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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF RISPERIDONE BY USING SOLID DISPERSION TECHNIQUE

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ABSTRACT

The present study was aimed to develop the formulation of sustained release tablets of Risperidone using solid dispersion technique. In this study solid dispersion of the drug were prepared by physical mixtuyre method, Kneading method and Co-precipitate method using Beta cyclodextrine and HP-Beta cyclodextrine and the drug was taken with carrier in the proportions of (1:1 and 1:2). The rate of dissolution of Risperidone was increased with the proportion of (1:2) (Drug: Beta cyclodextrine) Co-precipitate method when compared to the other formulations. The sustained release tablets were prepared by using CP2 formulation. F8 is the better formulation when compared to all formulations. The optimized formulation was subjected to different kinetic models including zero order, first order, Higuchi model and Korsemeyer Peppa's model and the formulation was found to follow first order release kinetics.

KEYWORDS: Solid dispersions, Sustained release, Risperidone, HPMC K4M, HPMC K15M, HPMC K100M.

INTRODUCTION

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.[1]

Oral drug delivery is one of the simple and easy modes of drug administration. The enhancement of oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. The rate and extent of dissolution of the active ingredient from any solid dosage form determines rate and extent of absorption of the drug. In the case of poorly soluble drugs dissolution is the rate limiting step in the process of drug absorption. Potential bioavailability problems are arising with extremely hydrophobic drugs due to incomplete absorption from the GIT. The concept of solid dispersion has been widely and successfully applied to improve the solubility, dissolution rate and consequently the bioavailability of poorly soluble drugs. In solid dispersion method drug is dispersed in inert water soluble carrier at solid state.[2,3]

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.[4] 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.[5]

MATERIALS AND METHODS

Materials

Risperidone, Beta cyclodextrine and HP-Betacyclodextrine were obtained as a gift sample from Pharmatrain, Hyderabad, India. HPMC K4M, HPMC K15M, HPMC K100M, DCP, Talc, Mg.Stearate was gift sample from Sunlife sciences, Hyderabad. All other reagents and solvents used were of analytical grade satisfying pharmacopoeias specifications.

Standard Calibration Curve of Risperidone in 6.8phosphate buffer

Standard Stock Solution: A stock solution containing 1000 µg/ml of pure drug was prepared by dissolving 100 mg of Risperidone in sufficient methanol and make up to the mark with 6.8phosphate buffer in a 100ml volumetric flask.

Stock Solution: From the standard stock solution, 10 ml of the stock solution was further diluted to 100 ml with water into a 100 ml volumetric flask and diluted up to the mark with 6.8phosphate buffer. Aliquots of 0.2, 0.4, 0.6, 0.8 and 1 ml of stock solution were pipette out into 10ml volumetric flasks. The volume was made up to the mark with 6.8phosphate buffer. These dilutions give 2, 4, 6, 8, and 10 µg/ml concentration of Risperidone respectively. The absorbance was measured in the UV-Visible spectrophotometer at 238 nm using 6.8phosphate buffer as blank and graph of concentration versus absorbance was plotted.

Preparation of solid dispersions

1. Solid dispersion of Risperidone was prepared by Physical mixture method, Kneading method and Co-precipitate method. The composition is shown in below table. **Physical mixture method:** Drug with polymers in different molar ratios (1:1 and 1:2) were mixed in a mortar for about one hour with constant trituration, passed through sieve No. 80 and stored in desiccators over fused calcium chloride.
2. **Kneading method:** Drug with polymers in different molar ratios (1:1 and 1:2) was taken. First cyclodextrin is added to the mortar, small quantity of 50% ethanol is added while triturating to get slurry like consistency. Then slowly drug is incorporated into the slurry and trituration is further continued for one hour. Slurry is then air dried at 25°C for 24 hours, pulverized and passed through sieve No. 80 and stored in desiccators over fused calciumchloride.
3. **Co-precipitate method:** Drug was dissolved in ethanol at room temperature and polymer was dissolved in distilled water. Different molar ratios of Drug with polymers (1:1 and 1:2) were taken. The mixture was stirred at room temperature, for one hour and then slowly evaporated on a boiling water bath. The inclusion complex precipitated as a crystalline powder was pulverized and passed through sieve No. 80 and stored in a desiccator till free from any traces of the organic solvent.

Table 1: Formulation of solid dispersions.

Ingredients	Formulation code											
	PM1	PM2	PM3	PM4	KM1	KM2	KM3	KM4	CP1	CP2	CP3	CP4
Risperidone	4	4	4	4	4	4	4	4	4	4	4	4
β-Cyclodextrine	4	8	-	-	4	8	-	-	4	8	-	-
HP-β-Cyclodextrine	-	-	4	8	-	-	4	8	-	-	4	8

Evaluation of Solid dispersions

Drug Content Estimation: Solid dispersion powder equivalent to 10 mg of the medicament was taken into a 10ml volumetric flask and dissolved in methanol and make up to the mark with 6.8phosphate buffer. The solution was subsequently diluted with 6.8phosphate buffer and assayed for the drug content by the UV spectrophotometric method at 238 nm.

***In vitro* dissolution studies for Risperidone solid dispersions**

Dissolution Profile

- Apparatus: USP - type II (Paddle)
- Medium: 900 ml of 6.8phosphate buffer
- Speed: 50 rpm
- Temperature of Medium : 37°C ±1°C
- Sampling time points: 5,10,15, 20, 30 , 40, 50 & 60 min
- Withdrawn the 5 ml samples were withdrawn through a filter (0.45 µ) at different intervals of time, suitably diluted and assayed for Risperidone at 238 nm UV spectrophotometer & replace with same volume of buffer. The dissolution experiments were conducted in triplicate.

Preparation of Risperidone tablets

The Risperidone SR tablets were prepared by following the General Methodology as given below:

1. All ingredients (Drug+Beta cyclodextrin complexes + polymer + DCP) were weighed accurately and co sifted by passing through #22 sieve, blended in a Poly Bag for 5 min.
2. The above blend was lubricated with # 40 Sieve passed Talc and Magnesium stearate.
3. The final blend was then compressed into tablets using 16 station tablet compression machine with an average hardness of 6.0kg/cm^2,by using 8mm to 12mm dies

Table 2: Formulation of Risperidone tablets.

Ingredients	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
(CP2) Drug: Beta cyclodextrin(1:2)	12	12	12	12	12	12	12	12	12
HPMC K4M	16	24	32	-	-	-	-	-	-
HPMC K15M	-	-	-	16	24	32	-	-	-
HPMC K100M	-	-	-	-	-	-	16	24	32
DCP	128	120	112	128	120	112	128	120	112
Talc	2	2	2	2	2	2	2	2	2
Mg.Stearate	2	2	2	2	2	2	2	2	2
Total wt (mg)	160	160	160	160	160	160	160	160	160

MICROMERITIC PROPERTIES OF PRE-COMPRESSED POWDER

The flow characteristics of the different batches pre-compressed powder were measured by determining their angle of repose using fixed-base cone method. A glass funnel was secured with its tip positioned at a fixed height (H) above graph paper placed on a horizontal surface. The sample was poured through the funnel until the apex of the conical pile touched to the tip of the funnel. The height and radius of the heap was measured. The experiment was repeated in triplicate, the angle of repose (tan θ) was calculated using the formula;

Angle of repose[θ] =tan -1(h/r)

H = cone height, r = radius of circular base formed by the granules on the ground.

The bulk and tapped densities of the pre-compressed powder were evaluated by using the bulk density apparatus. Known weights of formulated granules were transferred into a 50cc graduated measuring cylinder. The cylinder was fixed on bulk density apparatus and the timer knob was set for 500 tapings. Then, the initial bulk volume and final volume after 500 tapings were noted. The experiment was repeated in triplicate. The respective densities of different batches of granules were calculated by using the following formulas;

$$\text{Bulk density [gm /cc]} = \frac{\text{Mass of the sample (g)}}{\text{Bulk volume (ml)}}$$

$$\text{Tapped density [gm/cc]} = \frac{\text{Mass of the sample(g)}}{\text{True volume (ml)}}$$

Compressibility index or Carr‟s index value of precompressed was computed according to the following equation;

$$\text{Carr's index (CI \%)} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

Hausner‟s ratio of pre-compressed powder was determined by comparing the tapped density to the bulk density by using the equation;

Hausner's ratio = Tapped density / Bulk density

POST COMPRESSION PARAMETERS

Weight variation, Hardness and Friability

The uniformity of weights of tablets was determined according to the method mentioned in USP.[11] Weighed 20 tablets individually in an electronic balance and their average weight were determined. The standard deviation was calculated using the following formula;

Average weight (gm) = Total weight of the tablets /20

Standard deviation (%) = (Iw – Aw / Aw) x 100

[Where, Iw = Individual weight of the tablets, Aw = Average weight of the tablets]

For each formulation, the hardness of 10 randomly selected tablets was examined using a Pfizer hardness tester (A-101 Secor India). The tablet hardness or crushing strength was measured in kg/cm^2.

The percentage of friability was evaluated by using Roche friabilator (USP EF-2 Electro Lab). Ten or twenty tablets from each batch were weighed and placed in the plastic chamber. The chamber rotated for 4 minutes or 100 revolutions. After 100 revolutions tablets were removed from the chamber and reweighed. The percentage of weight loss or friability was determined by the following formula;

Friability (%) = Loss in weight of tablets / Initial weight x 100

Drug content uniformity

Ten tablets were weighed and powdered, a quantity of powder equivalent to 10 mg of Risperidone was transferred to a 10 ml volumetric flask and 2 ml methanol is added. The drug is dissolved in methanol by vigorously shaking the stoppered flask for 15 minutes. Then the volume is adjusted to the mark with 6.8phosphate buffer and the liquid is filtered. From prepared solution take 0.1ml soluion in 10ml volumetric flask and make up to mark with 6.8phosphate buffer. The Risperidone content was determined by measuring the absorbance at 238 nm after appropriate dilution. The drug content was calculated using the standard calibration curve. The mean percent drug content was calculated as an average of three determinations.

The actual drug content was determined by using the following relationship;

Assay = test absorbance/standard absorbance *standard concentration/sample concentration *purity of drug/100 * 100

In-vitro drug release studies

In vitro dissolution of Risperidone tablets were studied in USP XXIII type-II dissolution apparatus (LABINDIA) employing a paddle stirrer at 50 rpm. 900 ml of 6.8phosphate buffer was used as dissolution medium. The temperature of dissolution medium was maintained at 37 ± 1^{o} C throughout the experiment. One tablet was used in each test. Samples of dissolution medium (5ml) were withdrawn by means of syringe fitted with pre-filter at known intervals of time and analyzed for drug release by measuring the absorbance at 238 nm. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium. Cumulative percent Risperidone released was calculated and plotted against time.

% Drug release= test absorbance/standard absorbance*weight of standard/dilution of standard*dilution of sample/label claim*purity of drug/100*100

Mechanism of drug release kinetics studies

The data obtained from the in-vitro dissolution studies was subjected to kinetic treatment to obtain the order of release and best fit model for the formulations. The in-vitro drug release drug release data of the formulations was analyzed with various kinetic equations like zero-order (% release v/s time), first- order (Log % retained v/s time), Higuchi matrix (cumulative % drug released vs. square root of time) and Korsemeyer and Peppas equation (Log cumulative percent drug released versus log time).[13] The coefficients of correlation (r) values were calculated for the linear curves obtained by regression analysis of the above plots.

Zero-order kinetics: The drug release followed by zero-order was estimated by using the following equation;

Qt = Q0 + K0 t

Where Q is the amount of drug dissolved in time t, Q0 is the initial amount of drug in the solution (most times Q =0), and K0 is the zero order release constant. When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics with a slope equal to Ko.

First-order kinetics: The drug release followed to first-order was estimated by using the following equation;

Log c = Log Co – Kt / 2.303

Where: C = Amount of drug remained at time (t). Co = Initial amount of drug, K=First-order rate constant (hr-1).

When the calculated data was plotted as log cumulative percent drug remaining versus time obtained a straight line that indicates that the release follows first order kinetics. The constant "K" can be obtained by multiplying 2.303 with slop values.

Higuchi's matrix model: This model explains the release of drug from matrix devices mainly by diffusion of drug from the matrix layer. The drug release from the formulations was determined by using the following Higuchi"s classical diffusion equation.

Q = [DE / Ʇ (2A- E Cs) Cst] ½

Where; Q = Amount of drug released at time (t), D = Diffusion co-efficient of the drug in the matrix, A = Total amount of drug in unit volume of matrix, Cs = the solubility of the drug in the matrix, E = Porosity of the matrix, τ = Tortuosity and t = time (hrs.) of which Q amount of drug is released.

The above equation can be simplified if one assumes that D, Cs and A are constant. The equation becomes,

Q=Kt½

When the data was plotted by cumulative percentage of drug release versus square root of time shows a straight line. This was indicates that the drug was released by diffusion mechanism.

Korsemeyer and Peppas model: This model was generally used to analyze the release of the drug from polymeric dosage forms, when the release mechanism is not well known or when more than one type of release occurs corresponding to time (t). In order to understand the mode of drug release from swellable matrices, the data is fitted to the following Peppas equation,

Mt / M∞ = K t n

Where, Mt is the amount of drug released at time (t). M∞ is the amount of drug released at infinite time (t). K is the kinetic rate constant depends on structural and a geometric characteristic of the product and n is the diffusional exponent which indicates the release mechanism. The above equation can be simplified by applying log on both sides then we get:

Log Mt / M∞ = Log K + n Log t

When the data is plotted as log percentage of drug release versus log time shows a straight line with a slope equal to „n" (diffusional co-efficient) and the „K" (coefficient of correlation) can be obtained from y-intercept.

RESULTS AND DISCUSSION

Construction of Standard calibration curve of Risperidone in 6.8 phosphate buffer

The absorbance of the solution was measured at 238nm, using UV spectrometer with water as blank. The values are shown in below table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml.

Table 3: Calibration curve for Risperidone in 6.8 phosphate buffer.

Concentration(µg/ml)	Absorbance
0	0
2	0.091
4	0.188
6	0.281
8	0.382
10	0.469

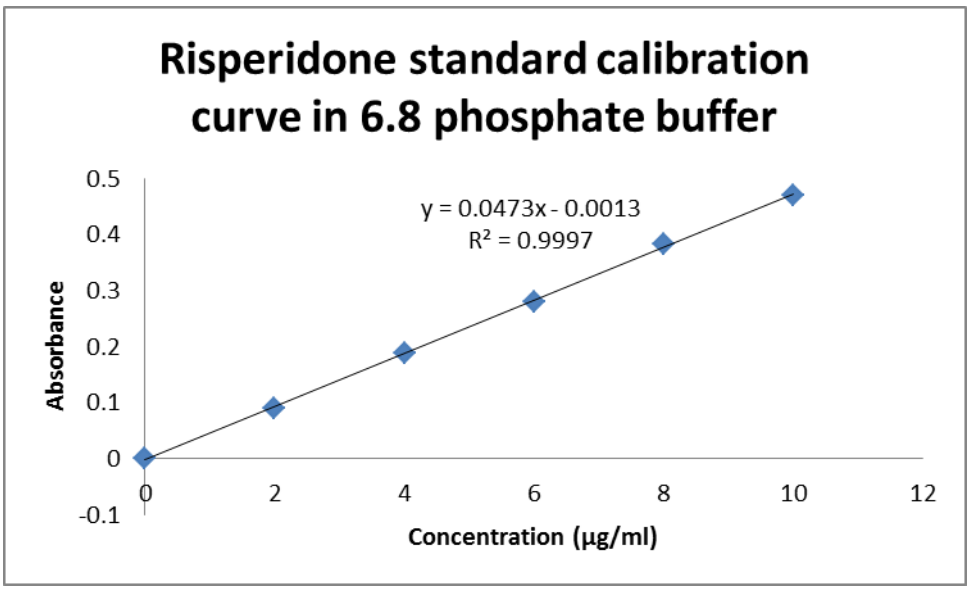

Figure 5: Calibration curve for Risperidone in 6.8phosphate buffer.

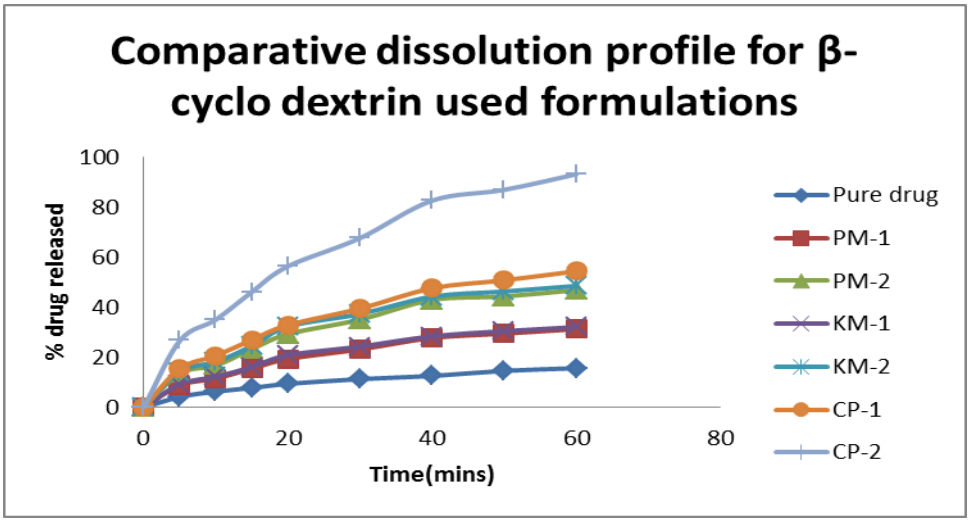

Figure 7: Comparative dissolution profile for pure drug and β-cyclodextrin used formulations.

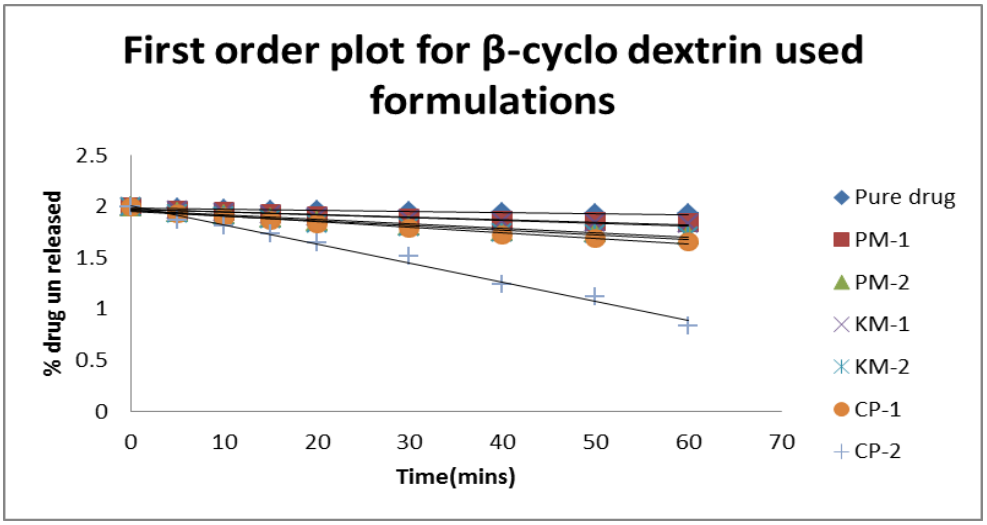

Figure 8: First order plot for pure drug and β-cyclodextrin used formulations.

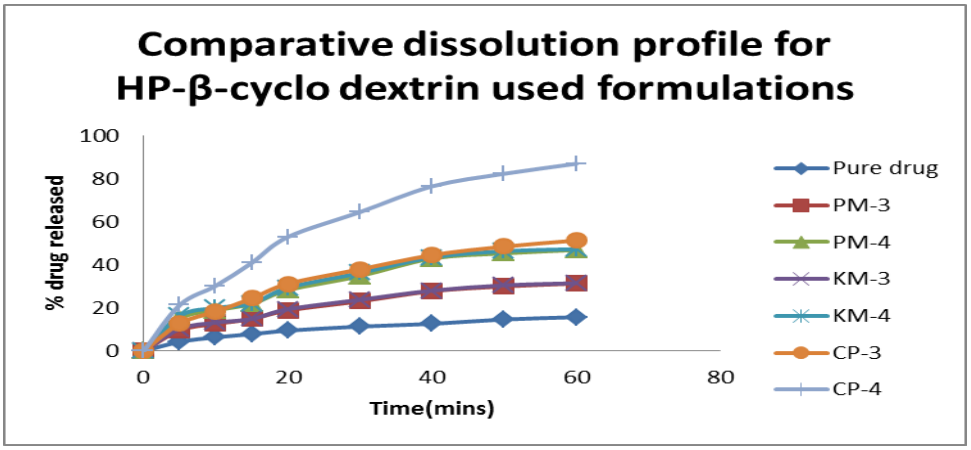

Figure 9: Comparative dissolution profile for pure drug and HP-β-cyclodextrin used formulations.

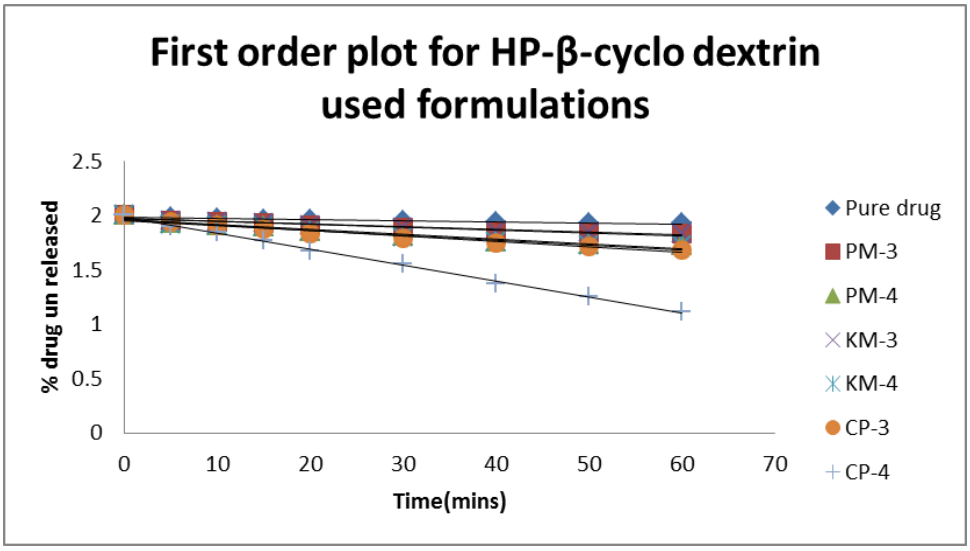

Figure 10: First order plot for pure drug and HP-β-cyclodextrin used formulations.

Table 4: Pre compression studies.

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
F1	0.37	0.41	9.75	1.1	21.61
F2	0.43	0.52	17.3	1.41	22.62
F3	0.40	0.46	13.0	1.50	22.29
F4	0.44	0.51	13.7	1.25	20.29
F5	0.39	0.47	17.0	1.56	28.23
F6	0.42	0.52	19.2	1.45	23.24
F7	0.41	0.50	18.0	1.50	27.4
F8	0.41	0.51	19.6	1.53	22.26
F9	0.44	0.52	15.3	1.40	23.62

Pre compression studies Risperidone tablet blend

- The prepared tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table
- The bulk density and the tapped density for all formulations were found to be almost similar.
- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.0 respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be within range which indicating passable flow.

Table 5: Post compression studies.

Formulation Code	% weight vaiation	Thickness	% friability	% Drug Content	Hardness (Kg/cm^2)
F1	pass	4.03	0.14	98.9	6.2
F2	pass	3.93	0.11	100.2	5.7
F3	pass	4.06	0.14	101.3	5.56
F4	pass	4.06	0.15	101.5	6.03
F5	pass	4.03	0.62	100.1	6.15
F6	pass	4.1	0.15	100.7	6.43
F7	pass	3.99	0.23	99.3	6.37
F8	pass	4.15	0.19	100.2	6.23
F9	pass	4.0	0.17	99.7	5.98

Post compression studies for Risperidone tablets

- The variation in weight was within the range of ±7.5% complying with pharmacopoeia specifications of USP.
- The thickness of tablets was found to be between 3.93-4.15 mm.
- The hardness for different formulations was found to be between 5.56 to 6.43kg/cm^2, indicating satisfactory mechanical strength
- The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet.
- The drug content was found to be within limits 98 to 102%.

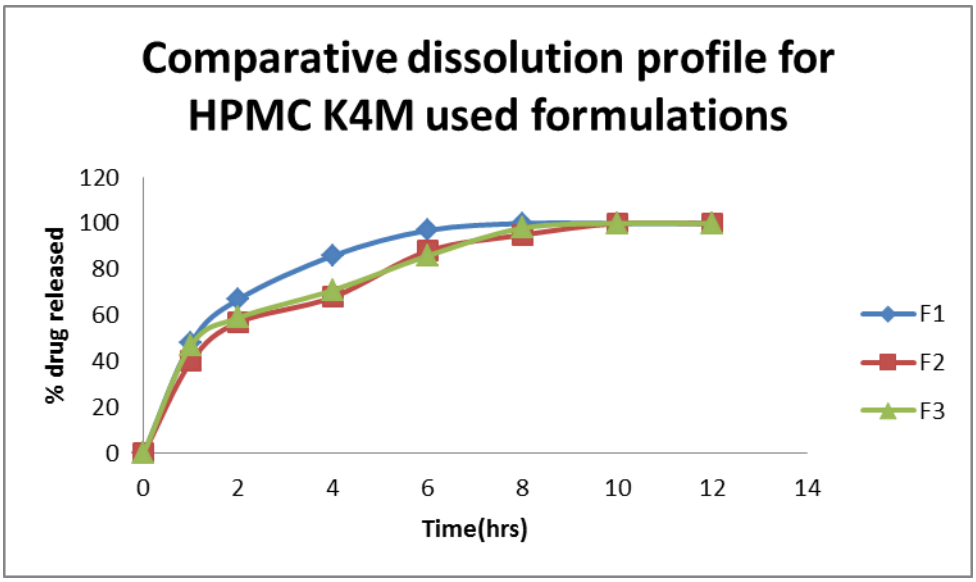

Figure 14: Comparative dissolution profile for F1, F2 and F3 formulations.

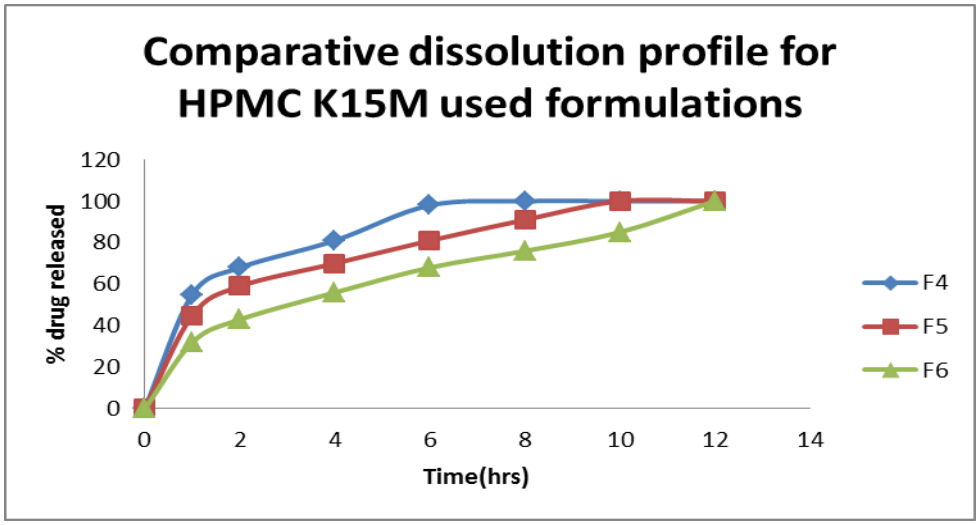

Figure 15: Comparative dissolution profile for F4, F5 and F6 formulations.

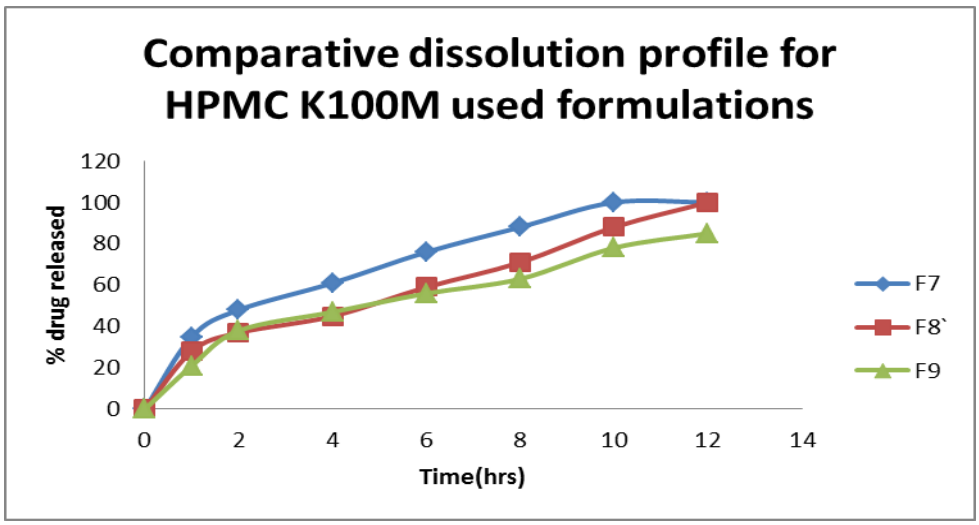

Figure 16: Comparative dissolution profile for F7, F8 and F9 formulations.

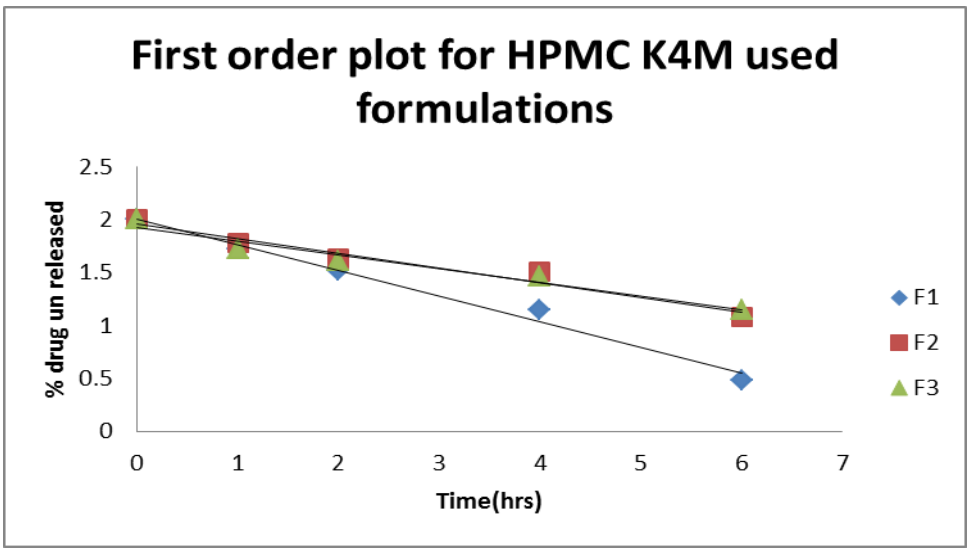

Figure 17: First order plot for F1, F2 and F3 formulations.

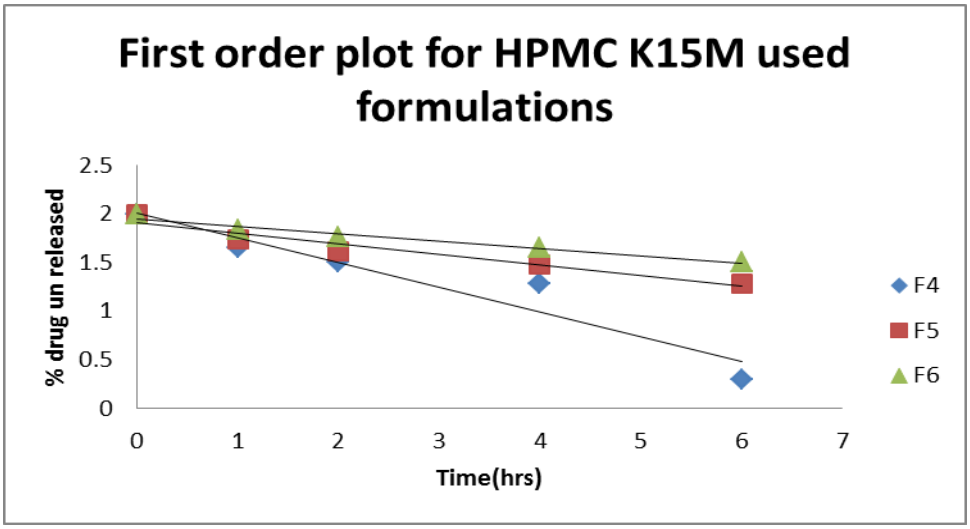

Figure 18: First order plot for F4, F5 and F6 formulations.

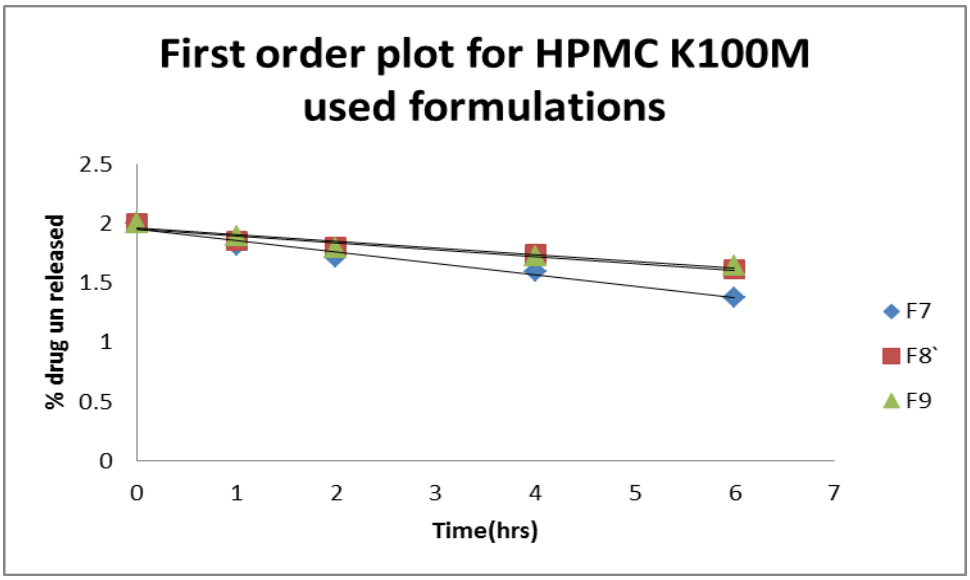

Figure 19: First order plot for F7, F8 and F9 formulations.

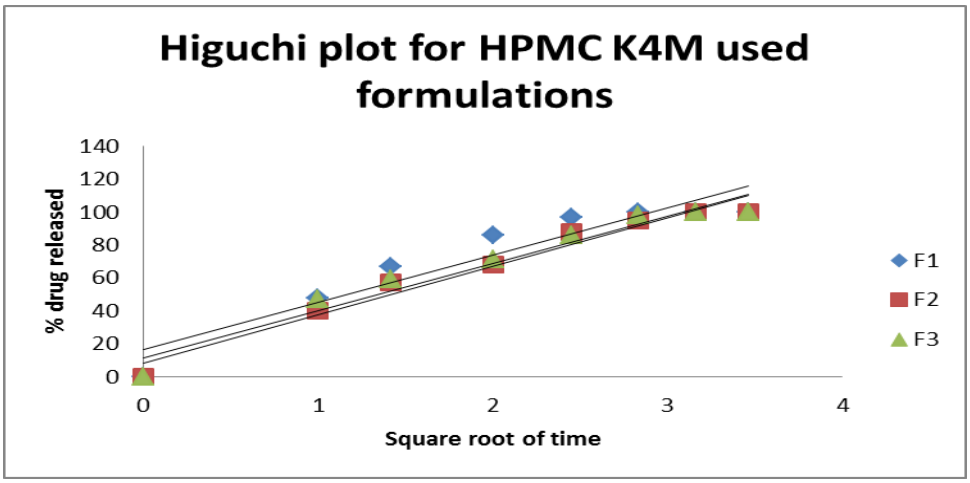

Figure 13: Higuchi plot for F1, F2 and F3 formulations.

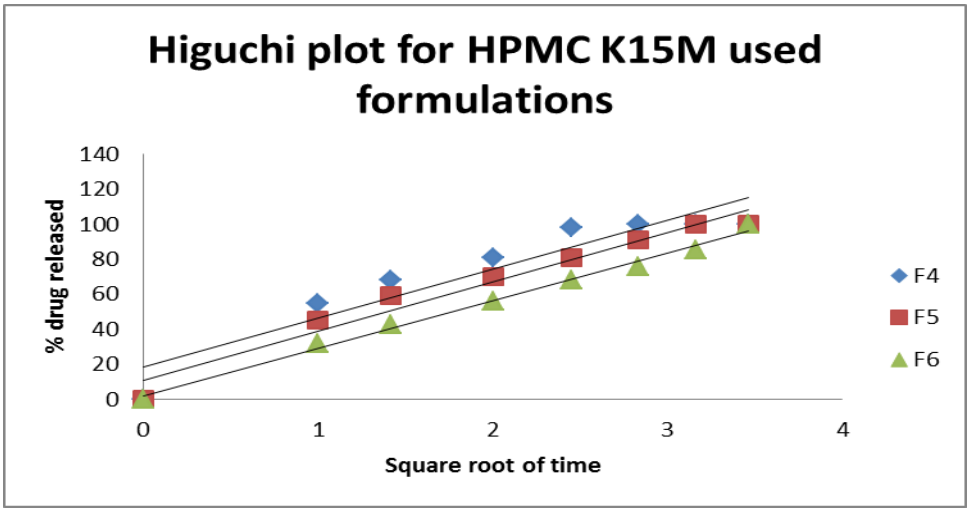

Figure 14: Higuchi plot for F4, F5 and F6 formulations.

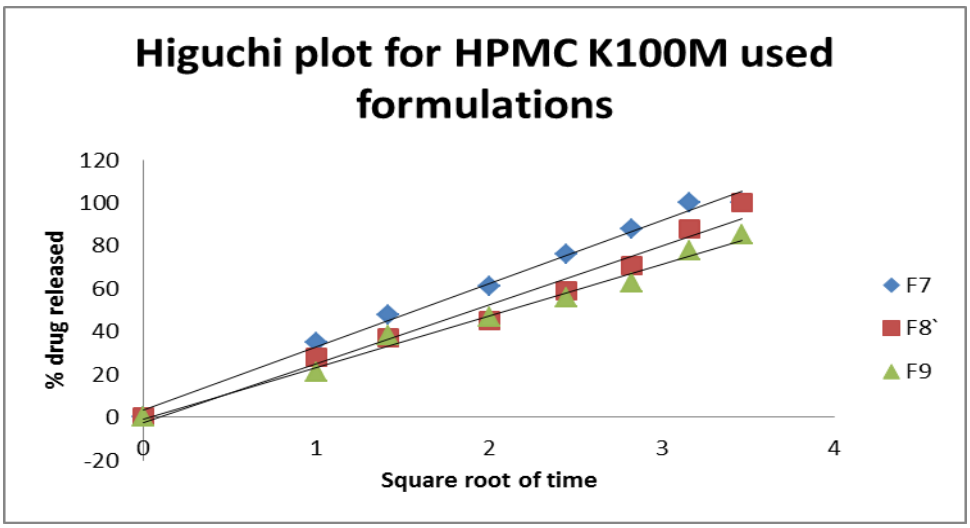

Figure 15: Higuchi plot for F7, F8 and F9 formulations.

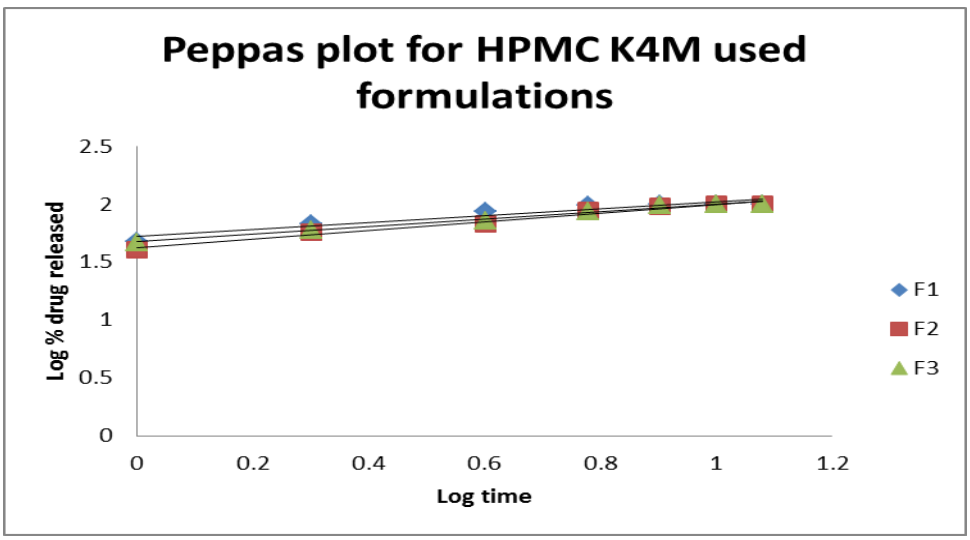

Figure 16: Peppas plot for F1, F2 and F3 formulations.

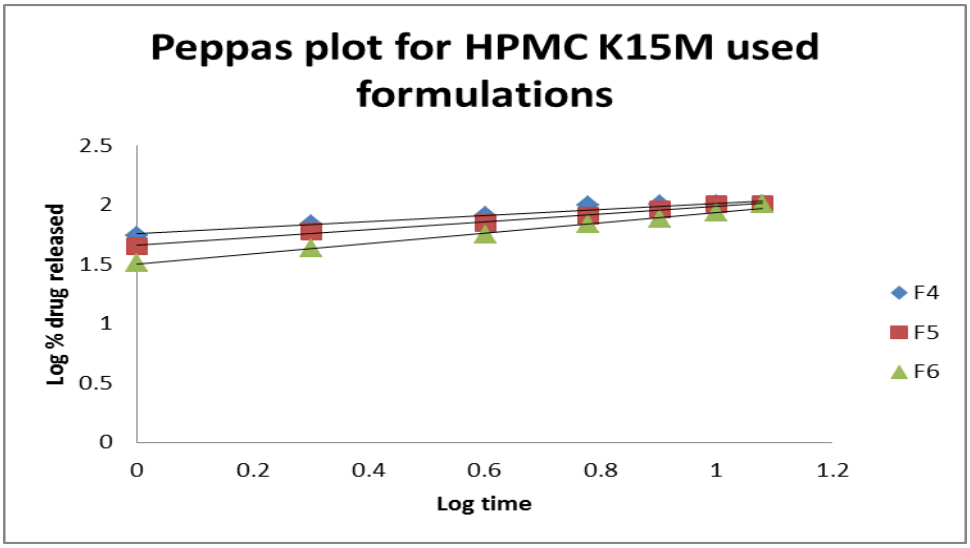

Figure 17: Peppas plot for F4, F5 and F6 formulations.

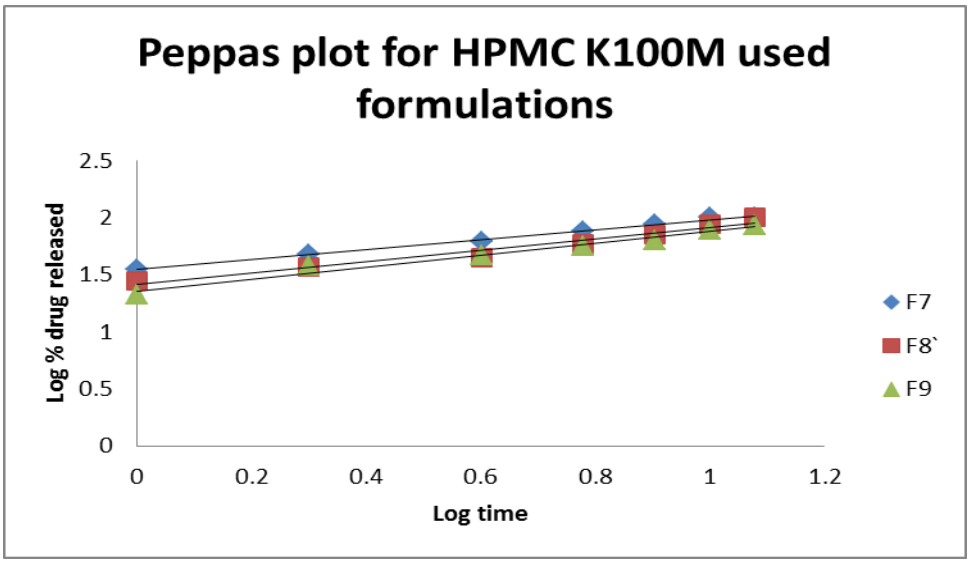

Figure 18: Peppas plot for F7, F8 and F9 formulations.

Table 6: R2 and N result table for Risperidone SR tablets.

Formulation code	R2 value				N value
	Zero order	First order	Higuchi	Peppas	
F1	0.819	0.993	0.946	0.964	0.299
F2	0.897	0.981	0.983	0.989	0.379
F3	0.881	0.979	0.976	0.992	0.324
F4	0.812	0.961	0.941	0.977	0.256
F5	0.892	0.968	0.981	0.996	0.327
F6	0.954	0.978	0.996	0.996	0.439
F7	0.941	0.985	0.996	0.997	0.437
F8	0.966	0.979	0.987	0.981	0.503
F9	0.962	0.967	0.994	0.987	0.520

SUMMARY AND CONCLUSION

1. Suitable analytical method based on UV-Visible spectrophotometer was developed for Risperidone. λ_{max} of 238 nm was identified in phosphate buffer solution, pH 6.8.
2. Prepared Risperidone solid dispersions in different ratios by Physical mixture method, Kneading method and Co-precipitate method.
3. From the above solid dispersions Risperidone: Beta cyclodextrin (1:2) CP2 has given better release in in-vitro dissolution studies.
4. From the FT-IR spectra the interference was verified and found that Risperidone did not interfere with the excipients used.
5. Direct compression method was established to manufacture sustained release tablets of Risperidone.
6. Evaluation parameters like hardness, friability, weight variation and drug content indicate that values were within permissible limit for all formulations.
7. *In vitro* drug release study was carried out and based on the results; F8 was identified as the best formulation among all the other formulations.

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