Formulation and Characterization of Cariprazine Nanoemulsion as Oral Route

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Abstract

Cariprazine is a antipsycotic drug with low aqueous solubility. Nanoemulsion (NE) is one of the popular methods that has been used to solve the dispersibility problems of many drugs. Cariprazine was formulated as a NE utilizing oleic acid as an oil phase, tween 80 and tween 60 as surfactants and ethanol as a co-surfactant. six formulas were prepared, and different tests were performed to ensure the stability of the NEs, such as particle size, polydispersity index, dilution test, drug content, viscosity and in-vitro drug release. Results of characterization showed that cariprazine nanoemulsion (F3) was selected as the best formula, since it has a particle size of (27)nm, low PDI (0.371), good dilution without drug precipitation , higher percent of drug content (98.9%) with acceptable viscosity , and complete release of the drug after (40 min.) with significantly higher ($P<0.05$) dissolution rate in comparison with the pure drug powder. The selected formula (F3) subjected to further investigations as drug and excipient compatibility study by Fourier transform infrared spectroscopy (FTIR) The outcomes of the (FTIR) indicates that there was no interaction between cariprazine and other NE components. Therefore, these excipients were found to be compatible with cariprazine. In conclusion, the NE was found to be an efficient method to enhance water solubility.

INTRODUCTION

Nanoemulsion is defined as a novel and advance drug delivery system that has a great devotion to the delivery of drugs. Nanoemulsions, also is known as submicron emulsions, are submicron sized colloidal particulate systems deliberated as thermodynamically and kinetically stable isotropic dispersions, which consist of two immiscible liquids like water and oil, stabilized by an interfacial film forming agent consisting of a suitable surfactant and co-surfactant to form a single phase. It leads to improve the solubility of poorly soluble drugs (lipophilic drugs) which results in an improvement of the bioavailability of these drugs (1) . Cariprazine is an oral antipsychotic approved in the US and EU for the treatment of schizophrenia. Cariprazine differs from other antipsychotics in that it is a dopamine D3- and D2-receptor partial agonist (2) . Cariprazine and its active metabolites reached steady state within 4 weeks, and exposure was dose proportional over the range of 3–9 mg/day. Once-daily cariprazine was generally well tolerated in adult patients with schizophrenia (3). It is rapidly absorbed, reaching peak concentrations between 3 and 4 hours after oral dosing in healthy subjects, but did not affect the extent of its absorption after a single 2 mg oral dose. Practically insoluble in water, soluble in organic solvents, half-life was 2–5 days (4) .

Materials and Methods

Materials

Cariprazine powder was purchased from Baoji Guokang Bio- Technology Co.LtdTween 80

was purchased from Riedel-De-Haen, Germany.Tween 60 was provided from Avonchem, England.Dialysis membrane(12000 Da) provided from Schcuhardt , Germany. All other chemicals and solvents were of analytical reagent grade.

Methods

Pseudo-ternary phase diagrams construction

Construction of the pseudo-ternary phase diagrams was done by using aqueous titration method. Based on the solubility studies, oleic acid was selected as an oil phase, tween 80 and tween 60 were selected as surfactant and ethanol were selected as a co-surfactant, and deionized water (DDW) used as an aqueous phase. The oil: surfactant: co-surfactant (Smix) mixed at different ratio. For each phase diagram, oil and Smix (at a specific ratios) were mixed gradually at different ratios (ranging between 1:9 to 9:1) in different glass vials (5)

Preparation of cariprazine nanoemulsion

Different o/w nano emulsion formulations (Table 1) were prepared using the Smix and oil ratios according to pseudo-ternary phase diagrams. The preparation of primary cariprazine nanoemulsion occur through dissolving (3 mg) of the drug in the selected oil, then magnetic stirrer was used then the selected Smix added slowly in a fixed proportion until clear solution was gained followed by the addition of deionized distal water dropwise to the clear solution with continuous stirring ((~500 rpm) at room temperature till formation of clear emulsion. The prepared emulsions then were ultrasonicated using a 20 kHz sonicator for 10 min to produce very small droplet size NEs. (6).

Table 1. Composition of different cariprazine nanoemulsion

Formula	Cariprazine w/w	Oleic acid % w/w	Surfactant	Co-surfactant	S mix ratio	S mix % w/w	DDW% w/w
F1	0.03 %	10 %	Tween 80	Ethanol	1:1	60	30
F2	0.03 %	10 %	Tween 80	Ethanol	2:1	60	30
F3	0.03 %	10 %	Tween 80	Ethanol	3:1	60	30
F4	0.03 %	10 %	Tween 60	Ethanol	1:2	60	30
F5	0.03 %	10 %	Tween 60	Ethanol	2:1	60	30
F6	0.03 %	10 %	Tween 60	Ethanol	3:1	60	30

Characterization of the prepared nanoemulsion:

Particle size and polydispersity index (PDI)

The droplet size of NE was determined by analyzing the fluctuations in light scattering due to the Brownian motion of the particle using the dynamic light scattering technique (Zetasizer Nano) Nanoemulsion was diluted with distilled water (100-fold) and gently stirred (to increase the homogeneity) before measurement (7) . While the measurement of (PDI) gives information about the uniformity of droplet size within the formulated NE. The lower PDI value (near zero) indicates a monodisperse droplet population, whereas a PDI value closer to 1 indicates a wide range of droplet size (8) .

Dilution test

Aqueous dilution test was done, 1 mL of each nanoemulsion formula from (F1-F8) diluted to 50 mL, 100 mL and 500 mL with distilled water at 37° C with constant stirring and was

maintained at 50 rpm. turbidity, clarity and the phase separation for each formula was observed visually (9)

Drug content

Accurately, 10 ml of each NE formula which contains (3mg) of cariprazine was dissolved in 100 ml ethanol, then filtered using 0.45 μm filter syringe and suitably diluted. The contents of cariprazine was determined using UV/Vis spectrophotometer at the selected λ max (10).

Viscosity measurement

Viscosity is very important for stability and efficient drug release. Nanoemulsion carrier formulations are basically oil-in-water and so in addition to being less greasy than water-in-oil formulations, often possess lower apparent viscosities. They are therefore expected to exhibit faster release of active ingredients.

The low viscosity of systems shows that it is o/w type and high viscosity shows that it is w/o type system. Measurements were performed using viscometer spindle number 2 that was immersed in 100- ml sample of each prepared NE formulas and rotated at different speeds (11)

In vitro drug dissolution study

The in vitro release of cariprazive loaded NE occur using USP dissolution apparatus type – II (paddle method).

Ten ml of each formula which contains (3mg) of cariprazine was poured in the dialysis bag (Molecular cut off 12000Da), then this bag immersed in 500 ml of dissolution medium.

The dissolution medium was (0.1N HCl with 1% tween 80), the dissolution apparatus set at 37 ± 0.5 °C, and the rotation speed was 50 rpm . Nanoemulsion containing cariprazine equivalent to one dose(10ml) was placed in a dialysis bag, and five ml of dissolution medium was withdrawn at 5, 10, 15, 30, 45, 60, 90 and 120 min time intervals and the samples then filtered using a 0.45 μm filter syringe and analyzed by UV/Vis spectrophotometer at the λ max of the drug the study was done in triplicate (12) .

Selection of the optimum formula

The choice of the optimum formula was accomplished, and this achieved according to the droplet size, PDI, dilution test, drug content, viscosity, and in vitro release studies.

Evaluation of the selected cariprazine optimum formula

Fourier transform infrared spectroscopy (FTIR)

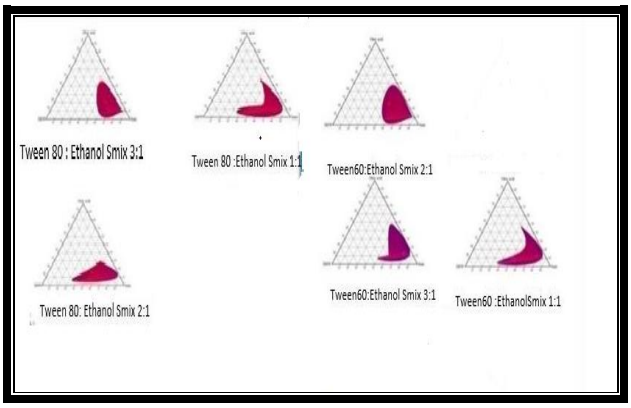
The Fourier transform infrared spectroscopy (FT-IR) spectra were recorded for pure drug and optimized formulation using KBr pellet technique. The pellets were prepared using KBr hydraulic press under hydraulic pressure of 150 kg/cm2 . The spectra were scanned over 3600-400 cm−1 at ambient temperature with a resolution of 4 cm−1, using FT-IR 2500 apparatus and spectra were recorded (13) .

Results and Discussion

Construction of pseudo-ternary phase diagrams

Figures 1 showed the pseudo-ternary phase diagram for the o/w NEs using oleic acid as an oil phase, tween 80 and tween60 as a surfactant and ethanol as a co-surfactant.

Figure (1): Pseudo-ternary phase diagrams showing the (o/w) nanoemulsion (colored area) regions of oleic acid at different Smix ratios.



Characterization of the prepared nanoemulsions:

Particle Size and Polydispersity Index (PDI)

Table (2) showed the results of droplet size measurement and poly dispersity index. Also, in regard to particle size, the results showed that when the concentration of surfactant increased the particles size reduced, since this high surfactant concentration decreases surface tension and stabilizes newly developed surfaces during homogenization and production of smaller particles , these results may be also due to accumulation of surfactant molecules at the interface provides better stabilization against droplet aggregation and helps in lowering the flocculation rate, as well as greater penetration of the oil phase in the hydrophobic region of the surfactant, lead to reduction the droplet size (14) ,while the PDI refers to the quality of a polydispersity index and it is not stable. The low value of PDI (0.289- 0.461) is considered to be desirable for uniform distribution, stability and high of the dispersion (15) .

Table 2. Particle size and poly pisprersity index of the NE formulas.

Formulas	Particle size (nm)	PDI
F1	202.1 nm	0.289
F2	66.8 nm	0.461
F3	27.1 nm	0.371
F4	61.5 nm	0.398
F5	48.7 nm	0.321
F6	36.6 nm	0.369

Dilution test

All nanoemulsion formulas (F1-F6) showed fine bluish to clear nanoemulsion indicating o/w type, proved that they could be diluted in GI fluids and maintaining the nanosized character without drug precipitation. Thus, it is anticipated that absorption will be enhanced(16) .

Drug content

Results shown in table (3) indicated that all nanoemulsion formulas agreed with the requirements of the British Pharmacopeia range (92.5 % - 98.9 %) indicating that, there was no precipitation of drug in any of prepared formulations.

Table 3. Drug content percentage of the prepared nanoemulsion

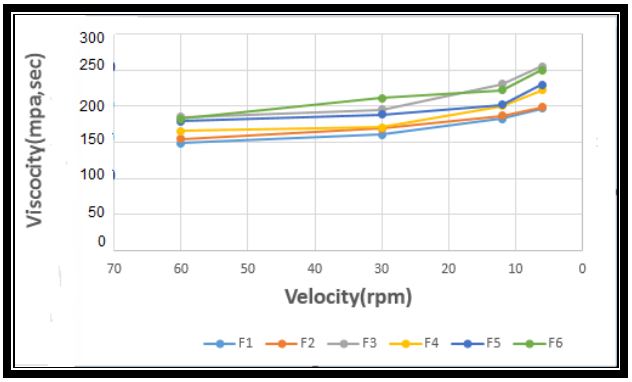
Formulas	Drug content
F1	92.5
F2	94.4
F3	98.9
F4	96.1
F5	95.8
F6	97.3

Viscosity measurements

Figure (2), it was demonstrated as the concentration of the surfactant increased; the viscosity increased this may be due to entrapping of the water molecules in cross-

linking surfactants chains and also highest surfactant concentration would make the dispersion medium more rigid (17) . The results also showed that the viscosity decreased as the rotation speed increased.

Figure 2. Viscosities data of prepared cariprazine nanoemulsion formulas (F1-F6).



In vitro drug dissolution study

The release of cariprazine from the formula that contain tween 80 as surfactant (F3) was higher than that contain tween 60 (F6) which could be explained by the smaller droplet size of formulas containing tween 80 as compared to that formulas which contain tween 60 leading to greater rate of dissolution. This may be attributed to the fact that the reduction of drug particle size caused an increase in the surface area and consequently enhanced the contact between nanoparticles and dissolution medium. The obtained results are in good accordance with Noyes–Whitney equation which states that the increase in saturation solubility and the decrease in particle size lead to an increased dissolution rate(18) , as showen in figure 3,4

Figure (3): In vitro drug release profile of cariprazine formulation nanoemulsion in 0.1N HCl at 37°C (F1,F2,F3) containing 1%tween 80

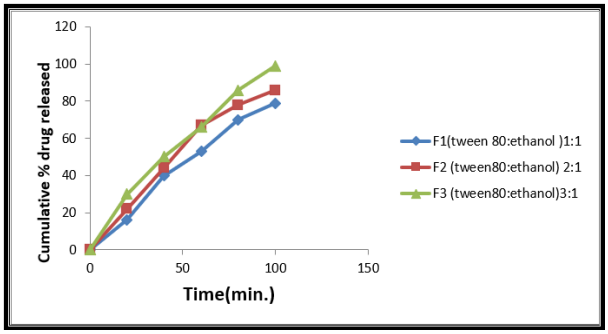
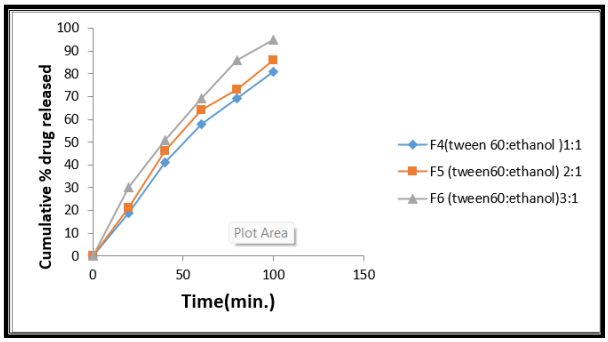


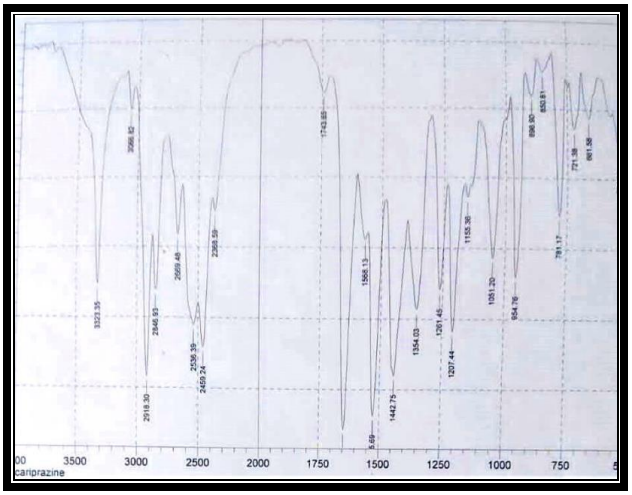
Figure (4): In vitro drug release profile of cariprazine formulation nanoemulsion in 0.1N HCl at 37°C (F4,F5,F6) containing 1%tween 80



Fourier transform infrared spectroscopy (FTIR)

The spectrum of the selected formulas F3 represented in figure 5, apear main peaks of drug that indicate no interaction between drug and excepeints during formulation of nanoemulsion.

Figure (5): FTIR of the selected formula , F3



Conclusion

Nanoemulsion formulas prepared with oleic acid as an oil phase, tween 80,tween 60 as a surfactant ,ethanol as a co-surfactant in the dissolution media compared to pure drug powder. F3 with oleic acid oil and Smix at ratio of 3:1 was selected best formula. No chemical interaction between cariprazine and other components in the preparation of nanoemulsion. The present study proved nanoemulsion technology is an efficient method of administering for insoluble drugs like cariprazine in liquid dosage form.

Reference

1- Manjit Jaiswal , Rupesh Dudhe . Nanoemulsion an advanced mode of drug delivery system. Biotech journal . 2015 ; 5(2): 123–127.

2- Leslie Citrome. Cariprazine for acute and maintenance treatment of adults with schizophrenia: an evidence-based review and place. Neuro-psychiatr Dis Treat. 2018; 14: 2563–2577.

3- Tadakatsu Nakamura, Tomoko Kubota. Clinical pharmacology study of cariprazine. Drug Design, Development and Therapy.2016; 10:116-129.

4- Maru alt. Clinical pharmacology of atypical antipsychotics: an update. Experimental and Clinical Science. 2014; 13: 1163-1191.

5- Su R, Yang L, Wang Y, Yu S, Guo Y, Deng J, et al. Formulation, development, and optimization of a novel octyldodecanol-based nanoemulsion for transdermal delivery of ceramide IIIB. Int J Nanomedicine. 2017;12: 5203–21. 11

6- Miastkowska MA, Banach M, Pulit-Prociak J, Sikora ES, Głogowska A, Zielina M. Statistical Analysis of Optimal Ultrasound Emulsification Parameters in Thistle-Oil Nanoemulsions. J Surfactants Deterg. 2017; 20(1): 233-246.

7- Alshahrani SM. Anti-inflammatory Studies of Ostrich Oil Based Nanoemulsion. Journal of Oleo Science.2019; 208(3):203–8.

8- Siddique AB, Ebrahim H, Mohyeldin M, Qusa M, Batarseh Y, Fayyad A, et al. Novel liquid-liquid extraction and self-emulsion methods for simplified isolation of extra-virgin olive oil phenolics with emphasis on oleocanthal and its oral anti-breast cancer activity. PLoS One. 2019; 14(4).

9- Maraie NK, Almajidi YQ. Application of Nanoemulsion Technology for Preparation and Evaluation of Intranasal Mucoadhesive Nano- In-situ Gel for Ondansetron HCl. Journal of Global Pharma Technology. 2018; 10(03): 431-42.

10- Sanjana Reddy, Tripura Sundari. Formulation and Evaluation for Nanoemulsion of Solubility Enhancement of Febuxostat International Journal of

Scientific Development and Research. 2019; 4(1): 2455- 2631.

11- Sumaya B. Hamed, Shaimaa N. Abd Alhammid. Formulation and Characterization of Felodipine as an Oral Nanoemulsions. Iraqi Journal Pharmaceutical Science. 2021; 30(1) ; 209-217.

12-Manyarara TE, Khoza S, Dube A, Maponga CC. Formulation and characterization of a paediatric nanoemulsion dosage form with modified oral drug delivery system for improved dissolution rate of nevirapine. MRS Advances. 2018;3(37):2203-19.

13- Prakash S, Suryadevera V , Anne R , Reddyvalam LS , Kunam V. Development and Characterization of A Novel Nanosuspension Based Drug Delivery System of Valsartan: A Poorly Soluble Drug. Asian Journal of Pharmaceutics. January-March 2015; 9:29-34.

14- Silva HD, Cerqueira MA, Vicente AA. Influence of surfactant and processing conditions in the stability of oil-in-water nanoemulsions. J Food Eng. 2015; 167:89–98 .

15- Danaei M, Dehghankhold M, Ataei S, Hasanzadeh Davarani F, Javanmard R, Dokhani A, et al. Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. Pharmaceutics. 2018; 10(2):1–17.

16- Al-sakini SJ, Maraie NK. Optimization and in Vitro Evaluation of the Release of Class II Drug From Its Nanocubosomal Dispersion. Int J Appl Pharm. 2019;11(2):86–90.

17- Megha Singh, Santosh Kumar. Formulation and Evaluation of Hydroxyzine Loaded Nanoemulsion. International Journal of Pharmacy and Pharmaceutical Research. 2012; 25(4): 221-240.

18- Heba A. Fatohy, , Alaa A. Abdul-Rasool. Effect of Different Diluent and Binder Types on the Preparation of Bisoprolol Fumarate as Tablet Dosage Form. Iraqi journal of Pharmaceutical Sciences. 2013; 22(1): 32-39.