Optimizing microfluidic preparation parameters of nanosuspension to evaluate stability in nanoprecipitation of stable-iodine (^{127}I)

Nooshin KianvashRad¹ · Elham Barkhordari² · Seyed Hossein Mostafavi^{3,4} · Mahdi Aghajani^{5,6}

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Abstract

The aim of the current study was the development of nanosuspension stability in nanoprecipitation using microfluidic devices. Also, it is desirable to understand how the microfluidic preparation parameters influenced the stability of the stable-iodine (^{127}I) nanosuspension. In optimization process through artificial neural networks (ANNs), the relations between input and output variables were investigated for 37 samples obtained by microfluidic nanoprecipitation process. Solvent temperature, antisolvent flow rate, and solvent flow rate were used as input variables, and the sedimentation time and polydispersity index (PDI) were considered as output parameters. Sedimentation time as an indicator of physical stability of nanosuspension was evaluated by observation of a densely packed sediment. Also, size and PDI of different samples were determined by dynamic light scattering. The size of the optimized sample was confirmed by transmission electron microscopy. The result obtained from modeling showed that increasing solvent temperature and antisolvent flow rate led to a decrease in PDI and an increase in the sedimentation time. The antisolvent flow rate was determined as the most important factor that affected the sedimentation time and PDI. Increasing the solvent flow rate was identified as an adverse factor which increased PDI or decreased formulation's sedimentation time. Optimization using ANN showed that microfluidic preparation parameters of nanosuspension as input variables had potential impacts on output parameters.

Keywords Nanoprecipitation · Microfluidic · Optimization · Stability · Stable-iodine

1 Introduction

Nanocrystals retain crystalline property and contain 100% pure drug. After dispersing in the aqueous media, they are called nanosuspension. Nanosuspensions have shown a variety of advantages such as increased dissolution velocity because of increasing surface (high surface to volume ratio), increased saturation solubility, and the capability of being scaled up [1–6]. At the time of radioactive iodine release in a nuclear event, accurate and on-time prescription of stable-iodine (^{127}I) can significantly reduce

uptaking of radioactive iodine in the thyroid glands of the people near to the nuclear event (1). Considering a competition between stable-iodine (^{127}I) and radio-iodine to absorb in the thyroid gland, consuming the nanosuspension formulation of stable-iodine (^{127}I) can increase the uptake rate of usual form of stable-iodine (^{127}I) compared to radio-iodine. This phenomena causes a decrease in the uptake of radio-iodine [7].

PDI is an important parameter that defines the physical stability of nanosuspensions and must be low enough to create long-term stability for nanosuspensions; PDI

✉ Mahdi Aghajani, m.aghajani@bpums.ac.ir; mehadinano88@gmail.com | ¹Department of Medical Nanotechnology, Faculty of Advanced Sciences and Technology, Islamic Azad University, Pharmaceutical Sciences Branch (IAUPS), Tehran, Iran. ²Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ³Department of Bioengineering, University of California, Riverside, CA 92521, USA. ⁴Department of Medical Nanotechnology, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran. ⁵Department of Nanotechnology, The Persian Gulf Nuclear Medicine Research Center, The Persian Gulf Biomedical Sciences Institute, Bushehr University of Medical Sciences, Bushehr, Iran. ⁶School of Advanced Technologies in Medicine, Golestan University of Medical Sciences, Gorgan, Iran.

in nanosuspensions, determines their physicochemical behavior such as saturation solubility, dissolution rate and physical stability [8, 9]. Selection of evaluation techniques for pharmaceutical nanosuspensions stability depends on the physical or chemical stability, forms of consumption, and properties of the drug [10]. Although nanosuspension technology was extensively evaluated, its stability still requires further studies in connection with parameters of the preparation process (in particular, microfluidic preparation as a simple and alternative method) [11, 12].

In over the past few decades, the knowledge in the field of controlling the nucleation and growing crystals in solution has been increased extensively. Also, the bottom-up method has been expanded for the production of ultrafine particles (UFPs) through controlling crystallization process at the molecular level. As an example, microfluidic method as the bottom-up process which can help to produce nanoparticles with a specific size, uniform particle size distribution and favorable structure under the controlled reactions [9, 11, 13]. Some of the flow instabilities that usually occur in nature are Kelvin–Helmholtz instability, Rayleigh–Taylor instability, and Karman Vortex Street. In case of microfluidic flows, these parameters do not induce instability due to the very small characteristic length and velocity scales, and high surface area to volume ratio [15, 16]. In microfluidic device, fluids flow in the channels that are much smaller than 1 mm. If two streams exist in the microfluidic device and one of them containing drug molecules in its solvent and the other one containing antisolvent of the drug, drug molecules begin to nucleate in diffusion layer (i.e. nucleation) because of the diffusion into antisolvent (see Fig. 1). Then, early formed nuclei begin to grow and finally precipitate in solution. It is also possible to control the speed of growth and precipitation process with surfactants, polymers or stabilizers, which are in the antisolvent flow [11, 14, 15].

In this study, an increase in the stability of nanoparticle formulation obtained from stable-iodine nanoprecipitation in microfluidic channel was considered. Optimization process of nanoprecipitation to improve PDI and sedimentation time was done in artificial neural networks (ANNs). In order to do the procedure, a certain number of formulations were prepared using microfluidic channels. The possibility of creating formulations with high efficiency is established by achieving favored conditions (less PDI and more sedimentation time). A previous study [7], showed that ANNs is able to create the qualified model to demonstrate the effects of an independent experimental variable on the dependent variable (particle size). Finally, after an analysis of results, a sample was created with an optimized particle size (namely, a nanosuspension formulation with minimum size). Recently, usage of ANNs was proposed to determine the factors that control the sedimentation time,

Fig. 1 Nanoprecipitation process in microfluidic devices; Flow rates of antisolvent and solvent are 0.5–2.5 and 0.5–1 ml/min, respectively. Stable-iodine (^{127}I) molecules in the microfluidic channel are diffused to antisolvent flow and then nucleation occurs

PDI and size of the nanoparticle [14, 16, 17]. Another study has also shown experimental factors such as solvent and antisolvent flow rate, solvent temperature and surfactant concentration have an important effect on PDI [8]. In a study on nanoprecipitation of hydrocortisone performed by Ali et al. [9] they observed a decrease in stability of nanosuspension without a stabilizer. Also, they found out that surfactant concentration has no effect on particle size distribution or PDI. In the study conducted by Abbasi et al. [16] it was shown that the optimized formulation, namely minimum value of PDI and size, was obtained by nanoprecipitation in the high values of solvent flow rate (i.e., 120 ml/h), surfactant concentration (i.e., > 0.9 mg/ml), and stirring rate (i.e., 500 rpm). In the current work, the effects of independent parameters including the solvent flow rate, solvent temperature and antisolvent flow rate on sedimentation time of nanosuspensions and effects of these parameters on PDI were modeled with ANNs.

2 Materials and methods

2.1 Materials

Potassium Iodide (KI) powder was purchased from Merck chemicals (Germany). Ethanol 99/6% (V/V) and Tween 80 (polysorbate 80) were purchased from Jahan Alkol Teb Arak co. (JATA) and Sigma-Aldrich (Germany), respectively.

2.2 Nanoprecipitation using microfluidic devices

Due to the effect of temperature on the dissolution of stable-iodine in the preparation of the supersaturated solution, we used the heating element and temperature

controller (Fanavaran Nano-Meghyas, Iran) to set the desired temperature for a syringe that contained the supersaturated solution of stable-iodine (30–80 °C). After drawing the supersaturated solution into the syringe, we waited until the temperature of the solution and syringe was same as each other and fixed. Surfactant solution (Tween 80) with ethanol as the antisolvent (at a controlled lab temperature, namely 24 ± 2 °C) was drawn into the syringe and placed on the hydrodynamic pump (Fanavaran Nano-Meghyas, Iran) for injection. Hydrodynamic pumps (used for injection of solvent and antisolvent solutions) were set at a constant volume and specific speed for injection of these solutions (flow rate of antisolvent and solvent at 0.5–2.5 and 0.5–1 ml/min, respectively). And then, each of syringes was connected to two input of microfluidic tools. In the next stage, hydrodynamic pumps injected solvent and antisolvent solution with a specified speed into the Y-shaped microfluidic tool. At final stage, nanosuspension formulation of stable-iodine (^{127}I) was collected from the output of this microfluidic tool.

Experimentally, 37 samples were prepared at random values for the three input variables (namely solvent temperature (°C)), and flow rate of antisolvent and solvent (ml/min)), while sedimentation time and PDI of these samples were considered as output variables. Then, the prepared samples were preserved at a controlled lab temperature to measure their PDI freshly by DLS instrument. Subsequently, in order to evaluate the sedimentation time as an index of physical stability of nanosuspension formulation, the samples were maintained at controlled lab temperature (i.e. 24 ± 2 °C), meanwhile the sediment property (a densely packed sediment) in nanosuspension visually

examined daily in each 8 h intervals. At the end, the sedimentation time and PDI data were used to understand the effect of the input variables on output variables according to the model obtained using ANNs modeling.

2.3 Artificial neural networks modeling

In this study, we used the commercialized ANNs software (Inform V4.02, Intelligensys, UK). This software is based on the connection between neurons for modeling of inputs and outputs, which have a complicated relevance. The results of the ANNs software are three-dimensional graphs that show input parameters established in the low, medium and high values. In this study, preparation of stable-iodine (^{127}I) nanosuspension consisted of three independent input parameters (i.e. solvent flow rate (ml/min), antisolvent flow rate (ml/min), solvent temperature (°C)), and two output dependent parameters (i.e. PDI and sedimentation time). The response surfaces (namely, 3D graphs) were applied to evaluate the variations in sedimentation time and PDI of nanosuspension against variations of two input variables, while another input variable was fixed at low, medium or high values [18, 19].

From the 37 samples that mentioned above, a data set of 29 preparations were used as training data set to train the ANN about relationships between input and output variables. Also, three data sets suggested by ANN software were applied as test data sets for the prevention of over-training during the learning process (namely, 10% of training data sets). Training parameters applied for modeling sedimentation time and PDI are shown in Table 1, details of the parameters have been described previously [19,

Table 1 The training parameters used with INForm v4.02

		PDI	Sedimentation time
Network structure	No. of hidden layers	1	1
	No. of nodes in hidden layer	3	3
Backpropagation type		Angle driven learning	Batch
Backpropagation parameters	Momentum factor	0.8	0.8
	Learning rate	0.7	0.7
Targets	Maximum iterations	1000	1000
	MS error	0.0001	0.0001
	Random seed	10,000	10,000
Smart stop	Minimum iterations	20	20
	Test error weighting	0.1	0.1
	Iteration overshoot	200	200
	Auto weight	On	On
	Smart stop enabled	On	On
Transfer function	Output	Tanh	Linear
	Hidden layer	Asymmetric Sigmoid	Tanh

20]. Then, to evaluate the predictive ability of the created model by ANN, eight remaining data sets were used as an unseen (validation) data set. Table 2 shows the unseen data set used for sedimentation time and PDI. In fact, the created model with better predictability shows correlation coefficient (R^2) near to one for the unseen data set [21, 22].

2.4 Measurement of the nanosuspensions' PDI and sedimentation time

For optimizing the nanosuspension stability, 37 samples (nanosuspension of stable-iodine (^{127}I)) was prepared to evaluate the effect of changing the variable factors on PDI and sedimentation time. According to the usage of ANNs modeling, the best condition for optimization of nanosuspension stability was obtained.

2.4.1 Dynamic light scattering (DLS)

PDI in obtained samples and optimized formulation was measured using Zetasizer (Malvern, UK) with a Malvern PCS software (version 1.27). The temperature for all formulations was set at $24 \pm 2^\circ\text{C}$. The formulations were measured freshly without any dilution.

2.4.2 Evaluation of sedimentation time

To evaluate the sedimentation time of preparations and optimum formulation, the samples were examined through visual observation daily, at a lab temp ($24 \pm 2^\circ\text{C}$). Since nanosuspension of stable-iodine (^{127}I) is a deflocculated nanosuspension [7], sedimentation time of formulation can be easily determined by visual observation of a densely packed sediment during a certain period of time as the sedimentation time. In other words, sedimentation time of samples was considered as phase separation time of nanoparticles in nanosuspension, representing an indicator of physical stability [10].

2.4.3 Transmission electron microscopy (TEM)

Particle size and morphology in the optimum formulation was measured by TEM (ZEISS EM 10C, Germany). After the sample was dispersed by ultrasonic for 3 min, two drops of the sample were put on a carbon-coated copper grid and placed in dry air (at lab temp) for 15 min. Then, the sample grid was put on a holder for monitoring by TEM at a voltage of 80 kV.

2.5 Evaluation of entrapment efficiency (EE%)

The spectrophotometric detection was used to determine the percentage of entrapment efficiency at a detection wavelength 226 nm. Optimized formulation of stable-iodine (^{127}I) was centrifuged (10,000 rpm for 20 min) and free stable-iodine (^{127}I) amount in the supernatant was measured at 226 nm. Entrapment efficiency of stable-iodine (^{127}I) was calculated by the following equation [23]:

$$\text{EE\%} = \frac{\text{Initial stable iodine}(^{127}\text{I}) \text{ amount} - \text{free stable iodine}(^{127}\text{I})\text{amount}}{\text{Initial stable iodine } (^{127}\text{I}) \text{ amount}} \times 100$$

3 Results and discussion

Prediction and prevention of the sedimentation in the nanosuspensions formulation is an important issue that must be considered. In addition to the type of stabilizers that are effective on the sedimentation of nanosuspensions, some other factors also contribute to instability of nanosuspensions [12]. According to previous studies, it was shown that factors such as polydispersity index (PDI) and parameters involved in the preparation method of nanosuspension are related to changes in physical stability [8, 14].

Table 2 The unseen data sets used in ANNs modeling

Antisolvent rate (ml/min)	Solvent rate (ml/min)	Temperature ($^\circ\text{C}$)	PDI-observed	PDI-predicted	Sedimentation time (day)-observed	Sedimentation time (day)-predicted
2.5	0.5	70	0.151	0.148	98.2	98.3
0.8	1.0	30	0.501	0.497	8.2	9.2
2.5	0.8	50	0.252	0.263	47.5	47.0
1.0	0.5	60	0.370	0.362	23.6	34.3
0.6	0.8	50	0.463	0.457	12.8	13.0
1.0	1.0	50	0.354	0.326	24.5	25.1
0.5	1.0	30	0.512	0.508	7.1	7.4

After modeling a set of experimental data by the use of ANN software, the achieved model consisted of the R^2 values of 0.96, 0.81 and 0.91 in modeling the PDI, and R^2 values of 0.93, 0.97 and 0.95 in modeling the sedimentation time, respectively for training, test, and unseen data. Concerning the complexity of the relationship between input and output variables in the preparation of nanosuspension of stable-iodine, the amounts stated above provided a satisfied predictable model. Then, this model was used to study the influence of the various input variables (consist of antisolvent flow rate, solvent flow rate, and solvent temperature) on the output variables (consist of PDI and Sedimentation time of nanosuspension). For the evaluation of the relationship between inputs and outputs in the model achieved by ANNs, a conventional approach such as sensitivity analysis can be used as the first choice. But here we used a semi-quantitative method for the study of interactions between input and output variables which have been reported formerly [19]. In summary, in this method for one input variable which has been fixed in a special value (namely a low, a mid-range and a high value), the effect of the two other input variables on the output variable will be shown by the use of 3D graphs created by ANNs software.

3.1 Evaluating the effect of input variables on sedimentation time by ANNs modeling

Since nanosuspension of stable-iodine (^{127}I) is a deflocculated suspension, we used visual observation of sediment to evaluate stability of samples obtained, as mentioned in previous studies [7, 10, 14]. In a deflocculated suspension, a densely packed sediment with a slow sedimentation rate has a hard structure and cannot be re-dispersed after shaking.

Here, to evaluate the effect of flow rate of the solvent or antisolvent on sedimentation time of nanosuspension of stable-iodine (^{127}I), we have fixed the variable of solvent temperature in low, mid-range and high values (respectively; 35, 55 and 75 °C). The results are shown in Fig. 2 as three-dimensional graphs. Concerning the details, enhancing antisolvent flow rate increases sedimentation time. In the previous report by the same group, it was stated that the time of sedimentation for nanoparticles prepared with this nanoprecipitation method is in direct relation to the rate of antisolvent [14]. It is also clear that with the increase of the flow rate of the solvent, sedimentation time reduces. In fact, by increasing the flow rate of antisolvent, the particle size distribution in the nanosuspension of stable-iodine (^{127}I) will be more uniform and thus will prevent the phenomenon of Ostwald ripening. This results in more stability of nanoparticles, namely, an increase in sedimentation time. In contrast, with the

increase of solvent flow rate, monodispersity of the particle size distribution in nanosuspension is decreased (due to an increase in the PDI), which ultimately reduces the stability and the sedimentation time of the formulation [14, 24, 25]. The second reason for this result may be related to a decrease in presence of drug molecules during the process of nucleation around the growing particles, with an increase in the antisolvent flow rate [26].

As demonstrated in Fig. 3, the flow rate of the solvent in high, mid-range and low amounts (i.e. 0.95, 0.75, and 0.55 ml/min, respectively) has been fixed against the antisolvent flow rate and temperature in order to create the 3D graphs of sedimentation time. As indicated in Fig. 2, for each fixed data set, an increase in antisolvent flow rate leads to a considerable increase in stability. Moreover, the increase in solvent temperature leads to an increase in sedimentation time. In fact, the high value of solvent temperature may cause decreasing PDI. So, an increase in the physical stability in the nanosuspension obtained will be achieved [8]. Considering the details, the maximum sedimentation time is obtained in high levels of antisolvent flow rate and solvent temperature. The decreasing PDI is probably due to an increase in the mixing of solvent and antisolvent flow inside the microfluidic channel before the extraction of the solution from its end. In fact, increased temperature of the solvent helps better mixing of water and ethanol; this, in turn, will lead to the increased mixing of solvent and antisolvent by means of diffusion. Therefore, before the solvent exits the microfluidic channel, a great amount of it is exposed to the antisolvent, which results in a further precipitation of stable-iodine in the form of nanoparticles. Following this, the solvent extracted from microfluidic contains less amount of dissolved iodine to precipitate by other processes and form particles with non-uniform size distribution. Since in the microfluidic, the mixing occurs only through diffusion, the precipitated particles have a uniform and homogeneous size distribution. Therefore, by increasing the solvent temperature, and subsequently increasing the precipitation within the microfluidic, the obtained nanosuspension of stable-iodine (^{127}I) has more uniform particle size distribution (i.e. less PDI), as reported in previous studies [8, 14].

In Fig. 4, the effect of solvent flow rate and solvent temperature on the sedimentation time in the nanosuspensions of stable-iodine (^{127}I) has been shown in which the antisolvent flow rate in values of 0.7, 1.5 and 2.3 ml/min have been fixed. The direct relationship of the solvent temperature with the sedimentation time is clear, as mentioned in Fig. 3. In addition, high levels of antisolvent flow rate lead to high sedimentation time. Also, it is important to note that in contrast with the high value of solvent flow rate, stability is minimal, which indicates the importance of the two parameters of the solvent temperature

Fig. 2 3D plots of sedimentation time predicted by the ANNs modeling; model fixed at low, mid-range and high values of the solvent temperature

and antisolvent flow rate in the stability of the obtained nanosuspension. With attention to detail and comparing Figs. 2 and 4, it is obvious that the impact of antisolvent flow rate on the enhancement of sedimentation time and stability of stable-iodine nanosuspensions is more effective than the solvent temperature impact. Reduction of the sedimentation time of nanosuspension against increase of the solvent flow rate can be justified by the higher rates of the solvent flow lead to the precipitation of more particles per unit volume of antisolvent. As a result, the presence of a greater number of particles per unit volume of antisolvent leads to more non-uniform particle size distribution and so sedimentation time will be reduced. Here, it should

be pointed out that the constant high concentrations of surfactant used in this study is important in the stability.

As shown in Figs. 2, 3 and 4, the least stability has been observed in low amounts of the solvent temperature and antisolvent flow rate, regardless of the solvent flow rate and the concentration of surfactant. This indicates the importance of these two factors on the stability of prepared nanosuspension. Also, minimum of sedimentation time in low values of solvent temperature or antisolvent flow rate against high flow rate of solvent is in a certain value. This phenomenon is due to the high amount of surfactant used in the study. In fact, the high amount of concentration of surfactant that used in the study causes an increase in physical stability of nanosuspension and

Fig. 3 3D plots of sedimentation time predicted by the ANNs modeling; model fixed at low, mid-range and high values of the solvent flow rate

decrease the particle growth [27, 28]. In a study conducted by Hany S.M. Ali and colleagues on the study of parameters relating to microfluidic precipitation process to prepare hydrocortisone nanosuspension, they reported that at low levels or absence of surfactant, nanosuspension stability has been decreased [9]. It is known that the presence of a surfactant/stabilizer as an important factor in the formulation of nanosuspension may results in the prevention of agglomeration or aggregation of drug nanoparticles, due to decreasing the high surface energy on these particles [2].

3.2 Evaluating the effect of input parameters on PDI by ANNs

In the prepared samples, the PDI of stable-iodine (^{127}I) nanosuspension showed the clear variations against changing the antisolvent and solvent flow rate and solvent temperature. Nanosuspension PDI is an important parameter that defines the physical stability and must be low enough so that long-term stability of nanosuspensions is possible. Approximate values of 0.1 to 0.25 shows good particle size distribution with a narrow width, while amounts more than 0.5 shows the particle size distribution with high width [9, 16]. In fact, dispersed systems due to

Fig. 4 3D plots of sedimentation time predicted by the ANNs modeling; model fixed at low, mid-range and high values of the antisolvent flow rate

the Oswald ripening phenomenon that causes the growth of crystal and production of the microparticle show physical instability. In this process, smaller particles, because of more solubility, dissolve and following that crystallization generates the creation of microparticles. The phenomenon of Oswald may not happen in the nanosuspensions because nanosuspensions can be produced by the uniform particle size distribution (low PDI) that causes long-term physical stability [29].

Here, to evaluate the effect of solvent flow rate, antisolvent flow rate, and solvent temperature on PDI of

stable-iodine (^{127}I) nanosuspension, the solvent temperature was fixed at amounts of low, mid-range, and high (respectively 35, 55 and 75 °C). The 3D graphs obtained are shown in Fig. 5. Also, solvent flow rate and antisolvent flow rate were fixed at amounts of low, mid-range and high (0.55, 0.75 and 0.95 ml/min for solvent flow rate respectively, and 0.7, 1.5 and 2.3 ml/min for antisolvent flow rate respectively). The resulting graphs are shown in Figs. 6 and 7.

As can be seen in Figs. 5, 6 and 7, an increase in antisolvent flow rate reduces the value of nanosuspensions' PDI.

Fig. 5 3D plots of PDI predicted by the ANNs modeling; Model fixed at low, mid-range and high values of the solvent temperature

An increase in PDI against enhancing the value of solvent flow rate is clear. In addition, high level of solvent temperature leads to a decrease in the nanosuspensions' PDI. The results achieved by the effect of variable input parameters on PDI (in relation to increase or decrease in stability) contradict with the results related to the effect of these parameters on sedimentation time. In fact, a decrease in PDI due to an increase in solvent temperature, as mentioned earlier, is because of the more mixing solvent and antisolvent flow through the diffusion in microfluidic channel. Thereby it causes an increase in precipitation of stable-iodine in the form of iodine nanoparticles. Subsequently, the solvent removed from the microfluidic channel has a smaller amount of dissolved iodine. Therefore, by an increase in solvent temperature and subsequently increasing precipitation in the microfluidic channel, more uniform particle

size distribution would be obtained in stable-iodine (^{127}I) nanosuspension (i.e. less PDI) [8].

The effect of antisolvent/solvent flow rate on PDI in a microfluidic channel is probably one of the following two methods which lead to the uniform particle size distribution:

- (1) Increasing stable-iodine molecules diffusion into antisolvent flow due to the rapid passing of antisolvent: When antisolvent flow passes rapidly near the solvent flow, it causes a greater amount of stable-iodine (^{127}I) molecules in solvent diffuse into the antisolvent flow. In fact, it causes more precipitation of stable-iodine before leaving the channel. In the other words, in the collector container, less stable-iodine (^{127}I) molecules are in contact with solvent and will sediment

Fig. 6 3D plots of PDI predicted by the ANNs modeling; model fixed at low, mid-range and high values of the solvent flow rate

by other processes. Since a large amount of stable-iodine (^{127}I) molecules precipitate within the micro-fluidic channel only through the phenomenon of diffusion, a more uniform distribution of particle size is created. This precipitation has uniform particle size distribution in comparison with precipitation in the collector container. Therefore, it creates a nanosuspension formulation with lower PDI, as noted above for the solvent temperature [14, 30, 31].

- (2) Less diffusion of stable-iodine (^{127}I) molecules to the antisolvent flow per unit volume:

In fact, with less diffusion of dissolved stable-iodine (^{127}I) molecules per unit volume of antisolvent flow against increasing the antisolvent flow rate, the presence of these molecules reduces around growing

drug nuclei. It leads to a nanosuspension sample with a smaller value in PDI [8, 11, 26].

3.3 Evaluation of optimized formulation

Concerning previous explanations, effects of different values of solvent/antisolvent flow rate and solvent temperature on PDI and sedimentation time were found. It was observed that increasing antisolvent flow rate and solvent temperature causes improvement in stability of stable-iodine nanosuspension, and increasing solvent flow rate leads to a decrease in its stability.

According to the results mentioned above, a favorable condition to prepare the optimum sample was obtained. Here, optimum nanosuspension was considered a sample

Fig. 7 3D plots of PDI predicted by the ANNs modeling; model fixed at low, mid-range and high values of the antisolvent flow rate

with maximum stability. Also, considering the previous studies [7, 8, 14], a high concentration of Tween 80 was suggested to reduce the particle size and an increase in the stability. So, we have considered the amount of 1290 mg/5 ml ethanol for surfactant concentration in the samples. In the following, to prepare the optimum sample, and according to the results of ANNs modeling, preparation conditions were selected as follows:

Solvent temperature: 80 °C; Solvent flow rate: 0.5 ml/min; Antisolvent flow rate: 2.5 ml/min.

The generated nanosuspension have suitable stability (i.e. 129 days with PDI=0.122), and the particle size was 40 nm that was measured with DLS and confirmed with TEM (Fig. 8). Also, the percentage of entrapment efficiency was determined to be 81%.

Fig. 8 Picture of transmission electron microscopy from stable-iodine (^{127}I) nanoparticle

4 Conclusion

In this study, Optimization using ANN shows that microfluidic preparation parameters of nanosuspension as input variables have potential impacts on output parameters to affect stability. 3D graphs of ANNs modeling showed that three input parameters (i.e. flow rate of solvent and antisolvent and solvent temperature), affect significantly PDI and sedimentation time of nanosuspension formulation. The antisolvent flow rate and the solvent temperature had a direct relationship with the stability of stable-iodine (^{127}I) nanosuspension. It was also found that it is necessary to keep the amount of solvent flow rate in a lower value, and to set the amount of solvent temperature, antisolvent flow rate, and surfactant concentration in a higher amount to create the maximum stability of stable-iodine (^{127}I) nanosuspension.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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