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Preparation and characterization of azelnidipine-loaded D-α-tocopheryl polyethylene glycol succinate (TPGS) / solutol micelles

Ali Kathem Ala Allah[1], Shaimaa Nazar Abd Alhammid [2,*]

[1]Babylon Health Directorate, Hillah, Iraq
[2]Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq

***Corresponding author:** Shaimaa Nazar Abd Alhammid, Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq; Tel.: +964-(0)7703951999
E-mail: Shaimaa.Abd@copharm.uobaghdad.edu.iq

Abstract

Azelnidipine is a calcium-channel antagonist classified as a “class 2” drug with high permeability and low aqueous solubility. It is used in the treatment of angina pectoris and hypertension without reflex tachycardia. Improvement of the solubility of azelnidipine and increasing drug’s bioavailability can be achieved through the drug encapsulation in solutol / D-α-tocopheryl polyethylene glycol succinate (TPGS) micelles. Six formulas were prepared by direct dissolution after using different amounts of solutol and TPGS. TPGS and solutol act as solubilizers, permeation enhancers, and P-glycoprotein inhibitors. The particle size, particle size distribution, zeta potential, and entrapment efficiency were determined. Depending on particle size and entrapment efficiency, formula #6 was selected and subjected to *in vitro* dilution stability and *in vitro* release studies. The results obtained showed that formula #6 was the best formula, with a high entrapment efficiency percentage equal to 86.5%±0.58% and a small particle size equal to 21.9±7.75 nm that did not change significantly after dilution up to 100-fold; a fact that reveals the high thermodynamic and kinetic stability of the optimum formula. The formula #6 release profile showed a controlled release of the drug from micelles when compared to plain drug release. Based on these results, polymeric nanomicelles are regarded as a promising delivery system for azelnidipine.

KEYWORDS
Azelnidipine, TPGS, solutol HS15, micelles, drug delivery

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1. INTRODUCTION

Polymeric micelles are spontaneously self-assembled structures composed of amphiphilic molecules, with two main types of segments: hydrophilic and hydrophobic. Their preparation, solubilizing capacity, and nano-size range made them interesting nanocarriers for oral administration routes [1].

Azelnidipine is a calcium channel antagonist with high permeability and low aqueous solubility, that is used in the treatment of angina pectoris and hypertension without causing reflex tachycardia [2].

D-α-tocopherol polyethylene glycol succinate (TPGS) is an amphiphilic copolymer composed of an hydrophilic polyethylene glycol head and a lipophilic tail of vitamin E that is used as a nanocarrier in order to increase drug solubility. Solutol HS15 (polyoxyethylene esters of 12-hydroxystearic acid) is a non-ionic polymer used for enhancing the solubility and stability of insoluble drugs, especially when combined with TPGS [1].

The aim of this study was the enhancement of the solubility of azelnidipine by using TPGS / solutol HS15 mixed micelles nanocarriers, leading to the enhancement of the drug bioavailability.

2. MATERIALS AND METHODS

Chemicals: Azelnidipine, TPGS, and solutol HS15 were purchased from HyperChem (Hangzhou, China). All other chemicals and solvents were of analytical grade.

Preparation of polymeric micelles: Different amounts of the two amphiphilic copolymers (solutol HS15 and TPGS) were used in order to prepare six formulas of azelnidipine-loaded mixed micelles as shown in Table 1. Solutol HS15 and TPGS were dissolved in 10 mL of distilled water in a glass vial, and then 8 mg of azelnidipine dissolved in the solutol HS15/TPGS solution by using a magnetic stirrer at 37°C with the stirring continuing until the complete dissolution of azelnidipine was achieved. After that, the sonication of this mixture was undertaken by using a bath sonicator. Finally, the filtration the mixture using 0.22-μm syringe filters was performed so as to obtain a clear and uniform micellar solution [1].

Particle size, polydispersity index (PDI), and zeta potential measurement: The particle size, the PDI, and the zeta potential of the prepared formulas were measured by a Zetasizer Nano (Malvern Pananalytical, UK) and was performed in triplicate at 25°C [3].

Entrapment efficiency percentage (%EE) measurement: In this study, each formula was centrifuged and then 1 mL of the supernatant was filtered through a 0.45-μm syringe filter and diluted, and the amount entrapped was measured directly by a UV-Vis spectrophotometer [4]. The %EE values were calculated by the following equation [5]:

$$\%EE = \frac{amount\ of\ drug\ in\ the\ micelles}{total\ amount\ of\ drug\ initially\ added} \times 100$$

Dilution stability: Formula #6 was diluted up to 100-fold by using a phosphate buffer at pH 7.4

The in vitro drug release study: The study was performed by using a USP dissolution test apparatus with a rotating paddle [6]. Briefly, capsules containing freeze-dried azelnidipine-loaded TPGS / solutol HS15 micelles (formula #6) or plain azelnidipine were immersed into the vessels of the dissolution testing apparatus containing 500 mL phosphate buffer at pH 6.8 with 0.5% SLS so as to maintain sink conditions, and the system was kept at 37±0.5°C with continuous stirring at 50 rpm. After that, samples equal to 5 mL were withdrawn from the release medium at predetermined time intervals, and were replaced immediately with a fresh buffer solution, and the amount of the released azelnidipine was determined by UV-Vis spectrophotometer [7]. Later, the percentage of the cumulative amount released was calculated and plotted against time [8]. The drug release profile from formula #6 was fitted by using several kinetic models such as zero-order, first-order, Higuchi's, Hixson-Crowell's, and Korsmeyer-Peppas's so as to determine the best-fit model and mechanism of azelnidipine release.

Statistical analysis: The results were expressed as the mean ± standard deviation (SD) of three independent measurements. One-way ANOVA was performed for the statistical analysis by using GraphPad Prism version 9; *P*-values <0.05 were considered as statistically significant [9].

3. RESULTS AND DISCUSSION

Method of polymeric micelles' preparation: The direct dissolution method is regarded as a suitable method for the preparation of these six formulas, because of the higher water solubility of the two copolymers (TPGS and solutol HS15). The use of two copolymers increases the solubility, %EE, and stability of the prepared micelles by the formation of hydrophobic bonds between the micelle's core and the hydrophobic drug (azelnidipine).

Particle size, PDI, and zeta potential determination: The small-size micelles were prepared by a combination of TPGS and solutol HS15 as shown in Table 1, and this increased the solubility, intestinal permeability, and bioavailability, and prolonged the *in vivo* circulation time. There is a significant decrease in particle size (P<0.05) when the concentration of TPGS increases and the concentration of solutol HS15 remains constant in the formulas (#1 compared to #4, #2 compared to #5, and #3 compared to #6) [1]. The narrow size distribution of the prepared formulas (as shown in Table 1) reveals the homogeneity and stability of the prepared formulas (*in vitro* and *in vivo* stability). The zeta potential of the prepared formulas was negatively charged and near neutral (Table 1), and this enhanced the mucus-penetrating prop-

erties of the micelles. Moreover, the presence of polyethylene glycol in the micelles shell generates an external crown that increases the stability of the micelles (steric stabilizer).

%EE determination: The %EE of the prepared formulas is shown in Table 1. There is a significant increase (P<0.05) in %EE when the concentration of TPGS increases and the concentration of solutol HS15 remains constant in the formulas (#1 compared to #4, #2 compared to #5, and #3 compared to #6) [1].

Selection of the optimum formula: Formula #6 which consists of 8 mg of azelnidipine, 100 mg of TPGS, and 100 mg solutol HS15 regarded as the best formula depending on particle size (21.9±7.75 nm), PDI, and %EE (86.5%±0.58%). It was, therefore, subjected to further characterization.

Dilution stability: There was no precipitation and turbidity observed, thereby suggesting a formula stability.

In vitro release study: Azelnidipine was released from the polymeric micelles at a much slower rate than from the plain drug. Within 1 h, almost all of the azelnidipine was released from the plain drug, while 86.66% of the drug was released from TPGS/solutol HS15 micelles at 2.5 h. This refers to the stability of the micelles core, which controls the release of the drug; it increases the contact time with the intestinal mucosa, prevents drug precipitation in the gastrointestinal tract, and increases the extent of the absorbed drug [10]. The formula #6 release profile was best fitted to the Hixon-Crowell's release kinetic model. In this study, the n value was equal to 0.789; it can, thus, be suggested that the mechanism of azelnidipine release from the TPGS/solutol HS15 micelles was through an anomalous non-Fickian diffusion, which indicates an azelnidipine release taking place as a combination of diffusion and erosion of the TPGS / solutol HS15 polymers.

Table 1. Formulas of the azelnidipine-loaded D-α-tocopheryl polyethylene glycol succinate (TPGS) / solutol HS15 micelles, and the results of the assessment of their particle size, polydispersity index (PDI), zeta potential, and entrapment efficiency percentage (%EE). Note: Q.S., *quantum satis*.

Formulas of the TPGS/solutol HS15 micelles				
Formula code	**Azelnidipine** (mg)	**TPGS** (mg)	**Solutol HS15** (mg)	**Deionized water** (up to 10 mL)
Formula #1	8	50	50	Q.S.
Formula #2	8	50	75	Q.S.
Formula #3	8	50	100	Q.S.
Formula #4	8	100	50	Q.S.
Formula #5	8	100	75	Q.S.
Formula #6	8	100	100	Q.S.
Particle size, PDI, zeta potential, and %EE of the formulas devised				
Formula code	**Particle size** (nm)	**PDI**	**Zeta potential** (mV)	**%EE**
Formula #1	365.37±68.49	0.55±0.12	-12.76±6.06	41.64±1.24
Formula #2	166.57±19.27	0.31±0.08	-6.67±2.66	49.5±0.9
Formula #3	151.8±13.67	0.25±0.02	-5.67±5.5	54.07±0.37
Formula #4	36.52±5.21	0.24±0.18	-9.63±6.71	80.13±0.3
Formula #5	19.26±3.10	0.16±0.04	-4.13±5.76	83.78±0.66
Formula #6	21.9±7.75	0.27±0.13	-7.23±5.58	86.5±0.58

4. CONCLUSION

Based on our findings, the direct dissolution method is the proper method for the preparation of these formulas. Formula #6 is the best one, with small particle size, high %EE, and a controlled release profile that increases the azelnidipine bioavailability and is, therefore, regarded as a promising delivery system for azelnidipine.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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