Improvement of the Solubility and Dissolution Characteristics of Risperidone via Nanosuspension Formulations.

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Abstract

Risperidone is an atypical antipsychotic drug that is used for treating schizophrenia, bipolar mania, and autism. Risperidone rebalances dopamine and serotonin to improve thinking, mood, and behavior by working on dopamine and serotonin 5 receptors antagonist. Risperidone has poor solubility and high permeability through the intestine, so it belongs to Biopharmaceutical Classification System (BCS) class II exhibits poor oral biopharmaceutical properties. The aim of the present work was to improve solubility and dissolution of risperidone by preparing nanosuspension using different stabilizers and different solvents in a method known as solvent-antisolvent precipitation method. Twenty-eight formulations were prepared and evaluated particle size, PDI, (EE), zeta potential, and in-vitro dissolution studies. The results showed that particle size of nanosuspension was nanosized for all formulations. The best formula (F13) has particle size (40.9) nm containing a (Soluplus) as a stabilizer in ratio 1:1 with drug by using acetone as a solvent in ratio 1:5 with water which was act as anti-solvent with stirring speed 1000 rpm and E.E % was 98%. For self-dispersible dry nanosuspension, the selected formula (F13) shown fast dispersibility of less than 1 min. and complete in-vitro dissolution to about 30 min. in 0.1N HCl. XRD and DSC indicate the transformation of a crystalline form of risperidone into an amorphous form. The stability studies of the best formula (F13) suggest that estimated shelf life was about 4 years.

In conclusion; the formulation of poorly water-soluble risperidone as nanosuspension significantly improved the dissolution rate of drug and enhanced its solubility.

Keywords: Risperidone, Nanosuspension, Solubility, Particle size.

Introduction

Biopharmaceutical Classification is such a system that provides a profile for each drug substance based on its permeability and solubility at several media. Accordingly, drugs are classified into four groups and become a benchmark in the regulation of bioequivalence of oral drug products. These classes are the following (1): class I (highly soluble, highly permeable), class II (poorly soluble, highly permeable), class III (highly soluble, poorly permeable), and class IV (poorly soluble, poorly permeable). Decrease particle size leads to increase solubility and enhance dissolution. Many techniques were used to decrease particle size. Nanotechnology-based approaches used to enhancement of drug solubility rely on reducing drug size to nanoparticles (2). Nanosuspension is one of nanotechnology approaches, which is a biphasic system consisting of pure drug particles dispersed in an aqueous vehicle in which the diameter of the

1Corresponding author E-mail: hyderimad@gmail.com
Received: 19/2/2021
Accepted: 25/7/2021

Iraqi Journal of Pharmaceutical Science 43
suspended particle is less than 1µm in size (3). An essential role of stabilizers is to compensate for the additional non-bound energy of newly revealed surfaces. Rigorously wetting drug particulates, hindering Ostwald ripening, and agglomeration of nanosuspension particulates are the most important advantages of adding pharmaceutical stabilizers (4). The widely used techniques of stabilization are steric and/or electrostatic stabilization, both ionic surfactants and charged polymers act as electrostatic stabilizers and non-ionic surfactants act as steric stabilizers (5). Maintenance of stability of nanocrystalline structure is of great significance results from polymer steric stabilization Most widely applied pharmaceutical excipients as polymeric stabilizers are (Soluplus, poloxamer 188, poloxamer 407, and PVP K30) K30). Risperidone is a benzisoxazole atypical antipsychotic, reported being an antagonist at dopamine D2, serotonin (5-HT2), adrenergic (α1 and α2), and histamine (H1) receptors. It is given orally for the treatment of schizophrenia and other psychoses and in short-term treatment of acute manic or mixed episodes associated with bipolar disorder. Risperidone is effective for treating positive and negative symptoms of schizophrenia owing to its affinity for its loose binding affinity for dopamine D2 receptors and additional 5-HT antagonism compared to first-generation antipsychotics, which are strong, non-specific dopamine D2 receptor antagonists(6). Figure 1. Chemical structure of risperidone
(6)
This study aimed to formulate risperidone nanosuspension by the use of solvent-antisolvent technique. An attempt to enhance risperidone solubility and improve dissolution rate.

Materials and Method

Materials
Risperidone, soluplus purchased from BASF/ Switzerland and all other solvents, Disodium hydrogen phosphate, Potassium dihydrogen phosphate, and other stabilizers purchased from China.

Preparation of risperidone nanosuspension by liquid solvent-antisolvent precipitation
2 mg of risperidone was dissolved in 1 mL methanol (acetone or ethanol) which is an organic solvent and sonicated in an ultrasonic bath for 15 min. On the other hand, 5mL of deionized water containing, stabilizers (Soluplus, poloxamer 188, poloxamer 407, and PVP K30) in ratio 1:1 that act as the antisolvent system. The following step is the addition of organic solvent slowly into aqueous solution at rate of (0.5 mL per min) of using a syringe pump, under mechanical agitation at different speeds (300, 1000, or 2000 rpm) with aid of a hotplate magnetic stirrer at room temperature (7). Then, evaporation of the organic solvent was done after stirring the sample at low stirring speeds for a half-hour at 25°C temperature to get coveted nanosuspension (8). Change in solvent and anti-solvent volume and stirring speed was done to formulate different risperidone nanosuspension preparation formulas shown in Table (1).

Determination of saturation solubility
Solubility of saturation is determined by putting an excessive amount of pure risperidone powder determined in 10 mL in various media where 0.1N HCl with 2% w/v Brij 35, water with 2% w/v Brij 35, phosphate buffer pH 6.8 with 2% w/v Brij 35, and methanol were used. Excess amount of drug was added to all of prepared media and kept in an (incubator shaker) at 25 °C, and after three days, prepared solution has been put in a centrifuge at 4000 rpm for duration of 10 min. Then, filtration by filter syringe of 0.45µm and dilution with particular solution of supernatants was done afterward. Absorbance was calculated according to calibration curves and it is determined at a wavelength for each media using UV- spectrophotometer(Carry win UV, Varian, Australia) and solubility (9).

Measurement of particle size and polydispersity index
Size of particle and index of polydispersity were determined by using the Nano Brook 90Plus particle size analyzer which is a dynamic light scattering, act by measuring the intensity of light scattered by the molecules in the sample as a function of time, at a scattering angle of 90°, and a constant temperature of 25 °C. Dilute suspensions prepared, a short ultrasonication is sometimes auxiliary to separate loosely-held agglomerates. 2 or 3 mL of nanosuspension is required to make the measurements. Disposable, acrylic square cells used for aqueous and alcohol suspensions (10).
Table 1. Composition of risperidone nanosuspension using different parameters

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<tr>
<th></th>
<th>Stabilizer</th>
<th>Ratio</th>
<th>Solvent</th>
<th>Ratio</th>
<th>Stirring Speed(rpm)</th>
<th></th>
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<th>Ratio</th>
<th>Solvent</th>
<th>Ratio</th>
<th>Stirring Speed(rpm)</th>
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<td>1000</td>
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<td>PVP k-30</td>
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<td>Acetone</td>
<td>1: 5</td>
<td>1000</td>
</tr>
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<td>methanol</td>
<td>1: 5</td>
<td>1000</td>
<td>F16</td>
<td>PVP k-30</td>
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<td>F17</td>
<td>Poloxamer188</td>
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<td>Poloxamer407</td>
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<td>F18</td>
<td>Poloxamer188</td>
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<td>F19</td>
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<td>Poloxamer407</td>
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<td>F27</td>
<td>Poloxamer407</td>
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<td>300</td>
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<td>Poloxamer407</td>
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<td>methanol</td>
<td>1: 5</td>
<td>2000</td>
</tr>
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**Determination of entrapment efficiency of a drug (EE) in Nanosuspension**

Nanosuspensions of different ratios were centrifuged at about 5000 rpm for 20 min. at 4°C using a cooling ultracentrifuge. The amount of free drug was detected by calculating the absorbance of an appropriately diluted sample of supernatant at 280 nm using a UV-spectrophotometer (Carry win UV, Varian, Australia). For each formula, the experiment was repeated three times and the average was calculated. (EE) could be calculated by the following equation:

\[ \text{EE} = \frac{\text{the total drug in a formula} - \text{free drug}}{\text{total drug in formula}} \times 100\% \]  

(1)

**In vitro dissolution of risperidone nanosuspensions**

Dissolution study of prepared nanosuspension was done under sink condition using paddle-type II according to USP pharmacopeia. Briefly, freshly an accurately weighed plain drug (2mg), and prepared nanosuspensions of (F1, F2, F5, F6, F13, and F21) formulas were placed in a pretreated dialysis bag (dialysis membrane); soaked in dissolution media overnight before use; and fitted with a paddle then dispersed in 900mL of 0.1N HCl with 2% w/v Brij35 solution as dissolution medium. The paddle has been built up to be rotated at 100 rpm maintained at 37 ± 0.5°C. An aliquot of 5mL samples was withdrawn from the receiver compartment at predetermined time intervals (5, 10, 15, 20, 30, 45, 60, 120) min and replenished with the equivalent volume of fresh dissolution medium to preserve the constant volume. And then, samples were analyzed for risperidone content spectrophotometrically after proper dilution using UV-spectrophotometer scanning at 200-400nm. The experiment repeated in triplicate for each formulation (11).

**Zeta potential evaluation of nanosuspension**

Zeta-potential evaluated by the use of zetasizer (Zetasizer Nano ZS, Malvern instrument, Worcestershire, UK) (12). The characteristics of surface charge were studied to assess the stability of the prepared nanosuspension and lyophilized nanoparticle formulas. The minimum limit needed for electrostatic stabilization of nanosuspension is ± 30 mv and for steric stabilization of ± 20 mv (13).

**Freeze drying of nanosuspension**

Freeze drying was used to convert the optimum formula to dry powder, later for further evaluation. Mannitol used as a cryoprotectant at 3% w/v. About 400mL of optimized formula was prepared and freeze-dried to yield a dry powder for evaluation. Four flasks froze in a deep freezer at -20°C for 24 hr. The frozen flasks were attached to the vacuum port of the device, then four flasks each containing 100mL of nanosuspension, instrument operated till dry powder yielded. Sublimation of solvent from frozen samples took 48 -72hr (14).**

**Effect of stirring speed on the particle size of risperidone nanosuspension**

Three different speeds were used to show their effect on the formulation of risperidone Nanosuspension. Speeds of 300 and 2000 rpm used in the formulas (F21-F28) were used to study this effect.**

**Effect of solvent/antisolvent ratio change on the particle size of risperidone nanosuspension**

Study the effect of change in solvent/anti-solvent ratio in nanosuspension where the change in volume of deionized water (anti-solvent) from 50 mL to 100 mL and 150 mL. Formulas (F5-F12) were used (12).

**Effect of polymer type when using different solvents on the particle size of risperidone nanosuspension**

By changing the solvent (methanol) in formulas (F1-F5) to acetone and ethanol. Formulas (F13-F20) were used (12).

**Characterization of lyophilized powder**

**Saturation solubility of lyophilized powder**

Three dissolving solvents water, 0.1 N HCl with pH 1.2, and phosphate buffer pH 6.8 were used to investigate the saturation solubility of lyophilized formula (F13). An excess amount of drug was added to each test tube containing the above-mentioned solvents then were shaken for at least 48hr in a water bath shaker at 25 °C. Then filter with a conventional filter paper before reading for each sample. Sample test tubes were centrifuged at 6000 rpm for 15 min. The absorbance of the supernatant was recorded and a calibration curve was used to determine the amount of drug dissolved in the specific volume of each dissolving media (17).

**The in-vitro dissolution profile of lyophilized risperidone nanoparticle**

In-vitro dissolution test of risperidone lyophilized powder was estimated using (paddle assembly) type II dissolution test apparatus. Accurately weighed lyophilized powder equivalent to 2 mg of risperidone was placed on a pretreated dialysis bag and fitted to the paddle which rotates at 100 rpm at 37 °C ± 0.5 in 900mL of dissolution medium 0.1N HCl. An aliquot of 5-milliliter samples was withdrawn from the receiver compartment at predetermined time intervals and refilled the
equal volume of fresh dissolution medium to conserve the constant volume. The same procedure was applied on lyophilized powder with the same conditions at 100 rpm rotation of paddle containing phosphate buffer (pH 6.8). Then samples were filtered by 0.45μm filter syringe and assayed spectrophotometrically by UV–spectrophotometer. Results obtained were compared using similarity factors and the experiment was repeated in triplicate (18).

**Differential scanning calorimetry (DSC)**

DSC can be used to evaluate the crystalline state of drug especially when converted to a lyophilized powder. 8-10 mg sample of the pure risperidone and lyophilized powder of the selected formulations heated at a scanning rate of 10°C/min. This done under dry nitrogen flow (100 mL/min) between 30 and 300° against an empty aluminum pan as a reference using DSC- Shimadzu 60 with TDA trend line software (19).

**X-ray powder diffraction (XRPD) analysis**

Patterns for pure risperidone and nanoparticles were analyzed using an XRD-6000, Shimadzu-Japan. The continuous scan range of 5-80 degree. 40 (kV) was for the operating voltage, 30mA for the current, scan step size of 0.050° (20), and scan step time of 60 sec (20).

**Scanning electron microscopy (SEM) study**

The morphology of pure drug and lyophilized formula were examined by (VEGA3Tuscan) by direct deposition of powder on double-sided carbon tape and coated with gold at 1K, 2K, 5K, and 500x magnification then coated with gold (21).

**Stability study**

In specific capsules, the selected formula powder was filled and stored at three various 40°C, 50°C, and 60°C temperatures degrees for 90 days, at an interval of 14 days, samples were dissolved in 100 ml methanol. And then, the drug concentration was measured spectrophotometrically at λ max considering this solvent as blank. K at 25°C was predicted from the Arrhenius plot and the date of expiration was determined (22).

**Statistical analysis**

The results experiments were expressed as a mean triplicate sample ± standard deviation (SD) and the analysis was done with the help of one-way analysis of variance (ANOVA) using SPSS software at which the results would be significant when p < 0.05, and the results would be non-significant if p> 0.05 (23). Difference factor (f1), similarity factors (f2) were also calculated to compare dissolution profiles, using DD Solver program. The difference factor (f1) measures the percent error between two curves over all time points. The similarity factor (f 2) was introduced by Moore and Flanner (24).

**Results and Discussion**

**Determination of risperidone saturation solubility**

The solubility study was performed in four different media, 0.1N HCl, phosphate buffer pH 6.8 methanol, and distilled water. Risperidone is a weak base with pKa value of 8.76 and expected to be more soluble in an acidic medium of about 1.3 mg/mL. In contrast, risperidone solubility in phosphate buffer was very low with a solubility value of 0.61mg/mL. risperidone was soluble in organic solvent(methanol) in 6.1mg/mL. On the other hand, the water solubility of risperidone was the lowest at about 0.019 mg /mL which considered practically insoluble.

**Characterization of the prepared risperidone nanosuspension**

**Determination of the particle size and polydispersity index**

The estimated average particle size was in the range of (40.9 nm – 1286 nm) and were illustrated in Table (2). On the contrary, the PDI which measures the size distribution of the nanoparticles; were ranged from (0.1-0.62) depending on formulation variables, (0.1) indicating good uniformity, a monodisperse system in the particle size distribution of nanoparticles while (0.62) indicated polydisperse system.

**Effect of stirring speed of the anti-solvent system**

When the stirring was 300 rpm the process failed to nanosizing the stabilizer around the drug due to the stuffiest energy required to achieve the mixing. Besides that, high stirring speed (2000 rpm) not always favored due to high agitation with the formation of foams that separate drug particles from the vehicle medium which act as an obstacle in the preparation process, thus an optimum speed (1000 rpm)is required to have optimum drug particles within the acceptable range (25).

**Effect of solvent/antisolvent ratio**

The results illustrated in Figure (2). It can be seen that when the ratio increases between the solvent and water increase particle size due to decrease the quality of mixing of media because of the decrease in specific stirrer speed to the solution that need to nucleation causing growth formation and increase flocculation (26). Increase in water volume decrease stabilizer in water leading to decrease stabilization and increase particle size. Formulas from F5to F12 were significant differences (p<0.05) in particle size and PDI of these formulas.
Table 2. Particle size, polydispersity index, and E.E. of formulas from 28 formula data are expressed as Mean ± SD, p <0.05. Standard deviation (SD) (mean±SD) n=3.

<table>
<thead>
<tr>
<th>Formula</th>
<th>Particle Size (nm)</th>
<th>PDI</th>
<th>E.E, Zeta potential</th>
<th>Particle Size (nm)</th>
<th>PDI</th>
<th>E.E%</th>
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<td>51.2</td>
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</table>

Figure 2. The effect of solvent/antisolvent on the particle size features on the prepared risperidone nanosuspension

**Effect of polymer type on particle size when using different solvents**

Acetone and ethanol were used in the preparation of nanosuspension in the formulas (F13-F20) and compared to the formulas prepared with methanol (F1, F2, F3, and F4). For acetone, as shown in Figure (3), the ratio of the drug to the stabilizer was fixed to a 1:1 ratio to study the effect of the type of the solvent. Formula F13 in which acetone was used as a solvent and soluplus as a stabilizer showed the smallest particle size among all formulations with other stabilizers within an optimum range of 40 nm and a PDI was 0.101 which indicate a good uniform particle size distribution. For formulas, F15 and F17 showed almost similar results of particle size 335 nm and 260 nm and a PDI of 0.34 and 0.32 which indicate almost homogenous particle size distribution. While F19 formula showed a bigger particle size of 502 nm and PDI of 0.308 which is similar to other formulas. This due to the strength of solvents polarity, where the acetone considered less polar and best miscible with water than methanol or ethanol, So risperidone highly solubility in acetone (27). Compared with other solvents (methanol, ethanol) that gave a good miscibility degree to a solvent carry the drug and facilitate diffusion when mixed by dripping with antisolvent media that contain a stabilizer leading to the formation of highly stabilizing nanosuspension by reducing the surface energy of the fine particles and effective energy barrier to prevent agglomeration and crystal growth. Besides, there is a fact that the soluplus is soluble up to (50%, 45%, and 25%) than water in acetone methanol and...
ethanol consecutively, where the process of precipitation method and before the solvent was evaporated the solvent could be contributed by made complete dissolved miscible component whether it was the drug or the stabilizer (28).

**Figure 3. Effect of polymer type when using acetone on particle size for F13, F15, F17, and F19**

For methanol as a solvent result in Figure (4) showed that formulas F1 and F2 showed particle sizes of 51 nm and 77.8 nm respectively but the F2 formula showed more uniform particle size distribution with PDI of 0.17. Formulas F3 and F4 presented a similar pattern of particle size and their distribution form of 233.5 nm and 245.5 nm respectively, and a PDI was 0.353 and 0.465 respectively. These results indicate similar superiority in using both stabilizers soluplus and PVP k30.

**Figure 4. Effect of polymer type when using methanol on the particle size of F1, F2, F3, and F4**

For ethanol as a solvent, results are shown in Figure (5). F14 formula where soluplus used showed the smallest significant particle size of 92 nm (P<0.05) and provided a uniform particle size distribution within the formulation with a PDI of 0.101. While F16 formula where PVP K30 was used presented particle size 160.3 nm with almost a uniform homogenous size distribution with PDI of 0.34. Formulas F18 and F20 showed about the same results when used poloxamer 188 and poloxamer 407 with a particle size of 450 nm with PDI of 0.36 and 490 nm with PDI of 0.32 respectively.
**Risperidone nanosuspension**

**In – vitro drug release study**

The dissolution profile of the prepared risperidone nanosuspension formulas is illustrated in Figure (6). The results showed a significant increase in the dissolution rate of the risperidone nanosuspension formulas which reach 100% release within 45 min when compared to the pure drug that reached 56% release within the same time frame. Also, the F13 formula presented the fastest complete release within 35 min, while pure drug showed the slowest incomplete release profile within the specified time.

To validate these findings, the fit factors have been used and expressed by two factors; \( f_1 \) the difference factor, and \( f_2 \) the similarity factor. For two dissolution profiles to be considered similar and bioequivalent, \( f_1 \) should be between 0 to 15 whereas, \( f_2 \) should be in the range of 50 to 100.

The similarity between F13 of the best release profile with the pure drug release profile showed the similarity value (\( f_2 \)) was 23.7 which is less than 50 which indicates a significant improvement in the release behavior. Also, the difference factor value was 84.2 which confirmed the previous similarity test results and conclude the greater and faster release pattern of the best formula F13.

F13 formula was selected to investigate the best release profile in two different mediums 0.1N HCl and 6.8 phosphates and the comparison was shown in Figure (7). It can be seen that the F13 formula showed a faster release profile in 0.1N HCl than phosphate buffer pH 6.8. In terms of validation, the similarity and difference factors were calculated and provided that, the similarity factor obtained was equal to 26.7 and the difference factor was equal to 84.4. According to these data results, 0.1N HCl is considered the best medium for drug release of the selected F13 formula. This comparison in similarity and difference factor were significantly improved.

**Selection of the best formula**

According to the previous results of all required tests of particle size determination, polydispersity index, entrapment efficiency and *in vitro* drug release it can be concluded that the F13 nanosuspension formula was the best formula with the smallest particle size of 40.9 nm and PDI value of 0.101 and zeta potential -18 showed highest drug entrapment efficiency of about 98.7 which will be subjected for further characterization after lyophilization and converted to nanoparticle by determining zeta potential, powder x-ray properties, drug excipient compatibility, in vitro drug release after lyophilization by freeze-drying process.

**Solidification of risperidone nanosuspension by freeze-drying**

The selected optimized formula F13 was freeze-dried to obtain the powder form of the prepared nanosuspension, enhanced amorphization, and subjected for further studies of solubility and *in vitro* drug release.

**Characterization of the lyophilized selected formula**

**Self-dispersibility of freeze-dried powder in aqueous medium**

The selected F13 lyophilized powder was tested for self-dispersibility in aqueous media. The
powder was completely dispersed within seconds in the aqueous media. The dispersed formula was tested for the particle size and polydispersity index and the results showed that the particle size was 60.5 nm which is higher than the particle size of the same formula when it was nanosuspension and the PDI of the lyophilized powder was 0.115 which is also higher which was 0.101.

The Zeta potential of the lyophilized F13 formula showed -18.96 mv which is similar to the value obtained before lyophilization which indicates the robust formulation by the action of the selected polymer with risperidone drug particles and last durable after freeze-drying.

These results indicate that the lyophilized F13 formula provided an accepted effective property of the nanosuspension formula which makes it potential for further study.

**Solubility study of the selected lyophilized formula**

Solubility study done at three different media; water, 0.1N HCl, and phosphate buffer pH 6.8(all with 2% w/v Brij 35). The results illustrated in Figure (8) and showed risperidone water solubility has significantly increased by about 105 times when compared with the one before lyophilization. Risperidone showed higher solubility in 0.1N HCl that results in higher and faster drug release when compared to the pure drug about 13.5 folds these were responsible for the significantly enhanced (p<0.05) saturation solubility.

**In – vitro drug release study of the lyophilized selected formula**

The dissolution study of the selected lyophilized F13 formula was performed in 0.1N HCl with 2% w/v Brij35 and compared with the pure drug and the results presented in Figure (9). It can be seen that lyophilized F13 formula nanosuspension showed a very characteristic enhancement in drug release when compared to the pure drug with faster and complete drug release within 30 min when compared to the pure drug.

This advancement in drug release was confirmed by using the similarity factor and showed 27.4 ($f_2<50$) and the different factor was 83.6 ($f_1>50$) which is explained due to better dissolution characteristics which in turn theoretically will boost the dissolution and absorption rate of risperidone nanosuspension and eventually its bioavailability.

**Differential scanning calorimetry (DSC)**

Lyophilized F13 was selected to investigate the crystalline purity after lyophilization and the result is presented in Figure (10). The Figure shows a sharp peak at 170°C, and it is similar as reported and indicates the purity of the drug (29). On the other hand, an endothermic broad peak at 162°C is shown for the lyophilized risperidone. Broad endothermic peak is including lower in melting points, broadening, shifting, and reducing in intensities supported the suggestion of a reduction in the crystalline state of risperidone optimized formula with a significant increment in the amorphous state that formed in lyophilization (30).
X-ray powder diffraction (XRPD)

The diffractograms of pure drug and lyophilized F13 were shown in Figures (11) and (12), respectively. It can be seen that there is a significant change in the X-ray pattern after the preparation of the nanosuspension formulation. The pure drug showed high intense peaks at 14°, 15°, 19°, 21°, 22°, 23°, 24°, 33°, and 34° that indicates a high degree of crystallinity of the pure risperidone. Although, after the preparation of the lyophilized powder, laser intensity peaks are observed which indicates a significant change in the crystallinity nature of the drug to be more amorphous. It has been noted that the emergence of new peaks at 31°, 39°, and 43° are related to the mannitol that has been added to the lyophilized powder (31). These changes indicate higher stability of the prepared lyophilized powder with the enhancement of water wettability and dissolution profile (32).
Figure 12. XRD diffraction of the lyophilized F13

**Scanning electron microscopy (SEM)**

The SEM pictures are shown in Figures (13) and (14). The SEM of the pure powder showed coarse agglomerates of risperidone crystals that packed together forming larger particles. Lyophilized F13 showed a homogenous dispersion of small flake irregular particles within a nanosized range contributed to cryoprotectants employed in nanoparticles where the freeze-drying process could influence the morphology. The surface area of nanoparticles affects dissolution. The larger surface area could increase the dissolution rate of nanoparticles \(^{(33)}\).

Figure 13. SEM of risperidone pure powder
Stability study of the selected F13 lyophilized powder

The prepared risperidone lyophilized powder was investigated for stability study at three accelerated temperatures 40°C, 50°C, and 60°C for 16 consecutive weeks. The F13 lyophilized powder was subjected to the study and the results are illustrated in Figure (15).

Table 3. The degradation constant of the selected formula f13 lyophilized powder

<table>
<thead>
<tr>
<th>Temperature in °C</th>
<th>K(week⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 °C</td>
<td>1.84 x 10⁻³</td>
</tr>
<tr>
<td>50 °C</td>
<td>3.454 x 10⁻³</td>
</tr>
<tr>
<td>60 °C</td>
<td>7.83 x 10⁻³</td>
</tr>
</tbody>
</table>

The degradation constant was calculated through constructing Arrhenius plot as shown in Figure (16). T90% was determined according to the previously mentioned equation and found to be 205.09 weeks that equal to 3.9 years.
Conclusions
The solvent antisolvent-precipitation method is effective, easy to operate, and less cost. Nanosuspension is a promising approach to improve the solubility, dissolution rate. Risperidone nanoparticle was successfully prepared using soluplus as a stabilizer at ratios (1:1) using acetone as a solvent that gave a higher in-vitro release profiles compared to pure drug powder with an expiration date of about to 4 years for self-dispersible dry nanoparticles. The conclusion was that the formulation of risperidone nanosuspension can improve solubility and dissolution and might improve bioavailability.

References