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Original Article

Lasmiditan nanoemulsion as intranasal in situ gel: Relative bioavailability study

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ABSTRACT

The purpose of this research was to compare the traditional aqueous-LAS-suspension (AQS) with the two successful intranasal formulations that use the recently created antimigraine drug Lasmiditan (LAS) as nanoemulsion-based in situ gel (NEIG a and b), in order to determine its relative bioavailability (F-relative) via using rabbits. In this investigation, 18 male rabbits weighing 2.0 to 2.5 kg were employed. The dose of LAS was determined based on the body surface area (BSA) normalization method, which is equivalent to 216µl~4drops of NEIG a, NEIG b, and AQS, each containing 80 mg of LAS per milliliter given separately to the randomly selected rabbit using a parallel design for the study. Serial blood samples were taken out and subjected to drug analysis using the HPLC method previously developed and validated by L. Santosh Kumar. Primary pharmacokinetics parameters, including maximum drug concentration in plasma (C-max), time to reach C-max (T-max), and area under the concentration-time curve from time zero to affinity (AUCt0-∞) were calculated. The results showed that C-max, T-max, and AUC0- ∞ for NEIG a and NEIG b were 8066±242 ng/ml, 0.75±0.05 h, 19616.86±589 ng. h/ml, and 7975.67±239 ng/ml, 1.0±0.05 h, 17912.36±537 ng. h/ml respectively compared with the traditional AQS which is equal to 4181.09±125 ng/ml, 2±0.2 h, and 8852.27±266 ng. h/ml respectively. It was discovered that NEIG a and b had better Intranasal delivery of LAS and can significantly ($p<0.05$) affect its pharmacokinetic profile and improve its bioavailability by more than 2.5 folds when compared to oral AQS (as a control), according to the results of the pharmacokinetic investigation. The current investigations confirm the potential of LAS as NEIG a and b to increase F, establishing them as a promising intranasal new formula with a faster onset of action and greater bioavailability than the oral dosage form (AQS).

Keywords: Bioavailability study, Nanoemulsion-based in situ gel (NEIG), Lasmiditan, C-max, T-max

Introduction

The oral medication lasmiditan (LAS) was approved by the Food and Drug Administration in October 2019 for the treatment of acute migraines [1]; however, LAS suffers from low oral bioavailability, which is around 40%, due to its extensively metabolized by non-CYP enzymes (extensive pre-systemic-metabolism), and because LAS is a substrate of the P-glycoprotein (p-gp) efflux system in the intestinal wall [2, 3].

The extremely permeable membranes and numerous blood vessels in the nose allow drugs to be absorbed swiftly within minutes after nasal administration [4, 5]. Also, medicines that are poorly absorbed orally due to instability or breakdown in the gastrointestinal tract may gain effect from administration via the nasal route instead. This route is also advantageous for medicines that are metabolized in the gastrointestinal tract, have strong P-glycoprotein efflux, or have high first-pass metabolism in the liver [6]. Medications administered by the intranasal route have efficacy comparable to intravenous administration and typically have superior efficacy to subcutaneous or intramuscular routes [7].

The stability of nanoemulsion (NE) over other systems has led to its consideration as a drug delivery vehicle for intranasal administration. They are clear solutions that contain oil,

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surfactant, cosurfactant, and water in varying proportions, with the oil globules either dispersed in water (o/w) or in oils (w/o). The droplet size in these systems ranges from 20 to 200 nm and they are solitary, optically isotropic, and thermodynamically stable [8, 9].

The low bioavailability of LAS prompted researchers to consider developing a novel dosage form that could improve bioavailability (by avoiding extensive pre-systemic metabolism and P-gp efflux system) through intranasal delivery of the drug.

In contrast, intranasally given medicines have a short residence period at the site of administration because of the nose cavity's architectural and physiological characteristics. Time for medication absorption is further constrained by the rapidity of mucociliary clearance (MC) [10, 11]. Therefore, the issue of short residence time in the nasal cavity must be taken into account during the design of intranasal formulations. Moreover, a droplet-sized formulation that promotes greater transmembrane transport can increase the drug's bioavailability.

Based In situ systems, which are liquid aqueous solutions before administration but transform into gel under physiological circumstances, are regarded as contemporary advances in hydrogel drug delivery research [12, 13]. The most popular pH-induced gelling agent is Carbopol 934, which prolongs the drug's stay on the nasal mucosa and slows down the body's natural elimination [14-16].

By using nanotechnology to formulate LAS as a nasal NE and avoiding mucociliary clearance which is regarded as the main barrier to drug delivery via including a pH-sensitive polymer like Carbopol-934 in the formulas to solve the issues associated with poor oral bioavailability of LAS as an oral tablet also for achieving in-situ gelling properties [17].

The previous findings revealed that NEIG **a** and NEIG **b** achieved 100% permeation within 20 min and then released within 25 and 35 min respectively so both achieve 3.3 folds permeation percentages compared with an AQS.

This study includes the application of an in vivo research plane via using rabbits to estimate the bioavailability of the LAS as AQS relative to the two successful intranasal formulations of LAS as NEIG **a** &**b** as well as calculating the primary and secondary pharmacokinetic parameters which include the rate (T max) and extent (C max) of systemic drug absorption, total AUC accompanied with calculation of elimination rate constant (Ke) and half time of elimination ($t_{0.5}$).

Materials and Methods

Lasmiditan was purchased from Yongchi Chemical Technology Co, LTD, China. Labrasol ALF, Transcutol, and Cremophor® EL were purchased from Gattefosse (France). Oleic acid and Carbopol 934 were purchased from Central Drug House (CDH®). HPLC-grade Methanol, Acetonitrile, and Isopropyl alcohol were purchased from Merk. A Millipore filter syringe was purchased from Chm Lab, Spain. HPLC-grade Water, and the rest of the chemicals, and reagents were of analytical grade.

In situ gel formulation

The selected NE **a** and **b** were subjected to be formulated as 0.5 % in situ gel as shown in **Table 1**. A calculated weight of Carbopol 934 (pH-induced in situ gelling polymer) was sprinkled over the water content of the NE, allowed to hydrate overnight then dropped gradually with continuous stirring at ~500 rpm over a homogeneous transparent yellow previously weighed mixture of oleic acid (OA), cremophore EL (CE) or labrasol ALF (LR), and transcutol (TC) till gets the NEIG **a** and **b** respectively [18, 19].

The prepared NEIG **a** and **b** after passing all the in vitro, and ex vivo evaluations, were finally subjected to an in vivo research plan.

Table 1. Composition of LAS NEIG

Formula code	OA% (W/W)	Surfactant type	Co-surfactant type	S-Mix Ratio	S-Mix % (W/W)	DD% (W/W)
NEIG a	10	CremophoreEL	Transcutol	1:2	50	40
NEIG b	15	Labrasol ALF	Transcutol	3:1	55	30

In vivo research plan for pharmacokinetics study

It was conducted according to the institutional guidelines of the Animal Ethics Committee of the College of Pharmacy at the University of Baghdad. During the collection of blood samples, 6- male, white albino rabbits weighing 2.0-2.5 kg were captured in a rabbit hutch. Afterward, a table was held in a horizontal position with the rabbits placed on it. The oral and nasal dosages for rabbits were estimated, and the animal received a comparable dose of LAS. BSA normalization method and the human equivalent dose (HED) of pharmaceuticals including the species (Km) factor (body weight in kg divided by BSA in m^2) were used to calculate the animal nasal and oral doses for the rabbit as follows [20-22]:

$$\text{HED (mg)} = (\text{Animal Km} / \text{Human Km}) \times \text{Animal Dose(mg)} \quad (1)$$

LAS single daily dose is advised to be (0.28 mg/kg for adults), and the values of Km were 37 and 12 for adult humans and rabbits respectively [23, 24].

Hence, the LAS dose for rabbits based on the BSA normalization method was 1.72 mg and reached 17.26 mg after multiplying by 10 (safety factor) [25].

18 albino male rabbits weighing between 2 and 2.5 kg were employed in the in vivo study. Based on the results of the in vitro and ex vivo studies, NEIG **a** and **b** were selected for the in vivo examination together with the AQS. Before the experiment began, the rabbits fasted for 24 hours. They were then divided into three groups, each with six rabbits. At a dosage of 0.863

mg/kg, Group I received LAS as AQS (reference). Group II received NEIG-a intranasally at a dosage of 0.863 mg/kg~4 drops as well as group III received NEIG-b intranasally at the same dose. 2ml blood samples were collected in EDTA tubes before the medication was administered (control sample), and then again at 0.25, 0.5,0.75, 1.0, 2.0, 3.0, 5.0, 7.0, 12, and 19 h after the drug was administered, then centrifuged [26, 27]. Prior to analysis utilizing the HPLC technique previously established and confirmed by L. Santosh Kumar, samples were kept at -20C° [28].

Parameters involved in pharmacokinetics

The pharmacokinetics of LAS was analyzed in a non-compartmental fashion. Using the plasma concentration-time curve (Cp versus T curve), we were able to calculate C max and T max following oral and intranasal delivery. $T_{0.5}$ is calculated by dividing the value of Ln 2 over Ke and the last is predicted from the slope of the straight section of the terminal phase (where the slope is equal to - Ke/2.303) [29, 30]. Extrapolation of the area to affinity (AUC t_{0}-$_{\infty}$) was estimated by adding the last measured Cp divided by Ke to the value of AUC $t_{0\text{-}19}$ according to the following Eq. 2 [31]. This was done for each individual rabbit by calculating the area under the Cp-time curve from time 0-19 h (AUC $t_{0\text{-}19}$).

$$AUC_{0-\alpha} = AUC_{0-19} + [C_{last} / Ke] \quad (2)$$

Where; Cp 19 is the concentration of LAS after 19 h.
Eq. 3 was used to determine F relative [32, 33]:

$$F_{relative}=(AUC_{NEIG2} / AUC_{oral} \times Dose_{oral} / Dose_{NEIG2}) \times 100 \quad (3)$$

Statistical analysis

One-way analysis of variance (ANOVA) was used to compare the results of pharmacokinetics parameters to determine whether or not there were statistically significant differences between groups when comparing means; p-values were considered significant at a level of ($P < 0.05$), and non-significant at a level of ($p > 0.05$).

Results and Discussion

In vivo pharmacokinetics study

A reproducible, sensitive, and rapid HPLC method was used to determine the concentration of LAS in rabbit blood [34, 35]. **Figure 1** shows the retention time and peak chromatograms of LAS (standard solution), hydrochlorothiazide (internal standard solution), and plasma sample(control) to be equal to 2.8, 6.08, and 4.33min respectively. The chromatographic conditions were developed and validated previously by L. Santosh Kumar [28].

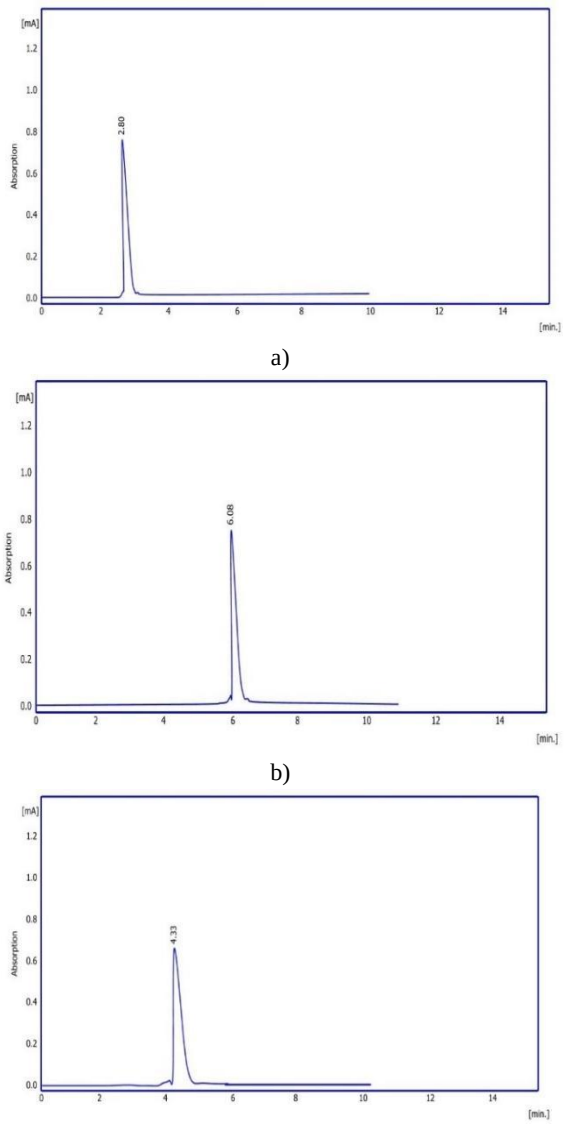
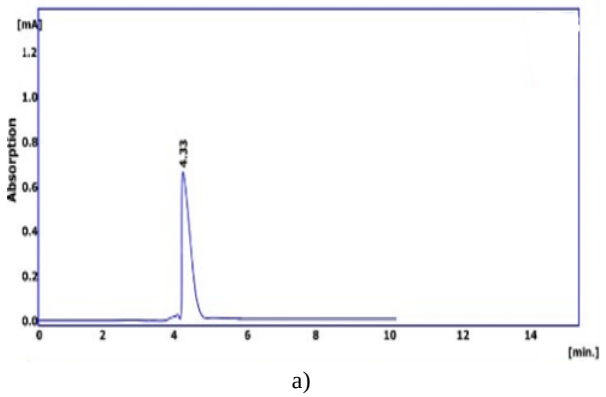
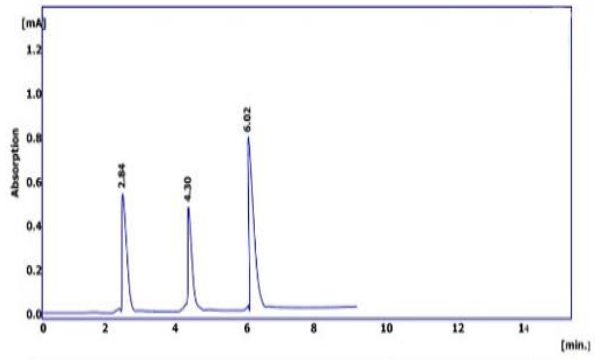


Figure 1. Representative HPLC chromatograms of standard, internal standard, and control plasma samples as a, b, and c respectively

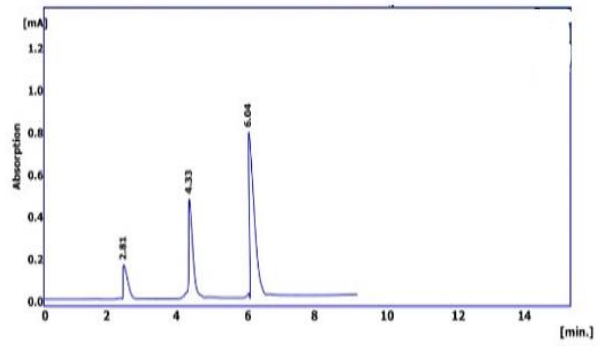
Figures 2a-2c represents the chromatograms of blank and test plasma samples, It is clear that the peaks were completely separated, and there is no interaction or overlap.



a)



b)



c)

Figure 2. Chromatograms plasma sample. a) Blank sample (before administration of drug -LAS), b) first sample at 0.25h, and c) plasma sample at 19 h (last one).

The calibration curve of LAS in plasma (spiked plasma sample) was represented in **Figure 3**, a straight line with high regression coefficient (R^2= 0.9999) was obtained by plotting the area under the peak of **standard/internal standard** versus the concentration, this indicates that the calibration curve obeys Beer's law within the range of concentration used [36, 37].

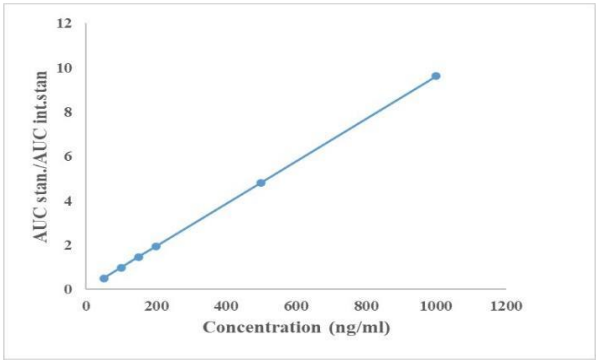


Figure 3. Calibration curve of LAS in plasma by HPLC method

Table 2 illustrates the arithmetic mean and standard deviation values of plasma drug concentration (ng/ml) of LAS (Mean Cp) at the selected time intervals for 18 rabbits having different weights (2-2.5kg) and every 6 rabbits randomly receiving a single dose of LAS (17.26 mg) as traditional AQS and the other two groups each 6 rabbits randomly receiving a single intranasal dose of the prepared NEIG a and b respectively.

Table 2. Mean CP of LAS at different time intervals following administration of the prepared NEIG a, NEIG b, and the oral AQS as a single dose.

Time (h)	Mean-Cp ORAL-AQS	Mean-Cp IN-NEIG a	Mean-Cp IN-NEIG b
0.25	909.15± 27.3	6986.65±209	5895.2± 177
0.5	1169.7± 35	7618±228	7283.9± 218
0.75	2363.98±71	8066±242	7737.75± 232
1	3114.8±93	7330±219	7975.67±239
2	4181.09±125	4990±150	4215.4± 126
3.6	648.23± 19	1742±52.3	1177.07±35
5	187.34± 5.6	236.5±7	188.72± 5.6
7	108.5± 3	190.85±5.7	126.52± 4
12	72.36± 2	105.28± 3	69.24±2
19	----------	77.8±2.3	38.99±1.1

n=6 (mean ±SD)

The pharmacokinetic study results revealed that intranasal application of LAS as NEIG **a** and **b** can significantly ($p<0.05$) modify its pharmacokinetic profile and can increase its bioavailability by more than **2.5 folds** in comparison with the oral LAS AQS (control) as shown in **Table 3** and **Figure 4** listed below.

Table 3. Pharmacokinetics parameters of a single intranasal dose of LAS as optimized NEIG a, NEIG b, and single oral AQS (8%LAS).

Kinetic parameters	Oral-LAS (control)	Intranasal LAS (NEIG a)	Intranasal LAS (NEIG b)
Cmax(ng/ml)	4181.09±125	8066±242	7975.67±239
T max(h)	2±0.2	0.75±0.05	1±0.05
AUC $t_{0-\infty(ng.h/ml)}$	8852.67±266	19616.86±589	17912.36±537
Ke(h-)	0.125±0.002	0.116±0.001	0.113±0.001
T 0.5 (h)	5.544± 0.17	5.97± 0.18	6.1± 0.18

n=6 (mean ±SD)

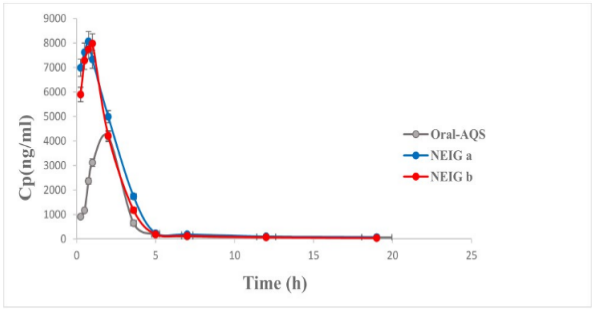


Figure 4. The profile of Mean Cp versus time during the pharmacokinetic experiment applied on 18 rabbits each 6 were given a single dose of LAS as NEIG a, the other 6 were given NEIG b (both given intranasally), and the last group received aqueous drug suspension AQS (given orally).

The results in **Table 3**, and **Figure 4** illustrated that the profile of the Mean Cp versus time which was constructed on a semilog paper for the optimized LAS formulas as NEIG **a** and **b** are superimposed with no significant difference ($p<0.05$), both formulas achieve rapid onset of action (lower T max value=0.75 and 1) with higher extent of LAS absorption (C max=8066 and

7975.67 ng/ml) accompanied by the higher value of total AUC (19616.86 and 17912.36 ng. h/ml) respectively.

The new intranasal formulations both gain the goal of increasing the bioavailability of LAS compared with a lower F value when administered orally.

The in vivo results are comparable with the invitro release and ex vivo permeation of the selected two prepared formulas of LAS as NEIG **a** and **b** which exert 100% permeation and are released within 20 and 35 min respectively compared with only 30% permeation and released of the traditional AQS during the same time interval so these optimized formulas given intranasally will be significantly better($P<0.05$) permeated, released and bioavailable than the AQS given orally.

Increased permeability is a result of the physicochemical characteristics of the drug molecule known as NEIG, which include reduced particle size, high lipoidal characteristics, and the presence of CE, LR, and TC [38].

Oligosaccharide chains in the mucus membrane include a high proportion of carboxyl groups that form hydrogen bonds with them, creating a dense network between the polymer and mucus membrane, increasing the residence time of dug in the nasal mucosa when in situ gelling agents are present [39-41].

Finally, switching the route of administration accompanied by the use of advanced nanotechnology together with an in-situ gelling formula helps to get acceptable, effective, safe, bioavailable formulas with the best patient compliance.

The two successful formulas of LAS NEIG a and NEIG b will be entered into a safety study to select one of them to be the gold one ready to be subjected to clinical study.

Conclusion

The most efficient new drug delivery technology was used for the formulation of LAS as NEIG a and b using two different pseudo ternary systems for formulation of NE, then including of pH-sensitive gelling agent (Carbopol 934).

This novel combination of NE with in situ gelling polymer attains the goal of increasing the bioavailability of LAS which is about 40% via the oral route to approximately 100% via the nasal route through the use of this nanosized lipophilic particles which achieve rapid permeation and released of LAS accompanied with increasing the residence time in the nasal cavity which considered as the main challenge for intranasal preparation.

The LAS's bioavailability was increased in comparison to the AQS by more than two and a half times.

The main flaws of the commonly used orally market pill might be fixed by using this mixture. In fact, it won't eliminate the necessity for future clinical testing of this innovative recipe, which might provide other crucial information to physicians.

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Conflict of interest: None

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Ethics statement: The University of Baghdad-College of Pharmacy Research Ethics Committee has reviewed the responses to comply with the ethical principles of the International Ethical Guidelines for Health-related Research with the approval number: REACUBCP2542022A.

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