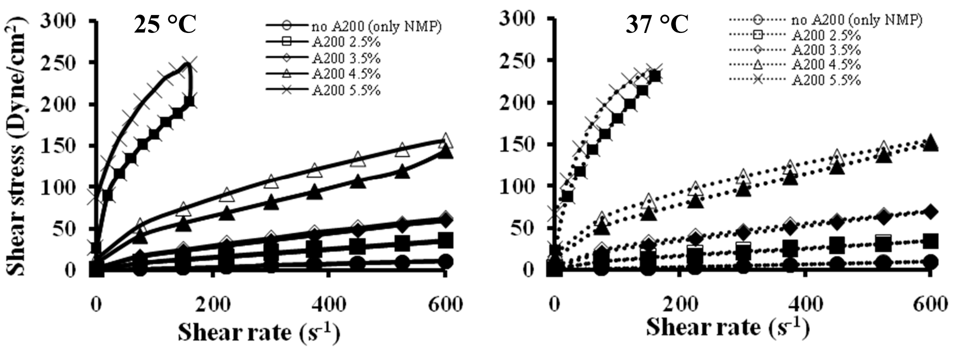

Fig. 3 Flow curve of systems containing aerosil 200 (A200) in NMP at 25 °C and 37°C. Open symbols represent the up-curve, and closed symbols represent the down-curve.

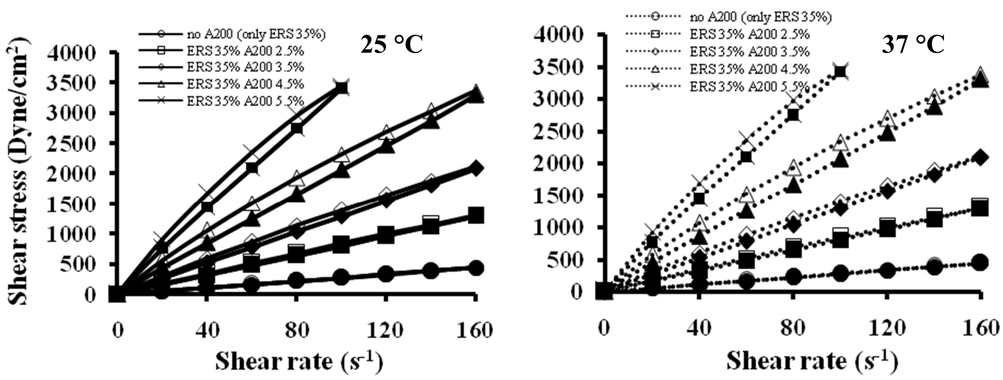

Fig. 4 Flow curve of systems containing aerosil 200 (A200) and ERS at 25 °C and 37°C. Open symbols represent the up-curve, and closed symbols represent the down-curve.

The work required to expel each sample from a syringe are shown in Table 1 and 2. Significant increase in the work of syringing was observed as the amount of each aerosil was increased. Syringeability of the systems containing aerosil 200 was higher than that containing aerosil R972.

Table. 1 Syringeability of systems containing aerosil 200 in NMP and ERS.

Systems	Syringeability (work, N.mm)				
	Concentration of Aerosil 200 (%w/w)				
	0	2.5	3.5	4.5	5.5
NMP	4.34 ± 0.09	4.73 ± 0.18	5.11 ± 0.03	5.19 ± 0.31	7.74 ± 0.27
35% ERS in NMP	8.21 ± 0.50	15.03 ± 1.12	23.38 ± 0.80	32.73 ± 1.84	50.88 ± 7.55

Table. 2 Syringeability of aerosil R972 in *N*-methyl-pyrrolidone (NMP) and the eudragit systems.

Systems	Syringeability (work, N.mm)				
	Concentration of Aerosil R972 (%w/w)				
	0	2.5	3.5	4.5	5.5
NMP	4.34 ± 0.09	4.46 ± 0.35	4.64 ± 0.22	4.70 ± 0.16	4.83 ± 0.16
35% ERS in NMP	8.21 ± 0.50	13.09 ± 0.90	21.23 ± 1.35	25.09 ± 0.67	38.11 ± 6.96

Conclusion

In this study, the effect of hydrophilic and hydrophobic aerosil on physical properties of NMP and ERS was investigated. The results showed that the amount of aerosil 200 and aerosil R972 could enhance the viscosity, rheology and syringeability of systems comprising NMP and ERS

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