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Research Article

FORMULATION AND EVALUATION OF NOVEL BRAIN TARGETING DRUG LOADED IN LIPID-BASED NANOPARTICLES THROUGH INTRANASAL ROUTE FOR ALZHEIMER

Dalia A. Elaty Mostafa *[1], Amira Mostafa Hashad [1], Amal Youssef M. Abdelreheem [2]
[1]Faculty of pharmacy, Pharmaceutics department, October University for Modern Sciences and Arts (MSA) university, Cairo, Egypt
[2]Associate Professor in National Organization of Drug Control and Research. (NODCAR) Cairo, Egypt
*Corresponding Author Email: damostafa@msa.eun.eg

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ABSTRACT

Objective: Alzheimer's disease is a slowly progressive disease that takes 7 to 10 years from onset to death. Design and development of different lipid-based drug delivery systems (Niosomes) loaded with rivastigmine tartarate is used to solve the problem of the extensive rapid metabolism of rivastigmine. Niosomes as a nanocarriers of rivastigmine will increase its bioavailability and brain targeting. Methods: Niosomes are prepared using Hand Shaking Method (Thin Film Hydration Technique). Span 60 and cholesterol are dissolved in organic mix solvent, until forming clear solution in a round bottom flask. Then, the solvent is evaporated under decreased pressure, temperature and 70 rpm in a rotary evaporator leaving solid surfactant and cholesterol as thin film formed on the wall of the flask. This layer is then rehydrated by using aqueous solution containing drug with continuous shaking which cause swelling of surfactant layer. Swelled amphiphiles eventually fold and form vesicles that could entrap the drug. The Prepared nanoparticles were characterized for pH, particle size, surface morphology, entrapment efficiency and in vitro release study. Results The average particle size was 100.7 nm with polydispersity index of 0.232. The zeta potential of the optimized formulation F2 was determined and found to be -19 mV. Surface properties of the nanoparticles were studied by Transmission electron microscopy (TEM) and nanoparticles found to have smooth surface. The Drug entrapment efficiency was found to be in between 83.5 to 86.53% indicated fairly good drug loading in the formulations indicated increased bioavailability of the drug. optimized formulation F2 showed 60 % drug release in 240 minutes indicate sustained release of drug. Conclusion: Rivastigmine could be prepared as a novel niosomes systems to enhance its bioavailability.

Keywords: Rivastigmine, Niosomes, in-vitro drug release, Hand Shaking Method, Transmission electron microscopy.

INTRODUCTION

Alzheimer's disease (AD) is a progressive, irreversible disorder of the brain which slowly destroys memory, thinking ability, and even the ability of carrying out the simplest tasks [1]. Alzheimer's disease (AD) is a critical neurodegenerative illness characterized by memory loss and diminished performance, language, and visuospatial skills [2]. Epidemiological data show that the occurrence of Alzheimer's disease (AD) increases with age and doubles every 5 y after 65 y of age [3]. There were about 26.6 million cases of Alzheimer's disease in the world in 2006 and it is predictable that the worldwide dominance of Alzheimer's disease will grow fourfold to 106.8 million by the year 2050 [4]. The neuropathological features of Alzheimer's disease involve extracellular senile plaques constituted of β-amyloid (Aβ) pledges, intracellular neurofibrillary tangles (NFTs), and cerebral atrophy [5]. Rivastigmine tartrate is used to treat mild to moderate dementia related to Alzheimer's disease or Parkinson's disease [6]. Niosomes are nonionic surfactant based unilamellar or multilamellar vesicles in which an aqueous solution of solute is entirely enclosed by a membrane resulting from the organization of surfactant macromolecules as bilayers. It is possible to encapsulate hydrophilic as well as lipophophillic drugs in niosomes. The lipophilic nature of constituent lipids in niosomes helps in the penetration of the drugs encapsulated inside into the deeper tissues [7]. The aim of the present study is to formulate niosomes vesicles of Rivastigmine tartrate to enhance its uptake and avoid extensive first pass effect.

MATERIALS AND METHODS

Rivastigmine Tartrate, Hikma Pharma Company, Giza, Egypt. Absolute ethanol, calcium chloride dehydrate ($CaCl_2.2H_2O$), chloroform, cholesterol, methanol, potassium chloride, span 60, sodium chloride is purchased from Sigma- Aldrich. All other chemicals were of analytical grade and were used without further purification.

UV scanning for λ max of Rivastigmine tartrate

Rivastigmine tartrate is very soluble in water and soluble in methanol. Methanol was used in UV scanning of rivastigmine tartrate and for construction of standard calibration curves. 100 mg of rivastigmine tartrate is dissolved in 100 ml methanol to form stock solution. Spectrophotometrically scanning for wave length between 200-400 nm is then done by using blank of methanol. The best wave length with the highest absorbance value was taken as λ of the detection of the drug.

Construction of standard calibration curves of Rivastigmine tartrate

Calibration curve was made by using methanol serial dilutions were prepared from stock solutions in methanol. The absorbance of each solution was measured spectrophotometrically at the predetermined λ using blank of methanol. To obtain the calibration curve, the measured

absorbance was plotted against its concentration. Linear regression analysis was performed to obtain least square line [8].

Preparation of rivastigmine loaded niosomes

Rivastigmine tartrate niosomes vesicles prepared in six formulae by using Hand Shaking Method. Thin Film Hydration Technique: Surfactant and cholesterol are dissolved in some of the organic mix solvent, which contain chloroform and methanol, until forming clear solution in a round bottom flask. Then, the solvent is evaporated under decreased pressure, temperature and 70 rpm in a rotary evaporator leaving solid surfactant and cholesterol as thin film formed on the wall of the flask. This layer is then rehydrated by using aqueous solution containing drug with continuous shaking which cause swelling of surfactant layer. Swelled amphiphiles eventually fold and form vesicles that could entrap the drugs [9].

Table 1: Composition of niosomal formulations at various ratios of cholesterol: span 40; span 60 and span 80:

	Drug	Cholesterol		Surfactant
Formula (1)	50 mg	39.57 mg	Span 40	41.4 mg
Formula (2)	50 mg	39.57 mg	Span 60	44.01 mg
Formula (3)	50 mg	39.57 mg	Span 80	42.8 mg

Evaluation of niosomes

The formulae were inspected visually for appearance, consistency, clarity, fluidity, transparency, and homogeneity.

Physical examination

By visual inspection to the niosomes to detect the homogeneity and stability.

Particle Shape and Morphology

Shape and morphology of niosomes determined by optical microscopy and Transmission Electron Microscopy (TEM) [10].

Measurement of pH

pH of prepared formulae was measured to insure its adequacy for intranasal administration. The measurement was carried out by using portable digital pH meter calibrated by standard buffers of pH 4.7 and 10. Both calibration and sample measurements were done at temperature simulated to temperature of intranasal cavity through dipping the sample beaker in water bath of 37ºC ±1 [11].

Particle Size

The particle size of the niosomes suspension determined by optical microscopy. A drop of niosomes suspension was placed on a glass slide. A cover slip was placed over the niosomes suspension and evaluated the average vesicle size by an ordinary optical microscope using a recalibrated ocular eye piece micrometer [12].

Entrapment Efficiency Percent EE%

The entrapment efficiency of niosomes loaded rivastigmine tartrate was determined by ultracentrifugation method. 2 ml of formula dissolved in 2 ml of methanol was centrifuged for 30 min at 4 ºC and 14000 rpm. Niosomes vesicles were obtained from the supernatant after filtration. 1 ml of the supernatant is dissolved in methanol to provide 10 ml that was further analyzed for drug content using UV spectrophotometer. By using the previously constructed calibration curve, the amount of entrapped rivastigmine tartrate was determined. Entrapment Efficiency was expressed as percentage of total drug entrapped by using the formula: Where, C = amount of drug found after dissolving the vesicles and T = total amount of added drug [13].

$$EE\% = C / T \times 100$$

Zeta potential

Malvern Zetasizer was used to determine zeta potential of niosomes suspension. The predetermined dispersant refractory index and viscosity of formula were incorporated into the computer software of the analyzer. Zeta potential was determined by using clear disposable zeta cell at 25ºC ± 1 and the measurements were made in triplicate [14].

Determination of saturated solubility of rivastigmine tartrat

In tightly capped vial at ambient temperature 25 ± 1 ºC, known excess of rivastigmine tartrate which was enough to give supernatant solution in 5 ml of simulated intranasal fluid at pH 5.5 was shaken by electric shaker for 48 hours then allowed to settle for two hours. The decanted supernatant was filtered through Millipore filters which were 0.45 µm. one milliliter of filtrate was properly diluted with known amount of simulated intranasal fluid at pH 5.5 and measured spectrophotometrically at the prescanned λ for rivastigmine tartrate. Simulated intranasal fluid at pH 5.5 is considered as a blank for the experiment. The amount of dissolved rivastigmine tartrate was determined by using previously constructed calibration curve of rivastigmine in simulated intranasal fluid at pH 5.5. Saturated Solubility is important to determine sink conditions of the release study that should be maintained at: C1 < Cs x 0.2; Where C1 = final concentration of rivastigmine tartrate after complete release in the release medium, and Cs = Saturated Solubility [15].

In Vitro Release Study

In vitro release of rivastigmine tartrate from the formulae was performed using the USP dissolution tester apparatus I (rotating basket) as follows: accurately measured 5 ml of each medicated and plain formula were placed in a silastic membrane bag (presoaked in a freshly prepared simulated intranasal fluid at pH 5.5 overnight) that was well tightened and hanged up in the rotating shaft of the apparatus I. The final concentration of rivastigmine tartrate after complete release in the release media was considered and maintained below than Cs x 0.2, in compliance with the sink condition. Bags were rotated at 100 rpm in a covered dissolution vessel (closed system) which contain 100 ml of the freshly prepared release medium and thermostatically adjusted at a temperature of 37±1 ºC. At a predetermined time, intervals (every 15 minutes during the first hour, every 30 minutes for the next one hour and every 60 minutes for the next two hours), 1 ml sample of rivastigmine tartrate release medium was withdrawn from the sink solution, filtered and analyzed for rivastigmine tartrate content by

measuring the absorbance at predetermined wavelength using the release medium as a blank. Meanwhile similar volume of the release medium was added to maintain the volume constant and compensate the withdrawn one. Each experiment was done in triplicate. Blank experiments using plain formula instead of medicated formula was carried out at the same time of the test experiments using same procedures and conditions. The percentage of the drug released were calculated from the previously constructed calibration curve of rivastigmine tartrate in the release medium [16].

RESULTS AND DISCUSSION

UV Scanning for λ max of Rivastigmine tartrate

The best absorbance of rivastigmine tartare was found to be λ max 263.60 nm, as shown in Figure 1.

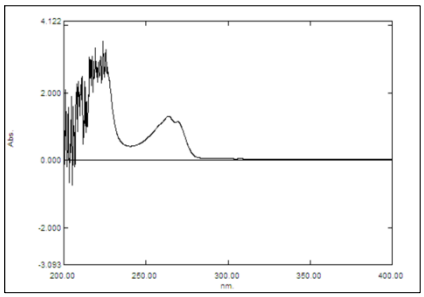

Figure 1: λ max of UV scanning of Rivastigmine tartarate

Table 2: Standard Calibration Data of rivastigmine tartrate in methanol.

Sample Number	Concentration (µg/ml)	Absorbance
1	200	0.201
2	300	0.321
3	400	0.431
4	500	0.542
5	600	0.649
6	700	0.763
7	800	0.891

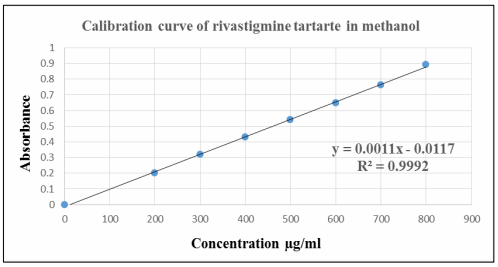

Figure 2: Rivastigmine tartrate standard calibration curve in methanol.

Table 3: Regression equation of Rivastigmine tartrate in methanol.

Medium	Regression Equation	R^2	K	Linearity Range
Methanol	Y=0.0011x - 0.0117	0.9992	0.99888 µg/ml.	200–800 µg/ml.

Table 2: Composition of Niosomes formulations at various ratios of cholesterol: span 40; span 60 and span 80:

	Drug	Cholesterol		Surfactant
Formula (1)	50 mg	39.57 mg	Span 40	41.4 mg
Formula (2)	50 mg	39.57 mg	Span 60	44.01 mg
Formula (3)	50 mg	39.57 mg	Span 80	42.8 mg

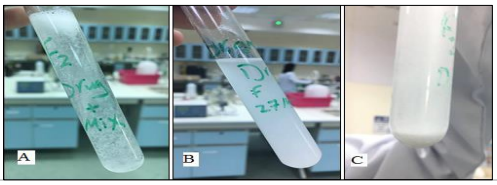

Figure 3: Suspension formed of three formulae

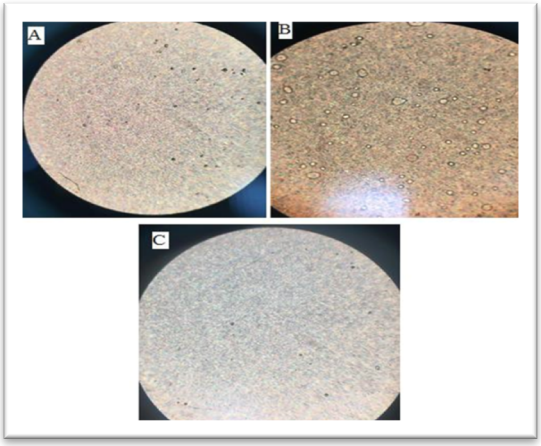

Figure 4: Niosomes vesicles of rivastigmine tartrate formula under Optical light microscope.

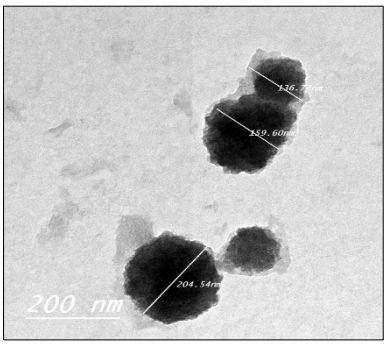

Figure 5: Aggregated Niosomes vesicles of rivastigmine tartrate of 200 nm under Transmission Electron Microscope.

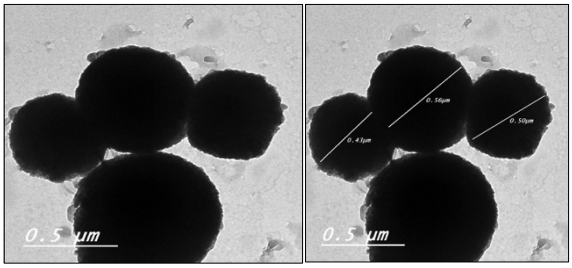

Figure 6: Aggregated Niosomes vesicles of rivastigmine tartrate of 0.5 µm size

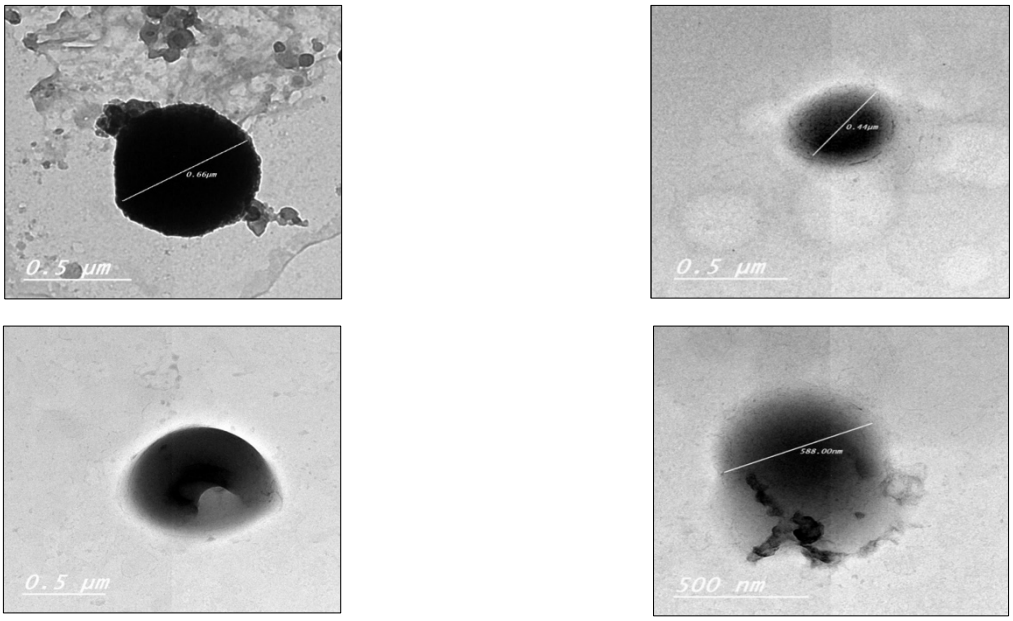

Figure 7: Separated Niosomes vesicles of rivastigmine tartrate of approximately 0.5 µm size under Transmission Electron Microscope.

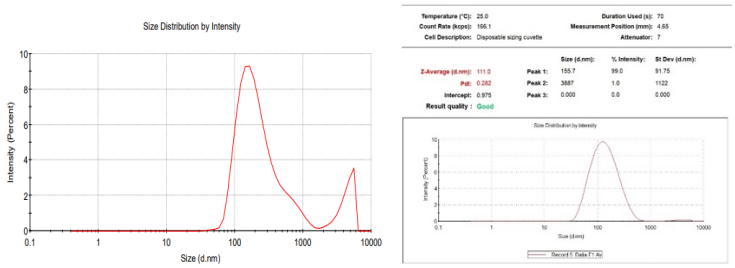

Figure 8: Particle size analysis of niosomes

Niosomes Formula	Zeta Potential		Conductivity (mS/cm)
	Zeta Deviation (mV)	Peak Position (mV)	
Formula (2)	3.79	-19.3	0.137

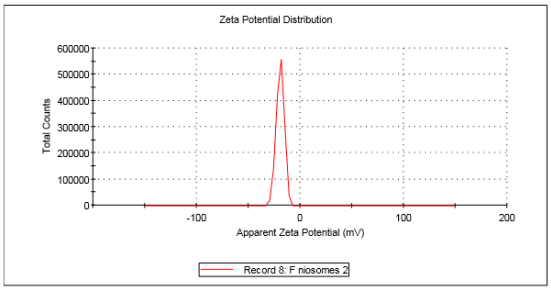

Figure 9: Zeta Potential Distribution of Formula (2)

Table 4: % of Cumulative drug release

	% of Cumulative drug release		
Time(min)	F1	F2	F3
0	0 ±0.12	0±0.89	0±0.78
15	11.5±0.32	10±0.35	8±0.98
30	21.89±0.15	22±0.32	20±0.54
45	30.6±0.34	29±0.54	25±0.34
60	40.4±0.56	36±0.23	39±0.23
90	49.8±0.78	48±0.11	45±0.33
120	58.7±0.32	55±0.21	58±0.45
180	66.8±0.26	67±0.45	66±0.67
240	68±0.34	75±0.11	69±0.67

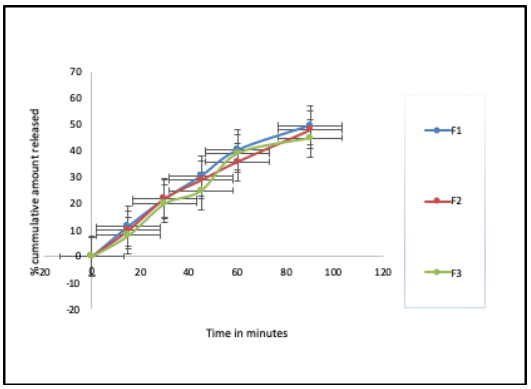

Figure 10: In-Vitro drug release of Niosomes rivastigmine.

Preparation and evaluation of niosomes

Visual examination

Visual inspection of niosomes suspension which contain span 60 (formula 2) showed opaque white color suspension. The suspension formed was homogenous and water like fluidity; other formulae which contain span 40 and span 80 provided less suitable suspensions. The appearance of the suspension of the three formulae is shown in figure 3.

Shape and Morphology

Shape and morphology of niosomes formulations were determined by optical microscopy. It was clearly observed from Figure 4, that niosomes are spherical in shape. It is demonstrated that the vesicles are well identified and present in a nearly perfect sphere-like shape having a large internal aqueous space relative to the sphere diameter [17].

Transmission Electron Microscopy (TEM)

Sample of the formula of rivastigmine tartrate loaded niosomes was examined by TEM after negatively stained with 1% aqueous solution of PTA, as shown in figures (5,6 and 7). Niosomes vesicles of formula appeared as spherical morphology with different sizes and also some flocculated /aggregates vesicles appeared. That clarified and emphasized what had been seen by optical light microscope.

pH measurement

The pH of Formula (1) was 4.2, Formula (2) was 4.3 and formula (3) was 4.8. Therefore, the pH of the three formulae was adjusted to be 5.5 to avoid nasal irritation and increase patient compliance.

Particle size and poly dispersity index

Particle size and poly dispersity index of Niosomes formulation at different ratio of cholesterol and surfactant was shown in Figure 8. Mean particle size of the Niosomes formulation was found to be in the range of 113nm. The poly dispersity index was ranged from 0.282 to 0. 453.It was clearly depicted that particle size of niosomes formulations was increased on increasing the cholesterol content. Cholesterol content provides strength to the nonpolar tail of nonionic surfactant. At low cholesterol content, it is to be expected that the cholesterol and nonionic surfactant are in close packing with increasing curvature and reducing size. As the cholesterol content increases, it would reduce the content of surfactants and also increased the hydrophobicity of bilayer membrane thus increasing vesicles radius in a way to establish more thermodynamic stable form. Rigid structure of bilayer membrane due to cholesterol content also provides resistance to reduce size due to sonication and results in vesicles with bigger size [18].

Entrapment efficiency

Cholesterol content added in the formula gives more rigidity to the lipid layer which provide higher stability to the niosomes vesicles which leading to the reduction of the possibility of vesicles fusion by resisting high ultracentrifugation rotational energy, as the result the entrapment efficacy of rivastigmine tartarte encapsulated into niosomes is entrapment efficiency (EE%) was ranged from 84.389% to 86%. In order to attain high encapsulation efficiency, several factors, including the type of surfactant, the ratio of cholesterol added the higher entrapment may be due to the solid nature, hydrophobicity and high phase transition temperature of the Span 60. [19]

Spans 60 has the highest transition temperature (Tc = 53 ◦C) amongst all spans (16 ◦C for Span 20, 42 ◦C for Span 40 and -12 ◦C for Span 80) [20]. The span having the higher phase transition temperature provides the higher entrapment for the drug and vice versa [21,22].

These findings are in agreement with previous researchers' work, where the increase in the alkyl chain length span 60 (C18) > Span 20 (C12) led to increase in the encapsulation efficiency (%EE) [23,24].

Additionally, the lower the HLB of the surfactant the higher will be the drug entrapment efficiency and stability [25,26].

Zeta potential

Zeta potential is considered an indicator for Niosomes vesicles stability. Nanoparticles with value greater than (+30 mv) or less than (-30 mv) typically have high degrees of stability as higher zeta potential indicate higher stability with low coagulation/flocculation probability. On the other hand, dispersions with low zeta potential values will eventually aggregate due to van derwaal inner particle attraction. The formula in this study has a zeta potential of value equal (-19.3 mv) which considered be good but not completely stable as its value is not greater than (+30 mv) or less than (-30 mv) and this is caused by absence of charged particles in the formula. The results can be shown in figure (9). The negative value of zeta potential indicates a negative charge on the droplets [27,28].

In-Vitro drug release of niosomes rivastigmine tartarte

Saturated solubility of rivastigmine tartrate in freshly prepared simulated intranasal fluid at pH 5.5 (release media) was considered as an important factor that may affect rivastigmine tartrate release study. Saturated solubility was found to be 2 mg/ml and that was considered in the sink conditions of rivastigmine tartrate release study to determine the used amount of the release media and/or formula. In vitro release of Rivastigmine tartrate best formula F2 from the Niosomes formula in freshly prepared simulated intranasal fluid at pH 5.5 at 37 ºC ± 1, was performed over a period of 4 hours. Sink conditions were guaranteed in which saturated solubility (2 mg/ml) is less than final concentration of rivastigmine tartrate in release medium (0.15 mg/ml). percentage of rivastigmine tartrate in release media was determined spectrophotometrically at λ max 263.60 as shown in figure (10). It was shown that the release of niosomes structure. The release study shows that the rivastigmine niosomes structure was sustained release; all formulations show slow drug release over 240 minutes with a maximum release reach to 65% which may be due to high entrapment efficiency. This can be explained by the fact that niosomes exhibit an alkyl chain length-dependent release and the higher the chain length, the lower the release rate [29]. This confirms that cholesterol in the formulation acts as a membrane stabilizing agent that helps to sustain drug release [30,31].

CONCLUSION

Three formulae of niosomes vesicles were prepared and loaded with rivastigmine tartrate. Those formulae were prepared by hand shaking method with three different surfactants (Span 40.60 and 80). Cholesterol and surfactants were added by molar ratio, but the second formula which contain surfactant of span 60 (formula 2) showed the best formed suspension. Therefore, this formula was chosen to be examined. The formed suspension was homogenous and opaque white in color. Under optical light microscope, formula showed well identified spherical vesicles with various sizes. Entrapment efficiency percentage of the prepared formula was (84 - 89%) and zeta potential was found to be (-19.3 mV) without using stabilizers or charged molecules. In-Vitro release studies proved that the prepared niosomes loaded with rivastigmine tartrate is considered to be a successful intranasal drug delivery system which can be further proven by future bioequivalence and In-vivo studies.

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