

FORMULATION AND EVALUATION OF RISPERIDONE-MANNITOL SOLID DISPERSIONS

VENKATESKUMAR KRISHNAMOORTHY^{1*}, VERMA PRIYA
RANJAN PRASAD², SUCHANDRA SEN¹

¹ Department of Pharmaceutics, KMCH College of Pharmacy,
Coimbatore-641048, India

² Department of Pharmaceutical Sciences, Birla Institute of Technology,
Mesra, Ranchi, 835215, India

* corresponding author: venkeyy@gmail.com

Abstract

The aim of the study was to enhance the dissolution of Risperidone (RSP) by the solid dispersion technique using mannitol as hydrophilic carrier. Solid dispersions of RSP were prepared by the dispersion method in drug: carrier ratios of 1:1, 1:2, 1:4, 1:6, 1:8 and 1:10, and were evaluated by drug content, *in-vitro* release studies, Powder X-Ray diffraction (PXRD), Differential Scanning Calorimetry (DSC), Fourier Transform Infra Red Spectroscopy (FT-IR), Near Infra Red (NIR), Raman, Particle size analysis, wettability studies. Phase solubility results exhibited a linear increase in solubility with the increase in carrier content and temperature. The sign and magnitude of thermodynamic parameters like Gibbs free energy, enthalpy and entropy indicated the spontaneity of solubilization. All dispersions showed increased dissolution rate in comparison to pure RSP and dispersions with the highest concentration of mannitol exhibited the fastest dissolution among all samples. Dissolution parameters were used for comparing the dissolution profiles of all dispersions and pure RSP as follows: the amount of drug released at 05 and 30 min (Q_{05} and Q_{30}), per cent dissolution efficiency (% DE), Dissolution rate constant (DRC), Dissolution half-life ($t_{50\%}$ and $t_{85\%}$ values were found to correlate with the release studies. The release data were found to fit best with the Korsmeyer-Peppas model. The results of XRD, DSC, FT-IR, Near Infrared, Raman and Particle size analysis revealed the reduction in drug's crystallinity, particle size reduction and the compatibility of drug and carrier. Wettability studies proved the increased wettability of RSP in dispersions the change in surface morphology of dispersions was evident from *in-vitro* dispersion studies.

Rezumat

Scopul prezentului studiu a fost evaluarea posibilităților de creștere a solubilității risperidonei prin tehnica dispersiei solide, folosind manitolul ca transportor hidrofil.

Dispersiile solide de risperidonă s-au realizat folosind rapoartele molare substanță activă:transportor 1:1, 1:2, 1:4, 1:6, 1:8 și 1:10 și au fost evaluate în ceea ce privește conținutul de substanță activă și cedarea *in vitro*. Au fost efectuate studii de difracție cu Raze X (Power X Ray), colorimetrie diferențială, spectroscopie în infraroșu cu transformata Fourier, analiza în domeniul infraroșu apropiat, Raman și determinarea dimensiunii particulelor, precum și studii de umectare.

Rezultatele obținute au demonstrat influența pozitivă a prezenței manitolului asupra parametrilor studiați și a solubilității substanței active.

Keywords: Risperidone (RSP), solid dispersion, mannitol, X-Ray diffraction, Differential scanning calorimetry, Near Infra Red spectroscopy.

Introduction

Water insoluble drugs are often incompletely absorbed after oral administration because of their limited solubility and slow dissolution. Owing to these problems it results in variable dissolution profiles and hence poor bioavailability. Several approaches such as micronization, salt formation, addition of surfactant, complexation, dendrimers for drug solubilization, formation of solid solutions/dispersions with hydrophilic carriers, self micro emulsifying drug delivery systems, spray drying, nano approaches pro-drug approaches and salt synthesis methods has been reported to improve the aqueous solubility and its slow dissolution. Among the approaches, solid dispersions forming is one of the successful methods used to improve the aqueous solubility, dissolution and oral bioavailability [1-3].

Risperidone ($C_{23}H_{27}N_4O_2$) is an atypical antipsychotic agent indicated for the treatment of schizophrenia with reduced side effects especially extra-pyramidal symptoms. Risperidone is practically insoluble in water having a molecular weight of 410.5 g/mol and shows good permeability with log P of 2.7. It also exhibits pH dependant solubility and highly bounding to plasma protein (90 %) [4-6]. Therefore, RSP shows dissolution rate limited absorption that gives rise to difficulties in pharmaceutical formulations for oral delivery, which may lead to variable bioavailability. This factor motivated the development of drug delivery technologies to overcome the obstacle of solubilization and it explains the rationale for the selection of Risperidone as the model drug.

Very few attempts to enhance the aqueous solubility and dissolution of RSP have been reported in literature using complexation techniques with cyclodextrin and amberlite resins [7-10]. The present work reports the potential of the water soluble carrier (mannitol) in enhancing the dissolution properties of RSP. The selected solid dispersions were subjected to various evaluation techniques like physico chemical, solid state characterization and wetting studies to determine their suitability to develop into fast release dosage forms with increased dissolution and oral bio availability. By opting for this approach an attempt has been made to develop dosage forms with improved oral absorption, increased therapeutic efficiency with significant reduction in the production cost.

Materials and Methods

Risperidone was obtained as a generous gift sample from M/s. Torrent Laboratories, Ahmedabad, India. Mannitol was purchased from M/s. SD Fine Chemicals, Ltd., (Mumbai, India). All the other reagents used were of analytical grade.

The abbreviations used throughout the study are: MAN - Mannitol, SDs - Solid Dispersions, PM - Physical Mixture, XRD - X-Ray Diffraction, DSC - Differential Scanning Calorimetry, FT-IR - Fourier Transform Infrared Spectroscopy, NIR - Near Infra Red Spectroscopy, OD - Optical Density, h - Hour, min - Minute, mL - Milliliters, ΔG - Gibbs Free Energy, ΔH - Enthalpy, ΔS - Entropy, % DE - Dissolution efficiency, DRC - Dissolution rate constant, RDR - Relative Dissolution Rate, $t_{50\%}$ - Dissolution Half Life, Q_{05} - Amount of Drug released at time intervals, FWHM - Full Width Half Maximum Values

Preparation of Solid Dispersions and Physical Mixtures

Solid dispersions (SDs) of RSP were prepared by varying the content of the hydrophilic carrier (mannitol) and keeping the amount of RSP constant in all SDs. The drug: carrier ratios used for optimization were 1:1, 1:2, 1:4, 1:6, 1:8 and 1:10. Physical mixtures were prepared by blending the drug and specific carrier at 1:1 ratio in a mortar.

Dispersion Method

Formulation of solid dispersions using mannitol was done by the dispersion method. The required amount of carrier (as per specific drug: carrier) was weighed and powdered in a mortar. RSP was dissolved in ethanol in order to form a clear solution. The drug solution was gradually added to the powdered carrier with constant trituration till it formed a porous mass. The mass was dried in oven at 45°C for 4 h. The mass was pulverized and passed through sieve No.80 to get uniform sized particles [11,12].

Phase Solubility Analysis

The drug and carrier were accurately weighed at specific drug: carrier ratio (from 1:1-1:10) were added to 25 mL of water in screw capped bottles sealed and shaken in an orbital incubator shaker (Remi, Mumbai) for 24 h at 37°C and 25°C [10]. The container with pure RSP and water was used as control. After 24 h the solutions were filtered through a 0.45 μm membrane filter. The filtrate was suitably diluted and analyzed spectrophotometrically (UV Vis 1700 spectrophotometer, Shimadzu, Japan) at 237 nm. The solubility measurements were performed in triplicate. From the solubility values various thermodynamic parameters were calculated [13-17].

Drug Content

The assay of the weighed amount of SDs was carried out to determine the drug content. The weighed samples (about 10 mg) were dissolved in 10 mL of 0.1 N HCl and stirred by vortex mixer. The solution was subjected to serial dilution, filtered using Whatman filter paper. The content was estimated spectrophotometrically (UV-Vis 1700, Shimadzu, Japan) at 237 nm using a standard curve with $OD = [OD=0.0757 \times \text{Concentration} - 0.0015]$ ($r=0.9998$; $p<0.001$).

***In vitro* Dissolution Studies**

In vitro dissolution tests for pure RSP and its solid dispersions equivalent to 10 mg of RSP were carried out with the USP 23 dissolution test apparatus (Type II paddle) at 37° C and 100 rpm using 900 mL of 0.1 N HCL as dissolution medium (n=3). Five mL of test samples were withdrawn at predetermined time intervals and replaced with an equal volume of fresh dissolution medium. The samples were filtered, suitably diluted and assayed spectrophotometrically for RSP content at 237 nm and the amount of RSP in each sample was calculated with reference to the regression equation generated from the suitably constructed calibration curve of RSP.

Analysis of dissolution data

The dissolution data was analyzed by various dissolution parameters calculated such as amount released at 5 and 30 min (Q_{05} and Q_{30}), percent dissolution efficiency (%DE), dissolution rate constant (DRC), relative dissolution rate (RDR) and time to release 50 % and 85 % of RSP ($t_{50\%}$ and $t_{85\%}$). The q values at different time interval, RDR, $t_{50\%}$ and $t_{85\%}$ can be obtained from percent dissolution vs. time profile/data. DE is defined as the area under the dissolution curve up to the time t, expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [16-19].

Mathematical Modelling of Release

The *in-vitro* drug release data were fitted to various release kinetic models as follows: zero order, first-order, Higuchi, Hixson-Crowell cube root and Korsmeyer-Peppas model [20-22].

Selection of Best Releasing Dispersions

Based on the *in-vitro* release dissolution profiles, and various dissolution parameters the best releasing dispersions were selected from the formulations.

Solid State Characterization

Powder X-ray Diffraction Studies

Powder X-Ray diffraction (PXRD) patterns were traced by employing an X-ray Diffractometer (Philips, England) for pure drug,

physical mixtures at 1:1 ratio and selected SDs using Ni filtered Cu K (α) radiation, a voltage of 40 kV, a current of 20 mA and receiving slit of 0.2 inch. The samples were analyzed over 2θ range from 2°C - 50°C at the rate of 2°C per min at 0.02° at 2θ step size.

Differential Scanning Calorimetry Studies

Differential scanning calorimetric (DSC) analysis of the drug, carrier, and selected solid dispersions were carried out on the samples using a DSC (Q 10 DSC TA, Instruments, Waters Inc., Newcastle, USA) with liquid nitrogen accessory. The analysis was performed under purge of nitrogen gas (50 mL/min). High purity Indium was used to calibrate the heat flow and heat capacity of the instruments. The sample (5-10mg), placed in flat bottomed aluminum pan, was firmly crimped with lid to provide an adequate seal. The sample was heated from ambient temperature to 400°C at a pre programmed heating rate of $10^\circ\text{C min}^{-1}$.

Fourier Transform Infrared Spectroscopic Studies

Fourier transform infrared (FT-IR) spectroscopy was employed to further characterize the possible interactions between the drug and the carrier in the solid state on an FT-IR spectrophotometer (Jasco-FTIR-1700 spectrophotometer, Japan) by the conventional KBr pellet method. FT- IR spectra of pure RSP, carriers, along with their physical mixtures (1:1) and optimized solid dispersions (from each carrier) were analyzed in a similar manner. Physical mixtures were prepared by blending individual components in a glass mortar.

Near Infra Red Analysis (NIR)

NIR spectra of pure drug and selected samples were recorded on an 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.

Confocal Raman Spectroscopic Analysis

The Raman spectra of samples and pure drug were recorded on a Confocal Raman spectrophotometer (WITEC Alpha 300, Confocal Raman Nd: YAG laser (532 nm), USA).

Particle Size Analysis

The particle size measurements were carried out using a Malvern Mastersizer S (Malvern Instruments, Worcestershire, 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.

Wetting Studies

Formulation of Tablets

The tablets of pure RSP and selected SDs were formulated by using 10 mg of pure RSP 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., Mumbai, India) at a compression pressure of 5 kg/cm². Each tablet weighed around 150 mg.

Wettability Studies

The wetting time was determined by placing a piece of tissue paper folded twice in a small Petri dish containing 6mL of water. A tablet was placed on the tissue paper and a small amount of methylene blue was placed on the upper surface of tablet. The time required by the color to reach the upper surface of the tablet was recorded as the wetting time [23-25].

Water Absorption Studies

The initial weight of the tablet was noted down and it was placed on a Petri dish with 10 mL of water. The tablet was left as such for 30 min; excess water was drained from the tablets by tissue paper and reweighed. The experiment was conducted in triplicate [23-25]. The water absorption ratio was calculated from the initial weight and the final weight of the tablet by using the following equation

$$R = 100 * \frac{W_a - W_b}{W_b} \quad (1)$$

Where, W_a is the weight of the tablet before water absorption

W_b is the weight of the tablet after water absorption

R is the water absorption ratio.

In-vitro Dispersion Studies

A compressed tablet from the selected dispersion was added to 10mL of 0.1 HCl and the time taken by the tablet to disperse in the medium was noted down and compared with that of the pure drug. The tests were carried out in triplicate [23-25].

Statistical Evaluations

The relevance of the difference in the *in vitro* dissolution profiles and pharmacokinetic parameters was evaluated statistically. The data were tested by two way analysis of variance.

Results and Discussion

Phase solubility analysis

The solubility of RSP in distilled water was found to be low indicating its poor water solubility. The solubility values showed a linear increase in drug solubility with the increase in carrier levels and with temperature. The enhancement of drug solubility in the hydrophilic carrier could also be equally well related to the formation of weak soluble complexes and the co-solvent effect of the carrier. Hydrophilic carriers are known to interact with the drug molecules mainly by electrostatic forces and occasionally by other types of forces like hydrogen bonds. The thermodynamic parameters of the physical mixture of drug and carriers are shown in Table I. The values of apparent stability constant, (K_a) were computed for 1:1 drug-carrier interactions and all the curves obtained in the present studies were of A_L type. The values of ΔG and ΔH were found to be negative and the positive entropy ΔS values of physical mixture with mannitol unequivocally demonstrated the spontaneity and solubilization effect of the carrier. These findings were found to be in accordance with the earlier reports on similar phase solubility studies using such carriers [13-17].

Table I

Thermodynamic parameters of risperidone physical mixtures with mannitol

No.	Carrier	Temp (°C)	Slope	Intercept	K_a	ΔG^a (kJ/mol)	ΔH^b (kJ/mol)	ΔS^c (kJ/mol)
01.	MAN	25	697.75	-17.119	0.058	-2.627	-2.627	2.618
		37	869.39	-18.182	0.055	-2.723	-2.723	2.714

ΔG^a – Gibbs free energy; ΔH^b – Enthalpy; ΔS^c – Entropy.

Drug Content

The theoretical drug content in solid dispersions with mannitol was calculated based on the weight ratio of drug and carrier. The drug content values of all solid dispersions in hydrophilic carriers are presented in Table II. The actual drug content in dispersions ranged between 97.22-103.40% and it exhibited a good agreement with the theoretical drug content.

Table II

Drug content data of risperidone mannitol solid dispersions

Carrier	Drug : Carrier					
	1:1	1:2	1:4	1:6	1:8	1:10
Mannitol	99.93 (0.738)	97.22 (0.250)	100.50 (0.226)	103.25 (0.651)	100.87 (0.738)	103.40 (0.663)

Values in parenthesis include standard deviation

In-vitro Release Studies

The results of the release studies revealed that about 60 % of pure RSP was released from its pure powder in 60 min which is due to its poor aqueous solubility. All dispersions with mannitol exhibited significant improvement in release rate than pure RSP. The release profiles of dispersions are illustrated in Figure 1. The dissolution parameters of dispersions at different drug: carrier ratio levels are listed in Table III.

The release of RSP was found to increase with the increase in the amount of mannitol in dispersions. It was noticed that there was a significant difference ($p < 0.001$) in the release rate between the pure RSP and solid dispersions with the varying concentration of each carrier. The parameters namely, the amount of drug released at 5 and 30min (Q_{05} and Q_{30}), %DE and RDR values of the dispersions were found to increase whereas parameters like DRC, $t_{50\%}$ and $t_{85\%}$ values were found to decrease with the increase in carrier content. The value of %DE_{60min} for pure drug was enhanced from a low value of 47.79% (for pure RSP) to 84.89% (for mannitol) in sample dispersions.

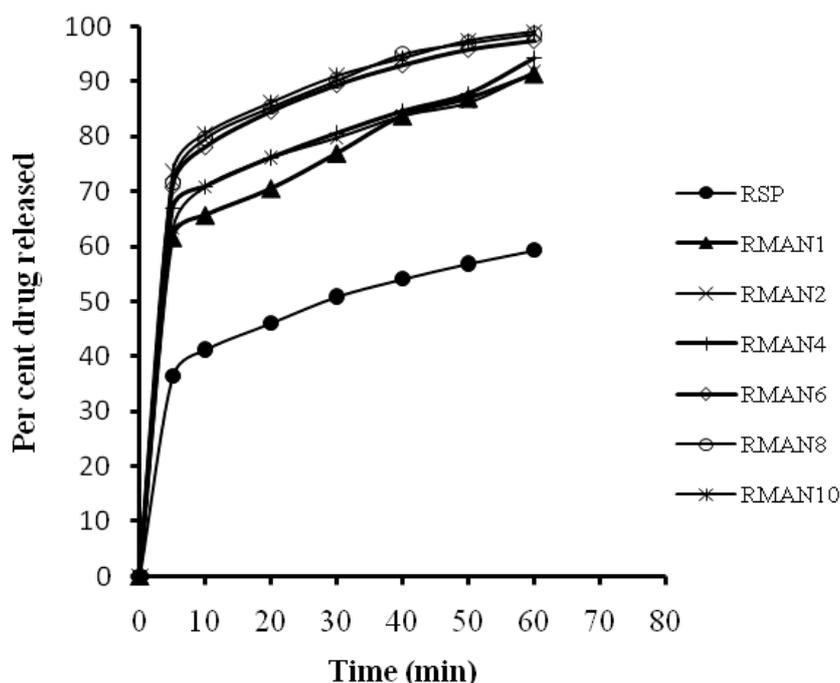


Figure 1

Dissolution profiles of risperidone-mannitol SDs compared with pure RSP. All data points represent the mean value ($n=3$)

Table III
Dissolution parameters of risperidone mannitol solid dispersions

Code	Composition RSP: Carrier	Q ₀₅ ^a (mg)	Q ₃₀ ^a (mg)	%DE ^b	RDR ^c 05	RDR ^c 30	DRC ^d	t _{50%} ^e (min)	t _{85%} ^f (min)
RSP	1:0	3.64	5.09	47.79	-	-	0.025	30	>60
RMAN1	1:1	6.16	7.69	74.00	1.69	1.53	0.020	4.0	45.0
RMAN2	1:2	6.32	7.97	75.90	1.73	1.59	0.016	3.75	44.0
RMAN4	1:4	6.68	8.05	77.12	1.84	1.60	0.010	3.50	40.0
RMAN6	1:6	7.08	8.93	82.73	1.94	1.65	0.008	3.0	21.5
RMAN8	1:8	7.20	9.01	83.76	1.97	1.66	0.006	3.0	21.0
RMAN10	1:10	7.36	9.06	84.89	2.02	1.67	-0.012	2.5	20.0

^aQ₀₅ and Q₃₀: Amount released at 05 min and 30 min in mg. ^b% DE : per cent dissolution efficiency.

^cRDR : Relative dissolution rate at specific time intervals ^dDRC: Dissolution rate constant.

^et_{50%} : Time taken to release 50 % of drug ^ft_{85%} : Time taken to release 85 % of drug.

Analogous to DE values, the maximum RDR values at 5 and 30 min was found to be high for dispersions (2.02-1.67). The DRC values of the dispersions were also found to decrease from pure drug value (0.025) with rise in the amount of carrier in dispersions. The dissolution half life (t_{50%}) and t_{85%} values of the binary systems was found to decrease from more than 60 min (pure RSP) to 2.5 and 20 min respectively.

The correlation plot of % DE and t_{50%} of SDs is shown in Figure 2. The dissolution efficiency and t_{50%} data showed a significant difference between the test products (p<0.001).

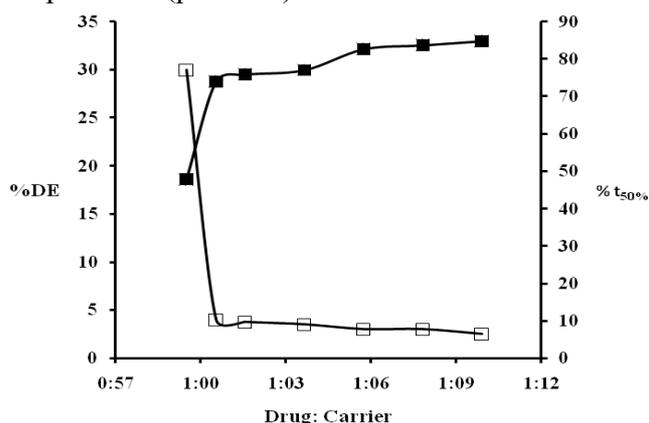


Figure 2

Correlation plot of percent dissolution efficiency and dissolution half life (t_{50%})

■ - % DE, □ - t_{50%}

The improvement of the dissolution rate of RSP in mannitol dispersions may be attributed to the formation of hydrophilic diffusion layer, change in surface hydrophobicity of RSP particles and increased wettability of RSP in dispersions [7-10, 15-18, 26, 27]. The other additional factors that might have contributed for the higher release rate may be

summarized as the solubilization effect of carrier, particle size reduction, change in crystal quality and augmentation of aqueous solubility by the said carriers. These observations were also well supported by the *in-vitro* wettability and disintegration tests which showed that a polymer rich layer was formed around the tablet and slow diffusion was clearly observed and tablets surface was found to decrease gradually during the dissolution process [7-10, 15-18, 26-28].

Release Kinetic Analysis

The regression parameters obtained after fitting the *in vitro* release data in to various kinetic models are presented in Table IV. The goodness of fit for various models investigated for the solid dispersions are ranked in the order of Korsmeyer-Peppas > Higuchi=Hixson Crowell> Zero Order > First order. It was observed that the release data was found to fit best into the Korsmeyer Peppas model as its correlation coefficient values were found to dominate over the “*r*” values in other models. Since the release exponent “*n*” values of the dispersions were found to be within 0.45 a Fickian Type of drug release was indicated for RSP release from its dispersions.

Table IV
Release kinetic parameters of risperidone mannitol solid dispersions

Batch	Mathematical models for drug release										
	Zero-Order		First-Order			Korsmeyer Peppas		Higuchi		Hixson-Crowell	
	r^2	K_0	r^2	K_1	Slope	r^2	<i>n</i>	r^2	Slope	r^2	Slope
RSP	0.801	0.700	0.142	0.023	0.010	0.994	0.210	0.865	6.741	0.726	0.007
RMAN1	0.770	1.028	0.013	0.0031	0.001	0.985	0.317	0.824	10.01	0.812	0.150
RMAN2	0.730	0.978	0.019	0.006	0.003	0.979	0.316	0.779	9.81	0.747	0.014
RMAN4	0.732	0.995	0.014	0.0008	0.003	0.977	0.321	0.774	9.924	0.769	0.015
RMAN6	0.719	1.063	0.210	-0.018	-0.008	0.978	0.349	0.768	10.75	0.830	0.021
RMAN8	0.711	1.058	0.168	-0.024	-0.01	0.975	0.351	0.758	10.75	0.827	0.021
RMAN10	0.704	1.048	0.221	-0.032	-0.014	0.972	0.350	0.747	10.67	0.864	0.009

The mathematical modeling of the release data and the findings were found to be in accordance with the possible mechanisms suggested for higher release rate from the dispersions. The hydrophilic mannitol on absorbing the dissolution medium forms a hydrophilic diffusion layer around the drug particle, changes its surface hydrophobicity and it diffuses across the hydrophilic layer to reach the bulk of the dissolution medium. These observations were found to be in accordance with the earlier published reports [20-22].

Solid State Characterization

The selected solid dispersions were further subjected to solid state characterization technique to determine the possible factors that might have contributed for improved release rate from dispersions.

Powder X-ray diffraction spectroscopy

XRD spectra of pure drug, mannitol, physical mixture at (1:1 ratio) and selected dispersion (RMAN 10) are depicted in Figure 3. The diffraction spectrum of solid dispersion compared with the pure drug, carrier and physical mixture indicates the changes produced in crystal structure of RSP. Numerous distinctive sharp, narrow high peaks with high relative intensity and (Full Width Half Maximum (FWHM) values appeared in RSP spectra at 7.5, 10.5, 12.5, 17.4 and 19.7 and 23.7 positions and this finding demonstrated the high crystalline nature of pure RSP [7-10, 28-30].

The spectra of carrier were found to possess few broad peaks and they reflected its amorphous nature. The prominent peaks of pure RSP were also found to present in spectra of physical mixture of RSP and carrier proving the absence of interaction between RSP and mannitol. The diffraction peaks of the pure RSP in selected solid dispersions (RMAN 10) were found to be broader in nature with reduced sharpness, decreased relative intensity, less peak height and low FWHM values.

These findings clearly prove the changes in drug's crystal quality and its structural disorientation in sample dispersions. The changes produced in the drugs crystal structure would have attributed for the dissolution enhancement of the RSP from selected dispersions [7-10,28-30].

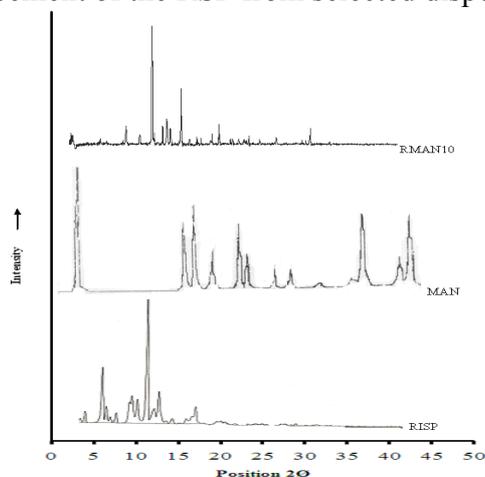


Figure 3

X-RD spectra of pure risperidone, mannitol, physical mixture (PM) at 1:1 ratio and solid dispersions (SDs) RMAN 10 at 1:10 ratio

DSC Analysis

DSC thermograms of RSP, carrier (Mannitol) and selected dispersion (RMAN 10) are compared in figure 4. A sharp endothermic peak appeared in pure RSP thermogram with the following peak parameters: onset at 183.69°C, peak at 187.20°C, with an area of 150.06mJ and Delta H value of 50.020 which is indicative of its high crystalline nature [7-10,28-30].

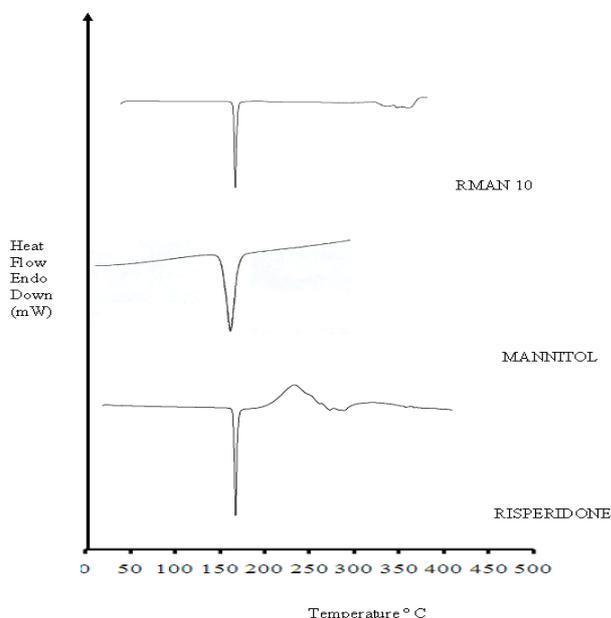


Figure 4

DSC thermograms of pure risperidone, mannitol and solid dispersions (SDs) RMAN at 1:10 ratio

A broad single endothermic peak was observed at 155°C (for mannitol) which indicated the nature of carriers. The thermograms of binary systems with mannitol as carrier showed no endothermic peak corresponding to pure RSP. It is quite probable that the drug might have dissolved in the carrier structure forming a solid solution in the carrier. The peaks present in the sample thermograms may all be related to that of carriers used in the formulation. The variation in peak properties and thermal behavior of sample thermogram clearly indicates crystallinity reduction in RSP molecule present in sample dispersions.

Fourier Transform infrared spectroscopy

The FT-IR spectra of SDs in mannitol compared with the corresponding physical mixture and pure RSP are shown in figure 5. The following characteristic peaks were observed for pure RSP: 2968 and 2931

cm^{-1} (aliphatic C-H stretching); 1590 and 1551 cm^{-1} (C=N stretching, 1462 and 1431 cm^{-1} (aromatic C=C stretching); 820 cm^{-1} (C-Cl stretching) [7-10, 28-30]. The presence of prominent peaks of pure RSP in thermograms of physical mixture and as well as in selected solid dispersions reveals the compatibility between drug and carrier.

It was also noticed that the peaks corresponding to pure RSP in solid dispersions were found to be broad in nature and with sharpness getting reduced gradually with the increase in the amount of mannitol. It was also stated that few principle peaks in dispersions (with mannitol) were found to be absent at higher concentration of carrier structure suggesting that drug may be present in dissolved form or as a solid solution in the carrier structure. This spectral behavior of solid dispersions may be attributed to change in crystal quality of RSP due to induced change in the orientation of the crystal lattice of pure RSP in dispersions. Thus the spectral study results prove that some structural changes had taken place in RSP molecule in present in solid dispersions.

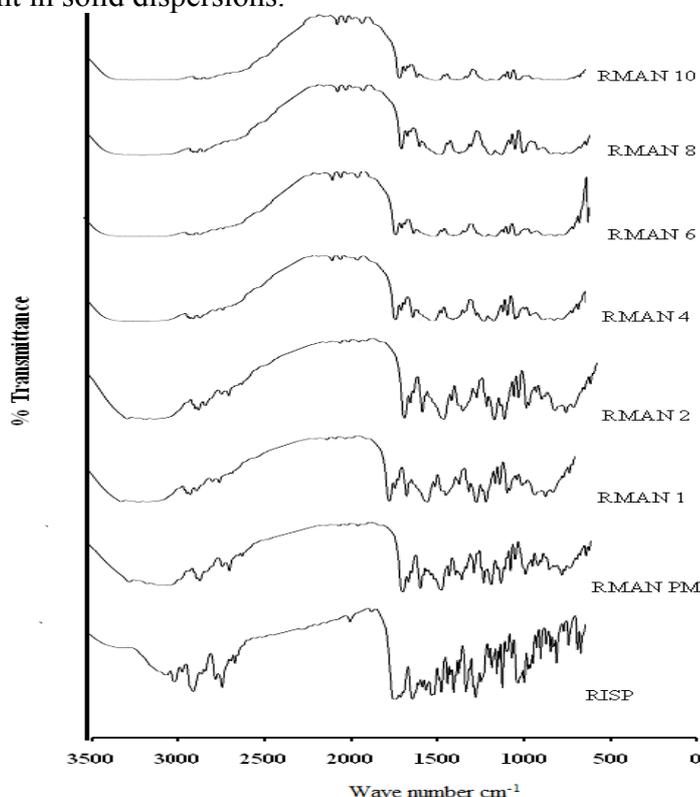


Figure 5

FT-IR spectra of pure risperidone, physical mixture (PM) at 1:1 ratio, solid dispersions (SDs) RMAN1, RMAN2, RMAN4, RMAN6, RMAN8 and RMAN10

Near Infra Red analysis

The near infrared spectra of pure RSP and the selected dispersion (RMAN 10) were compared in Figure 6. The characteristic peaks for pure RSP were found at 1200nm, 1410 and 1710nm. The specific peaks of the pure RSP were found to be broader in nature with a slight shift in their peak position towards the lower wavelength number in sample spectra. These findings suggest the reduction of crystallinity of pure drug present in dispersions. Thus, these results suggest the change in crystal quality of RSP in solid dispersions [7-10, 28-30].

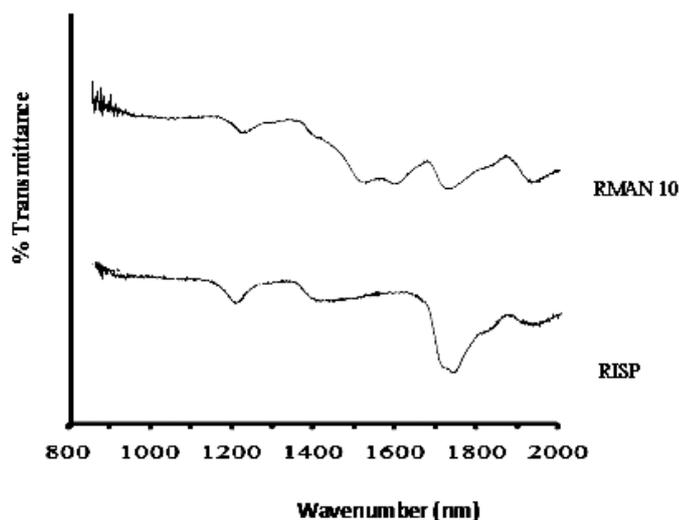


Figure 6

Near infrared spectra of pure risperidone and selected solid dispersions (SDs) RMAN10

Raman Analysis

The Raman spectra of pure RSP and selected solid dispersion (RMAN 10) are compared in figure 7. The characteristic peaks of pure RSP were found to appear at the following peak positions: 303cm^{-1} , 367cm^{-1} , 1145cm^{-1} , 1282cm^{-1} , 1393cm^{-1} , 1533cm^{-1} , 2930cm^{-1} and 3060cm^{-1} [11-14,37-42]. The characteristic peak of pure RSP at 2930cm^{-1} was found to be present in spectra of selected solid dispersions, but with decreased sharpness, reduced height and slight shift in peak positions. These observations clearly demonstrate the change in the crystalline nature of pure RSP in selected solid dispersions [7-10, 28-30].

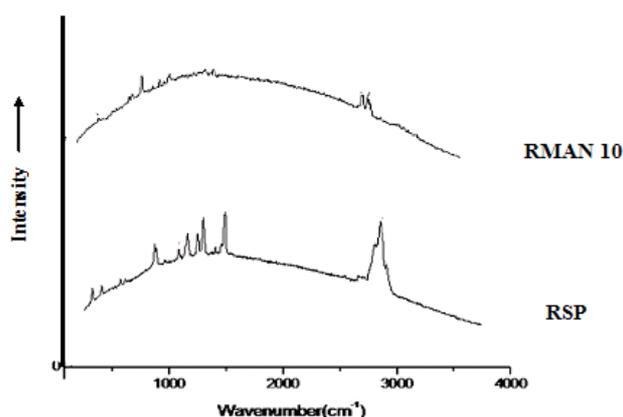


Figure 7

Raman spectra of pure risperidone and selected solid dispersions (SDs) RMAN 10

Particle size analysis

The particle size data and particle size distribution of pure RSP and selected dispersion are presented in Table V. The particle size of pure RSP was found to be 255 μm (D10), 407 μm (D50) and 650 μm (D90) and particle sizes distribution was higher in pure drug. The particle size at D10, D50 and D90 and its distribution in selected SDs were found to be lower than the corresponding parameters of pure RSP. The particle size distributions were regarded as narrow, as the span, calculated as $D90-D10/D50$, was below 1.7 for all SDs. These findings confirm the particle size reduction of RSP present in selected dispersions [31].

Table V
Particle size analysis data of risperidone and selected solid dispersions

Batch	Particle Size (μm)			Particle Size distribution (μm)
	D10	D50	D90	
RSP	1.80	307	583	1.89
RMAN 10	1.97	3.10	4.95	0.97

Wettability Studies

The wettability data of pure RSP drug and selected dispersions are presented in table VI. The wetting time and *in vitro* dispersion time were found to be more than 60 min for pure RSP with low water absorption ratio of 12.80. Further, the tablets prepared with pure RSP did not show any sign

of structural changes and compactness was maintained though out the study period. These observations clearly indicate the high hydrophobicity and poor wettability of pure RSP [29-31].

The wetting time and *in vitro* dispersion time of the selected solid dispersions (RMAN 10) was found to be 22 and 28 min which was found to be much less than the pure RSP. The water absorption value of the selected dispersions was also found to be high for selected dispersions (15.18) than pure RSP. These findings prove the water absorbing potential and hydrophilic nature of carrier. The wettability results proved the increased wettability of RSP and the high water absorption potential of the carriers used in dispersions. These observations clearly explained the role of hydrophilic carriers in enhancing the RSP release from its solid dispersions [23-25].

Table VI

Wettability data of risperidone and selected solid dispersions			
Batch	Wetting time (min)	Water Absorption Ratio	<i>In vitro</i> Dispersion Time (min)
RSP	> 60 min (4.26)	12.86 (2.16)	> 60 min (1.12)
RMAN 10	20 (2.36)	14.18 (1.84)	28 (1.96)

Mechanisms for Enhanced Release

Based on the results of the various evaluation techniques used for the evaluation of the sample dispersions the following mechanisms were suggested for increased release of RSP from SDs are: solubilization effect of the hydrophilic carrier, (phase solubility data), particle size reduction, change in surface hydrophobicity of drug particles due to carriers, change in crystal quality of RSP, change in crystal disorientation (phase transition from crystalline to amorphous form), formation of solid solution in the carrier structure, increased wettability and increased water absorption due to hydrophilic carriers. The foresaid postulations were found to be in accordance with earlier published reports using such hydrophilic carriers [32-34].

Conclusions

The hydrophilic carrier used in the current study enhanced the aqueous solubility, dissolution characteristics and bioavailability of poorly soluble drug RSP. Mannitol was found to be a promising solubility enhancing agent for poor water soluble drugs.

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