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Some variables Affecting Preparation of Nanosuspension-based Gel of Paliperidone

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Abstract

An intranasal drug delivery system offers a non-invasive, effective, reliable, direct, and alternative route to the CNS via the neural connections between the nasal mucosa and the brain. Paliperidone is mainly used to treat schizophrenia and disorder. It's practically insoluble in water class II with low bioavailability 28%. Therefore, the aim of the preparation of nano nasal suspension gel is to deliver paliperidone to brain via neural connections of nasal mucosa and the brain, and then enhance the uptake and bioavailability of the drug near and at the site of action. Different variables were investigated in this study, in order to recognize the best formula which contains 6 mg Paliperidone, 18 mg soluplus® at 500 rpm string speed, that aims the drug to deliver by the brain through the nasal administration .Among these variables are, stabilizers types soluplus®, Polyvinylpyrrolidone K30, Hydroxypropyl methylcellulose E5,and Poloxamer 188, besides to drug-stabilizer ratios, and stirring speed .The prepared nanosuspension, were evaluated according to their particles sizes, poly dispersity index, and dissolution behavior in simulated nasal fluid pH 6.5.The *in-vitro* results of the study revealed that, lowest particle size diameter was with the drug loaded by soluplus® of (1:3), (71.28 nm), compared with Polyvinylpyrrolidone K30of (1:3), (146.2 nm.), Poloxamer188 of (1:3), (393.1nm.), and Hydroxypropyl methyl cellulose E5 of (1:3), (251.2 nm.), respectively. Furthermore, the poly dispersity index demonstrates that soluplus® was the lowest (0.031), compared with Polyvinylpyrrolidone K30 (0.163), Polyxamer188 (0.2428), and Hydroxypropyl methylcellulose E5 (0.309), respectively. While the calculated entrapment efficiency % of the all paliperidone prepared nano suspension were ranged from 81.94% to 99.99 %. According to the particle size diameter, the formula F6 loaded by soluplus® of (1:3), was chosen for dissolution behavior of paliperidone in simulated nasal fluid pH 6.5, it gave 98% drug released, and estimated time for 50%, and 75% paliperidone released at 40.3 and 73.2 minutes, respectively.

Keywords: Nanosuspension, Paliperidone, Polyvinylpyrrolidone K30, Poloxamer 188, Soluplus.

Introduction

Nose-to-brain nano suspension delivery systems have emerged as a promising avenue for enhancing the therapeutic efficacy of drugs targeting the central nervous system (CNS). This innovative approach leverages the unique anatomical and physiological characteristics of the nasal cavity, such as its large surface area, high vascularization, and direct connection to the brain via the olfactory and trigeminal nerves, to bypass the blood-brain barrier (BBB) and deliver therapeutics directly to the brain [(1)]. Nanosuspensions, consisting of drug particles suspended in a colloidal dispersion stabilized by surfactants or stabilizers at the nanoscale, offer several advantages for nose-to-brain delivery. Their small particle size facilitates rapid absorption across the nasal mucosa, while their high surface area-to-volume ratio enhances drug dissolution and bioavailability [(2)].

Additionally, nanosuspensions can encapsulate both hydrophilic and hydrophobic drugs, enabling the delivery of a wide range of therapeutic agents to the CNS. The application of nanotechnology in nose-to-brain drug delivery has garnered significant attention due to its potential to overcome the limitations of conventional delivery methods, such as poor BBB permeability and systemic side effects [(3)]. By directly targeting the brain, nanosuspensions offer the possibility of reducing drug doses, minimizing off-target effects, and improving patient compliance [(4)]. Several studies have demonstrated the feasibility and effectiveness of nose - to-brain nanosuspension delivery for various

CNS disorders, including Alzheimer's disease, Parkinson's disease, brain tumors, and neuroinflammation [5].

These studies have highlighted the ability of nanosuspensions to enhance drug accumulation in the brain, prolong therapeutic action, and improve therapeutic outcomes compared to traditional administration routes [6]. Paliperidone is a second-generation (atypical) antipsychotic medication widely used in the treatment of schizophrenia disorders. It belongs to the class of benzisoxazole derivatives and is the primary active metabolite of risperidone. Paliperidone acts primarily through antagonizing of dopamine D2 and serotonin 5-HT2A receptors in the brain, leading to its therapeutic effects in managing psychotic symptoms [7]. Paliperidone, (Fig. 1) has M.Wt. 426 g\mole, it is practically insoluble in water (30 mg./L), class II, and log p 2.39. The pharmacokinetic properties of paliperidone, including its relatively long half-life t½ (23 hrs.), with oral bioavailability 28 % [8].

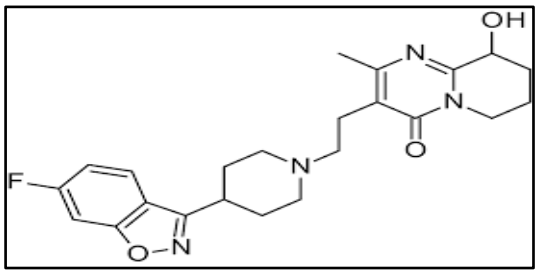

Figure1.Chemical structure of paliperidone (PAL) [8]

This study aims to formulate paliperidone as a nano suspension using solvent - anti solvent technique, in order to improve the rate of solubility, dissolution rate, as suggested formula for Nose to brain drug delivery.

Literature Survey

1-Intranasal (IN) administration is an attractive way of attaining high drug levels in the brain, which has been suggested as an alternative approach to the traditional parenteral and oral routes for the direct delivery of drugs to the brain [9].

2-Nguyen TT. Maeng HJ. showed in pharmacokinetic and pharmacodynamic study that nanosuspension NS hold tremendous potential for nose-to-brain drug due to increasing the absorption and bioavailability of many poorly soluble drugs by intranasal administration [10].

3-Also, Gulsun T, Borna SE, considered a dispersion of nanosuspension drug in suitable polymers and / or surfactants with sizes lower than one micron in diameter are the best and effective for drug dissolution in nasal to brain site delivery [11].

4- Ying Chong Chen, Yuling Liu, Jin Xie found that the bioavailability of Breviscapine nanosuspension as anticoagulant in the brain was significantly improved due to the direct nose-to-brain route. Therefore, this nanosuspension-based in situ gel is convenient and effective intranasal administration [12].

5-Smita Kakad, Sanjay Kshirsagar, declared that the Pharmacokinetic parameters of Efavirenz targeting potential of 99.46 %, suggest direct nose to transport of Efavirenz nanosuspension particles. This revealed the best possible alternative route for neuro –AIDS treatment [13].

6- P. Saha, H Kathuria, MM Pandey , demonstrated that the Nanosuspensions of Rotigotine RTG provide high drug solubility that can effectively combat the problem of nanosuspension stability for at least 3 months. Furthermore, the amorphous conversion of RTG significantly enhanced the drug's *in vitro* dissolution with that of pure drug suspension. Finally, enhanced the efficiency of nose-to-brain delivery targeting delivery [14].

7- PC Pires, M Rodrigues et al. detected in a study that, the pH adjustment, surfactants, and solvent, besides cosolvent play an important role in the preparation of nano suspensions of Clozapine, Curcumin and Baicalein targeting as nasal to brain delivery system [15].

8- In another study, S. Ourani-Pourdashti, E Mirzaei, suggested that niosomal methotrexate (MTX) in situ gel formulation, gave optimum niosomal MTX with particle size, zeta potential, and entrapment efficiency (EE%), equal to 130.5 nm, −38.5 mV, and 91.39 %, respectively, which could be a suitable candidate for drug delivery to the brain [16].

Materials and Methods

Materials

PAL powder was purchased from Heowns Biochem Technologies. LLC. in Tianjin, China. Liquid Tween 60 was obtained from Scharlau S.L. Spain. Hangzhou Hyper Chemicals Limited of Zhejiang, China, provided Poloxamer 188, PVP K30, Soluplus®, and HPMC E5 powder. HIMEDIA (Mumbai, India) provided the dialysis membrane 70. All remaining chemicals and solvents were of analytical reagent-grade quality.

Methods

Preparation of PAL nanosuspension

The nano suspension precipitation method is used to create nano suspensions of PAL with varying stabilizer and surfactant concentrations. In brief, 6 mg of PAL was dissolved in an organic solvent (2 mL ethanol). Using different stabilizer like HPMC-E5, Soluplus PVP K30, and poloxamer -188, in various drug-to-stabilizer ratios (1:1, 1:2,

and 1:3), or in conjunction with a co-surfactant liquid (tween 60), that acts as an anti-solvent system. Subsequently, the drug's organic solution was introduced into the stabilizer/surfactant aqueous solution at a rate of 0.5mL/min using a syringe, under varying speed mechanical agitation of (250,500,1000 rpm).To create the powdered nanoparticles, the organic solvent was allowed to evaporate at room temperature and subsequently lyophilized using a freeze drying equipment (Copley, UK).The composition and variable conditions of the preparation of different formulas of PAL nano suspension are listed in Table. 1 [17,18]

Characterization of the Prepared Nanosuspensions

Particle size and polydispersity index (PDI)

The average particle size and polydispersity index (PDI) of all the generated formulations were examined in triplicate using a particle size analyzer. This analyzer determines the variation in light scattering at a temperature of 25°C and a scattering angle of 90°. The PDI was calculated to determine the width of the size distribution of each formula. It serves as an indicator of the extent of dispersion or variability in the particle size [19].

Determination of Zeta potential

Zeta potential was measured using a zeta seizer apparatus, which measures the electrophoretic mobility of particle charges and converts them into an electrical potential known as zeta potential. The samples were prepared for measurement in triplicate, using the previously indicated procedure for detecting particle size [20].

Table 1. Composition of paliperidone nanosuspension formulas using different stabilizer types, ratios, co-stabilizer, and stirring speeds using the same solvent-antisolvent system type and ratio

Formula no.	Paliperidone (mg)	HPMCE5 (mg)	Soluplus® (mg)	PVP K30 (mg)	Poloxamer188 (mg)	Tween 60 (mg)	Ethanol (mL)	D.W (mL)	Speed (rpm)
F1	6	6	-	-	-	-	2	10	500
F2	6	12	-	-	-	-	2	10	500
F3	6	18	-	-	-	-	2	10	500
F4	6	-	6	-	-	-	2	10	500
F5	6	-	12	-	-	-	2	10	500
F6	6	-	18		-	-	2	10	500
F7	6	-	-	6	-	-	2	10	500
F8	6	-	-	12	-	-	2	10	500
F9	6	-	-	18	-	-	2	10	500
F10	6	-	-	-	6	-	2	10	500
F11	6	-	-	-	12	-	2	10	500
F12	6	-	-	-	18	-	2	10	500
F13	6	12	-	-	-	6	2	10	500
F14	6	-	12	-	-	6	2	10	500
F15	6	-	-	12	-	6	2	10	500
F16	6	-	-	-	12	6	2	10	500
F17	6	18	-	-	-	-	2	10	250
F18	6	18	-	-	-	-	2	10	1000
F19	6	-	18	-	-	-	2	10	250
F20	6	-	18	-	-	-	2	10	1000
F21	6	-	-	18	-	-	2	10	250
F22	6	-	-	18	-		2	10	1000
F23	6	-	-	-	18	-	2	10	250
F24	6	-	-	-	18	-	2	10	1000

Determination of entrapment efficiency

The entrapment efficiency was quantified to accurately determine the quantity of drug encapsulated inside the stabilized nanoparticles. A volume of 4 mL of the polymeric nanoparticle dispersion was introduced into a micro ultrafilter with a molecular weight cut off (MWCO) of 10 kDa and subjected to centrifugation at 4000 rpm for 15 minutes. The amount of free drug was measured using spectrophotometry at a wavelength of 237 nm after diluting 0.1 mL of the filtered solution with deionized water. The entrapment efficiency was determined by utilizing the following equation:

$$\%EE = \frac{A\,(total) - A(free)}{A(total)} \text{ x100} \quad \text{..... (Eq.1)}$$

Where: % EE: is entrapment efficiency percentage, A (total) total amount of drug determined through measurement of drug content, and A (free) is a free amount of the drug that passes through Amicon ultrafilter, the measurements were done in triplicate.[21].

In -vitro dissolution studies

Nano suspension having drug amounts equivalent to 6 mg of PAL was taken and poured into a Dialysis bag of two compartments sealed their ends of the bag to avoid drug leakage out of the bag. The dialysis bag was then immersed in dissolving medium overnight before usage, fitted with a paddle, and then dispersed in 300 mL SNF (pH 6.5). kept at 37± 0.5 °C temperature and rotation speed of 100 rpm. The sink condition was maintained throughout the investigation. To maintain a consistent volume, an aliquot of 5mL samples was removed from the receiver compartment at specified time intervals (5, 10, 15, 30,45,60,90,105, and 120 minutes) and refilled with the equivalent volume of new dissolving media. After filtering the samples, the amount of drug was measured using a UV spectrophotometer at λ max 237 nm. [22].

Lyophilization of selected formula of PAL- nano suspension

The selected formula was lyophilized using Christ equipment. (ALPHA 1-4 LD plus) to collect nanoparticles in a dried powder condition from the nano suspension, as well as to complete the characterization of the nano suspension and demonstrate the effect of lyophilization on nano particle size. The selected formula was frozen for 24 hours at -70 °C in a refrigerator using 2% w/w mannitol as a cryoprotectant. The sample was subsequently freeze-dried in a vacuum freeze drier at a precise temperature of -58 °C using a pump working at a pressure of 150 millitorr for duration of 48-72 hours. The resulting powder was preserved for further analysis. [23].

Characterization of Paliperidone Lyophilized Nano Suspension

Differential Scanning Calorimeter (DSC)

The differential scanning calorimeter (DCS) is a thermal analysis tool used to investigate the thermal characteristics and/or physical changes of various compounds in order to validate the presence of any drug-excipient interactions. The test was carried out on the pure drug, and after that, the formula for the optimum nano particles was chosen. Each sample was placed in an aluminum pan and sealed. The pan was then heated in the DSC apparatus at a rate of 10°C per minute, starting from 30°C and reaching 300°C.The experiment was conducted in a nitrogen environment. [24].

Fourier Transform Infrared Spectroscopy (FTIR)

In order to get the FTIR spectra of pure PAL as well as lyophilized PAL nanoparticles, an FTIR-7600 (Australia spectrophotometer) was utilized. Following the combination of powders with potassium bromide, the mixture was then crushed into disks using a hydraulic press. The disks were then scanned from 4000 to 400 cm-1. [25].

X-ray Powder Diffractometry

Powder X-ray diffraction (XRD) was employed to determine the crystalline pattern of the drug and detect any physical changes that occurred during formulation. The test was conducted on both the pure drug and the optimized nano particle formula. The study utilized a powder X-ray diffractometer, which scanned continuously in the range of 2θ = 10 - 50. The operating voltage was set at 30 KV with a current of 20 mA. [26].

Morphological Characterization of Nanoparticles

The size and shape of the selected formula were examined using Field Emission- Scanning Electron Microscopy (FESEM). Double-sided carbon tapes were adhered to an aluminum stub for support. A desiccator was used to dry the nano suspensions after they had been deposited onto the tape. For a continuous 10 minutes, they were gold - sputtered. The aluminum stub was positioned using a scanning electron microscope with a vacuum chamber. The morphology of the particles of the selected nano suspension formula was examined by FESEM type (Tescan Mira3, France). The particles' surfaces underwent to examination [27].

Statistical Analysis

The results obtained from the experiments are presented as the average of three replicated samples, with a standard deviation of (±). These findings were analyzed using a one-way analysis of

variance (ANOVA) for statistical significance ($p < 0.05$).

Results and Discussion

Characterization of the prepared paliperidone nanosuspension

Determination of the particle size and polydispersity index

Table 2 showed that the estimated mean particle size fell within the specified range (71.28 nm – 404.2 nm). Conversely; the PDI quantifies the size distribution of the nano particles, were ranged from (0.028-0.55) depending on formulation variables, in the present study, among all the stabilizers and co-stabilizers, the soluplus was more effective in stabilizing the system and result in effective particle size reduction, which may be attributed to the extended hydrophilic nature of the Soluplus® in the system, while the standard PDI values range were 0- 0.05 for the mono disperse system, 0.05-0.08 for nearly mono disperse, 0.08-0.7 for that of mid-range poly disperse, and greater than 0.7 is a very poly disperse system [28].

Table 2. Some physical properties of the prepared paliperidone nanosuspension

Formula no.	Particle size ± SD	PDI ± SD	E.E. % ± SD
F1	199 ±.6.0	0.341±0.1	88.45±0.11
F2	215.2 ±8.7	0.386 ±0.23	91.24±0.23
F3	224.6 ± 9.2	0.438 ±0.35	95.45±0.27
F4	126.5±1.8	0.064 ±0.025	93.13±0.24
F5	99.33±6.3	0.070±0.029	94.86±0.36
F6	71.28 ±2.4	0.031±0.035	96.61±0.87
F7	121.2±7.3	0.209±0.2	91.01±0.17
F8	129.57±5.0	0.125±0.12	93.31±0.44
F9	146.2 ±19.2	0.163±0.23	94.56±0.51
F10	102.5±14.2	0.253±0.14	85.21±0.73
F11	217.1±12.1	0.329±0.36	92.32±0.29
F12	223.4±16.5	0.295±0.34	94.54±0.82
F13	257.8±14.1	0.550±0.49	97.02±0.51
F14	108.5±18.1	0.240±0.20	99.56±0.30
F15	244.7±16.3	0.409±0.45	96.54±0.88
F16	232.1±17.6	0.366±0.32	94.32±0.12
F17	314.5±21.3	0.328±0.29	87.21±0.32
F18	210.7±17.5	0.308±0.29	94.63±0. 6
F19	80.56±5.6	0.053±0.06	97.25±0.78
F20	87.55±7.2	0.028±0.24	96.36±0.81
F21	187.1±15.4	0.299±0.26	92.21±0.5
F22	212.8±9.8	0.327±0.28	94.4±.0.78
F23	282.2±18.2	0.452±0.37	88.7±0.20
F24	404.2±20.3	0.423±0.42	85.36±0.61

Determination of the entrapment efficiency of paliperidone –nanosuspension

The entrapment efficiency of the drug was ranged from 85.21% to 99.56% for the prepared formulas. The results demonstrated the entrapment efficiency of the produced nano particles increased significantly ($P < 0.05$) as a function of increasing the stabilizer ratio, and for all the stabilizers used in the present study. This result is consistent with the result obtained by Singh PR., which may be attributed to the fact that, an increase in the stabilizer ratio in the organic phase enhances drug entrapment by increasing the viscosity of the organic phase. This increase in viscosity hinders the diffusion of drug molecules from the organic phase to the aqueous phase, resulting in a greater amount of drugs being trapped in the nanoparticles [29]. It is evident that the drug entrapment efficiency was enhanced by raising the stabilizer concentration and adding surfactant. The drug's comparatively low affinity for the stabilizer matrix is indicated by the low drug entrapment efficiency values. According to the results of Balzus et al., who synthesize spray-dried nanoparticles containing corticosteroid, the most important element in entrapment efficiency is the concentration of stabilizer utilized [30].

Effect of stabilizer concentration on the particle size and polydispersity index

Figure 2 shows the influence of stabilizer concentration on particle size and PDI for four distinct stabilizers. HPMC E5, Soluplus®, PVP K30 and Poloxamer 188 with ratios 1:1, 1:2, and 1:3 for each one. The prepared formulas showed PDI in the range of (0.028-0.55), these low values of the prepared formulas indicated good particles stability of the nano suspension. Besides to that, the results showed that the particle size decrease as increasing the concentration of Soluplus® (1:3), only which may be referred to the effect of high hydrophilicity of soluplus compared with other stabilizers that led to decrease in the particle size of nanosuspension [31]. While for PVP (Plasdone) of (1:3), 146.2 nm, poloxamer 188 of (1:3), 223.4 nm and HPMC of (1:3), 224.6 nm, the later three stabilizers showed an increase in particle size upon increasing the stabilizer ratio or content which may be as a result of the effect of aggregation of stabilizer around drug particles due to different solubility of the drug and other stabilizers in the same solvent used in the preparation of paliperidone nanosuspension particles. The selection of appropriate stabilizers and their concentration are crucial factors in regulating the size and stability of the nano suspension during nano precipitation and solvent evaporation methods [32].

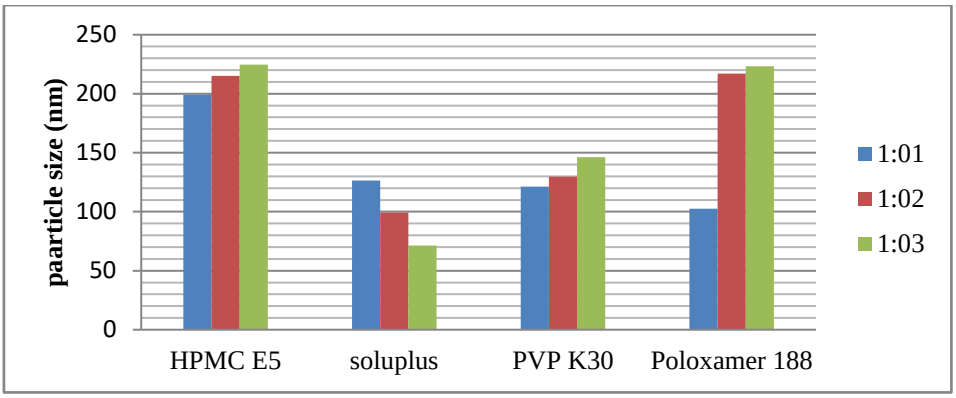

Figure 2. Effect of different stabilizers ratios on the nano particle size

Effect of stabilizer type on particle size and PDI

There are four distinct stabilizers. (HPMC E5, Soluplus®, PVP K30, and poloxamer 188) were used in formulas (F3, F6, F9 and F12), which they are prepared using magnetic stirrer, revealed that smallest particle size (71.28nm) was obtained when using Soluplus® as a stabilizer (F6), as shown in sampling data of Malvern Panalytical run report (Figure 3), compared with the other stabilizers used. This effect may be attributed to the fact that. Soluplus® is a graft co-stabilizer that possesses amphiphilic characteristics. The polyethylene glycol backbone represents the hydrophilic element, whereas the vinyl caprolactam/vinyl acetate side chain represents the hydrophobic part. The amphipathic structure of soluplus particles makes it a unique surface-active and wetting agent, effectively reducing the interfacial tension between the hydrophobic surface of the particles and the aqueous anti-solvent. This facilitates the interaction between the surface and water, while also preserving the small size of the produced particles [33].

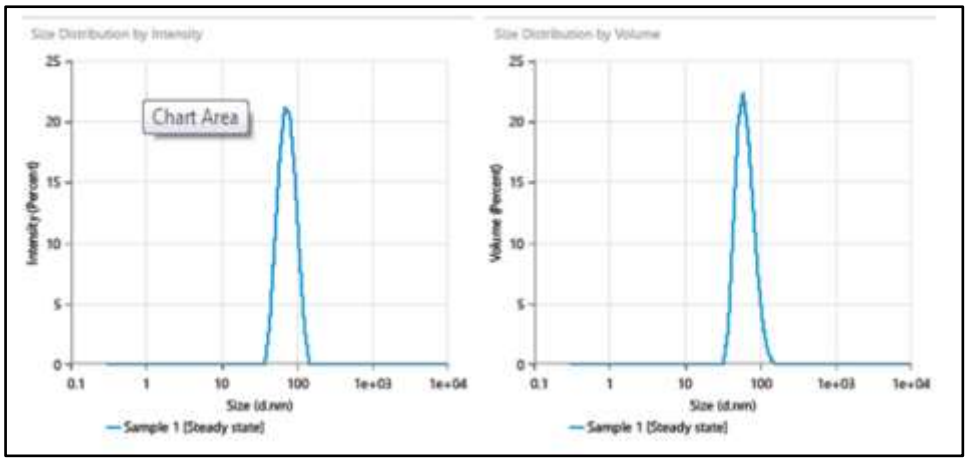

Figure 3. Particle size of the prepared PAL- Soluplus® nano particles in formula 6.

Effect of co-stabilizer on particle size and PDI

Formulas (F13 to F16) were prepared to illustrate the effect of the incorporation of co-stabilizer tween 60 on the particle size of the prepared paliperidone nanoparticles as shown in figure (4). Tween 60 is a non-ionic surfactant act by a steering stabilization mechanism. Its incorporation in the prepared nano particle formulas is significantly ($p<0.05$) increases the particle size for HPMC E5 from (224.6 nm) to (257.8 nm), for Soluplus® from (71.28 nm) to (108.5 nm), for PVP K30 from 146.2 nm. to 244.7 nm. and for Poloxamer 188 from 223.4 nm. to 232.1 nm. respectively. This increment may be due to disruption of the coverage provided by the original stabilizer, and that causes the particles to aggregate and increase in their particle's sizes [34]

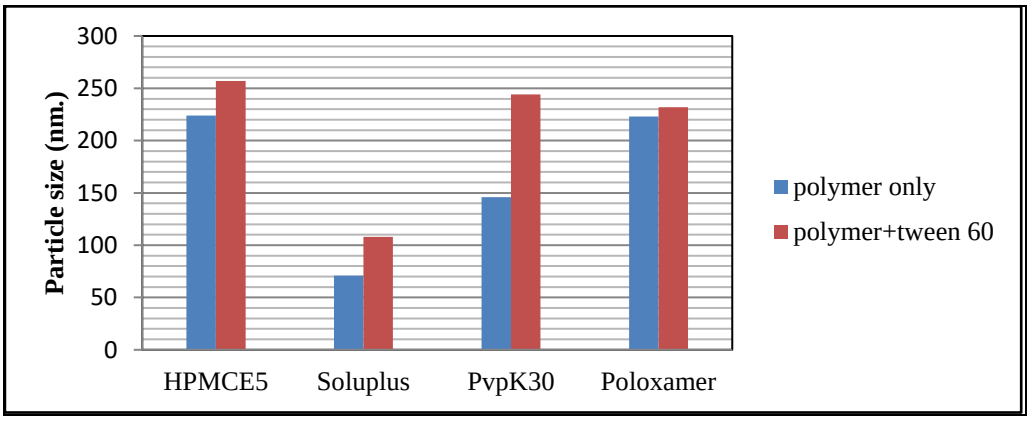

Figure 4. Effect of co-stabilizer addition (tween 60) on the particle size of different stabilizers

Effect of stirring speed of the anti-solvent system

Figure5. demonstrates that the stirring speeds of 250 and 1000 rpm used in the method was unsuccessful in reducing the particles to the nano scale. This might be attributed to the presence of a stabilizer around the drug, which increased the energy required for effective mixing. In addition, a high stirring speed of 1000 rpm is not always beneficial because it can cause excessive agitation and the formation of foams that hinder the preparation process by separating drug particles from the vehicle medium. Therefore, an optimal speed of 500 rpm was determined to achieve PAL particles within the acceptable nano average range [35].

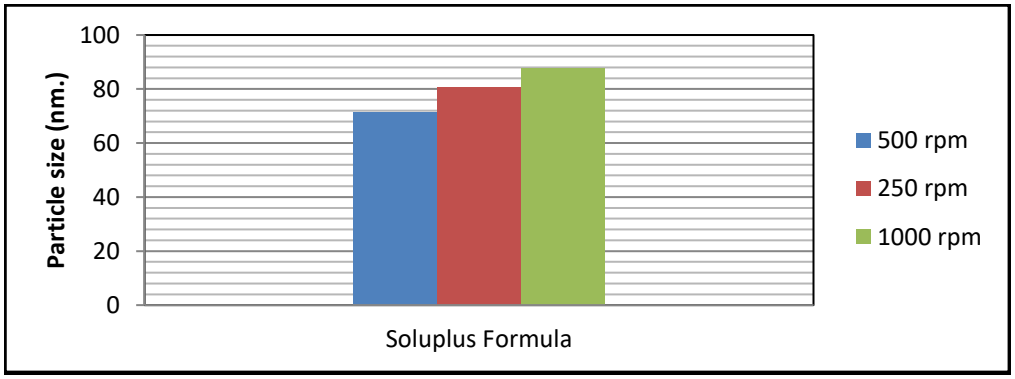

Figure 5. Effect of different stirring speed method on the prepared nanoparticle size of Soluplus formula

Zeta potential of selected formula

The zeta potential of the selected formula of PAL nano suspension (F6) was (- 0.83 mV) as shown in figure (6). Zeta potential measurements revealed that the molecule's surface charge was negative which depends on the particular system being used. This result may be attributed to the presence of Soluplus® as stabilizer that determines or governs enough degree of repulsion between adjacent, similarly charged particles of the dispersed nanosuspension [36]. Besides that the majority of nanosuspension particles dispersed in water acquires negative charge due to preferential adsorption of the hydroxyl ions towards these nanosuspension particles [37].

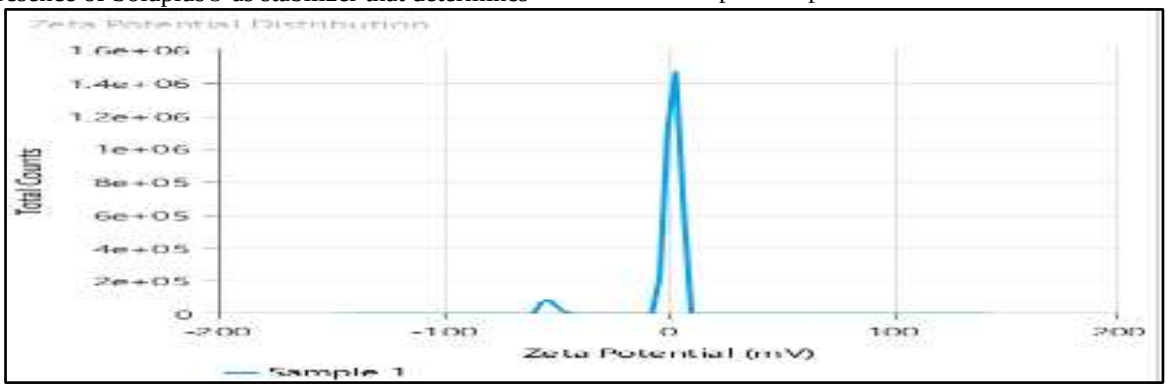

Figure 6. Zeta potential for PAL nanosuspension F6

In vitro release of paliperidone from nanosuspension

Figures 7 illustrate the effect of different type of stabilizers as a stabilizer used on the cumulative release profiles of paliperidone from nano suspension in comparison with pure drug. All dissolution profiles of the paliperidone from different stabilizers used in a ratio 1:3 formulas showed a significant increase ($p < 0.05$) in the dissolution rate compared to pure paliperidone drug, this behavior referred to the nature of these stabilizers as hydrophilic and solubility enhancing stabilizers. While paliperidone as a powder belongs to hydrophobic solubility drug classification [38]. On the other hand, and to investigate the cumulative release of paliperidone from different Soluplus® ratios, the obtained results in figure 8, indicated that formula 6 with 1;3 drug–stabilizer ratio gave 98% paliperidone released in 2 hours, compared with formulas HPMC E5 , PVP K30, Poloxamers 188 , and pure powder, respectively. In figure (4) nanosuspension formula composed of Soluplus® with 1:3 ratio, exhibited better drug release with the highest dissolution rate about 100% in 120 min. compared to 11.5% release of pure drug which may be owed to the existence of Soluplus®, hence it has a faster dissolution rate due to the larger effective surface area of PAL [39]. It is observed from the figures of dissolution drug release that increasing stabilizer concentration can lead to significant increase in the dissolution rate of PAL compared with low stabilizer concentration, this may refer to the higher hydrophilicity of Soluplus which is polyvinyl caprolactam derivative and act as amphiphilic stabilizer with an excellent solubilizing capacity (HLB value 14) for poorly water soluble drugs that permits more polar hydrophilic property towards water and increase the solubilizing rate of paliperidone in the nanosuspension [40].

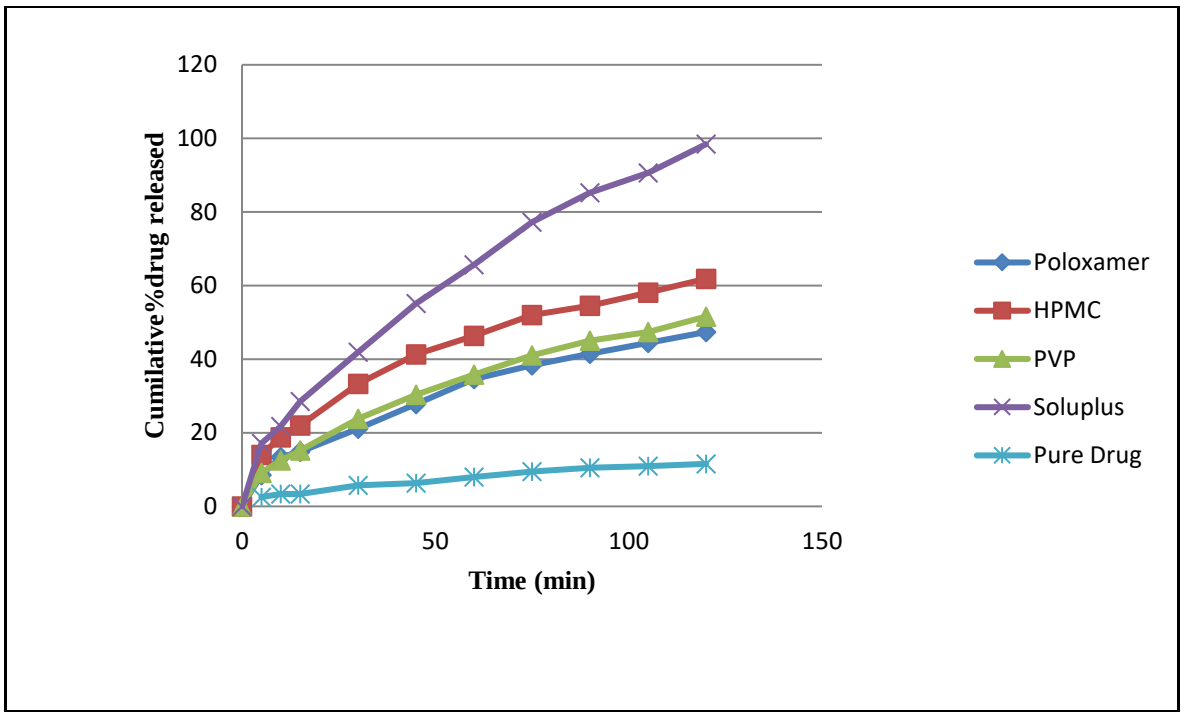

Figure 7. Effect of stabilizer type on cumulative percent PAL released profile in SNF dissolution medium pH 6.5 maintained at 37°C.

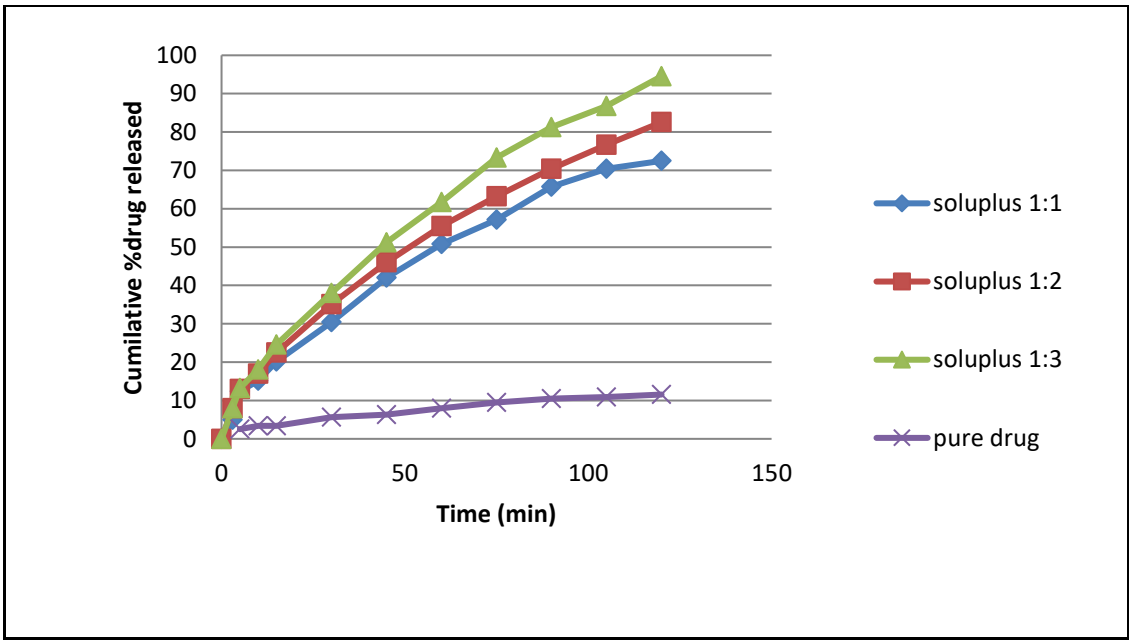

Figure 8. Effect of paliperidone: soluplus® ratios on cumulative percent PAL released profile in SNF dissolution medium pH 6.5 maintained at 37°C.

Differential scanning calorimetry (DSC)

DSC studies were performed on the individual components in order to study the interaction between PAL and the Soluplus® in the solid state. The lyophilized F6 sample was chosen to examine the crystalline clarity of the PAL nanosuspension after the lyophilization process. The thermogram of pure PAL powder exhibited a sharp endothermic peak at 163.82 °C, as shown in (figure 9), while the thermogram of lyophilized PAL nano particles (F6) exhibited a sharp endothermic peak at 163.82°Cdisappeared, indicating that paliperidone has changed into an amorphous form. The substance became amorphous and lost its crystallinity [41].

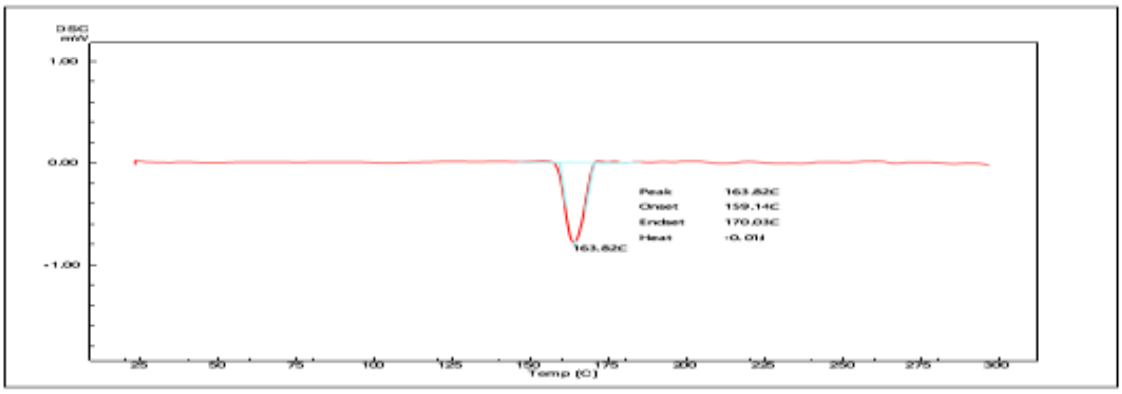

Figure 9. DSC of pure PAL

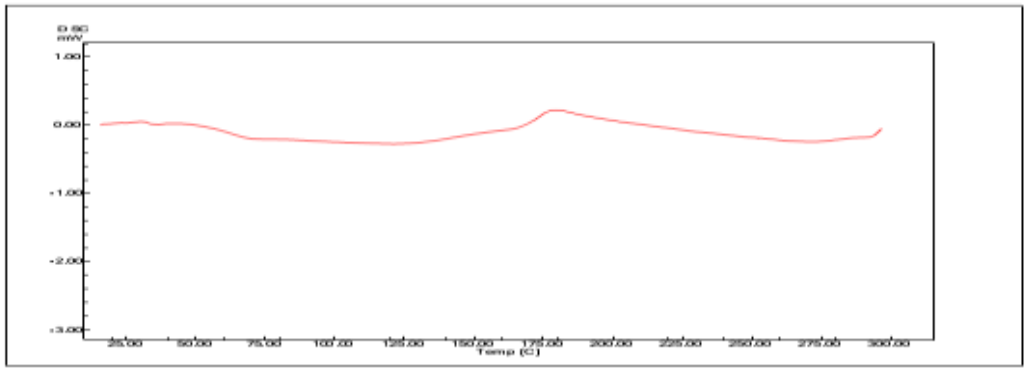

Figure 10. DSC of lyophilized PAL nanosuspensions (F6)

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectrum of pure drug (figure 11) had shown the characteristic stretching bands of C-F at 1271, O-H at 3290, C-N at 1335, C=O (Aromatic carbonyl) at 1627, C-O at 1535, aromatic C-H at 3043, and SP3 C-H at 2934 cm-1, which they are retained to the FTIR spectra of the PAL pure powder as shown in (figure 11). While the spectrum of lyophilized PAL–Soluplus® (F6) illustrated in figure (12), revealed the same bands, which they are specific to the main functional groups of pure PAL powder. These bands appeared in the chart as C-F at 1247.94, O-H at 3275.13, C-N at 1330.88, C=O (Aromatic carbonyl) at 1625.99, C-O at 1535.34, and SP3 C-H at 2933.7 cm-1. These similar bands indicating the compatibility between the PAL and, Soluplus® with no specific chemical interaction [42].

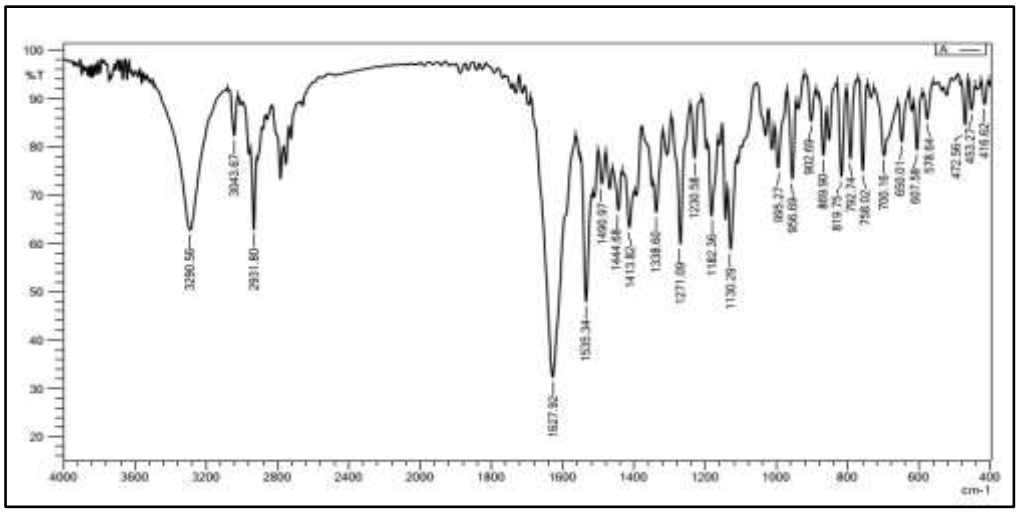

Figure 11. FTIR of pure PAL drug

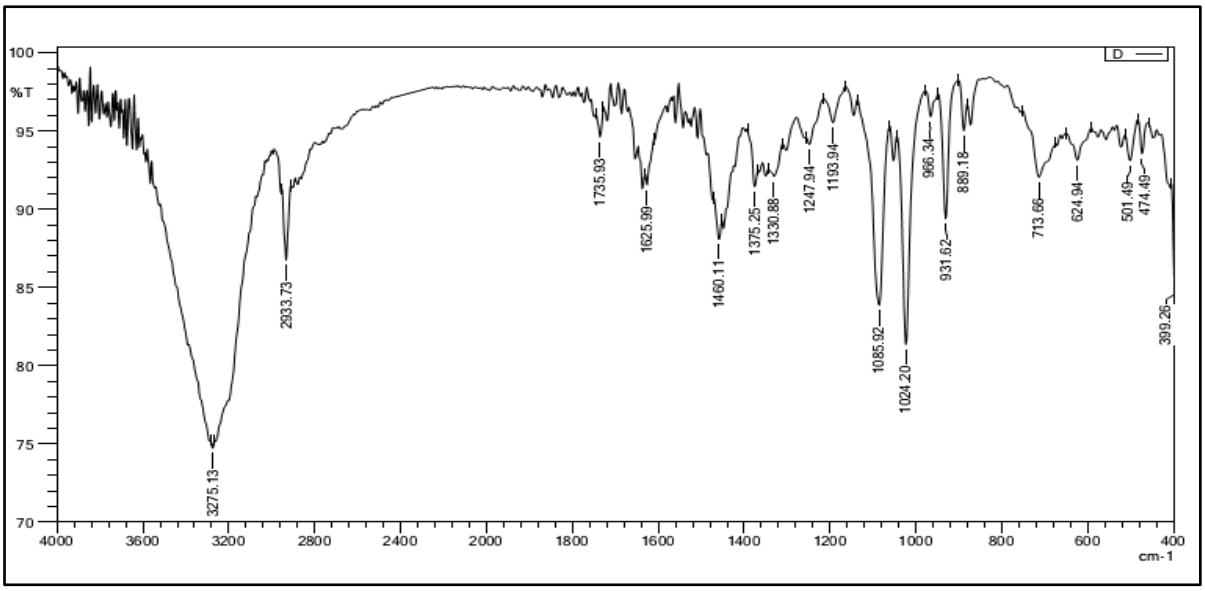

Figure 12. FTIR of lyophilized PAL in selected formula 6

X-ray powder diffraction (XRPD)

X-Ray diffraction analyses were conducted to confirm the crystalline nature of PAL using Soluplus®, as indicated by the DSC data. The diffraction patterns of the pure drug and lyophilized F6 were presented in Figures (13) and (14), respectively. An observable alteration in the X-ray pattern was noted following the creation of the nano suspension formulation. The pure PAL drug exhibited strong peaks at 14°, 15°, 19°, 21°, 22°, 23°, 24°, 33°, and 34°, indicating a high level of crystallinity. However, after the lyophilized powder was prepared, lower intensity peaks were observed, suggesting a significant transformation of the drug from a crystalline state to a more amorphous form. The appearance of additional peaks at 33°, 36°, and 41° is attributed to the presence of mannitol in the lyophilized powder [43]. The observed modifications suggest an increased level of stability in the lyophilized powder, accompanied by improvements in water wet ability and dissolution profile [44].

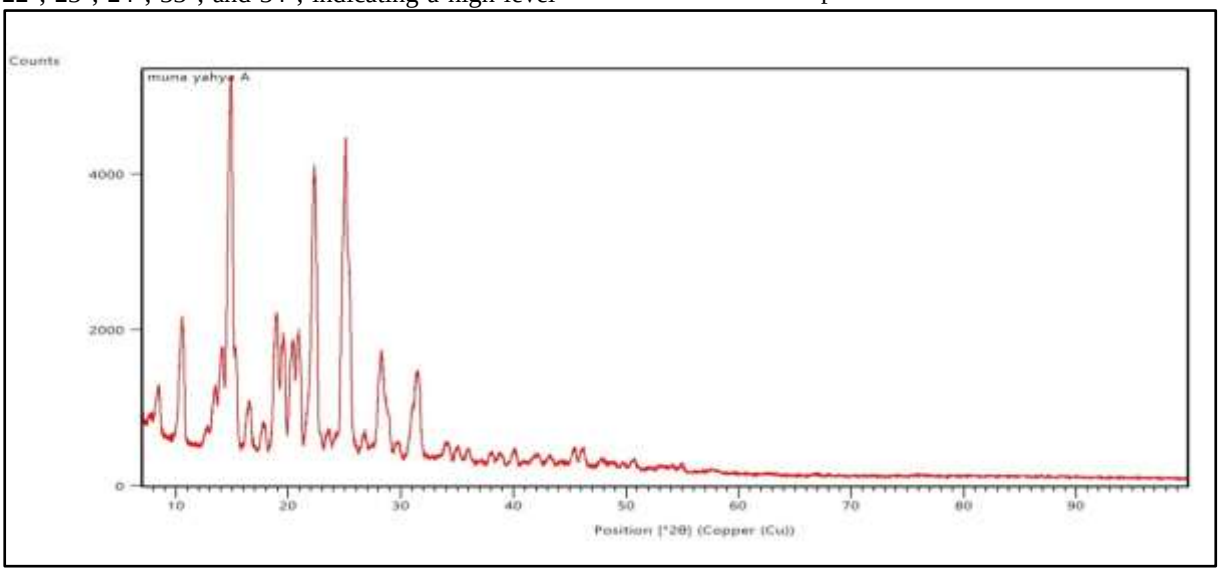

Figure 13. XRD Diffraction of pure PAL

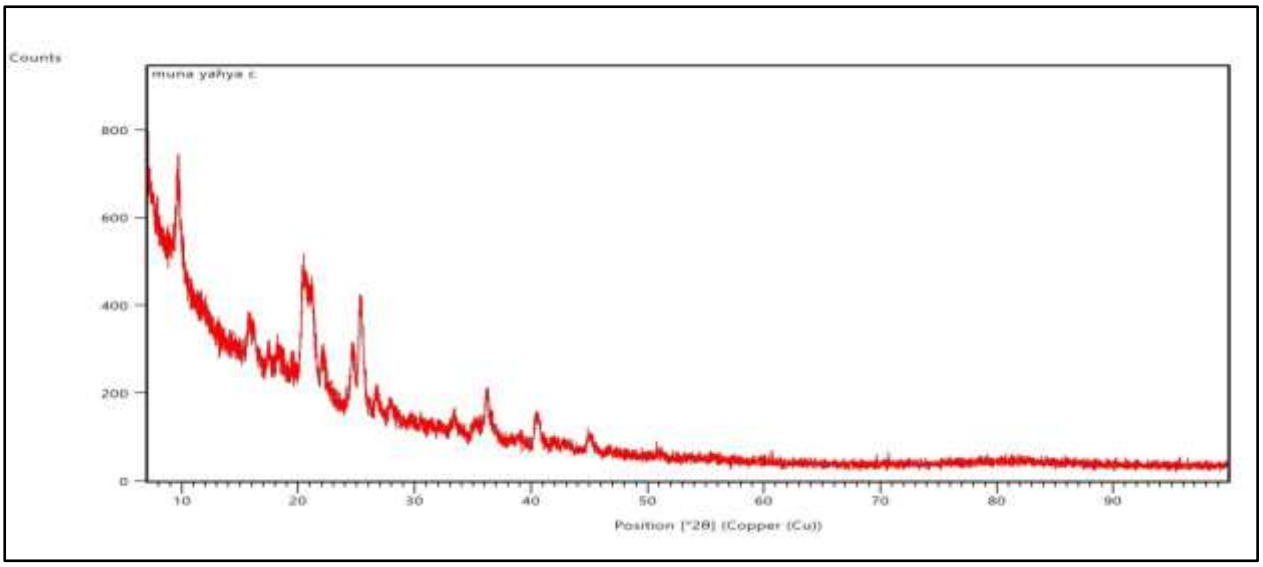

Figure 14. XRD diffraction of lyophilized Selected Formula 6

Field emission scanning electron microscopy (FESEM)

The images of FESEM for the selected formula (F6) were obtained. Figure (15) shows that there is a uniform particle size of the PAL with Soluplus ® , with smooth nature of the nano particles with dimensions 68.97nm. , 71.2 nm. and 74.2nm. The obtained results may be attributed to the suitable stirring speed (500 rpm), compared with other stirring speeds (250 and 1000 rpm) used in the study [41, 45].

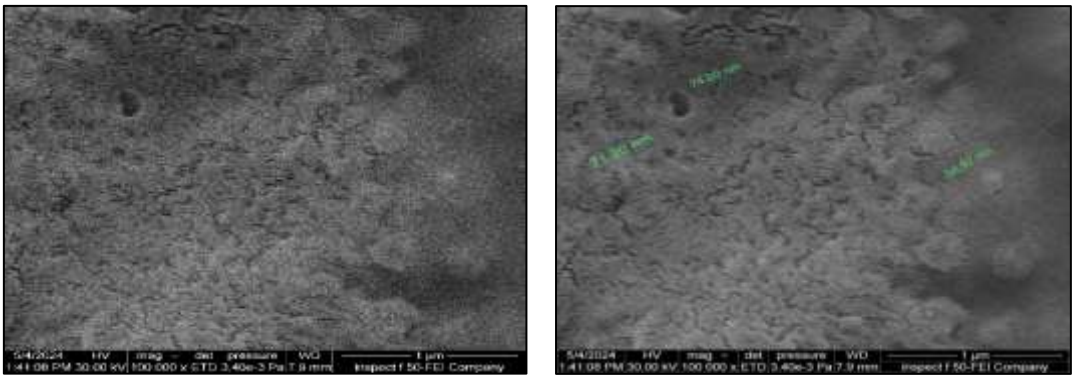

Figure 15. FESEM of lyophilized selected formula 6

Conclusions

The solvent anti solvent-precipitation method is efficient, simple to use, and cost-effective. Nanosuspension is a highly promising method for enhancing the solubility and dissolution rate of substances. The PAL nanosuspension was effectively synthesized by employing Soluplus® as a stabilizer in a 1:3 ratio, with ethanol acting as the solvent., with stirring speed (500 rpm), that gave a higher in-vitro dissolution release profiles compared to pure drug powder. The conclusion was that the formulation of paliperidone nanosuspension can improve solubility and dissolution rates, and promised improve bioavailability.

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Conflicts of Interest

There was no conflict of interest regarding the publication of this manuscript.

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Ethics Statements

This study did not need ethical approval from an ethics committee.

Author Contribution

The contributors of this study include MunaYehia and Fatima J. Al_Gawhari who both agree to the publication of this study.

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بعض المتغيرات المؤثرة على تحضير المعلق النانوي كأساس هلامي للباليبيريدون

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الخلاصة

نظام توصيل الدواء عن طريق الأنف طريقًا غير جراحي وفعال وموثوق ومباشر وبديل اخر للجهاز العصبي المركزي عبر الوصلات العصبية بين الغشاء المخاطي للأنف والدماغ. البيريدون يستخدم بشكل رئيسي لعلاج الفصام . غير قابل للذوبان عمليا في الماء من صنف الدرجة الثانية مع توافر حيوي منخفض ٢٨٪ . لذلك، فإن هدف الدراسة لتحضير البالي بيريدون كمعلق نانوي انفي لتهديفه نحو الدماغ عبر الوصلات العصبية للغشاء المخاطي للأنف والدماغ، وذالك لتقوية امتصاصه والتوافر الحيوي للدواء قرب وعند موقع العمل . ومن بين العوامل المستعملة في الدراسة انواع البوليمرات كالسولو بلس والبولي فينل بايروليدون كي ٣٠ والهايدروكسي بروبيل مثيل سللبلوز اي ٥ والبولوكسامر ١٨٨ اضافة الى نسبة الدواء الى البوليمر وسرعة التحريك.أن المعلق النانوي المحضر والذي يحنوي على ٦ ملغم. بالي بيريدون قييم طبقا الى حجم الجزيئات ومؤشر التشتت المتعدد وسلوك الذوبان في سائل انفي متزامن في رقم هيدروجيني ٦,٥ . النتائج لهذه الدراسة أظهرت أن أقل قطر لحجم الجسيمات كان مع الدواء المحمل بالسولوبلاس بمقدار (١:٣)، (٧١,٢٨ نانومتر)، مقارنة مع البولي فينل بايروليدون كي ٣٠ (١:٣) (١٤٦,٢ نانومتر)، بولوكسامر١٨٨ (١:٣). (٣٩٣,١ نانومتر)، وهيدروكسي بروبيل مثيل سللبلوزاي ٥ (١:٣)، (٢٥١,٢ نانومتر)، على التوالي. بالاضافة على ذلك، يوضح مؤشر التشتت المتعدد أن السولوبلاس كان الأدنى (٠,٠٣١)، مقارنة بـ بولي فينل بايروليدون كي ٣٠ (0.16) ، وبولوكسامر ١٨٨ (0.2428)، و الهيدروكسي بروبيل مثيل سللبلوز اي ٥ (٠,٣٠٩) ، على التوالي. بينما كانت النسبئة المئوية لكفاءة الاحتجاز للبالي بيريدون في الجسيمات النانوية بمعدل ٨١,٩٤٪ ال ٩٩,٩٩٪ .

وطبقا الى ذالك فان قطر حجم الجسيمات، للتركيبة F6المحملة بالسولوبلاس بنسبة (١:٣)، وسرعة تحريك ٥٠٠ دورة في الدقيقة اختيرت لسلوك ذوبان البالي بيريدون في السائل الأنفي المتزامن في رقم هيدروجيني ٦,٥ ، وقد أعطت ٩٨٪ من الدواء المتحرر، مع الوقت المقدر لـتحرر ٥٠٪، و ٧٥% بالي بيريدون عند ٤٠,٣ و ٧٣,٢ دقيقة على التوالي .

الكلمات المفتاحية: معلق نانوي، بالبيريديون ، بولي فينل بايروليدون ، بولكسامير ١٨٨، سولوبلاس