Available Online through
www.ijpbs.com (or) www.ijpbsonline.com

IJPBS |Volume 3| Issue 3 |JUL-SEP|2013|290-298

Research Article
Pharmaceutical Sciences

FORMULATION AND EVALUATION OF RISPERIDONE SUSTAINED RELEASE TABLETS

Santosh Duddelli[1], Vedavathi T, Ajay Kumar[†], Zuheb ur rahman*, R Shireesh kiran[1]

[1]*Department of Pharmaceutics, CMR College of Pharmacy, Medchal, Hyderabad, A.P, India*

† Project coordinator, Richer Pharmaceuticals, Hyderabad.

***Corresponding Author Email:** zuheburrahman@gmail.com

ABSTRACT

Schizophrenia affects around 0.3–0.7% of people or 24 million people worldwide as of 2011. It occurs 1.4 times more frequently in males than females and typically appears earlier in men the peak ages of onset are 20–28 years for males and 26–32 years for females. Onset in childhood is much rare. The aim of the current investigation is to design oral twice a daily sustained release matrix tablets of Risperidone 4mg, used for the treatment of Schizophrenia which can release the drug for 10 to 12 hours. The tablets were prepared by the Wet granulation method using varying concentrations of sustained release polymers HPMC, Eudragit and Ethyl cellulose. The compatibility of the polymers was ruled out by FT-IR studies and found to be compatible. Total 9 formulations were prepared. The Risperidone powder and the powder-blends of tablets were evaluated for their physical properties like angle of repose, bulk density and compressibility index and found to be good and satisfactory. The manufactured tablets were evaluated for in process and finished product quality control tests including appearance, dimensions, weight variation, hardness, friability, drug content, and in vitro drug release. The dissolution medium used was pH 6.8 Phosphate buffer. All formulations showed acceptable pharmaco-technical properties and complied with in-house specifications for tested parameters. The results of dissolution studies indicated all formulations released up to 12hours and formulation containing Ethyl cellulose (5%) i.e. F7 was the most successful formulation with 96.72% drug release at the end of 12 hours. Based on mathematical models the formulation F7 fitted into zero order and korsmeyer- peppas plot with 0.942 and 0.999 regression values respectively and show fickian diffusion mechanism release.

KEY WORDS

Schizophrenia; Risperidone; Sustained release polymers; sustained release; matrix tablets formulation; evaluation; in vitro release.

INTRODUCTION

Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects.[1] The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. The desire to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.[2]

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the reparations. Hydrophilic

polymer matrix is widely used for formulating an SR dosage form. [3,4,5, 6] Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained release or controlled release drug delivery systems[7]. Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers.

By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poor water soluble drugs.

Risperidone is a potent antipsychotic drug which is mainly used to treat schizophrenia (including adolescent schizophrenia), schizoaffective disorder, the mixed and manic states associated with bipolar disorder, and irritability in people with autism. 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 behavior in severe dementia and manic episodes associated with bipolar I disorder. Risperidone is effective for treating the positive and negative symptoms of schizophrenia owing to its affinity for its “loose” binding affinity for dopamine D2 receptors and additional 5-HT antagonism compared to first generation antipsychotics, which are strong, non-specific dopamine D2 receptor antagonists.[8]

Sustained release tablets can be prepared by direct compression method using hydrophilic polymers such as HPC, HPMCK4M, and Sodium alginate.

MATERIALS AND METHODS

MATERIALS

Risperidone was obtained as a gift sample from Aurobindo pharma, Hyderabad. Ethycellulose, Eudragit and Hydroxy propyl methyl cellulose K4M was obtained as a gift sample from Loba Chem Pvt.Ltd, Mumbai. Starch, Di-calcium phosphate, Isopropyl alcohol, Talc, Magnesium stearate was purchased from S.D.Fine Chem.Ltd., Mumbai. All other chemicals and solvents were purchased from analytical grade.

METHODS

Wet Granulation method: The drug and the excipients were passed through sieve no: 40 except lubricant and glidant. Weighed amount of drug and excipients (diluent, binder and sustained release agents) were mixed using Isopropyl alcohol as granulating agent. The blend was subjected to drying at 60^{o}c for 5hrs, for removal of moisture. After drying the powder is collected and the remaining excipients i.e. Glidant and lubricant were added (perceived through sieve no: 80) and was compressed by using flat faced punches in CADMACH 16 punches tablet punching machine. Round punches measuring 8.7mm diameter were used for compression. Tablet of 200mg was prepared by adjusting hardness and volume screw of compression machine properly. (**Figure No: 1**)

EVALUATION PARAMETERS

1. Bulk density:

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml. (**Table No: 2**)

Bulk density = Weight of powder / Bulk volume

2. Tapped density:

It is the ratio of total mass of powder to the tapped volume of powder. It is determined by placing a graduated cylinder containing known weight of powder, mechanical tapper apparatus operated for fixed number of taps until the powder bed volume has reached a minimum volume. (**Table No: 2**)

Tapped density = Weight of powder / Tapped volume

3. Carr's Index (I):

It is measured by using values of bulk density and tapped density. (**Table No: 2**)

$$\frac{\text{Tappeddensity - Bulk density}}{\text{Tappeddensity}} \times 100$$

4. Hausner's ratio:

Hausner's ratio is the ratio of tapped density to bulk density. (**Table No: 2**)

$$\text{Hausner's Ratio} = \frac{\text{TappedDensity}}{\textit{Bulk Density}}$$

5. Angle of Repose:

The frictional forces in a loose powder can be measured by the angle of repose, θ. (**Table No: 2**)

$$\theta = \tan^{-1} (h/r)$$

Where h=height of the heap

r=radius of the heap

It is determined by pouring the powder a conical on a level, flat surface, measured the included angle with the horizontal.

6. Hardness:

The hardness of the tablet was determined by using a Monsanto hardness tester. It is expressed in **Kg / cm^2.**

7. Thickness:

The thickness of the tablets was measured by Digital Vernier Caliper. It is expressed in **mm**.

8. Weight Variation:

Ten tablets were selected randomly from the lot and weighed individually to check for weight variation. The following %deviation in weight variation is allowed.

9. Friability (F):

The friability of the tablet was determined using Roche Friabilator. It is expressed in **%**. 10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 mins. The tablets were weighed again. Friability of tablet should not exceed 1%.

10. Determination of drug content

Weigh and powdered 10 tablets in a mortar. From this powder equivalent to 10 mg of Chlorzoxazone was taken in a volumetric flask to this 5 ml of methanol was added and then the solution was subjected to sonication for about 10min for complete solubilization of drug and the solution was made up to the mark with methanol, filtered and further appropriate dilutions were made with phosphate buffer pH 6.8 and the drug content was estimated by measuring the absorbance at 280 nm by using UV-Visible spectrophotometer.

11. Drug-Excipient Interaction Studies

This type of interactions was studied with the help of Shimadzu FTIR spectrophotometer, in which KBR pellet method used to determine the interactions.

12. In vitro dissolution studies

The dissolution studies were performed using USP 24 type II paddle apparatus, employing paddle stirrer rotating at 75 rpm, 900 ml of phosphate buffer pH 6.8 as a dissolution medium at 37 ± 0.5°C. 5 ml aliquots of dissolution medium was withdrawn at specified time intervals and the volume of the dissolution medium was maintained by adding the same volume of fresh dissolution medium. The absorbance of the withdrawn samples was measured spectro photometrically at 280 nm. (**Table No: 4**)

13. Stability studies

The stability studies were conducted for satisfactory formulation as ICH guidelines. The satisfactory formulation sealed in aluminum packaging and kept in humidity chamber containing 30±2°C with 65±5% RH for 2months.Samples were analyzed for drug content and in vitro drug release profile. (**Table No: 5**)

14. Drug release kinetics

To analyze the mechanism of drug release from the tablets, the results of *in vitro* release data were plotted in various kinetic models like zero order, Higuchi model and Korsmeyer- peppas. (**Table No: 6**)

RESULTS AND DISCUSSION

Evaluation parameters

Tablets of different formulations were subjected to various physicochemical evaluation parameters such as weight variation, hardness, friability, thickness, drug content, and diameter. The results of these studies were found to be within the limits and given in **Table No.3**.

Compatibility studies

The standard spectrum of Risperidone shown in fig.7 was compared by FTIR spectrum of physical mixtures **Fig 8, 9, and 10**. FTIR studies proved that the drug is compatible with excipients**.**

In vitro dissolution studies

Dissolution is carried out in USP 2 type apparatus at 50rpm in the volume of 900ml dissolution media (phosphate buffer pH 6.8) for 12hours. The dissolution rate was found to decrease linearly with increasing concentration of Sustained release agent. Formulations F1, F2, and F3 which contained HPMC shows % drug release of 93.71%, 87.69%,and 82.11% Formulations F4, F5, and F6 which contained Eudragit shows % drug release of 94.57%, 88.98%, and 83.83% respectively. Formulations F7, F8, and F9 which contained Ethyl cellulose shows % drug release of 96.72%, 90.27%, and 82.54% respectively. The % drug release of all the formulations **Table 21** (F1-F3), **Table 22** (F4-F5) and **Table No: 4** (F7-F9) and the comparative release profile in **Fig.2**.

Release kinetics

Different models like zero order, first order, higuchi's, and peppas plots were drawn for formulation F-7. The regression coefficient (r^2) value for zero order, first order, higuchi's, and peppas plots (**Figures No: 3-6 and Table No: 6**) for formulation F-7 was found to be 0.942, 0.933, 0.966, and 0.999 respectively. The formulation F-7 follows zero order release and peppas plot. Since the regression coefficient of peppas was 0.999 and slope 'n' value is less than 0.5 which confirms that the drug release through the matrix was fickian diffusion.

Stability studies

F7 formulation was subjected to stability studies. It was suggested that there was no significant change physical parameters such as weight variation, hardness, friability, thickness; drug content. This is shown in **Table No 5**.

CONCLUSION

The incorporation of drugs into polymer matrices is considered a valid tool in order to optimize insufficient features of the drug molecule, like solubility, stability or toxic effects. In the present work, the incorporation of Risperidone was performed in inert HPMC, Eudragit and Ethyl cellulose to retard the release of drug as sustained release polymers. All polymers are used in different concentrations to achieve sustained release of the drug. The Risperidone powder and the powder-blends of tablets were evaluated for their physical properties like angle of repose, bulk density and compressibility index and found to be good and satisfactory. The manufactured tablets were evaluated for in process and finished product quality control tests including appearance, dimensions, weight variation, hardness, friability, drug content uniformity and concluded to be within limits. Hardness values ranged from 5.7 to 5.9 kg/cm2 , weight variation ranged from 198±1.3 mg to 203.5±1.72 mg, thickness of all the tablets ranges between 3.8±0.02 mm to 3.9±0.04 mm and friability values were in range of 0.1 – 0.2%. The maximum drug content among all the formulations was 101.48±0.5 and minimum % drug content from the all formulation was 96.23±1.22. From the dissolution studies, it was observed that all batches gave the release by diffusion-dissolution controlled mechanism. The dispersion of the drug in the polymer network altered its dissolution profile at ph 6.8, thus making it possible to obtain a gradual and prolonged release. The dissolution profile data shows that F7 (ethyl cellulose 5%) has more prominent linear release compared to other formulations. Based on mathematical models, it was concluded that F7 fitted into zero order and korsmeyer- peppas plot with fickian diffusion mechanism release.

ACKNOWLEDGEMENT

This study was supported by Richer Pharmaceuticals, kukatpally, Hyderabad.

REFERENCES

1. Lieberman HA, Lachman L and Schwartz JB., Pharmaceutical Dosage Forms: Tablets, Volume 3, 2nd edition, 199-287.
2. Kuno Y, Kojima M, Ando S, Nakagami H, Evaluation of rapidly disintegrating tablets manufactured by phase transition of sugar alcohols, J Control Release, 105, 2005, 16-22.
3. Vidyadhara S, Rao PR., Prasad JA., Indian J. Pharm Sci, 66, 188-192 (2004).
4. Reddy KR., Mutalik S, Reddy S, AAPS Pharm. Sci. Tech., 4, 1-9, (2003)
5. Mohammed AD., James LF., Michael HR., John EH., Rajabi-Siahboomi AR., Phar. Dev. Tech., 4, 313-324 (1999).
6. Lee BJ, Ryu SG, Cui JH, Drug Dev. Ind. Pharm., 25, 493-501 (1999).
7. Gwen MJ and Joseph RR, In Banker GS and Rhodes CT, Eds., Modern Pharmaceutics, 3rd Edn, Vol. 72, Marcel Dekker Inc. New York, 1996, 575.
8. http://www.drugbank.ca/drugs/DB00734.

Table No 1: Formulation of Different Batches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Model drug (Risperidone)	4	4	4	4	4	4	4	4	4
Starch	129.5	122	114.5	129.5	122	114.5	129.5	122	114.5
Ethyl Cellulose N-20	-	-	-	-	-	-	7.5 (5%)	15 (10%)	22.5 (15%)
Eudragit S-100	-	-	-	7.5 (5%)	15 (10%)	22.5 (15%)	-	-	-
HPMC K_4M	7.5 (5%)	15 (10%)	22.5 (15%)	-	-	-	-	-	-
Di-calcium Phosphate	50	50	50	50	50	50	50	50	50
Magnesium Stearate (4%)	6	6	6	6	6	6	6	6	6
Talc (2%)	3	3	3	3	3	3	3	3	3

Table No 2: Pre-compression studies of the blend

Property	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of repose	24.15	24.2	24.61	24.23	24	23.6	22.61	22.9	23.42
Bulk density gm/cm^3	0.405	0.43	0.41	0.39	0.43	0.41	0.42	0.45	0.41
Tapped density gm/cm^3	0.47	0.511	0.496	0.462	0.515	0.48	0.496	0.52	0.478
% Compressibility	13.82	15.85	17.33	15.58	16.50	14.58	15.32	13.46	14.22
hausner's ratio	1.16	1.18	1.20	1.18	1.19	1.17	1.18	1.15	1.16

Table No 3: Post compression studies of Risperidone Sustained Release tablets

Formulation	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Thickness (mm)	Drug content Uniformity (%)
F1	5.85±0.37	0.139	203.5±1.72	3.85±0.02	98.18±0.86
F2	5.85±0.45	0.1	200.5±1.8	3.86±0.04	96.23±1.22
F3	5.8±0.52	0.1	202±1.54	3.86±0.019	98.05±1.58
F4	5.9±0.52	0.27	204±1.3	3.5±0.04	98.62±1.51
F5	5.87±0.49	0.139	201±1.9	3.85±0.03	97.59±0.52
F6	5.9±0.61	0.139	199±1.42	3.86±0.03	100.11±1.78
F7	5.85±0.32	0.29	199.5±1.8	3.85±0.03	99.5±0.5
F8	5.9±0.68	0.17	198±1.3	3.86±0.02	98.83±1.04
F9	5.85±0.44	0.15	202±1.6	3.85±0.02	101.48±0.5

Table No 4: Dissolution tables of formulations in 6.8phosphate buffer

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	46.42±0.92	36.11±1.16	31.38±1.27	42.99±0.37	33.96±0.09	37.40±0.13	55.027±0.030	42.13±0.66	25.36±0.44
4	57.17±0.67	52.01±0.79	41.70±1.03	56.31±0.31	47.28±1.72	45.13±0.95	70.073±0.32	55.02±0.61	43.84±0.17
6	71.79±1.33	64.05±0.51	57.17±0.67	64.05±87	58.46±1.26	52.01±0.79	73.08±0.67	64.48±0.46	51.58±0.61
8	79.10±1.16	72.22±1.32	64.05±1.51	76.52±0.72	70.07±0.9	59.32±0.62	82.54±1.12	73.51±0.84	60.61±0.62
10	88.12±0.95	80.82±1.12	73.08±1.03	86.4±0.15	79.10±0.24	71.79±1.33	89.84±0.28	81.68±0.26	72.22±0.29
12	93.71±0.82	87.69±0.96	82.11±1.09	94.57±0.28	88.98±0.93	83.83±0.05	96.72±0.16	90.27±0.62	82.54±0.91

STABILITY STUDIES

Table No.5 Stability studies: Drug content

Formulation	Initial amount	30±2°c/65 ± 5%RH after1month	30±2°c/65 ± 5%RH after2nd month
F7	96.72 ±0.38	96.1±0.45	95.9±0.35

Table No: 6 Kinetic Model Fitting for Formulation F7

Time in min	SQRT of time	Log time	%CDR	Log %CDR	Cu % Drug remain	Log Cu % Drug remain
0	0	0	0	0	100	2
120	11	1.04	28.4	1.45	71.6	1.85
240	15.5	1.19	44.1	1.64	55.9	1.74
360	19	1.27	62.6	1.79	37.4	1.57
480	21.9	1.34	79	1.89	21	1.32
600	24.5	1.38	89.7	1.95	10.3	1.01
720	26.8	1.42	96.7	1.98	3.3	0.51

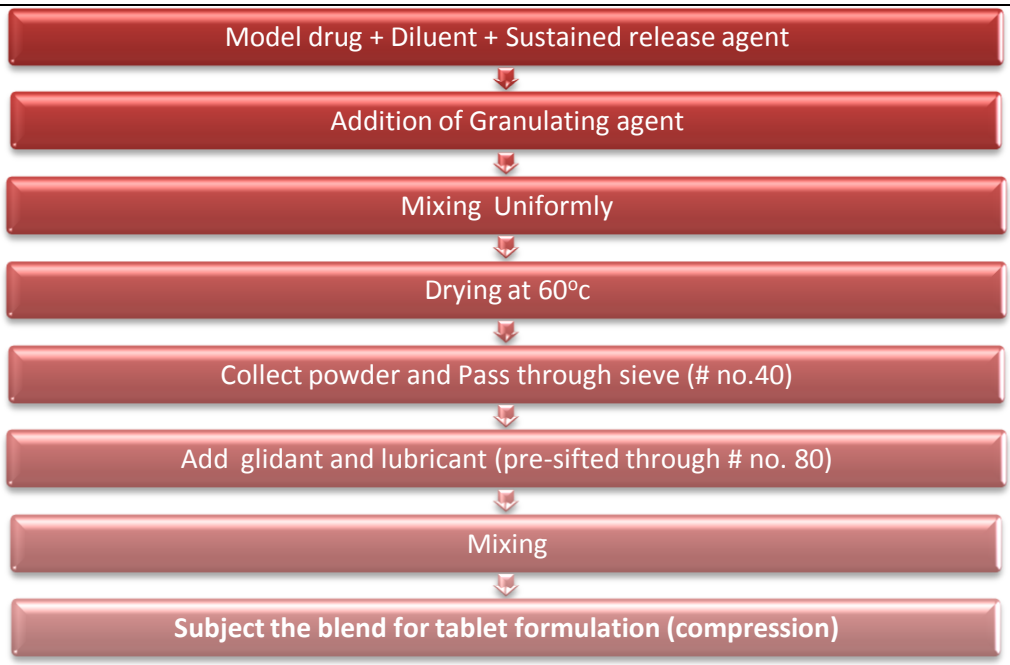

Figure No: 1 Representation of Wet granulation Technique for design of sustained release tablet

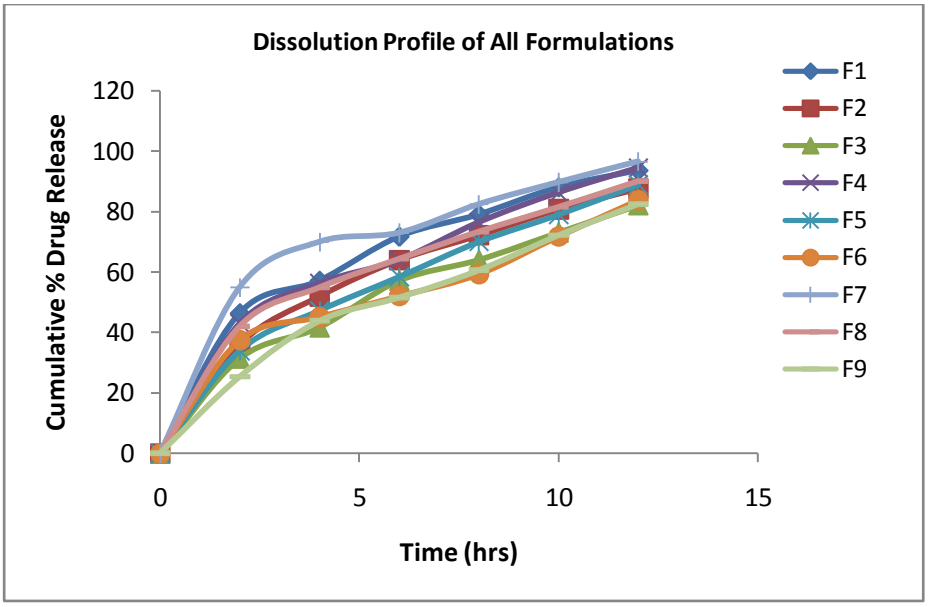

Figure No.2 Drug Release of All Risperidone SR Formulations

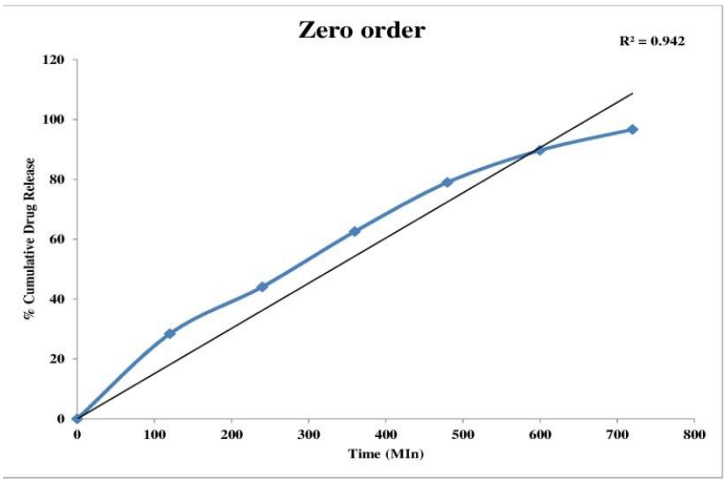

Figure No: 3 *In vitro* release profile of Risperidone from tablets of F7 fitted in zero order release

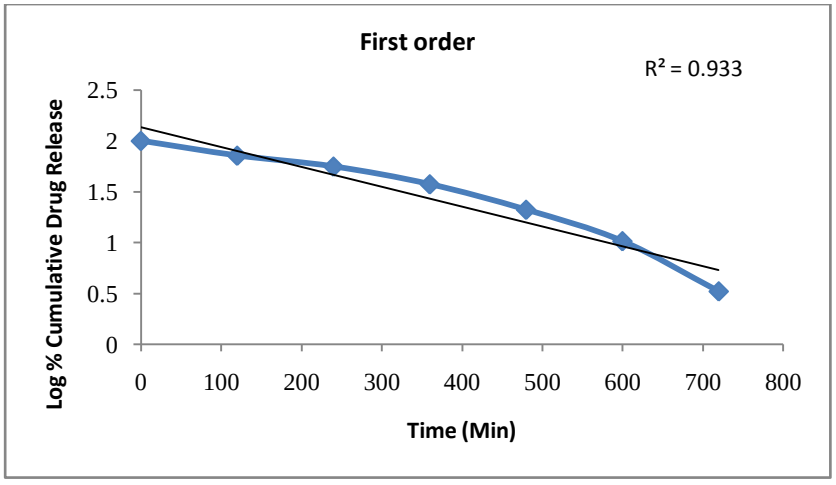

Figure No: 4 *In vitro* release profile of Risperidone from tablets of F7 fitted in first order release

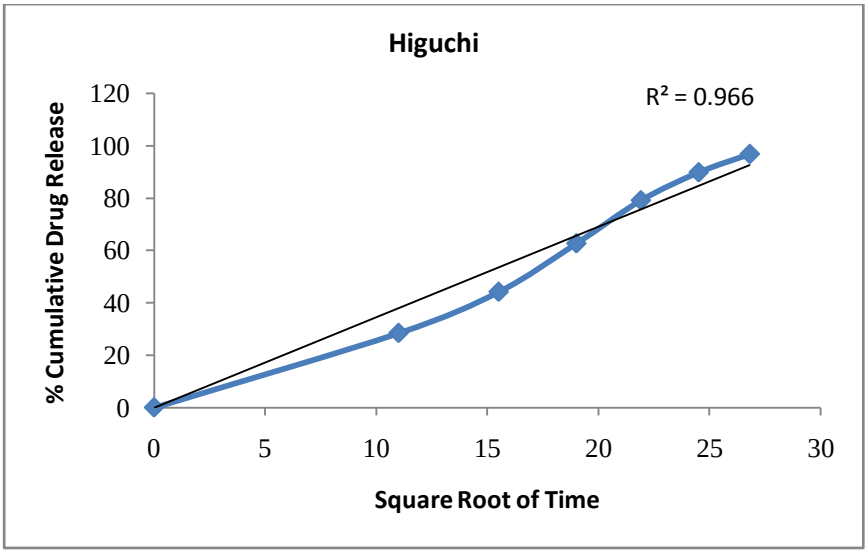

Figure No: 5 *in vitro* release profile of Risperidone from tablets of F7 fitted in Higuchi plot

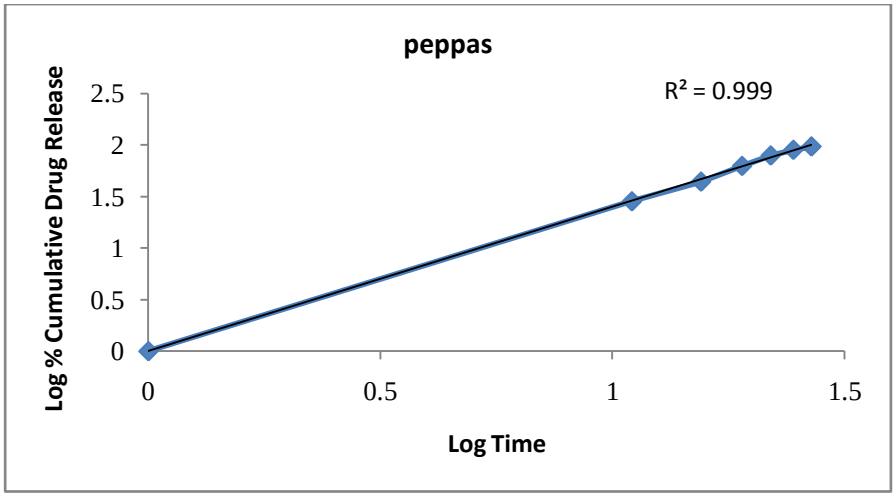

Figure No: 6 *In vitro* release profile of Risperidone from tablets of F7 fitted in Korsmeyer-Peppas plot

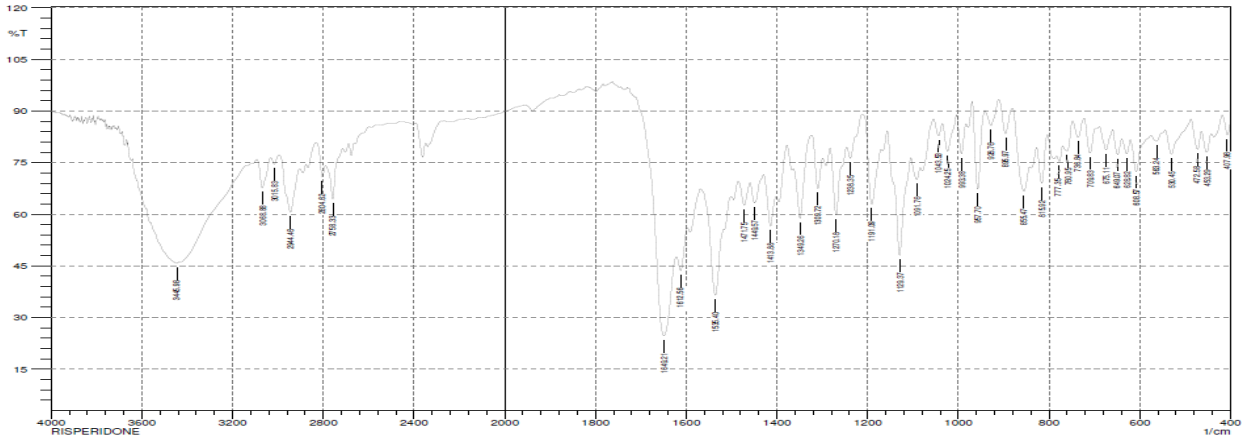

Figure No: 7 FT-IR Spectra of Risperidone

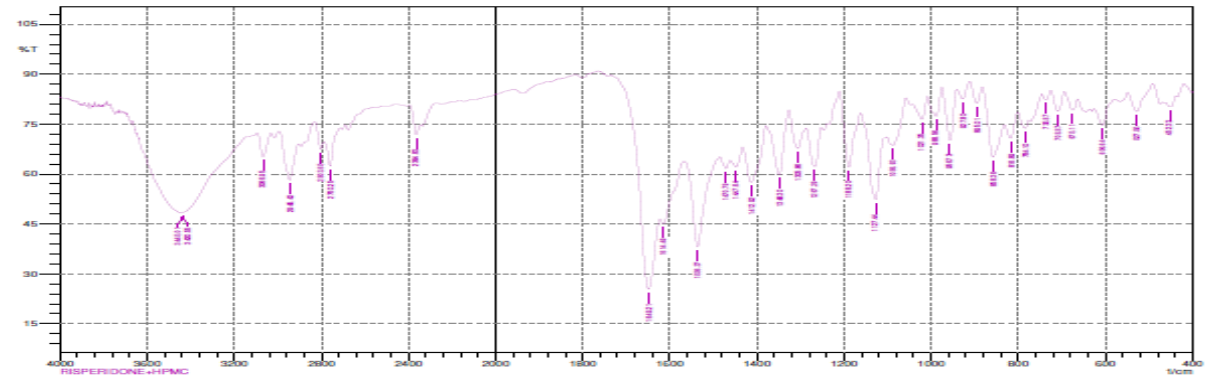

Figure No: 8 FT-IR Spectra of Risperidone+ HPMC

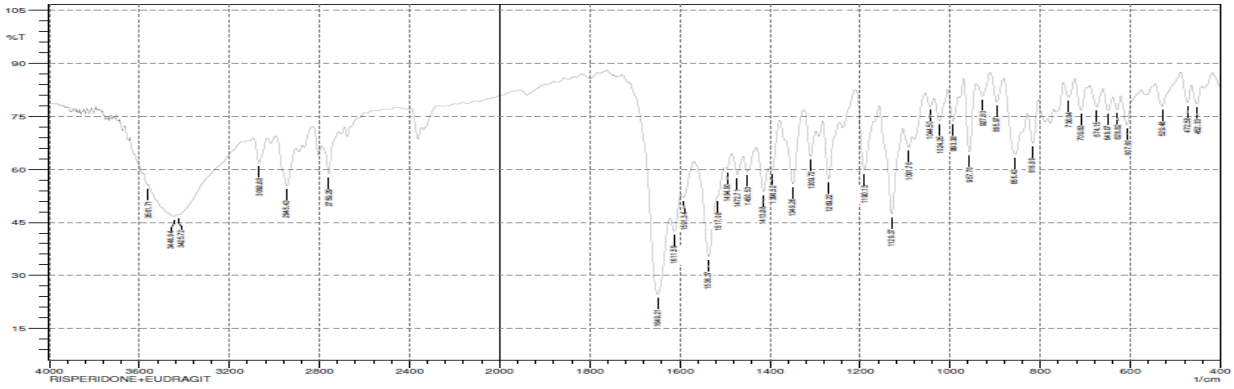

Figure No: 9 FT-IR Spectra of Risperidone+ Eudragit

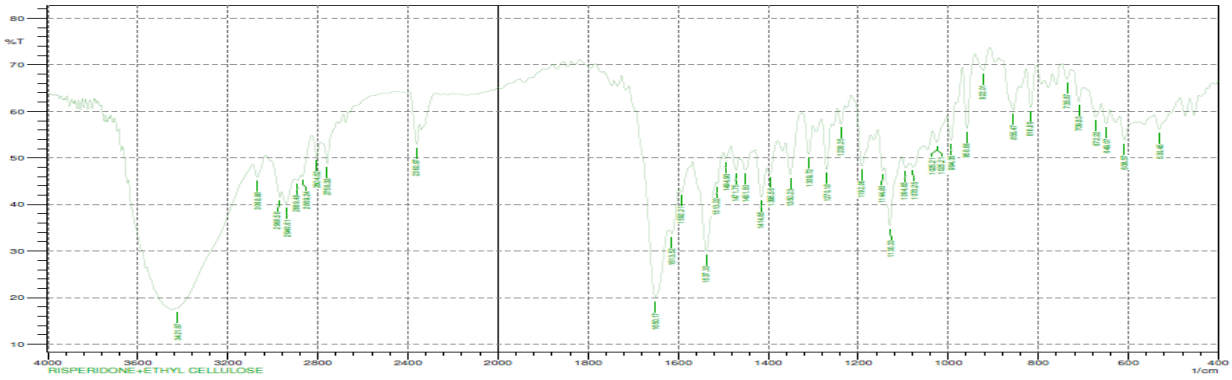

Figure No: 10 FT-IR Spectra of Risperidone+ Ethyl Cellulose

***Corresponding Author:**
Zuheb ur rahman*
Department of Pharmaceutics,
CMR College of Pharmacy,
Medchal, Hyderabad, A.P, India