J Nanostruct 15(3): 1130-1141, Summer 2025

RESEARCH PAPER

Formulation and Evaluation of Nanomicelles Loaded with Spironolactone as a Platform for Pediatric Oral Delivery

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ARTICLE INFO

Article History:
Received 27 April 2025
Accepted 28 June 2025
Published 01 July 2025

Keywords:
Dissolution rate
Nanomicelle
Oral delivery
Soluplus
Spironolactone

ABSTRACT

Spironolactone is a synthesized steroid potassium-sparing diuretic utilized in the management of heart failure and hypertension. Due to inadequate water solubility, spironolactone demonstrates low oral bioavailability. Thus, inclusion of spironolactone into a nano micelle system has been proposed to improve the solubility and dissolution rate. Nanomicelles were prepared via the solvent evaporation technique, utilizing different polymer types and relative ratios. The selected formulation was evaluated through FTIR, PXRD, DSC and TEM. FTIR and PXRD analyses confirmed the absence of chemical interaction between spironolactone and soluplus, while PXRD and DSC results indicated a transition of the crystalline spironolactone to an amorphous state. Polymeric nanomicelle has emerged as promising pharmaceutical drug carriers that improve the solubility and dissolution rate of spironolactone.

How to cite this article
Dehghankelishadi P, Dorkoosh FA. Formulation and Evaluation of Nanomicelles Loaded with Spironolactone as a Platform for Pediatric Oral Delivery. J Nanostruct, 2025; 15(3):1130-1141. DOI: 10.22052/JNS.2025.03.031

INTRODUCTION

Historically, around 60.0-70.0% of compounds are categorized as biopharmaceutical classification systems Class II (have low solubility and high permeability) and Class IV (low solubility/low permeability) [1]. Solubility and dissolution rate are critical factors in gastrointestinal absorption within oral medication delivery systems. Researchers have explored multiple strategies to improve medication solubility, including particle size reduction, solid dispersion, complexation, salt creation, self-emulsifying drug delivery systems, cosolvent incorporation, and cocrystal formation [1-3]. Due to its nano-scale and high solubility, nanomicelles have innovative properties [4-6]. Nanomicelles are colloidal dispersions with a hydrophobic centre and hydrophilic outer surface. Amphiphilic molecules aggregate at specific temperatures and concentrations, which may be surfactants, polymeric, or mixed structure [7]. The critical micelle concentration is the threshold concentration at which aggregation initiates, and micelles are created. The crucial micellar temperature is the temperature at which micellar molecules assemble; below this temperature, no micelles are produced, and they exist solely as monomers. The aggregation group of a micelle refers to the quantity of the monomer molecules that constitute it. The aggregation of amphiphilic molecules into micelles happens as hydrophobic segments are sequestered from the aqueous environment, facilitating hydrogen bond formation

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in water and reducing the system's free energy. Micelles function as drug transporters across many pharmacological domains, encapsulating lipophilic medications within their core while their surface engages with polar molecules [8-14]. Polymeric micelles are utilized in therapeutics due to their enhanced solubility, resulting in superior intestinal permeability. Polymeric micelles consist of amphiphilic block copolymers [7]. The core and shell structure of polymeric micelles are organized as follows: The hydrophobic core envelopes the insoluble component of the block copolymer. While the hydrophilic block of the copolymer shields the medication from water and stabilizethe polymeric micelles, the corona serves to prevent the reticuloendothelial system (RES) from recognizing them in vivo. One of the many benefits of polymeric micelles is increased permeability and retention (EPR) effect, a passive targeting mechanism that allows them to target tumors based on their physicochemical characteristics. Pharmaceutical drug carriers should have characteristics such as biodegradable, small particle size, a high loading capacity, prolonged circulation, and able to accumulate in the necessary pathological site in the body through the parenteral route [15]. It should be noted that polymeric micelles can enhance the water solubility of these medications by a factor of 10 to 5000. On the other hand, the medicine needs to have hydrophobic groups to bind with the receptor of interest [16-19]. Spironolactone is an aldosterone antagonist utilized as a potassium-sparing diuretic. Spironolactone is noteworthy for treating primary hyperaldosteronism and managing heart failure in adults and neonates. The treatment started with 1 mg per kg per day, with a maximum limit of 3.3 mg per kg per day, not exceeding 100 mg per day. Spironolactone is accessible in tablet form, necessitating the compounding of various suspension formulations from these pills. The issues arise from the low water solubility of spironolactone, 28 mg/L. Spironolactone belongs to a class of drugs characterized by extremely low water solubility and a delayed dissolution rate, leading to inconsistent and suboptimal oral bioavailability. [20-22]. A lot of efforts for improving the oral absorption of spironolactone have been published. Blouza et al. used nanoprecipitation to create spironolactone loaded nanocapsules for pediatric. These nanocapsule showed rapid and complete drug release in simulated gastric fluid [20]. Hallouard et al. have attempted to improve the solubility and administration of spironolactone by nanoemulsions through spontaneous surfactant diffusion. This process offered a promising extramporaneous hospital formulation [23]. The development of nanomicelle-based drug delivery systems for pediatric use holds immense potential. Despite spironolactone 's prior prescription for children, the absence of solid dosage forms tailored for pediatrics remains a challenge. This gap emphasizes the importance of innovative formulations that ensure precise dosing, better taste masking, and easy administration. Selecting appropriate polymers is essential for constructing micellar structures for effective drug delivery. Nanomicelle offer precise dosing, better taste masking and easy administration making [8, 24, 25]. This research aim to prepare spironolactone nanomicelle to enhance drug solubility and dissolution rate by preparing nanomicelles.

MATERIALS AND METHODS

Materials

Spironolactone (SL) was purchased from Zhejiang Shenzhou Pharmaceutical co, ltd, China; soluplus (SP) was obtained from BASF (Germany); D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) was obtained from Beijing Jin Ming Biotechnology Co. Ltd. China, Tween 20 was purchased from Loba Chemie Pvt. Ltd. India; ethanol was purchased from Chem-lab, Belgium, Dialysis membrane was 8000-14000 Da (USA).

Preparation of nanomicelles

Nanomicelles were prepared using the solvent evaporation technique, where in spironolactone was dissolved in 3mL of ethanol, which was added to the polymer(s) dispersion) soluplus, TPGS, tween 20). Then, the resulted mixture was stirred using magnetic stirrer and continued for duration of 3 h with stirring rate of 1000 rpm and controlled temperature of 40℃, facilitating solvent evaporation and ensuring the formation of nano micelle [26-28]. The formulas prepared from F1 to F24 with different polymer and polymer ratios are shown in Table 1.

Characterization of spironolactone nanomicelles

Particle size (P.S.) and polydispersity index (PDI)

The mean particle size and the polydispersity index (PDI) of the diluted formulation were

evaluated using a Malvern Zetasizer. The measured principle of particle size is based on quantifying the scattered light produced by dispersed particles undergoing Brownian motion [29-31].

Entrapment efficiency (EE)

An indirect method was used to calculate the concentration of free spironolactone. The amount of untrapped medication was determined using an ultrafiltration technique. In brief, 2 mL of the spironolactone nanomicelle formulation was introduced into a top part of plastic (Amicon) conical tube at 4000 rpm for 30 min with a molecular weight cutoff (MWCO) of 10 kDa [32]. The quantity of unencapsulated medication was quantified spectrophotometrically utilizing a UV light spectrophotometer, with absorbance measured at 237 nm [33]. The calibration curve of ethanol has been used to determine the quantity of spironolactone (Eq. 1) [34-36].

In-vitro Release

The formula with the low particle size/PDI and high EE% have been selected for in-vitro release, in which, 10mL of micellar preparation (equivalent to 5 mg of SL) was inserted into the dialysis bag

$$EE\% = \frac{(\text{total drug in formula} - \text{amount of free drug})}{\text{total drug in formula}} \times 100\% \quad (1)$$

Table 1. Composition of SL nanomicelles formulation.

Formula symbol	SL	SP	TPGS	Tween 20
F1	5	10	-	-
F2	5	20	-	-
F3	5	30	-	-
F4	5	40	-	-
F5	5	50	-	-
F6	5	100	-	-
F7	5	200	-	-
F8	5	10	-	15
F9	5	10	-	30
F10	5	40	-	10
F11	5	40	-	15
F12	5	40	-	20
F13	5	40	-	50
F14	5	40	-	100
F15	5	10	20	-
F16	5	40	10	-
F17	5	40	25	-
F18	5	50	25	-
F19	5	50	50	-
F20	5	25	50	-
F21	10	100	-	-
F22	12.5	100	-	-
F23	25	100	-	-
F24	50	100	-	-

(12000-14000 Da). The dialysis membrane was presoaked for the entire night in phosphate buffer pH 6.8 before start of the test. The bag containing micellar solution was closed and immersed in 500 mL phosphate buffer 6.8. The dissolution apparatus type II was utilized in the study where was maintained at 37℃, and rotation speed 50 rpm. At regular interval, 5 mL of the sample was taken out and replaced with fresh dissolution media to maintain sink condition. The sample was withdrawn at pre-determined time (5, 10, 15, 30, 45, 60, 90 min) and then samples were measured spectrophotometrically at 242 nm [37, 38]. The outcomes derived from the dissolution test were statistically verified by applying the similarity factor (f_2).

$$f_2 = 50 \times log\ [[1 + (1/\ n) \sum_{j=1}^{n} w|Rj - T|^2]^{0.5} \times 100]$$

The similarity factor ranges from 0 to 100. An F2 value of 50 signifies a comparable disintegration profile, whereas a value below 50 shows dissimilar profiles [39, 40].

Assessing the zeta potential

The Malvern Zeta Sizer, UK, was utilized to assess the zeta potential of the sample. 1 mL of the spironolactone nanomicelle was introduced into a capillary zeta cell, and the recorded zeta potential value was noted [41, 42].

Lyophilization of the selected formula

The chosen formula has been frozen and then dried to obtain a dry powder for further evaluation. To produce a dry powder for evaluation, 10 mL of the optimal formula was prepared and subjected to freeze-drying. Round-bottom flasks containing the selected formula were frozen in liquid nitrogen at -60°C for 30 min. The apparatus's vacuum port was linked to the frozen flasks. The lyophilizer (Christ, Germany) was operated until dry powder was generated. The process of sublimation of the water from samples necessitates roughly 12 to 18 h [20, 23, 43, 44].

Transmission electron microscopy (TEM)

The morphology of spironolactone-loaded polymeric nanomicelles was analyzed using TEM measurement (Morgagni FEI 268/Holan). A droplet of micelles was deposited on a carbon-coated copper grid, dried, and dyed with 1% phosphors-tungstic acid [45].

Differential scanning calorimetric (DSC)

Thermodynamic properties of spironolactone and the selected formula were tested using a DSC-60 plus apparatus (Shimadzu, Japan). A sample of around 5 mg was inserted in aluminum pans and heated from 30 to 300 °C at a rate of 10 °C/min, with nitrogen flowing at a rate of 50 mL/min [46, 47].

Fourier transform infrared spectroscopy (FTIR)

FTIR analysis was employed to examine the compatibility of pure spironolactone, a physical mixture, and the chosen formulation. Around 3 mg of sample was crushed with dry potassium bromide, and the resulting preparation was scanned across a wavenumber range of 4000 to 400 cm^{-1} to ascertain the potential interaction between SL and the polymer [44, 48].

Powder X-ray diffraction (PXRD)

The crystalline composition of spironolactone and lyophilized nanomicelle-powder was analyzed utilizing powder-X-ray diffraction (XRD - 6000 Shimadzu - Japan). Measurements were performed using a Cu Kα filter at a voltage setting of 40 kV and an electrical current of 30 mA. The scanning was conducted within a 2θ range of 20 to 80 degree [49, 50].

RESULTS AND DISCUSSION

Particle size (P.S.) and polydispersity index (PDI)

Table 2 illustrate that as the concentration of soluplus increased from F1 to F7, the particle size decreased, except F 7 shows a much larger P.S. Formulation that contains Tween 20(F8 to F14) at different concentrations impacts the micelle size. Tween 20 is a non-ionic surfactant that reduces surface tension at low concentrations, stabilizing the micelle size. However, excessive surfactant concentration in F14 (100 mg Tween 20) showed signs of particle aggregation and swelling. In formulation of mixed micelles (F15 to F20), particle size reduced in F19, indicating strong synergy between the two surfactants in stabilizing the micelle. Whereas TPGS alone (unpublished data) or at low concentration, gives large particle sizes owing to its higher molecular weight. Increased TPGS content adversely affects Soluplus self-aggregation habits. A consistent increase in particle size was observed upon the

enhancement in the dose as seen in F21 (10mg) F22 (12.5mg) F23 (25mg) to F24 (50 mg) when compared to F6(5mg). At the highest dose, the particle size remains below 100 nm. PDI increase with increased concentration but remains below 0.3. This demonstrates stable and homogenous nanomicelle. The data shown in Table 2 indicate as the concentrations of Soluplus and Tween 20

Table 2. Particle size and PDI and EE values.

Formula symbol	SL mg	SP mg	TPGS mg	Tween 20 Mg	PS	PDI	EE
F1	5	10			89.87	0.241	95.16
F2	5	20			93.06	0.236	95.27
F3	5	30			95.31	0.258	95.83
F4	5	40			94.49	0.228	92.30
F5	5	50			107	0.286	92
F6	5	100			75.9	0.239	94.67
F7	5	200			136.6	0.048	.....
F8	5	10		15	88.23	0.199	94.57
F9	5	10		30	96.71	0.283	98.73
F10	5	40		10	119.5	0.013	83.75
F11	5	40		15	79.7	0.230	93.09
F12	5	40		20	131.2	0.086	92.5
F13	5	40		50	127.4	0.192	25.8
F14	5	40		100	165.9	0.343	.....
F15	5	10	20		78.55	0.259	91.87
F16	5	40	10		202	0.39	83.20
F17	5	40	25		132.8	0.102	83.75
F18	5	50	25		71.4	0.1112	84.61
F19	5	50	50		57.43	0.315	91.37
F20	5	25	50		75.45	0.2459	88.87
F21	10	100			72.92	0.0432	97.79
F22	12.5	100			79.54	0.0702	93.26
F23	25	100			78.54	0.0882	93.42
F24	50	100			85.12	0.0913	97.01

increased, the PDI declined, suggesting a high surfactant concentration. Tween20 and Soluplus stabilize freshly produced nanomicelles. The PDI results of the examined formulations were all below 0.3 except (F16, F19), signifying a uniform and narrow particle size distribution across most formulation

Entrapment efficiency (EE)

The EE values ranges from 83% to 98%, as shown in Table 2. The most effective variable in concentration of Soluplus (up to 95%.) and the addition of Tween 20 increased the EE (up to 98%) [51].

Selection of the optimized formulas of SL nanomicelles

The SL nanomicelle formula with the low particle size and good PDI and high entrapment efficiency were selected as optimal and retained for the in vitro release.

In-vitro release

Fig. 1 represents the release of the formula with low particle size and PDI and good EE%. F1 exhibit the lowest release rate of only 35 % at 60 min, F6 made of 100 mg soluplus achieve higher drug release percentage. F8 and F11 show progressive increase in percentage of release over time. According to these result, F6 has the smallest micelles size, the lowest PDI, high entrapment efficiency and high release rate when compared to the other formulae. Since the released profile towards pure SL powder showed significant improvement (F2=19.01), it was chosen as the optimal formula for release profile analysis. Fig. 1 indicates that F6 had a rate of 96%, but the pure drug only releases 33%.

Selection of the optimal formula of SL nanomicelles

F6 was chosen as the selected formula since it gave the fastest release compared to other formula and the drug itself. Further evaluation was conducted on this formula.

Zeta potential evaluation

Fig. 2 represent the findings of the zeta potential of the selected formula, which was -21.27 mV.

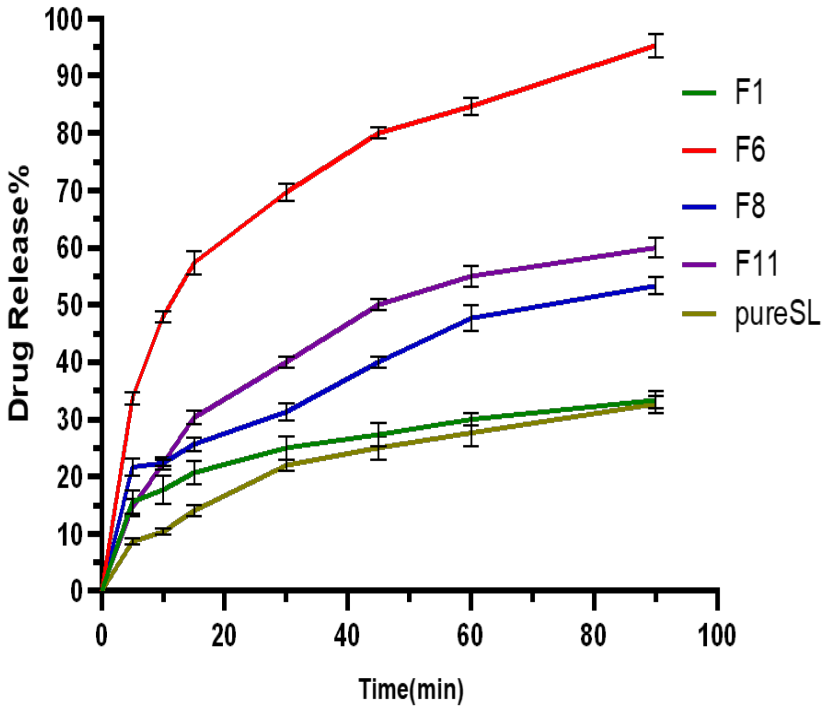

Fig. 1. *In*-vitro drug release of pure SL and nanomicelles formula.

Lyophilization of SL nanomicelle formula

The F6 formula that was dried by lyophilization (F6L) exhibits a white fluffy texture appearance.

TEM analysis

The TEM image of F6L nanomicelles in Fig. 3 exhibits a spherical shape, consisting of an outer shell and an inner core that encapsulates SL.

DSC analysis

The DSC thermogram of SL (Fig. 4) indicated melting values of 204.5 °C. No melting point peak

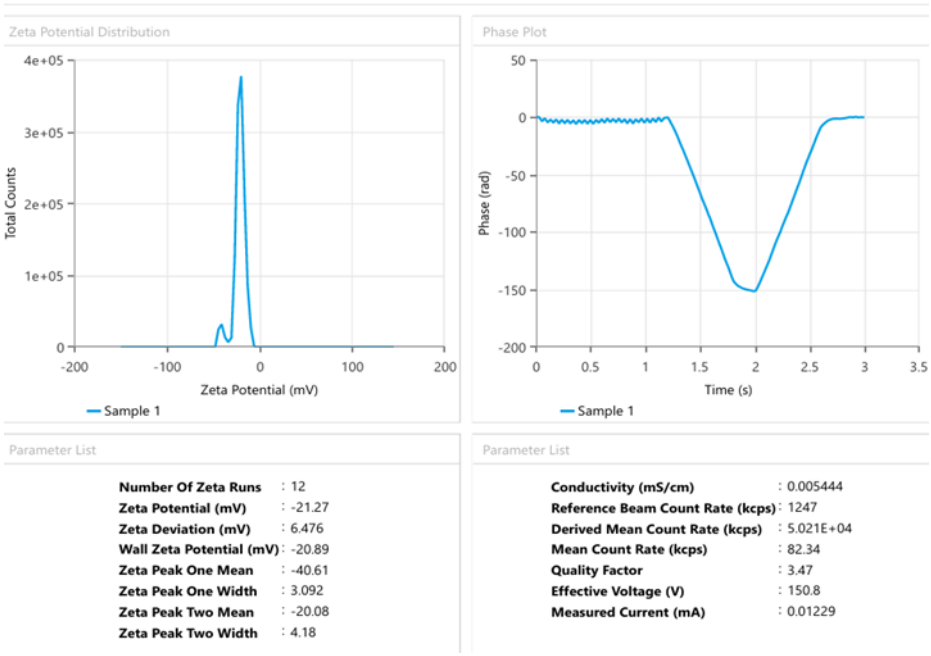

Fig. 2. Zeta potential of selected F6 formula.

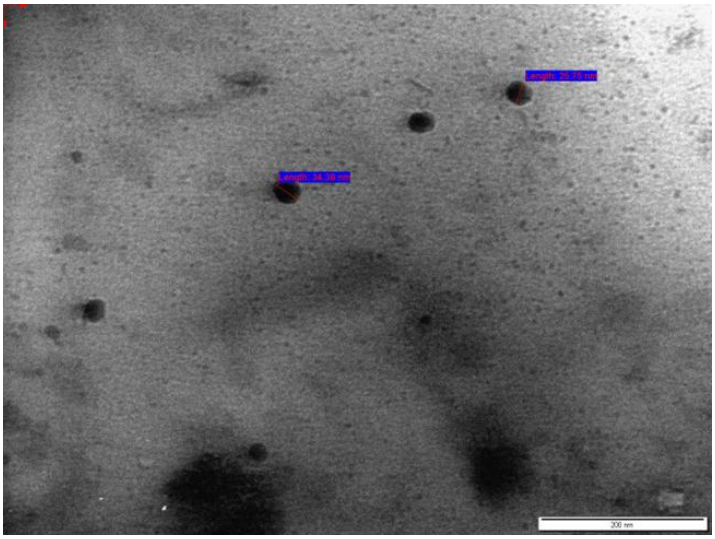

Fig. 3. TEM image of F6L nanomicelles.

of SL was detected in the DSC thermogram of F6 L.

FTIR analysis

In Fig. 5, FTIR spectrum of pure drug shows a C-H stretching vibration band centered at 2951 cm^{-1}, the band for stretching C=O carbonyl of lactone group at1766cm^{-1}, a stretching vibration of thio-acetyl carbonyl group at 1689 cm^{-1}, carbonyl

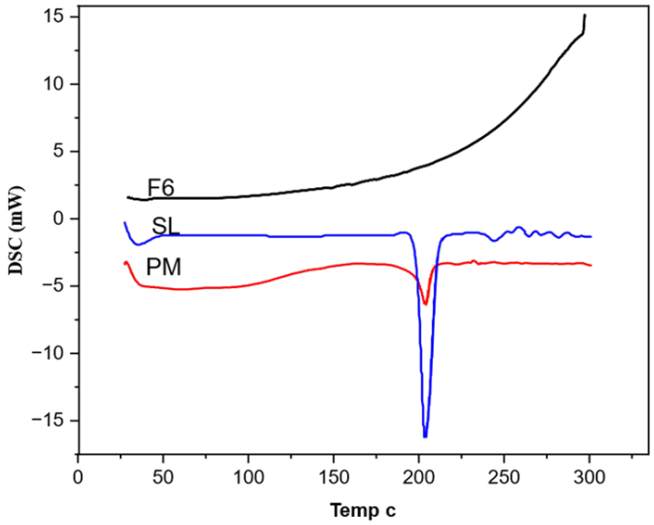

Fig. 4. DSC thermograms of SL, physical mixture and F6L.

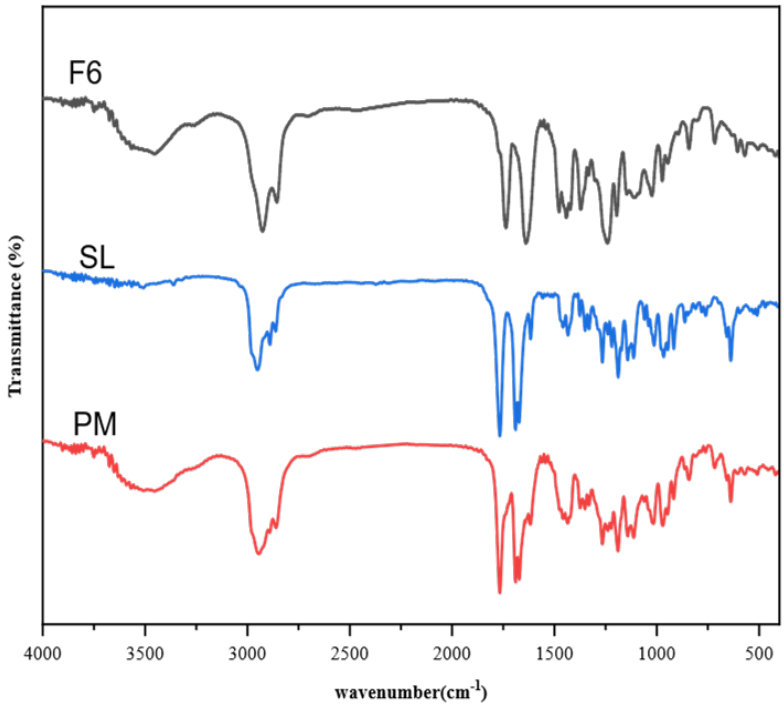

Fig. 5. FTIR spectra of SL, physical mixture and F6L.

stretching at 1672 cm^{-1}. Whereas Soluplus showed peaks at 2920, 2850, 1750 and 1650 cm^{-1} [52]. F6L exhibited similar absorption peaks suggesting its good compatibility with polymer.

PXRD analysis

As illustrated in Fig. 6, the pure drug exhibited crystalline peak at 2θ=10.1°, 13.2°, 14.6°, and 15.2°. In contrast, the distinctive diffraction peak patterns of F6L were broad and blunt, owing to reduced crystallinity and amorphous formation. Disappearance of drugs crystalline peak confirme the amorphousb state of the optimized formula.

The results demonstrate that an increase in Soluplus concentration initially leads to a reduction in micelle size, attributable to enhanced solubilization. At elevated concentrations, an excessive polymer results in the aggregation and enlargement of micelles (F7) [53]. Incorporating Tween 20 improved micelle stability at lower concentrations by diminishing surface tension; nevertheless, elevated concentrations (e.g., F14) led to aggregation. This corresponds with established surfactant behavior; in where elevated surfactant concentrations can disturb micelle architecture [54]. The combination of TPGS and Soluplus demonstrates how these surfactants stabilize micelles. TPGS's amphiphilic nature improves formation and stability of micelle. However, when TPGS was utilized alone or at low concentrations, high molecular weight limited the ability of formation of stable micelles, the TPGS alone did not offer sufficient stability and control over the size and shape of nanomicelle. This is due to the positioning of TPGS in the outer layer of the micelle [55, 56]. The imbalance between Soluplus and TPGS resulted in micelle aggregation and destabilization. In contrast, increasing the TPGS concentration had a detrimental effect on Soluplus's self-aggregation tendency. This result is most likely owing to reduced hydrophobic interactions between Soluplus core-forming blocks and the Vitamin E section of TPGS within the micellar core [57]. Increasing the spironolactone dose (10 mg to 50 mg) resulted in larger micelles, which is expected due to increased drug incorporation in the micelle core. Even at the highest dose, the particle size remains below 100 nm, which

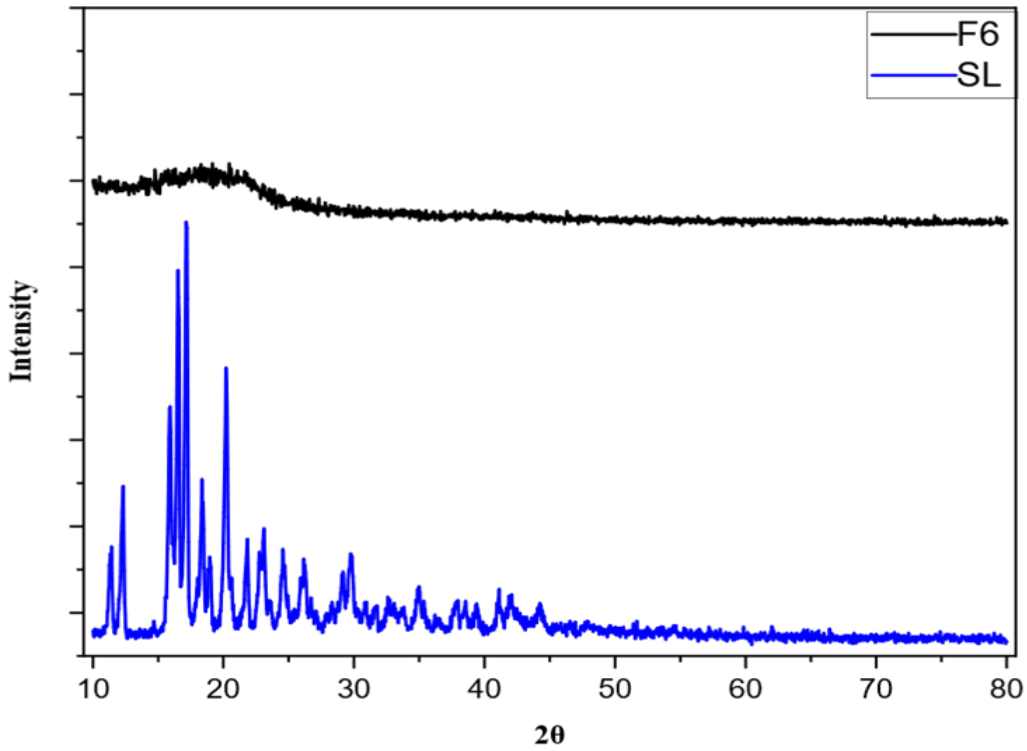

Fig. 6. XRD patterns of SL and F6.

improve absorption and extend circulation time [21, 57]. Soluplus and Tween 20 reduce PDI, facilitating the formation of nanomicelles with a stable and homogeneous particle size distribution, which is crucial for their use in drug delivery systems. The PDI values below 0.3 indicate a homogeneous distribution of nanomicelles [58]. The concentrations of Tween 20 and Soluplus significantly impacted entrapment efficiency. The maximum encapsulation efficiency (98%) was attained using Tween 20, indicating its function in enhancing the stability of the micelle core, however at excessive concentration of Tween 20 and Soluplus cause aggregation and precipitation. Mixed micelles that contains TPGS have EE % above 80% but not as soluplus incorporation [57]. Increasing the dose of spironolactone result in good EE due to high solubilization capacity of the micellar system at optimized surfactant ratios [57, 59, 60]. The in-vitro drug release profile proved that the nanomicelle encapsulation enhanced the solubility and dissolution of spironolactone relative to the pure drug powder. The accelerated release in F6 is due to the incorporation of Soluplus, which improves drug dispersion and micelle stabilization. Soluplus is an amphiphilic molecule that increases the aqueous solubility of poorly soluble drugs [11, 61]. A non-ionic stabilizer soluplus causes the reduction in zeta-potential values. Stability of nanomicelle could be improved by steric stabilization that creates a physical barrier around the nanomicelle. Thus, a formulation can maintain stability even with a low zeta potential if the steric stabilizer is effective. Moreover, pure soluplus micelles have a negative surface charge [62]. TEM image confirmed a well-defined spherical structure [27, 63]. The outcome of DSC indicated that SL was uniformly distributed among the nanomicelles in an amorphous state. The production of nanomicelles could alter the crystallinity state of SL [63-65]**.** The FTIR spectral indicated that there was no significant chemical interaction between the excipients and the medicine, confirming the drug's stability during the formulation process [43, 52, 66]. The XRD pattern of pure SL displayed distinct at 2θ scattered angles showing its crystalline nature. The distinctive diffraction peak for XRD pattern of F6L was broad and blunt, owing to reduced crystallinity and amorphous formation [36, 67]. This promising approach can improve solubility and dissolution rate of the spironolactone.

CONCLUSION

Our research demonstrated the effective trapping of SL within polymeric nanomicelles composed of two FDA-approved polymeric surfactants, specifically SP and TPGS, utilizing a solvent-evaporation method. The entrapment, stability, and morphology of SL nanomicelle were examined and validated using several techniques, including FT–IR, XRD, DSC, and TEM. This finding corroborates the domain of nanomicelles as a medication delivery method.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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