Acta Pharmaceutica Sciencia
53: 319-334 (2011)

Physicochemical characterization of risperidone solid dispersions

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Abstract

Solid dispersions of risperidone in SSG were prepared by dispersion method and evaluated by phase solubility, *in vitro*, XRD, DSC, IR, particle size, NIR, Raman analysis, wetting and permeation studies. Phase solubility results proved the solubilization and spontaneity effect of carrier. The release rate from dispersions was higher than pure drug and it was found to increase with increase in carrier content. Based on release rate and dissolution parameters RSSG10 was found to be the best releasing dispersions in the lot. XRD, DSC, NIR and Raman analysis confirmed the crystallinity reduction in dispersions. IR analysis proved the compatibility between the drug and carrier. Particle size reduction was proved by the particle size analysis. Wettability and water absorption studies confirmed the increased wettability. The apparent permeability co-efficient of sample across the natural and synthetic membranes were found to better than pure drug. The possible mechanisms for high release rate from samples were postulated and it was well supported by characterization findings.

Keywords: Risperidone, dissolution efficiency, dissolution rate constant, relative dissolution rate, X-ray diffraction, differential scanning calorimetry

Introduction

It has been estimated that nearly 35-40% of drugs suffer from poor aqueous solubility and formulation of poor water soluble drugs in to oral dosage forms still remains as one of the major challenges to formulation scientists in industry (Serajuddin 1999). Solubility is an important physicochemical factor that affects the absorption of drug from gastrointestinal tract that leads to poor oral bioavailability, high intra and inter subject variability, increase in dose, reduction in therapeutic efficiency and finally failure in formulation development (Chiou and Riegelman 1971, Ford 1986, Aungst 1993). Increased bioavailability for orally administered compounds can be achieved by manipulating the physico chemical properties of the drug of the drug compound and/or by adding excipient to the formulation that lead to an increased solubilization and each technique have its own pros, cons and limitations. One well recognized approach is the transformation of a crystalline drug into a high energy amorphous state (Chiou and Reigelman et al. 1969, Venkatesh et al. 2008).

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Solid dispersion is one of the common and simple techniques used to improve the dissolution rate and oral bioavailability of poorly soluble drugs. Several poor water soluble drugs have shown improved aqueous solubility, enhanced dissolution rate and better oral absorption when incorporated in solid dispersion form by using various hydrophilic carriers. Solid dispersion is a technique in which the hydrophobic drug will be dispersed in the carrier structure. Since the drug is present in the amorphous form in carrier its aqueous solubility and dissolution rate gets enhanced significantly (Venkatesh et al. 2008).

Superdisintegrants are a class of pharmaceutical excipient used for development of fast release dosage forms mainly due to their high water absorbing capacity. The majority of this research has been directed at the function-related properties of the superdisintegrants with special emphasis on correlating these properties to disintegrant efficiency and drug release (Bolhius et al. 1997, Sunilkumar et al. 2007).

Risperidone a widely used atypical antipsychotic drug and it was reported to be the only drug approved by FDA for the treatment of schizophrenia in 13–17 years age group of children and bipolar mania. Most of the antipsychotic drugs are lipophilic in nature and this property is very essential for its action in central nervous system. Due to its high lipophilicity all such antipsychotic drugs suffer from poor water solubility and low oral bioavailability.

Risperidone ($C_{23}H_{27}N_4O_2$) is an atypical antipsychotic agent having a molecular weight of 410.5 g/mol (Wishart et al. 2006). The poor aqueous solubility, low oral dose (4-8 mg), log p 2.7 values provide a platform for potential bioavailability problems (Titusville 2005, Francois 2006). These factors provided a strong rationale to select risperidone as the model drug for solubility and dissolution enhancement by solid dispersions technique.

The primary objective of this study was to enhance the aqueous solubility and dissolution rate of poor water soluble antipsychotic drug risperidone by using SSG as a carrier and to evaluate the dispersions by various physicochemical characterization techniques.

Material and Methods

Materials

Risperidone was obtained as gift sample from M/s. Torrent Laboratories, Ahmedabad, Microlabs, Bangalore and Sun pharmaceuticals, Ahmedabad, India. Sodium starch glycollate (SSG) and polyethylene Glycol 6000 (PEG 6000), were procured from Loba Chemie Ltd., India. Potassium dihydrogen orthophosphate, microcrystalline cellulose, magnesium stearate, sodium hydroxide and mannitol were purchased from SD Fine Chemicals Ltd., India. All other solvents and reagents used were of Analytical grade.

Phase solubility analysis

The drug and carrier was accurately weighed at specific drug: carrier ratio and added to 25 mL of water in screw capped bottles and shaken in Orbital incubator shaker (Remi, Mumbai) for 24 h at 37°C and 24°C. The container with pure drug and water was used as control. After 24 h the solutions were filtered, diluted and absorbances were measured at 239 nm (UV-Vis 1700 spectrophotometer, Shimadzu, Japan) (Arias et al. 1999, Sudha et al. 2002, Levine 2005, Sammour et al. 2006).

Preparation of solid dispersions

Solid dispersions of risperidone were prepared by dispersion method varying the concentrations of sodium starch glycolate individually and by keeping the concentration of drug constant. The drug: carrier ratio tried were 1:1, 1:2, 1:4, 1:6, 1:8 and 1:10 w/w. Required amount of carrier were powdered well in a mortar and risperidone was dissolved in chloroform to form a clear solution. The drug solution was gradually added to the carriers with constant trituration till it forms a porous mass. The mass was dried in oven at 45°C for 4 h. The mass is pulverized and passed through sieve No.-80 to get uniform sized particles (Bolhius et al. 1997, Chowdhary and Rao 2000, Zhao et al. 2005, Rajushree et al. 2007).

Physicochemical characterization

Characterization of the dispersions was carried out by the methods described below:

Drug content studies

Assay of weighed amount of SDs were carried out to determine the drug content. Weighed samples were dissolved in 10 mL of the analytical media (0.1 N HCl) and the solutions were filtered using Whatman filter paper (0.45 µm, 13 mm, Whatman, USA). Next, the filtrate was diluted suitably and the content was estimated spectrophotometrically (UV-1700, Shimadzu, Japan) at 239 nm.

In vitro dissolution studies

The *in vitro* dissolution testing of each sample was determined on USP Dissolution rate (paddle type) apparatus (Campbell Electronics, India). Dissolution vessels contained using 900 mL of 0.1N HCl maintained at 37°C ± 0.5°C and paddle speed at 50 rpm. Dispersions equivalent to 10 mg of risperidone was added to dissolution flask and 5 mL samples was withdrawn at specific time intervals, diluted and absorbance were determined at 239 nm and analysed for drug content by using UV- Visible spectrophotometer (UV-Vis 1700 Shimadzu, Japan). The withdrawn sample was replenished with 5 mL of fresh media to maintain sink conditions. The content of risperidone was calculated from the standard curve [O.D. = 0.0757 x concn – 0.0015] ($r=0.9998$; $p < 0.001$).Three such determinations were carried out for each formulations. Various dissolution parameters namely the amount released at different time intervals Q05, Q30 min, per cent DE, DRC, RDR and dissolution half-life and T_{85}% (time taken to release 85 % of drug) were calculated from the *in vitro* release data and compared with pure drug. Based on the parameters and the release data, the best releasing dispersions were selected from the formulations (Bolhius et al. 1997, Chowdhary and Rao 2000, Zhao et al. 2005, Rajushree et al. 2007).

Fourier transform infrared spectroscopic studies (FT-IR)

FT- IR spectra of pure RSP, carrier, physical mixtures of drug and carrier (1:1) and dispersions were carried out using FT-IR spectrophotometer with KBr disc (Jasco - FTIR -1700 spectrophotometer, Japan). Physical mixtures were prepared by blending individual component in glass mortar.

X-ray diffraction studies (XRD)

X-Ray diffractometer (Philips, The Netherlands) consisting of 40 kV, 30 mA generator with a Cu-Kα radiation tube was used. Diffraction patterns of pure drug, physical mixtures and selected SDs were scanned over 2Ø range from 2°C-50°C at the rate of 2°C per min at 0.02° at 2Ø step size (Orkoula and Kontoyannis 2007 and 2008, Shukla et al. 2009a and 2009b).

Differential scanning calorimetry studies (DSC)

Thermal analysis was carried out using differential scanning calorimeter (Q 10 DSC TA, Instruments, Waters Inc., USA) with liquid nitrogen cooling accessory. The analysis was performed under purge of

nitrogen gas (50cc/min). High purity Indium was used to calibrate the heat flow and heat capacity of the instruments. Sample (5-10) mg, placed in flat bottomed aluminium pan, was firmly crimped with lid to provide an adequate seal. Sample was heated from ambient temperature to 400°C at pre programmed heating rate of 10°C min^{-1}.

Near infrared analysis (NIR)

NIR spectra of pure drug and selected dispersion were recorded in FT-IR spectrometer (Jasco FT-IR, Japan) in Diffuse Reflectance Mode (DRS). The samples were scanned in the wavelength range of 800 – 2000 nm and absorbance was measured in transmittance mode (Orkoula and Kontoyannis 2007, Ayala et al. 2007, Shukla et al. 2009a and 2009b).

Raman analysis

The Raman spectra of pure drug and selected sample were recorded in a WITEC alpha 300 Nd:YAG laser (532 nm) Confocal Laser Raman Spectrophotometer with the following characteristics: the laser excitation line used, was the 1064 nm of a Nd:YAG laser. A secondary filter was used to remove the Rayleigh line. The scattered light was collected at an angle of 180°. The system was equipped with a liquid N2 cooled Ge detector (D 418).The power of the incident laser beam was about 370mW on the sample's surface. Raman spectra from the samples that were in the form of powders, e.g. raw risperidone, were recorded by placing in aluminium cylindrical cups with 10 mm diameter and 4mmheight having a cavity in the centre of 2 mm diameter and 1mm depth (Breitenbach et al. 1999, Ayala et al. 2007, Orkoula and Kontoyannis 2007 and 2008, Shukla et al., 2009).

Particle size analysis

The particle size measurements were carried out using a Malvern Mastersizer S (Malvern Instruments, UK) with a MS7 magnetically stirred dry sampling system and a 300 mm lens. A pressure of 2 Bar was used in order to disperse the particles. The particle size will be reported as D10, D50 and D90. From the values the particle size distribution was calculated form the value (Thybo et al. 2008).

Formulation of tablets

The tablets of pure RSP and selected dispersion were formulated by using 10 mg of pure drug and SDs equivalent to 10 mg of RSP. Sufficient quantity of microcrystalline cellulose (diluent) and magnesium stearate (lubricant) was added and mixed well in a mortar. The mixture was directly compressed in a 10 station rotary tablet punching machine (Rimek, Ltd., India) at a compression pressure of 5 kg/cm^2. Each tablet weighed around 250 mg.

Wetting time studies

Five circular tissue papers were placed in a petri dish of 10 cm diameter. Ten millilitres of water containing 0.5 % methylene blue, a water-soluble dye, was added to petri dish. The dye solution was used to identify complete wetting of the tablet surface. A tablet was carefully placed on the surface of the tissue paper in the petri dish at ambient temperature. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicates of three. Wetting time was recorded with digital watch (Gohel 2003, Mohapatra et al. 2008, Sunilkumar et al. 2008).

Water absorption ratio studies

The weight of the tablet prior to placement in the petri dish was noted (Wb), utilizing a Metler Toledo Digital balance. The wetted tablet was removed and reweighed (Wa). Water absorption ratio R, was then determined using the equation (Mohopatra et al. 2008, Sunilkumar et al. 2008)

$$R = 100 * \frac{W_a - W_b}{W_b} \quad ----- \text{Eq.3.10}$$

In vitro dispersion studies

A tablet was added to 10 mL of phosphate buffer pH 7.4 at 37°C. The time required for complete dispersion was noted down. Three such determinations were carried out (Fukami et al. 2006, Mohapatra et al. 2008, Shoukri et al. 2009).

Permeation studies

Preparation of egg membrane

The outer shell membrane of the egg of *Gallus domesticus* that just locate inside the shell exactly under the hard calcified layer was prepared by immersing the egg in 0.01 N HCl for 6 h to dissolve the calcified layer without any further process. The membrane was cut cautiously to cut cautiously to expel the contents of the egg and washed with normal saline solution. The inner membrane was repeatedly washed with water and stored in distilled water (Ansari et al. 2006, Corti et al. 2006a and 2006b).

Preparation of onion membrane

The middle membrane of the *Allium cepa L.* (onion) were pealed or separated with caution by gradual application of water in filler to avoid damage to the membrane. The stripped membranes (3 cm^2) without any crack or orifice were selected and stored in cold water till further studies (Ansari et al. 2006).

Preparation of tomato membrane

Tomatoes were boiled in hot water for about 15 min. The softened outer layer of tomato was removed carefully and repeatedly washed with water to remove the fleshy parts of tomato. The washed membranes were stored in cold water till further studies (Ansari et al. 2006).

Through natural membrane

All the membranes were inspected by a microscope to assure about their integrity and uniformity. Their thickness was measured by a calliper, and membranes with thickness similar to cellophane membrane were used for further studies. The required length of egg/onion/tomato membrane was cut and tied /glued to the bottom (grounded) layer of the diffusion cell with thread to form an inner compartment.

Ten mL of 0.1 N HCL was added to the inner compartment and placed in a beaker containing 100 mL of 0.1 N HCL which acts as outer compartment. Care was taken to make sure that the level of media in both compartments is equal. A magnetic bead was added to the outer compartment to stir the contents during the studies. The entire assembly was placed in a magnetic stirrer (Remi Ltd, Mumbai, India) and temperature was maintained at 37±1°C. Weighed amount of the pure drug was added to the inner compartment of the diffusion cell and the studies were performed for duration of 30 min. At predetermined time intervals, samples were withdrawn and the same volume of media was replenished to maintain sink condition. The solutions were suitably diluted and the absorbance was measured spectrophotometrically at 259 nm (UV-1700 Shimadzu, Japan). The procedure was repeated with the selected SDs from each carrier and with each of the membrane viz. Egg, onion, tomato, cellulose acetate and cellulose nitrate (Ansari et al. 2006, Corti et al. 2006a and 2006b).

Through cellulose nitrate and cellulose acetate

Cellulose acetate and cellulose nitrate membrane were procured as readymade membranes and rinsed in distilled water prior to studies. The cellulose nitrate and acetate membrane was glued to the bottom

(grounded) layer of the diffusion cell and the procedure was repeated like the diffusion studies performed using egg and other natural membranes (Ansari et al., 2006). The apparent permeability co-efficient (Papp) was calculated using the equation

$$P_{app} = \frac{d_q}{d_t} * \frac{1}{A * C_0} \quad ----- \text{Eq. 3.11}$$

where, dQ/dt is the linear appearance rate of mass in the receiver solution transported during sink conditions, A is the surface area of the membrane, and C0 is the initial drug concentration in donor compartment (Ansari et al. 2006, Corti et al. 2006a and 2006b).

Results and Discussion

Drug Content Studies

The drug content in the dispersions was found to be in the range of 98.6 % - 103.5 % which indicates the uniform distribution of the drug in samples and the suitability of the method used for formulation.

Phase solubility analysis

The phase solubility and thermodynamic parameters of samples at specified temperatures are shown in Table 1. The solubility of RSP was found to be higher when mixed with carriers and it tends to increase with the concentration of carrier. The enhancement of drug solubility in hydrophilic carrier could also be equally well related to the co-solvent effect of the carrier. The thermodynamic parameters of physical mixtures like ΔG and ΔH values were found to be negative and entropy ΔS values was positive in nature. These observations indicated the spontaneity and solubilization effect of the carriers. These findings were found to be in accordance with the earlier reports on similar phase solubility studies using such carriers (Arias et al. 1996, Cirri et.al. 2004, Levine 2006, Sammour et al. 2006).

Table 1. Content uniformity data

Carrier	Drug: Carrier					
	1:1	1:2	1:4	1:6	1:8	1:10
SSG	98.65 (0.847)	96.13 (0.984)	103.40 (0.331)	103.25 (0.751)	100.87 (0.125)	99.42 (0.166)

In vitro release studies

The dissolution profiles of risperidone–SSG solid dispersions were shown in Fig. 1. The release rate of RSP from dispersions was found to be higher than pure drug and found to increase with increase with the amount of carrier in dispersions. The dissolution parameters (Table 3) namely, amount released, % DE and RDR values were found to be increase whereas the parameters like t_{50}%, t_{85}% and DRC were found to decrease from samples RSSG1- RSSG10. Based on these findings batch RSSG 10 was chosen as the optimized batch in the lot.

The pattern of drug release from the dispersions was ranked as follows RSSG 10>RSSG 8>RSSG6>RSSG4>RSSG2>RSSG1>Pure Drug.

Table 2. Thermodynamic parameters of risperidone physical mixtures with sodium starch glycollate

S. No	Carrier	Temp. °C	Slope	Intercept	Ka	ΔG kJ/mol	Δ H kJ/mol	ΔS J/mol
01	SSG	25	1321.68	-46.026	0.0217	-2.5320	-2.5320	2.5235
		37	1300.89	-41.982	0.0238	-2.6395	-2.6395	2.6310

Ka = (Slope)/ Intercept * (1-Slope); ΔG (kJ) = (R*ln Ka * 1/T)/1000; R – Gas Constant -8.314 J/mol ; K T = Temp + 273°C; Ka – Stability Constant; ΔH (kJ) = (ln Ka * R/T)/1000; S (kJ) = [(ΔH-ΔG)/T] /1000

The increased dissolution rate from dispersions was attributed to high water absorption capacity and rapid dispersive nature of carrier in the dissolution medium. Due to this unique property of the carrier, the wetting nature of the dispersions increases, bringing more drug particles in to intimate contact with the dissolution medium and thereby increasing the dissolution rate. This phenomenon would have played a significant role in the dissolution behavior of dispersions with SSG as carrier (Bolhius et al. 1997, Chowdhary and Rao 2000, Zhao et al. 2005, Rajushree et al. 2007).

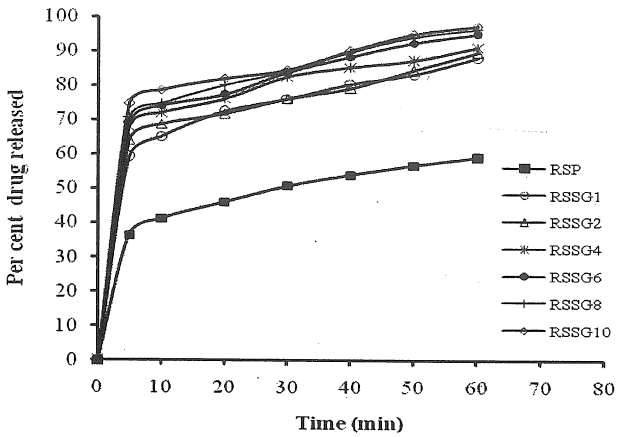

Figure 1. Dissolution profiles of risperidone- SSG solid dispersions compared with pure drug. All data points represent the mean of 3 values, n=3

The release rate from the dispersions was found to have significant difference between the samples at 5 % level ($p>0.05$) in comparison to the pure drug and the effect of carrier and its concentration. The findings of the release studies were well supported by related works utilizing SSG as carriers which showed an increase in solubility as well as dissolution rate of other drugs.

The relevance difference in dissolution parameters was evaluated statistically. When examined by two way analysis of variance the dissolution parameters showed a significant difference between the test samples ($p< 0.001$) with the same carrier. Hence it can be inferred that the products are not same but are different in their formulations.

The kinetic release data of the dispersions was shown in Table 4. The release data was found to fit best in to the korsemeyer peppas model as its correlation co-efficient "r value was found to predominate over the "r" values in other models. Since the release exponent values were found to fall within 0.0-0.5, fickian type release behavior was assigned for drug release from the dispersions (Seipmann and Peppas 2001, Zhao et al. 2006, Sunilkumar et al. 2007, Chandak and Verma 2008a and 2008b).

Table 3. Dissolution parameters of risperidone- SSG solid dispersions

Code	Composition RSP:SSG	Q 05 (mg)	Q 30 (mg)	DE %	RDR 05	RDR 30	DRC	$t_{50\%}$ (min)	$t_{85\%}$ (min)
PD	1:0	3.64 (0.37)	5.09 (0.35)	47.79	-	-	0.025 (0.001)	30	>60
RSSG1	1:1	5.92 (0.30)	7.62 (0.25)	72.54	1.62	1.49	0.023 (0.016)	4.50	55.0
RSSG2	1:2	6.40 (0.30)	7.62 (0.25)	73.39	1.75	1.51	0.018 (0.320)	3.75	51.5
RSSG4	1:4	6.80 (0.39)	8.26 (0.18)	77.54	1.86	1.54	0.012 (0.006)	3.75	41.0
RSSG6	1:6	6.92 (0.14)	8.34 (0.14)	77.65	1.90	1.60	0.010 (0.014)	3.75	33.5
RSSG8	1:8	7.00 (0.14)	8.42 (0.32)	80.39	1.92	1.63	0.004 (0.320)	3.50	31.5
RSSG10	1:10	7.40 (0.14)	8.69 (0.12)	81.28	2.03	1.64	-0.008 (0.300)	3.50	27.5

Values in parenthesis indicates Standard deviation; Q 05= Amount released at 05 min (mg); Q 30= Amount released at 05 min (mg); DE= Dissolution efficiency; DRC= Dissolution rate constant; RDR= Relative dissolution rate at specific time intervals; $t_{50\%}$= Dissolution half-life; $t_{85\%}$= Time taken to release 85 % of drug from dispersions

Table 4. Release kinetics of risperidone–SSG solid dispersions

Code	Composition RSP:SSG	Zero order		First order		Korsmeyer-Peppas	
		r^2	K_0 (min^{-1})	r^2	K_1 (min^{-1})	r^2	n
PD	1:0	0.801 (0.042)	0.700 (0.030)	0.142 (0.030)	0.023 (0.003)	0.994 (0.002)	0.210 (0.010)
RSSG1	1:1	0.752 (0.049)	0.970 (0.092)	0.036 (0.030)	0.009 (0.005)	0.984 (0.008)	0.307 (0.014)
RSSG2	1:2	0.728 (0.009)	0.9425 (0.023)	0.028 (0.013)	0.008 (0.002)	0.973 (0.002)	0.304 (0.006)
RSSG4	1:4	0.707 (0.029)	0.956 (0.036)	0.0025 (0.002)	0.006 (0.002)	0.971 (0.007)	0.317 (0.004)
RSSG6	1:6	0.727 (0.012)	1.021 (0.039)	0.020 (0.025)	-0.005 (0.008)	0.976 (0.002)	0.331 (0.008)
RSSG8	1:8	0.724 (0.010)	1.032 (0.037)	0.112 (0.142)	-0.017 (0.022)	0.975 (0.006)	0.336 (0.013)
RSSG10	1:10	0.692 (0.050)	0.9978 (0.075)	0.0957 (0.129)	-0.010 (0.027)	0.962 (0.004)	0.334 (0.005)

Values in parenthesis indicates SD (n=3); Ko= Zero order release constant; K_1= First order release rate constant

Solid state characterization

Drug excipient compatibility studies

The FT-IR spectra of RSSG 10 and PM at 1:1 ratio were compared with the spectra of RSP (Fig. 2). The FT-IR spectra of pure risperidone showed the following characteristic peaks at specific positions; 3058 cm^{-1} (aromatic stretching); 2941.7 and 2757 cm^{-1} (aliphatic stretching); 1652 cm^{-1} (C=0 stretching); 1535 cm^{-1} (C=C stretching); 1448 cm^{-1} (C=N stretching); 1412 cm^{-1} (aliphatic C-H bending); 1351 cm-1 (C-N stretching); 958, 866 and 817 cm^{-1} (aromatic C-H bending). The characteristic peaks of risperidone were also found to present in PM and SDs indicating the compatibility between drug and carrier. The peaks were also found to lose its sharpness and broader in nature as the concentration of the carrier was increased in samples. These findings may be attributed to the presence of drug in the dissolved form or as solid solution. The FT-IR analysis results suggests that some structural changes had taken place in drug molecule and those changes might have assisted in improving the release rate from dispersions (Skooge et al.

2003, Shukla et al. 2009a and 2009b, Orkoula and Kontoyannis 2007 and 2008, Khan et al. 2009a, 2009b and 2010).

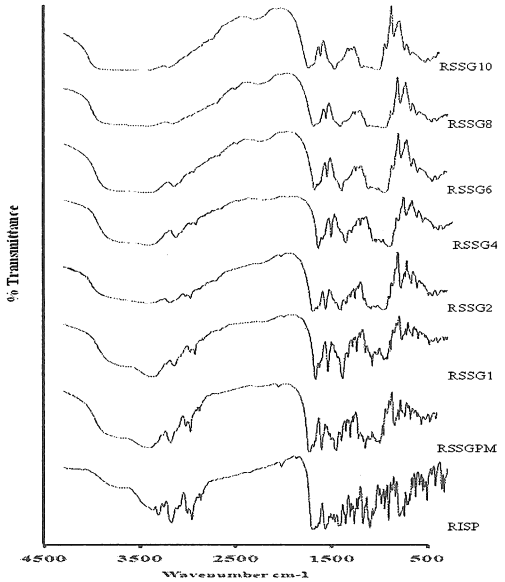

Figure 2. FT-IR spectra of pure risperidone, physical mixtures (PM) at 1:1 ratio, solid dispersions RSSG1, RSSG2, RSSG4, RSSG6, RSSG8 and RSSG10

X-ray diffraction studies

X-ray diffraction of pure RSP, SSG and selected SDs (RSSG 10) are presented in Fig. 3. The Numerous distinctive sharp, narrow peaks occurred at 7.56, 10.5, 11.2, 13.56, 14.22 and 19.7 2Ø positions which is indicative of its crystalline nature (Shukla et al. 2009a and 2009b, Orkoula and Kontoyannis 2007 and 2008, Khan et al. 2009a, 2009b and 2010).

The X-ray diffractogram of SSG exhibited two intense peaks (Ganesh et al. 2009) indicative of its nature. Few broader peaks with less relative intensity, peak height and high FWHM values than pure drug were observed in the diffractogram of selected SDs (RSSG10). These observations suggest that reduction of crystallinity of pure drug had occurred in SDs and part of the drug structure may have been converted to the amorphous state, and this finding would have contributed for the increased release rate from SDs.

Differential scanning calorimetry studies

DSC thermograms of pure RSP, carrier and selected SDs (RSSG10) are illustrated in Fig. 4. A sharp endothermic peak was observed for pure drug with the following parameters; Onset at 169.◦C, peak at 171.20◦C, with an area of 237.04 mJ and Delta H value of 91.27 J/g. These values clearly indicate the high crystalline nature of risperidone. A broad endothermic peak appeared in SSG thermogram indicative of its nature (Ganesh et al. 2009).

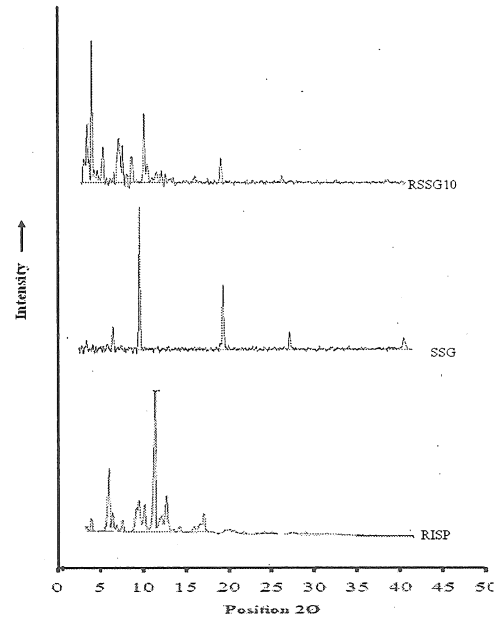

Figure 3. X-RD spectra of pure risperidone, SSG, physical mixtures (PM) at 1:1 ratio and solid dispersion (SDs) RSSG 10 at 1:10 ratio

A broad endothermic curve at 75°C and a little much reduced broad endothermic peak (onset at 168◦C, peak at 170◦C, peak area 7.790 mJ and Delta H value of 3.387) was observed in sample thermogram. The peak height, peak area and Delta H values were found to be less in comparison with that of pure drug. The variation in peak properties and thermal behavior of sample thermogram ratify that some structural changes had taken place in drug molecule during the formulation process and it may be attributed to crystallinity reduction or phase transition from crystalline to amorphous form. This phenomenon in drug molecule would have assisted in increased release rate from the samples (Orkoula and Kontoyannis 2007 and 2008, Shukla et al. 2009a and 2009b, Khan et al. 2009 a, 2009 b and 2010).

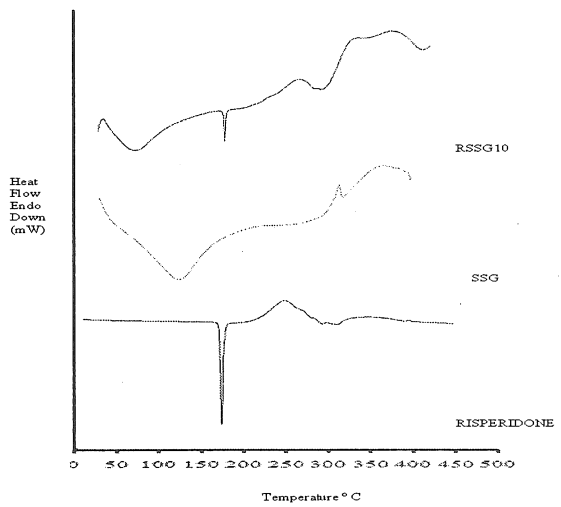

Figure 4. DSC thermograms of pure risperidone, SSG and selected solid dispersions (RSSG 10) at 1:10 ratio.

Near infrared analysis

The near infrared spectra of pure drug and selected dispersion (RSSG 10) were illustrated in Fig. 5. The characteristic peaks for pure risperidone were found to be at 1200 nm, 1410 and 1710 nm (Orkoula et al. 2007 and 2008, Khan et al. 2010). The specific peaks of the pure drug were found to broader in nature with a slight shift in their peak position towards the lower wavelength was observed in sample spectra. These findings suggest the reduction of crystallinity of drug present in dispersions. The structural changes in the drug molecule would have assisted in increasing the release rate from dispersions (Orkoula and Kontoyannis 2007 and 2008, Shukla et al. 2009, Khan et al. 2009a, 2009b and 2010).

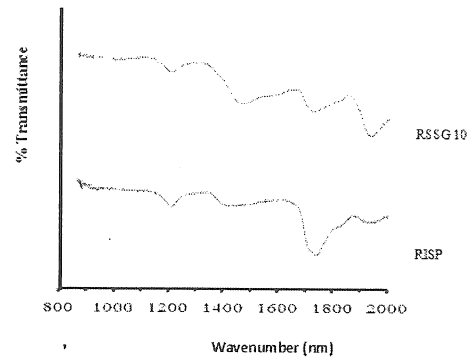

Figure 5. Near infrared spectra of pure risperidone and selected dispersion (RSSG10)

Raman analysis

The Raman spectra of pure drug and selected dispersions (RSSG 10) are presented in Fig. 6. The characteristic peaks of pure drug appeared at the following wave numbers; 303 cm^{-1}, 367 cm^{-1}, 1145 cm^{-1}, 1282 cm^{-1}, 1393 cm^{-1},1533 cm^{-1}, 2930 cm^{-1} and 3060 cm^{-1}. The characteristic peak of pure drug at 2930 cm^{-1} was found to present in sample (RSSG 10) spectra too, but in much reduced height, sharpness and slight shift in their peak positions. These observations clearly suggest that some structural changes had taken place in drug molecule when dispersed in hydrophilic carriers (Orkoula and Kontoyannis 2007 and 2008, Shukla et al. 2009, Khan et al. 2009a, 2009b and 2010).

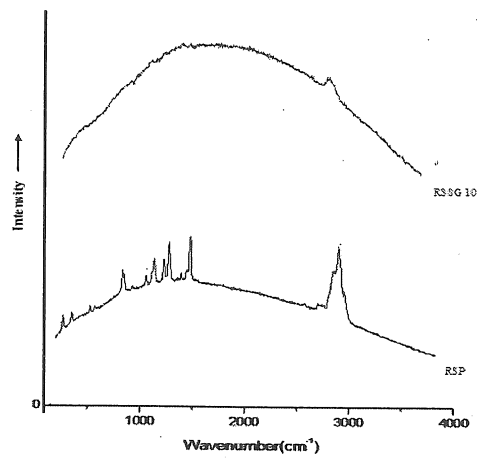

Figure 6. Raman spectra of risperidone and selected dispersion (RSSG 10).

Particle size analysis

The particle size data and particle size distribution of pure RSP and selected dispersion (RSSG 10) are shown in Table 5. The particle size of pure RSP was found to be 255, 407 and 650 μm and particle size distribution of about 582.17. The particle size and its distribution in selected SDs were found to be much less than the corresponding parameters of the pure drug. These findings prove the particle size reduction of drug in SDs (Thybo et al. 2008).

Table 5. Particle size analysis data of RSP and selected dispersion (RSSG 10)

Batch	Particle Size (μm)			Particle Size distribution (μm)
	D10	D50	D90	
RSP	1.80	307	583	1.89
RSSG10	5.53	8.84	14.1	0.97

Wettability studies

The wetting time and *in vitro* dispersion time (Table 6) of pure RSP was found to be more than 60 min. The water absorption ratio of risperidone was found to be (14.86) due to its high hydrophobicity. Due to its low water solubility it tends to absorb less amount of water during water absorption studies and it was also noticed that tablets prepared with pure RSP alone did not showed any sign of structural changes and little fragments were found at the end of the study period. These observations clearly indicate the poor wettability and hydrophobic nature of the drug (Wishart et al. 2006, Shukla et al. 2009a and 2009b).

The wetting time (20 min) and *in vitro* dispersion time (35 min) of dispersion RSSG10 was found to be higher than pure drug (more than 60 min). The water absorption ratio of selected dispersion (RSSG 10) was also found to show a higher value (16.85) than pure drug (14.85) and it may be related to water absorption potential of the carrier. Further, the tablet was also found to absorb water slowly forming a viscous sticky layer at the bottom surface and getting gradually dispersed in water. These observations from the wetting studies were found to be in agreement with the established reports utilizing SSG as carrier (Mohapatra et al. 2008, Sunilkumar et al. 2008, Shoukri et al. 2009).

Table 6. Wettability data of RSP and selected dispersions (RSSG 10)

Batch	Wetting time (min)	Water Absorption ratio	*In vitro* dispersion time (min)
PD	> 60 min (4.26)	14.86 (2.16)	> 60 min (1.12)
RSSG10	20 (3.14)	16.85 (1.36)	23 (1.66)

Permeation Studies

The amount of RSP permeated and apparent permeability co-efficient of dispersions RSSG10 compared with pure drug across the tested membranes are shown in Table 7. The amount permeated and the apparent permeability co-efficient of selected SDs (RSSG 10) are found to higher than pure drug and the results clearly indicate the efficiency of the samples. This behavior may be due to the increased dissolution rate and wettability in samples. These findings confirm the enhanced increased permeation potential capacity of the samples when formulated as solid dispersions (Ansari et al. 2006, Corti et al. 2006a and 2006b).

Table 7. Permeation co-efficient data of RSP and RSSG 10

Membrane	RSP		RSSG10	
	Amount Permeated (mg/mL)	P App ($cm\ s^{-1}$)	Amount Permeated (mg/mL)	P App (cm^{s-1})
Egg	0.0064	0.0004	0.0076	0.0008
Onion	0.0027	0.0001	0.0040	0.0008
Tomato	0.0011	0.0010	0.0069	0.0014
Cellulose acetate	0.0078	0.0006	0.0174	0.0012
Cellulose nitrate	0.0059	0.0002	0.0076	0.0008

Mechanism for enhanced release data

Based on the physicochemical characterization findings of the selected dispersions (RSSG 10) the following possible mechanisms were postulated for increased release rate from dispersions.

- Solubilisation effect and spontaneity of the hydrophilic carrier. (Phase solubility data).
- Increase wettability (Wetting time).
- Increased water absorption by the carriers (Water absorption studies).
- Crystallinity reduction (XRD, DSC, TSC & IR analysis).
- Phase Transition – from crystalline to amorphous form. (DSC & TSC analysis).
- Increased permeation capacity. (Permeation studies across natural, semi synthetic and cell lines.

The suggested possible mechanism for increased release rate from the solid dispersions were found to correlate well with the physico-chemical characterization of the dispersions and with the published reports on various solid dispersions and the general mechanism of drug release from the dispersions (Corrigan 1985, Ford 1986, Serajjudin 1999, Craig 2002, Leuner and Dressman 2002, Zhao et al. 2005, Rajushree et al. 2007, Sunilkumar et al. 2007, Balasubramaniam et al. 2008, Dhirendra et al. 2009, Venkates et al. 2008).

Conclusion

Thus it can be concluded that the dissolution rate of poor water soluble drug can be enhanced significantly by utilizing superdisintegrants like SSG and by a simple technique. These findings could be further explored for development of fast release dosage forms of drugs with low aqueous solubility in near future.

Acknowledgement

We express our thanks to M/s. Kovai Medical Center Research and Educational Trust (KMCRET) for providing all facilities and infrastructure for carrying out this work. We also thank Dept of Environmental Sciences, Pondicherry University for assisting us in XRD analysis of our samples. Thanks are also Due to staff of SAIF, IIT Chennai for helping us to perform NIR and Raman analysis.

Declaration of Interest

The authors report no declarations of interest.

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Received: 02.08.2010

Accepted: 11.07.2011