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ORIGINAL STUDY

D-∝-TPGS/Poloxamer 188 Mixed Micelles for the Oral Delivery of Azelnidipine: Preparation and In Vitro Evaluation

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ABSTRACT

Azelnidipine is a calcium channel blocker with low water solubility and high lipophilicity and is intended for treating angina pectoris and hypertension. This study aimed to increase and enhances the solubility of azelnidipine through its incorporation in *D*-∝-tocopheryl polyethylene glycol/polyxamer188 (TPGS/P188) micelles for oral administration and substantially increasing the extent of drug absorption.

Nine formulations (A_1-A_9) were prepared by direct dissolution method using a combination of D-∝- TPGS 1000 succinate and Poloxamer 188. The size of the particle, polydispersity index (PDI), surface charge, and entrapment capacity were measured. The optimum formula was subjected to further characterization including in-vitro release study, Fourier transform infrared spectroscopy (FTIR), X-ray diffraction study (XRD), Differential scanning calorimetry (DSC), and atomic force microscopy (AFM). The study showed that A_9 was the optimum formula depending on the particle size (24.22 ± 7.61), polydispersity index (0.24 ± 0.09), zeta potential (-4.35 ± 3.7), and entrapment efficiency percentage (84.35 ± 0.65). The small particle size, narrow size distribution, high entrapment efficiency, and negative near-neutral Zeta potential of formula A9 significantly improve the drug transport and absorption via intestinal epithelium. they are of prime importance for both in vitro and in vivo stability of Azelindipine-loaded micelles.

The profile of release showed controlled release characteristics of azelnidipine from formula (A_9) compared to plain drug release. The controlled release of Azelindipine could avoid precipitation of the drug in the gut and improve its absorption. whereas rapid release of Class 2 drugs might lead to precipitation of the drug in GIT environment before absorption. Solubility study showed enhancement of the drug solubility in micellar solution, this can improve significantly the bioavailability. FTIR showed azelnidipine compatibility with TPGS/P188 copolymers and absence of chemical interaction.

DSC and XRD showed the transformation of azelnidipine into an amorphous form and confirmed its localization inside the micelles. AFM study showed smooth spherical morphology of formula (A_9). Depending on these results, formula (A_9) is regarded as a promising nanocarrier for azelnidipine delivery.

Keywords: Azelnidipine, TPGS/P188 micelles, TPGS, Poloxamer 188

1. Introduction

The oral administration route offers a valuable choice for curing different diseases due to its unique benefits, including sustained or controllable delivery, patient compliance, cost-effectiveness, easiness of administration, possibility for solid dosage formulations, and an increased immune response for vaccines delivery. It is considered as the most widely used route for drug delivery. It is also greatly used for chronic drug administration, including antitumor, antidiabetic drugs, and antihypertensive compounds [1].

The new technologies employed in drug discovery led to find many new powerful substances. The development of new drugs alone is not sufficient to ensure

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progress in drug therapy. Unfortunately, more than 40% of the drugs coming out of the drug discovery and development processes are not suitable for oral delivery due to their poor oral bioavailability that is insufficient drug is presented to the site of action with subsequent lack of pharmacological action. Therefore, there is an increasing need to develop a drug carrier system that overcomes these drawbacks. This carrier system should have no toxicity (acute and chronic), have a sufficient drug loading capacity and the possibility of drug targeting and controlled release characteristic. It should also provide chemical and physical stability of the incorporated drug [2].

Pharmaceutical nanotechnology is the alternative strategy to overcome bioavailability problems by generating various products with extra advantages at the nanoscale that deliver pharmaceutical compounds to the body according to desire and need [3].

The first advantage is the improvement of solubility and dissolution speed, because of the high surface area/volume ratio offered by nano sized particles. The second advantage is the improvement of drug delivery where the small particle size can prolong the residence time of the drug in the systemic circulation, change drug distribution, and improve drug targeting [4].

Polymeric nano-micelles are an important drug carrier system and have been used recently to fulfill the above nanotechnology advantages. Polymeric nanomicelles are composed of diblock or triblock polymers which self-associated into core-shell nano-sized structures where the lipophilic segment acts as a reservoir for lipophilic drugs and the hydrophilic segment acts as stabilizing corona [5].

Azelnidipine is a calcium channel antagonist used to treat hypertension and angina pectoris where it induces a gradual decrease in blood pressure without reflex tachycardia. The chemical structure of azelnidipine was shown in (Fig. 1). It is a lipophilic compound with low water solubility and high permeability [6].

D-α-tocopherol polyethylene glycol is an amphiphilic polymer that was approved by FDA as safe pharmaceutical excipient and it is consisted of vitamin E covalently bonded to polyethylene glycol (PEG) 1000 via esterification reaction. It is a biocompatible and biodegradable molecule that is widely combined with other amphiphilic polymers to form micelles. It is used in nano carriers as emulsifier, solubilizer, stabilizer, and absorption enhancer [7]. Chen *et al.* that enhance the paclitaxel oral bioavailability by 3.8 fold using TPGS micelles compared to commercial formulation (Taxol) [8].

Poloxamer-188 is triblock amphiphilic polymers consist of two hydrophilic segments connected to a

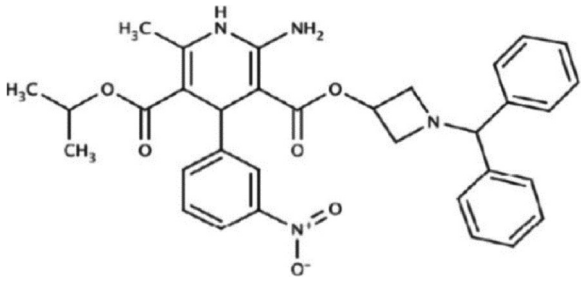

Fig. 1. Chemical structure of AZEL.

lipophilic center core that is used as a micellar carrier to produce small-size micelles with sufficient stability [9]. It combines with other amphiphilic molecules such as TPGS to produce an active carrier system that improves the bioavailability of oral low water-soluble drugs such as ebastine [10].

The aim of the study is the improvement of the solubility of azelnidipine (BCS class two drug) by using TPGS/P188 mixed micelles nanocarriers, which leads to the enhancement of the drug bioavailability.

2. Materials and methods

Azelnidipine and TPGS were obtained from Hangzhou, Hyperchem (China). Poloxamer 188 was obtained from Sigma-Aldrich (Germany). All other chemicals and solvents were of analytical grade.

2.1. Preparation of polymeric micelles

Formulations (A_1–A_9) were prepared by direct dissolution method using different amounts of two amphiphilic polymers TPGS and P188 as shown in (Table 1).

Briefly, TPGS and P188 were dissolved in ten milliliters of distilled water in glass vial, after that, eight milligrams of the drug dissolved in TPGS\P188 solution using magnetic stirrer at 37°C and the stirring continued until complete dissolution of the azelnidipine. Finally, sonication of the mixture using a bath sonicator followed by filtration using 0.22 μm filter syringe to get a clear and uniform micellar solution [11].

2.2. Determination of the optimum stirring rate and time

Two stirring rates and stirring times (1000 rpm for 0.5 h and 2000 rpm for 1h) were used to determine the optimum magnetic stirring rate and time for the preparation of azelnidipine-loaded TPGS/P188 micelles.

Table 1. Formulas of TPGS/P188 micelles.

Formula code	Amount of Azelnidipine mg	Amount of TPGS mg	Amount of P188 mg	Distilled water up to 10 ml
A_1	8	50	50	Q.S
A_2	8	50	75	Q.S
A_3	8	50	100	Q.S
A_4	8	75	50	Q.S
A_5	8	75	75	Q.S
A_6	8	75	100	Q.S
A_7	8	100	50	Q.S
A_8	8	100	75	Q.S
A_9	8	100	100	Q.S

2.3. Particle size and PDI measurement

The particle size and PDI of the formulated formulas were determined by Zetasizer (Malvern Instrument, UK). Every test was achieved in three times at 25˚C [12].

2.4. Zeta potential measurement

The zeta potentinal of the TPGS/P188 polymeric micelles was measured by Zeta sizer. The test was achieved in three times at 25˚C [13].

2.5. Entrapment efficiency percentages measurements

The encapsulation efficiency percentages were determined for formulations (A_1-A_9) where each formula was centrifuged (4000 RPM for 10 min) using EBA-20, Zentrifugen, HeHich Lab technology, Germany. Then 1ml of the supernatant filtered through 0.45μm syringe filter, suitably diluted, and the amount loaded measured directly by UV-Vis spectrophotometer (UV-1650 SHIMADZU (Japan), at wavelength 250 nm). The encapsulation capacity percentages were measured by using formula [14]:

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

2.6. The in-vitro drug release study

The in-vitro drug release study of Azelnidipine from TPGS\P188 micelles (A_9) was achieved using a USP dissolution test apparatus with a rotating paddle and compared with the plain drug release [15].

Briefly, capsule containing freeze dried azelnidipine loaded TPGS\P188 micelles (A_9) or plain azelnidipine drug were immersed into vessels of dissolution testing apparatus containing 500 ml phosphate buffer pH 6.8 with 0.5% sodium lauryl sulfate to maintain sink condition and the system was kept at 37 ± 0.5˚C with continuous stirring at fifty rpm. After that, samples equal to five milliliters were withdrawn taken from the release medium at regular periods of time, and replaced immediately with a new buffer solution, and the amount of Azelindipine released was determined by UV-Vis spectrophotometer. Later, the % of the cumulative amount released was calculated and respective time [16].

The drug release profile from A_9 was fitted using several kinetic models such as zero-order, first-order, Higuchi's, Hixson-Crowell's, and Korsmeyer-Peppas's to determine the best-fit model and mechanism of azelnidipine release [17].

2.7. Saturation solubility study

The solubility of azelnidipine in water and in the best formula (A9) was investigated by adding excess amount of azelnidipine to certain volume of water and blank micellar solution (blank best formula A9). The mixtures were agitated on a shaker water bath for 48 hours at room temperature to attain equilibrium. The mixtures were rotated at 10000 rpm for thirty minutes to remove the undissolved azelnidipine. The supernatant thus obtained was suitably diluted and the solubility of azelnidipine in water and micellar solution was determined using UV- spectrophotometer. The factor of solubility (Sf) was then measured using the equation:

$$Sf = \frac{smic}{sw}$$

Sf: factor of solubility

Smic: the solubility of azelnidipine in nano micelles

Sw: solubility of azelnidipine in water.

2.8. FTIR spectroscopy study

FT-IR study was performed using FTIR spectroscopy (IRPrestige-21, SHIMADZU, Japan) to check the identity of the azelnidipine and to identify its interaction

Table 2. Particle size, polydispersity index, zeta potential, and entrapment efficiency percentage of the formulas ($A_1 - A_9$).

Formula code	PS (nm)	PDI	ZP (mV)	EE%
A_1	229.73 ± 27.98	0.96 ± 0.69	−11.76 ± 11.04	40.61 ± 1.11
A_2	44.14 ± 16.349	0.24 ± 0.03	−6.5 ± 2.95	47.41 ± 0.81
A_3	75.01 ± 2.17	0.4 ± 0.28	−4.86 ± 1.65	55.26 ± 0.54
A_4	72.37 ± 9.94	0.2 ± 0.13	−8.25 ± 10.45	62.91 ± 1.14
A_5	31.85 ± 9.06	0.25 ± 0.08	−4.04 ± 3.31	63.8 ± 0.6
A_6	34.66 ± 12.87	0.25 ± 0.03	−3.31 ± 4.56	65.75 ± 1.52
A_7	39.24 ± 9.50	0.28 ± 0.07	−9.61 ± 2.91	81 ± 0.5
A_8	22.04 ± 2.10	0.2 ± 0.01	−8.64 ± 5.01	81.99 ± 0.66
A_9	24.22 ± 7.61	0.24 ± 0.09	−4.35 ± 3.7	84.35 ± 0.65

with TPGS/P188 polymers. The IR spectra of azelnidipine, TPGS, P188 and formula (A_9) were obtained using KBr disk process and scanning range between 400–4000 cm^{-1} at scanning rate of 2 cm^{-1} [18].

2.9. DSC study

The probability of any interaction between azelnidipine, TPGS, and P188 was evaluated by running thermal analysis of the drug, TPGS, P188, and lyophilized formula (A_9) using DSC apparatus (DSC-60, SHIMADZU, Japan). Every sample was measured precisely and kept in aluminum pan and an empty pan was used as reference.

The thermograms of each compound were determined at 10°C/min heating rate in the temperature range of 30°C–350°C under the nitrogen gas flow [19].

2.10. X-Ray Diffraction (XRD) study

PXRD was achieved to determine crystalline or amorphous properties of azelnidipine entrapped in TPGS/P188 micelles. These studies were conducted by X-ray diffractometer (Aeris XRD System Malvern Panalytical, Netherland). The samples were hold in the sample holders followed by scanning from 2° to 50° and a scanning rate of 2° per min. The samples that used in the study were pure azelnidipine, TPGS, P188, and lyophilized formula (A_9) [20].

2.11. AFM study

The morphology, size, and roughness of azelnidipine-loaded micelles (A_9) were visualized by AFM (Core AFM 2023 model, Nanosurf AG, Switzerland). The Sample was dropped on a microscope slide and dried at ambient temperature and the AFM images were collected in tapping mode [21].

2.12. Analytical statistics study

The results were determined as mean ± standard deviation (SD) of three independent tests. One-way ANOVA was performed for statistical study using graph prism version 9. P-values < 0.05 were regarded as a statistically significant [22].

3. Results

3.1. Method of polymeric micelles preparation

The formulas (A_1–A_9) were prepared by direct dissolution method depending on the physicochemical properties of the azelnidipine, TPGS, and P188.

3.2. Determination of the optimum stirring rate and time

Stirring rate 1000 rpm for 0.5 h give turbid dispersion while stirring rate 2000 rpm for 1 h gives clear micellar solution.

3.3. Particle size and PDI measurements

The size of particle of the prepared formulation from (22.04 ± 2.1) nm to (229.73 ± 27.98) nm as shown in (Table 2). Also, The PDI of the prepared formulas from (0.2 ∓ 0.01) to (0.96 ∓ 0.69) as shown in (Table 2)

3.4. The polymer concentration effect on the particle size

There is a significant decrease in particle size $P < 0.05$ when TPGS concentration increase and P188 concentration remain constant in the formulation A_1, A_4 and A_7 when compared to each other's, in the formulation A_2, A_5 and A_8 when compared to each

Table 3. The mechanism and the kinetic of the release data of Azelnidipine from A_9.

	Azelnidipine release kinetic				
Formula	Zero order R^2	First order R^2	Higuchi's R^2	Hixson Crowell's R^2	Korsmeyer-Peppas's n value
9	0.9574	0.9535	0.9446	0.9808	0.754

other's, and in the formulation A_3, A_6 and A_9 when compared to each other's.

3.5. The surface charge measurements

The surface charge of the prepared formulas was negatively charged and near neutral as shown in (Table 2)

3.6. Encapsulation efficiency percentages measurements

The entrapment efficiency percentage from (40.61 ± 1.11) to (84.35 ± 0.65) is shown in (Table 2).

3.7. The polymer concentration effect on encapsulation efficiency

There is a significant increase in encapsulation efficiency $P < 0.05$ when the concentration of TPGS increase and the concentration of P188 remain constant in the formulation A_1, A_4 and A_7 when compared to each other's, the formulation A_2, A_5 and A_8 when compared to each other's, and the formulation A_3, A_6 and A_9 when compared to each other's.

3.8. The optimum formula selection

Formulation (A_9) which consists of 8 milligrams of Azelnidipine, 100 milligrams TPGS, and 100 milligrams P188 regarded as the optimum formula depending on particle size (24.22 ± 7.61), polydispersity index, and entrapment efficiency percentage (84.35 ± 0.65) therefore, subjected for further characterization.

3.9. In vitro release study

This study compares the release of azelnidipine from TPGS/P188 nanomicelles (A_9) with the release from plain drug and performed using 500ml phosphate buffer pH 6.8 with 0.5% sodium lauryl sulfate to maintain sink condition and prevent drug precipitation. The azelnidipine was released from polymeric micelles at much slower rate than from plain drug. Within one hour, almost all of azelnidipine was released from plain drug, while more than 93% of azelnidipine was released from TPGS/P188 nanomicelles after 2.5 hours as shown in (Fig. 2) Formula (A_9) release profile was best fitted to Hixon-Crowell's release kinetic model as shown in (Table 3). In this study, the n value equal to 0.754.

Table 4. FTIR spectrum of azelnidipine.

Theoretical values wave number (cm^{-1})	Chemical group
1693.5	C=O stretching
1282.66	C-N stretching
1525.69	N-H bending
1614.82	C=C stretching
1658.78	N-O recognize the identity

3.10. Saturation solubility study

According to the solubility study, the solubility of azelnidipine in water equal to 0.905 μg/ml and the drug solubility in micellar solution equal to 745.69 μg/ml (solubility in A_9). There are 823.96 fold increases in the solubility of azelnidipine in the TPGS/P188 polymeric micelles when compared to the solubility of azelnidipine in water.

3.11. FTIR study

FTIR spectra of azelnidipine, TPGS, P188, and azelnidipine-loaded TPGS/P188 micelles (A_9) were shown in (Figs. 3 to 6), respectively. From the azelnidipine Spectrum, all peaks are within the reported range, Table 4. All the major peaks of azelnidipine can also be seen in selected formula.

3.12. Differential scanning calorimetry study

The physical state, the physicochemical interaction, and thermal behavior of azelnidipine, P188, TPGS, mannitol, and formula (A_9) were evaluated by DSC as shown in (Figs. 7 to 11) respectively. Azelnidipine exhibited a sharp endothermic peak at 200°C. The characteristic peak of azelnidipine completely disappeared in the polymeric micelles formula (A_9). The drug-loaded TPGS/P188 formula (A_9) micelles showed an endothermic peak at 172.47.

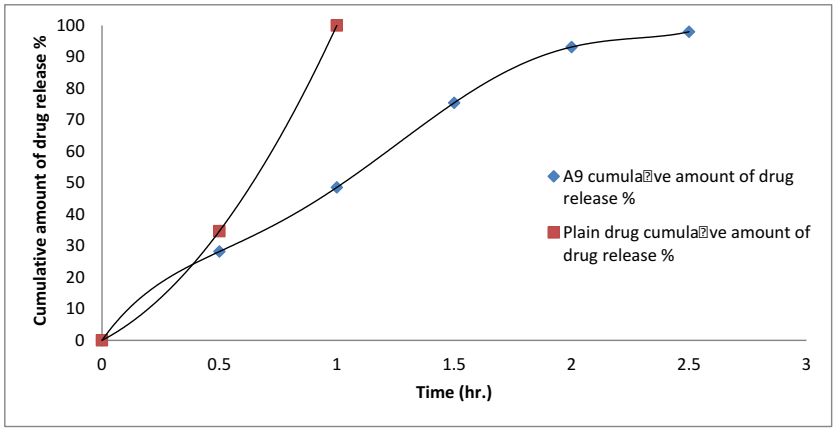

Fig. 2. The cumulative amount of drug release % of formula A_9 and plain drug as a function of time in phosphate buffer pH 6.8.

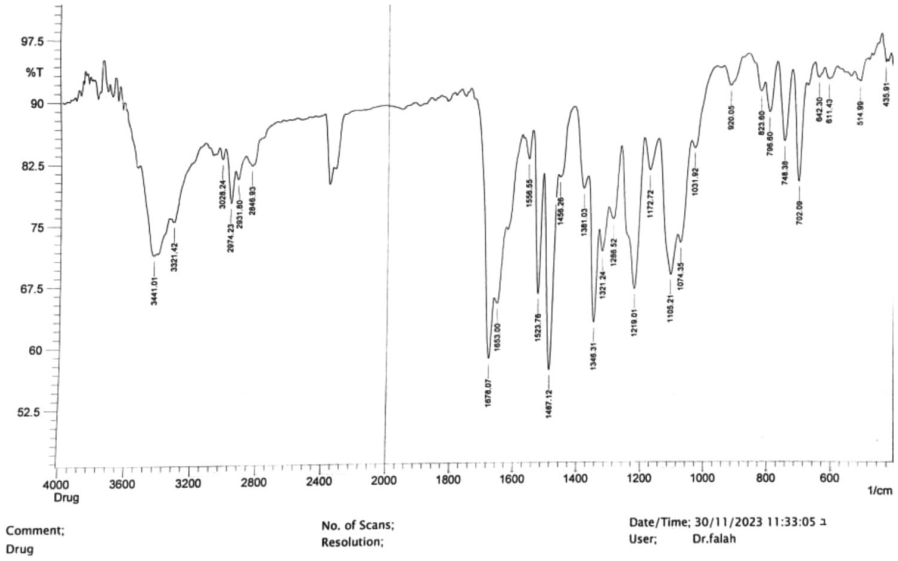

Fig. 3. FTIR spectrum of azelnidipine.

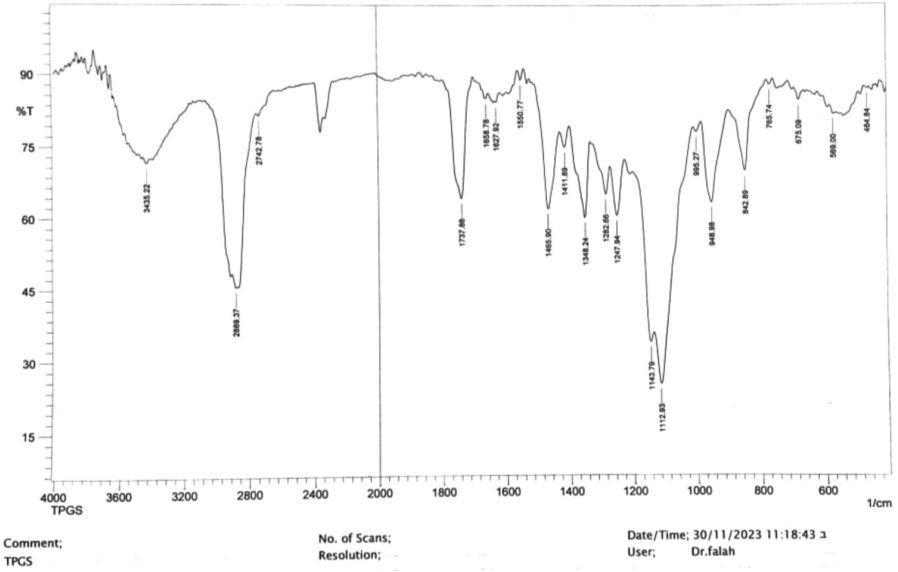

Fig. 4. FTIR spectrum of TPGS.

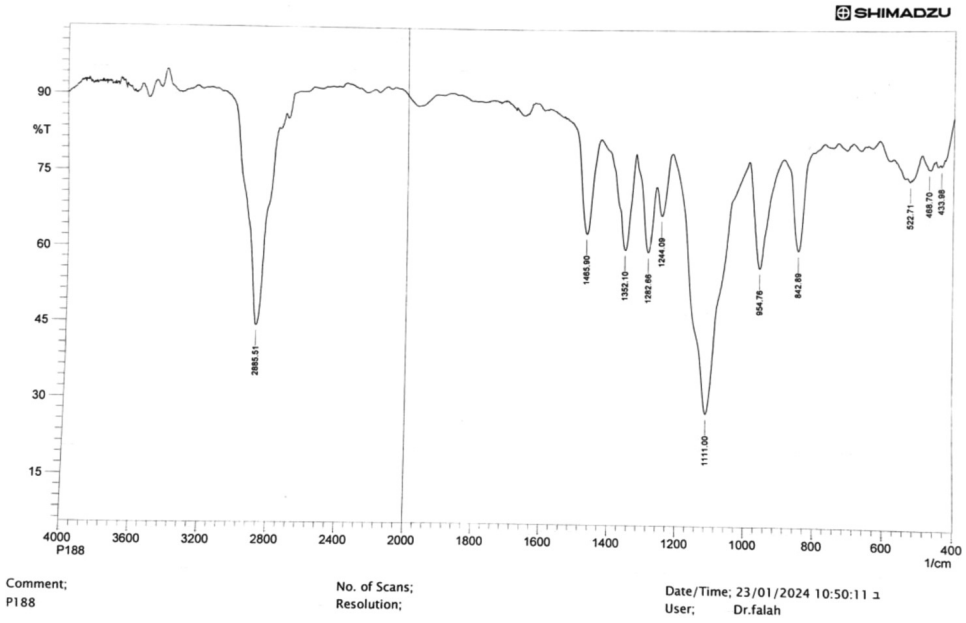

Fig. 5. FTIR spectrum of P188.

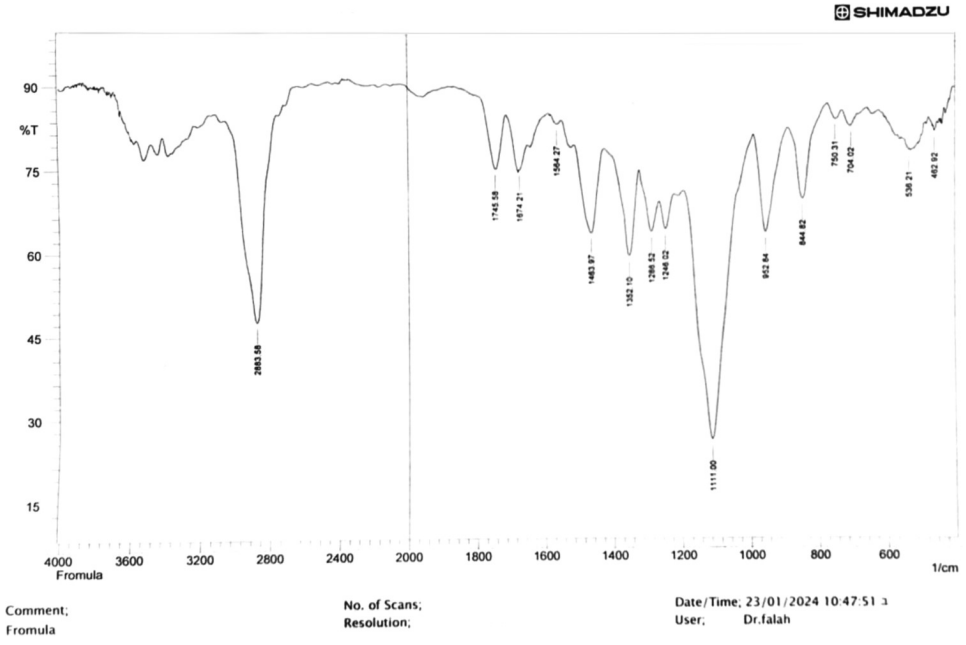

Fig. 6. FTIR spectrum of formula (A_9).

3.13. X-ray study

The crystallinity of azelnidipine, TPGS, P188, and azelnidipine loaded formula (A_9) was evaluated by XRD as shown in (Figs. 12 to 15) respectively. From the diffraction patterns, azelnidipine has sharp, intense diffraction peaks at two thetas equal to 21.3274, 22.5484, 12.4834, and 14.2324 respectively. There are no sharp diffraction peaks observed in the polymeric micelles formula (A_9).

3.14. Atomic Force Microscopy (AFM)

AFM imaging of formula (A_9) was shown in (Fig. 16), which showed smooth spherical morphology and agreed with the Size measured by PCS.

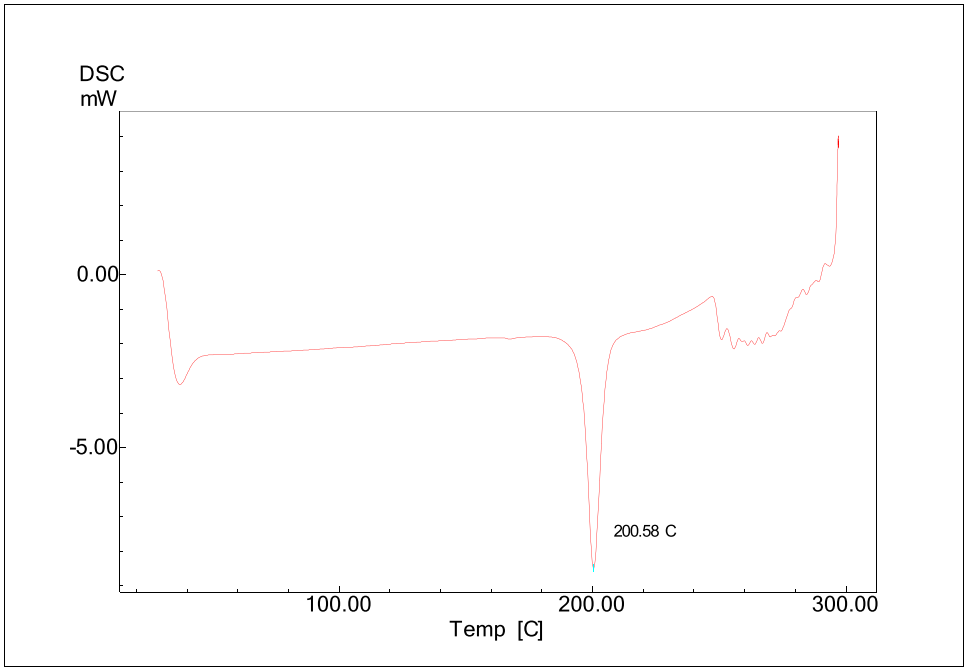

Fig. 7. DSC thermogram of azelnidipine.

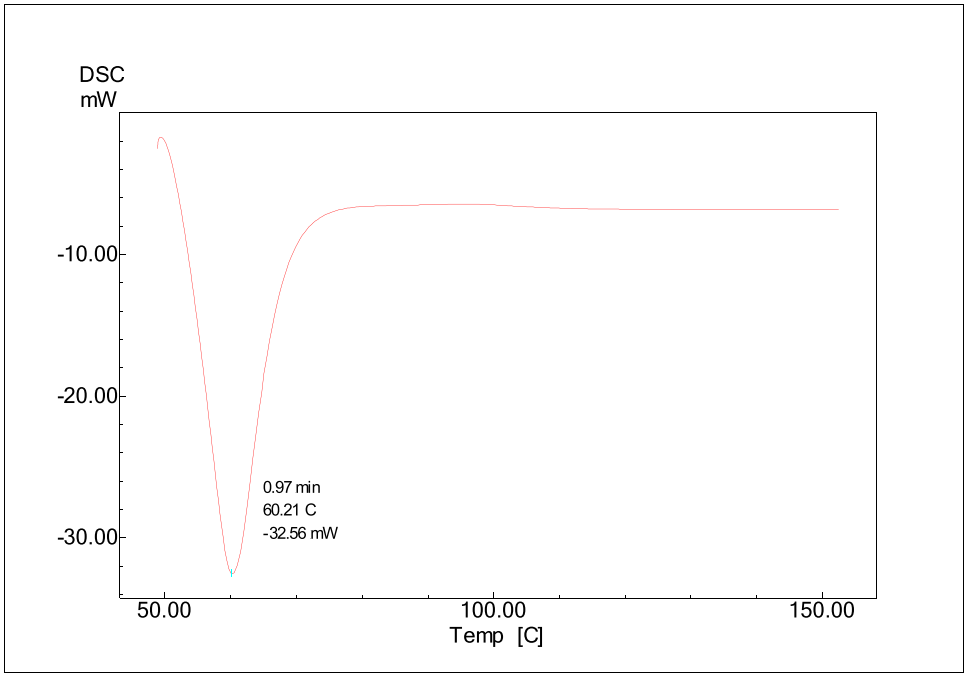

Fig. 8. DSC thermogram of P188.

4. Discussion

4.1. Method of polymeric micelles preparation

This method is appropriate for polymers having high water-solubility such as TPGS and P188, also it can be used for mildly hydrophobic polymers such as P188. In this method, the combination of two copolymers (TPGS and P188) has been used to increase the solubility, stability, and the entrapment efficiency of the prepared formulas due to increase in the number of the available amphiphilic unimer that assemble into micelles as compared to single copolymer which have limited number of unimers [23].

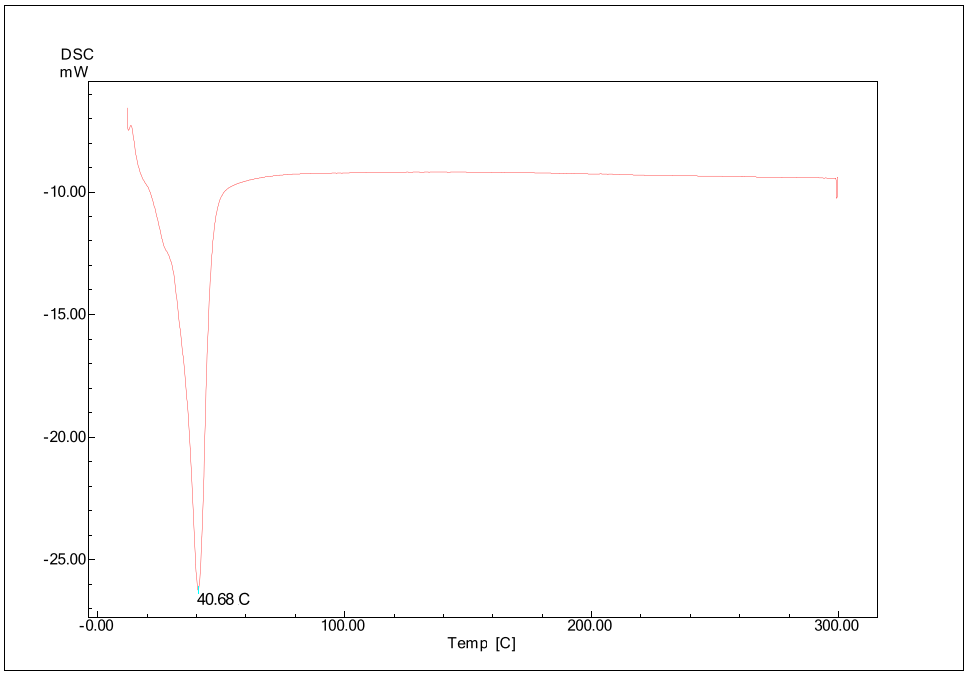

Fig. 9. DSC thermogram of TPGS.

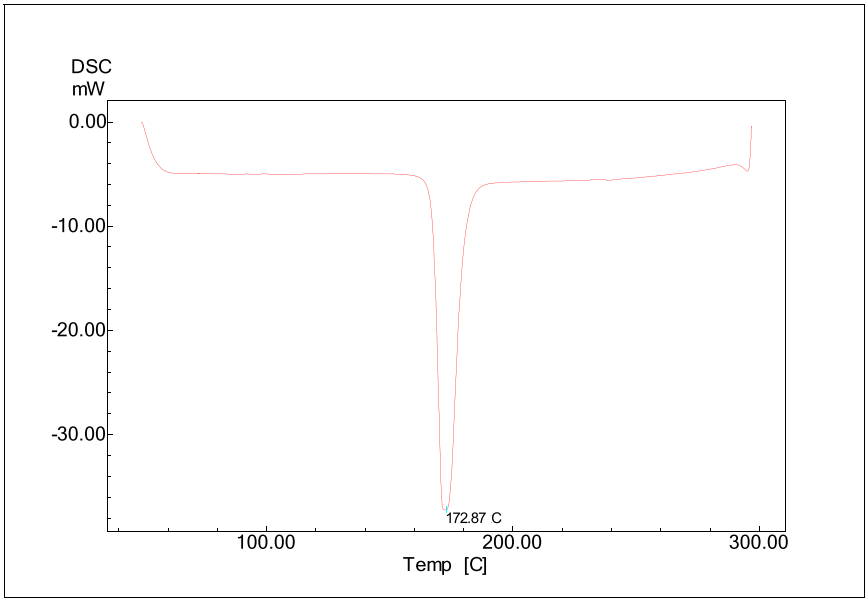

Fig. 10. DSC thermogram of mannitol.

4.2. Determination of the optimum stirring rate and time

Polymeric micelles form by spontaneous assembly in aqueous solution upon solubilization of amphiphilic copolymers, as the formation of micelles was an entropy-driven method. Therefore, energy input is important and required when azelnidipine is mixed with amphiphilic copolymers. The stirring rate 2000 rpm for 1h give the required energy which lead to solubilization and transfer of azelnidipine into the micellar core.

4.3. The particle size and PDI

The use of two polymers TPGS and P188 produce high numbers of small size micelles and this increase the solubility of the drug, facilitate its intestinal transport by paracellular or transcellular routes, increase

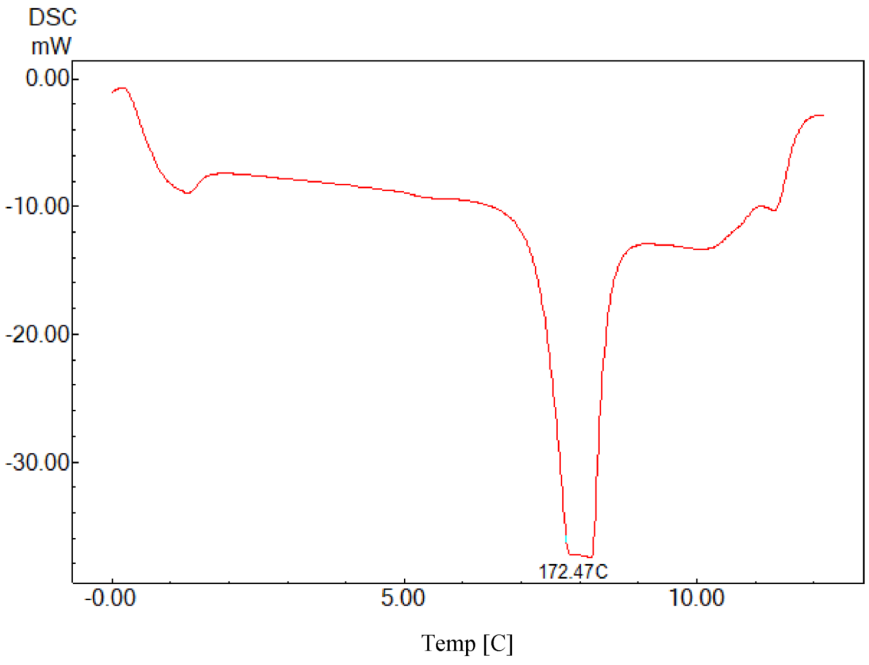

Fig. 11. DSC thermogram of Formula A_9.

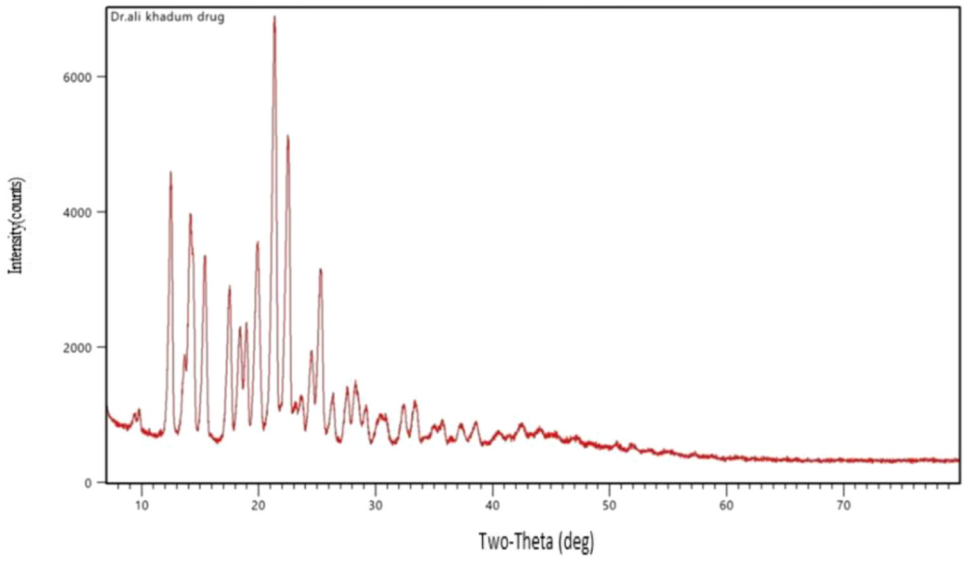

Fig. 12. XRD diffractogram of azelnidipine.

the extent of the absorbed drug and prolong its circulation time in blood [24]. The narrow PDI enhance the stability of the selective formula through storage period and prevent particle growth after administration (in vivo stability) [25].

4.4. The polymer concentration effect on particle size

Formulations (A_1, A_4, A_7) when compared to each other, formulation (A_2, A_5, A_8) when compared to each other, and formulations (A_3, A_6, A_9) when compared to each other. There is a significant decrease in particle size ($P < 0.05$) when the TPGS concentration increase and the P188 concentration remain constant.

This is owing to the capacity of TPGS to solubilize hydrophobic drugs, also, it acts as an emulsifier and this agrees with previously published research [26].

4.5. Surface charge determination

The negative near-neutral surface charge of the prepared formulations is due to the presence of the

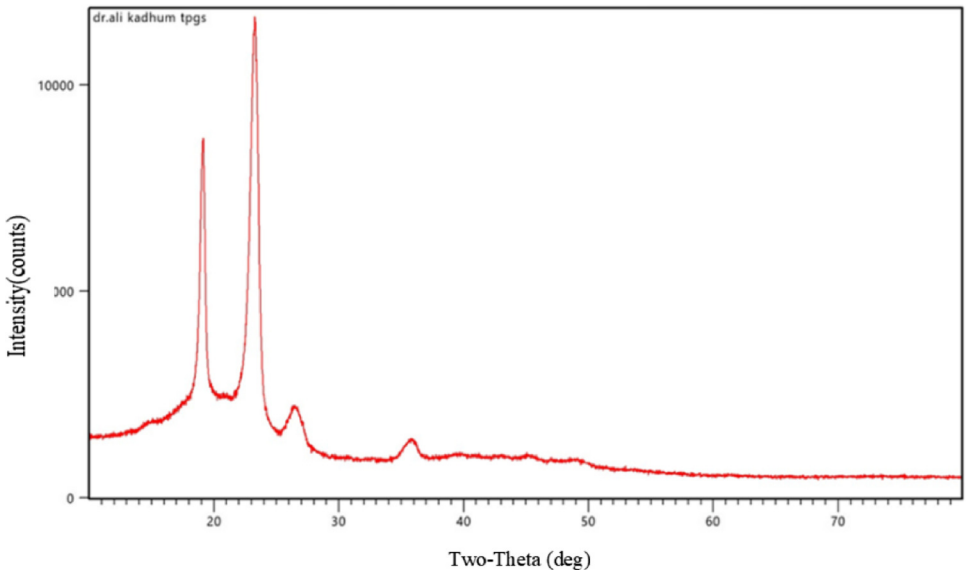

Fig. 13. XRD diffractogram of TPGS.

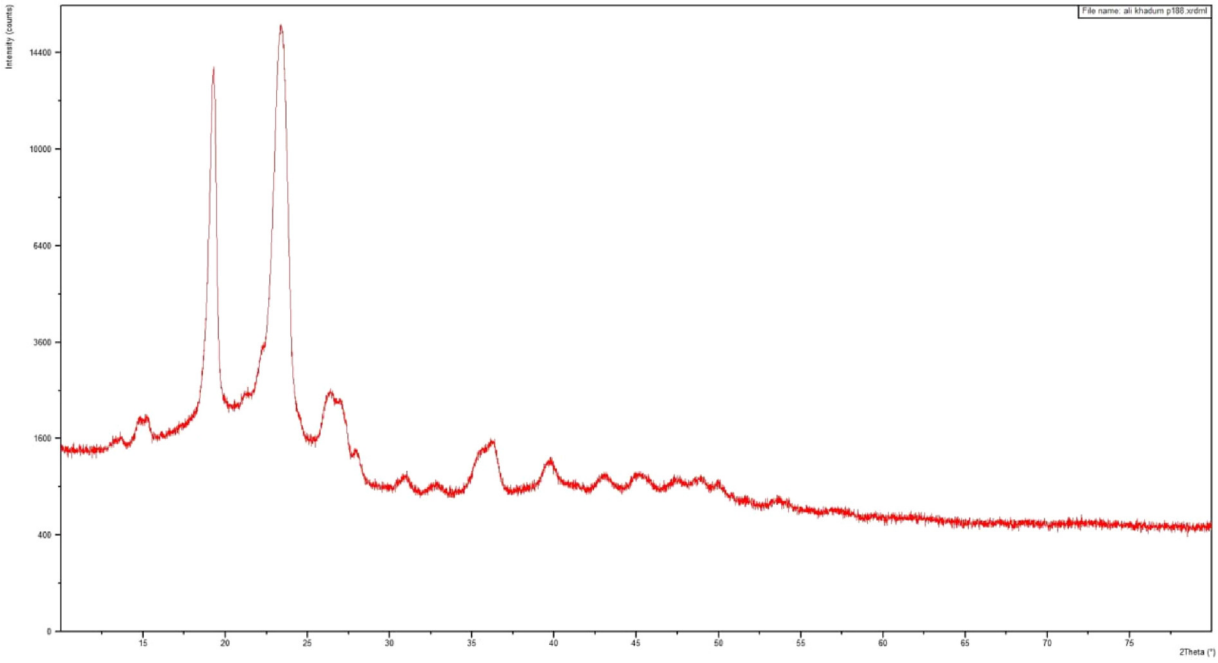

Fig. 14. XRD diffractogram of P188.

non-ionic polyethylene glycol in the micelles surface, which confers the stability of the micelles (storage stability and in vivo stability) [27].

4.6. Entrapment efficiency percentages determination

The entrapment efficiency of lipophilic drugs such as azelnidipine depends on the hydrophobic interaction with the micelles core, the size of the lipophilic part of the polymer, and the type of substituents in the hydrophobic chain [28]. The suitability of TPGs and P188 and the Selection of the proper preparation method that ensures efficient incorporation of the drug inside the micelles depend on the entrapment efficiency determination [29].

4.7. ThePolymer concentration effect on entrapment efficiency

There is a significant increase in encapsulation efficiency ($P < 0.05$) when TPGS concentration increases

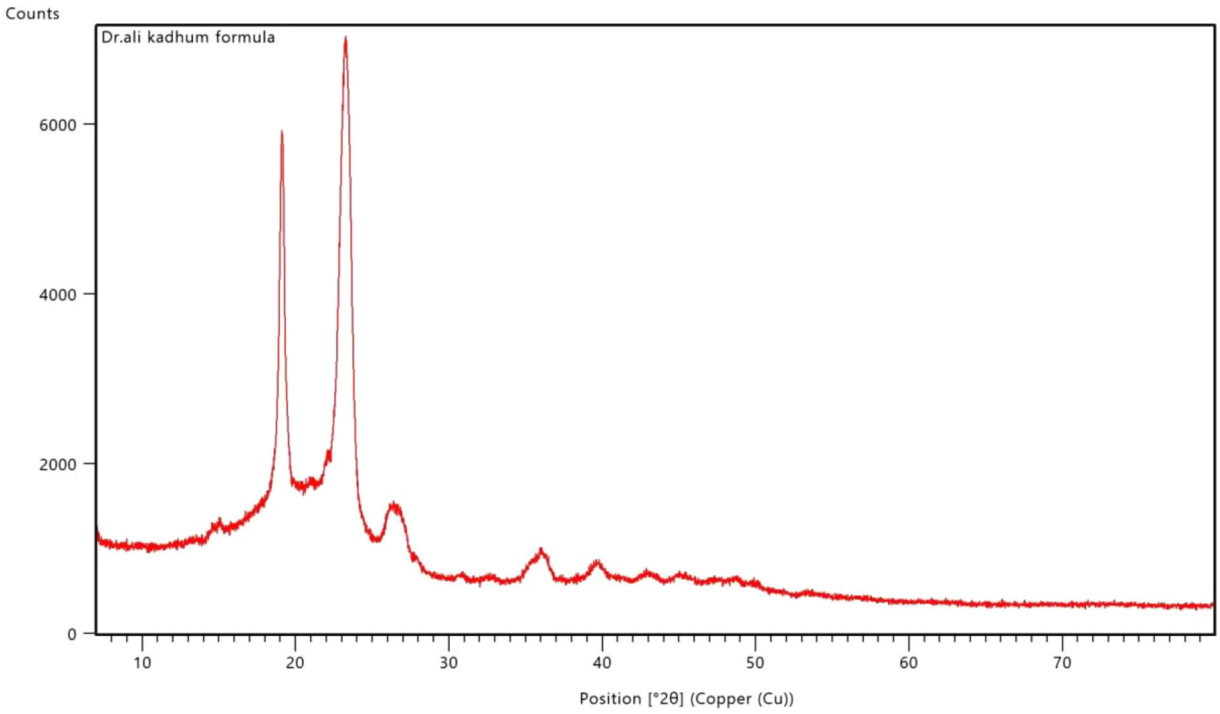

Fig. 15. XRD diffractogram of Formula (A_9).

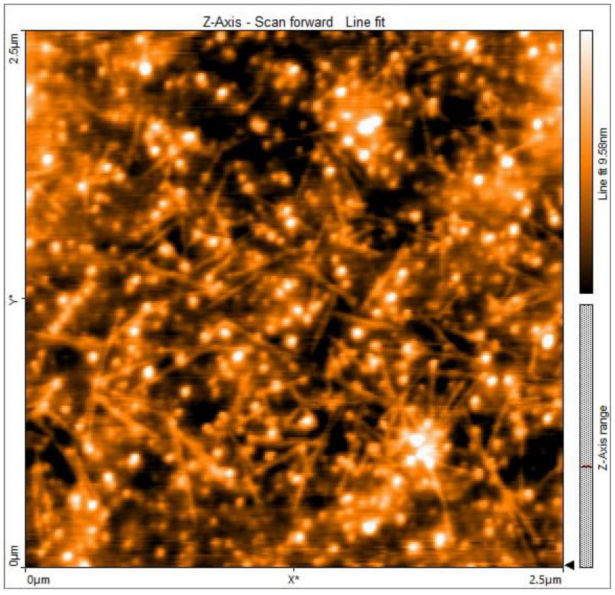

Fig. 16. Atomic force microscopic image of formula (A_9).

and P188 concentration remains constant for formulations (A_1, A_4, A_7) when compared to each other, formulations (A_2, A_5, A_8) when compared to each other, and formulations (A_3, A_6, A_9) when compared to each other.

These outcomes are because TPGS acts as an emulsifier and solubilizer which increases the amount of the drug incorporated in the nanomicelles by producing a large number of micelles with stable core that encapsulate high amount of the drug and this agrees with that reported by other researchers [26].

4.8. Selection of the best formula

The selection of the best formulas depending on the particle size, the zeta potential, PDI, and entrapment efficiency because these factors regarded as major determinant of drug passage and absorption through intestinal barrier. These properties of prime effect on the stability of polymeric nanomicelles (in-vitro and in vivo).

4.9. In-vitro release study

The slower speed release of azelnidipine from polymeric micelles (A_9) as compared to plain drug release indicates that azelnidipine was encapsulated inside the polymeric micelles core and the stability of structure of the micelles core made it difficult for azelnidipine to release rapidly from the core of the nanomicelles, subsequently inducing a controlled release of azelnidipine [30]. The controlled release of azelnidipine from polymeric micelles could avoid the precipitation in the lumen of GIT and this gives a benefit for oral absorption of the drug in-vivo whereas rapid release of lipophilic drugs might cause precipitation of the drugs in the gastrointestinal tract

before absorption [31]. It can be concluded that the mechanism of azelnidipine release from TPGS/P188 micelles was anomalous non-Fickian diffusion, which indicates azelnidipine release as a combination of the diffusion and erosion of the polymer matrix [32].

4.10. Saturation solubility study

The increase in the solubility of azelnidipine in micelles when compared to solubility in water because of the two amphiphilic polymers (TPGS and P188) produce small particle size, increase the number of available building blocks which associate to form micelles that incorporate a high amount of the drug in the lipophilic core, and also the high solubilizing power of TPGS/P188 copolymers.

Kumar *et al.* produced curcumin-encapsulated micelles that were small in size 15–18 nm and the solubility increased in the order 10^3 to 10^4.

4.11. FTIR study

FTIR study is one of the most powerful techniques that is used for chemical identification of drugs. From the azelnidipine spectrum, the presence of characteristic peaks within the reported range in azelnidipine indicates the drug purity and confirms its stability during the process. The presence of all major azelnidipine peaks in selected formula, indicates no chemical interaction between azelnidipine, TPGS, and P188 [33].

4.12. Differential scanning calorimetry study

Azelnidipine presented a sharp endothermic peak of around 200°C, which is attributable to its melting point [34]. The characteristic peak of azelnidipine completely disappeared in the polymeric micelles formula (A_9) depicting its conversion into an amorphous form and confirming the localization of azelnidipine inside the micelles [35]. The drug-loaded TPGS/P188 formula (A_9) micelles showed an endothermic peak at 172.96 that is near to the melting point of mannitol [35].

4.13. X-ray diffraction study

From the diffraction patterns, azelnidipine has sharp, intense diffraction peaks at two thetas equal to 21.3274, 22.5484, 12.4834, and 14.2324 respectively which confirm the crystallinity of azelnidipine. There are no sharp diffraction peaks appeared in the polymeric micelles formula (A_9) indicating azelnidipine entrapment in amorphous state where the intensified interaction between drug and the hydrophobic core of the micelles led to the disappearance of the crystalline order of the drug [36].

4.14. AFM study

AFM is a high-resolution technique used for determining the morphology and size of nanocarriers such as polymeric micelles in tapping mode which minimizes the sample distortion associated with tip movement [37]. AFM imaging of formula (A_9) showed smooth spherical morphology and agreed with the Size measured by PCS [38].

5. Conclusion

In this research, azelnidipine-loaded TPGS/P188 micelles were successfully prepared by direct dissolution method to improve the solubility and bioavailability of the drug. The best formula (A_9) with small particle size, narrow PDI, high encapsulation efficiency, and exhibited controlled release profile as desired to achieve its prolonged therapeutic activity. Based on these results, the TPGS/P188 micelles (A_9) are regarded as a promising nanocarriers for the delivery of azelnidipine.

Author contributions

Each author contributed equally to the creation of this manuscript

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Not applicable.

Conflict of interest statement

No material conflict of interest to disclose

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