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Formulation and Evaluation of Risperidone Fast Disintegrating Tablets by Using Co-processed Superdisintegrants

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Abstract In the present work, an attempt has been made to develop fast disintegrating tablets of Risperidone. Novel method of co processed super disintegrates technology was employed to formulate the tablets. All the formulations were prepared by direct compression method using 8mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F8 formulation showed maximum % drug release i.e., 101.4 % in 2 min hence it is considered as optimized formulation. The F8 formulation contains CP3 as super disintegrate in the concentration of 20 mg. (CP 3 contains SSG and CCS in 1:3 ratio).

Keywords Risperidone, Co processed super disintegrants, Sodium starch glycol late, Cross carmellose sodium.

Introduction

Various Approaches for Fast Dissolving Tablets

The fast-dissolving property of the tablet is attributable to a quick ingress of water into the tablet matrix resulting in its rapid disintegration. Hence, the basic approaches to developing fast dissolving tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation [1]. Various technologies used in the manufacture of Fast dissolving tablets but mainly we selected co-processed superdisintegrants were used.

Co-processing is based on the novel concept of two or more excipients interacting at the sub particle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual. Co-processing excipients lead to the formulation of excipient granules with superior properties, compared with physical mixtures of components or individual components, like improved flow properties, improved compressibility, better dilution potential, fill weight uniformity, and reduced lubricant sensitivity [2-3].

Risperidone, a benzisoxazole derivative, is an atypical antipsychotic drug with high affinity for 5- hydrotryptamine (5-HT) and dopamine D2 receptors. It is used primarily in the management of schizophrenia, inappropriate behaviour in severe dementia and manic episodes associated with bipolar I disorder. Aim of this research work was to develop mouth dissolving tablet that disintegrates rapidly in mouth by using co-processed superdisintegrants and enhance the solubility of the drug facilitating for quick release [4-5].

Materials and Methods

Materials Risperidone was obtained from hetero Laboratories, Hyderabad, India. Microcrystalline cellulose, Sodium starch glycollate, Croscarmellose sodium and Magnesium stearate from Merck Specialities Pvt Ltd, Mumbai, India.

Preformulation Studies

preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies and flow properties [6].

Construction of Risperidone calibration curve with phosphate buffer PH 6.8

100 mg of Risperidone was dissolved in 100 ml of phosphate buffer PH 6.8 to give a concentration of 1 mg/ml (1000 µgm/ml). From the above standard solution (1000 µgm/ml) 1ml was taken and diluted to 100ml with phosphate buffer PH 6.8 to give a concentration of 0.01mg/ml (10 µgm/ml). From this stock solution aliquots of 0.2, 0.4, 0.6,0.8 and 1 ml were pipette out in 10ml volumetric flask and the volume was made up to the mark with phosphate buffer PH 6.8 to produce concentration of 2,4,6,8 and 10 µgm/ml respectively. The absorbance (abs) of each conc. was measured at respective (λ_{max}) *i.e.*, 278 nm.

Drug- excipient compatibility studies by FT-IR [7-8]

The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The potassium bromide pellets were prepared on KBr press by grounding the solid powder sample with 100 times the quantity of KBr in a mortar. The finely grounded powder was then introduced into a stainless steel die and was compressed between polished steel anvils at a pressure of about 8t/in^2. The spectra were recorded over the wave number of 8000 to 400cm^{-1}.

Flow Properties

Angle of Repose

It is performed to determine the flow rate of powder done by the funnel method. The powder was poured into a funnel which is fixed from height of 2cm of the plane surface. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculating Angle of repose using following formula:

$$\Theta = \tan^{-1} H/R$$

Θ=angle of repose

H=height of powder cone, R=radius of powder cone

Angle of Repose less than 30^0 shows the free flowing property of the material.

Loose bulk Density (LBD)

Loose bulk density was obtained by dividing the mass of powder by the bulk volume in cm^3. The sample of about 50 cm^3 of powder, previously been passed through a standard sieve no. 20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2 second intervals on to hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm^3 of the sample contained in the cylinder. It was calculated by using equation given below:

Df = M /Vp

Where, Df = bulk density

M = weight of sample in grams

Vp = final volume of powder in cm^3

Tapped bulk density (TBD)

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times if the difference between these two volumes is less than 2%. If it is more than 2%, tapping was continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2 % (in a bulk density apparatus). It is expressed in g/ml and is given by

Do = M /Vp

Where, Do = Tapped density,

M = weight of sample in grams

Vp = final volume of powder after tapping in cm^3

Carr's consolidation index:

The Carr index is an indication of the compressibility of a powder. This is calculated by the formula

$$C=100(1- \rho_b/\rho_t)$$

Where, ρ_b is the bulk density , ρ_t is the tapped bulk density

A Carr index greater than 25 is considered to be an indication of poor flowability, and below 15, of good flowability.

Hausner's ratio

The Hausner ratio is a number that is correlated to the flowability of a powder or granular material. The Hausner ratio is calculated by the formula

$$H= \rho_{b/} \rho_b$$

Where, ρ_b is the bulk density

ρ_b is the tapped bulk density

Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.

Formulation of Oro dispersible tablets of Risperidone:

Preparation of co processed super disintegrates:

Co processed super disintegrates were prepared by using sodium starch glycollate and cross carmellose sodium. The super disintegrates were mixed in different concentrations and labeled as CP1,CP2,CP3.The blend of super disintegrates was mixed thoroughly for a period of 15 min, collected and used for preparing formulations in different concentrations.

Table 1: Composition of co processed super disintegrates

Ingredients	CP1	CP2	CP3
SSG(mg)	100	100	100
CCS(mg)	100	200	300

CP = Co processed super disintegrate

Preparation of tablets

Composition of Risperidone Dispersible Tablet by direct compression is shown in table 6.4. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 8mm flat punch, B tooling. Each tablet contains 3 mg Risperidone and other pharmaceutical ingredients.

Table 2: Composition of various tablet formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Risperidone (mg)	3	3	3	3	3	3	3	3	3
CP 1(mg)	10	20	30	-	-	-	-	-	-
CP 2(mg)	-	-	-	10	20	30	-	-	-
CP 3(mg)	-	-	-	-	-	-	10	20	30
Mg St(mg)	2	2	2	2	2	2	2	2	2
Talc(mg)	2	2	2	2	2	2	2	2	2
MCC(mg)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total wt(mg)	100	100	100	100	100	100	100	100	100

Post Compression Parameters

Evaluation of uncoated tablets [9-12]

Shape and colour

The tablets were examined under a lens for the shape of the tablet and colour by keeping the tablets in light.

Uniformity of thickness:

Randomly 10 tablets were taken from formulation batch and their thickness (mm) was measured using a Vernier calipers.

Hardness test:

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. Six tablets were randomly picked from each formulation.

Friability test:

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche friabilator (Lab India, FT 1020). It is expressed in percentage (%). Ten tablets were initially weighed [$W_{(initial)}$] and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again [$W_{(final)}$]. The percentage friability was then calculated by,

$$F = \frac{[W(\text{initial}) - W(\text{final})]}{W(\text{initial})} X100$$

Weight variation test

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The % deviation in weight variation is shown in table.

Drug Content estimation

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch.

Four tablets were weighed and crushed in the mortar. The powder equivalent to 1.25 mg of the drug were weighed and dissolved in 100ml phosphate buffer PH 6.8 to give a concentration of 12.5 µg/ml. 2ml of this solution was taken

and diluted to 10ml to give a concentration of 2.5µg/ml. The absorbance of the prepared solution was measured at 278nm using UV Visible spectrophotometer (Lab India, UV-3200).

***In -vitro* dissolution studies [13-16]**

In-vitro release studies were carried out using a modified USP XXIII dissolution test apparatus (Lab India, DS-800). The dissolution fluid was 500ml of phosphate buffer pH 6.8 at a speed of 50rpm at a temperature of 37^0c were used in each test. Samples of dissolution medium (5ml) were withdrawn for every 2min and assayed for Risperidone by measuring absorbance at 278 nm. For all the tests 5ml of the test medium were collected at specified time intervals and replaced with same volume of phosphate buffer PH 6.8. Details:

Application of Release Rate Kinetics to Dissolution Data [17-19]

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$\text{Log } (100\text{-}F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t/ M_\infty = K\ t^n$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

Hixson-Crowell release model:

$(100\text{-}Q_t)^{1/3} = 100^{1/3} – K_{HC}.t$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

Results and Discussion

Standard Calibration curve of Risperidone:

It was found that the estimation of Risperidone by UV spectrophotometric method at λ_{max} 278.0 nm in pH 6.8 Phosphate buffer had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 2- 10µg/ml. The regression equation generated was y = 0.0376x +0.0436.

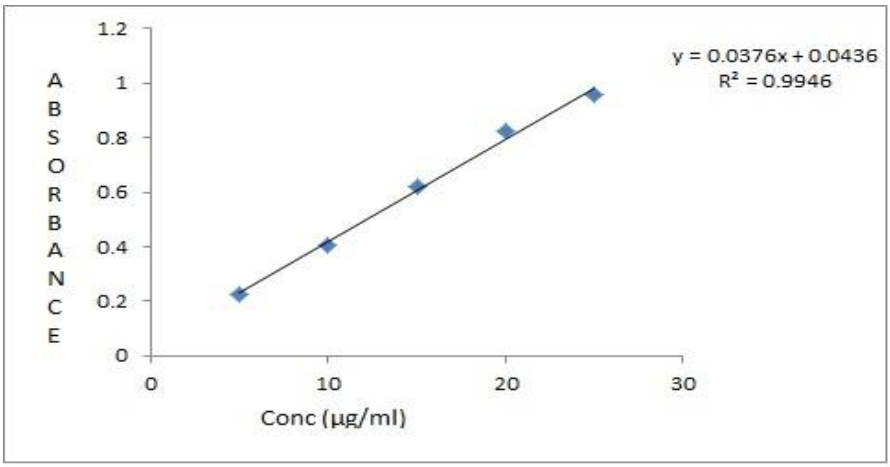

Figure 1: Standard graph of Risperidone in pH 6.8 Phosphate buffer

Evaluation Parameters for Fast Dissolving Tablets of Risperidone:

Pre-compression parameters:

The data's were shown in Table 3. The values for angle of repose were found in the range of 25°-30°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41 to 0.50 (gm/cc) and 0.50 to 0.58 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 13.06% to 18.18%. The Hausner ration fall in range of 1.14 to 1.22. From the results, it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Table 3: Pre-compression parameters

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle of Repose(Ɵ)
F_1	0.45	0.55	18.18	1.22	27.91
F_2	0.47	0.55	14.54	1.17	28.23
F_3	0.50	0.58	13.79	1.16	29.34
F_4	0.46	0.55	16.36	1.19	26.71
F_5	0.50	0.58	13.79	1.16	29.34
F_6	0.47	0.55	14.54	1.17	28.23
F_7	0.50	0.58	13.79	1.16	29.34
F_8	0.41	0.50	18	1.21	26.78
F_9	0.41	0.50	18	1.21	26.78

Post compression Parameters:

Weight variation test

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 4. The average weight of the tablet is approximately in range of 107 to 98.5, so the permissible limit is ±10% (110-90mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test

Hardness of the three tablets of each batch was checked by using Monsanto hardness tester and the data's were shown in Table 4. The results showed that the hardness of the tablets is in range of 2.5 to 3.00 kg/cm^2, which was within IP limits.

Thickness

Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table-4 .The result showed that thickness of the tablet is raging from 3.56 to 3.64.

Friability

Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 4. The average friability of all the formulations lies in the range of 0.30 to 0.51% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

***In vitro* disintegration time**

Tablets of each batch were evaluated for *in vitro* disintegration time and the data's were shown in the Table 4. The results showed that the disintegration time of prepared tablets were in the range of 12.66 to 30.33 seconds.

Assay

Assay studies were performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the % drug content values within 97.23 -99.25 %.

Table 4: Post-Compression parameters**:**

Formulation Code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Disintegration Time (sec)	Friability (%)	Assay (%)
F1	105	2.5	3.59	20.33	0.43	97.23
F2	104	2.6	3.64	22.66	0.34	98.55
F3	110	2.5	3.59	30.33	0.49	98.16
F4	109	2.6	3.58	19.00	0.47	99.34
F5	99.4	2.3	3.59	30.33	0.49	98.16
F6	102	2.7	3.64	22.66	0.34	98.55
F7	101	2.5	3.59	30.33	0.49	98.16
F8	107	2.6	3.56	17.00	0.34	99.25
F9	102	2.5	3.56	17.00	0.34	99.25

Table 5: *In vitro* dissolution data

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	25.4	31.7	30.8	24.3	39.5	14.9	48.3	101.16	99.45
4	39.6	34.5	36.72	31.6	76.3	28.4	82.9	101.8	100.33
6	48.6	41.9	56.16	49.3	96.2	33.1	98.7		
8	64.3	62.4	87.4	58.3	99.7	59.7			
10	76.4	89.1	98.5	74.3		79.3			
15	97.1	99.5		88.1		88.9			
20	97.6			94.6		93.5			
25				98.1		98.1			
30									

***In vitro* Dissolution studies:**

Invitro dissolution studies were carried out by using 500 ml of pH 6.8 Phosphate buffer in USP dissolution apparatus by using paddle method. The dissolution studies were carried out for about 30 min. The dissolution data for all the formulations were given in the Table 5.

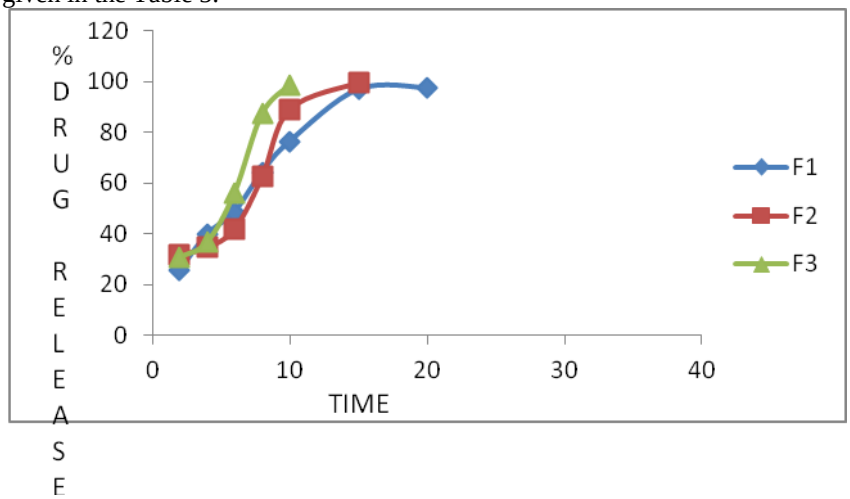

Figure 2: Dissolution profile of formulations prepared with CP1 as super disintegrate

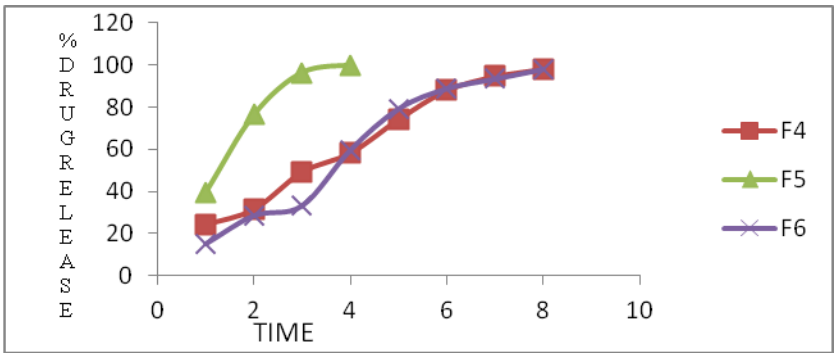

Figure 3: Dissolution profile of formulations prepared with CP2 as super disintegrate

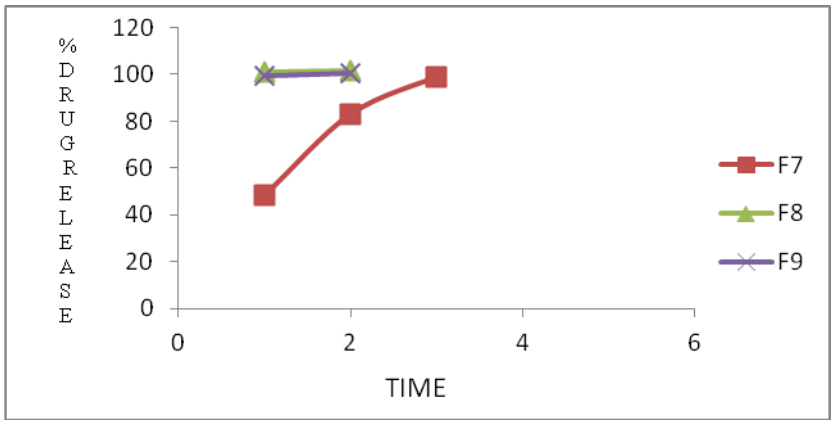

Figure 4: Dissolution profile of formulations prepared with CP3 as super disintegrate

From the tabular column 5 it was evident that the formulations prepared with super disintegrate CP3 showed maximum % drug release in 2 min i.e.101.96% and 101.1% (F8,F9 formulations and the concentration of super disintegrate is 20mg,30 mg). So the principle of coproceesed super disintegrates was found to be useful to produce oro dispersible tablets .F8 formulation was considered as optimized formulation as it contains less concentration of super disintegrate.

Fourier Transform-Infrared Spectroscopy:

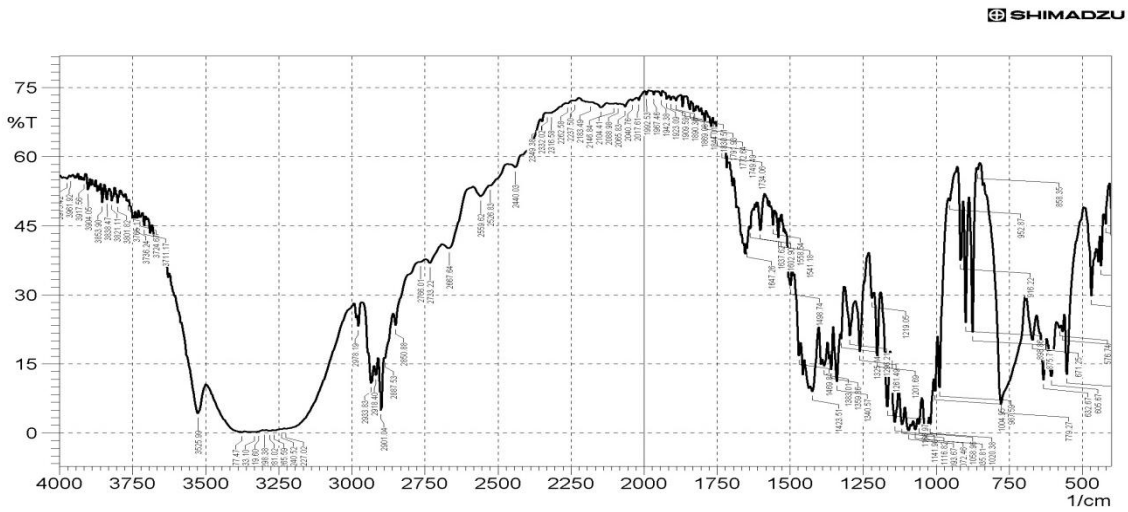

Figure 5: FT-TR Spectrum of Resperidone pure drug.

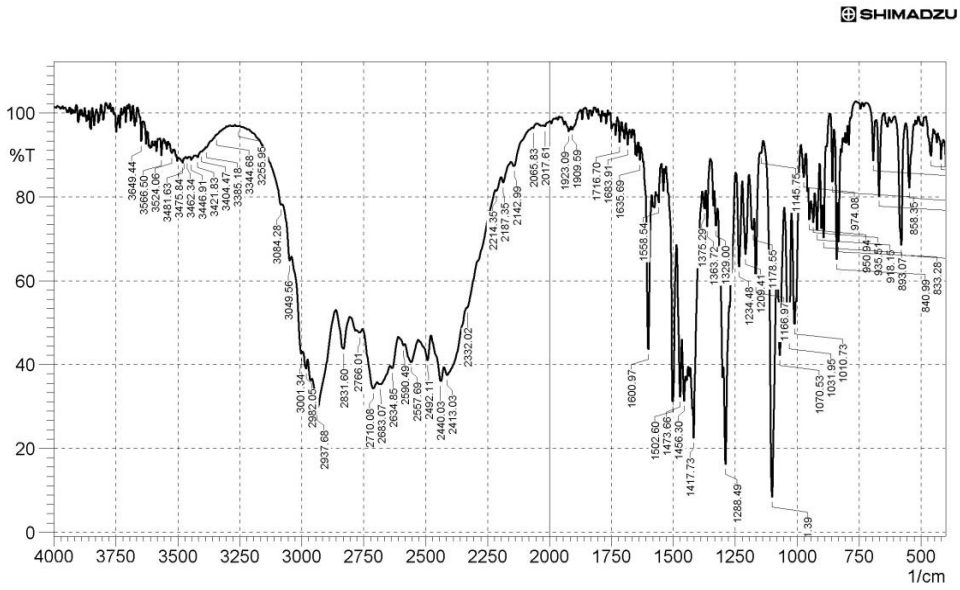

Figure 6: FT-IR Spectrum of Optimized Formulation

From the FTIR data it was evident that the drug and super disintegrates, other excipients doses not have any interactions**.** Hence they were compatible.

Conclusion

In the present work, an attempt has been made to develop fast disintegrating tablets of Risperidone. Novel method of co processed super disintegrates technology was employed to formulate the tablets. All the formulations were prepared by direct compression method using 8mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed god flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F8 formulation showed maximum % drug release *i.e.*, 101.4 % in 2 min hence it is considered as optimized formulation. The F8 formulation contains CP3 as super disintegrate in the concentration of 20 mg. (CP 3 contains SSG and CCS in 1:3 ratio).

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