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Physical and chemical stability of drug nanoparticles ☆

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ABSTRACT

As nano-sizing is becoming a more common approach for pharmaceutical product development, researchers are taking advantage of the unique inherent properties of nanoparticles for a wide variety of applications. This article reviews the physical and chemical stability of drug nanoparticles, including their mechanisms and corresponding characterization techniques. A few common strategies to overcome stability issues are also discussed.

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1. Introduction

With significant attention focused on nanoscience and nanotechnology in recent years, nanomaterial-based drug delivery has been propelled to the forefront by researchers from both academia and industry [1–3]. Various nano-structured materials were produced and applied to drug delivery such as nanoparticles [4], nanocapsules [5],

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nanotubes [6], micelles [7], microemulsions [8] and liposomes [9]. In general, the term "nanoparticles" refers to particles with sizes between 1 and 100 nm. However, submicron particles are also commonly referred as nanoparticles in the field of pharmaceutics and medicine [10–14]. Nanoparticles are categorized as nanocrystals [10], polymeric [15], liposomal [9] and solid lipid nanoparticles (SLN) [16] depending on their composition, function and morphology. Given the extensive available literature reviews on SLN, polymeric and liposomal nanoparticles [4,9,15–18], this article will focus only on nanocrystals (pure drug nanoparticles).

The unique nano-scale structure of nanoparticles provides significant increases in surface area to volume ratio which results in notably different behavior, both *in-vitro* and *in-vivo*, as compared to the traditional microparticles [10–12]. Consequently, drug nanocrystals have been extensively used in a variety of dosage forms for different purposes [10,11,14,19,20], such as improving the oral bioavailability of poorly water-soluble drugs by utilizing enhanced solubility and dissolution rate of nanoparticles [21–23]. In the field of pulmonary drug delivery, the nanoparticles are able to deliver the drugs into the deep lungs, which is of great importance for systemically absorbed drugs [11,14]. In addition, injection of poorly water-soluble nanosuspension drugs is an emerging and rapidly growing field that has drawn increasing attention due to its benefits in reducing toxicity and increasing drug efficacy through elimination of co-solvent in the formulation [10,20].

Despite the advantages of drug nanocrystals, they present various drawbacks including complex manufacturing [12,24–26], nanotoxicity [27] and stability issues [10,19,20]. Stability is one of the critical aspects in ensuring safety and efficacy of drug products. In intravenously administered nanosuspensions, for example, formation of larger particles (>5 μm) could lead to capillary blockade and embolism [20], and thus drug particle size and size distribution need to be closely monitored during storage. The stability issues of drug nanoparticles could arise during manufacturing, storage and shipping. For instance, the high pressure or temperature produced during manufacturing can cause crystallinity change to the drug particles [12,26,28]. Storage and shipping of the drug products may also bring about a variety of stability problems such as sedimentation, agglomeration and crystal growth [29–31]. Therefore, stability issues associated with drug nanocrystals deserve significant attention during pharmaceutical product development. This article reviews existing literature on drug nanoparticle stability, including theory/mechanisms, methods used to tackle the stability problems and characterization techniques, and provides recommendations to improve the current practices. Since the stability issues related to nanoparticle dry powders are usually trivial, this review will only focus on stability of nanosuspensions (drug nanoparticles dispersed in a liquid medium).

2. Stability of drug nanoparticles

2.1. Effect of dosage form on stability

The unique characteristics of drug nanoparticles have enabled their extensive application in various dosage forms including oral, parenteral, ocular, pulmonary, dermal and other specialized delivery systems [10,11,13,20,32]. Although different dosage forms may share some common stability issues, such as sedimentation, particle agglomeration or crystal growth, their effects on drug products are quite different. For instance, particle agglomeration could be a major issue in pulmonary drug delivery since it affects deposition amount/site, and thus drug efficacy. On the other hand, agglomeration in intravenous formulations can cause blood capillary blockage and obstruct blood flow. Moreover, the selection of stabilizers is also closely related to dispersion medium, dosage form and strictly choices on the approved stabilizers for oral dosage form whereas the excipients allowed for inhalation are very limited [33].

Drug nanoparticles exist in the final drug products either in dry powder or suspension form. Examples of the dry powder form include the dry powder inhaler, lyophilized powder for injection and oral tablets or capsules. Solid dosage forms usually have good storage stability profiles, which is why a common strategy to enhance nanosuspension stability is to transform the suspension into solid form [19,25]. Most of the reported stability concerns arise from nanosuspensions in which the drug nanoparticles are dispersed in a medium with or without stabilizers. In addition, mechanisms involved in the stability of small and large biomolecule formulations are different due to their molecular structure differences. A small molecule drug is defined as a low molecular weight non-polymeric organic compound while large biomolecules refer to large bioactive molecules such as protein/peptide. One of the major issues with protein/peptide stability is to maintain the 3-dimensional molecular conformation, such as secondary and tertiary structure in order to keep their biological activities [34,35], whereas there is no such concern for small organic molecules.

2.2. General stability issues related to nanosuspensions

Stability issues associated with nanosuspensions have been widely investigated and can be categorized as physical and chemical stability. The common physical stability issues include sedimentation/creaming, agglomeration, crystal growth and change of crystallinity state.

2.2.1. Sedimentation or creaming

Drug particles can either settle down or cream up in the formulation medium depending on their density relative to the medium. The sedimentation rate is described by Stokes' law [36,37] which indicates the important role of particle size, medium viscosity and density difference between medium and dispersed phase in determining the sedimentation rate. Decreasing particle size is the most common strategy used to reduce particle settling. Matching drug particles density with medium or increasing medium viscosity are the other widely used approaches to alleviate sedimentation problems [37,38]. Fig. 1 shows different sedimentation types that occur in suspension formulations.

In a deflocculated suspension (Fig. 1a), particles settle independently as small size entities resulting in a slow sedimentation rate. However, densely packed sediment, known as caking [39], is usually formed due to the pressure applied on each individual particle. This sediment is very difficult to be re-dispersed by agitation [36,37,39] and would be detrimental to the drug products performance. In the flocculated suspension (Fig. 1b), the agglomerated particles settle as loose aggregates instead of as individual particles [36,37]. The loose aggregates have a larger size compared to the single particle, and thus higher sedimentation rate. The loose structure of the rapidly settling flocs contains a significant amount of entrapped medium and this structure is preserved in the sediment. The final flocculation volume is therefore relatively large and the flocs can be easily broken and re-dispersed by simple agitation. K.P. Johnston et al. [40,41] have recently attempted to achieve stable nanosuspensions via a novel design of flocs structure called "open flocs", as illustrated in Fig. 1c. Thin film freezing was used to produce BSA nanorods with aspect ratio of approximately 24. These BSA nanorods were found to be highly stable when dispersed into hydrofluoroalkane (HFA) propellant, with no apparent sedimentation observed for 1 year. Due to the high aspect ratio of BSA nanorods and relatively strong attractive Van der Waals (VDW) forces at the contact sites between the particles, primary nanorods were locked together rapidly as an open structure upon addition of HFA, inhibiting collapse of the flocs [41]. The low-density open flocs structure was then filled with liquid HFA medium,

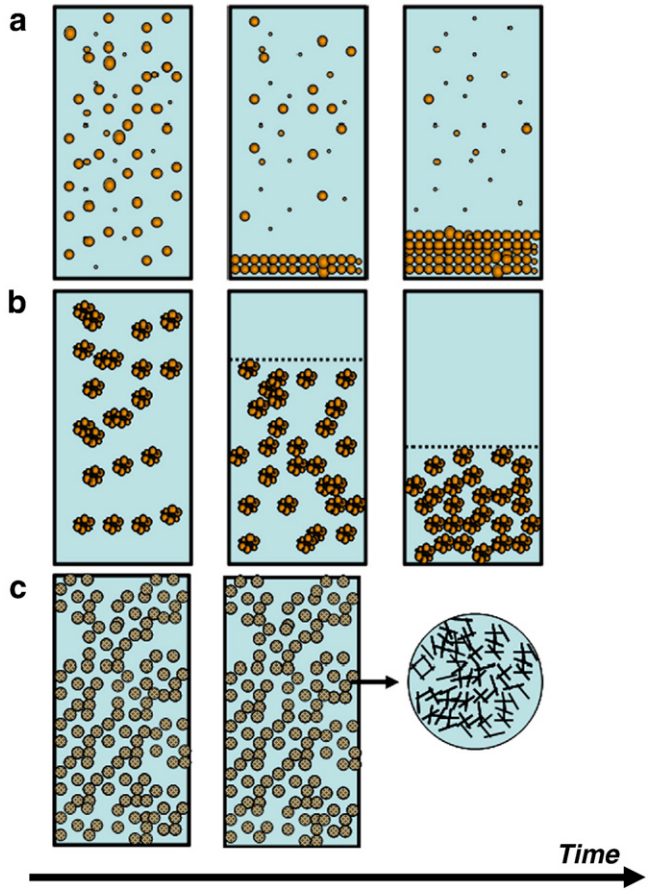

Fig. 1. Sedimentation in (a) deflocculated suspension; (b) flocculated suspension; and (c) open flocs-based suspension.

and plate shaped itraconazole nanoparticles with aspect ratios between 5 and 10 [40].

Although sedimentation is one of the key issues for colloidal suspension, the reported studies examining sedimentation issues in aqueous-based nanosuspensions are very scarce. This could be due to (i) surfactants are generally used in most of the nanosuspensions to inhibit particle agglomeration in the medium, which alleviates the sedimentation issues and (ii) the small nano-sized particles significantly reduce the sedimentation rate. In addition, many of the aqueous nanosuspensions are transformed to dry solid form by spray drying or freeze drying to circumvent the long-term sedimentation issue. Unfortunately, this solidification process cannot be applied to non-aqueous nanosuspensions where sedimentation/creaming is commonly present. An example to illustrate this is metered dose inhaler (MDI) formulations where the nanoparticles are suspended in HFA propellants. Sedimentation or creaming is a key aspect affecting stability of these formulations. Particle engineering to optimize particle surface properties and morphology, e.g. hollow porous particles [42], and introduction of surfactant(s) is generally employed to alleviate the issue.

2.2.2. Agglomeration

The large surface area of nanoparticles creates high total surface energy, which is thermodynamically unfavorable. Accordingly, the particles tend to agglomerate to minimize the surface energy. Agglomeration can cause a variety of issues for nanosuspensions including rapid settling/creaming, crystal growth and inconsistent dosing. The most common strategy to tackle this issue is to introduce considerations, selection of stabilizers is based on their ability to provide wetting to surface of the particles and offer a barrier to prevent nanoparticles from agglomeration [13,19].

There are two main mechanisms through which colloidal suspensions can be stabilized in both aqueous and non-aqueous medium, i.e. electrostatic repulsion and steric stabilization [10,36,37]. These two mechanisms can be achieved by adding ionic and non-ionic stabilizers into the medium, respectively. Stabilization from electrostatic repulsion can be described by the classic Derjaguin–Landau–Verwey–Overbeek (DLVO) theory [43,44]. This theory mainly applies to aqueous suspension while its application in non-aqueous medium is still not well-understood [33]. The DLVO theory assumes that the forces acting on the colloidal particles in a medium include repulsive electrostatic forces and attractive VDW forces. The repulsive forces are originated from the overlapping of electrical double layer (EDL) surrounding the particles in the medium, and thus preventing colloidal agglomeration. The EDL consist of two layers: (i) stern layer composed of counter ions attracted toward the particle surface to maintain electrical neutrality of the system and (ii) Gouy layer which is essentially a diffusion layer of ions (Fig. 2).

The total potential energy (V_T) of particle–particle interaction is a sum of repulsion potential (V_R) generated from electric double layers and attraction potential (V_A) from the VDW forces. V_A is determined by the Hamaker constant, particle size and inter-particulate distance while V_R depends on particle size, distance between the particles, zeta potential, ion concentration and dielectric constant of the medium. V_R is extremely sensitive to ion concentration in the medium. As the ion strength is increased in the medium, the thickness of EDL decreases due to screening of the surface charge [36,37]. This causes decrease in V_R, increasing the susceptibility of the dispersed particles to form aggregates. Zeta potential (ZP) is electric potential at the shear plane which is the boundary of the surrounding liquid layer attached to the moving particles in the medium. ZP is a key parameter widely used to predict suspension stability. The higher the ZP, the more stable the suspension is.

In the case of steric stabilization, amphiphilic non-ionic stabilizers are usually utilized to provide steric stabilization which is dominated by solvation effect. As the non-ionic stabilizers are introduced into nanosuspensions, they are absorbed onto the drug particles through an anchor segment that strongly interacts with the dispersed particles, while the other well-solvated tail segment extends into the bulk medium (Fig. 3).

As two colloidal particles approach each other, the stabilizing segments may interpenetrate, squeezing the bulk medium molecules out of the inter-particulate space as illustrated in Fig. 3. This interpenetration is thermodynamically disfavored when a good solvent is used as the bulk medium to stabilize the tail [36]. Accordingly, provided that the stabilizers can be absorbed onto the particle surface through the anchor segment, strong enthalpic interaction (good solvation) between the solvent and the stabilizing segment of the stabilizer is the key factor to achieve steric stabilization and prevent particles from agglomeration in the medium [36,37]. In addition to solvation, the stabilizing moiety needs to be sufficiently long and dense to maintain a steric barrier that is capable of minimizing particle–particle interaction to a level that the VDW attractive forces are less than the repulsive steric forces [43–45].

The main drawback associated with the steric stabilization is the constant need to tailor the anchoring tail according to the particular drug of interest. Due to the lack of fundamental understanding of interaction between the stabilizers and dispersed nanoparticles, current surfactant screening approaches to achieve a successful steric stabilization are mostly empirical and could be very burdensome [45–49]. In addition, the solvation of the stabilizing segment is susceptible to variation in temperature. Stabilizer concentration could also play a role in causing suspension instability by affecting the absorption

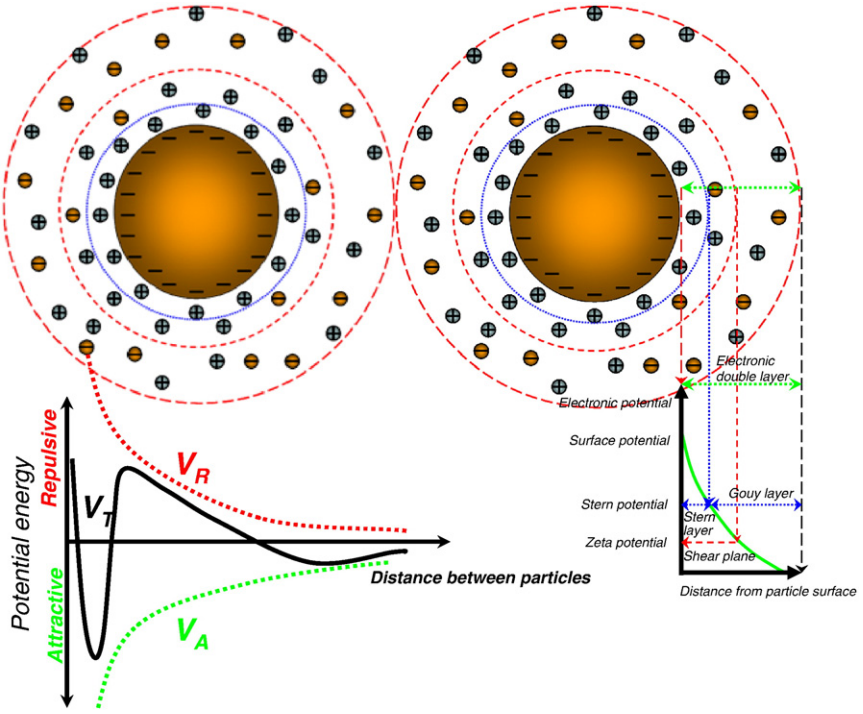

Fig. 2. Illustration of classical DLVO theory. Attractive forces are dominant at very small and large distances, leading to primary and secondary minimum, while repulsive forces are prevailing at intermediate distances and create net repulsion between the dispersed particles, thus preventing particle agglomeration.

[50] used Pluronic® F127 to stabilize paclitaxel nanosuspensions. It was reported that stabilizers had high affinity to nanocrystals surface at concentrations below critical micelle concentration (CMC), and increasing concentrations above CMC caused loss of F127 affinity to the nanocrystals and thus unstable formulation. This was because F127 monomers on the nanocrystals surface started to aggregate with each other to form micelles as the concentration was increased to the CMC level, leading to a lower affinity to the drug crystals. Temperature was also shown to affect the stabilizer affinity to drug crystals. This is expected since the CMC level is dependent on temperature.

It is apparent that combination of the two stabilization mechanisms can be very beneficial in achieving a stable colloidal dispersion. In addition, the combination of a non-ionic stabilizer with an ionic stabilizer reduces the self repulsion between the ionic surfactant molecules, leading to closer packing of the stabilizer molecules [10,51].

Besides the steric and electrostatic stabilization mechanisms, some other stabilization mechanisms have also been reported. Makhlof et al. produced indomethacin (IMC) nanocrystals using the emulsion solvent diffusion technique [52]. The nanoparticles were stabilized using various cyclodextrins (CyDs) without adding any surfactants. The stabilizing effect was attributed to the formation of a CyD network in the aqueous medium via intermolecular interaction of CyD molecules. The network-like structure was believed to prevent aggregation and crystal growth of IMC nanoparticles initially produced from the solvent diffusion process. Similar stabilization mechanism was also observed in another study where budesonide microsuspension was stabilized with hydroxypropyl-beta-cyclodextrin in HFA medium [53]. Another approach to enhance suspension stability that has increasingly been utilized is engineering of particle morphology. One breakthrough in this area was the porous particle

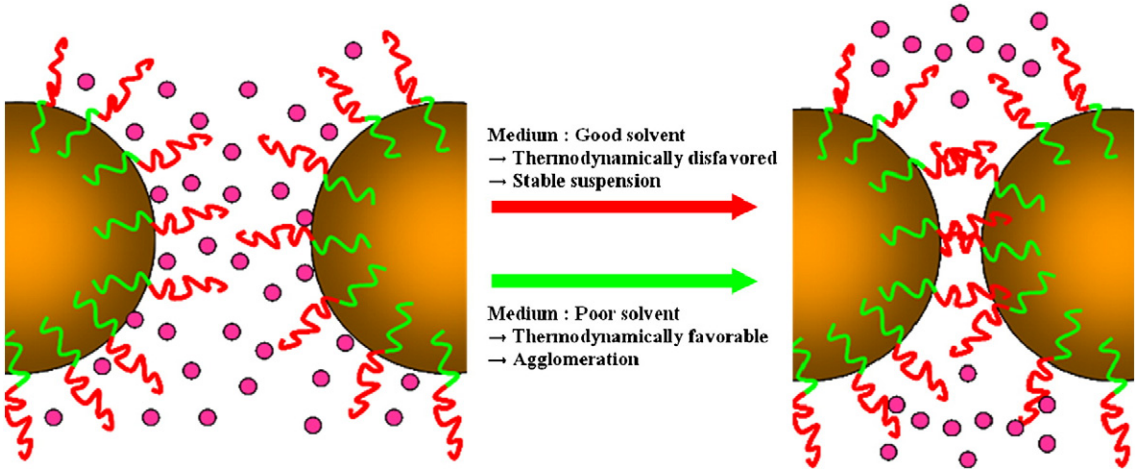

Fig. 3. Steric stabilization mechanisms according to Gibbs free energy: $\Delta G = \Delta H - T\Delta S$. A positive ΔG indicates stable suspension while negative ΔG induces particle agglomeration. If the medium is a good solvent for the stabilizing moiety, the adsorbed stabilizing layers on the dispersed particles cannot interpenetrate each other when the particles collide. This reduces the number of configurations available to the adsorbed stabilizing tails, resulting in a negative entropy change and positive ΔG. On the other hand, if the dispersion medium

concept that was first introduced by Edwards et al. [54]. The porous particles include hollow porous particle [42] and porous nanoparticle-aggregate particles (PNAPs) [14]. Unfortunately, most of the work has been focused on microsuspension or polymeric colloidal formulations and has not been applied to pure drug nanoparticles.

Table 1 summarizes a few published studies on pharmaceutical nanosuspensions. Due to the vast amount of literature work on the pharmaceutical nanosuspensions, this review will focus only on the studies that provide a more profound enlightenment on the stabilizer selection for nanosuspensions. The summary table shows that most of nanosuspensions were generated in aqueous medium, with only a limited number of nanosuspensions made in non-aqueous environment. The commonly used ionic stabilizers in aqueous medium include sodium dodecyl sulfate (SDS), sodium lauryl sulfate (SLS), lecithin and docusate sodium. The non-ionic surfactants used in aqueous medium are usually selected from Pluronic® surfactants, Tween 80, polyethylene glycol (PEG), polyvinyl alcohol (PVA) polyvinylpyrrolidone (PVP) and cellulose polymers such as hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC).

The stabilizers are not only used to provide short- and long-term storage stability for nanosuspensions, but also to achieve successful formation and stabilization of nanocrystals during particle production. Lee et al. designed and synthesized various amino acid copolymers containing lysine as the hydrophilic segments with alanine, phenylalanine or leucine as hydrophobic moieties [49]. Wet comminution was used to produce naproxen nanosuspensions in presence of HPC and amino acid copolymers. Lysine copolymer with alanine was unable to produce submicron particles while the other copolymers with phenylalanine and leucine were capable of forming the nanoparticles. The size of nanocrystals was proven to be constant over 1 month storage and the crystallinity was also shown to be preserved after the wet comminution process. Furthermore, hydrophobicity of the copolymers was identified as the key factor in achieving the stable nanosuspensions, attributed to strong polymer adsorption onto the hydrophobic drug surfaces. Although this work did not provide an in-depth discussion on how the copolymers interacted with the drug nanoparticles, it illustrated the importance of careful selection of the anchor group (that is attached to the drug surface) in facilitating the production of a stable nanosuspesion. In the subsequent study [45], they attempted to understand the nature of interactions between polymeric stabilizers and drugs with different surface energies. Nanocrystals of seven model drugs with PVP K30 and HPC as stabilizers were generated using wet comminution. It was expected that a close match of surface energy between the stabilizers and drug crystals would promote the absorption of stabilizers onto drug particles, and thus help in reducing the particle size during the wet comminution process. Although surface energy did not seem to correlate well with particle size for HPC stabilized system, some trend was observed for PVP stabilized suspension with only one exception.

A further study with seven stabilizers (non-ionic stabilizers: HPC, PVP K30, Pluronic® F127 & F68, PEG and ionic stabilizers: SDS and benzethoinum chloride) and eleven model drugs was conducted by the same group in order to provide more understanding on the stabilization mechanism [48]. Again, the general trend between surface energy and particle size reduction was not observed in this work. PEG was unsuccessful in reducing the particle size of most drug candidates while the other non-ionic stabilizers proved to be effective in reducing the size of five drug candidates that had similar surface energies to the stabilizers. F68 was shown to be the most effective stabilizer (successfully stabilizing nine drug candidates), which could be due to its strong chain adsorption onto the drug crystals through the hydrophobic polypropylene glycol (PPG) units. F127 was found to be less efficient than F68 likely because the short processing time led to inefficient physical adsorption of higher molecular weight F127 to the drug surface. This study demonstrated that a combination of ionic stabilization, A few combinations of SDS or benzethoinum chloride with various non-ionic stabilizers resulted in positive stability effects while the others did not. The effects of physicochemical properties of the drugs on the stabilization were also explored in this study. In general, drugs with lower aqueous solubility, higher molecular weight and higher melting point were shown to have higher chance for successful nanosuspension formation.

Van Eerdenbrugh et al. conducted an expanded study using 13 stabilizers at 3 different concentrations to stabilize 9 drug compounds [47]. The particles were generated using the wet milling technique. The success rate in producing nanosuspensions using polysaccharide based stabilizers [HPMC, methylcellulose (MC), hydroxyethylcellulose (HEC), HPC, carboxymethylcellulose sodium (NaCMC), alginic acid sodium (NaAlg)] was limited by the high viscosity of these polymeric stabilizer solutions. Increasing concentration of these stabilizers did not appear to be helpful. In contrast, the other stabilizers [PVP K30, PVP K90, PVA, Pluronic® F68, polyvinyl alcohol–polyethylene glycol graft copolymer (K-IR), Tween 80 and D-α-tocopherol polyethylene glycol 1000 succinate (TPGS)] did not encounter the viscosity issue. PVA was ineffective in producing the nanosuspension and the success probability of PVP K30, PVP K90, F68 and K-IR is highly dependent on their concentration. Higher concentrations (25 wt.% and 100 wt.%) increased the stabilizing efficacy significantly. Tween 80 and TGPS were proven to be the most effective stabilizers. Addition of TGPS (at concentrations >25 wt.%) allowed nanosuspension formation for all tested drug compounds. No correlation was observed between drug physicochemical properties (molecular weight, melting point, log p, solubility and density) and nanosuspension formation success rate. It was demonstrated that surface hydrophobicity of the drug candidates was the driving force for nanoparticles agglomeration, thus lowering the success rate of nanosuspension production.

Mishra et al. explored nanosuspension stability issues during both production and storage [29]. Hesperetin nanosuspensions were produced using HPH with Pluronic® F68, alkyl polyglycoside (Plantacare 2000) and inulin lauryl carbamate (Inutec SP1), or Tween 80 as stabilizers. It was demonstrated that all stabilizers were suitable for successful production of hesperetin nanosuspensions. The size of nanocrystals was dependent on power density applied in the homogenization process and the hardness of the crystals. The effect of stabilizers on the particle size was negligible. Short-term stability over a period of 30 days was examined in order to evaluate the stabilizer efficiency. ZP was measured as a key parameter to predict the stability. In distilled water, the ZP values of all the nanosuspensions fell between −30 and −50 mV and the values dropped significantly in the original dispersion medium. This can be explained by the fact that adsorbed layers of large molecules shifted the shear plane to a longer distance from the particle surface, thus reducing the measured value of zeta potential (Fig. 4). However, the low ZP value does not point to an unstable suspension in this case, which could be due to the additional presence of steric stabilization mechanism. Both Inutec and Plantacare stabilized nanosuspensions also showed significant reduction of ZP measured from water to dispersion medium, indicating a thick absorbed steric layer and good stability. F68 exhibited only slight decrease in ZP, indicating a relatively thin stabilization layer. The ZP value of Tween 80 was only −13 mv in the dispersion medium, pointing to a potentially problematic stabilization. The study demonstrated that zeta potential measurement is a good predictor for storage stability. Nanosuspensions stabilized by Inutec and Plantacare were stable at all storage conditions (4, 25 and 40 °C) up to 30 days while F68 stabilized nanosuspensions were shown to be less stable. The Tween 80 formulation stability was the poorest. Pardeike et al. [30] conducted a similar study using phospholipase A2 inhibitor PX-18 nanosuspensions produced by HPH with Tween 80 as stabilizer. In this work, ZP of

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