Advances in Nano Research, *Vol. 14, No.1 (2023) 17-25*
https://doi.org/10.12989/anr.2023.14.1.017

Efficacy of nano-drugs in muscle injury rehabilitation and fatigue relief

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(*Received January 7, 2022, Revised July 11, 2022, Accepted July 12, 2022*)

Abstract. Gold nanoparticles have recognized a promising drug carriers in many diseases. These nanoparticles could carry anti-inflammatory drugs in the case of muscle injury and for fatigue relief. On the other hand, specific surface of this kind of nanoparticles could be critical in amount of drug they could carry. Therefore, in this study, we explore different methodology and influencing parameters on the specific surface of gold nanoparticles. After specifying the main parameters, different machine learning and artificial neural network are adopted to model the effects of different parameters. Furthermore, response surface methodology is utilized to obtain a quadrilateral relationship between different parameters and specific surface. The results indicate that concentration of the gold salt solution is the most important parameter in increasing the size of gold nanoparticle and, as a consequence, increasing specific surface. Moreover, the ability of gold nanoparticles in prolonging retention of the drugs is discussed in detail.
Keywords: drug delivery; fatigue relief; gold nano-particle; machine learning; muscle injury; nano-medicine

1. Introduction

Muscle injury and rupture are frequent among athletes. The process of the muscle rehabilitation is complicated and the human body take care of it in most cases. In simple words, the skeletal muscles contain both satellite cells (SCs) as well as fibro/adipogenic progenitors (FAPs). These cells have a prominent effect in recovery of injured muscle. However, they need other blood cells to be activated (Zou *et al*. 2019, Zhuo *et al*. 2020, Lai *et al*. 2021, Li and Wang 2021, Tang *et al*. 2021, Yang *et al*. 2022b). In the first phase after muscle injury, Neutrophils blood cells release some enzymes to alleviate muscle damage (Lai *et al*. 2020, Cao *et al*. 2022, Xue *et al*. 2022a, b, Zhang *et al*. 2022). Afterwards, monocytes differentiate to M1 macrophages to produce inflammation. These chemicals lead to proliferation of SCs and FAPs in the injured muscle. After some days, proliferation of SCs stop and FAPs die due to presence of M1 macrophages. In this stage, the M1 macrophages converts to M2 macrophages which assist SCs differentiation to muscle fibers. In normal condition, human body could cure muscle damages. However, if any disturbance in M1 and M2 releasing occurs it may results in chronically damaged muscles. Therefore, research studies are focusing on the anti-inflammation drugs (Raimondo and Mooney 2018).

Raimondo and Mooney *et al*. (2018) reported that IL-4 cytokine is a common anti-inflammatory therapeutic which is utilized in different cases. This cytokine has a short half-life in the human body. Thus for prolongation its presence in body they suggested using gold nanoparticles (AuNPs) as drug carriers. Moreover, using AuNPs has another advantage which uniformly distribute the drug in the injured area. Using this method they reported that there were sees 40% increase in the muscle force in comparison to the muscle treated with vehicle alone. Mackey *et al*. (2012) reviewed the effects of anti-inflammatory drug in treatment of strain muscle injuries. They collected articles on this matter and suggested that and with comprehensive investigation it was concluded that non-steroidal anti-inflammatory drugs have both positive and negative effects in curing muscle injuries. However, the number reports in favor of positive effects is superior to negative effects. Bayer *et al*. (2017) reported the effect of timing in treating muscle injuries. They found that early therapy only two days after injury results in sooner pain-free recovery and returning to exercise sport in comparison to delayed therapy started 9 days after injury. It is also found that immobilization of patient for 9 days have adverse effects on the curing muscle injury. Kim *et al*. (2017) utilized polymer nanoparticles to enhance ultrasonographic imaging contrast. The injection this kind of nanoparticles also applies anti-inflammatory and anti-apoptotic results. Da Rocha *et al*. (2020) evaluated the effects of AuNPs and micro-currents on the muscle injury therapy on Wistar rats. They found that combination of gold nanoparticles and micro-current gives the best results among other examined methods. This method significantly improved the inflammation and oxidative stress parameters. dos Santos Haupenthal *et al*. (2020) used several methodology for repairing injury in Wister rats. They examined 8 groups each contains 10 rats with different therapies including diclofenac linked to AuNPs. It is found that combination of Therapeutic Pulsed Ultrasound and AuNPs with diclofenac accelerates curing of the muscles with decreasing inflammations in the injured muscle.

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http://www.techno-press.org/?journal=journal=anr&subpage=5
ISSN: 2287-237X (Print), 2287-2388 (Online)

The above references indicated that using gold nanoparticle as anti-inflammatory drug carriers is a promising method to insure that enough and well-maintained drugs delivered to the injured area. In fact, beside gold nanoparticles there are several other drug carriers produced and tested. The ability to produce different size nano particles is the most challenging goal in experimental studies (Moradi *et al*. 2022). The drug carrying capacity of AuNPs depends on many factors including specific surface (Ahmad *et al*. 2014) and functionalized surface (Nicol *et al*. 2015) of the nanoparticles. Ahmad *et al*. (2014) synthesized different size of gold nanoparticles using different concentration of gold salt. The main parameter affecting the final particles sizes in their study in the concentration which had an inverse effect on the AuNPs. They successfully produced nanoparticles from 2.9nm to 53.7nm by changing the molarity of gold salt. Other parameters affecting the size and shape of AuNPs are temperature (Hatakeyama *et al*. 2011, Mountrichas *et al*. 2014, Tran *et al*. 2016), rate of adding (Sivaraman *et al*. 2010) and pH of the solution (Seol *et al*. 2011, Singh and Srivastava 2015). Hatakeyama *et al*. (2011) examined the effect of temperature on size and shape of AUNPs in liquid polyethylene glycol (PEG) medium. They observed that changing solution temperature from 20°C to 60°C results in change of NP sizes from 2nm to 8nm. Moreover, alternation in temperature leads to change in shape of the NPs from spherical for low temperature to stretched shapes for higher temperatures. Mountrichas *et al*. (2014) considered the effects of temperature on the synthesis of AuNPs and found contradicting results for hybrid polymer/ metal nano-particles as increasing in temperature from 60°C to 30°C cause increase in size of particles from 10.2nm to 45.8nm. They also argued about the speed of the process and uniformity of the particle shapes in different temperatures. Tran *et al*. (2016) explored effects of both temperature and concentration of gold salt on the size and shape of the AuNPs. They reported that effect of the concentration is more important than effect of temperature. The time of the reaction significantly affected by the concentration of the solution. Sivaraman *et al*. (2010) showed the effect of pH and slow addition of chloroauric acid in tannic acid. They produced 2-10nm AuNPs using this method. Seol *et al*. (2011) utilized high microwave power to reduce the size of synthesized nano-particles and make their size distribution more uniform.

As discussed above, there are several parameters affecting the size, shape and size distribution of gold nanoparticles namely concentration of gold salt, pH and temperature. There are very limited number of study in which all of this parameters considered. Considering all of the influencing parameters in studies is highly complicated. Therefore, another approach using artificial intelligence method is proposed to overcome this complexity and to have an insight on the general effect of each parameters. Using artificial intelligence (AI) methods has become widespread in solving nonlinear problems in engineering and health systems (Seong-Woo *et al*. 2001, Yegnanarayana 2009, Jiang *et al*. 2017, Ho *et al*. 2019, Coccia 2020, Singh *et al*. 2020, Troyanskaya *et al*. 2020, Liu *et al*. 2021a, Mahmood *et al*. 2021, Jung *et al*. 2022). This method and the methods on this basis have demonstrated superior ability in terms of time in comparison to numerical methods (Amelirad and Assempour 2019, Amelirad and Assempour 2021). This methods could be used to predict outputs of a system having the influencing factor and parameters. On the other hand, simple fitting of data using quadratic function (Ma *et al*. 2022, Zhao *et al*. 2022, Hou *et al*. 2021, Huang *et al*. 2021a, b, Jiao *et al*. 2021, Liu *et al*. 2021b, Moradi *et al*. 2021, Xu *et al*. 2021, Dong *et al*. 2022, Luo *et al*. 2022a, Michael *et al*. 2022, Wang *et al*. 2022b, Yang *et al*. 2022a, Yu *et al*. 2022) is very useful in finding optimum condition for a process employing response surface method (RSM) (Wong 1985, Habib *et al*. 2019, Dehghani *et al*. 2021, Moradi *et al*. 2022).

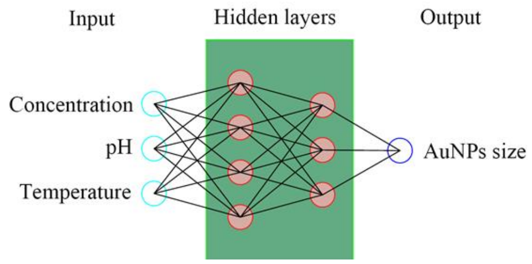


Fig. 1 Artificial neural network design for investigation of effects of different parameters on AuNPs size

Therefore, in this study, we explore different methodology and influencing parameters in producing AuNPs on the specific surface of gold nanoparticles. After specifying the main parameters, different machine learning and artificial neural network are adopted to model the effects of different parameters. Furthermore, response surface methodology is utilized to obtain a quadrilateral relationship between different parameters and specific surface and further point out the optimum condition. Moreover, the ability of gold nanoparticles in prolonging retention of the drugs is discussed in detail.

2 Related research

Finding optimum condition to have larger surface area of AuNPs is performed using optimization algorithm and artificial neural network and machine learning methods. All of this method require a set of valid input data from experimental or simulation sources to be trained at first. After training (calculating the unknown parameters in each method), the model is employed for further prediction of the output which in the case of the current study is the specific surface of gold nanoparticles to be used in the case of muscle injury and fatigue relief problems. On this basis, we explore different published experimental articles on synthesis of AuNPs in different condition and collected the required data for training our models. In this regard, the data presented in Refs. (Hatakeyama *et al*. 2011, Seol *et al*. 2011, Mountrichas *et al*. 2014, González-Mendoza and Cabrera-Lara 2015, Nicol *et al*. 2015, Silveira *et al*. 2016) are extracted.

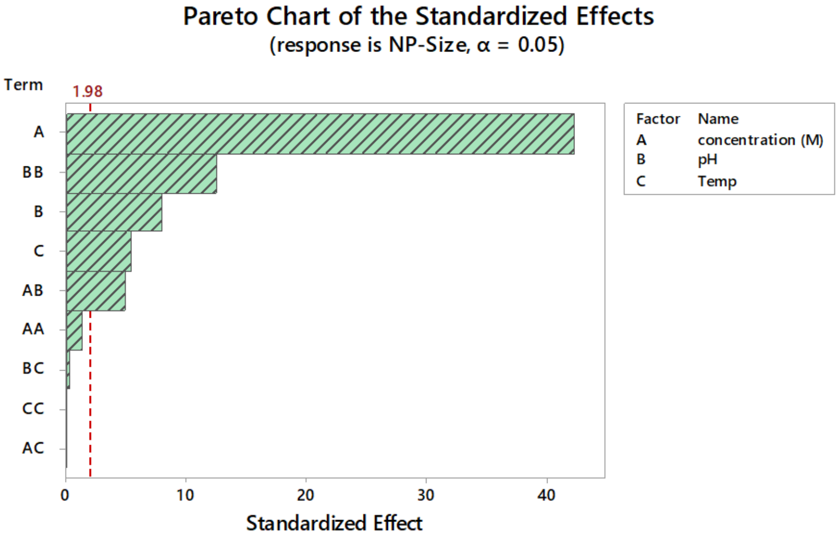


Fig. 2 Pareto chart to find out about the most important parameters in synthesizing AuNPs

Response surface method is a method of optimizing experimental condition based on a set of conducted experimental data. In the first step in this method, a high degree polynomial (commonly quadratic form) is fitted to the provided data (Fan *et al*. 2022, Luo *et al*. 2022b, Wang *et al*. 2022a, Xia *et al*. 2022). Afterwards, based on this fitted polynomial an optimization procedure is performed to find the optimal condition. This method is simple and present acceptable results. However, if the relation between the factors and the desired output does not follow a quadratic relationship, it could result an unrealistic prediction by RSM method. Thus, caution should be exercised in employing this method by precise investigation of the accuracy level (Habibi *et al*. 2016, 2018a, b, 2019b, d, e, Ebrahimi *et al*. 2019, Esmailpoor Hajilak *et al*. 2019, Pourjabari *et al*. 2019, Safarpour *et al*. 2019a, Zhu *et al*. 2022).

On the other hand, the artificial neural networks are extremely powerful in modeling non-linear behaviors of systems (Shariati *et al*. 2012, 2016a, b, 2019, 2020a, b, c, d, e, f, g, 2021a, b). Indeed, given a set of data, an ANN could tune its parameters to reach very low level of errors. ANNs are multilayer networks as demonstrated in Fig. 1.

As seen in this figure, a four-layer network is utilized to predict the gold nanoparticle size as a function of three input factors namely concentration, pH and temperature. There are two hidden layers for internal calculation of the neural network (Habibi *et al*. 2017, 2019a, c, Safarpour *et al*. 2018, 2019b, 2020, Alipour *et al*. 2020, Ebrahimi *et al*. 2020, Ghazanfari *et al*. 2020, Chen *et al*. 2022).

3. Results

Using RSM has advantage of finding the most important factor in synthesis gold nanoparticles. In doing so, the Pareto chart is extremely useful. In Fig. 2, the Pareto chart of influencing parameters is depicted. As can be observed in this figure, the most important parameter determining the size of the gold nanoparticles is the concentration of gold salt in the solution. The importance of this factor is much higher than pH and temperature of the solution as it could be deduced that using only the concentration of the gold salt one can control the size of the nanoparticles. The second key parameter is the pH of the solution and the third one is the temperature. It is worth mentioning that only these three parameters are considered in this examination. There are also other parameters investigated in other studies including the temperature change rate and rate of change in pH of the solution.

As mentioned earlier, the RSM used quadratic polynomial to fit the provided data by experiment which could be not sufficient for representation of the behavior. Therefore, the differences between nanoparticle size as calculated by RSM and the experimental values should be examined. The residuals of all values of the nanoparticle size are presented in different ways in Fig. 3. As seen, the residuals mostly fall between -8 and 8nm which is acceptable for this kind of analysis.

Analysis of variance of effects of different parameters on the gold nanoparticles is presented in Table 1. The P-value in this table presents the importance of each parameter. From this table it could be deduces that the product of concentration and pH is the most important in controlling gold nanoparticle size.

Predictions made by RSM fitting method could be further extended to other unknown experimentally condition to design experiments in the case a specific gold nano-particle size is needed for the muscle injury treatment and fatigue relief. Fig. 4 presents three-dimensional surfaces showing the effect of pH, concentration and temperature on the gold nanoparticle size. The vertical axis is the gold nanoparticle size and the horizontal axes are concentration of gold salt and pH of the solution. At constant values of pH, the presented surface show that increase in concentration of the salt results in increase in AuNP size. This dependency on the concentration is approximately linear. On the other hand, increase in the temperature of the reaction leads to slight increase in the size of the nanoparticles. This increase is almost constant in all

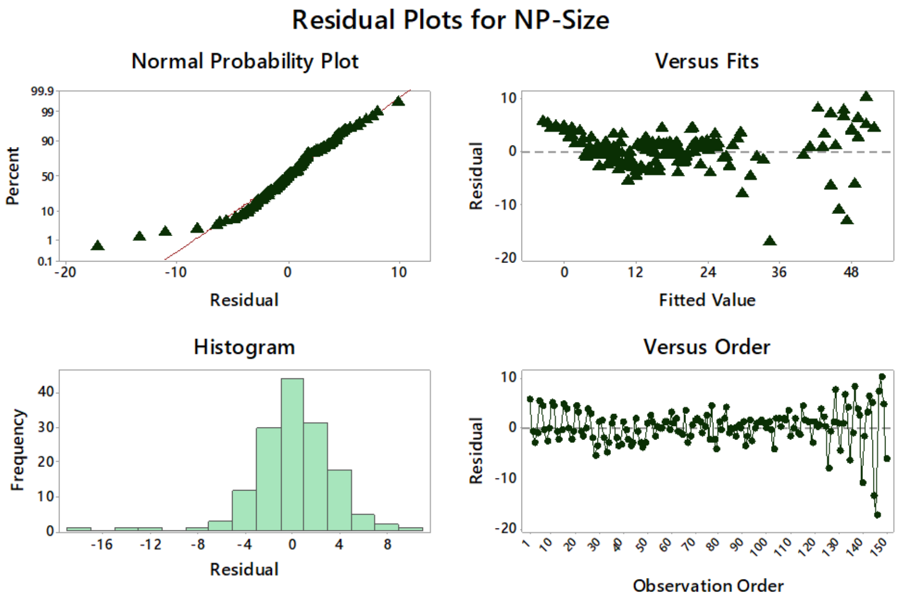


Fig. 3 Differences between values calculated by RSM and experimental results for AuNPs size

Table 1 Analysis of variance of influencing factor in synthesis of AuNPs

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Model	9	27989.4	3109.9	228.66	0
Linear	3	25454.3	8484.8	623.86	0
concentration (M)	1	24203.9	24203.9	1779.64	0
pH	1	860.2	860.2	63.25	0
Temp	1	390.2	390.2	28.69	0
Square	3	2119.3	706.4	51.94	0
concentration (M)*concentration (M)	1	22.4	22.4	1.65	0.202
pH*pH	1	2096.8	2096.8	154.17	0
Temp*Temp	1	0.1	0.1	0.01	0.927
2-Way Interaction	3	317.3	105.8	7.78	0
concentration (M)*pH	1	316.3	316.3	23.26	0
concentration (M)*Temp	1	0	0	0	0.959
pH*Temp	1	1	1	0.07	0.789
Error	140	1904.1	13.6		
Total	149	29893.4			

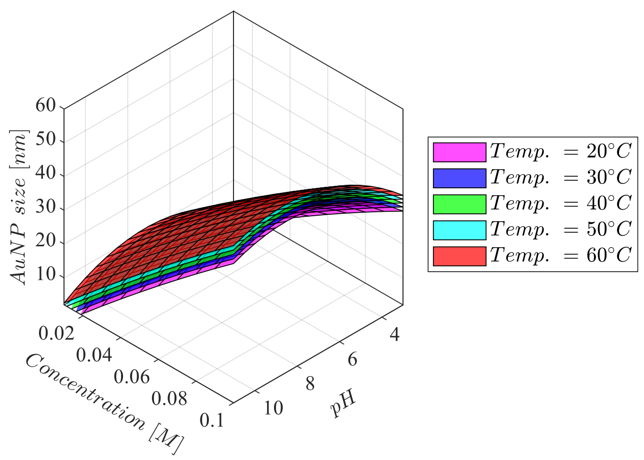
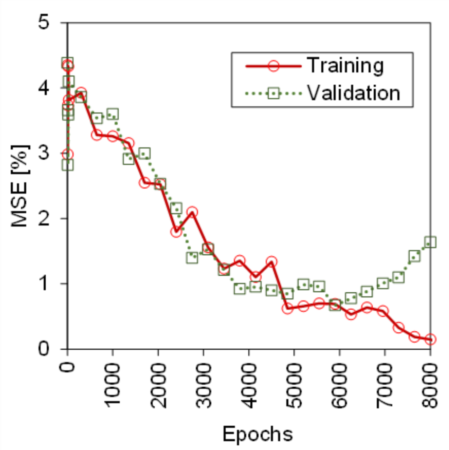
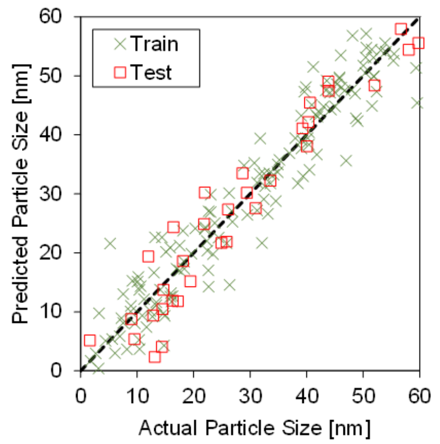


Fig. 4 Dependency of AuNPs size on concentration, pH and temperature as calculated by RSM



(a)



(b)

Fig. 5 (a) Artificial neural network training and validation MSE. (b) Predicted AuNPs size in comparison to experimental results

concentration and pH values.

Furthermore, at constant concentrations the dependency of AuNP size on the pH is quadratic with maximum values happening at the $pH = 7$. Change in the temperature does not alter this quadratic behavior and in all temperature condition the value of pH in which maximum particle size is obtained occur near pH=7. In higher values of pH it is seen that particle sizes are larger than lower values of pH. Therefore, to obtain larger gold nanoparticle it is recommended to shift the pH of the reaction solution toward higher pH and vice versa.

As discussed above, the RSM residual values are fall between -8 and 8 which is acceptable for finding optimum condition of the process. However, predicted values should be improved in the case we need more accuracy. Fitting experimental data using polynomial functions of other function may be not a perfect idea since it could happen some instances in which no function provide good results. In such cases, the methods based on ANN could be extremely beneficial in terms of modeling nonlinear behaviors of different processes. The results of the ANN method is presented in the following. In general, the provided experimental dataset is divided into two separate data sets namely train and test data set. As it could be deduced from the naming, the train data set is utilized to train the ANN. Training ANN is a term used for tuning the weights and biases in hidden layer of neural network. The ability of the ANN to reach low values of mean squared error (MSE) is a well-known fact. However, it should be noted that the train of the network to be continued up to over-fitting data. To avoid over-fitting data, the results predicted by ANN should be checked regularly to observe the accommodation of the MSE for data other than training data. In doing so, a third set of valid experimental data is separated from training data set for validation process.

In Fig. 5(a), the values of MSE for both training and validation process are presented as function of iterations (epochs). The values of MSE is similar for both training and validation process until epoch 6000 where an obvious diverge between two curves is observed. At this point, further tuning of the weights and biases of the ANN results in over-fitting of the training data which means that the ANN would be only present good result for training set only. However, we interest in ANNs having the ability to predict other outputs as accurate as training set. Therefore, the training process should be stopped at epoch 6000 and at this point the network is regarded as trained and validated.

For further examining, the ANN is tested using test data for observing the correlation between predicted and measured AuNP sizes. As seen in Fig. 5b, the correlation between both train data sets and test data sets are satisfactory which are $R^2 = 0.958$ and $R^2 = 0.942$, respectively. In this condition, the trained ANN could be confidently used for prediction of gold nanoparticle size prediction based on pH, concentration and temperature of the process.

4. Conclusions

This study covers an important aspect of utilization of nanoparticles in the case of muscle injury and fatigue relief. As the conventional drugs preventing inflammation of the muscle injury section are unstable, using gold nanoparticles could be a promising method in treatment of such injuries. Therefore, we explored different methodology and influencing parameters on the specific surface of gold nanoparticles which is vital in drug delivery capability of these nanoparticles. After specifying the main parameters, artificial neural network are adopted to model the effects of different parameters. Furthermore, response surface methodology is utilized to obtain a quadrilateral relationship between different parameters and specific surface. The results indicate that concentration and pH of the reaction solution are the most parameters in increasing specific surface. Moreover, the ability of gold nanoparticles in prolonging retention of the drugs is discussed in detail. The main results could be encapsulated in the followings:

•With high values of the correlation factors, the trained ANN could be confidently used for prediction of gold nanoparticle size prediction based on pH, concentration and temperature of the process.

• The most important parameter determining the size of the gold nanoparticles is the concentration of gold salt in the solution.

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