Nanoprecipitation and nanoformulation of polymers: from history to powerful possibilities beyond poly(lactic acid)

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Nanoprecipitation is a facile, mild, and low energy input process for the preparation of polymeric nanoparticles. Basic requirements, as well as common techniques for the self-assembly of non-charged and non-amphiphilic macromolecules into defined nanoparticles are described. At present, the primary focus of polymer nanoprecipitation research lays on poly(lactic acid) (PLA) and its copolymer poly(lactic-*co*-glycolic acid) (PLGA). This contribution thus emphasises on polymers beyond PLA systems, such as common industrial- or tailored lab-made polymers, and their ability to form well-defined, functional nanoparticles for a variety of applications now and in the past two centuries. Moreover, in combination with high-throughput devices such as microfluidics, pipetting robots, inkjet printers, and automated analytical instrumentation, the abilities of nanoprecipitation may broaden tremendously with significant effects on new applications.

1 Introduction

It is known that nanoparticles may possess extraordinary, often tunable properties dramatically different from their bulk material;[1–3] consequently, there is an enormous demand for tailor-made functional nanoparticle systems. Inorganic, organic, or hybride nanoparticular materials are used in various application fields such as medicine, pharmaceutics, analytics, catalysis, coatings, and several others. The production of such nanoparticle systems requires specific characteristics of the materials used. Essentially, the various nanoparticle preparation techniques can be sorted into two general categories. The first category involves the *in situ* reactive synthesis of nanoparticles, starting from solubilized small molecule precursors (*e.g.* preparation of gold nanoparticles, emulsion polymerization techniques). In the second category, the shaping of the bulk material into nanostructures (*e.g.* nanoprecipitation, emulsion/solvent diffusion technique, spray drying, salting out, milling processes) yields nanoparticles based on low as well as high molar mass compounds. In this context, polymeric nanoparticles represent particularly rich opportunities to tune and control the outcome of the nanoparticle materials, since they can be processed with

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various functionalities as well as characteristics and can thus cover broad application fields. A detailed overview on methods available for the preparation of polymeric nanoparticles is provided by Lassalle and Ferreira on the example of poly(lactic acid) (PLA), a well established polymer for drug delivery systems.[4]

The term nanoprecipitation refers to a quite simple processing method for the fabrication of polymeric nanoparticles. Generally, the method describes the precipitation of a dissolved material as nanoscale particle after exposure to a non-solvent that is miscible with the solvent. In contrast, the emulsion/solvent diffusion technique uses partially miscible solvents.[5]

While the nomenclature is still of a relatively recent vintage, the application of polymer nanoprecipitation as a processing technique has a considerably longer history. In fact, the utility of nanoprecipitation was recognized far earlier than the concept of nanotechnology.[6] Generally speaking, the application of nanoprecipitation can be divided into two broad categories: (a) applications where nanoprecipitation is used as a formulation technique for preparing multicomponent, value-added dispersions as the desired end-product, and (b) applications where nanoprecipitation is used as intermediate step of polymer processing.

Well over a century ago, the diverse ingenuity of nanoprecipitation was beginning to be revealed, based on natural polymers. The creativity of these early polymer nanoprecipitation investigators is reflected in the broad scope of the materials science addressed in the patents of the time. Guttapercha-derived varnish formulations,[7] artificial ivory,[8] waterproofing materials from milkweed pulp,[9] and stabilizing pigments used in marine paints[10] were all examples of patented nanoprecipitated polymeric systems from the later half of the 19th century. In one of the first health-related applications, colloids of natural rubber were proposed as an antidote to strychnine poisoning (at least as demonstrated in frogs).[11] As part of this very early work on colloids, the future Nobel laureate Theodor Svedberg published a patent for the colloids of clinically important excipients such as mastic (arabic gum) already in 1909.[12]

Running roughly in parallel with these nanoprecipitated end-product-driven systems, researchers were also investigating nanoprecipitation as a processing tool for polymers—both as a means for preparing useful industrial intermediates, as well as a basic research tool. Already as early as 1862, nanoprecipitation was used as a tool to investigate the composition of the resins obtained from the Port Jackson Fig (*Ficus rubiginosa*).[13] This approach to purify and refine natural elastomers is later revisited in numerous industrial applications, such as gutta percha,[14] in reconverting vulcanized rubber waste material,[15,16] and in improving the bleaching and purification process for natural rubber.[14] This role as a tool for polymer processing would remain the focus of nanoprecipitation for decades to come.[17,18]

The level of interest in nanoprecipitation waned for some decades, and the method regained recognition in the 50's as a means of preparing colloids for stabilizing pigments,[19,20] as well as industrially important components in paints, lacquers, and other coatings.[21]

While it had already been reported at least as early as the 1940's as a way for isolation of purified analytical samples of synthetic polymers,[22–24] nanoprecipitation regained a heightened level of patent interest in the 1950's and 60's—this time as a cost effective tool for purifying synthetic polyolefins.[25–27] One of the challenges of *in situ* synthesis of polyolefins on an industrial scale is the isolation of the pure polymer afterwards from the solvent; while these could be stripped off using pressurized steam, considerable heating, and/or the application of a vacuum, by simply crashing out the polymer with a miscible non-solvent, the polymer could be acquired as a purified powder, in a simple, low-energy process.

In the late 80's and early 90's, Fessi *et al.* patented the nanoprecipitation technique as a process for the preparation of dispersible colloidal systems of a polymeric substance in the form of nanoparticles.[28,29] The technique is also known as solvent diffusion, solvent shifting, and diafiltration method, and is in this context commonly applied to polymeric systems. The precipitation is claimed to work with basically all solvents that are sufficiently volatile in a polymer concentration range from 0.1 and 10%. In contrast to low molar mass compounds, surfactants for the stabilization of the nanoparticle suspensions are generally not necessary.

In the recent literature, the majority of the reported polymer systems that are formed into nanoparticles *via* nanoprecipitation is based on block copolymers since these systems usually possess amphiphilic character and form a core–shell structure due to their micelle-like behavior.[30] The appeal to nanoprecipitation of amphiphilic block copolymers is that the size of the driving force controlling assembly of the nanoparticles is a direct function of the size of the phase separation of the blocks, and can be reasonably predicted *a priori*; the size and morphology of the nanoparticles can be controlled by tuning the block lengths. Various systems contain hydrophobic polymer units and poly(ethylene glycol) as hydrophilic segment, leading to di-, tri-, or higher polyblock copolymers. Such amphiliphic carriers were already successfully applied to deliver hydrophobic drugs such as doxorubicin,[31] clomazepam,[32] and adriamycine,[33] or to encapsulate pharmaceutically relevant proteins.[34] A further class of

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polymers undergoing nanoprecipitation are charged macromolecules that are able to form complexes in the nanoscale range, so called polyplexes, with oppositely charged molecules such as genes and proteins.[35] Efficient gene delivery systems, based on *e.g.* poly(ethylene imines), diethylamino ethyl (DEAE) dextran, or poly(lysine), were already developed and are under consideration for *in vivo* studies.[36] Less prominent examples for gene therapy materials prepared by nanoprecipitation are so-called proticles, *i.e.* protamine–oligonucleotide complexes.[37,38] Drug conjugates can also be formed by polyplex formation as demonstrated for ibuprofen and DEAE dextran.[39]

In contrast to this, polymer systems having no classical amphiphilicity and a neutral charge can also be processed into nanoparticles *via* nanoprecipitation. The most prominent examples are PLA and poly(lactic-*co*-glycolic acid) (PLGA) that are used as biocompatible nanocontainer materials in drug delivery devices.[40–43] Poly(ε-caprolactone) (PCL) as an alternative biocompatible and biodegradable polyester is also known to form nanoparticles during nanoprecipitation while efficiently incorporating cosmetics-related lipophilic molecules,[44] drugs,[45–47] or pesticides.[48]

Recent developments and general findings in understanding and improving the nanoprecipitation technique of the mentioned polyesters will shortly be discussed. However, this contribution will focus on polymer systems beyond PLA, PLGA, and PCL that are also transformable into nanoparticles and show interesting and useful functionalities for various applications.

2 Theoretical background, the "ouzo effect", and processing parameters

Nanoparticle formation *via* nanoprecipitation is assumed to be due to the nucleation of small aggregates of macromolecules followed by aggregation of these nuclei. The aggregation stops as soon as the colloidal stability is reached. A theory describing the nucleation in supersaturated solutions into nanodispersions is proposed by Lamer.[49] The resulting size at the end of aggregation is strongly correlated with the polymer concentration and, consequently, the viscosity of the solution.[50] The viscosity should be sufficiently low to suppress entanglements between the polymer chains, which, when present, are sufficient to fail the creation of nanoparticles.[51] Moreover, the character of the polymer is responsible to prevent the growth of the nanoparticles through Ostwald ripening, otherwise, stabilizing agents need to be added.[50] Since the total amount of polymer is distributed homogeneously throughout the solution during nanoprecipitation, the preferred shape of the particles is a sphere.

The concentration, where the polymer solution is sufficiently dilute to be metastable resulting in nucleation of the polymers, is the so-called "ouzo" region. This effect is named by the Greek aperitif that becomes cloudy by spontaneous emulsification of water and anethole.[51] Besides nanoprecipitation, in terms of polymer chemistry, such a spontaneous emulsification can also be used for polymerization techniques to form polymeric nanoparticles[52] or to generate oligomers for postcondensation into nanocapsules.[51] In all cases, the hydrophobic substance becomes greatly supersaturated upon addition of a hydrophilic substance, which results in the formation of small aggregates or droplets. This concept is not limited to polymers but can also be used for the preparation of lower molar mass substances such as β-carotene or oils.[53]

A phase diagram for the PCL particle formation in acetone/water (solvent/non-solvent) shows the limited regions where the "ouzo" effect and, thus, nanoprecipitation is possible (Fig. 1).[54] Metastable dispersions can only be generated between the spinodal and the binodal curves. Zone BI indicates the "ouzo" region where nanoparticles can be obtained. Zones BII and BIII represent flocculation and dissolution of the PCL, respectively, whereas in region A the polymer is not completely dissolved in acetone. The diagram further evidences that the maximum polymer concentration of the "ouzo" boundary decreased exponentially with the solvent/non-solvent ratio.

Due to the fact that the diffusion coefficient of the solvents needs to be sufficient to produce spontaneous emulsification, and thus nucleation, the dielectric constants ε of the solvents are also involved in finding the optimal processing conditions for uniformly sized nanoparticles.[55] As a typical example, the effect of the type of solvent/non-solvent can be described for PLA/PLGA. A general finding is that solvents with lower dielectric constants result in larger particles. However, the combination of solvent/non-solvent seems to have an even greater influence on the diffusion rate and, thus, on the particle size. The affinity of the solvent for the non-solvent is of importance and can be described with the interaction parameter, χ.[55] For this, the Hildebrand solubility parameters for the solvent (δ_s) and non-solvent (δ_{ns}) and the molar volume of the solvent (V_{ns}) need to be known: $\chi = V_{ns} \cdot (\delta_s - \delta_{ns})^2/RT$. A plot of χ over particle size shows that the higher the interaction parameter, the larger are the particles. The interaction between the solvent and the polymer itself also needs to be considered. It is claimed that a high affinity between the solvent and the polymers leads to a higher concentration of solvent remaining in the supersaturated polymer region. The solvent motion to the non-solvent is hampered, resulting in smaller particle sizes. In general, polar and aprotic solvents show this behavior, therefore, they are promising solvents for applications such as the nanoencapsulation of peptides or proteins. In addition, DMSO is the solvent of choice in terms of protein stability and solubility.

From the processing point of view, there are basically two different routes to manufacture polymeric nanoparticles *via* nanoprecipitation, namely the dialysis and the dropping

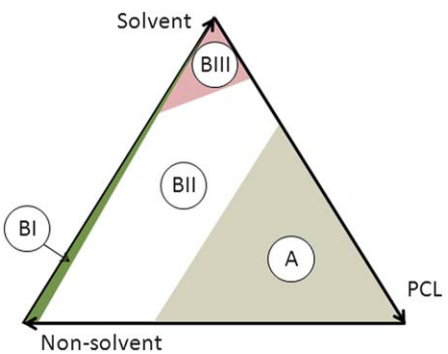

Fig. 1 Ternary phase diagram of PCL in acetone/water (solvent/non-solvent) showing the domain of nanoprecipitation (BI), of flocculation (BII), of dissolution of PCL (BIII), and of insolubility of (A). Redrawn from ref. 54.

technique, as illustrated in Fig. 2.[56] The use of a dialysis membrane is advantageous to ensure a complete exchange of the polymer solvent against the non-solvent, where the choice of solvent is only limited to the membrane characteristics and, of course, the miscibility with the non-solvent. However, this process is comparatively time-consuming, and may not be used for less stable particle systems. The dropwise addition of the polymer solution to the non-solvent and *vice versa* is usually applied when using comparatively volatile solvents that allow the easy evaporation (also at higher temperatures) leading to pure nanoparticle suspensions. The course of the preparation, *i.e.* the manner of diffusion, strongly influences the size of the particles.[57] In general for all techniques, the choice of solvent and non-solvent, the quality of the solvents (pH, salt concentrations),[58] and the polymer concentration have an important impact on the resulting particle suspensions.[55]

3 Advantages and limitations of nanoprecipitation

Because of the fact that no external energy input is essential for the nanoparticle formation (*e.g.* no required high shearing homogenization, milling, or sonication), nanoprecipitation can be regarded as a mild and sensitive procedure, with modest equipment requirements and low energy costs.[50] In contrast to emulsion/solvent diffusion, no surfactants are necessary that might influence the surface characteristics or cause toxic effects. Moreover, a broad variety of benign solvents, such as DMSO or acetone, can be used. The use of already prepared polymers ensures the quality of the nanospheres without any residual monomers that might be present using emulsion polymerization techniques. The size and shape of the particles can only hardly be predicted but it is comparatively easy to influence the particle formation by changing concentration, solvent/non-solvent, and preparation technique.

In contrast to emulsion/solvent evaporation, which usually involves the use of highly volatile organic solvents such as dichloromethane or hexane, nanoprecipiation may also utilize non-volatile solvents, *i.e.* solvents that are not easily removable only by stirring or evaporation assisted with gentle heating, such as DMSO, DMA, DMF, 2-pyrrolidone, or NMP. In such cases, the solvents need to be removed carefully, which can be a challenging task in particular for high polymer–solvent affinities. Problems may arise if substances that possess a similar polarity such as the polymer need to be embedded into the nanoparticle. In general, water soluble drugs are usually poorly incorporated into the polymer matrix, however, there are also some attempts to entrap hydrophilic drugs efficiently into nanoparticles by changing the pH value (*e.g.* for procaine hydrochloride encapsulation)[59] or by choosing the appropriate type of solvent/non-solvent (*e.g.*, polar and aprotic solvents for protein encapsulation).[60]

4 PLA, PLGA, and PCL particles

Although originally invented for a broad variety of polymers, nanoprecipitation is up to now mainly applied for the biodegradable polyesters PLA, PLGA, and PCL in drug delivery systems for research and industrial applications. Many reviews were published in the last years demonstrating the enormous potential of the polyesters as gene- and drug delivery systems.[4,48,61] It could be shown that PLA/PLGA particles *in vitro* and *in vivo* can escape from the endo-lysosomal compartments during the cellular uptake into the cytosol while releasing the therapeutic agents. Various hydrophobic as well as hydrophilic drugs can be efficiently encapsulated into the polymer matrix resulting in nanoparticles that release their payload slowly over time.[62] The release kinetics strongly depend on the drug itself and the processing parameters. In this way, hydrophobic drugs such as clonazepam, paclitaxel, cyclosporin A, indomethacin, valproic acid, ketoprofen, digitoxin, cyclosporine, risperidone, tamoxifen,[45–47,63,64] but also hydrophilic payloads, *e.g.* insulin, vancomycin, phenobarbital, peptides, or proteins, only to mention a few, can be immobilized in the polyester matrix.[65–68] Nanoprecipitation is also advantageous for protein immobilization by adsorption on the particle surfaces, since no surfactants are present that might otherwise inhibit or affect the adsorption.[69] Even dendritic cells loaded with HIV-1 p24 proteins were shown to adsorb onto PLA nanoparticles that later induce an enhanced cellular immune response against HIV-1 after vaccination.[70]

For the encapsulation of therapeutic genes into polymeric carriers *via* nanoprecipitation of uncharged material, a pre-complexation of the DNA or RNA, *e.g.* with dioleoyl trimethylammonium propane (DOTAP), is essential in order to ensure

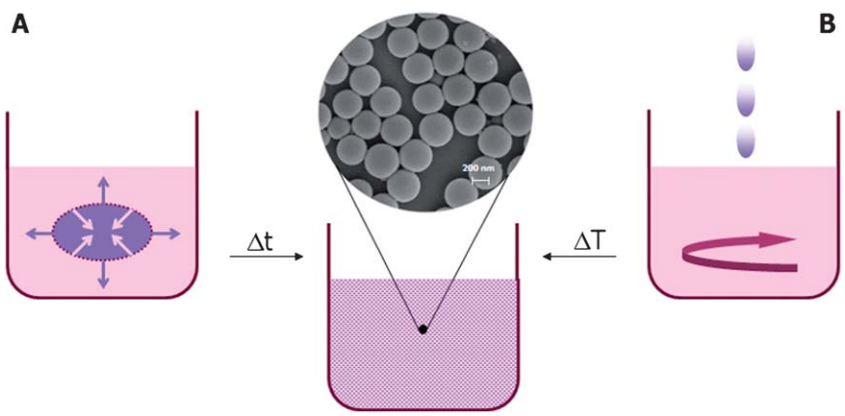

Fig. 2 Schematic representation of the preparation of nanoparticles *via* nanoprecipitation applying dialysis in a membrane (A) and dropping technique under stirring (B), respectively. Reproduced from ref. 56.

their solubility in organic solvents and to enhance the encapsulation efficiency due to the more hydrophobic character. PLGA particles coated with chitosan show an even higher gene loading efficiency and a prolonged release profile.[71]

5 Other polymer systems

Comparing to nanoprecipitation of biodegradable synthetic polyesters (shortly discussed in section 4) with over 80 publications in the last 2 years alone, there are only few examples showing the use of nanoprecipitation as the method of choice for nanoparticle formation of other polymers. Such a development is remarkable due to the fact that the patent from Fessi *et al.* in 1989 covers a wide range of polymers, not only PLA, PLGA, and PCL, but also other lactones and cellulose ethers and -esters (cellulose butyrate acetate, ethylcellulose, hydroxymethylpropylcellulose phthalate, cellulose acetophthalate), naturally occurring polymers (gelatin, arabic gum), poly(vinyl alcohol acetophthalate), copolymers of acrylate and methacrylate (EUDRAGIT®), poly(vinylpyrrolidone-vinyl acetate), maleic acid derivatives, and a few more.[28] However, in spite of this structural versatility, the different categories remain comparatively unexplored with respect to their development of functional nanoparticles.

The usage of polymeric nanoparticles for biological applications requires appreciable biocompatibility; as a consequence, polysaccharides are promising polymers for drug delivery- and sensing devices. For example, pullulan acetate is functionalized with folic acid to improve the cancer-targeting activity and loaded with epirubicin as cytotoxic agent for pharmaceutic applications.[72] A further possibility is the use of vitamin H as cancer cell targeting.[73] The hydrophobic character of the polymers allows the formation of regular nanospheres that all show specific interaction with cancer cell lines.

Another class of nanoparticles based on polysaccharides are functionalized dextrans. A broad range of functionalities could be attached by simple alkylation or esterification in order to tune the hydrophobicity[74,75] or to attach, *e.g.*, cross-linkable substituents,[76] drugs (ibuprofen, naproxen),[77] and photoactive groups.[78] The labeling of hydrophobic dextran acetate with different fluorescent dyes and subsequent nanoprecipitation in the desired ratio of the polymers leads to nanosensors that can be used for ratiometric pH measurements *in vitro*.[79] Besides the bacterially produced polysaccharides, modified plant polysaccharides such as cellulose acetate or starch acetate are also able to self-assemble during nanoprecipitation.[57,80] In order to encapsulate fragrances such as camphor, eucalyptol, menthol, or limonene, a blend of ethylcellulose, hydroxypropylcellulose, and poly(vinylalcohol), which is dissolved in ethanol containing the ingredients, is dialyzed against water.[81] Pure cellulose nanoparticles can be achieved from trimethylsilyl cellulose due to spontaneous hydrolysis of the ether functionalities during dialysis in *N*,*N*-dimethylacetamide (DMA) against water.[82] The wood component xylan is also transformable into nanospheres, whereas the hydrophobicity of the resulting xylan-drug conjugates is claimed to be tunable by introducing sulfate groups.[83] Guar gum as alternative biopolymer is shown to form nanoparticles that bear lipase and model dyes, however, surfactants and crosslinkers are essential to encapsulate the payload.[84]

The formation of nanoparticles *via* nanoprecipitation is also known for a broad variety of synthetic polymers. Poly(methyl methacrylates), such as EUDRAGIT®, form well-defined nanoparticle suspensions from acetone, ethanol, DMA, or THF solutions and are able to entrap ibuprofen, indomethacin, and propranolol.[50,85,86] Also other completely hydrophobic polymers (poly(styrene) (PS), poly(vinyl carbazole), poly(styrene-*co*-acrylic acid), poly(vinyl acetate), poly(carbonate)) that are synthesised on industrial scale self-assemble during the defined precipitation process applying different solvents and techniques. However, up to now there are no applications reported.[56] Controlled and living polymerization techniques were used to fabricate tailor-made polymers with defined molar mass, low polydispersity indices, and versatile functionalities. In this manner, nanoparticular glucopolymers were produced by a combination of nitroxide-mediated polymerization (NMP) and "click" chemistry to attach glucose functionalities on the poly(pentafluorostyrene) backbone.[87] Potential biocompatible, nanoscale sensor systems are available by living cationic polymerization resulting in poly(oxazoline)s bearing combinations of dyes and ene-functionalities for thiol–ene "click" reactions.[88]

A different approach is the use of nanoprecipitation for controlled polymerizations. In this way, polymeric nanoparticles are formed *in situ* while precipitating during polymerization, however, only with the aid of surfactants.[52]

6 Modern technology platforms

A central challenge in the development of polymeric nanoparticles for drug delivery applications or sensor materials is the difficulty to control the mixing processes during nanoprecipitation and, thus, to regulate dimensions and physicochemical properties of the nanoparticles with good accuracy.[89] Indeed, there are several attempts to keep the conditions as constant as possible such as a continuity of mixing and dropping speed or the choice of the dialysis membrane. In its most facile format, polymer nanoprecipitation can consist of manually dispensing a polymer solution into a miscible nonsolvent—as simple as pipetting one liquid into another. For certain on–off, qualitative experiments, this may be more than sufficient, and there is little sense in seeking out more complex experiment designs when they are unnecessary. While this is an attractive prospect in terms of simplicity and cost of investment, there are some practical limitations in terms of process reproducibility, the rate of addition, the presence or absence of mixing, and a host of other basic parameters, which can affect the morphology of the resulting nanoparticles.[90–93] As a consequence, the lack of control over these basic variables means that there is ample opportunity for imparting a significant amount of operator variability. Moreover, when exploring even modest materials spaces involving a few hundred samples, this variability between samples is amplified. Thus, automatically controlled devices are advantageous and guarantee a good control over processing parameters while following a high-throughput (HT) approach. This may facilitate the development and optimization of polymeric nanoparticles enormously.

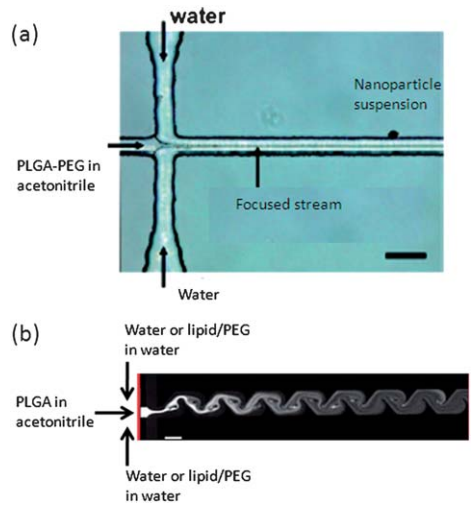

Fig. 3 Nanoprecipitation by hydrodynamic flow focusing using a microfluidic device for the preparation of nanoparticle suspensions. (a) Photography of the mixing and precipitation process of PLGA–PEG (scale bar 50 μm),[89] and (b) multifluidic rapid mixing of PLGA and lipids forming multicompartment nanoparticles (scale bar 100 μm).[94]

6.1 Microfluidics

The microfluidic platform provides a promising tool for the controlled synthesis of polymeric nanoparticles. The hydrodynamic flow ensures a rapid and well tunable mixing of solvent/non-solvent in the microfluidic channels.[89] The concept was first shown for a PLGA-*b*-PEG copolymer in acetonitrile/water (Fig. 3a). By varying flow rates, polymer composition, and polymer concentration, it is possible to optimize the size and polydispersity, and to control the drug loading and release of the resulting nanoparticles. The mixing process can be further optimized by minimizing the mixing time to provide a homogeneous environment for the growth of nanoparticles.[94] For this purpose, micromixing structures can be applied in the microfluidic devices. A micromixing structure that contributes from both diffusion and convection at high flow rates is the in-plane Tesla mixer. By using such a device, the formation of pure PLGA particles and multicompartment particles consisting of PLGA/lipid with or without PEG is demonstrated in Fig. 3b. Though showing the precipitation of accustomed biodegradable homo- and copolymers, the concept of using microdevice technologies can easily be adopted for alternative, hydrophobic polymers and the high definition screening thereof.

6.2 Pipetting robot

For large numbers of samples, or where precise processing conditions are needed, a certain amount of automation is inevitably required. One of the recent developments in this high-throughput (HT) preparation and screening is the concept of the 'nanoformulator',[95] where devices such as pipetting robots are employed for the purpose of nanoprecipitation. Automation of routine tasks has been a transformative development in lab work elsewhere,[96,97] but the advent of automation to nanoprecipitation work is surprisingly recent. Pipetting robots were one of the earliest developments in laboratory automation and have become ubiquitous in clinical settings, where the dispensing of liquids in microlitre quantities in a highly reproducible way is critical to the quality of the data. Moreover, a traceable, digital record of the processing conditions under which the formulation was prepared is provided.

As an illustrative example, a pipetting robot has recently been used to study the formation of nanoparticles (EUDRAGIT® S100) by polymeric nanoprecipitation (Fig. 4).[98] Like many other high-throughput laboratory tools, the default experiment layout of the robot is preset to handle the Society for Biomolecular Screening (SBS) formatted 96-well and 384-well plates, meaning that the resulting samples are readily amenable to downstream HT screening. Moreover, in order to handle a broad range of fluids with different physical properties such as different viscosities and surface tensions, the pipetting settings can be adjusted in terms of push-out speed, aspiration speed, mixing settings, premotion pauses, *etc.* With control over these variables, one can further explore formulation–process–property relationships more deeply and thoroughly. The characterization of the particle suspensions can be performed subsequently using spectroscopic and dynamic light scattering plate readers. Another possibility is the use of inkjet dispensers to microdispense the solutions in the desired manner.[99]

7 Conclusion

Nanoprecipitation provides a facile, mild, and low energy consuming method to prepare polymeric nanoparticle suspensions. Parameters influencing the particle formation are discussed as well as advantages but also disadvantages over other

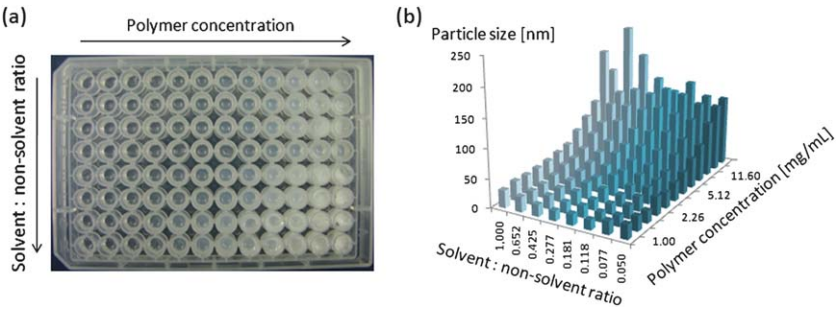

Fig. 4 Automated pipetting robot used for the nanoprecipitation of EUDRAGIT® S100 from acetone in water resulting (a) in nanoparticle formulations deposited in a 96 well plate that can be analyzed using a DLS plate reader for (b) particle size analysis.[98]

methods to prepare polymeric nanoparticles. However, up to now the formulation of PLA and PLGA based particles is in the main focus of research for diverse applications. The minor knowledge about the self-assembly of other synthetic polymers requires a clarification to allow a generic application of such a facile technique to a wide range of polymers. This contribution provides an overview about alternative polymer systems that are able to form nanoparticles *via* nanoprecipitation in order to open the scope for unconventional, multifunctional polymers to be shaped into nanoparticles. It seems that almost each hydrophobic polymer may be able to precipitate in the nanoscale applying the appropriate conditions. Moreover, methods are described to transform the simple dropping or dialysis processes into industrially more relevant testing devices for continuous repetition of the formulation (microfluidics) and high-throughput experimentation (pipetting robot, inkjet printing).

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