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Short Communication. Nanotechnology

EFFECTS OF ANTI-SOLVENT FLOW RATE IN THE MICROFLUIDIC PREPARATION OF NANOPARTICLE FOR BIOMEDICINE APPLICATION

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ABSTRACT Microfluidic technology, as a new and efficient method, can be used to provide nanomaterials in biomedical applications and to evaluate the crystallization process for the generation of nanoparticles. In crystallization approach using anti-solvent flow, can precisely control the physical properties of the nanoparticles obtained, including particle size, polydispersity index (PDI), stability and encapsulation efficiency. This operating and convenient method has led to an increase in the researchers' attention to nanoparticle manufacturing in this method for pharmaceutical and medical applications. In the current short communication, effects of anti-solvent flow rate as an important parameter in crystallization using microfluidic devices is presented on the particle size, PDI and stability of nanoparticle intended for biomedical applications.

KEYWORDS : Anti-solvent; Microfluidic: Nanoparticle; Size; PDI; Stability.

INTRODUCTION

The Laminar patterns observed in microfluidic channels lead to the controlled diffusion of the molecules across the interface of flows. In the past decade, the microfluidic devices have been expanded to create nanoparticles by controlling the nucleation and growing crystals in solution that starts at the molecular level. Microfluidic approach as a bottom-up preparation method can help to overcome limitations in the traditional preparations for the generation of nanoparticles under controlled reactions of interface (1, 2). Microfluidics have been developed to product monodispersed nanoparticles with homogenous reaction environment and improved reproducibility. In microfluidic devices, solvent and anti-solvent solutions flow in the channels with a diameter of 100 microns to 1 mm. The ability of this system to manipulate liquids at the micro/nano scale and variation in reaction conditions continuously, makes it attractive for nanoparticle synthesis. In this method, the effects of independent parameters including the solvent flow rate, solvent temperature and anti-solvent flow rate on sedimentation time, particle size, PDI, and entrapment efficiency were studied and compared (3-5). Previous studies were reported to prepare nanocrystals, micro- and nano-emulsions, polymeric and metal nanoparticles, liposomes and SLNs (6). In the microfluidic channel, the flow of liquids is laminar and a diffusion interface forms in the central part of the channel. In diffusion interface (diffusion layer), the molecules dissolved in the solvent diffuse to anti-solvent flow and begin to nucleation and grow in size. Also, growth and precipitation rate of created nuclei can be controlled by the use of surfactants or polymers at anti-solvent (7). The aim of current short communication is to inform the reader for the effects of the variables in the microfluidic preparation of nanoparticle, in particular the anti-solvent parameter, on the size, PDI and stability. Here, recent studies carried out by this group on the evaluation of microfluidic preparation parameters in nanosuspension with an emphasis on anti-solvent flow as the most important parameter, are presented (7-9). The effects of anti-solvent flow in the preparation of nanosuspensions using microfluidics are similar to others work on the preparation of nano- and micro-emulsions, and polymeric and lipid nanoparticles using this method (3, 6, 10-12).

Preparation of nanoparticle in a Y-junction microfluidic channel

Microfluidic channel with continuous flow was used in the studies to create rapid mixing/nanoprecipitation using a solvent-miscible antisolvent liquid towards a solvent solution. This nanoprecipitation process results in the production of small nanoparticles (10~100 nm) and polydispersity index in the range of 0.1 to 0.4. Nanoprecipitation in channel was carried out with flow of saturated solution of drug as solvent and flow of anti-solvent which was pumped through microfluidic channel. Details of the channels have been given previously (7). Hydrodynamic micropumps were set at a special flow rates to inject the solvent solution (0.5-1 ml/min; at predetermined temperatures (30-80 °C)) and anti-solvent solution (0.5-2.5 ml/min; at a controlled lab temperature (24±2 °C)) into the Y-junction microfluidic channel. Different concentrations of Tween 80 as surfactant (10-270 mg/ml) were used at the anti-solvent solution. At final stage, supersaturation is created with rapid diffusion of the drug molecules into anti-solvent flow and production of nanoparticles with nucleation/growth (see Fig. 1).

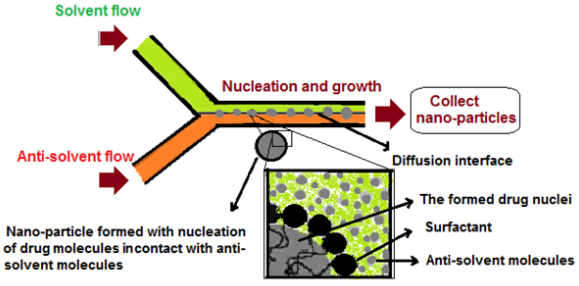

Figure 1. A schematic of the anti-solvent precipitation process in Y-junction microfluidic channel.

RESULTS AND DISCUSSION

Our previous studies demonstrated the ability of the Y-junction microfluidic channel in the nanoprecipitation of acetaminophen and stable-iodine (127I) molecules. In these studies, we evaluated the effects of microfluidic preparation input parameters (i.e., solvent temperature, solvent and antisolvent flow rate and concentration of surfactant) on the output parameter(s) (i.e., particle size, PDI and sedimentation time (related to physical stability)) of acetaminophen and stable-iodine (127I) nanosuspensions. Also, considering the complicated and non-linear relationships between the input parameters and the output parameter(s), we used the artificial neural networks (ANNs) software (INForm V4.02, Intelligensys, UK) to study and predict these relationships. For this purpose, the effect of two input parameters on the output parameter was shown using 3D graphs provided by the software, while the other parameters were fixed at certain values of low, mid-range and high (7-9).

According to studies, it was found that parameters including the anti-solvent flow rate, solvent temperature and solvent flow rate are related to the physical stability, particle size and polydispersity index of the nanosuspension obtained through anti-solvent

precipitation in microfluidic channel.

In a study on the preparation and optimization of acetaminophen nanosuspension through nanoprecipitation using microfluidic devices (7), it was shown that antisolvent flow rate and solvent temperature had a direct relationship with sedimentation time (i.e., physical stability), while solvent flow rate had a reverse relationship with the sedimentation time. Also, It was determined that in order to obtain an optimal sample (i.e., a sample with maximum stability), it is necessary to adjust the anti-solvent flow rate, solvent temperature and surfactant concentration at the highest value. In fact, when the anti-solvent flow rate increases, it leads to a decrease in the PDI of nanosuspension and a narrow particle size distribution. Consequently, the physical stability of nanosuspension increases due to the lack of Ostwald ripening. In addition, by increasing the solvent temperature, the diffusion rate of the drug molecules into the anti-solvent flow per unit volume of antisolvent will be increased, resulting in formation of more drug nuclei. As a result, more homogenous dispersions will be created for higher solvent temperatures, which results in the higher physical stability in the nanosuspension.

In a study on the controller factors of polydispersity index (PDI) in the acetaminophen nanosuspension prepared using microfluidic channel (8), ANNs modeling 3D-graphs were used to evaluate the interactions between the input parameters and the output parameter (i.e., PDI). In this work, comparing the 3D-graphs indicated that the anti-solvent flow rate and the solvent temperature had a reverse effect on the PDI, while solvent flow rate had a direct relationship with PDI. Also, it was found that generally, the surfactant concentration had a reverse relationship but less influential on the PDI. In general, it was determined that a sample with minimum PDI can be created at the high values of anti-solvent flow rate and solvent temperature against a low value of solvent flow rate.

Considering the effect of anti-solvent and solvent flow rate, it can be stated that increasing the anti-solvent flow rate leads to the smaller PDI which is in agreement with our previous study. In fact, increasing the anti-solvent flow rate results in the fewer diffusion of drug molecules to the anti-solvent flow per unit volume of antisolvent. Consequently, the drug molecules around growing drug nuclei will decrease. As a result, a sample of nanosuspension with a fewer value of PDI will be obtained. Also, a reason for this can be the formation of more nucleation sites per unit volume of antisolvent, as explained above. Therefore, the fewer drug molecules will precipitate per nucleation site that causes a more homogeneous distribution for the particle size (less PDI). In this study, an increase in the anti-solvent flow rate promoted the effect of surfactant concentration on the PDI. This is because the surfactant was dissolved in anti-solvent (i.e., water) in this study. Therefore, with increasing anti-solvent flow rate, more surfactant molecules enter the microfluidic channel. Consequently, the concentration of surfactant in the final sample is increased and leads to a more monodispersed sample (i.e., less PDI).

Overall, this study showed that the anti-solvent flow rate and solvent temperature are the dominant factors that influence the distribution of nanoparticles in the nanosuspension. Since the temperature factor is not suitable for some specimens in biomedical applications, it is, therefore, necessary to consider the parameter of anti-solvent flow rate as an important factor in the preparation of nanoparticles using microfluidic channels, especially to reduce particle size and increase stability in the final product.

In another study on size control in the nanoprecipitation process of stable-iodine (127I) using microchannel reactor (9), the 3D-graphs showed the determining effect of input parameters including solvent and anti-solvent flow rate, surfactant concentration, and solvent temperature on the output parameter (particle size). This study showed that an increase in the flow rate of anti-solvent results in a considerable decrease in the size of nanoparticles. Also, a direct and indirect relationship between solvent temperature and particles size was observed at low and high values of solvent temperature, respectively. In addition, it was determined that The particle size decreased with increasing concentration of surfactant at low values of solvent temperature, while increasing concentration at high solvent temperature led to an increase in the particle size. In this study, there was an indirect and direct relationship between solvent temperature and nanoparticle size in low and high values of solvent temperature, respectively.

Here, enhancement of anti-solvent flow rate reduces the solubility of drug molecules by an increase in mixing with solvent through diffusion. Consequently, the level of supersaturation decrease that results in a higher nucleation rate than growth rate. As a result, smaller nano-sized particles will be produced. As discussed above, an increase in the anti-solvent flow rate leads to an increase in the diffusion of molecules from the solvent flow to unit volume of anti-solvent. This phenomenon can result in less concentration of solute around the growing drug nuclei and the formation of smaller nanoparticles. According to the results of the study, the direct relationship between the solvent temperature and particle size can be due to increased solubility of the solute and a difficult supersaturation level at the high values of solvent temperature. Therefore, it leads to a low nucleation rate and an increase in the particle size. In contrast, the indirect relationship between the solvent temperature and particle size can be due to an increase in the nucleation rate relative to the growth rate, which leads to a reduction in the particle size. This phenomenon can be due to the fact that nucleation is a favorable process energetically. On the other hand, the increase in solvent temperature will increase the diffusion of molecules into the anti-solvent flow per unit volume, which will result in more nucleation sites and smaller particle size, as mentioned above. Also, since surfactant acts as a steric barrier against the growth of particles, thus increasing the concentration of surfactant results in an increase in nucleation rate than growth rate. On the other hand, at the high values of solvent temperature, an increase in surfactant concentration leads to an increase in surfactant molecules uncontrollably on the surface of particles and a decrease in their mobility. As a result, a larger particle size will be shown by dynamic light scattering analysis.

CONCLUSION

In the studies mentioned, the anti-solvent flow rate parameter was used as the most important factor in reducing particle size and polydispersity index (PDI) and increasing the stability of nanoparticles in the nanosuspension formulations obtained through nanoprecipitation using microfluidic channel. The results of these studies can be applied to polymer, lipid and SLN nanoparticles, as well as nano- and micro- emulsions for pharmaceutical and medical applications that are prepared and optimized using these microfluidic channels. Here, it should be noted that the preparation of nanoparticles using microfluidic channels is a simple, cost-effective, rapid, and scale-up capability approach for biomedical applications.

Declaration of interest

The authors declare that they have no conflicts of interest to disclose.

REFERENCES

1. Zhao C-X, He L, Qiao SZ, Middelberg AP. Nanoparticle synthesis in microreactors. Chemical Engineering Science. 2011;66(7):1463-79.
2. Ali HS, York P, Blagden N. Preparation of hydrocortisone nanosuspension through a bottom-up nanoprecipitation technique using microfluidic reactors. International journal of pharmaceutics. 2009;375(1-2):107-13.
3. Baby T, Liu Y, Middelberg AP, Zhao C-X. Fundamental studies on throughput capacities of hydrodynamic flow-focusing microfluidics for producing monodisperse polymer nanoparticles. Chemical Engineering Science. 2017;169:128-39.
4. Lonare AA, Patel SR. Antisolvent crystallization of poorly water soluble drugs. International Journal of Chemical Engineering and Applications. 2013;4(5):337.
5. Xu J, Zhang S, Machado A, Lecommandoux S, Sandre O, Gu F, et al. Controllable microfluidic production of drug-loaded PLGA nanoparticles using partially water-miscible mixed solvent microdroplets as a precursor. Scientific Reports. 2017;7(1):4794.
6. Xia H, Seah Y, Liu Y, Wang W, Toh AG, Wang Z. Anti-solvent precipitation of solid lipid nanoparticles using a microfluidic oscillator mixer. Microfluidics and Nanofluidics.

2015;19(2):283-90.
7. Aghajani M, Shahverdi AR, Rezayat SM, Amini MA, Amani A. Preparation and optimization of acetaminophen nanosuspension through nanoprecipitation using microfluidic devices: an artificial neural networks study. Pharmaceutical development and technology. 2013;18(3):609-18.
8. Aghajani M, Shahverdi AR, Amani A. The use of artificial neural networks for optimizing polydispersity index (PDI) in nanoprecipitation process of acetaminophen in microfluidic devices. AAPS PharmSciTech. 2012;13(4):1293-301.
9. Aghajani MH, Pashazadeh AM, Mostafavi SH, Abbasi S, Hajibagheri-Fard M-J, Assadi M, et al. Size Control in the Nanoprecipitation Process of Stable Iodine (127 I) Using Microchannel Reactor—Optimization by Artificial Neural Networks. AAPS PharmSciTech. 2015;16(5):1059-68.
10. Mahdi Jafari S, He Y, Bhandari B. Nano-emulsion production by sonication and microfluidization—a comparison. International Journal of Food Properties. 2006;9(3):475-85.
11. Maenaka H, Yamada M, Yasuda M, Seki M. Continuous and size-dependent sorting of emulsion droplets using hydrodynamics in pinched microchannels. Langmuir. 2008;24(8):4405-10.
12. Belliveau NM, Huft J, Lin PJ, Chen S, Leung AK, Leaver TJ, et al. Microfluidic synthesis of highly potent limit-size lipid nanoparticles for in vivo delivery of siRNA. Molecular Therapy-Nucleic Acids. 2012;1.