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Optimization of Processing Parameters for the Preparation of Nimodipine-Loaded Transferosomes by Solvent Evaporation-Hydration Method

Samir Hasson Aziz Ramadhan[1*] and Khalid Kadhem Al-Kinani[2]

[1] Ministry of Health, National Baghdad Center for Drugs Control and Research, Directorate of Technical Affairs, Iraq.

[2]Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

***Corresponding author**

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Abstract

Nimodipine is a vasodilating drug approved for the prevention of cerebral vasospasm, a major risk factor that causes deaths in patients diagnosed with subarachnoid hemorrhage. The current marketed products of this drug are administered either orally in frequent, multiple daily doses, or by infusion through central vein. Therefore, delivery of nimodipine through the skin via transferosomes can overcome such difficulties because the transdermal route is non-invasive; associated with prolonged duration of drug and reduced dosing frequency. Solvent evaporation-hydration method followed by sonication was applied for the preparation of transferosomes. The aim of the present study is to investigate and optimize the processing parameters of this method through the utilization of Design-Expert® software. Box-Behnken statistical design was selected for this purpose to study the film formation temperature, speed of rotation, and hydration time as independent variables, each at three levels. The vesicles sizes (VS), polydispersity index (PDI), and entrapment efficiency (EE) of nimodipine were the dependent variables. After statistical analysis of the obtained data, a batch was formulated according to the selected, optimized variables, and then the responses were compared to those predicted by the software. This batch was subjected to further characterization by transmission electron microscopy (TEM), degree of deformability and permeation through an excised skin of rat. The study showed that transferosomal formulations were within nanoscale range for VS 95.4 – 914.0 nm with PDI 0.0897 – 0.624 and EE 65.2 – 98.3%. The chosen response ranges to optimize the processing parameters were 200.0 - 250.0 nm for VS, 0.1 – 0.4% for PDI and 80.0 - 100.0% for EE. The resulted values of the batch formulation were comparable as 197.0 nm, 0.09% and 91.4%, respectively. In addition, TEM revealed bilayer vesicular structure, degree of deformability was 0.98 and permeation calculated as the flux of nimodipine was 113 µg/cm^2/h. In summary, this study demonstrates that in addition to addressing qualitative and quantitative concerns, optimizing the processing parameters can yield nimodipine-loaded transferosomes to achieve the desired properties of the transferosomes.

Keywords: Transferosomes, Nimodipine, Box-Behenken, Design, Solvent Evaporation-Hydration.

Introduction

The administration of drugs through the skin possesses great prospective [(1)]. Such transdermal delivery of drugs is non-invasive; appropriate for unconscious or vomiting patients, enhances their compliance, skipping first-pass metabolism, thus bioavailability of the drug is increased; while the dose, dosing frequency and the risk of toxic side effects is reduced [(2)]. Lipid-based nano-vesicles can facilitate the passage of drugs through stratum corneum and skin appendages, increase contact time, control the release and protects the drug from physical and chemical instability [(3)]. The developed types of these biocompatible carriers include transferosomes [(4)], ethosomes [(5)] , invasomes [(6)], novasomes [(7)] ufosomes [(8)] and cubosomes [(9)]. As the first ultradeformable vesicles, transferosomes were introduced, composed of phospholipid (as for liposomes) as well as an edge activator (surfactant) which is responsible for the elasticity and flexibility properties [(10)]. Therefore, transferosomes change in shape and modulated as the vesicles pass skin to reach the systemic circulation [(11)]. When applied onto skin, the flexibility of transferosomes resists the possibility of their rupture [(12)]. This type of vesicles gained attention for the delivery of medicinal small molecules and peptides [(13)].

Research through quality by design (QbD) approach during pharmaceutical development of new products is useful to improve methods so that the critical formulation and processes parameters are identified.

Consistent quality therefore will be reached and drug product with the desired properties is then obtained [14]. The critical process parameters (CPPs) are among the elements stated by the international Conference of Harmonization (ICH) guideline for pharmaceutical development [15,16]. Therefore, optimization of such parameters during the preparation of vesicular nano-carriers, such as transferosomes is valuable for the design of formulations [17]. Furthermore, the application of QbD experiments in the pharmaceutical industry permits robust manufacturing which lead to an optimized products, enhances the regulatory confidence and reduces post-approval changes [18].

Nimodipine is a calcium channel blocking vasodilator drug, which reduces the risk of delayed cerebral ischemia associated with subarachnoid hemorrhage [19]. The approved oral dosage forms of the drug require multiple administration due to extensive first-pass metabolism with variable bioavailability range from 3 to 30% [20]. On the other hand, injectable products of nimodipine were associated with adverse events and/or complications, including hypotension, thrombosis caused by catheter indwelling, and new intracerebral hemorrhage [21]. Subarachnoid hemorrhage which is diagnosed and evaluated with computed tomographic angiography [22] may cause brain injury with the loss of consciousness [23]. Therefore, transdermal delivery of nimodipine through the nano-sized carriers can provide an alternative pathway and additional advantage to those mentioned previously. Mainly, these carriers are formulated with lipids materials that resemble those of the skin [24].

The method of solvent evaporation and lipid film formation/hydration followed by application of ultrasound energy for homogenization had been described for the preparation of transferosomes.

The objective of this work is to study and optimize the processing parameters of solvent evaporation-hydration method for the preparation of nimodipine-loaded transferosomes.

Materials and Methods

Materials

Nimodipine was purchased from Leyan (China), while phospholipon® 90% was purchased from Henan (China). Sodium deoxycholate supplier was BDH (UK). Chloroform and ethanol purchased from Supelco (UK). Monobasic potassium phosphate, sodium hydroxide and sodium lauryl sulphate were from (Alpha, India).

Instruments

The instruments which were used in this work include rotary evaporator apparatus (Buchi, Switzerland), ultrasound water bath (Soniclean, Australia), zetasizer (Malvern, UK), centrifuge (Eppendorf, Germany), UV-visible spectrometer (Shimadzu, Japan), Franz diffusion cell apparatus (Copley, UK) and Transmission electron microscope (Zeiss, Germany).

Methods

Experimental design

Box-Behenken design was applied in this study through the utilization of Design-Expert® Software Version 13 (Stat-Ease Inc. Minneapolis, MN). A 15 formulation runs with each of the processing parameters at three levels were generated. The studied parameters included film formation temperature (A), speed of rotation (B) and hydration time (C) as independent variables. On the other hand, the obtained responses as dependent variables were vesicles size (VS), polydispersity index (PDI) and entrapment efficiency (EE). Table 1 includes the formulation runs suggested by the software.

Table 1. The formulation runs with the process parameters and their responses.

Run	Temperature (A)	Speed (B)	Time (C)	VS	PDI	EE
#	°C	rpm	Hour	nm	---	%
1	45	50	3	348.8	0.3566	89.1
2	50	50	2	810	0.5928	65.2
3	45	75	2	344.8	0.16625	92.5
4	45	75	2	321.9	0.1814	94.4
5	40	50	2	98.67	0.0897	82.3
6	45	100	1	329.5	0.204	96.1
7	45	100	3	302.4	0.2538	98.3
8	50	100	2	914	0.624	74.5
9	45	75	2	332.7	0.1462	93.7
10	50	75	3	871	0.431	72.1
11	40	100	2	103.7	0.0921	85.2
12	45	50	1	315.4	0.1454	85.2
13	40	75	1	98.45	0.1327	81.9
14	40	75	3	95.4	0.17622	83.6
15	50	75	1	852	0.518	69.5

Preparation of transferosomes

Solvent evaporation followed by hydration was conducted for the preparation of nimodipine-loaded transferosomes. The method imitated by dissolving 30 mg nimodipine, 150 mg Phospholipon® 90% and 15 mg sodium deoxycholate in chloroform and methanol (3:1) mixture, then the rotary evaporator was switched on with the water bath at the temperature of 40, 45 or 50°C, and the specified speed at 50, 75 or 75 rpm with reduced pressure. Afterward, the formed film was left for two hours to ensure full dryness. Hydration of the film gained through shaking with 10 mL phosphate buffer pH 7.4 for 1, 2 or 3 hours. Nimodipine concertation in the transferosomal dispersion was 3 mg/mL. Sonication was applied for 3 minutes in ultrasound water bath [25].

Characterization of transferosomes

Vesicles size (VS)

The principle of dynamic light scattering was applied by the zetasizer instrument for the determination of the vesicles sizes. The samples of transferosomal dispersions were diluted with water prior analysis [26].

Polydispersity index (PDI)

The heterogeneity or polydispersity index (PDI) was obtained simultaneously during analysis by dynamic light scattering from a two-parameter fit to correlation data as dimensionless value [27].

Entrapment efficiency (EE) of nimodipine

To test the entrapment efficiency of nimodipine by transferosomes, aliquots from the dispersion was centrifuged in Amicon® tubes (MWCO 10000) at 15000 rpm for 60 minutes [28]. Both of the filtered and retained drug (free and total, respectively) was calculated using the following equation [29] after the measurement of UV absorbance at 238 nm in 1-cm cuvette by the spectrometer:

$$EE(\%) = \frac{\textbf{Total quantity of nimodipin} - \textbf{Free quantity of nimodipine}}{\textbf{Total quantity of nimodipine}} \times 100$$

Optimization of transfersomes

The optimized formulation composed from nimodipine, phospholipon® 90% and sodium deoxycholate was prepared according to the suggested processing parameters of the above method and characterized for VS, PDI and EE. Furthermore, studies of morphology, deformability and steady-state flux (Jss) of nimodipine was implemented for the optimized formulation [30].

Morphological examination

The structure of the optimized nimodipine-loaded transfersomes was imaged through transmission electron microscopy (TEM). A mini-drop of the transferosomal dispersion was put on the grid for drying prior the imaging [29].

Deformability index

Deformability is crucial for transferosomes since it reflects its ability to traverse through the layers of skin with retained integrity. An extrusion technique was followed for the measurement of deformability of optimized formulation. Onto glass flask, 0.20 μm membrane was fitted with stainless-steel holder and with the aid of vacuum pump, the transferosomal dispersion passed. The vesicles sizes were measured before and after extrusion by the zetasizer [31]. The deformability index was obtained by dividing the measured sizes after extrusion by those recorded before this process.

Determination of nimodipine ex. vivo steady-state flux (Jss)

The steady-state flux (Jss) for the optimized formulation was determined utilizing Franz diffusion cell with an area of 3.14 cm^2. The cell was assembled in beaker filled with water acted as modified thermal jacket. In the donor chamber of the cell, 3 mL of the transferosomal dispersion (contains 8.2 mg of nimodipine in transferosomes) was loaded, while the 12-mL receiver chamber was filled with phosphate buffer pH 6.8 containing 1% sodium lauryl sulphate at temperature of 35±0.5ºC. An excised and washed skin of Wister rat males was placed between the chambers [32]. A volume of 0.25 mL from the receiver medium at 1, 2, 4, 6, 12, 16, and 24 hours was sampled with replacement [33]. The permeated quantities of the drug were determined from the UV absorbance at 238 nm in 1-cm cuvette by the spectrometer after dilution of samples [34] and the steady flux (Jss) of nimodipine was determined as the slope of line for permeated quantities versus time plot.

Results and Discussion

Experimental design

The vesicles size (VS), polydispersity index (PDI) as well as the entrapment efficiency of nimodipine (EE) for the 15 formulation runs are seen in Table 1, while the summary of calculated statistical parameters obtained for the responses are stated in Table 2. Quadratic models were selected for VS and EE, while logarithmic linear model was suitable for PDI. The F values were significant for the three models. The processing parameters or independent variables, namely film formation temperature (A), speed of rotation (B) and hydration time (C) in these models appeared to behave differently. For VS, the parameters A, B and C are found with their squared and products of terms, which indicate the presence of interactions between these parameters. On the other hand, the model for PDI appeared logarithmic and without any interactions between the terms A, B and C. Finally, the model for EE was found quadratic, normally

scaled, without interactions. Since the predicted and adjusted R^2 values for the three models were in reasonable closeness, and adequate precision values more than 4, the selected models were satisfactory for the description of relationship between the independent and dependent variables, which in turn can be successfully implemented for optimization of formulation. Box-Behnken design is considered as a subtype of three-level fractionate factorial designs, with an additional advantages of modeling as 1st or 2nd order response surfaces and being more cost-effective than three-level full factorial designs [35].

Table 2. Statistical parameters of various responses for the models.

Response	Model source	Model F- value	Lack of fit F value	Predicted R2	Adjusted R2	Adequate precision
VS	Quadratic	250.91	0.1383	0.9675	0.9938	42.2007
PDI	Linear	16.65	9.75	0.6666	0.7693	11.3596
EE	Quadratic	67.13	3.65	0.8861	0.9770	25.6536

Vesicles size

The following polynomial quadratic model was suggested for vesicles size:

$$VS = +333.13 +381.35A +9.59B +2.78C +24.74AB +5.51AC -15.13 BC +151.82 A^2 -3.36B^2 -5.74C^2$$

The model revealed that the film formation temperature was significantly the most influential parameter on the vesicles size than the other two. The higher the film formation temperature (of water bath), the larger is the vesicles size. This effect of the film formation temperature was almost constant at different speeds of rotation as shown in the contour and response surface plots (Figure. 1). The effect of the negative interaction and parabolic terms BC, B^2 and C^2 were minor. The effect of temperature had not been investigated widely in the preparation of transferosomes. However, that showed that temperatures more than 50°C did not significantly affected VS of liposomes. One study for transferosomes showed that the lipid film formed only at certain temperature [37]. The extremely larger VS in our study when the 50°C temperature used may be attributed to the more fluidic nature of phospholipids at such temperature which lead to the formation of multilayered vesicles such that might had been difficult to break by sonication. Regarding the speed of rotation, more time for contact of the film with the water in the bath would occur at lower speeds, while such time was not enough at higher speeds. This effect might resulted in the larger VS due to the unideal liquid for gel transitions of the lipid [38]. The hydration time was the least affecting parameter.

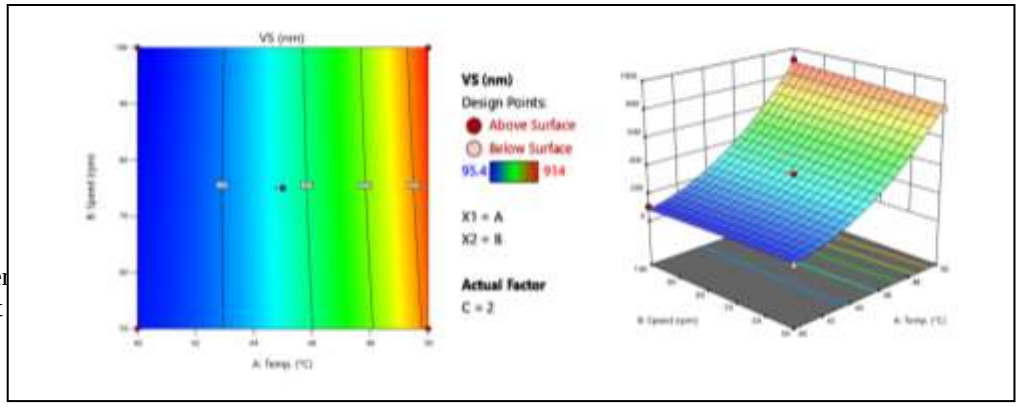

Figure 1. Contour and response surface plots for the effect of processing parameters on VS.

Polydispersity index (PDI)

The linear model created as the polynomial equation to describe the PDI was:

$$Log_{10}(PDI) = -0.6483 +0.3289A +0.0041B +0.0660C$$

The film formation temperature is the dominant parameter affected the PDI, while the speed of rotation was the least one. Overall, the raising film formation temperature, speed of rotation and the hydration time increased the PDI. Nevertheless, the contour and response surface plots (Figure. 2) showed that the high PDI only seen at 50°C, while vast range of the film formation temperature gave low PDI. A uniform distribution of size which is expressed as the PDI was not more than 0.7 in this study, and even less than 0.3 for most formulation

runs, thus it can be acceptable as monodispersed system [39]. Thus, aggregation of vesicles was negligible during its preparation [40]. The hydration time here was the least affecting parameter.

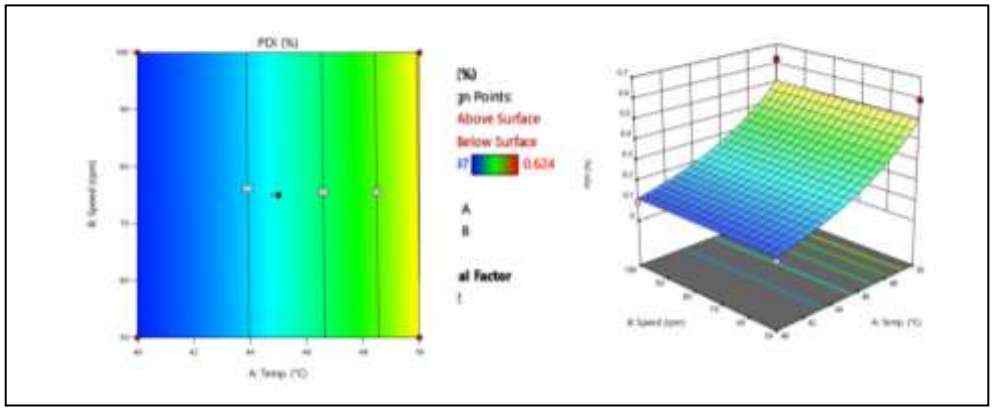

Figure 2. Contour and response surface plots for the effect of processing parameters on PDI.

Entrapment efficiency of nimodipine

The resulted quadratic model as polynomial equation for entrapment efficiency was:

$$EE = +93.53 - 6.46A + 4.04B + 1.30C + 1.60AB + 0.2250AC - 0.4250BC - 16.07A^2 - 0.6667B^2 - 0.6917C^2$$

Notably, the coefficients of the model referred that the film formation temperature appeared as the most striking parameter. However, the product (AB, AC and BC) as well as the squared terms (A^2, B^2 and C^2) clearly pointed that all parameters interacted. Contour and response surface plots for entrapment efficiency in Figure. 3 revealed an elliptical shape, reflected such interaction. The highest entrapment efficiency was reached at the mid-range of temperatures, which broadened at faster speed of rotation. This can be explained by the fact that processing near the transition temperature of the phospholipid might support the entrapment of drug during the changes from the gel phase to liquid crystal phase. The interaction effect was also concluded in the study of liposomes [41].

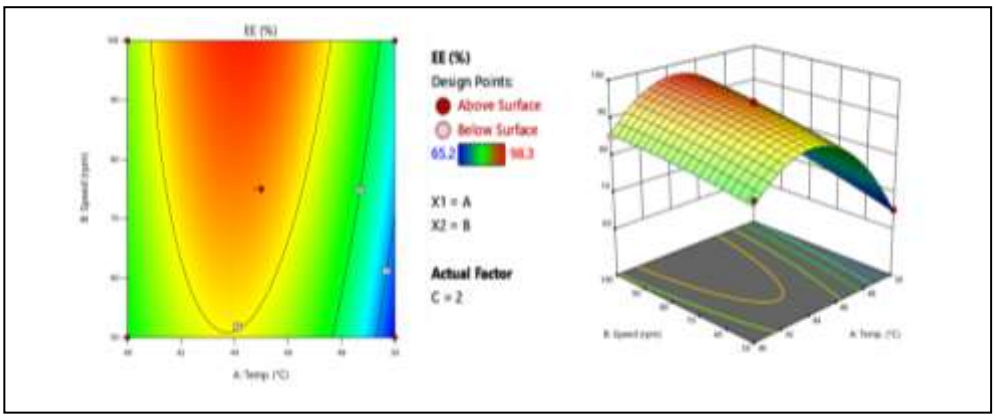

Figure 3. Contour and response surface plots for the effect of processing parameters on EE.

Preparation and characterization of the optimized transferosomes

The desirability values for numerical optimization of processing parameters were selected in the range of the applied conditions. The best suggested solution by the software to optimize nimodipine-loaded transferosomes were 42.5°C for film formation temperature, 55 rpm for the speed of rotation and 2.7 hours for the hydration time as independent variables. An optimized formulation was prepared according to the selected conditions and characterized. Table 3 illustrates the good agreement between the predicted and observed values for this formulation.

Table 3. Predicted and experimental responses of the optimized formulation.

Response	Predicted value	Observed value
Vesicles size (nm)	186.9	197.0
Polydispersity index (---)	0.179	0.099
Entrapment efficiency (%)	90.4	91.4

Morphological examination

The images obtained for TEM in Figure. 4 revealed vesicular, bilayer structures of the optimized transferosomes. In addition, the size of an individual transferosome was approximately near to that measured by zetasizer.

Deformability index

Calculation of deformability index is needed as it reflects the ability of transferosomes to traverse skin with a retained integrity. The index of the optimized formulation found 0.98 which revealed the elastic property of the transferosomes.

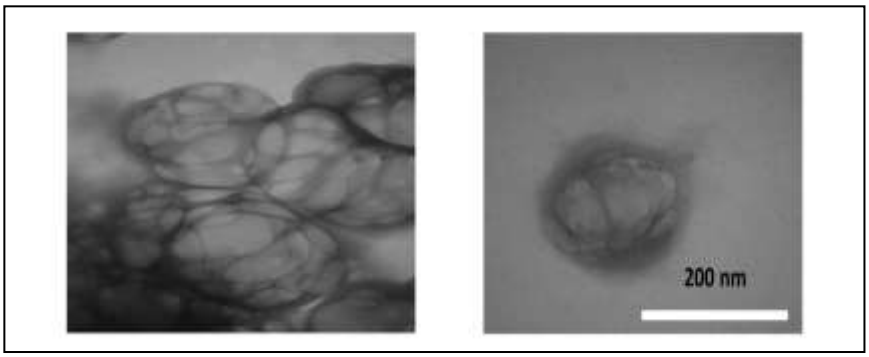

Figure 4. TEM images of nimodipine-loaded transferosomes.

Steady-state flux (Jss)

The characteristic flexibility and elasticity provided through the inclusion of edge activator in the body of transferosomes is enhanced with surfactant role of such molecule to permeate drugs [42]. Therefore, these vesicles are not limited for topical application, but intended for an enhanced transdermal delivery [43]. The flux of nimodipine was calculated from the slope of line in Figure 5 and found 113 µg/cm^2/hr. The nano-deformable properties of transferosomes enhanced the flux by the osmotic gradient which is the mechanism of penetration; however, the prolonged permeation time of the drug might be due to their slow escape from the upper layers of the skin. In addition, the lipophilic nature of the drug and its abundant content in the vesicles lead to decreased thermodynamic activity and slowed down its permeability [44].

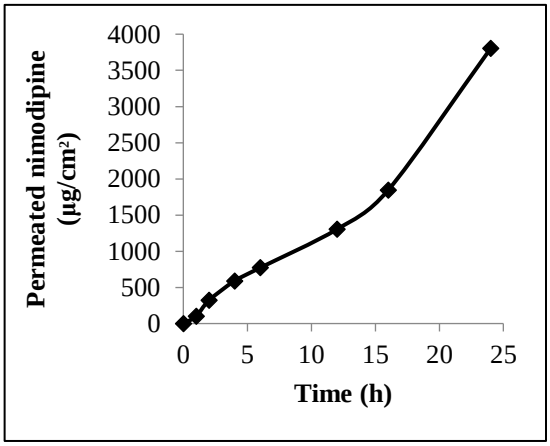

Figure 5: The *ex. vivo* permeation profile of nimodipine from transferosomes.

Conclusion

In order to deliver nimodipine transdermally, transferosomes were chosen due to their distinct characteristics. The statistical optimization for the processing parameters through Box-Behenken design was applied and formulation runs were suggested for the optimization process. The studied dependent variables were vesicles size, polydispersity index and entrapment efficiency due to its fundamental importance in all nano-sized systems to attain the desired transdermal delivery. The mathematical models were chosen to best suited for each outcome response. The predicted and experimental results were comparable. Further

studies for deformability, imaging and steady-state flux of nimodipine proved that transferosomes can be considered as potential carriers for nimodipine due to their capability to enhance the permeation through skin in an almost controlled manner. These advantages provide convenient administration for patients as well as possible reduction of side effects associated with nimodipine.

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Conflicts of Interest

The authors clearly declare that they do not have any conflict of interest with any scientific and/or commercial organization.

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Ethics Statements

The skin of Wistar rat was used after the College of Pharmacy University of Baghdad Research Ethical Committee issued the certificate with the approval number RECAUBCP142024K.

Author Contribution

The authors contributed their roles as follows: study conception, design, experimental work and data collection by Samir Hasson Aziz Ramadhan. Analysis and interpretation of the study results was done by Samir Hasson Aziz Ramadhan and Khalid Kadhem Al-Kinani. Draft manuscript preparation: Samir Hasson Aziz Ramadhan. Both authors reviewed the results and confirmed it.

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تحسين عوامل التحضير للحويصلات الناقلة المحملة بنيموديبين بطريقة تبخير المذيب ـ الترطيب

سامر حسون عزيز رمضان[١] و خالد كاظم الكناني[٢]

[١] وزارة الصحة ،المركز الوطني للرقابة و البحوث الدوائية، بغداد، العراق.

[٢] فرع الصيدلانيات، كلية الصيدلة، جامعة بغداد، بغداد، العراق.

الخلاصة

نيموديبين هو دواء معتمد للوقاية من التقلص الوعائي الدماغي لدى المرضى المصابين بنزيف تحت العنكبوتية. المنتجات المسوقة للدواء يتم إعطاءها عن طريق الفم بجرعات متكررة أو التسريب المستمر عبر الوريد المركزي ، لذا فإن توصيل نيموديبين عبر الجلد بإستخدام الحويصلات الناقلة يمكنه التغلب على هذه الصعوبات. تم تطبيق طريقة تبخيرالمذيب-ترطيب متبوعة بالأمواج فوق الصوتية لتحضير هذه الحويصلات. الهدف من هذه الدراسة تحري وتحسين عوامل التحضير لهذه الطريقة بإستخدام تطبيق خبير التصميم و إختيار التصميم الإحصائي بوكس- بينكن لتحري درجة حرارة تكوّن الحويصلات ، سرعة الدوران و زمن الترطيب كمتغيرات مستقلة ، بينما كانت أحجام الحويصلات، ومؤشر تعدد التشتت ، وكفاءة تحميل نيموديبين هي المتغيرات التابعة. بعد التحليل الإحصائي للبيانات ، تم تصييغ وجبة وفقا للمتغيرات المختارة والمحسنة و مقارنة النتائج مع تلك التي تنبأ بها التطبيق. أظهرت الدراسة أن حجم الجسيمات الناقلة يتراوح من ٩٥,٤ إلى ٩١٤,٠ نانومتر مع مؤشر تعدد التشتت من ٠,٠٨٩٧ إلى ٠,٦٢٤ و كفاءة التحميل من ٦٥,٢ إلى ٩٨,٣٪. تم تحديد نطاقات المتغيرات التابعة لتحسين المعالجة لتكون من ٢٠٠,٠ إلى ٢٥٠,٠ نانومتر لحجم الحويصلات ، ٠,١ - ٠,٤٪ لمؤشر تعدد التشتت و٨٠,٠ - ١٠٠,٠٪ لكفاءة الإحتواء وكانت القيم الناتجة للوجبة ١٩٧,٠ نانومتر و٠,٠٩٪ و٩١,٤٪ على التوالي. بالإضافة إلى ذلك، أظهر صورة المجهر الإلكتروني النافذ عن بنية حويصلية ثنائية الطبقة، وكانت درجة التشوه ٠,٩٨ و النفاذ المتدفق لنيموديبين من خلال جلد الجرذان ٣١١ ميكروغرام / سم ٢ / ساعة. أظهرت الدراسة إمكانية تحسين العوامل المؤثرة على طريقة تحضير الحويصلات الشحمية الناقلة لنيموديبين بواسطة تصميم التجارب لأجل الوصول إلى الخصائص المطلوبة.

الكلمات المفتاحية: الحويصلات الناقلة ، نيموديبين ، تصميم ، بوكس ـ بينكن ، تبخير المذيب ـ الترطيب .