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An Integral Approach to Master Physicochemical Properties in the Solid Chain of a Colloidal Pharmaceutical Product

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In a wide range of industrial applications particle design is governed by the process precipitation followed by isolation like filtration or washing and drying. Particle characteristics play a crucial role on the behavior of the suspension during all production steps. This especially counts for pigments or dye stuff as well as for life science products. Particularly in the pharmaceutical industry bioavailability of a product is of utmost importance, which is often improved by designing colloidal particle collectives with a high surface area, however, often compromising the solid-liquid separation efficiency. This study is concerned with the interaction between crystallization, sedimentation, and washing efficiency all impacted by physical chemical properties of the particles itself, but also on the liquid phases used. The effect of dosage time of the reactants, stirrer speed, ionic strength, and pH-value are investigated in the precipitation process and on their impact on the solid-liquid separation behavior.

Keywords colloids; microparticles; precipitation; sedimentation; washing

INTRODUCTION

The production of colloidal dispersions is widely encountered in the chemical and pharmaceutical industry for the production of pigments and dye stuffs, life science products like pharmaceuticals and plant protection agents, and in the mineral industry for the separation and purification of ores (1). Therefore, colloid stability and aggregation phenomena are crucial for the solid-liquid separation, because they influence parameters as cake resistance, cake structure, and the sedimentation behavior. Conventional processes like sweep coagulation or flocculation by means of polymer bridging are limited to applications like microfiltration for water treatment, where the separated product purity plays a diminishing role.

A colloidal dispersion in a continuous phase is stable, if an electrostatic charge is present on the particle surface or in the environment of the particles, which is strong enough to hold the particles apart. The relevant stabilization mechanism is the electrostatic stabilization, while other mechanisms also exist like steric or electrosteric stabilization (2). It happens due to counter ions compensating the charge. These ions are not attached to the particle surface, but form diffuse ion layers around each particle. The result is repulsion between these ion layers which stabilizes the dispersion. The stabilization strongly depends on the size of the defuse double layer that is influenced by the valency and concentration of the surroundings ions. For a detailed description of the diffuse layer theory, see (3–5). The ζ-potential is a measure for the strength of the repulsive force and within for the stability of the suspension. It is defined as the electric potential measured at the shear plane. If the particles move close together the presence of attractive van der Waals force between the particles destabilize the dispersion. A very high ion concentration means a compressed and therefore smaller double layer. The particles move closer and the attractive force leads to agglomeration. The effect of both forces, repulsive and attractive, is described in detail by the famous DLVO-theory (6,7).

The stability of a suspension influences their sedimentation behavior significantly. Stokes (8) showed that a single, spherical particle with the diameter x in a liquid environment will settle with the velocity v_{St} if the flow is creeping and the particle motion is stationary. This Stokes velocity represents the relative velocity between the particles and the fluid, and can be calculated with the well known formula

$$v_{St} = \frac{(\rho_s - \rho_l)Cg}{18\eta_l}x^2. \tag{1}$$

The centrifugal number C, or the C-value, is equal to 1 in the gravity field of the earth and can be increased by a centrifugal field. Although this formula is developed for spheres it can be used to approximate the settling velocity

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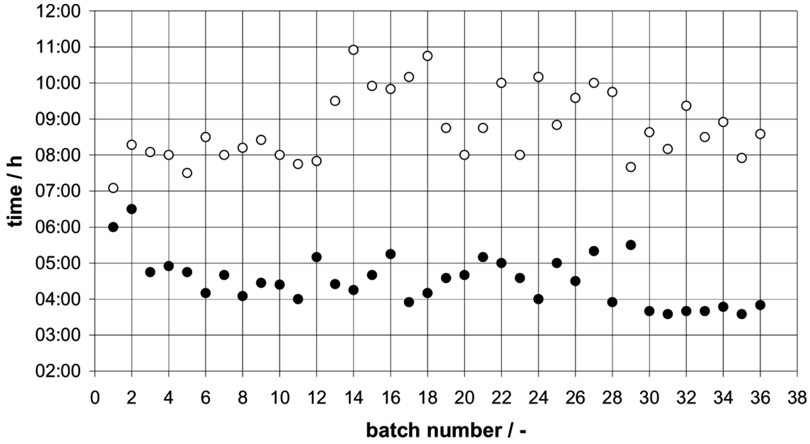

FIG. 1. Physicochemical properties affecting the cycle time of a sedimentation process (bold points: suspension directly after the precipitation, empty points: suspension after the third washing step).

of agglomerates, if they are stable and do not change their size during sedimentation. Then x denotes the diameter of the agglomerate and ρ_s its agglomerate density. Therefore even in destabilized suspensions the Stokes formula can be used for calculating the agglomerate settling speed as long as the agglomeration is stable.

Instead of observing single particles, it is often only possible to measure the settling speed of a separation front between the suspension and the clear part of the liquid. The most famous approach for an approximation connecting the sedimentation speed of the separation front v_{sed} with the stokes velocity v_{St} is given by Richardson and Zaki (9), who proposed the empirical equation,

$$v_{sed} = v_{St}(1 - c_V)^{4.65}. \tag{2}$$

The given exponent depends on the Reynolds number, but the value 4.65 is valid for the Stokes regime ($Re \leq 0.25$). Additionally, Beiser et al. (10) and Feist et al. (11) have shown, how significantly the sedimentation velocity depends on the stabilization of the suspension. They used a sedimentation scale and a manometer centrifuge, which exploits the mass difference between the fluid and the liquid. Another possibility to get knowledge about the settling behavior is the observation of the separation front, which is in these presented studies done by the LUMiFuge® (12). It observes the extinction of light caused by the suspension. From this data the suspension and the clear liquid can be distinguished. Due to measurements up to every 2 seconds one gets the evolution of the clear liquid and with it the speed of the separation front. Especially the different behavior in sedimentation of suspensions produced by changing parameters can be compared. Additionally, in the described industrial process the separation behavior is of utmost importance. Therefore, we especially investigate the sedimentation behavior of the separation front, instead of measuring the particle size distribution, like it can be found in literature, see (13–15).

The motivation for this study is given by the necessity to integrate precipitation, sedimentation and washing to master physical chemical properties in the solid liquid chain to design a robust process, superior particle properties and improved sedimentation behaviour. Figure 1 illustrates the motivation for this study from the production point of view.

The precipitated product is separated by means of an accelerated sedimentation process. The cycle time for this process is captured by the bold symbols. The sediment is subsequently washed in a re-suspending process with a solvent, whereby the ionic load of the product is reduced. The cycle time for the re-suspended slurry, which has the same solid concentration as the precipitate, is shown by the empty symbols. The settling time is nearly twice as long as the first sedimentation cycle. Additionally the variations can be explained by slightly varying process parameters, which is unavoidable in most industry processes. Unfortunately in this case these changes have a big influence on the sedimentation behavior and on the separation times during production. In literature there are various reports in which parameters influence the flake size in precipitation processes and within the sedimentation behavior. Pascoe et al. (13,14) report a significant change of the flake size during flocculation of a hematite-sodium oleate suspension, depending on the pH-value and on the stirrer speed. Additionally Patil et al. (15) add the flocculation time to the significant parameters for the flake size. By Eq. (1) it is clear that the size of a particle has a big influence on its settling velocity. These results stress the necessity to investigate the influencing parameters to stabilize the precipitation for a homogeneous separation.

EXPERIMENTAL SET UP AND MEASUREMENT TECHNIQUES

The Precipitation Reaction

The precipitation reaction is conducted in such a way that two reactants are dosed into a stirred reactor at constant temperature. The schematic experimental precipitation set-up is given in Fig. 2.

Therein the following precipitation reaction takes place,

$$(R_1 + L_1 + CP) + (R_2 + L_2) \rightarrow P + L + G + I, \qquad (3)$$

where R_1 denotes the reactant 1 which is dissolved in liquid 1 (L_1), CP the carrier particles, and R_2 the reactant 2 dissolved in liquid 2 (L_2). The terms in the first bracket of Eq. (3) form the reactant suspension and those in the second bracket the reactant solution. On the product side P means all settling particles including the precipitated particles, which are free or agglomerated with the carrier particles and the unused carrier particles, L is the liquid phase, G the gas phase, and I denotes 6 different ions within the suspension. Three of these ions (I_1, I_2, I_3) had to be washed out until a certain limit was reached. The outflow of the gas phase G results in variations of the pH-value of suspensions. For simplification the right hand side of Eq. (3) can be defined as,

$$S_0 := P + L + G + I, \qquad (4)$$

where S_0 now denotes the suspension obtained directly after the precipitation and before the solid-liquid separation and washing steps.

Washing Steps

In each washing step we have tried to remove most of the ions from the solid product P. De-ionized water is used as wash liquid, but the amount can be varied from step to step. The procedure is explained in detail in Fig. 3.

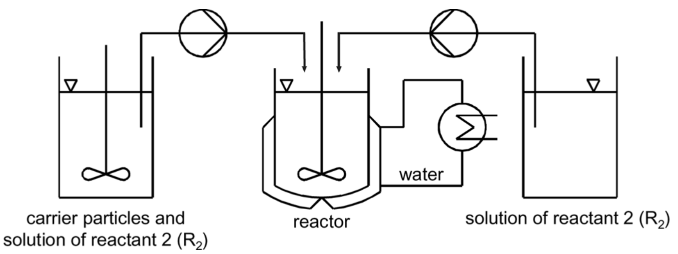

FIG. 2. Schematic experimental set-up for the precipitation reaction.

After the first centrifugation, the clear solution 1 (CS_1) is withdrawn from the vessel and its electrical conductivity (EC) and ion concentrations is measured. The wet solid 1 (WS_1) is washed with wash liquid 1 by re-suspending it, to form the suspension 1 (S_1). The percentage of wash liquid is calculated by,

$$WR = \frac{w}{w + m} \qquad (5)$$

where WR denotes the washing ratio, w the amount of wash liquid, and m the amount of wet solid. Equation (5) is applied for all washing steps. The centrifugation and washing steps are performed until reaching wet solid 4 (WS_4), in which the concentrations of three of the Ions have to be below certain limits.

Measurement Techniques

The solid-liquid separation, particularly the sedimentation behavior of the suspension S0, and after each wash step, S1 to S3, is investigated using the analytical centrifuge LUMiFuge®. The aim is to rate and compose the sedimentation behavior of each single suspension under variation of the precipitation parameters to investigate their influences. Every two seconds the LUMiFuge® gives a transmission profile of the sample that is used to evaluate the position, where the separation front is located. With these positions one can calculate the settling speed of the separation front. The experiments are done with two or four samples to calculate the median and the standard deviation. The particle size distribution is measured by Helos 3000 to get knowledge about the size and the agglomeration ability of the particles and the AcoustoSizer II is used to measure the ζ-potential. Finally the ionic conductivity and the ion concentration are measured to evaluate the quality of our washing steps.

RESULTS AND DISCUSSION

Particle Size Distribution

To investigate the agglomeration behavior of the product under certain conditions we measured the particle size distribution in different dilution liquids, one with a high ionic

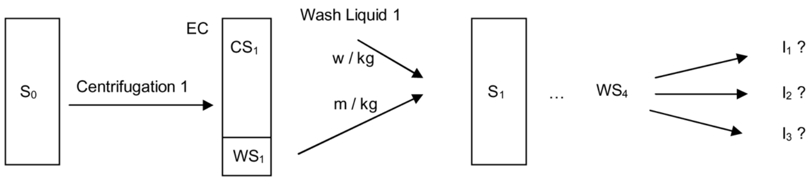

FIG. 3. Sequence of the centrifugation and wash steps.

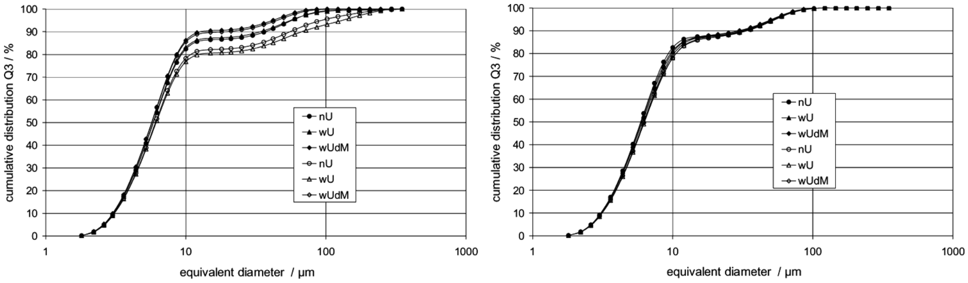

FIG. 4. Particle size distribution of suspension S_0 without ultrasonic (nU), with 120 s ultrasonic dispersion (wU) before the measurement and with ultrasonic dispersion directly during the measurement (wU dM). Left diagram: Dilution liquid: 70% mother liquor and 30% de-ionized water; right diagram: 100% de-ionized water.

concentration, see Fig. 4 left, and one with hardly any ion in it, see Fig. 4 right. In each measurement cycle we varied the sample preparations, with variation of the mechanical stress before the measurement. The obtained stress sequence was first, without ultrasonic, second, with 120 s ultrasonic directly before, and third, ultrasonic during the measurement. This cycle was once repeated with the same sample. Referring to Fig. 4 left, 120 s ultrasonic before the measurement have nearly no effect on the particle size distribution compared to the measurement without ultrasonic. Using ultrasonic during the measurement the average particle size becomes much smaller, because the agglomerates are broken off. Repeating of the cycle with the same sample shows that the particles tend to re-agglomerate and that the agglomerates become even bigger than the original ones have been. The re-agglomeration is due to the high ion concentration which compresses the ionic double layer and the bigger agglomerates are explained by reordering effects. Ultrasonic during the measurement is again able to destroy the agglomerates, which leads to the same particle size distribution as in the first cycle. The measurement with 100% de-ionized water, Fig. 4 right, shows a different behavior. Here the ultrasonic has nearly no influence. The particles and agglomerates have the same size distribution independent on treatment, particularly they do not agglomerate again to bigger particles.

From these results one recognizes that the agglomeration ability of the particles in the mother liquid, that means at suspension S0, is very high. It is supposed, that even if a separation step in the production plant destroys the agglomerates, the particles will agglomerate again and within have a better separation behavior, as long as the ion concentration in the liquid is high enough. However, the more the wash steps the less the ions are in the new mother liquid and the smaller are the agglomerates. Additionally the re-agglomeration is very poor, and the settling speed is relative slow. This is also shown by the poor separation efficiency shown in Fig. 1.

Stirrer Speed, Dosage Times, and Dosage Type

The precipitation reaction has been studied on 0.25 L reactor by varying the stirrer speed, the dosage time of the reactants, and with it the pH-value during precipitation. The suspensions were analyzed with respect to the sedimentation behavior. The investigated dosage time t was 2 h, 4 h, 6 h, 8 h, 10 h, and 12 h. The stirrer speed n was changed between 123 rpm, 200 rpm, and 300 rpm for 4 h dosage time. The pH-regime was accomplished by varying the flow rates of the basic reactant suspension and the acidic reactant solution. The impact of the precipitation conditions on the sedimentation behavior was studied at 23 g.

The results for the investigation on the type of dosage are shown in Table 1. We varied the type of dosage from dosing only the reactant solution via a stoichiometric dosing up to only dosing the reactant suspension. Together

TABLE 1
Settling velocity of the separation front in dependence on the dosage type. The dosage time was 4 h and the stirrer speed 123 rpm

Type of dosage	regime	Settling velocity in 10 e-5 m/s
reactant suspension and solution are dosed stoichiometric	neutral regime	6.79 ± 0.037
reactant solution is dosed slower	basic regime	6.44 ± 0.065
only reactant solution is dosed	basic regime	7.38 ± 0.140
reactant suspension is dosed slower	acid regime	2.47 ± 0.005
only reactant suspension is dosed	acid regime	1.17 ± 0.175

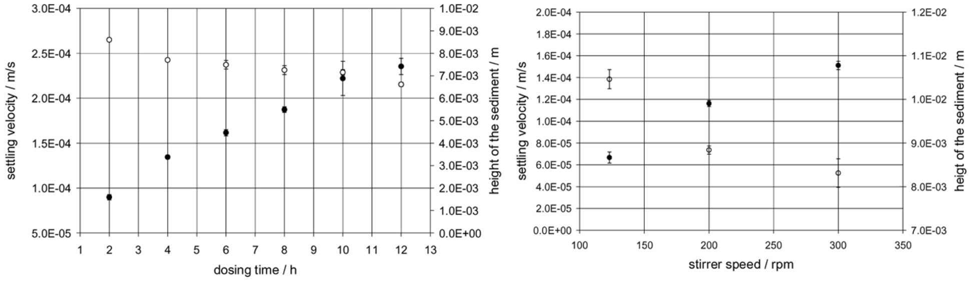

FIG. 5. Left diagram: Effect of dosage time t. Right diagram: Effect of the stirrer speed on the sedimentation behavior. The first y-axis shows the settling velocity of the separation front (bold symbols), the second y-axis the height of the sediment (light symbols).

with this variation, we varied the pH-regime of the precipitation from a basic regime to an acid regime. The settling velocity from the product particles produced in the acid regime is up to four times slower, then the settling velocity achieved in the basic regime. This can be explained with a stronger outgasing of the gas phase G and bigger agglomerates.

The effect of dosage time at a stoichiometric ratio of 1:1 and the stirrer speed is illustrated in Fig. 5. It shows the settling velocity and the height of the sediment of the suspensions S0 obtained after the precipitation reactions at dosage times of 2 h, 4 h, 6 h, 8 h, 10 h, and 12 h, as well as for stirrer speed values of 123 rpm, 200 rpm, and 300 rpm. At the first y-axis the settling velocity of the separation front and at the second y-axis the height of the sediment is given. The sedimentation velocity rises, the longer the dosage time and the higher the stirrer speed was. Additionally the sediment is high at low sedimentation speed and because of equal mass concentrations less compact than for a high sedimentation speed. During the precipitation a longer dosage time causes more compact and bigger flakes, as it was reported by (15), too. This can be attributed to the mechanical energy which is entered into the system by longer stirring. Another reason could be outgasing and thus shifting the pH and a better mixture of the reactants. However, the influence of the pH-regime is not very obvious for the stirrer speed of 123 rpm at lab scale. One reason for the faster sedimentation at higher stirrer speeds is the fracture of the flakes. Due to the re-agglomeration ability, shown in the left diagram, of Fig. 4, bigger and more compact agglomerates are formed in the suspension, which can form more dense sediments and settle faster without being affected strongly from hindering effects. This coincident with Pascoe et al. (13,14) who explained the shear flocculation and also found bigger agglomerates for higher stirrer speeds. Another reason for obtaining better sedimentation results with higher stirrer speeds could be the effect of mixing leading to stronger outgasing of the gas phase G. This, like for the case explained in Fig. 5(a), increases the pH-value of the suspensions due to the pH dependent chemical equilibrium.

Zeta-Potential Variation

Figure 6 compares the sedimentation results at different pH-values of suspension S_3 and the progress of the ζ-potential as a function of the pH-value. The reason for not choosing S_0 was due to its very high ion concentration, where the pH-value could not be changed even with large amounts of acid or base. Additionally the ionic strength of the surrounding liquid is too high for the limit of the measurement technique of the AcoustoSizer.

Starting at 7.5, the pH-value was reduced by adding HCl until a pH-value of 2 was reached. At certain values the ζ-potential and the sedimentation behavior is measured. According to Fig. 6 left, at the beginning the ζ-potential is about $-10\,\text{mV}$ and the suspension should be just a bit stabilized. Lowering the pH-value the isoelectric point, nearly at pH 6, is reached and the suspension is destabilized.

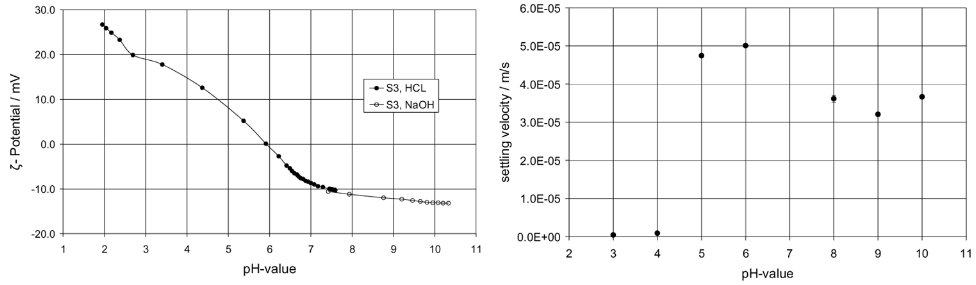

FIG. 6. Left diagram: Zeta potential vs. pH-value of suspension three (S_3), right diagram: settling speed at different pH-values.

A further decrease leads to a ζ-potential of about 20 mV at a pH-value of 2 and 3, where the suspension is supposed to be stabilized again. The second experiment was done by adding NaOH to increase the pH-value. In that region the ζ-potential of the suspension has approximately the same ζ-potential it is about −11 mV.

Comparing this ζ-potential progressing with the settling velocity of the separation front, (see Fig. 6 right), it shows the (from the prior results expected) behavior. Suspensions with pH-values of 2 and 3, which have the flattest curves, are the most stable suspensions compared to those at higher pH-values. These two suspensions are even investigated with a C-value of 800, because no sedimentation could be observed under investigations with 23 g. The particles are so small that they did not settle in a field with a C-value of 23. Therefore, at pH-values of 2 and 3 the suspension is very stable and the agglomeration effects are prevented. At the pH-values of 5 and 6, the fastest sedimentation speed is reached. This is expected from the ζ-potential curve, (see Fig. 6 left), because the isoelectric point of S_3 is nearly at pH 6 where no stabilization is expected. A further increase in pH to values 8, 9, and 10 gave similar sedimentation behaviors for these three suspensions, as may be expected from the ζ-potential progress of S_3 as well. As a result, it can be concluded that the ζ-potential progress in dependence of the pH-value can be directly correlated with the settling velocity of the separation front.

Washing Steps

The influence of different washing ratios WR were examined with respect to the sedimentation behavior of the suspensions and the amount of retained ions within the dry solid products after each wash step. In Fig. 7 the sedimentation behavior of S1 is shown under variation of the washing ratios, which are 90, 80, 70, and 50%.

It is obvious that the suspension with the highest wash liquid ratio has the best sedimentation result. The results become worse for increasing concentrations of solid phase. This could be attributed to the concentration effect for the zone sedimentation region, where high particle concentrations are encountered. That is in accordance with the well known theory (9), (10), because the higher the volume concentration, the higher the hindering during sedimentation. At a washing ratio of 50% the concentration is so high that there is no free sedimentation, but just a compression of the sediment. Suspensions after the second and third wash steps showed similar behavior.

The electrical conductivities of the supernatant were measured in order to predict the concentrations of ions washed from the solid phase.

Figure 8 compares the electrical conductivity values of solutions containing equal concentrations of I_1 and I_2 taken from the literature. As is obvious, the literature values fit our results well. I_3 either prefers to be at the particle surface so that its concentration in clear solutions is low, or its concentration is not high in general, depending on the pH-value and equilibrium conditions of the suspension. To summarize, I_3 does not contribute to the electrical conductivity of clear solutions significantly. Therefore, predictions about the concentrations of I_1 and I_2 can be made by measuring the electrical conductivity of the clear solutions and comparing them to the literature values. The remaining amount of these ions in the solid phase can then be calculated. For I_3, however, this is not possible since the value of pH affects the concentration of this ion.

After the first centrifugation step, the electrical conductivity of clear solution 1, CS_1, was measured. The result is the point on Fig. 9 having the washing ratio of 0% because CS_1 is obtained before the first wash step. The linear curve named "first washstep" belongs to the second clear solutions. The linearity of this curve means that the amount of wash liquid used is linearly proportional to the amounts of 11 and I2 removed. That is because the 11 and I2 are removed by dilution washing. The curves branching out from the second wash step belong to the third and the

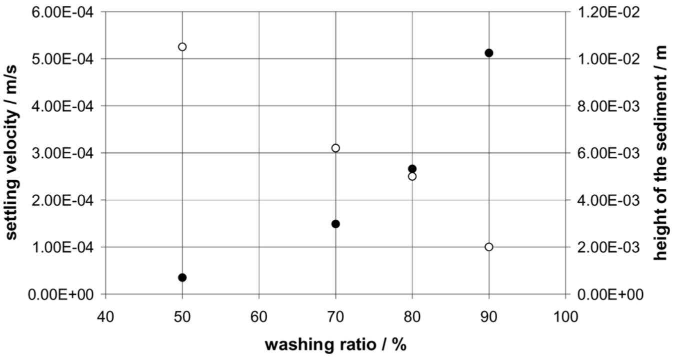

FIG. 7. Effect of the dilution on the sedimentation behavior after 1st washing step (S_1) (bold symbols: settling velocity of the separation front, light symbols: height of the sediment).

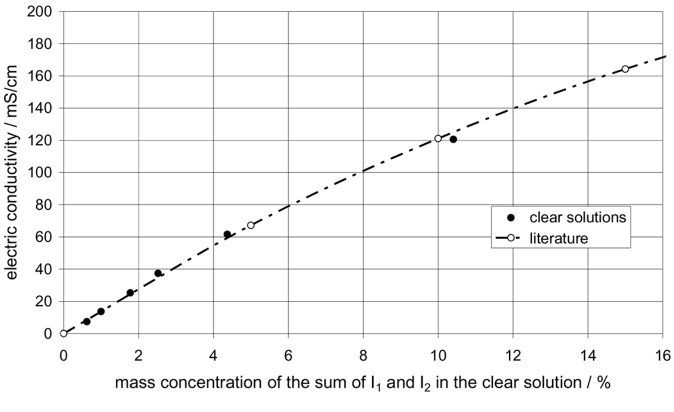

FIG. 8. Comparison of the electrical conductivity values between the literature data.

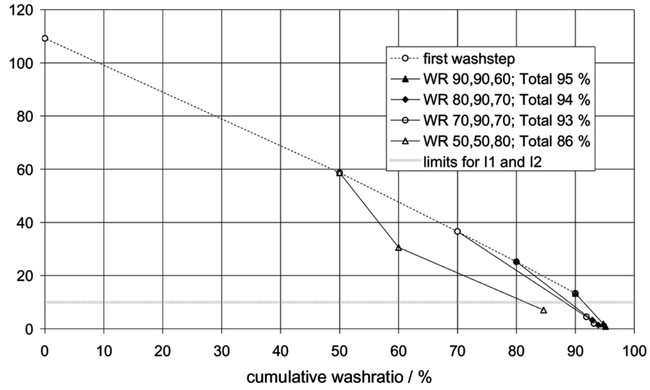

FIG. 9. Electrical conductivity of the supernatant in dependence of the washing ratio.

fourth clear solutions. The final clear solutions of the first three sets of experiments, which have similar values of the total washing ratio, have approximately the same electrical conductivity. The fourth set with 86% total wash ratio has more ions within the clear solution after the third wash step (fourth clear solution) due to the less amount of wash liquid used. This is explained with the proportionality of the removed ion amounts with the wash liquid amount used. It can be said, that for I_1 and I_2 only two washing steps with only 86% total amount of water is needed. Therefore the electrical conductivity is a good measure to control the amount of Ion I_1 and I_2 in the washed product.

CONCLUSIONS

The influence of physicochemical properties on the sedimentation behavior of a pharmaceutical product has been studied. The motivation was given by the fact that precipitation and sedimentation needs to be looked at in an integral approach. Additionally the product tends to agglomerate very fast if the liquid has a high ion-concentration.

To understand the precipitation process better, precipitation reactions are performed with variation of some parameters, which were the dosage times, and the stirrer speed. The agglomeration behavior of the final product were investigated by measuring the particle size distribution under different mechanical stress prior to the measurement. It was found that these parameters influence the system in such a manner that outgasing of the gas phase and breaking of the flakes during the precipitation leads to more compact agglomerates and quicker sedimentation. These were obtained with longer dosage times, higher stirrer speeds, and precipitating in the basic region.

According to the results of the wash steps it can be said that higher values of the washing ratio or lower values of solid concentration for a suspension result in quicker sedimentation. This is simply explained with the concentration effect. The total amount of wash liquid could be reduced if the distinctive ions are washed out with only dilution. As for one ion it is a diffusion process that the total amount cannot be reduced, but the amount in every step can be shifted to use the high ion concentrations and agglomerated particles at the beginning of the purification process to separate a huge amount of liquid and only a small amount of liquid in the end, when the sedimentation takes a much longer time. Finally, the zeta-potential progression depending on the pH-value was directly compared with the sedimentation velocity of the settling front, to investigate the possibility for adjusting the pH-value during the production to obtain higher sedimentation velocities.

NOMENCLATURE

Symbol	Definition	Unit
C	Centrifugal number (C-value)	[–]
g	Gravitational acceleration (=9.81)	[m^2s^{-1}]
Re	Reynolds number	[–]
u_{sed}	Settling velocity of the separation front	[ms^{-1}]
u_{St}	Stokes velocity	[ms^{-1}]
x	Particle diameter	[m]
ρ	Density	[$kg\ m^{-3}$]

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