Original Article

Formulation and evaluation of maline based solid super-saturable self-emulsifying drug delivery system for risperidone

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Abstract

Objective: Solid super-saturable self-emulsifying drug delivery system of risperidone was formulated utilizing maline; a type of a deep eutectic choline based ionic liquid (DEIL), as oil phase in order to enhance the drug's solubility, dissolution, and intestinal penetration, and therefore its bioavailability.

Method: Maline was prepared using 1:1 molar ratio choline chloride and malonic acid. The SEDDs was formulated using maline as oil phase, tween80 or tween 20 as surfactant, and PEG600 or PG as co-surfactant in comparsion to conventional one using oleic acid as oil phase. Soluplus was utilized as drug precipitation inhibitor. For SEDDs solidification Aerosil 200 adsorbant was used as a carrier.

Results: The mean droplet size of the optimized formulation 210.3 nm with polydispersity of 0.357, zeta potential -3.47, drug content 100.21±0.47%. The optimum solid supersaturable SEDDs formula (SSM) showed excellent flow properties with Carr's Index of 8.77%, Hausner ratio of 1.09, and angle of repose at 38.72○. The FTIR, DSC and XRD results showed a good drug excipient compatability.Ex vivo permeation test on isolated sheap intestine revealed an inhancement in the risperidone amount permeated from the optimum formulation comparable to that of the pure drug and marketed tablet and even the conventional solid S-SEDDs formula.

Conclusion: The developed Maline based solid super-saturable self-emulsifying drug delivery system of risperidone can be considered as an innovative, economically feasible alternative to existing risperidone formulations and a promising method for enhancing the oral bioavailability of poor soluble drugs.

Keywords: Solid supersaturable self-emulsifying drug delivery system (Solid s-SEDDs), Deep-eutectic solvents (DES), Ionic liquids (ILs), Maline (M), choline chloride (ChCl), Malonic acid (M.A).

INTRODUCTION

Maline is a type of a deep eutectic choline based ionic liquid (DEIL) [1]. DES is a new generation of green solvents related to ionic liquids (ILs) characterized by considerable depressions in melting points compared to those of the pure constituents and has been recognized as an ideal substitute for organic solvents and ionic liquids (ILs)[2]. These DES has the distinctive properties of ILs including low volatility, high thermal and chemical stability, non-inflammability and conductivity.[3,4]

In DES, strong hydrogen bond interactions occur between a hydrogen bond acceptor (HBA) and hydrogen bond donor (HBD) with no chemical reactions occurring.[5] In case of maline, the choline chloride acts as hydrogen bond acceptor and malonic acid as hydrogen bond donor with 1:1 mloar ratio.[6]

The self emulsifying drug delivery systems (SEDDS) are complex lipid-based drug delivery systems containing a combination of drug, lipids (natural/synthetic oil), and surfactant/co-surfactant. These systems are often self-dispersing, allowing them to produce fine oil-in-water (O/W) emulsions with minimal agitation after dilution with an aqueous medium or gentle agitation induced by gastrointestinal motility in vivo.[7] Self-emulsifying drug delivery system (SEDDS) improves solubility and oral bioavailability of the incorporated drug with poor biopharmaceutical properties, as the small globules produced increase the interfacial area of a number of drugs by stimulating lymphatic transport and bypassing the metabolism of the first step. The SEDDS typically produces emulsion with a droplet size above 300 nm, however it may be vary from coarse to micron size that form transparent microemulsion with a droplet size of 100-250 nm, or even nano size that contain low quantity of surfactants with droplet size below 100 nm resulting in physically stable formulations comparing to the emulsions, which are sensitive

and metastable dispersed forms.[8]

Since the use of surfactant in SEDDS preparation is vital and usually used in high concentration (may need up to 60%) this may trigger local irritation in the gastrointestinal tract as well as moderate reversible alterations in the intestinal membrane, altering its permeability. Therefore, a super-saturable SEDD(S-SEDD) is preferably prepared in order to reduce the amount of surfactant along with the use of a polymeric precipitation inhibitor that stabilizes the drug supersaturated.[9]

The liquid SEDDS extensive application is challenging due to the inability to maintain stability during handling or storage as well as irreversible precipitation of drug or excipient[7]. To overcome these limitations, solid self-emulsifying drug delivery systems or solid supersaturable SEDDS have been developed. These systems are composed of powders converted from conventional liquid SEDDS that are then filled in capsules or formulated as solid dosage forms.[10]

The model drug Risperidone (RSD) is a class II BSC (low soluble /highly permeable) which is a psychotropic benzisoxazole derivative; approved by the United States Food and Drug Administration for schizophrenia treatment, bipolar disorder and irritability in children and adolescents ages. It is a selective monoaminergic antagonist, that is practically water insoluble, soluble in methanol and exhibits a pH dependent solubility.[11]

The aim of this work is utilizing maline (choline chloride based deep eutectic ionic liquid with malonic acid prepared in our laboratory) to prepare solid super saturable self-emulsifying drug delivery system that may enhance the solubility of the low water soluble drug risperidone hence enhancing its absorption and oral bioavailability leading to reduction of its dose and side effects.

Materials:

Choline chloride, Malonic, Risperidone and Areosil 200 were purchased from Hangzhou Hyper chemicals, China. Methanol, Propylene glycol, PEG 6000 and HCL were purchased from Thomas Baker, India. Oleic acid from Gainlind Chemical Comban, UK. Soluplus was purchased from BASF, Switzerland. Tween 20 and 80 from Central Drug House, India

Methods:

liquid self-emulsifying drug delivery (SEDD) preparation:

The preparation of liquid self-emulsifying drug delivery (SEDD) formulations of risperidone involved mixing 2mg of risperidone with our previously prepared maline[12] or oleic acid as oil phase, Smix of tween 80 or 20 as surfactant and propylene glycol or PEG600 as co-surfactant to prepare one milliliter formula in a screw-capped glass vial by using a vortex mixer and heating up to 40°C for 30 min in a water bath to facilitate homogenization. Then the formula cooled to room temperature[11].

Four formulas were prepared, two of them using oil:Smix ratio (1:9) with tween80 : propylene glycol (Smix) ratios (1:1), and the other two formulas using oil:Smix ratio (1:9) with tween20 : PEG600(Smix) ratios (1:1) (table1).

Table 1: Contents of the prepared liquid SEDD of risperidone:

Formula name	Oil:Smix ratio	Oil phase %	Surfactant %	Co-surfactant %	Smix ratio
LT1	1:9	Oleic acid 10%	Tween20 72%	PEG600 18%	1:4
LT2	1:9	Oleic acid 10%	Tween80 45%	PG 45%	1:1
LM1	1:9	Maline 10%	Tween20 72%	PEG600 18%	1:4
LM2	1:9	Maline 10%	Tween80 45%	PG 45%	1:1

Characterization and evaluation of the prepared risperidone liquid SEDD

I. The physical properties evaluation

a) Self emulsification time:

Using USP type II dissolution apparatus, the period of time needed to complete self-emulsification for all created liquid SEDDs formulae of risperidone (LT1, LT2, LM1 and LM2) was evaluated. 1 mL of each formulation was added to 500 mL of 0.1N HCl, pH 1.2, at 37°C with moderate stirring at 50 rpm until a clear, homogeneous phase was visually detected. According to the statistics presented in table 2, 1 minute is regarded to be the optimal formation time for transparent SEDD [13,14].

Table 2: Dispersibility test grading[14]

Grade	Appearance
A	Rapid forming emulsion (within 1 min), which appears to be clear and transparent.
B	Rapidly forming emulsion with slight less clear emulsion which has bluish appearance.
C	Emulsion is bright white or grayish white with a slight greasy appearance that is slow to emulsify.
D	Exhibit inadequate or little emulsification, resulting in the presence of large oil droplets on the surface.

Light transmittance:

The transmittance of light through each of the prepared liquid SEDD formulas (LT1, LT2, LM1 and LM2) was measured by taking 3mL from its dissolution medium and analyzed with UV- visible spectrophotometer at 650nm wavelength[15].

Measurement of droplet size distribution and polydispersity index

For the liquid SEDD formulas (LT1, LT2, LM1 and LM2), the particle size analyzer ABT-9000 nanolaser was used to evaluate the particle size distribution and polydispersity index (PDI). The lower the value of (PDI), the greater the droplet size homogeneity within the formulation[16].

Measurement of Zeta potential

Liquid SEDD formulations (LT1, LT2, LM1 and LM2) were evaluated using a zeta potential analyzer device (nano brook zeta plus). Typically, particles with +30mv or -30mv were regarded stable.[17]

Drug content determination

The drug content of the formulations (LT1, LT2, LM1 and LM2) was determined by adding 1 mL of each formula to 100 mL of methanol and vortexing the mixture for 5 minutes[13]. Samples were filtered through a 0.45 m filter media, and analyzed by HPLC at 280nm[18].

Thermodynamic study

1. Centrifugation Test

The liquid SEDDS formulations (LT1, LT2, LM1 and LM2) were centrifuged at 3000 rpm for 20 minutes and phase separation, creaming, and cracking were observed. The formulations that passed the centrifugation test will be subjected to another thermodynamic test.

2. Heating/Cooling Cycles Test

The formulations (LT1, LT2, LM1 and LM2) were kept at 40 degrees Celsius for 48 hours, then chilled at 4 degrees Celsius for another 48 hours (this cycle was repeated for three times). The test was conducted to determine the influence of aging on the stability of formulations.

3. Freezing/ Thawing Cycles Test

The formulations (LT1, LT2, LM1 and LM2) were frozen (-20○C) overnight and then maintained at 25 ○C (to be melted). This provides additional confirmation for thermodynamic stability of the produced liquid SEDD formulations[19].

Dilution test:

One milliliter of each of the generated liquid SEDD formulations (LT1, LT2, LM1 and LM2) was diluted to 100 mL with 0.1N HCl, phosphate buffer 6.8 and water, and then to 1,000 mL (each dissolution medium separately). After being diluted, the product was kept overnight to check for any indications of drug precipitation or phase separation.[20]

In vitro drug release study of risperidone liquid SEDDS:

In 900 mL of 0.1N HCl containing 0.1% w/w SLS, the in vitro release of liquid SEDDS formulations (LT1, LT2, LM1 and LM2) was evaluated. The temperature was maintained at 37 degrees Celsius using USP dissolution apparatus II rotating at 75 rpm. At predefined intervals of 5, 10, 20, 30, and 60 minutes, a 5 mL aliquot was withdrawn and replaced with a new dissolving media in order to maintain sink condition[13,17]. The aliquot was filtered using a 0.45m filter membrane, and the drug concentration was analyzed by HPLC[21]. The analysis was performed using a Shimadzu HPLC and a C18 (250mm×4.6 mm, 5µm) column. The mobile phase was 130mm ammonium acetate: methanol: acetonitrile (40:20:40) with flow rate of 1.2 ml/min, and the wavelength of the UV detector was at 280 nm[22].

Risperidone liquid supersaturable self-emulsifying formulas (liquid S-SEDD) preparation :

The liquid supersaturable formulae (S-SEDD) were developed from the liquid SEDD formulas (LT1, LT2, LM1 and LM2) by applying a precipitation inhibitor (soluplus).The preparation method include combining soluplus (with percentage of 2.5 and 5%) and 2mg risperidone in a mortar for 5 minutes. Then, this mixture was added to 0.25 milliliter homogenous mixture of (10% oleic acid or maline,45% tween 80 , 45% propylene glycol) or (10% oleic acid or maline, 72% tween20, 18% PEG 600), which is one forth (1/4) the contents of each of the liquid SEDD formula and vortexed at 40˚C until a clear liquid was achieved[23]. Eight liquid supersaturable formulas (S-SEDD) were prepared (Table 3).The SEDD formula (LM1) not succeeded to convert to supersaturable formula using 5% soluplus (LSM1 5%). Therefore, only seven formulas of the liquid SEDD succeeded to change to the supersaturable formula.

Table 3: liquid supersaturable self-emulsifying formula of risperidone

Formula no.	Content of	Soluplus %
LST1 2.5%	Liquid SEDD formula LT1	2.5
LST1 5%	Liquid SEDD formula LT1	5
LST2 2.5%	Liquid SEDD formula LT2	2.5
LST2 5%	Liquid SEDD formula LT2	5
LSM1 2.5%	Liquid SEDD formula LM1	2.5
LSM1 5%	Liquid SEDD formula LM1	5 (failed)
LSM2 2.5%	Liquid SEDD formula LM2	2.5
LSM2 5%	Liquid SEDD formula LM2	5

In vitro dissolution study for risperidone liquid supersaturable formulas (liquid S-SEDD):

Each of the prepared risperidone liquid supersaturable formulas were encapsulated in zero sized hard gelatin capsule and placed in a dissolution vessel of USP dissolution apparatus II (Paddle) containing 100 ml of 0.1N HCl for two hours , at 37○C and rotation speed 75 rpm. Then repeat the process in phosphate buffer pH 6.8 for 3 hours, at 37○C and rotation speed 75 rpm[24,25]. Five milliliters samples were withdrawn from the test medium without volume replenishing at (5, 10, 15, 30, 60, 30, 45, 60) min, 2 hrs, and 3 hrs, then filtered using 0.45um filter and analyzed using HPLC. The formulas gave the acceptable release were chosen for further work.

Risperidone solid supersaturable self-emulsifying drug delivery (solid S-SEDD) Preparation:

Risperidone solid supersaturable self-emulsifying formulations (solid S-SEDD) were formed by incorporating 0.25ml of each selected liquid supersaturable formulae which were chosen according to in vitro dissolution profile (LST1 2.5% and LSM2 2.5%) with gradual amount of the adsorbent (Aerosil 200) using mortar and pestle for 10 min until a free flow powder is obtained(table 4). The formed mixture was placed in the oven at 40°C for 12 hours to complete drying[26].

Table 4: Solid supersaturable self-emulsifying drug delivery system of risperidone:

Formula no.	Content of	Aerosil200
SSM	Liquid supersaturable SEDD formula LSM2 2.5%	500 mg
SST	Liquid supersaturable SEDD formula LST1 2.5%	1000 mg

Evaluation of the powder properties for the prepared solid supersaturable formulas (solid S-SEDD) of risperidone:

a) Angle of repose measurement:

The angle of repose of powder blend (SST and SSM) formulations was estimated using the fixed funnel method, with the funnel positioned approximately 2 cm above a horizontally set circular sheet of paper. The powder was poured down the funnel until the funnel's peak nearly touched the funnel's end[26]. Then, the powder cone diameter was measured, and from the following equation the angle of repose was calculated:

$\tan \theta = h/r$

Where: h = powder cone height; and r = powder cone radius.

b) (Carr's Index) Compressibility index and Hausner ratio:

These indices were calculated by determining the unsettled apparent bulk volume of a 2 g sample contained in a 10 mL measuring cylinder, followed by measuring the powder's final tapped volume after tapping the material until no more volume reduction occurred, as they will be used further for bulk density and tapped density calculation respectively[19]. The compressibility index (Carr's index), Hausner ratio and flow property expression of a powder are shown in Table 5 which are calculated as follows[27]:

$$\text{Bulk density (BD)} = \frac{powder\ blend\ weight}{powder\ blend\ bulk\ volume}$$

$$\text{Tapped density (TD)} = \frac{powder\ blend\ weight}{powder\ blend\ tapped\ volume}$$

$$\text{Hausner's ratio} = \frac{tapped\ density}{bulk\ density}$$

$$\text{Carr's index} = \frac{(tapped\ density - bulk\ density)\ X\ 100}{tapped\ density}$$

Table 5: Carr's Index, Hausner's Ratio, angle of repose and the corresponding flow property expression for powder:

Flowability	Carr's index (%)	Hausner ratio	Angle of repose (º)
Excellent	10	1.00–1.11	25–30
Good	11–15	1.12–1.18	31–35
Fair—aid not needed	16–20	1.19–1.25	36–40
Passable—may hang up	21–25	1.26–1.34	41–45
Poor—must agitate, vibrate	26–31	1.35–1.45	46–55
Very poor	32–37	1.46–1.59	56–65
Very, very poor	>38	>1.60	>66

In-vitro dissolution test for the prepared solid supersaturable self-emulsifying drug delivery system (solid S-SEDDs)

To determine which formula gives satisfactory drug release profile, the in vitro dissolution test was performed applying the same procedure described earlier.

Drug excipients compatibility:

a) FTIR Spectroscopy

The selected solid S-SEDD formula (SSM) that passed powder evaluation successfully was combined with potassium bromide and pressed into a disc shape. FTIR spectroscopy was used to investigate the disc (at a range of 4000 cm-1 to 400 cm-1)[19]

b) Differential scanning calorimetry (DSC):

The solid S-SEDD formula (SSM) was evaluated by DSC technique. The procedure involves placing the solid sample in tightly sealed aluminum pans and raising the temperature in the range of 0°C to 300°C at a rate of 20˚C/min in DSC instrument[11].

c) X-ray powder diffractometry analysis:

Powder X-ray diffractometer was used to evaluate the diffraction of X-rays from risperidone powder, solid S-SEDD formula powder (SSM), and physical mixtures of the formula component in the range 10–70° (2θ), at 40 (kV) voltage and 30 (mA) current[28].

Ex-vivo permeation test:

This study was conducted using Franz cell system and the small intestine of young male sheep. The intestine was excised, cleaned, and socked in PBS (pH 7.4) at 5 ±3○C for 12h, then, 3×3 cm pieces were cut, mounted on the Franz cells glass ring, and trimming the remaining corners. The intestine segment was positioned between the receptor and donor compartments, with the basal surface in touch with the receiving media and the apical surface in contact with the donor chamber. Receptor compartment contained 15 ml of PBS pH 7.4, while donor compartment was filled with certain amount of each powder formula equivalent to 2mg of risperidone dissolved in 1 ml of PBS pH 7.4. The cell contents was stirred using magnetic stirr bar at 700 rpm and 37 ±1○C. Aliquots of 3 ml were withdrawn at regular intervals (15 min, 30 min, 60 min, 90 min, 120min, 3hrs, 4hrs,5hrs and 6hrs)and replaced with equivalent amount of fresh medium[29,30].

The amount of drug permeated was quantified using UV visible spectrophotometric method at 280nm[31]. The cumulative amount of the drug was plotted against time to calculate the percentage of the dose permeated. The test was conducted for marketed risperidone, SSM (tested formula containing maline), SST (conventional formula containing oleic acid), risperidone dissolved in maline, and pure risperidone powder.

Results and discussion:

Preparation of liquid self-emulsifying drug delivery (SEDD):

From our previous study[12]; best maline deep eutectic ionic liquid was prepared using choline chloride: malonic acid 1:1 molar ratio. This maline was able to dissolve risperidone and succeeded to remain liquid at room temperature. Maline was used (as an oil phase) to prepare two formulas of liquid SEDDs for risperidone using oil; Smix ratio (1:9) and two Smix ratio (1:1) including tween 80: propylene glycol as well as tween 20:PEG600. These maline containing liquid SEDD were evaluated in comparison to two conventionally prepared liquid SEDD using oleic acid (as oil phase) and same oil: Smix ratio in addition to similar Smix ratio.

Evaluation of prepared risperidone liquid SEDD

I. Evaluation of the physical properties

a) Self-emulsification time:

The ability of efficient self-emulsification is crucial for SEDDS because the emulsification process is considered to be the rate-limiting step for drug absorption. This efficiency could be estimated by measuring the rate of emulsification time, which was done by visual observation, with one minute as the maximum time for the emulsification process to complete, assuming a maximum of one minute to complete the emulsification process, the pace of emulsification relies on the degree of interfacial tension decline, phase transition, and surfactant concentration[32].

All the prepared liquid SEDD formulas are graded (A) in relation to their visual appearance passing successfully as shown in Table 6, where the formula (LM2) containing maline as oil phase tween 80 as surfactant and propylene glycol as a co-surfactant achieved the lowest time of emulsification in comparsion to conventional liquid SEDD (LT1 and LT2) attributing to the ability in reducing the interfacial tension and thus excess diffusion of the aqueous phase into the oil occurs, causing interfacial disruption and discharge of droplets into the bulk aqueous phase. Similar results was observed with Candesartan cilexetil prepared as liquid SEDDs [33].

It was also noticed that the increased surfactant (tween 20) to co-surfactant (PEG 600) ratio in formulas LT1 and LT2 caused a slowing down in the emulsification process. This could be due to reduction in the flexibility of interfacial film that would cause slow down emulsification process. Similar results observed in cilostazol SEDDs[34].

Table 6: Visual classification for the prepared liquid SEDD formulas

SEDDs formula	emulsifying time/ class
LT1	26sec /A
LT2	24 sec /A
LM1	20sec /A
LM2	8sec / A

b) Light transmittance:

From the test results (table 7), the formulation showed high percent transmittance, indicates the formulations were transparent. The observed transparency of the prepared liquid SEDDs is due to the fact that the maximum size of the droplets of the dispersed phase is not larger than 1/4th of the wavelength of visible light. Thus, emulsion scatters little light and therefore appears transparent or translucent. A value closer to 100% indicated the formulations' transparency and stability, indicating a high surface area for drug release [35].

Table 7: Light transmittance measurement of SEDDs formula

SEDDs formula	Light transmittance
LT1	100%
LT2	99.3%
LM1	98.9%
LM2	100%

c) Measurement of droplet size distribution and polydispersity index

The droplet size is a crucial factor in the self-emulsification performance of the emulsion as it determines the rate and extent of drug release as well as drug absorption[33]. It was noticed from the results (table 8) that the relative proportion of surfactant to co-surfactant has variable effects on the droplet size. LM1 formula showed lower droplet size comparable to LM2 formula justified to the presence of higher amount of surfactant in LM1 formula which causes an interfacial film to stabilize and condense as a result of the surfactant monolayers presence at the interface of the oil and water[36,20]. However, LT1formula showed larger droplet size than LT2 formula because the surfactant is at a super-saturated concentration, additional surfactant could not weaken the interfacial tension, rather form an independent large diameter micelle[37]. Similar results were observed in the prepared Lutein SNEDDS[38]. The relatively small oil globules existence in LT2 formula as well as LM2 formula could

be attributed to the high concentration of co-surfactant (45% propylene glycol) that lowered the droplet size to 167.8 and 210.3 respectively[39].

The polydispersity index (PDI) is a dimensionless number which indicates the droplet size distribution in the system. The closer to zero the PDI value is, the more homogeneous the particle population, whereas values more than 0.5 indicate greater heterogeneity[40]. All the prepared formulas showed PDI range from 0.315 to 0.429 indicating their clarity, good homogeneity, and stability.

Table 8: Droplet size, polydispersity index and zeta potential measurements of SEDDs formula

SEDDs formula	Droplet size (nm)	Polydispersity index	Zeta potential (mV)
LT1	540	0.429	25.40
LT2	167.8	0.315	28.96
LM1	170	0.327	35.64
LM2	210.3	0.357	-3.47

d) Zeta potential measurement

Generally the significance of zeta potential is related to the short and long term stability of emulsions. A zeta potential value of −30 mV to +30 mV is considered to have sufficient repulsive force to attain better physical colloidal stability [41]. Also, zeta potential has a significant impact in the interaction with the mucus of the gastrointestinal system; positively charged droplets may interact more favorably with the mucus of the gastrointestinal tract due to the presence of negatively charged mucosal fluid within the intestinal cells. Due of the slightly negative charge of the droplet, aggregations will not occur[17]. The zeta potential results (table 8) show the formula stability that was less prone to form aggregates or increase in particle size. However, the LM2 shows a negative charge, this may be due to the maline composition as the negative sign usually indicates that free fatty acids presents in oil droplet[42], and since the droplets have a smaller negative potential, they are probably facilitate the intestinal absorption[42].

e) Determination of drug content:

The Drug content in all liquid SEDD formulas was determined (table 9) and shows that all got high drug content due to the high drug solubility in the oil phase, surfactant, and co-surfactant, with the proper combination[35].

Table 9: The drug content of the liquid SEDDs formulas

SEDDs Formula	% of the drug content
LT1	88.69±0.56
LT2	108.92 ±0.23
LM1	95.73±0.539
LM2	100.21±0.47

f) Thermodynamic study

The thermodynamic studies have always helped to determine the kinetic stability of the formulation and are very important for its performance. The main criteria to pass these tests are not to show any indication of creaming, cracking, coalescence, or phase separation. All the prepared formulations(Table 10) had passed the test, with no signs of phase separation and precipitation of drugs indicating their stability against the maintained storage conditions and the efficiency of the method to obtain stable SEDDs[43].

Table 10: Thermodynamic tests for the liquid SEDDs formula

SEDDs Formula	Centrifugation test	Heating-cooling cycles test	Freeze-thawing cycles test
LT1	pass	pass	pass
LT2	pass	pass	pass
LM1	pass	pass	pass
LM2	pass	pass	pass

g) Dilution test:

The dilution test is carried out for liquid SEDD formulas to ensure that the generated emulsion has identical characteristics at different dilutions, therefore providing a consistent drug release profile, and ensuring that the drug will not precipitate at higher dilutions in-vivo, which might considerably hinder drug absorption[44]. All the prepared formulas showed no signs of phase separation or drug precipitation in all dilution series after 24 h storage. The findings demonstrated that dilution of liquid SEDD formulations did not alter the rigidity of the surfactants layer at the nano droplet interface and revealed the stable o/w

nano-emulsion production[34].

In vitro drug release study of risperidone liquid SEDD formulas:

The release profiles (figure1) of risperidone SEDD formulas (LT1,LT2, LM1 and LM2) showed an initial gradual release within the first 10 min and the release continued for 60 min. Formula LM2 containing maline as oil phase showed significantly ($P< 0.05$) higher release percentage than LT2 (containing oleic acid as oil phase) as maline lipophilicity is less than oleic acid and the higher oil phase lipophilicity leads to hinder the drug release due to the reduced thermodynamic activity of the drug in the vehicle containing the most lipophilic oil phase[45]. Also the amount of surfactant used (45% tween80 in LM2 and LT2, while 72% tween20 in LM1 and LT1) influence the drug release as the surfactant is required for the formation of the interfacial barrier, a reduction in the amount of surfactant leads to lower drug release[46]. Therefore LT2 showed lowest drug release.

LM1 showed lower drug release than LM2 because of the reduced amount of co-surfactant, that might cause reduction in the flexibility of the interfacial barrier film leading to decrease drug release[47]. Same results were observed in cilostazol SEDDS drug release profile[34].

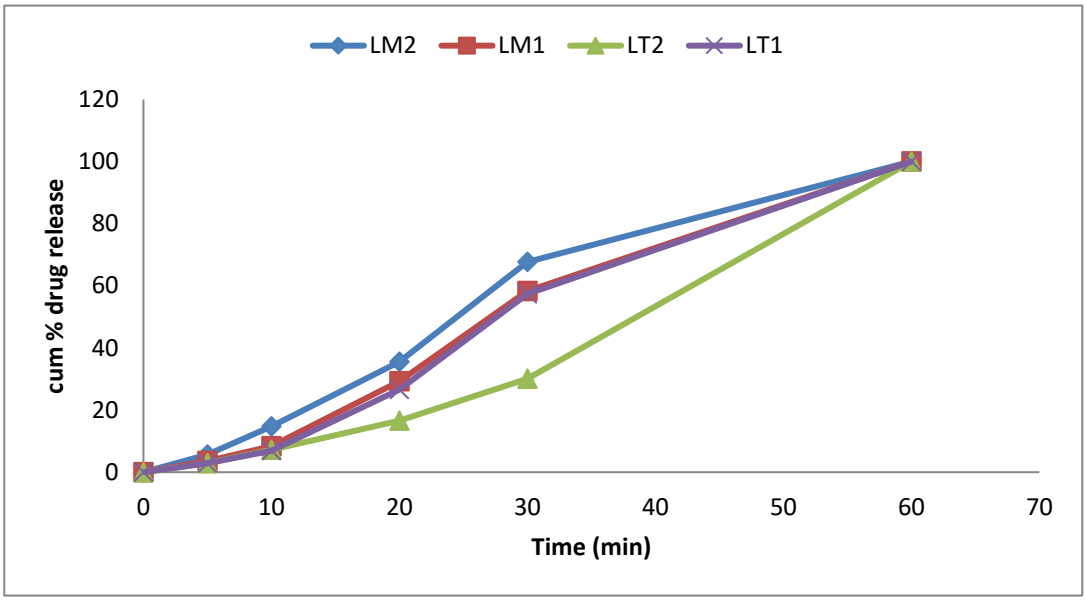

Figure 1: In vitro cumulative drug release of risperidone liquid SEDD in 0.1N HCl containing 0.1% SLS

Risperidone liquid supersaturable self-emulsifying formulas (liquid S-SEDD) preparation:

All the prepared formulas of risperidone liquid SEDD (LM2, LM1,LT2 and LT1) were prepared as super-saturable SEDD utilizing varied percentage of Soluplus as a precipitation inhibitor(2.5% and 5%) keeping the same contents but ¼ of their percentage in the formulas except the drug amount.

In vitro dissolution study for risperidone liquid supersaturable formulas (liquid S-SEDD):

The potential of soluplus to prevent risperidone precipitation from seven liquid supersaturable SEDD formulations was investigated under non-sink condition at pH 1.2 (using 0.1NHCl) for two hours and at PB pH 6.8 for 4 hours in order to achieve typical physiological pH conditions in GIT (fig 2). In pH 1.2; the formula LSM2 2.5%, LSM1 2.5% and LST1 2.5% exhibited a rapid initial peak release (>70%) during the first 30 minutes, demonstrating the rapid development of the self-microemulsion upon contact with the dissolution medium, while the other formulas showed delayed initial peak release in comparison to the former formulas which may be due to high formula viscosity[48].

The presence of soluplus enhanced the extent and rate of the drug release from the supersaturable SEDD formulas in comparison to liquid SEDD formulas which can be attribute to the polycaprolactam moiety of Soluplus, a hydrophobic compartment of an amphiphilic polymer, which may be incorporated and/or adsorbed into risperidone-loaded self-emulsifying droplets, forming a condensed structure, and the hydrophilic group of Soluplus, polyethylene glycol, which would provide sterical stabilization after dilution. The rate and extent of risperidone release decreased as the concentration of soluplus increased to 5% in formulas (LST1 5%, LSM2 5% and LST2 5%) because the soluplus amount exceeded the critical concentration at which the polymer forms its own micelle structure rather than being integrated into droplets or stabilizing nanoemulsion. Therefore, soluplus loose the packing of the interfacial layers leading to destabilizing risperidone loaded SEDD. These results were similar to tacrolimus supersaturable SEDD[23]. It is also the reason for the failure of the formula (LSM1 5%) to give supersaturation.

Risperidone release from the liquid supersaturable SEDD formulas containing soluplus showed pH independent profile in aspects of rate and extent in both media pH 1.2 and pH 6.8 indicating an improvement in the dissolution by producing nanosized dispersions [49].

From the obtained results formula LSM2 2.5% was chosen as the best liquid S-SEDD containing maline as well as formula LST1 2.5% was chosen as the best liquid S-SEDD prepared by the conventional way (containing oleic acid as an oil phase instead of maline).

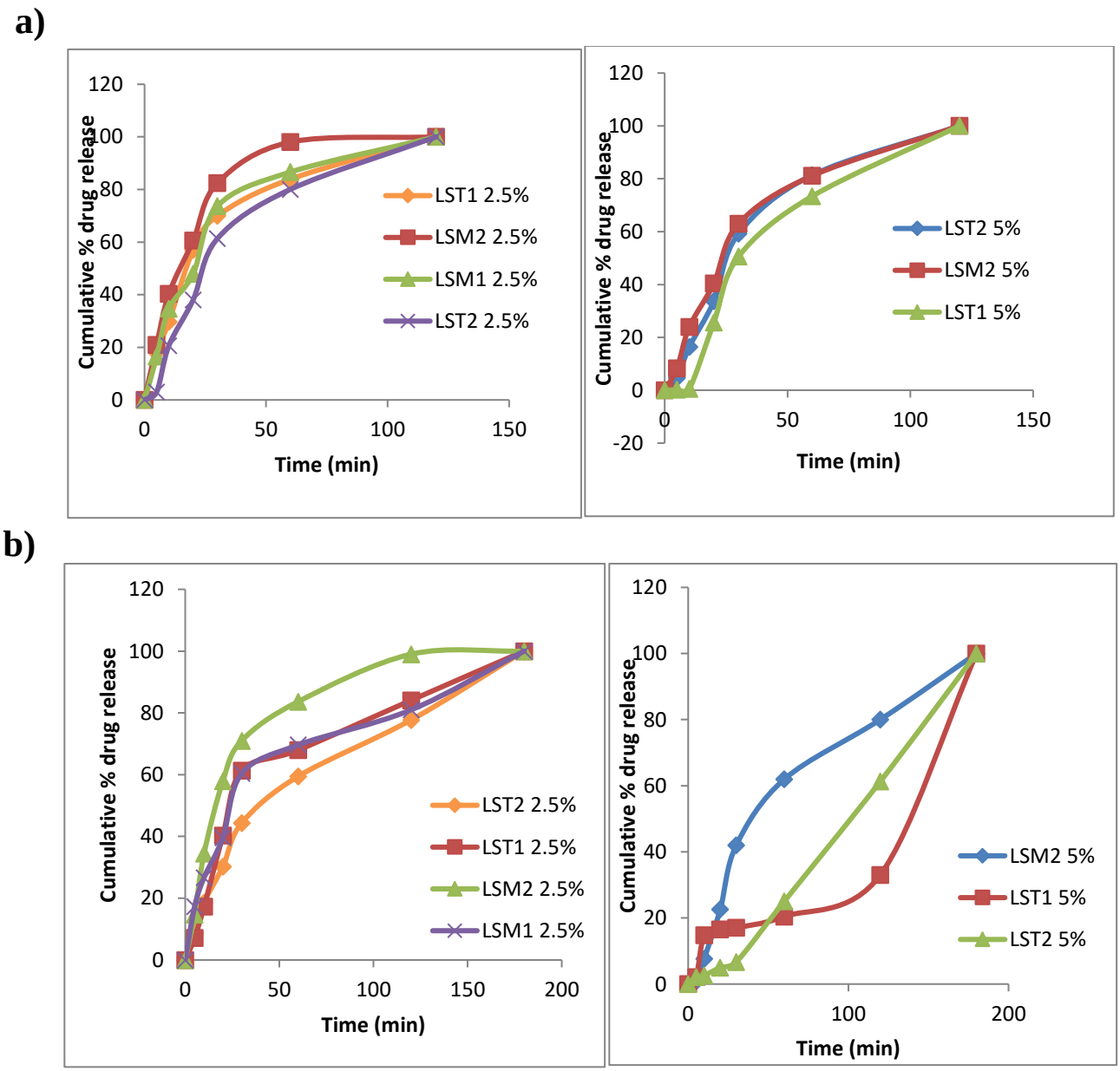

Figure 2: In vitro drug release of risperidone from liquid S-SEDDs containing soluplus (a) in 0.1N HCl and (b) in P.B pH 6.8.

Risperidone solid supersaturable self-emulsifying drug delivery (solid S-SEDD) Preparation:

Based on the in vitro drug release test results, the best liquid supersaturable formula (LSM2 2.5%) and the conventional formula (LST1 2.5%) were converted into solid supersaturable formula in order to improve stability as the solid dosage form is the most stable, convenient for handling and patient compliance, as well as overcoming limitations associated with the liquid SEDDs[50,7].The two formulas (LSM2 2.5% and LST1 2.5%)were converted to the solid S-SEDD by adding gradual amount of Aerosil 200 until showing a free flow powder. LSM2 2.5% formula needed 500mg while LST1 2.5% formula needed 1000mg

of Aerosil 200, this may be attributed to the high lipophilicity of oleic acid[51](oil phase in LST1 2.5% formula) that required double the amount of the adsorbent Aerosil 200 to change to free flowing powder (SST) therefore, the solid S-SEDD formula containing oleic acid (SST) required larger size of hard gelatin capsule to be incorporated in comparison to that containing maline (as an oil phase).

Evaluation of the flowability of the solid supersaturable formulas (solid S-SEDD) for risperidone:

Various micromeritics properties of solid S-SEDDs formulations were measured to evaluate the flowability characteristics of the resulted powder. The angle of repose, Carr's index and Hausner ratio were performed (table 11) for the two formulas and the solid S-SEDD formula containing maline (SSM) showed Carr's index 8.77%, Hausner ratio1.09 and angle of repose about 38.72º representing an excellent flowability and compressibility as its Hausner ratio is less than 1.25 and Carr's index within range of 5 to 18% considering it appropriate for the production of solid dosage form[52, 53]. While solid S-SEDD containing oleic acid (SST) showed Carr's index 33.5% , Hausner ratio1.5 and angle of repose about 43.6º suggesting passable flow properties[27], as the viscosity of oleic acid is higher than maline and required larger amount of Aerosil 200 so the SST formula particle size was larger and affect its flowability.

Table 11: Rheology parameters of the prepared solid SEDDs powder

Formula	Carr's Index	Flow character	Hausner ratio	Flow property	Angle of Repose	Flow property
SSM	8.77%	Excellent	1.09	Excellent	38.72º	Fair- aid not needed
SST	33.5%	Poor	1.5	Poor	43.6º	Passable-may hang up

In-vitro dissolution test:

The drug release form the prepared solid S-SEDD formulas was done by filling SSM and SST formulas each one separately in hard gelatin capsule(size 0 for SSM formula and 000 for SST formula) and placed in 0.1N HCl and phosphate buffer for 2hrs and 3hrs respectively. In pH 1.2 no difference in the drug release profile from the prepared solid S-SEDD containing maline (SSM) in comparison to its corresponding liquid S-SEDD (LSM2 2.5%), except that the liquid S-SEDD gave 80% release within 30min while SSM gave 80% release within 60 min.

Likewise, the prepared solid S-SEDD containing oleic acid (SST) reach 75% drug release within 60 min while its corresponding liquid S-SEDDS (formula LST1 2.5%) gave 75% drug release within 30 min. Same behavior was observed in pH 6.8 media for both formulas SST and SSM comparable to their corresponding liquid S-SEDD such delay may be attributed to the need of solid S-SEDD formula for more step such as desorption of the adsorbed Aerosil during dissolution process[54]. Also SST and SSM formulas gave similar dissolution in pH 1.2 while in pH 6.8 they gave identical dissolution in the first 30 min then SSM formula gave higher drug release than SST and both gave 100% release at the end of the experiment due to the presence of higher amount (double) of Aerosil in the SST.

Similar results were observed with solid SEDDs of azithromycin as well as with atorvastatin [54,55].

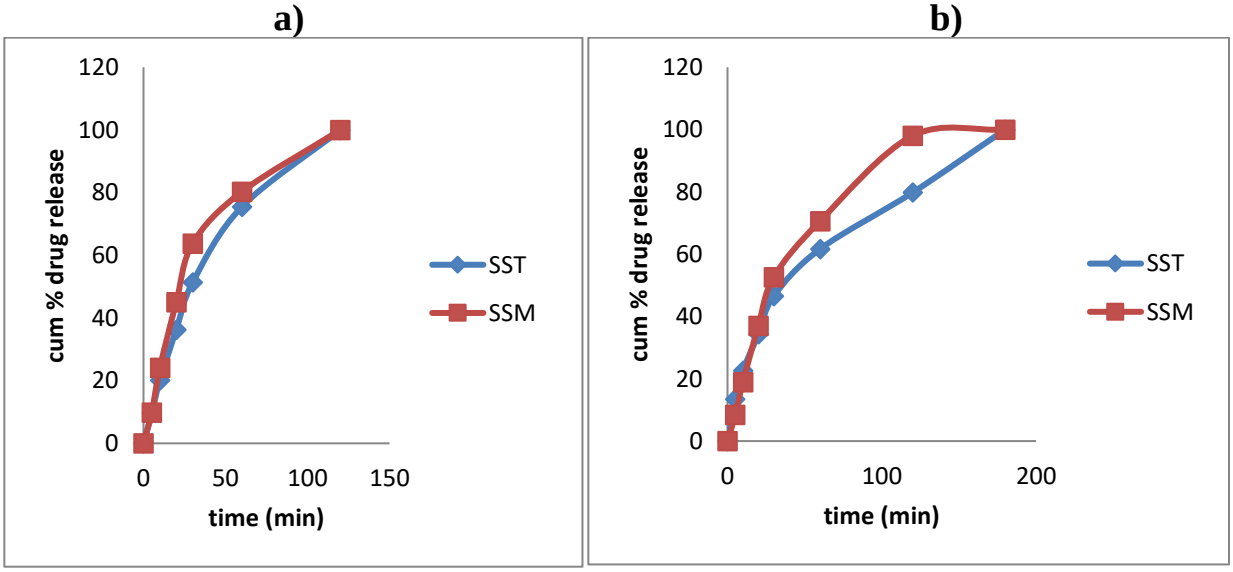

Figure 3: In vitro drug release of risperidone solid SEDDs in a) 0.1N HCl, b) phosphate buffer pH 6.8.

Drug excipients compatibility:

A. Drug excipients compatibility by FTIR Spectroscopy:

The FTIR spectra of risperidone, risperidone in maline, and SSM formula in figure 4 represented the main characteristic peak at 1651cm-1 related to the carbonyl group in its structure[18], which upon risperidone dissolution in maline shifted from 1651 to 1633cm-1 indicating the formation of hydrogen bonding between the maline and risperidone as was illustrated in our previous study[12].

The FTIR spectra of the SSM formula was investigated and compared to the risperidone dissolved in maline to confirm the chemical stability of drug structure and the absence of any change that could occur during the preparation of SEDDS and solidification process. The results showed the presence of all the stretching bands that was observed in the FTIR spectrum of risperidone with no major shifting or change of peaks, along with the absence of interfering peaks; indicating the compatibility between risperidone and the excipients[42].

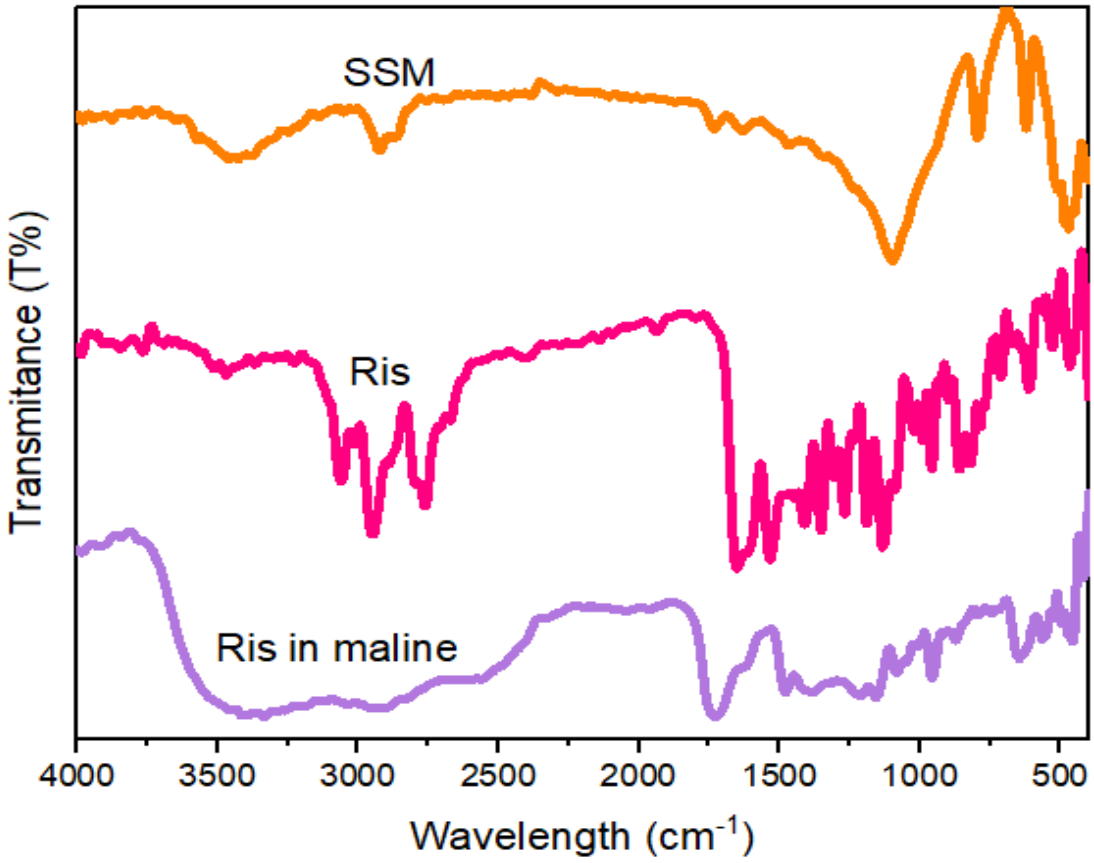

Figure 4: FTIR spectra of risperidone (Ris), risperidone in maline (Ris in maline) and the solid S-SEDD containing maline (SSM).

B. Differential scanning calorimetry (DSC):

The DSC thermogram of the pure risperidone showed a sharp endothermic peak at 170˚C corresponding to the drug melting point indicating the crystalline form of the drug[18]. A similar but less intense endothermic peak for risperidone was observed in the physical mixture suggesting a semi crystalline state. However, the SSM formula showed no endothermic peak at 170 ºC indicating the amorphous homogenous dispersion of risperidone in the formula and there is no crystallization of the drug[56]. The amorphous structure due to solubilizing effect of maline on risperidone which comply with the computational prediction described earlier.

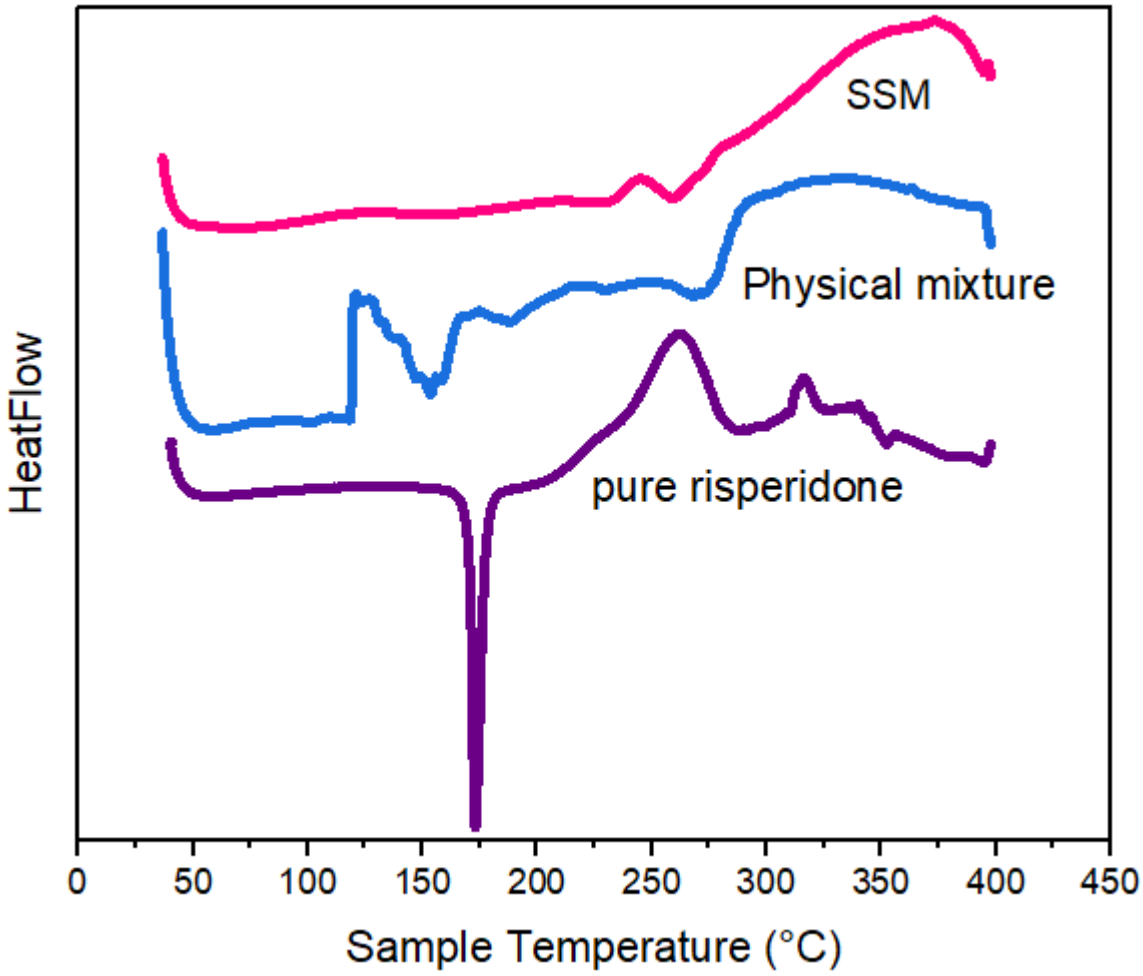

Figure 5: DSC thermogram of pure risperidone, SSM formula powder and the physical mixture of the content of SSM ormula.

X-ray powder diffractometry:

The X-ray diffractogram of pure risperidone powder (figure 6)showed sharp and intense peaks (crystalline state) for the pure drug at a range of scattering angle from 10 to 21◦ (2θ) [18], while the diffraction pattern of SSM formula showed the absence of these peaks indicating the amorphous homogenous dispersion of risperidone in the formula and no crystallization of the drug. The physical mixture of the formula represents less intense peaks indicating a semi crystalline state[11,57].

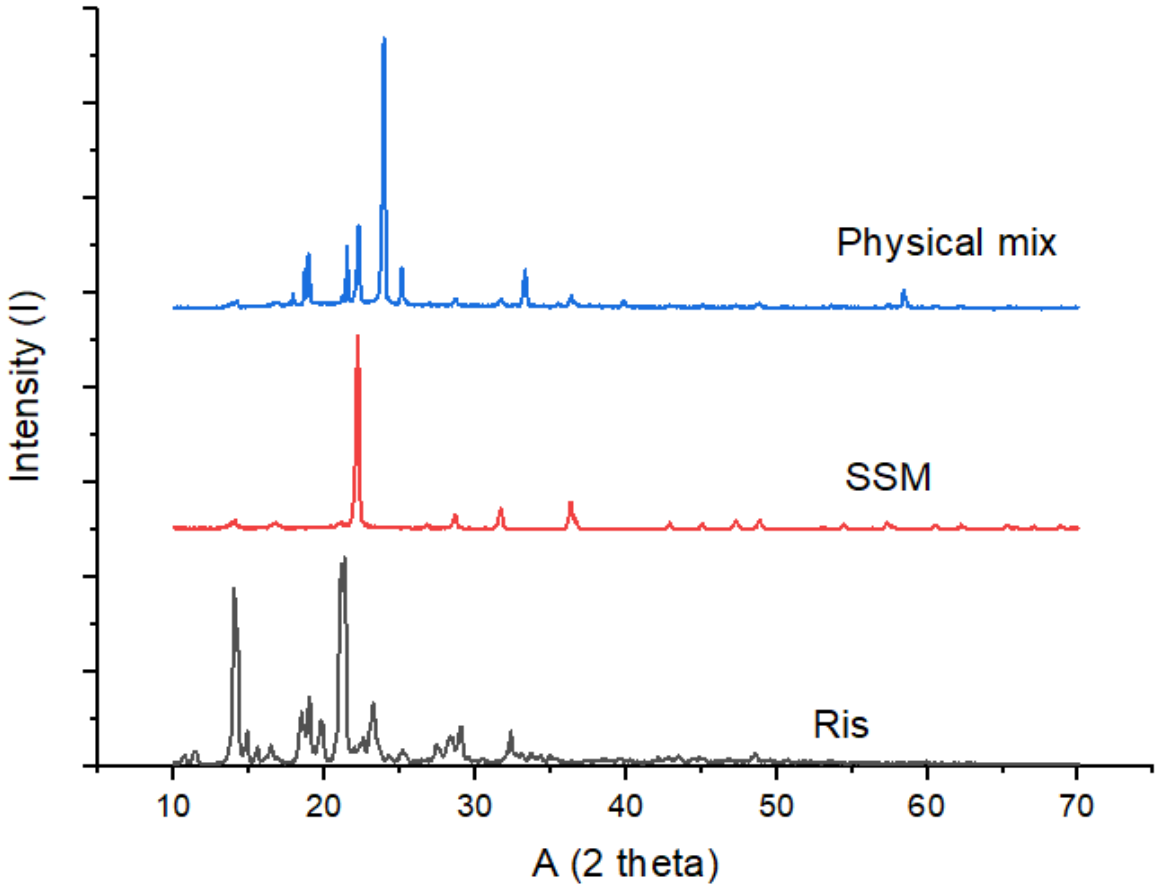

Figure 6: X-Ray diffraction of pure risperidone, SSM formula powder, and physical mixture of the SSM formula.

Ex-vivo permeation test:

The test was conducted for marketed risperidone tablet, SSM (maline containing formula), SST (conventional formula), risperidone dissolved in maline, and pure risperidone powder.

The results (figure 7) shows that the drug diffuses freely from SSM formula and the cumulative amount of risperidone permeated was 130.2µg within 6hrs, which is significantly ($P<0.05$) higher than the cumulative amount of risperidone permeated from conventional formula (SST) which was 99.5 µg, while the marketed formulation and risperidone dissolved in maline gave 86.1, 62.8µg, and the lowest permeation was for pure risperidone (27.9 µg).

From the results it was observed that the intestinal permeability of the SSM formula was significantly enhanced compared to the pure drug ($P<0.05$), as it was found that the optimized formulation SSM showed around 97.9% permeation percentage compared to pure risperidone with only 45% and 86.1% for marketed risperidone.The permeation enhancement was attributed to the solubilization effect of maline in addition to small droplet size that permits easy access through epithelial cells. Also, the presence of surfactant, co-surfactant which fluidize the intercellular lipid bilayer, leading to better membrane contact and improving the partitioning of the drug into the membrane[58,29]. The pure drug showed the lowest permeation due to its poor solubility.

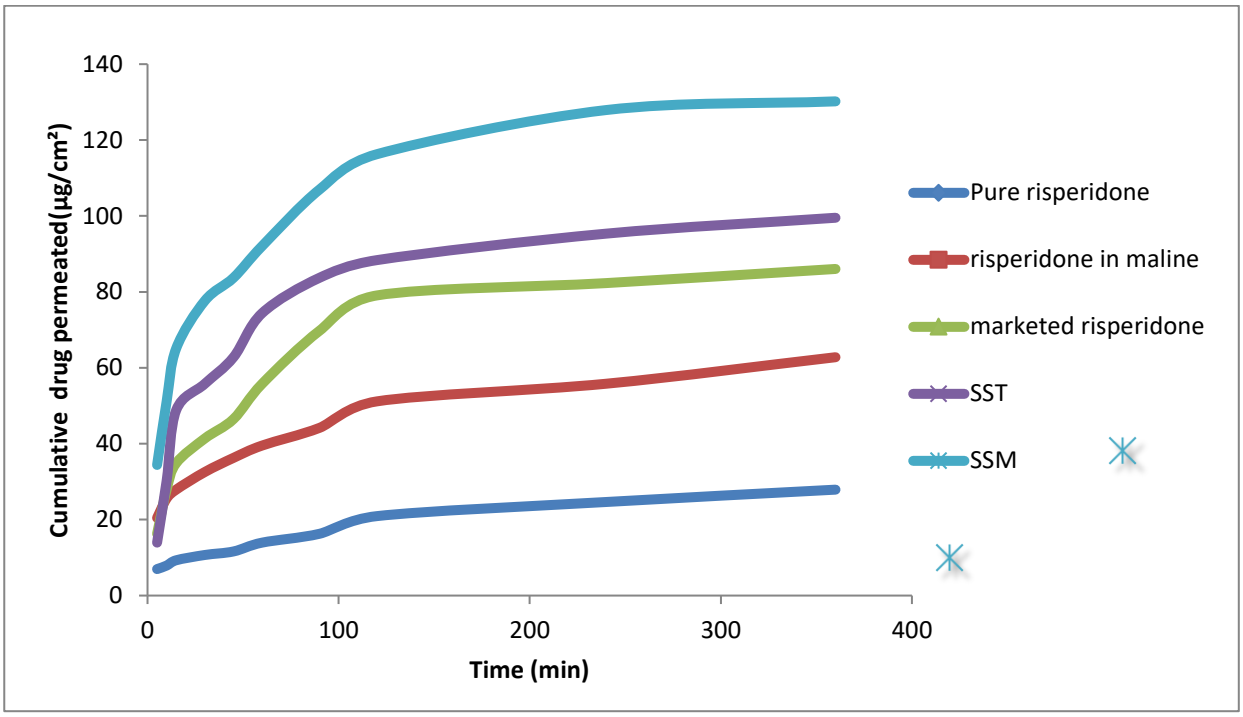

Figure 7: The cumulative amount of risperidone permeated through sheep intestinal sac from SSM, SST, risperidone dissolved in maline, marketed risperidone and pure risperidone.

Table 12: The parameters of permeability study for risperidone

Formula	Pure risperidone	Risperidone in maline	Marketed risperidone	SST	SSM
Permeated amount after 6 hrs(µg/cm²)	27.9	62.8	86.1	99.5	130.2
Permeation percentage	45%	47.1%	64.5%	74.7%	97.7%

Conclusion:

This work showed that preparation of supersaturable SEDD containing ionic liquid deep eutectic solvent as a green solvent can permanently solubilize risperidone, stabilize, enhance drug release and its intestinal permeation that reflect its ability to improve drug absorption and hence its oral bioavailability.

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