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Original Article

Formulation Considerations and *in vitro* Characterization of Polymeric Micelles Loaded with Asenapine Maleate

Zainab Eassa Jassim[1], Nawal Ayash Rajab[1,*], Hamid Akbari Javar[2]

[1]Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, IRAQ.
[2]Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, IRAN.

ABSTRACT

Objectives: An effort has been utilized to incorporate ASPM into polymeric micelles using single and mixed copolymers. **Materials and Methods:** A thin-film hydration approach was used to create the ASPM polymeric micelles, which comprised TPGS, Solutol®HS-15, and Pluronics. Micelles characterization was performed by particle size distribution, zeta potential, while Encapsulation Efficiency (EE%), Drug Loading (DL%) content and *in vitro* drug release were determined also by HPLC analysis. **Results:** The ASPM loaded micelles, specifically F1, F4, and F8, exhibited a mean particle size of less than 200 nm, characterized by a narrow size distribution. The encapsulation rate reached up to 72±1.571%, with a drug loading of 14.12±0.3%, and a zeta potential indicating a negative charge of approximately -2 mV. ASPM was continuously released from polymeric micelles in PBS medium (pH 7.4) for 6 hr at 37°C, F8 was selected as the optimized mixed polymeric micelle. **Conclusion:** Polymeric micelles composed of TPGS, Tetronic® and TPGS:Solutol®HS 15 at concentration (2% w/v) can effectively incorporate ASPM and prolong drug release.

Keywords: Asenapine maleate, Polymeric micelles, Copolymers, Thin-film hydration method.

Correspondence:
Dr. Nawal Ayash Rajab
Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, IRAQ.
Email: dr.nawalayash@copharm.uobaghdad.edu.iq

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INTRODUCTION

Schizophrenia is a complex, chronic mental disorder that presents substantial clinical and economic challenges to global healthcare systems.[1] Antipsychotics serve as the primary treatment modality for schizophrenia and bipolar disorder, offering a favorable tolerability profile and comprehensive symptom management.[2]

Asenapine Maleate (ASPM) is a second-generation antipsychotic approved in Europe in August 2009 for the treatment of schizophrenia and moderate to severe manic episodes associated with type I bipolar disorder in adults.[3,4]

Chemically, is a tetracyclic medication composed by a dibenzo-oxepino pyrrole structure,[5] It exhibits limited solubility in 0.1M HCl and demonstrates slight solubility in water. The protonated free base of ASPM exhibits a pKa of 8.6, indicating a strong affinity for the proton, which is not readily released. The log *p*-values are 4.9 for the neutral species and 1.4 for the cationic species, indicating the polar characteristics of the ASPM.[6]

Owing to the high hepato-gastrointestinal first-pass effect, the oral bioavailability of ASPM is limited to less than 2%.[7]

Polymeric Micelles (PMs) are spherical nanostructures consisting of a hydrophobic core and a hydrophilic shell. They are formed through the self-aggregation of polymeric amphiphiles in aqueous environments when the concentration exceeds the Critical Micelle Concentration (CMC), facilitating the encapsulation of hydrophobic drugs within the micellar core.[8]

They have attracted considerable attention for study and are among the most thoroughly researched systems. The micelle's core can encapsulate pharmaceuticals that exhibit low water solubility, thereby improving drug solubility, stability, pharmacokinetic profiles, and stabilizing degradable chemicals.[9]

Polymeric micelles capable of self-assembling in aquatic environments to create a hydrophilic exterior and hydrophobic inside have garnered considerable.[10]

The core functions as a reservoir for hydrophobic medications, thereby enhancing the biological activity of poorly water-soluble anticancer agents and improving therapeutic efficacy while reducing adverse side effects. The external coating protects the medication, improves stability, and enables a controlled release.[11]

D-alpha Tocopheryl Polyethylene Glycol 1000 Succinate (TPGS) is an ester derived from vitamin E succinate and Polyethylene Glycol (PEG) 1000, commonly employed as a solubilizer, stabilizer, and penetration enhancer. The substance has obtained Food and Drug

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Administration (FDA) approval as a novel non-ionic surfactant, defined by a Hydrophilic-Lipophilic Balance (HLB) value of 13.2, for application in diverse pharmaceutical formulations.[12] The properties of TPGS may enhance the permeability of drug carriers through the nasal mucosa, thereby improving the biodistribution of encapsulated medications to targeted sites while reducing toxicity and systemic exposure.[13]

Pluronic block copolymers are amphiphilic synthetic polymers consisting of hydrophilic (Polyethylene Oxide) (PEO) blocks and hydrophobic Poly (Propylene Oxide) (PPO) blocks arranged in a triblock structure: PEO-PPO-PEO.[14] The hydrophobic PPO segments create a hydrophobic core that facilitates the incorporation of hydrophobic drugs. The hydrophilic PEO corona prevents aggregation, protein adsorption, and recognition by the Reticuloendothelial System (RES).[15] Moreover, the aggregation behavior of binary Pluronics is dependent on PPO; Pluronics with similar PPO moieties show cooperative aggregation, while those with different PPO moieties exhibit non-cooperative binding.[16]

Pluronics® micelles have been extensively studied as carriers for a range of antitumoral agents and antibacterial compounds.[17] Pluronic polymers were discovered to augment the bioavailability of certain antibacterial medicines, hence enhancing their efficacy.[18] Some features of block copolymers used in this study was demonstrated in Table 1.

Tetronic® family of surfactants (BASF), known as poloxamines, represents a significant class of copolymers. These are Polyethylene Oxide (PEO)-Polypropylene Oxide (PPO) block copolymers distinguished by their four-arm star structure.[19]

This study aims to investigate the effect of type and concentration of copolymer on polymeric micellar formulation of Asenapine Maleate (ASPM) using different copolymer/surfactant to prepare single and mixed micelles and their effect on particle size, entrapment and *in vitro* release study.

MATERIALS AND METHODS

Materials

Asenapine maleate was purchased from Suzhou Zehou Biochemical Technology Co., Ltd., (China), TPGS (shanghai Aladdin Biochemical Technology Co., Ltd., China), Solutol® HS15, Pluronics® P-123, L-61 and L-62 were supplied from RHAWN Co., Ltd., (China), while P-65 and Tetronic® 701 were purchased from MERYER Co (China) and the rest of the chemicals and solvents utilized were of analytical grade.

Preparation of ASPM single and mixed micelles by thin film-hydration method

PMs were synthesized via the thin film hydration method, involving the precise measurement and dissolving of 0.5% w/v of ASPM and 2% w/v of copolymer (Table 2) in 20 mL of methanol within a round-bottom flask.[25] The solvent was gradually evaporated at 60°C under decreased pressure with a rotary evaporator (Stuart rotary evaporator, RE300DB, North Yorkshire, UK), rotating at 80 rpm, resulting in a thin dry layer of ASPM-copolymer matrix on the inner wall of the flask. The leftover solvent in the film was eliminated overnight at ambient temperature.[26] The dried film was rehydrated using 10 mL of Phosphate-Buffered Saline (PBS) at pH 7.4, maintained at a constant temperature of 40°C. The solution was agitated at 60 rpm for one hr in a rotary evaporator to obtain a polymeric micelle solution.[27] The micellar solution was filtered using a 0.22 µm nylon filter to remove undissolved agents or impurities. The prepared polymeric mixed micelles were subsequently stored at 4°C for further investigation.[28,29]

Characterization of the Prepared Polymeric Micelles

Determination of Critical Micelle Concentration (CMC)

The iodine UV spectroscopy method was utilized to determine the Critical Micelle Concentration (CMC) of each polymer and the composition of mixed micelles in PBS. A standard potassium iodide/iodine solution was prepared by dissolving 1 g of potassium iodide and 0.5 g of iodine in 50 mL of distilled water. Samples of each polymer and the combined micelles formulation were synthesized at concentrations ranging from 0.002 %w/v to 0.022% w/v.[30] Subsequently, 25 µL of potassium iodide/iodine solution was added to each sample produced. Iodine functioned as a hydrophobic probe, as solubilized iodine (I_2) exhibited a tendency to localize preferentially within the hydrophobic domains of the copolymer. I_3 is converted to I_2 as a result of the excess KI in the solution, which maintains a saturated concentration of I_2 in water.[31]

Samples were incubated in darkness for 12 hr at ambient temperature, after which the Ultraviolet (UV) absorbance of each concentration was measured at 366 nm. Experiments were performed in triplicate. To determine the CMC, absorbance

Table 1: Characteristics of block copolymers used in this study.

Copolymer	PO units	EO units	HLB	Reference
Pluronic®-123	62	36	8	20
Tetronic ® 701	14	2.1	1-7	21
Pluronic® L-61	31	5	3	22
Pluronic® L-62	35	11	7	23
Pluronic® P-65	30	50	17	24

was plotted against the logarithm of the concentration of the produced samples. The concentration at which a significant increase in absorbance was observed corresponded to the critical micelle concentration.[32]

Determination of Micellar Particle Size (PS), Polydispersity Index (PDI) and Zeta Potential (ZP)

Particle size, Polydispersity Index (PDI) and zeta potential were assessed using the Malvern Zetasizer, UK, employing the Dynamic Light Scattering (DLS) method with the original formula undiluted.[33,34] All measurements were repeated in triplicates (n=3).

Determination of Encapsulation Efficiency (EE) and Drug Loading (DL)

The Encapsulation Efficiency (EE) and Drug Loading (DL) of ASPM in micelles were quantified by centrifugation, 2 mL of each formula was centrifuged using Millipore filter membrane (Amicon®) ultra-4 tube with molecular weight cut-off of 10,000 Da (Sigma, Ireland).[35] After centrifugation at 4000 rpm for 30 min, micelles with the encapsulated drug remained in the outer chamber, and the free drug was filtered to the sample recovery chamber through the. The drug loading and the entrapped drug amount in micelles was measured by High-Performance Liquid Chromatography (HPLC) with ultraviolet detector at 230 nm.[36]

DL and EE were obtained by the following equations 1 and 2 respectively.[37]

$$DL\ (\%) = \frac{\text{Weight of drug in nanoparticles}}{\text{Total weight of drug loaded micelles}} \times 100 \text{ ---------- Equation 1}$$

$$EE\ (\%) = \frac{\text{Weight of the drug in nanoparticles}}{\text{weight of the feeding drugs}} \times 100 \text{ ---------- Equation 2}$$

High-Performance Liquid Chromatography (HPLC) Analysis Conditions

The HPLC was performed with a CECIL apparatus (UK) equipped with a UV detection (CECIL CE 4200-Adept, UK) and Harmony column (4.6×250 mm, pore size 5 µm, C18, Perkin Elmar) and temperature controller Varian Metathern®, USA. The Lab Solution software (Power Stream by Cecil instrument, Ltd., version 4.2) was used to manage instrument operation and data acquisition. The detection wavelength was 230 nm, the mobile phase consists of (acetonitrile/water with 0.2% Trifluoracetic Acid (TFA) 50:50 v/v) was filtered through 0.45 µm filter before injection. The flow rate was 1.0 mL/min and the retention time was determined through 10 min of run. The calibration curve was linear in the range of 10-150 µg/mL with a correlation coefficient of $R^2$0.9992. The area of each eluted peak was integrated and used for ASPM quantification. Specificity revealed that the retention time of drug was ranged from 4.6-5 min when drug was analyzed from solution and in the determination of drug concentration in polymeric micelles. For accuracy, recovery percent for all spiked samples at three levels (80, 100 and 120%) was ranged between 98.5 to 102.32 %. In precision, Intra-day percentage Relative Standard Deviation (RSD) ranged from 0.27% to 1.4% whereas the inter-day RSD was from 0.34% to 0.8% for three concentration 60, 80 and 150 (µg/mL). The LOD and LOQ values attained in the method analysis were 8.78 µg/mL and 26.61 µg/mL, respectively, based on the standard curve equation. Robustness was assessed by the percentage of recovery and RSD of the mean concentration of the analyte, at 150 µg/mL, when the column temperature raised to 40°C, the method proved to be robust considering these changes in chromatographic parameters. The analysis was performed in triplicate for each sample.

Table 2: Composition of polymeric micelles formulation.

Formula	ASPM (%) w/v	Copolymer/surfactant	Copolymer/surfactant (%) w/v
F1	0.5 %	TPGS	2%
F2	0.5 %	Solutol®HS15	2%
F3	0.5 %	P-123	2%
F4	0.5 %	Tetronic®	2%
F5	0.5 %	PL-61	2%
F6	0.5 %	PL-62	2%
F7	0.5 %	P-65	2%
F8	0.5 %	TPGS: Solutol®HS15	2%
F9	0.5 %	TPGS: P123	2%
F10	0.5 %	TPGS:Tetronic®	2%
F11	0.5 %	TPGS:PL-61	2%
F12	0.5 %	TPGS:PL-62	2%
F13	0.5 %	TPGS:P-65	2%

In vitro drug release from polymeric micelles

The *in vitro* drug release profile of ASPM from the chosen polymeric micelles was examined utilizing the dialysis membrane diffusion method. For this procedure, 1 mL of selected formulations at a concentration of 5 mg/mL was introduced into preconditioned dialysis bags with a molecular weight cutoff of approximately 8000-14000 Da (manufactured by MYM Biological technology company limited, Beijing).[38] These bags were then immersed separately in 100 mL of PBS (pH 7.4).[39] The solutions functioned as the release medium and were maintained at a constant temperature of 37±2°C, with continuous agitation at a speed of 50 rpm for 6 hr intervals.[40] At specified times, samples were extracted from the system and substituted with new release medium to sustain a consistent sink state.[41] The samples were filtered through a 0.45 µm syringe filter for subsequent analysis using a validated HPLC method. The data from these tests were analyzed to generate a graph depicting the correlation between the proportion of drug release and the time.[42]

Drug Release Mathematical Model

Several mathematical methods (zero-order, first-order, Higuchi, and Korsmeyer-Peppas models) were used to the collected release data of the formulation. The release kinetics were analyzed and the regression coefficient (R^2) values for each model were calculated using the DDsolver® add-in program. The model with the highest value of R^2 was selected as the optimum one.

Solubility enhancement determination

The solubilization characteristics of polymeric micelles were examined by introducing an excess of ASPM to 5 mL of both PBS and a blank micellar solution of the optimal formulation in separated sealed glass containers, thereafter maintained in a water bath shaker at 37°C. Following a 48-hr period, the samples were centrifuged at 6,000 rpm for 30 min, and the ASPM content in the supernatants was quantified using HPLC subsequent to appropriate dilution with methanol.[43] Then, the Solubility Factor (S_f) was calculated according the equation:

$$S_f = S_{mic} / S_{buf}$$

Where S_{mic} is the solubility of ASPM in micellar formulation and S_{buf} is the solubility of

Drug in buffer pH 7.4.

Differential Scanning Calorimetry (DSC)

Using Differential Scanning Calorimetry (DSC-50 Shimadzu, Japan), thermograms of pure drug, was recorded. The sample was put in an aluminum pan with a heating rate of 10°C/min from 25 to 300°C and the sample cell was constantly purged with nitrogen at a flow rate of 100 mL/min.[44]

Powder X-ray Diffraction Studies (PXRD)

XRD analysis was carried out to determine the crystallinity of the drug, X-ray powder diffraction patterns were obtained using Aeris-Malvern Panalytical's X-ray diffractometer (United Kingdom, The Netherlands). The diffraction pattern was measured with a voltage of 30 kV and a current of 40 mA in the range of 5°-90° (2θ) in a step scan mode.[45]

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy study was conducted to identify potential interaction among the formulation components. The FTIR spectra of the drug, copolymers and the physical mixture of the optimized formula were obtained using an FTIR-ATR spectrophotometer (Bruker, USA). The spectra were recorded using 32 scans with 4 cm^{-1} resolution in the 4000 cm^{-1} to 400 cm^{-1} spectral range.[46]

Field Emission Scanning Electron Microscopy (FESEM) Analysis

FE-SEM (Inspect F50, FEI Company, The Netherlands) was employed to examine the topography of ASPM-loaded polymeric micelles for the chosen optimal formulation. The liquid sample was initially dried and subsequently coated with a conductive substance (gold) to enhance the imaging at 30 kV with a magnification of 120,000.[47]

Storage Stability

The chemical and physical storage stability of selected micelle formula was monitored over three months in refrigerated conditions (4°C). The physical parameters were evaluated by light scattering analyses to determine the particle size, PDI, drug content was determined by HPLC, while the presence of any precipitate was visually checked against white and black backgrounds under light for each prepared formula.[48]

Statistics

We assigned GraphPad Prism, version 10.4.0, One-Way Analysis of Variance (ANOVA), and the Tukey test to assess the statistical differences between the experimental groups. When the p-value was less than 0.05, a significant difference was deemed to exist, and the data were shown as the mean ± the Standard Deviation (SD).[49]

RESULTS AND DISCUSSION

Critical micelle concentration determination

Hydrophilic-Lipophilic Balance (HLB) is an aspect of copolymers that impacts CMC.[50] CMC serves as a prerequisite for the micelles' kinetic and thermodynamic stability. The time behavior, polymer exchange rate, and micelle disassembly are all aspects of kinetic stability, whereas the building of the micellar system until equilibrium is reached is the focus of thermodynamic stability.[21] The plots of absorbance versus log concentration obtained after

the experiment for each surfactant and copolymer were shown in Figure 1, while the measured and the documented values of CMC were presented in Table 3.

Determination of Micellar Particle Size (PS), Polydispersity Index (PDI) and Zeta Potential (ZP)

Physical stability, drug release from micelles, cellular uptake, and biodistribution are all directly affected by micellar Particle Size (PS) and Polydispersity Index (PDI) Table 4 summarizes the findings of determining the features of drug-loaded micelles, including their mean diameter, polydispersity index and other properties.

At concentration of 2% w/v, the particle size of TPGS micelle and TPGS/copolymer micelles of ASPM was ranged from 10.103±0.899 nm to 401.7±93.265 nm with narrow PDI, this as seen in Figure 2, suggests micellar systems that are homogenous and uniform. (A and B). Zeta potential is used as an indicator of a colloidal dispersion's stability that is based on the surface charge of the particles in contact with water.[57]

Zeta potential was measured for F1, F4 and F8 micelle formula since they have the highest EE, and the values for these formulas were (-1.784±2.85 mV) (-1.54±1.23 mV) and (-2.52±1.83 mV) respectively which are nearly neutral. Nonionic amphiphilic polymers with PEG chains as the hydrophilic domain include Solutol and TPGS, during self-assembly, PEG chains produce micelles, which have a protective shell. Sterically stable systems have limited zeta potential applicability, and PEG works as a steric stabilizer overall. These systems are stable even if their zeta potential values are almost neutral.[58]

One of its numerous uses is as a cosurfactant for Pluronic mixed micelles; TPGS is a water-soluble version of vitamin E that works in tandem with Pluronic to create uniformly sized particles.[59]

The polymeric micelles were prepared by self-assembling a combination of Pluronics® and TPGS at a concentration greater than CMC. The micelles' central core is made of the hydrophobic Pluronics® block, while their outer shell is made of the hydrophilic TPGS block.

The integration, stability, and solubility of the encapsulated hydrophobic medicines are all enhanced by this structure.[41]

Solutol®HS15 micelle is also characterized by small particle 13.02±0.1803 nm with narrow PDI 0.0595±0.0299 as shown in Figures 2C and D. Micelles prepared using pluronics® P-123, L-61, L-62, P-65 and poloxamine 701 tetronic® gave particle size ranged from 44.26 ±31.33 nm to 277.63±63.96 nm with PDI ranged from 0.273±0.06715 to 0.6183±0.23 and characterized by multiple populations as shown in Figures 2E and 2F.

A high encapsulation efficiency of hydrophobic medicines in polymeric micelles is valuable, as it promotes their solubility, resulting in enhanced absorption and therapeutic efficacy. The %EE of ASPM-PM was ranged from 63.67±1.478% to 71.3±1.571% as shown in Table 4. The ANOVA analysis indicated that F1, F4 and F8 that are formulated using TPGS, Tetronic® and TPGS/solutol® HS-15 respectively had a non-significant impact ($p>0.05$) on the %EE of ASPM in the PM between them, while those formulas showed a significant difference ($p<0.05$) in comparison with other formula as shown in Figure 3.

However, a medicine binds to and is compatible with the micellar core determines how it is encapsulated. Encapsulation is enhanced when the medication exhibits higher affinity and compatibility with the micellar core, and decreased when the opposite is true.

Previous research has demonstrated that poorly soluble drugs can be incorporated into polymeric micelles via hydrophobic interactions, hydrogen bonding, and van der Waals forces, so from these results of encapsulation efficiency, F1, F4 and F8 were selected for further analysis such as *in vitro* drug release.

In vitro drug release from polymeric micelles

As mentioned earlier, the *in vitro* release of ASPM from polymeric micelles was analyzed using the HPLC technique. Additionally, at each time point, samples were tested in triplicate for the release study of the ASPM micelles. The dissolution behavior of

Table 3: The observed and documented CMC values.

Type of Copolymer / surfactant	Observed CMC in PBS %w/v	Documented CMC in water %w/v	References
TPGS	0.01	0.02	51
Solutol®HS15	0.016	0.005-0.02	52
Pluronic®-123	0.01	0.004	53
Poloxamine 701 Tetronic®	0.006	0.00277	54
Pluronic®-61	0.015	0.02	55
Pluronic®-62	0.018	0.1	36
Pluronic®-65	0.016	2.5	24
TPGS: Solutol®HS15 mixed solution	0.004	0.0000124	56

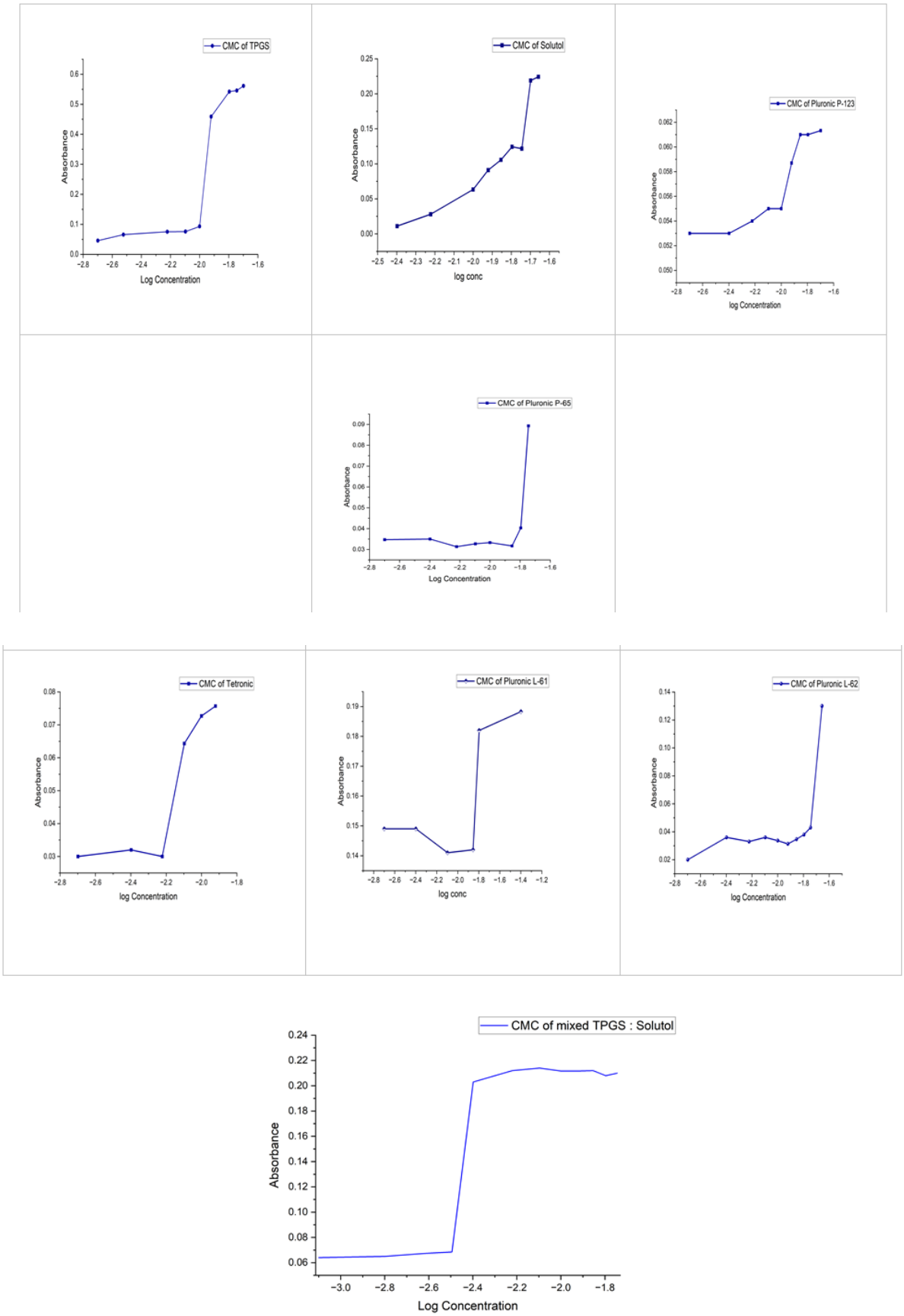

Figure 1: Measurement of CMC of Surfactant/copolymer single and mixed copolymer for the selected formula.

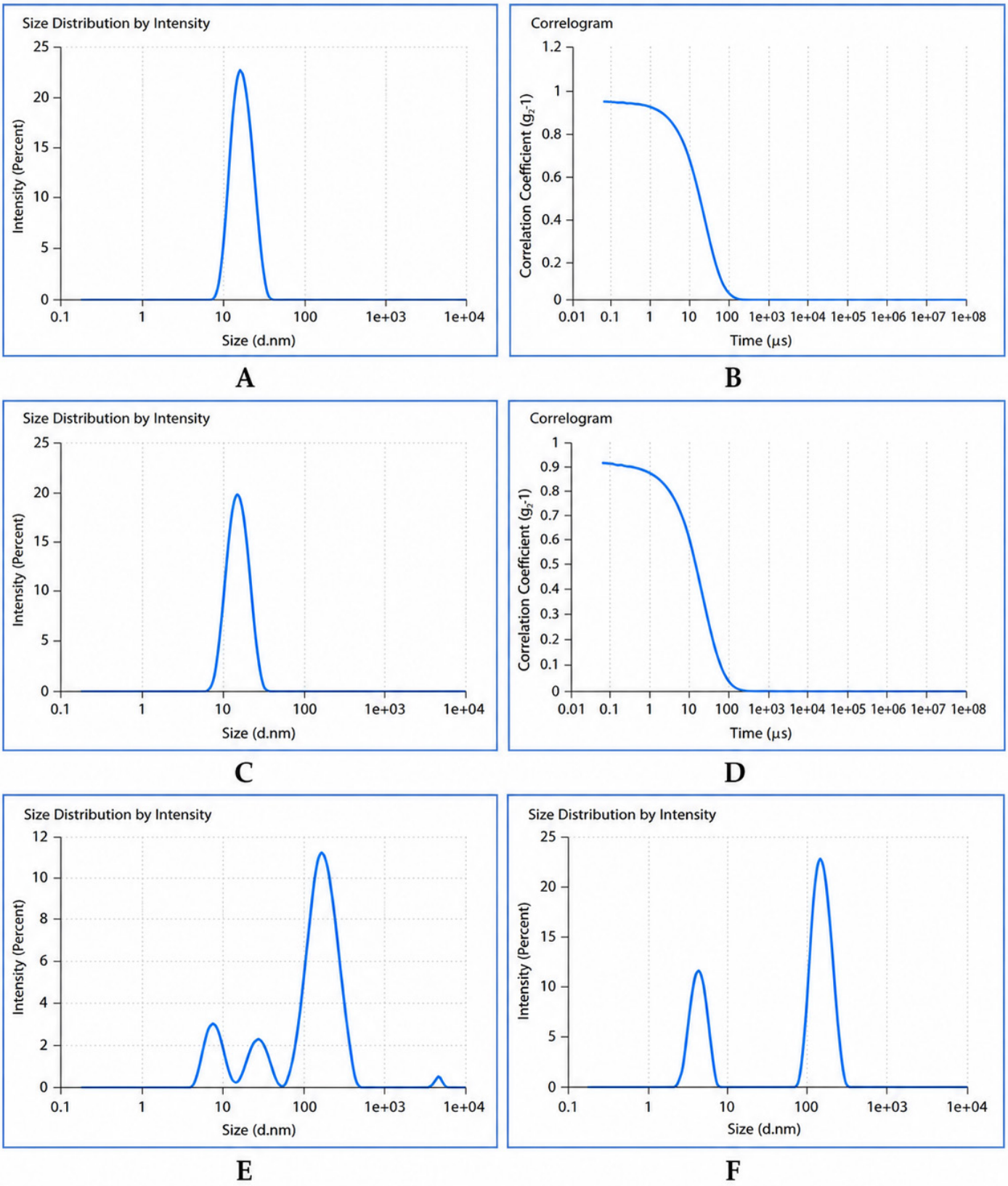

Figure 2: (A) and (B) Particle size distribution of TPGS and TPGS/copolymer micelles, (C) and (D) Particle size distribution of Solutol® HS 15 micelle (E) and (F) Particle size distribution of Pluronics® and Poloxamine 701 micelles. Determination of Encapsulation Efficiency (EE) and Drug Loading (DL).

the ASPM from the prepared micelles F1, F4 and F8 has been investigated during a 6 hr period under sink condition in PBS (pH 7.4) utilizing the dialysis bag method. The release profiles of ASPM are shown in Figure 4. F1, F4 and F8 Micelles prepared using TPGS 2%, Tetronic® and TPGS-solutol® HS-15 respectively were selected for dissolution study since they have the highest drug entrapment efficacy.

Overall, in 6 hr, less than 30±2.415% of ASPM was released from the micelles, F1 and F8 showed non-significant difference ($p>0.05$) in drug release at concentration 2% w/v of copolymer, while F4 showed burst effect in the 1st hr and to keep the maximum release below 20% during 6 hr of release study.

Based on these release properties, the results indicated sustained release behavior for ASPM polymeric micelle. Possible causes of the persistent release characteristic include hydrogen bonding

Table 4: Characterization of single and mixed polymeric micelles of ASPM.

Formula	Copolymer/ surfactant 2% w/v	P. Size (nm) Mean ± SD	PDI Mean ±SD	% EE Mean ±SD	%DL Mean ± SD	Physical Appearance after 24 hr	Physical Appearance after 3 months
F1	TPGS	11.3±1.02211	0.0343±0.0161	71.3± 1.571	14.263±0.3174	Clear	Clear
F2	Solutol®HS15	13.02±0.1803	0.0595±0.0299	65.3±1.471	12.404±0.31	Clear	Clear
F3	P-123	44.26±31.33	0.6183±0.23	52.4±0.49	10.48±0.34	Clear	Precipitate
F4	Tetronic®	160.8±35.321	0.294±0.075	68.6±1.248	13.7107±0.259	Clear	Clear
F5	PL-61	254.3±22.69	0.275±0.094	48.14±0.26	9.628±0.17	Clear	Precipitate
F6	PL-62	191±77.4854	0.273±0.06715	24.6±0.86	4.92±0.56	Clear	Precipitate
F7	P-65	277.63±63.96	0.412±0.0372	48.2±0.56	9.64±0.49	Clear	Precipitate
F8	TPGS: Solutol®HS15	11.79±0.8561	0.1078±0.0896	68.963±1.16	13.743±0.3235	Clear	Clear
F9	TPGS: P-123	13.454±0.721	0.13997±0.046	66.5±1.4391	13.3±0.2874	Clear	Clear
F10	TPGS:Tetronic®	10.103±0.899	0.047±0.01063	66.123±2.95	13.22±0.58412	Clear	Clear
F11	TPGS:PL-61	401.7±93.265	0.526±0.1266	66.05±2.684	13.2075±0.532	Clear	Clear
F12	TPGS:PL-62	334.23±23.95	0.2623±0.0234	69.01±4.245	13.8015±0.849	Clear	Clear
F13	TPGS:P-65	10.973±0.841	0.15253±0.096	63.67±1.478	12.73453±0.296	Clear	Clear

Data was expressed as $n=3$.

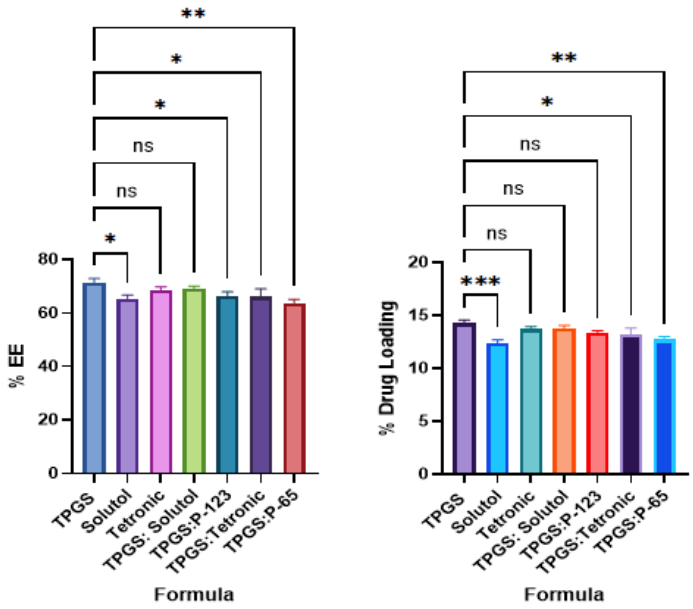

Figure 3: Entrapment efficiency and drug loading.

* Represents significant differences ($p<0.05$), ** represent highly significant ($p<0.001$), *** represent very highly significant ($p<0.0001$). Data are expressed as mean ± SD ($n=3$).

between molecules and the hydrophobicity of micelles' inner core.[60]

The release kinetic data for formulas was fitted with various release models using the DD solver MS Excel add-in application and demonstrated in Table 5. Korsmeyer-Peppas was the best-fitting release kinetics model with *n* value less than 0.45 indicating Fickian diffusion mechanism. From the data observed, the mentioned model was best fitted with F4 and F8 since they have the highest R^2, but F8 was considered the best formula since it is a mixed micelle preparation, so it will be considered for FTIR study.

Solubility enhancement determination

Solubility of ASPM in buffer solution pH 7.4 was 2.113±0.1 mg/mL, while its solubility in the blank micellar solution of the selected formula (F8) was 2.6±0.15. Drug is characterized by low solubility due to high lipophilic nature (log p 4.61±0.05), polymeric micelles well increase the water solubility by 1.23-fold. Loading ASPM within the micelles significantly increased its solubility.

Differential Scanning Calorimetry (DSC)

Figure 5 shows the DSC endothermic peaks of the drug, ASPM usually shows an intense endothermic peak at 142.5°C, indicating the melting point and crystalline nature of ASPM.

Powder X-ray Diffraction studies (PXRD)

The X-ray powder diffraction study the crystallinity of the pure drug ASPM, the diffractogram can be seen in Figure 6, ASPM in its pure form indicates high crystallinity with sharp, intense peaks throughout the measured temperatures, especially between 5° and 30°.

Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR spectrum of ASPM (Figure 7) revealed the characteristics absorption bands at 3039.78 cm^{-1} (aromatic C-H), 1699.13 cm^{-1} (C=O stretching), 1347.21 cm^{-1} (C-N stretching), 1186.34 cm^{-1} (C-O-C), 768.58 cm^{-1} (C-Cl stretching), and 1573.00 cm^{-1} (aromatic ring C=C stretching).[61]

The FTIR analysis of neat TPGS (Figure 5) revealed a distinct carbonyl ester peak at around 1742 cm^{-1}, attributed to the presence of both intermolecular and intramolecular hydrogen bonds among the hydroxyl groups of polyethylene glycol. Additionally, another notable FTIR peak for TPGS was identified at 1642 cm^{-1}, which corresponds to the unsaturated bonds (C=C) found in the vitamin E molecule. Furthermore, the FTIR peak detected at 3495 cm^{-1} is attributed to the presence of terminal hydroxyls within the TPGS molecule.[62]

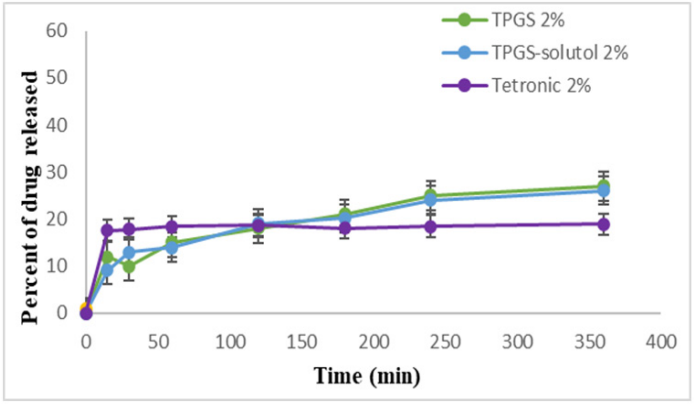

Figure 4: *In vitro* drug release of the ASPM-loaded micelles in phosphate-buffered saline (pH 7.4). Each point represents mean ± SD (*n*=3).

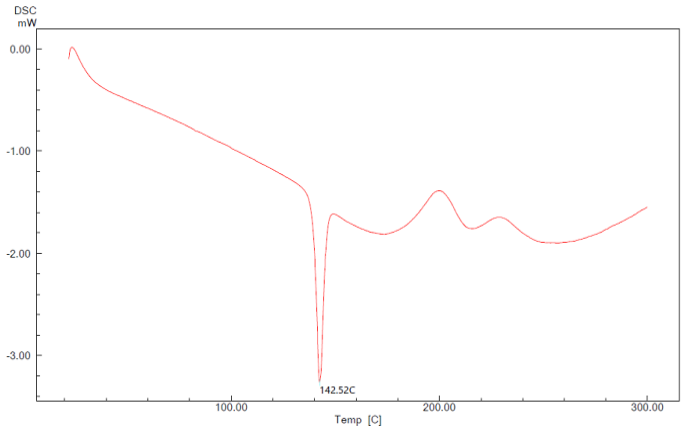

Figure 5: DSC thermograms of ASPM.

Table 5: Mathematical Models to Describe the Drug Release.

Model	F1 TPGS 2%	F4 Tetronic 2%	F8 TPGS: Solutol 2%
Zero order	0.3253	-2.0168	0.2785
First order	0.4473	-1.8112	0.4053
Higuchi	0.9007	-0.3271	0.9020
Korsmeyer-Peppas	0.9764	0.9988	0.9919
n	0.328	0.018	0.318
Hixson-Crowell	0.4089	-1.8795	0.3651

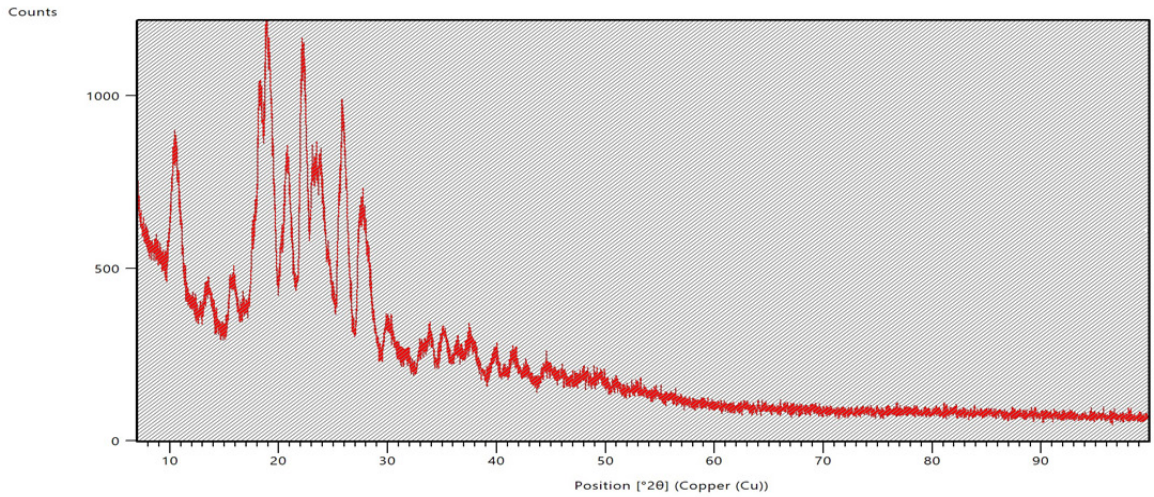

Figure 6: Powder X-ray diffractograms of pure drug ASPM.

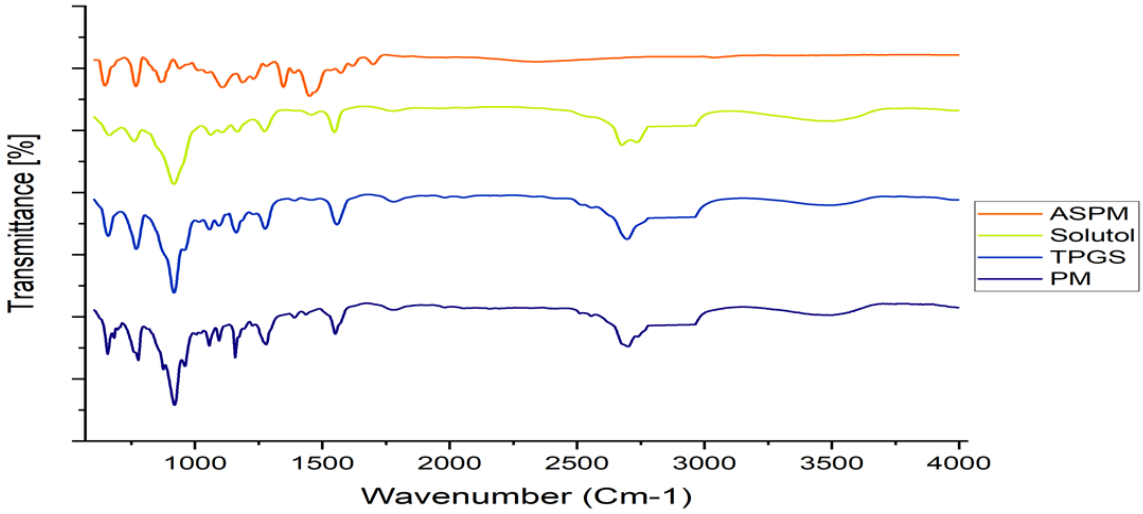

Figure 7: FTIR Spectrum of ASPM, Solutol, TPGS and physical mixture of drug and copolymers at ratio 1:1:1.

Table 6: Stability study of the selected ASPM micelles at 4°C each value represents the mean ± S.D (*n*=3).

Formula	Mean particle size (nm)±SD	PDI	% Drug content ±SD	Physical Appearance
F8	12.1±0.067	0.07±0.0223	74.87±17.3163	Clear

Solutol® HS15 which is the polyoxyl 15 hydroxylstearate, showed the characteristic stretching vibrations of C=O at 1732.26 cm^{-1} and the OH at 3495 cm^{-1} (Figure 5).[63]

The Physical Mixture (PM) of drug and copolymers of the selected formula at ratio also presented in (Figure 5), similar characteristics peaks for ASPM also appeared in the physical mixture and no additional peak was observed, thus confirming the lack of chemical interaction between copolymers and ASPM.

Field Emission Scanning Electron Microscope (FESEM) Analysis

Morphological observation of the pure powder of ASPM and the selected formula of polymeric micelle (F8) was shown in Figure 8. FESEM analysis of pure powder of ASPM (Figure 8a) showed a large particle with high particle size around 1.2 µm, while F8 revealed spherical shaped particles (Figure 8b) which exhibited narrow size distribution dispersed homogeneously in the aqueous phase with particle size near 50 nm.

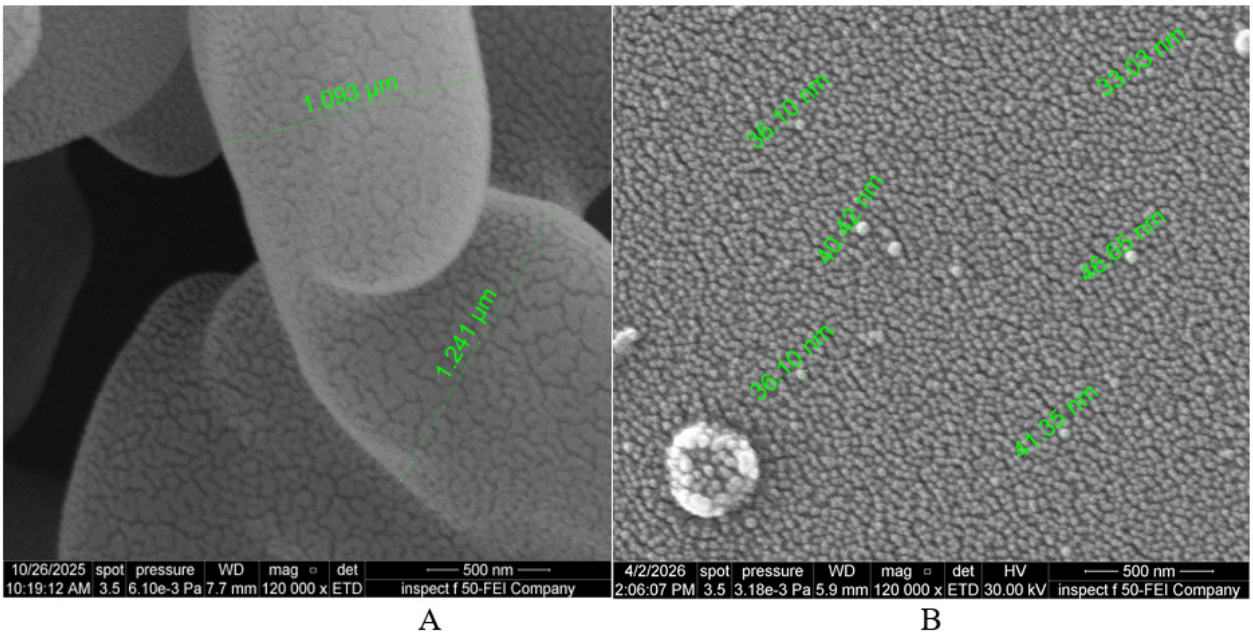

Figure 8: FESEM of pure powder of ASPM (a) and FESEM of selected formula of polymeric micelle F8.

Stability studies

The physical appearance of each formula (Table 4), was observed after 3 months in 4°C, and the results showed that F3, F5, F6 and F7 were precipitated after 3 months at concentration 2%w/v of P-123, L-61, L-62 and P-65 respectively. These findings assumed that preparation of polymeric micelles using single copolymer would not form a stable micelle.

The storage stability results related to particle size, PDI and drug content of selected formula F8 were summarized in Table 6.

CONCLUSION

Block copolymers, which are typically created by the self-assembly of amphiphilic or oppositely charged copolymers in buffer media, were ideal for loading ASPM into polymeric micelles by the thin film hydration approach. At a concentration of 2% w/v of TPGS, Tetronic ®, and TPGS-solutol ® HS-15 mixed micelles, the observations seen here suggest that the synthesized polymeric micelles produced a sustained release of ASPM over 6 hr. The development and behaviors of micelles in their media are greatly influenced by the type of interactions between the hydrophobic blocks of the copolymers.

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ABBREVIATIONS

ASPM: Asenapine maleate; **PMs:** Polymeric micelles; **HCl:** Hydrochloric acid; **CMC:** Critical micelle concentration; **TPGS:** D-alpha tocopheryl polyethylene glycol 1000 succinate; **PEG:** Polyethylene glycol; **FDA:** Food and drug administration; **HLB:** Hydrophilic-lipophilic balance; **PEO:** Poly (ethylene oxide); **PPO:** Poly (propylene oxide); **PBS:** Phosphate-buffered saline; **UV:** Ultraviolet; **PDI:** Polydispersity Index; **ZP:** Zeta Potential; **DLS:** Dynamic light scattering; **EE:** Encapsulation efficiency; **DL:** Drug loading; **HPLC:** High-Performance Liquid Chromatography; **TFA:** Trifluoracetic acid; **FTIR:** Fourier Transform Infrared; **ANOVA:** Analysis of variance; **SD:** Standard deviation; **DSC:** Differential scanning calorimetry; **PXRD:** Powder X-ray diffraction; **FESEM:** Field Emission Scanning Electron Microscope.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Zainab Eassa Jassim conceived and designed the study, performed the experiments, analyzed the data, and drafted the manuscript. Nawal A. Rajab contributed to data interpretation, assisted in experimental design, and critically revised the manuscript. Hamid Akbari Javar provided supervision, and final approval of the version to be published. All authors have read, reviewed the results and approved the final manuscript.

SUMMARY

Encapsulation of pharmaceuticals with low solubility is achieved when the polymers self-assemble form micelles of nanoscale size, with a hydrophobic core and a hydrophilic exterior, when hydrated with an aqueous medium. Thin film hydration method is simple method for single and mixed micelle formulation, since it produces stable micelles with a regulated size distribution, high drug loading capacity, and the ability to release drugs gradually over time. Particle sizes below 200 nm, a high encapsulation effectiveness of up to 72%, a drug loading of around 14% were observed in micelles made using TPGS, Solutol® HS-15, and pluronics using the thin-film hydration approach. For six hr in PBS (pH 7.4), the formulations demonstrated sustained ASPM release. Polymeric micelles using mixed copolymers at 2% w/v concentration was considered as an optimized formula in order to enhance the stability of ASPM incorporated in the hydrophobic core.

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