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Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING TABLETS OF RISPERIDONE SOLID DISPERSION

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ABSTRACT

Solubility is an important physicochemical factor affecting absorption of drug and its therapeutic effectiveness. Consequences of poor aqueous solubility would lead to failure in formulation development. The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. In the present investigation, an attempt was made to improve the solubility and dissolution rate of a poorly soluble drug, Risperidone by solid dispersion method using Beta-cyclodextrin, crospovidone and croscarmellose as carrier with varying drug: carrier ratios. The solid dispersions were formulated as fast dissolving tablets by using Doshion P544 resin (C), a taste masking agent with different superdisintegrants such as Croscarmellose and crospovidone and were subjected to various pre formulation and post formulations studies. All the formulations showed marked improvement in the solubility behaviour and improved drug release. The results concluded that fast dissolving tablets of poorly soluble drug, Risperidone showed enhanced dissolution, may lead to improved bioavailability and hence better patient compliance.

INTRODUCTION[6]

Solid dispersion are defined as dispersion of one ormore active ingredients in an inert carrier matrix at solid-state prepared by themelting (fusion), solvent or melting- solvent method. Several insoluble drugs have been shown to improve their dissolution character when incorporated into solid dispersion.Solid dispersion technique has been widely employed to improve the dissolution rate, solubility and oral adsorption of poorly water soluble drugs.

Preparation techniques of solid dispersions:

A. Solvent evaporation method
B.Melting method (Fusion method)
C.Kneading method
D.Melting solvent method
E.Supercritical fluid methods

Solvent evaporation method

In this method, physical mixture of two components are dissolved in a common solvent and followed by the evaporation of solvent. The advantages of this method are low temperature requirement for the preparation of dispersion and thermal decomposition of drugs and carriers can be prevented.

Swallowing problem is also common in young individuals because of their under developed muscular and nervous system. Other groups that may experience problems using conventional oral dosage forms include mentally ill and the developmentally disabled. In some cases such as motion sickness, sudden episodes of allergic attack or coughing and unavailabilityof drinking water, swallowingconventional tablet maybe difficult.

Recent advances in novel drug deliverysystems (NDDS) aim to enhance safety and efficacy of drug molecule by formulation and to achieve better patient compliance. One such approach is 'mouth dissolving tablets', which disintegrate or dissolve in saliva and are swallowed without water as tablet disintegrate in mouth, this could enhance the clinical effect of drug through pre gastric absorption from the mouth, pharynx, oesophagus. This leads to an increase in the bioavailabilitybyavoiding first pass liver metabolism. Mouth dissolving is also called as oro-dispersible tablets, melt-in-mouth, and fast dissolving tablet, rapimelts, porous tablets, quick dissolving or rapidly disintegrating tablets.

In the present investigation, an attempt was made to improve the solubility and dissolution rate of a poorly soluble drug, Risperidone by solid dispersion method using Beta-cyclodextrin, crospovidone and croscarmellose as carrier. The solid dispersions were formulated as fast dissolving tablets by using Doshion-P544 resin (C), a taste masking agent with different superdisintegrants such as Croscarmellose and crospovidone.

MATERIALS AND METHODS

Materials

Risperidone (Micro Labs,Bangalore), Crospovidone,croscarmellose and β-cyclodextrin (Yarrow Chem Products,Mumbai). Doshion P-544 C resins (Doshion ltd, Ahmedabad), Aspartame (ChetanaPhamaceuticals, Thrissur). All the other raw materials used were of Pharmacopoeial grade.

Methods

Preparation of solid dispersion of Risperidone[2]

Solid dispersion of Risperidone was prepared by solvent evaporation method. The drug was weighed and taken in china dish, dissolved in methanol and then the carrier was added in the ratio1:1, 1:3, 1:7and 1:9.The solvent was evaporated at room temperature and dried in hot air oven at 50^{0}C for 4 hours. The resultant mass was passed through sieve no-120 and stored in desiccator.

Evaluation of Solid Dispersion[2]

Fourier Transform Infra-Red Spectroscopy

FTIR transmission spectra were obtained using a Fourier Transform infrared spectrophotometer (FTIR, Shimadzu, Japan). Samples were prepared in KBr disks by means of hydrostatic press. The scanning range was 500 to 4000cm^{-1}.The characteristic peak was recorded.(Fig:5,6,7,8)

Differential Scanning Calorimeter (DSC)

Differential Scanning Calorimetry study was performed using Differential Scanning Calorimeter (Mettler Toledo DSC 822e) using crucible Al 40µL, at of 10^{0}c/min heating rate, under nitrogen environment. The temperature range used was 0 – 400^{0}c (Fig: 2, 3, 4)

Scanning Electron Microscopy

Shape and surface morphology characterization of risperidone, BCD and SD formulations was performed by scanning electron microscopy (SEM, JSM-6390 LV, JEOL, Tokyo, Japan) measured at the working distance of 15mm and an accelerated voltage of 20 kV.(Fig:1a,1b,1c)

Drug Content

A quantity of solid dispersion equivalent to 4mg of Risperidone was accurately weighed and dissolved in 0.1N HCl in a 100 ml volumetric flask.Then the volume was made upto 100ml with 0.1N HCl. From this serial dilution were made with 0.1NHCl.Theabsorbance of the resulting solution was measured at 239nm against blank (0.1N HCl).

In-vitro Dissolution Studies

Dissolution studies were carried in USP Apparatus II. Solid dispersion equivalent to 4mg of drug were added to 900ml of phosphate buffer pH6.6 stirred at 75rpm.Aliquotes of 5ml were withdrawn at specified time intervals and analyzed at 277nm.(Fig:9,10,11)

Preparation of fast dissolving tablets containing solid dispersions of Risperidone[1]

Fast dissolving tablets containing 4 mg of risperidone were prepared by direct compression method and the formula used in the study are shown in Table 1.Different superdisintegrants such as Crosprovidone and Croscarmellose were used. Doshion-P544 resin (C), a taste masking agent was used to mask the bitter taste of Risperidone. Mannitol and aspartame were used as sweetening agent. Risperidone was mixed in geometric proportions with sweeteners, diluents and lubricants. Blend was screened and compressed on rotary punching machine.(Table:1)

Evaluation of Fast Dissolving Tablets[1]

All the tablets were evaluated for different parameters such as weight variation, hardness, friability, uniformity of weight, disintegration time, wetting time, drug content and in vitro dissolution study.(Table:2)

Weight variation

Twenty tablets were randomly selected from each formulation and average weight was determined.Then individual tablet were weighed and individual was compared with average weight.

Friability

The friability of tablets was determined using friability test apparatus (Biolinkz, India). The tablets were weighed ($W_{initial}$) and placed in friabilator. The friabilator was operated at 25rpm for 4 minutes or 100revolutions. The tablets were dedusted and weighed again (W_{final}).The percentage friability was calculated by

$$F = \frac{W_{initial} - W_{final} \times 100}{W_{final}}$$

Hardness

The hardness of tablet was determined using Pfizer Hardness tester. It was expressed in kg/cm^2

Thickness

Twenty tablets were randomly selected from formulations and thickness was measured individually by Screw gauge. It was expressed in millimeter.

Disintegration Test

The disintegration time of fast dissolving tablets was determined using Disintegration test apparatus. (Fig: 13)

Wetting time

The wetting time of the tablets can be measuredusing a simple procedure. Five circular tissue papersof 10 cm diameter were placed in a petri dish witha 10 cm diameter. 10 ml of water was poured on the tissue paper placed in the petridish. A tablet is
carefully placed on the surface of the tissue paper.The time required for water to reach upper surfaceof the tablet is noted as a wetting time.

***In-vitro* dissolution study**

In-vitro dissolution study was done using USP type II apparatus which was rotated at 50rpm. Phosphate buffer pH (6.8) was taken as dissolution medium. Temperature of dissolution medium was maintained at 37±0.5^{0}c. Aliquotes of dissolution medium were withdrawn at specific time interval, filtered and was determined by Shimadzu Double beam spectrophotometer at 277nm.Dissolution studies of all formulations were done as presented in Fig: 12

Determination of Drug Content

Ten tablets were weighed and taken in mortar and crushed to make powder. A quantity of powder weighing equivalent to 4 mg of Risperidone was taken in 100 ml volumetric flask and 0.1 N HCl was added. Then the solution was filtered using membrane filter 0.45µm and then the solution was diluted up to 10µg and absorbance was measured at 277 nm. Then the amount of drug present was calculated using standard graph.

RESULTS AND DISCUSSION

Risperidone solid dispersions were prepared by solvent evaporation method in different drug – polymer concentrations and it was evaluated. FT-IR spectroscopic studies were conducted for possible drug: carrier interactions. FT-IR spectra of pure drug Risperidone and solid dispersions are shown indicating no significant evidence of chemical interaction between drug and carrier, which confirms the stability of drug with its solid dispersion. When guest molecules are incorporated in the ß-cyclodextrin cavity or in the crystal lattice, their melting, boiling, and sublimation points usually are shifted to a different temperature or disappear within the temperature range in which the ß-cyclodextrin lattice is decomposed. In Risperidone - β cyclodextrin inclusion complex DSC plot, two melting ranges were obtained. In one peak, melting process started at 106.38^{0}c and completed at 117.68^{0}c. In another peak, process was started at 212.24 ^{0}c and completed at 217.45^{0}c was suggested that Risperidone and β cyclodextrin used for the formulation was nothing but a mixture of both.SEM photograph was shown in figure 1. Drug content of all Solid dispersions was in the range of 90.1 to 99.8% which was in accordance with USP standards. In vitro dissolution Studies of all the formulations were performed and the cumulative percentage drug release was found increase from that of pure drug.

The different batches of Risperidone fast dissolving tablets were prepared by direct compression method using optimized Risperidone Solid Dispersion (1:3), various superdisintegrants like crospovidone and croscarmellose and it was evaluated.

Total of three formulations with fixed concentration of different super disintegrants and one control formulation without the addition superdisintegrants were prepared and evaluated. Weight variation of all formulations was observed which were within acceptable limit for uncoated tablets as per USP. Hardness of tablets was determined and was found to be in the range of 2.13 to 2.56kg/cm^2.Friability was observed between 0.18 to 0.34% which was within acceptable limits. The wetting times for all formulations from F1 to F4 were found to be 90 to 19 seconds respectively. The tablets were subjected for evaluation of *in vitro* disintegration time and was found to be 88 to 36 seconds. Percentage drug content of all formulations was found to be 94.0 to 101.5% of Risperidone which was within the acceptable limits.

Table 1: Formulation design of fast dissolving tablet of Risperidone Solid dispersion

Tablet Ingredients (mg)	F_1	F_2	F_3	F_4
Risperidone β-cyclodextrin solid dispersion (1:3)	16	16	16	16
Doshion-P544C	25	25	25	25
Mannitol	128	120	103	95
Camphor	5	5	5	5
Ac-di-sol	-	8	-	8
Aspartame	20	20	20	20
Crospovidone	-	-	25	25
Magnesium Stearate	2	2	2	2
Talc	2	2	2	2
Aerosil	2	2	2	2
Total	200	200	200	200

Table 2: Evaluation of Fast Dissolving Tablets

Parameter	F_1	F_2	F_3	F_4
Thickness(mm)	2.42	2.36	2.4	2.47
Friabilty(%)	0.32	0.27	0.34	0.18
Disintegration Time(sec)	88	61	72	36
Hardness(kg/cm^2)	2.56	2.31	2.32	2.13
Wetting Time(sec)	90	63	69	19

Table 3:Preformulation Studies of Blends

Parameter	F_1	F_2	F_3	F_4
Bulk density	0.43	0.41	0.45	0.40
Tapped density	0.58	0.58	0.66	0.66
Carrs index	26.19	29.25	31.83	39.9
Hausner's Ratio	1.35	1.41	1.46	1.66
Angle of repose	49^{0}05”	54^{0}02”	54^{0}12”	50^{0}20”

Table 4: Drug content studies of fast dissolving tablets of Risperidone solid dispersion

Batch No	Assay (%)
F_1	94.00
F_2	94.25
F_3	101.50
F_4	97.75

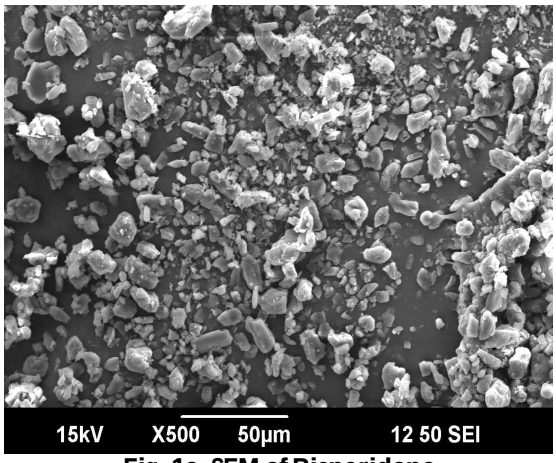

Fig. 1a: SEM of Risperidone

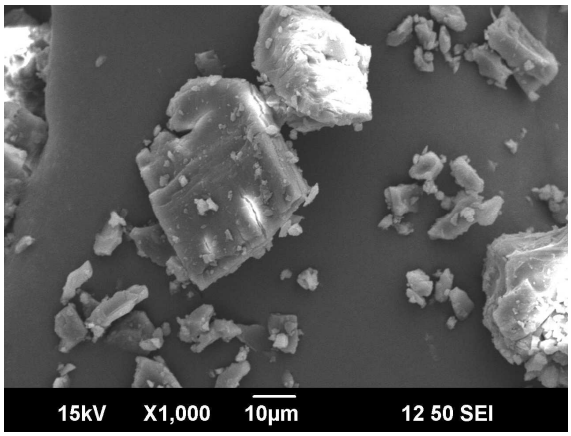

Fig. 1b: SEM of β-Cyclodextrin

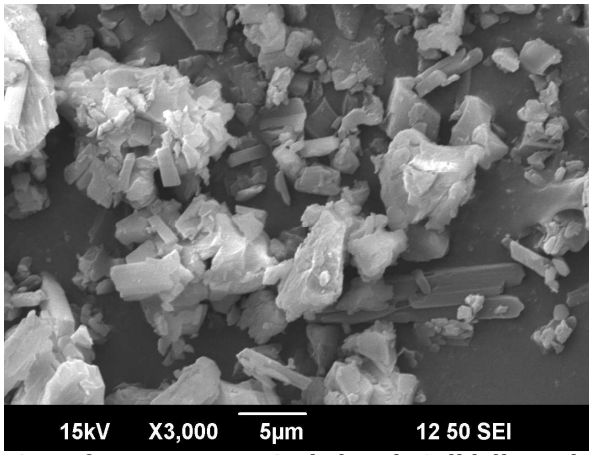

Fig. 1c: SEM of Risperidone:β-Cyclodextrin Solid dispersion(1:3)

SEM photomicrographs of Risperidone, B-CD and SDformulations

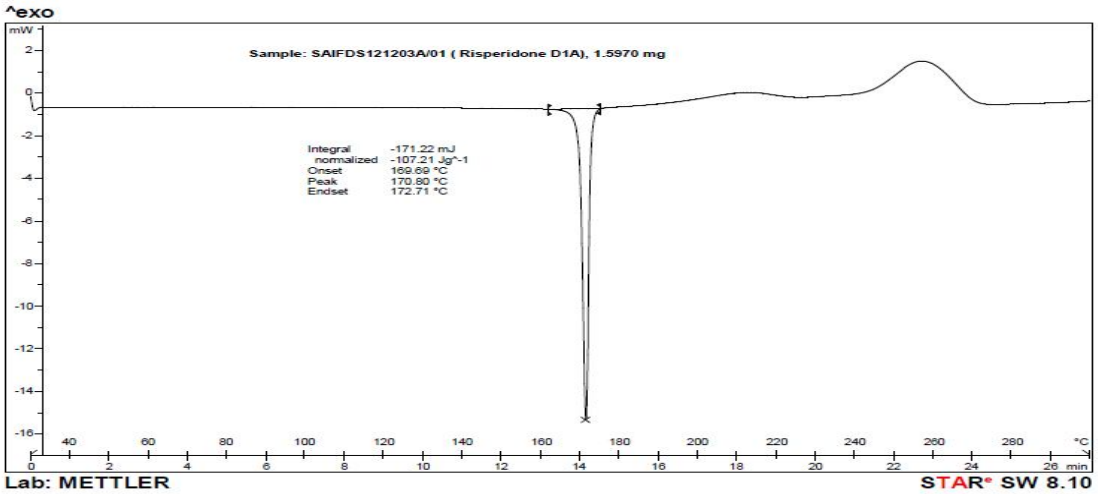

Fig. 2: DSC of Risperidone

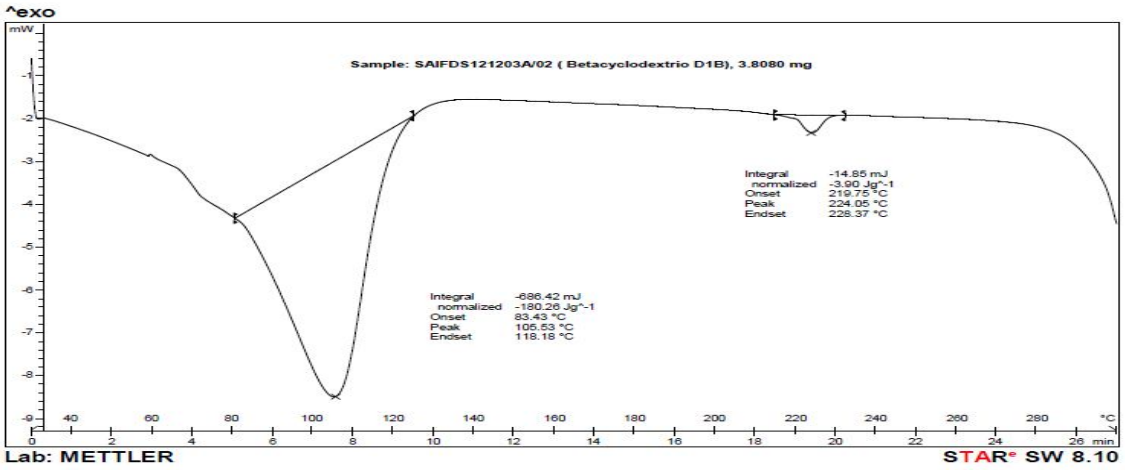

Fig. 3: DSC of β-Cyclodextrin

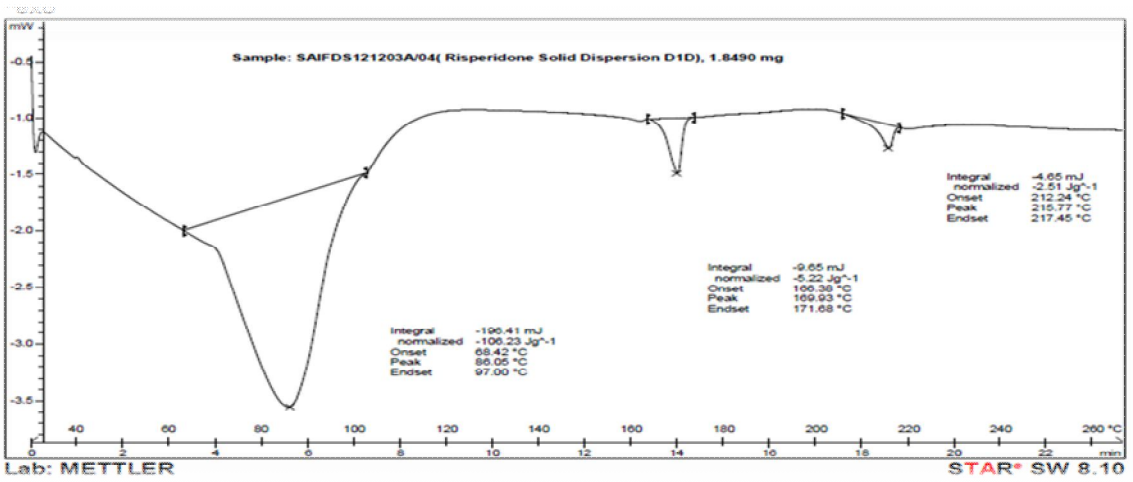

Fig. 4: DSC of Risperidone Solid Dispersion

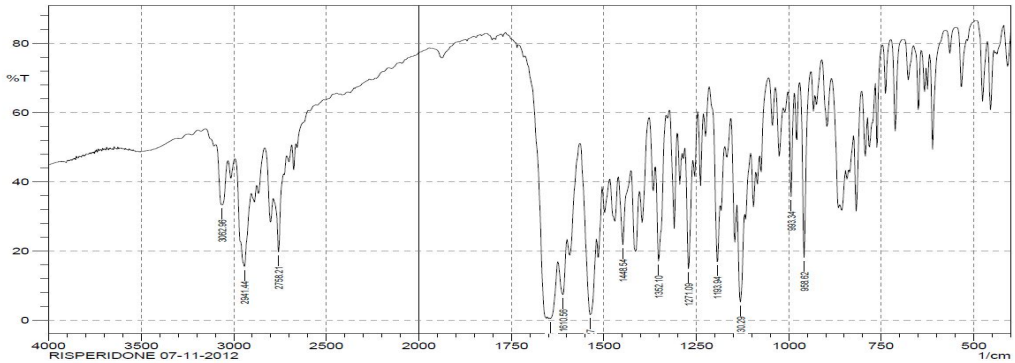

Fig. 5: FT-IR spectra of Risperidone

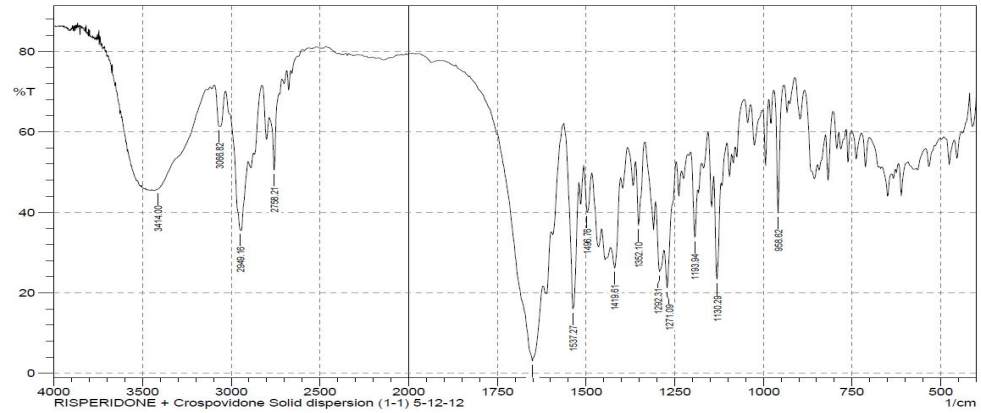

Fig. 6: FT-IR spectra of Risperidone +Crospovidone

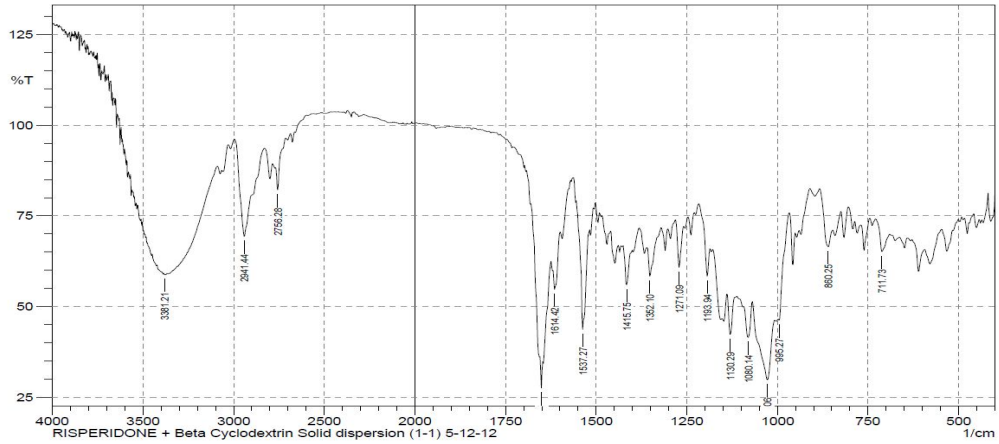

Fig. 7: FT-IR spectra of Risperidone + β-Cyclodextrin

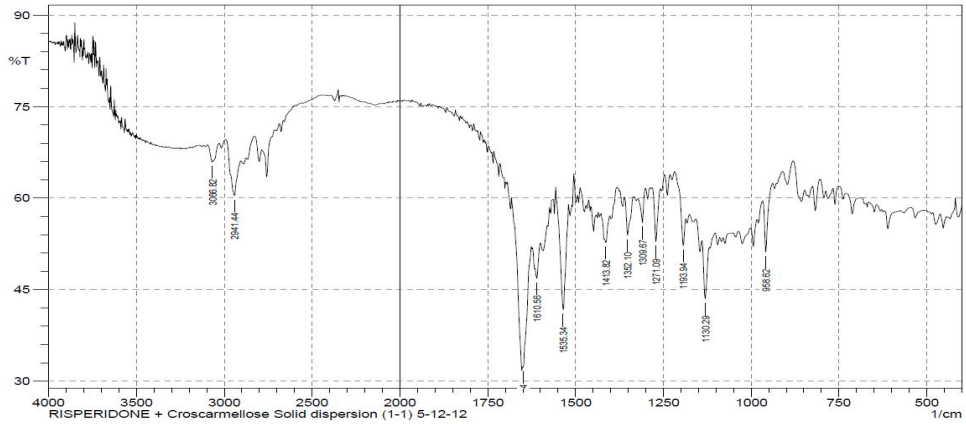

Fig. 8: FT-IR spectra of Risperidone + Croscarmellose

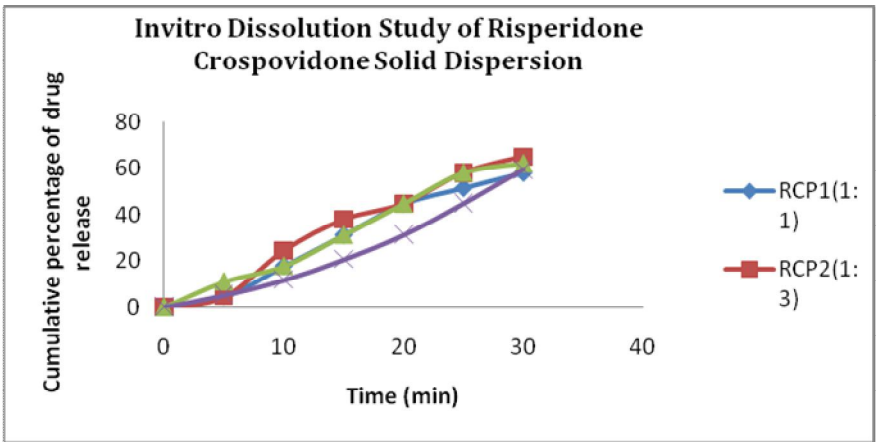

Fig. 9: In-vitro Dissolution Study of Risperidone: Crospovidone Solid dispersion

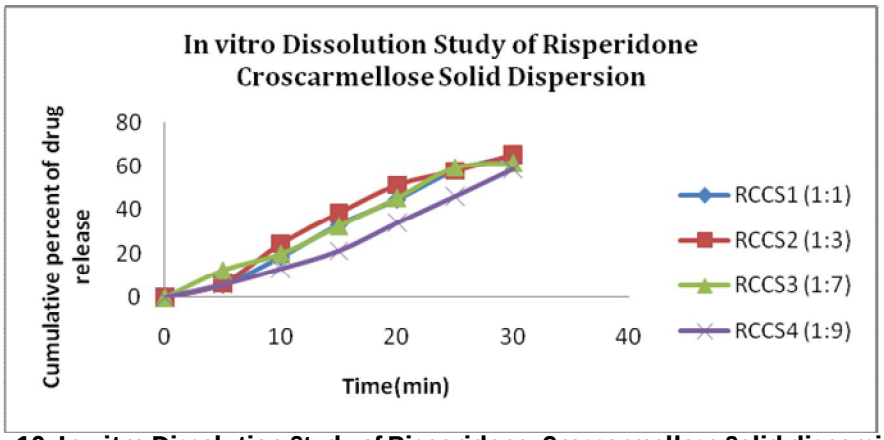

Fig. 10: In-vitro Dissolution Study of Risperidone: Croscarmellose Solid dispersion

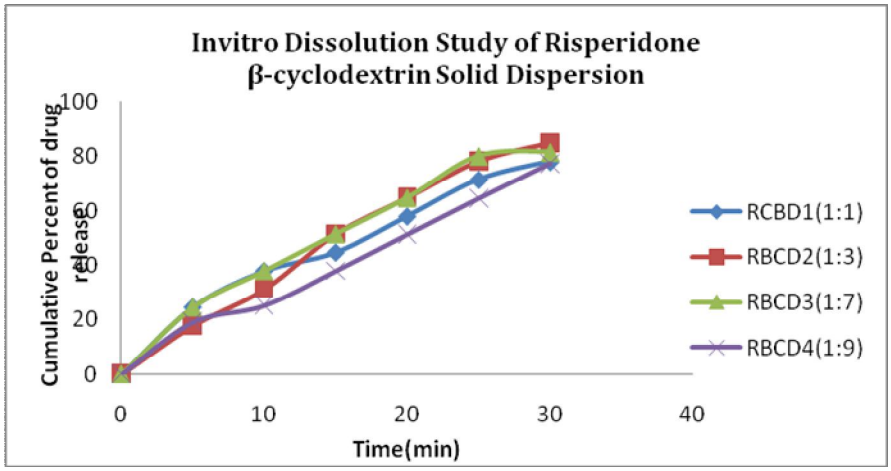

Fig. 11: In-vitro Dissolution Study of Risperidone: β-Cyclodextrin Solid dispersion

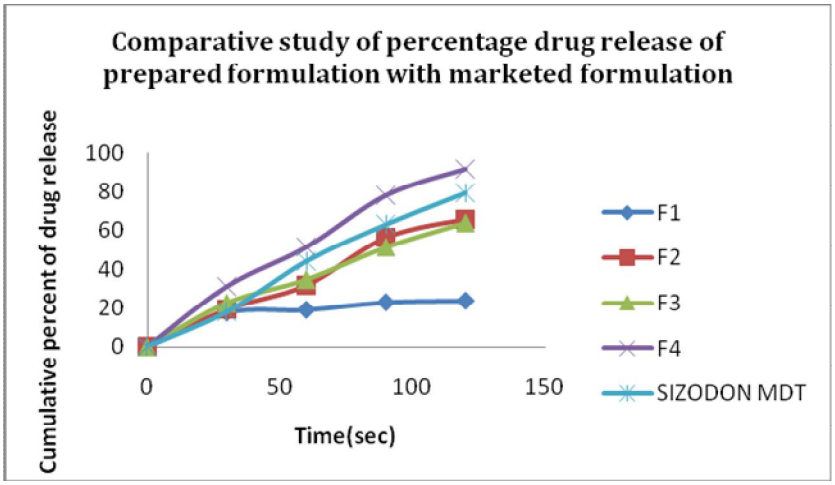

Fig. 12: Comparative study of drug release

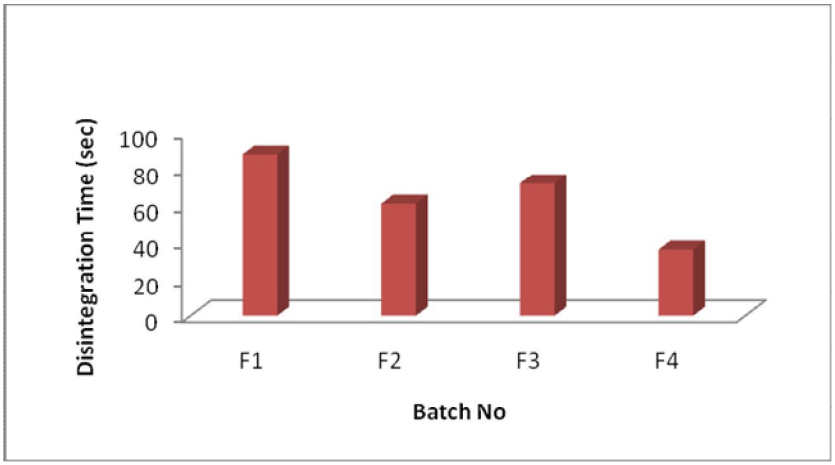

Fig. 13: Disintegration time (sec) of various batches containing differentsuperdisintegrants and its combination

CONCLUSION

It may be concluded that from the DSC, FT-IR, drug content and *in vitro* dissolution studies, solid dispersion of Risperidone with β-cyclodextrin(1:3) prepared by solvent evaporation method is the best formulation. Fast dissolving tablets of poorly soluble drug, Risperidone solid dispersion showed enhanced dissolution, which may lead to improved bioavailability and hence better patient compliance.

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