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Study of the stability of Kollidon® SR suspensions for pharmaceutical applications

José L. Arias[a,*], Amparo Gómez-Gallo[a], Ángel V. Delgado[b], Visitación Gallardo[a]

[a] Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Granada, Granada, Spain
[b] Department of Applied Physics, Faculty of Sciences, University of Granada, Granada, Spain

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ABSTRACT

Currently, great efforts are devoted to the design of drug delivery systems and many new polymers are investigated to make drug release fit the desired profiles. In this work, we investigate the formulation of colloidal aqueous suspensions based on the polymer Kollidon® SR for the oral administration of drugs. Such an investigation has never been carried out to our knowledge, as this polymer has only been used as soluble binder and film-forming agent for solid dosage forms. In this work, both the stability and redispersibility characteristics of Kollidon® SR aqueous suspensions are extensively investigated through thermodynamic and electrokinetic studies. The hydrophilic character of the polymer, and the surface charge and electrical double layer thickness play a key role in the stability of the suspensions, hence the need for a full characterization of the polymer. Kollidon® SR suspensions display a “free-layered” sedimentation determined by their hydrophilic character and their zeta potential values (indicating the electrokinetic charge on the particles). The electrostatic repulsion between the particles is responsible for the low sedimentation volume and easy redispersibility of the polymer.

1. Introduction

During recent years, an increase in the research efforts dedicated to finding new polymers suitable for drug delivery has been made possible, thanks to the design of improved colloidal systems for the transport and controlled release of drugs. These systems are intended to be able to selectively direct the drug to the target tissue at the required dose and time scale [1–3]. Whatever the colloidal material chosen, the control and prediction of the stability of its suspensions is crucial for its application as drug carriers. In this respect, the electrical properties of the solid/liquid interface are essential in determining the stability of the suspensions. Since high zeta potentials (ζ) give rise to significant electrostatic repulsions between the particles, this situation should correlate with small sedimentation volumes, low settling rates and difficult redispersion. The reverse will be true for low ζ.

In order to achieve the desired control over these properties, polymers and polyelectrolytes can be used, although simple electrolytes can also be employed with this aim, and in fact they are usually present in pharmaceutical suspensions [4]. Whatever the procedure used, it must be kept in mind that the electrokinetic potential and the electrical double layer thickness will play an essential role in the stability of the system. Hence the need for the investigation of the electrical state of the particles if a full characterization of the system is sought.

In the present work, a colloidal oral suspension based on the polymer Kollidon® SR is investigated as a potential drug vehicle. To our knowledge, such an investigation has never been carried out. In fact, this polymer (a biodegradable copolymer of vinylpyrrolidone and vinylacetate) is known to be suitable for the manufacture of pH-independent sustained-release matrix tablets. The key aspect of its structure is that the water-soluble polyvinylpyrrolidone leaches out when in contact with the gastric or intestinal fluids, thus creating channels for the slow diffusion of the active component through the polyvinylacetate matrix. Kollidon® SR contains no ionic groups and is therefore inert to drug substances. In addition, its sustained-release properties are unaffected by ions or salts. Kollidon® SR has demonstrated to have no acute toxicity and to be not irritating to the skin or mucous membranes. Moreover, it is only minimally absorbed following oral administration and is, therefore, largely excreted in the feces [5–7].

For these reasons, the present contribution will focus on the preparation and characterization of Kollidon® SR aqueous dispersions. A simultaneous analysis of their electrokinetic properties and their stability will also be performed, and the effects of both pH and ionic content of the dispersion medium will be investigated.

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* Corresponding author at: Departamento de Farmacia y Tecnología Farmacéutica, Facultad de Farmacia, Universidad de Granada, 18071 - Granada, Spain.
Tel.: +34 958 24 39 00; fax: +34 958 24 89 58.
E-mail address: jlarias@ugr.es (J.L. Arias).

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2. Materials and methods

2.1. Materials

All chemicals were of analytical quality from Panreac, Spain, except for Kollidon® SR (BASF, Germany), KOH and diiodomethane (Merck, Alemania) and formamide (Carlo Erba, Italy). Water used in the experiments was deionized and filtered (Milli-Q Academic, Millipore, France).

2.2. Methods

2.2.1. Preparation and characterization of Kollidon® SR microparticles

In order to reduce the size heterogeneity and the number of particles with a diameter over 10 μm in the sample, the original Kollidon® SR suspensions [10%, w/v] were subjected to filtration in a stirred filtration cell with a membrane of 10 μm pore size. The experiment was repeated at least three times on independent samples.

The size and shape of the particles were deduced from SEM pictures obtained with a Zeiss DSM 950 (Germany) scanning electron microscope set at 80 kV accelerating voltage. Mean particle diameters were also determined at 25.0 ± 0.5 °C by Quasi-Electric Light Scattering (QELS) using a Nanosizer (Coulter® N4MD, Coulter Electronics, Inc., Hialeah, FL, USA). The scattering angle was set at 90° and the measurement was made after suitable dilution of the aqueous suspensions.

The characterization of the chemistry of the polymer particles was carried out by means of Fourier transform infrared spectrometry data (Nicolet 20 SXB infrared spectrometer, USA) with a resolution of 2 cm^{-1}.

The surface electrical properties of Kollidon® SR particles [≈0.1%, w/v], were analyzed by electrophoresis measurements as a function of both pH (adjusted with either HCl or NaOH) and NaCl concentration, using a Zetasizer 2000 (Malvern Instruments, U.K.) electrophoresis device. Measurements were performed at 25.0 ± 0.5 °C, after 24 h of contact at this temperature under mechanical stirring (50 rpm). This technique was also used in the estimation of the effect of pH and electrolyte type and concentration on the stability of Kollidon® SR aqueous dispersions. For this purpose, the electrolyte concentrations were fixed between 10^{-5} and 10^{-1} M with NaCl, $CaCl_2{\cdot}4H_2O$ or $AlCl_3{\cdot}6H_2O$. The experimental uncertainty of the measurements was below 5%. The theory of O'Brien and White [8] was used to convert the electrophoretic mobility (u_e) into zeta potential (ζ) values.

The significance of the evaluation of the solids wettability is high for our purposes, not only regarding their dipersibility in aqueous media, but also considering the effect of hydrophilicity on the capture of the particles by the cells of the reticuloendothelial system. It appeared interesting to carry out such evaluation for our particles, previously selecting a surface thermodynamic model capable of quantifying the hydrophobicity of the solid by means of a physical quantity like the surface tension or surface-free energy, γ_S, of the solid. We will follow the model proposed by van Oss [9], which has proved its suitability in pharmaceutical suspensions, as shown by Arias et al. [10,11].

The model starts from the separation of γ_S into two components, γ_S^{LW} and γ_S^{AB}, accounting for the van der Waals and acid/base interfacial interactions:

$$\gamma_S = \gamma_S^{LW} + \gamma_S^{AB} \tag{1}$$

and the acid/base component is in turn considered as a harmonic mean of two additional quantities, γ_S^+ and γ_S^-, known, respectively as electron acceptor and electron donor components. Thus the polar contribution to the surface-free energy is controlled by the tendency of the solid to accept or give electrons:

$$\gamma_S^{AB} = 2\sqrt{\gamma_S^+\gamma_S^-} \tag{2}$$

The same applies to the liquid (or any other) phase present in the suspension, and, most important, to the solid/liquid interfacial-free energy:

$$\begin{aligned}
\gamma_{SL} &= \gamma_{SL}^{LW} + \gamma_{SL}^{AB}\\
\gamma_{SL}^{LW} &= \left(\sqrt{\gamma_S^{LW}} - \sqrt{\gamma_L^{LW}}\right)^2 = \gamma_S^{LW} + \gamma_L^{LW} - 2\sqrt{\gamma_S^{LW}\gamma_L^{LW}}\\
\gamma_{SL}^{AB} &= 2\left(\sqrt{\gamma_S^+\gamma_S^-} + \sqrt{\gamma_L^+\gamma_L^-} - \sqrt{\gamma_S^+\gamma_L^-} - \sqrt{\gamma_S^-\gamma_L^+}\right)\\
&= 2\left(\sqrt{\gamma_S^+} - \sqrt{\gamma_L^+}\right)\left(\sqrt{\gamma_S^-} - \sqrt{\gamma_L^-}\right)
\end{aligned} \tag{3}$$

If we now imagine a drop of liquid in equilibrium on a molecularly flat solid surface, the contact angle θ can be related to the LW and AB components of γ_S and γ_L [9,12], through Young's equation:

$$2\sqrt{\gamma_S^{LW}\gamma_L^{LW}} + 2\sqrt{\gamma_S^+\gamma_L^-} + 2\sqrt{\gamma_S^-\gamma_L^+} = \gamma_L\left(1+\cos\theta\right) \tag{4}$$

Note that if γ_L^{LW}, γ_L^+, γ_L^- are known for three probe liquids, and their corresponding contact angles are measured, a system of three equations like Eq. (4) can be formulated, the solution of which yields the unknown γ_S^{LW}, γ_S^+, γ_S^-. In our case, the liquids chosen were water ($\gamma_L^{LW} = 21.8\,\text{mJ/m}^2$, $\gamma_L^+ = \gamma_L^- = 25\,\text{mJ/m}^2$), formamide ($\gamma_L^{LW} = 39.0\,\text{mJ/m}^2$, $\gamma_L^+ = 2.28\,\text{mJ/m}^2$, $\gamma_L^- = 39.6\,\text{mJ/m}^2$) and diiodomethane ($\gamma_L^{LW} = 50.8$, $\gamma_L^+ = \gamma_L^- = 0\,\text{mJ/m}^2$). All γ_L data were taken from van Oss [9], and the contact angles were measured at 25.0 ± 0.5 °C using a Ramé-Hart 100-00 goniometer (USA) with a CCD camera and a digital image analysis of drop pictures. Pellets (1.3 cm radius) of the powdered dry solids were prepared by compression in a Spepac (U.K.) hydraulic press set to 8 ton, for 5 min.

2.2.2. Stability of Kollidon® SR aqueous dispersions

We used differential scanning calorimetry (DSC) and SEM observations to investigate the stability of Kollidon® SR aqueous dispersions under different experimental conditions (pH, shaking, light and temperature). The experiments were carried out in triplicate in all cases.

The effect of pH on the stability of the dispersions was studied after one week of contact with solutions of the desired pH. The effect of exposure to light was studied by placing one set of glassware under ambient light, and wrapping another set with aluminium foil, during one week in both cases. The effect of shaking on Kollidon® SR was tested by treating samples for 3 h in a Branson 5200E4 ultrasonic bath (USA) set at 450 W ultrasound power. In these cases, the samples were then desiccated at room temperature before running the DSC experiments. To check for the effect of temperature on polymer stability, samples were desiccated at 25.0 ± 0.5 °C and 40.0 ± 0.5 °C.

DSC analysis of the samples was performed with a Mettler FP85 DSC (Switzerland) at a heating rate of 5 °C min^{-1} in a temperature range of 30–300 °C. The sample weight was 6 mg. SEM pictures of desiccated dilute (≈0.1%, w/v) suspensions were used to provide complementary morphological information.

Apart from the electrokinetic evaluation, two methods were used to determine the colloidal stability of Kollidon® SR aqueous dispersions: one consisted in the measurement of the sediment volume, V_s, after keeping the suspensions in 100 mL cylinders (inner diameter: 2.4 cm) placed in a thermostatted bath at 25.0 ± 0.5 °C. The concentration of solids in the cylinders was 10% (w/v) in all cases. The flocculation ratio, F, was the quantity chosen for the characterization of the stability. This is defined as 100 (V_s/V_0), where V_0 is the initial volume of the suspension [13]. A complementary