Jordan Journal of Pharmaceutical Sciences, Volume 18, No. 3, 2025

In vivo Pharmacokinetic Comparison of Oral and Polymeric Nanoparticles Loaded in Transdermal Bilayer Dissolving Microneedles for Nimodipine delivery

Asmaa Mohammed Rashid[1], Mowafaq M. Ghareeb[*1]

[1]Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq

ABSTRACT

Background: Subarachnoid hemorrhage (SAH) is a disease that requires extensive treatment with medication that targets the brain and minimizes systemic adverse effects, preferably with a single daily medication. Nimodipine [NID] offers these properties to be used for this purpose.

Objective: The goal of the study was to accomplish a comparison in the pharmacokinetic parameters of oral nimodipine suspension and transdermal Polymeric Nanoparticles loaded bilayer dissolving microneedles to improve lower oral bioavailability.

Methods: Nimodipine was previously formulated as polymeric nanoparticles (PNPs) characterized by a particle size of 81.78 ± 0.6 nm, a polydispersity index of 0.046 ± 0.01, and a zeta potential of -18.96 mV. These nanoparticles were incorporated into bilayer dissolving microneedle patches (bDMNs) utilizing a casting technique, employing a 10% w/v polyvinyl alcohol (PVA) polymer matrix and 5% glycerin. A total of twelve male white albino rabbits, each weighing approximately 1500 ± 175 g, were randomly allocated into two groups of six animals. One group received an oral dose of nimodipine suspension via oral gavage, while the other group was administered the nimodipine-loaded transdermal bDMNs applied to the skin. The plasma concentration of nimodipine was quantified using reversed-phase high-performance liquid chromatography (RP-HPLC), following the establishment of a spiked calibration curve with plasma samples with the internal standard cilnidipine.

Results: The results displayed mean value of time and concentration needed to achieve the maximum effect were (C_{max}= 42.54 ±3.4 ng/ml, T_{max}= 1 ±0.02 h) for oral and (C_{max}=64.66 ±2.9 ng/ml, T_{max}=0.5±0.01h) for bDMN, respectively approving that the optimized transdermal bDMN exhibited higher plasma concentration with T_{max} lower than oral route, achieving (1.9) fold rise in the calculated relative bioavailability.

Conclusions: The transdermal bDMNs could offer a promising and effective method for NID delivery to improved lower oral bioavailability by enhancing the delivery through skin.

Keywords: Subarachnoid hemorrhage, transdermal, bilayer, bioavailability.

INTRODUCTION

Regardless of their post-ictus neurological condition, NID can enhance neurological outcomes by lowering the prevalence and severity of ischemia impairments [1]. In 1988, the FDA first gave its approval for clinical uses in treating SAH [2]. The parenteral NID formulation has a high absolute bioavailability (100 %) but it causes painful administration with the need for hospitalization resulting in low efficacy. Oral administration of the NID using current dosage form (tablets and capsule) has low plasma concentrations and required a high daily doses to achieve its therapeutic effect due to the extensive first-pass metabolism [3]. Additionally, drawbacks such low drug solubility, repeated daily oral doses were required ending with insufficient bioavailability (13-30%) and undesirable side effects.

[*]***Corresponding author: Mowafaq M. Ghareeb***
Mowafaq.abd@copharm.uobaghdad.edu.iq
Received: 14/07/2024 Accepted: 21/09/2024.
DOI: https://doi.org/10.35516/jjps.v18i3.2958

The study described using a combination technique involving bilayer dissolving microneedles (bDMNs) and Nano encapsulation for delivering a lipophilic model systemically via the skin [1]. As a result, a transdermal delivery bDMN-loaded was developed to overcome skin barrier stratum corneum (SC) while PNPs compromise a number of features, including increasing lower solubility, targeted drug delivery, regulate the skin permeability, prevention of incorporated drug from degradation in the biological environment, consequently reduced dose and side effects [4, 5].Therefore, selective manipulation of size, chemical composition, shape, internal structure, surface charge, and combination approaches allows for controlling drug release from PNPs.

There is consensus in the literature that physical approaches such as microneedles are necessary for PNPs to enhance the permeation through the SC [6]. The drug is usually released and carried to deeper layers of the epidermis by the hair follicles. The transporting PNPs via bDMN beyond SC, achieved by creating microsized channels within skin, thereby increasing the translocation of NPs as reservoirs of drugs deeper to skin [7].

As a results, transdermal drug delivery is an attractive option that deliver NID systemically achieving avoidance of first pass metabolism in addition to the advantages of bDMNs such as being noninvasive, painless self-administered dosage form .This study developed new bDMNs formulations of NID for transdermal application to improve lower oral bioavailability via preventing presystemic metabolism and lowering side effect of NID [4, 7].

The primary objective of this study was comparing the pharmacokinetic parameters of oral NID suspension with transdermal PNPs loaded bDMNs, to enhance oral bioavailability.

MATERIALS AND METHODS

Materials

Nimodipine (CAS Number: 66085-59-4) was purchased from Zhejiang Shenzhou pharmaceutical Co., LTD, China, soluplus was purchased from Sigma-Aldrich®, PVA and PVP was purchased from HI Media Laboratories, USA. HPLC grade Acetonitrile, HPLC grade Methanol and all other chemicals were obtained from Merck chemical division, Mumbai. Ethanol was purchased from Honeywell International Inc. USA.

Preparation of NID-NP-DMN

Nimodipine was previously formulated, characterized, and optimized, as shown in Table 1. The formulation contained one dose of the drug mixed with Soluplus (1:8, w/w), dissolved in 3 mL of ethanol, which was then added to an aqueous phase containing 0.25% PVP K15. The mixture was stirred until a uniform distribution was achieved, resulting in particles with a size of 81.78 ± 0.6 nm. Subsequently, the casting technique was employed to fabricate bDMNs (array 15 × 15, 500 µm height) using 10% PVA as the polymeric solution [8,9].

Table 1. Composition of NID-PN-DMN

Ingredients	Amount
Nimodipine	30mg
Soluplus *	240mg
Absolute ethanol	3ml
PVPK15**	0.075mg
D.W***	27ml
Glycerin	5%v/v
PVA	10%w/v
Soluplus®= polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer **PVPK15=polyvinylpyrrilodine K15, ***DW= deionized water	

Study Design

This study utilized twelve male white albino rabbits, which were randomly divided into two groups, each consist of six rabbits (n=6), with an average weight of 1500±175 g. The rabbits were confined in the animal facility of the Research Centre for Cancer Research and

Medical Genetics, Baghdad, Iraq, under a constant room temperature of 25°C±1°C, a 12h light/dark cycle for 7 days prior to the experiment to be acclimatized to laboratory conditions [10].

Dosing Regimen

Before administration, rabbits were subjected to food fasting for12 hr. The animals dose (3.08mg/kg) was calculated depending on human dose (1mg/kg), according to equation (1), the rabbits (1500 ± 175g) given oral dose of the NID suspension using an oral gavage as the control group while the second groups were administered NID by inserted transdermal bDMNs into the full thickness of dorsal skin after removing their back hair using an electric shaver [2].

$$HED\left(\frac{mg}{kg}\right) = AED\left(\frac{mg}{kg}\right) \times \frac{AnimalKm}{Human\ Km} \ldots\ldots\ldots\ldots\ldots\ldots Eq.1$$

Where, HED is the human equivalent dose, AED is the animal equivalent dose, and Km is the conversion factor (for human adults=37, and for rabbits =12) so the ratio will be 3.0 [3,4] .During administration, both groups were administered ketamine (Ketamine 10%, Alfasan Woerden, Holland) at a dose of 35 mg/kg, and xylazine (XYL-M2, VMD® HogeMauw 900 pharma, Belgium) at a dose of 5 mg/kg , the study concentrated on 48 h and divided the times of sample collection [7].

In vivo pharmacokinetic studies

The study was concentrating to evaluate the drug delivery of NID transdermaly through the application of NID-PNP Loaded bDMNs. Each sampling was timed, and a single dose was administered to both groups to assess the relative bioavailability of the oral NID suspension and transdermal NID-PNP-bDMN. A total of 1 mL of blood samples were taken from heart before administration (0 min) and at 5, 10, 20, 30, 45, 1hr, 2, 6, 12, 24 and 48 hr., post injection, was acquired from the myocardium through piercing at predefined time intervals .An EDTA-treated tubes were used in order to collect blood samples from the rabbits, which were then promptly separated. Plasma samples were obtained by centrifuging the blood samples (Hettich Zentrifugen EBA 20, Germany) at a speed of 3000 rpm for a duration of 15 min. Plasma samples were obtained from the supernatant liquid fraction, transported to Eppendorf tubes, and stored at -20 °C for analysis .All samples were sheltered from exposure to light to avert any potential photo-degradation of NID in the plasma [11].

A confirmed approach was used to evaluate the samples of plasma by using reversed high-performance liquid chromatography (RE-HPLC). Maximum concentration (C_{max}) and time to reach C_{max} (T_{max}) were also determined. The AUC_{0-48} were determined by calculating the integral of the plasma concentration-time curve from time 0 to 48 hrs. by applying Trapezoidal rule. The relative bioavailability value (F) was calculated using equation 2 [12, 13].

$$Relative\ Bioavailability = \frac{AUC\ NID-PNP-MN \times dose of\ \ NID\ suspension}{AUC\ NID\ suspension \times dose\ of\ NID-PNP-MN} * 100 \ldots\ldots\ldots\ldots Eq.2$$

Analytical method

Plasma concentration of NID was determined using RE- HPLC analysis according to the procedure that was developed and validated in term of linearity, precision, accuracy, lower limit of detection, and lower limit of quantification by ***Rajani B***. in estimating the NID in tablet dosage form as shown in Table.2 [14,15].

Table 2. Chromatographic Conditions

Parameter	Condition
Mobile phase	PB:Acetonitril(30:70)
Diluent	Methanol :DW(80:20)
Column	C18(4.6 x150mm, 5µ)
Column temperature	25^0C
Flow rate	1 ml/min
Retention time	3.79min
Run time	20 min
Wavelength	236nm
Injection volume	10 µL

Calibration Curves

Standard solutions containing NID were used to spike control plasma to create calibration standards at concentrations of 0.1, 0.5, 2.5,5,10, 20 and 60 ng/ml. A constant concentration 5ng/ml of cilnidipine as internal standard (IS) was added to all assay tubes. Zero-concentration plasma samples containing only the IS were included in each run. In addition, a plasma blank sample (without IS) was analyzed in each cycle [16].

Validation Method

Linearity and limits of detection and quantitation

The proposed method's linearity was confirmed by constructing calibration curves at (0.1 - 60 ng/ml) NID concentrations and plotting their relative peak area (against their respective concentrations using a linear least squares regression analysis, using cilnidipine as the internal standard [17].

Precision and Accuracy

Precision measured by calculating the relative standard deviation of intra-day repeatability and inter-day reproducibility while accuracy determining the percent recovery using three different concentrations as described by ***Rajani B*** [14,15].

Sample Extraction

To prevent photodegradation of NID, all experimental procedures—including plasma collection, sample preparation, and instrumental assays—were performed under dim yellow light. Extraction was carried out according to the method developed by Nascimento DFd et al. Briefly, 300 µL of plasma was mixed with 25 µL of the internal standard (cilnidipine, 5 ng/mL) and vortexed for one minute. Subsequently, 1000 µL of a hexane/ethyl acetate mixture (1:1, v/v) was added, followed by five minutes of vortex mixing. The samples were then centrifuged at 2000 g for five minutes at 37 °C. The upper organic layer (800 µL) was carefully collected, transferred to clean tubes, and dried in a vacuum desiccator (Christ Company, Germany) at 37 °C. The residue was reconstituted with 150 µL of acetonitrile (ACN) and vortex-mixed for one minute. The resulting solutions were transferred to microvials, sealed with caps, and placed in an autosampler rack. Finally, 10 µL aliquots were injected into the chromatographic system [17,18]

Statistical analysis:

The results were presented as mean values with their standard deviation (±SD; n=3). A difference was judged statistically (using T-test) significant or not if the P-value was < 0.05 using Prism GraphPad 8.4.3 Software. The pharmacokinetic parameters, C_{max}, T_{max}, and AUC_{0-48}, were calculated by means of PK solver 2.0[19]

RESULTS AND DISCUSSION

Validation Method

Linearity and limits of detection and quantitation

Least squares regression calibration curves were created by plotting the peak area ratios of NID to IS against nominal concentrations. The correlation coefficient (R^2) was 0.99994 over the point out that the calibration curve obeys Beer's law within the range of concentration range of 0.1–60 ng/ml used [20].

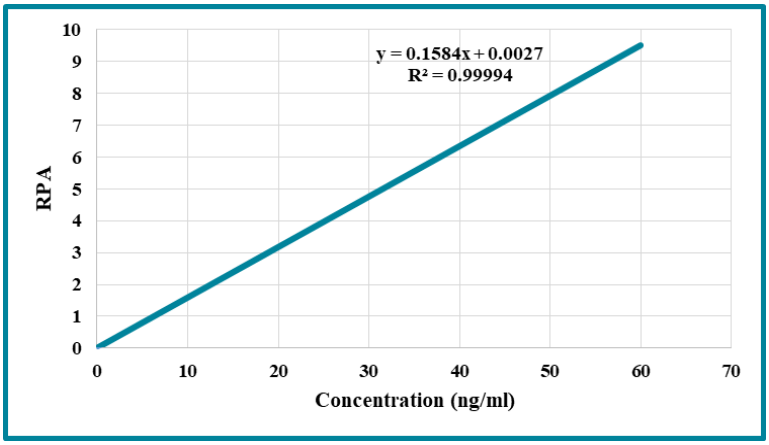

Figure 1. Calibration curve of NID with IS as an internal standard in the mobile phase (Potassium dihydrogen phosphate buffer: Acet) (30:70, v/v). (Error bars= SD, n=3)

The sample's chromatogram exhibited a good separation attained within 20 min using the conditions described. Sharp, symmetrical, and well-resolved peaks were detected for NID and IS. The elution order and the retention times for spiked plasma, NID besides IS were 1.47±0.002min, 3.79± 0.004 min and 6.18 ± 0.005 min respectively (Figure 2).

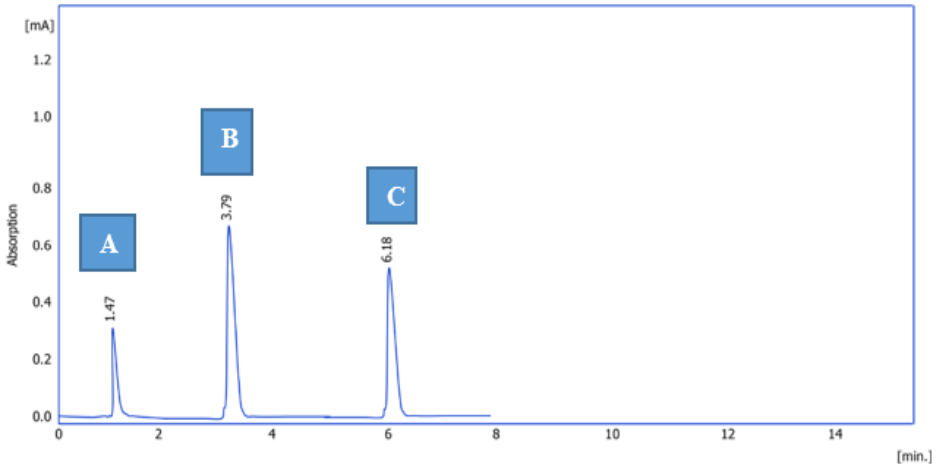

Figure 2. Chromatogram of known concentration of NID spiked with plasma (A), NID (B), and the internal standard (C) (n=3)

The HPLC method was considered to calculate plasma concentration of NID and method was valid (linearity R^2 = 0.9994) and both limits of detection and quantification (LOD and LOQ) were determined giving to the following equations as per ICH guidelines [21].

LOD = 3.3* ẟ/S ……Eq.3

LOQ = 10* ẟ/S ……Eq.4

Where ẟ is the standard deviation of y-intercept of calibration curves and S is the mean of slope of calibration curve [1, 21]. The lower limit of quantification (LOQ) for NID was 0.12 ng/ml, the lowest concentration on the calibration curves and the LOQ was 0.37 ng/ml.

Regarding precision and accuracy, the study revealed validation parameters that were consistent with results mentioned by ***Rajani B***. According to the standard guidelines, the proposed analysis method is precise since the mean values of %RSD for all were less than 20% and the recovery was 97.66% which is within range of 99%-101%indicating that the proposed method was accurate [14].

***In-vivo* Pharmacokinetics Results**

The *in-vivo* pharmacokinetics study achieved by administering one equivalent dose of NID oral suspension, and transdermal NID-NP-bDMNs followed by plasma sample collection to attain C_{max}, T_{max} and AUC as displayed in (Table 3) and plasma profiles (Figure 3) where the resulted average relative bioavailability of transdermal NID-NP-DMNs was 1.9 fold higher than oral NID suspension.

Table 3. Pharmacokinetics Parameters of Nimodipine

Pharmacokinetic parameters	NID oral suspension	Optimized transdermal NID-NP-bDMNs
C max (ng/ml)	42.54 ± 3.4	64.66 ± 2.9
T max (hr.)	1± 0.02	0.5 ± 0.01
AUC $_{0—48}$ (ng.h/ml)	27230.08±25.4	51947.56±18.3

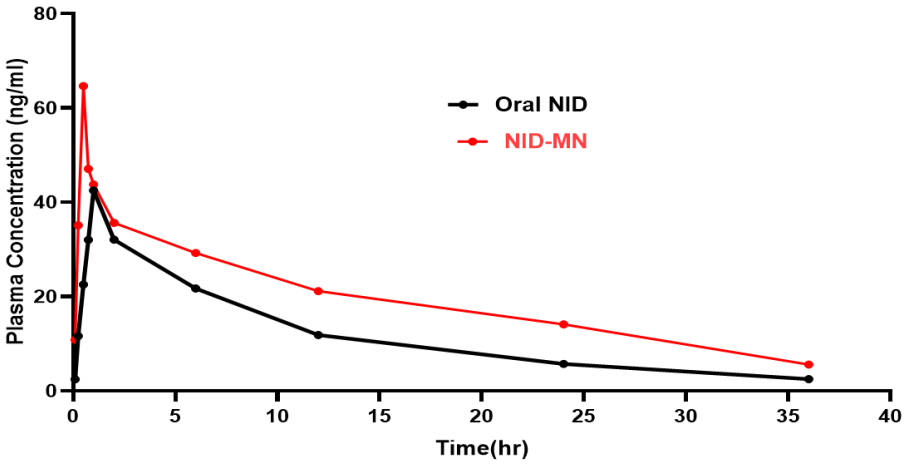

Figure 3. Comparative *in vivo* plasma profile of NID oral suspension and transdermal NID NP-bDMNs formula

Concerning the Nanocarriers, including polymeric nanoparticles, are specifically created to carry therapeutic drugs that exhibit distinct physicochemical properties and are composed of different polymer ratios. Extensive research has been conducted on dissolving microneedles to enhance the transdermal delivery of medicinal substances ended with several advantages; first, it effectively penetrates SC that acts as the primary obstacle to drug diffusion and second, to avoid the extensive first pass metabolism that resulting in rapid decline in plasma concentrations following oral NID administration [18, 23].

Statistical analysis revealed that (C_{max}= 42.54 ±3.4 ng/ml, T_{max}= 1 ±0.02 h) for oral NID while (C_{max}=64.66 ±2.9 ng/ml, T_{max}=0.42±0.01h) for b DMN, respectively. Plasma concentrations of NID are significantly higher (P= 0.022) with lower T_{max} following DMNs administration in contrast to low and inconsistent plasma levels of NID subsequent oral administration [24].

As a results, the pharmacokinetic analysis exhibited that the optimized transdermal NID-NP-bDMN had a 1.9 fold rise in the relative bioavailability compared to oral NID suspension. Additionally, an important factor that significantly enhances the lower oral bioavailability is the reduction in particle size with formulation of nanoparticles that leads to an increase the surface area of the NID, hence boosting the dissolving of medications that are poorly water soluble[2,21].

CONCLUSION

Nimodipine as an effective treatment for the avoidance of SAH, nevertheless the mechanism of action and dose limiting hypotension persist foremost areas of uncertainty. Recent advances in delivery have confirmed safety of drug delivery with less hypotension and significantly higher concentration at the target organ.

Results demonstrate that the convenient, painless, and less invasive bilayer dissolving microneedles employed as an alternative to injection and oral administration through enhanced transdermal delivery of NID offering an improvement of lower oral bioavailability, reduced side effect from intravenous administration and improved patient compliance.

The formulated NID-NP-loaded bDMN has a much higher relative bioavailability compared to the oral NID. Consequently, it is deemed as a more advantageous dosing form for the administration of NID in the treatment of SAH.

Acknowledgements

The data of this work was abstracted from a PH. thesis submitted to the department of Pharmaceutics / College of Pharmacy/University of Baghdad. The authors are extremely grateful to the College of Pharmacy/University of Baghdad for their valuable support in providing education and facilities that facilitated this work.

The authors would like to express their gratitude to Dr. Adnan Alswak (Research Centre for Cancer Researches and Medical Genetics) and Assist. Prof. Jasim Mohammed (Biotechnology Research Center) for their invaluable support in animal dosing and blood sample preparation throughout the study. Special thanks are also extended to Dr. Ali Al-Tamimi (Ministry of Science and Technology) for his valuable assistance with the HPLC analysis of blood samples.

Funding

This research did not receive any specific fund

Ethics Statements

The animal studies were conducted with the approval of the Institutional Animal Care and Use Committee (IACUC), College of Pharmacy, University of Baghdad, Iraq. Authorization was granted for the in vivo experiments on rabbits under protocol number RECAUBCP 2720236.

Author Contribution

Asmaa. M.R. Data collection, investigation, methodology, writing—original draft preparation. Mowafaq. M.G. Project administration, supervision, writing—review and approval of the final manuscript.

Abbreviations

Abbreviations	Meanings
AUC	area under curve
C	Celsius
Cmax	Maximum concentration
DMN	Dissolve microneedle
g	Gram
hr.	Hour
IS	internal slandered
Kg	kilogram
LOD	Limit of detection
LOQ	Limit of quantification
mg	milligram
µ	microliter
-min	minute
-ml	Milliliter
-mm	millimeter
-ng	Nano gram
NID	nimodipine
NPs	nanoparticles
PVA	Polyvinyl alcohol
PVPK15	polyvinylpyrrolidone
RE-HPLC	Reversed high-performance liquid chromatography.
-rpm	Round per minute
SAH	subarachnoid hemorrhage
SC	stratum corneum
Tmax	Maximum time
V/V	Volume by volume
W/V	Weight by volume

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مقارنة داخل الجسم الحي بين التوصيل الفموي والتوصيل عبرالجلد لجسيمات النيمودبين البوليمرية النانوية المحملة بابر دقيقة مذابة ثنائية الطبقات

اسماء محمدرشيد[1]، موفق محمد غريب[1]*

[1] قسم الصيدلانيات ،كلية الصيدلة ، جامعة بغداد ، بغداد ، العراق.

ملخص

الخلفية: نزيف تحت العنكبوتية (SAH) هو مرض يتطلب علاجا مكثفا بالأدوية والتي تستهدف الدماغ وتقلل من الآثارالجانبية الضارة ، ويفضل أن يكون ذلك باستخدام دواء يومي واحد. يقدم نيموديبين هذه الخصائص لاستخدامها لهذا الغرض

الهدف: هدفت الدراسة إلى مقارنة معايير الحركية الدوائية لمعلق نيموديبين الفموي مع الإبر الدقيقة الذائبة المحملة بجسيمات نانوية بوليمرية عبر الجلد من اجل زيادة التوافر الحيوي الفموي المنخفض.

الطريقة: تم تصييغ النيموديبين سابقا على شكل جسيمات نانوية بوليمرية ، تتميز بحجم جسيمات يبلغ 81.78 ± 0.6 نانومتر، ومؤشر تعدد تشتت يبلغ 0.046 ± 0.01، وجهد زيتا يبلغ −18.96 ملي فولت. وقد صب هذه الجسيمات النانوية في رقعات إبر دقيقة مذابة ثنائية الطبقات باستخدام تقنية الصب، باستخدام بوليمر البولي فينيل الكحول بنسبة 10% وزن/حجم و5% جلسرين .وُزّع اثني عشر أرنبًا أبيض ، ذكرًا من نوع ألبينو، يزن كل منها حوالي 1500 ± 175 غرامًا، عشوائيًا على مجموعتين من ستة حيوانات. تلقت إحدى المجموعتين جرعة فموية من معلق النيموديبين عن طريق التغذية الأنبوبية، بينما أُعطيت المجموعة الأخرى رقعات إبر دقيقة مذابة ثنائية الطبقات عبر الجلد، محملة بجسيمات نيموديبين النانوية . تم تحديد تركيز نيموديبين في البلازما باستخدام كروماتوغرافيا السائل عالية الأداء في الطور العكسي (RP-HPLC)، بعد إنشاء منحنى معايرة مدبب مع عينات البلازما ذات المعيار الداخلي للسيلينيديين.

النتائج: أظهرت النتائج أن الوقت والتركيز اللازمين لتحقيق أقصى تأثير كانا C_{max} = 42.54 ±3.4نانوغرام/مل، T_{max}=1 ± 0.2 ساعة للإعطاء الفموي، و C_{max} = 64.66 ± 2.9 نانوغرام/مل، T_{max}=0.5 ± 0.1 ساعة للإعطاء عن طريق الجلدعلى التوالي. لقد أظهر تحليل الحركية الدوائية أن تركيبة الابر الدقيقة المذابة ثنائية الطبقة والمحملة بالجسيمات النانوية عبر الجلد شهدت زيادة في التوافر الحيوي النسبي بمقدار 1،9 مرة مقارنةً بمعلق النيموديبين الفموي.

الخلاصة: يمكن أن يوفر التوصيل عبر الجلد باستخدام أن تقنية الابر الدقيقة المذابة ثنائية الطبقة والمحملة بالجسيمات النانوية طريقة واعدة وأكثر فعالية لتوصيل الدواء.

الكلمات الدالة: النزف تحت العنكبوتية، عبر الجلد، الطبقة المتقرنة ، ثنائي الطبقة ، التوافر الحيوي.

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* ***المؤلف المراسل: موفق محمد غريب***

Mowafaq.abd@copharm.uobaghdad.edu.iq

تاريخ استلام البحث 2024/07/14 وتاريخ قبوله للنشر 2024/09/21.