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Formulation and Evaluation of Resperidone Mini Tablets

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ABSTRACT

The present study was carried out to formulate Risperidone mini tablets filled into hard gelatin capsule, as it is administered for the treatment of psychosis. The preformulation studies of Risperidone were carried out and drug –polymer compatibility studies were performed by FT-IR spectra analysis. The precompression parameters revealed that all the 6 formulations had good flow Carr's index, Hausner's ratio and angle of repose within the limit. Risperidone is made up of a variety of polymers, such as HPMCK100M and HPMCK15M, as well as fillers like lactose and other excipients. Six formulations (F1,F2,F3,F4,F5, and F6) were carried out and evaluated. The thickness of all of the formulations ranges from 3.90 to 3.94mm, and the optimal batch's hardness was found to be 3.18kg/cm2. The optimized formulation had no variance in hardness, indicating that powder blending was homogeneous. F1, F2, F3, and F6 formulations were tested using K100M polymer, and F4, F5 using K15M polymer using an optimal amount of lactose. The best batch among those tested was F1, which had 90% drug release, could continue its activity until 20thhr, and was extremely cost-effective.

Keywords: Risperidone, mini tablets, HPMC, Sustained release and Zero order release. .

INTRODUCTION

Despite significant advancements in drug delivery, the oral route remains the preferred method for the administration of therapeutic agents because of the low cost of therapy and convenience of administration, which leads to better levels of patient compliance. Oral dose forms such as tablets and capsules provide a specific medication concentration in the systemic circulation while providing little control over drug administration and causing significant variability in plasma drug levels. Various techniques have been developed to improve medication release over a long period of time with a single oral dose and no changes in plasma drug profile.

Sustained release systems, extended drug release systems, and controlled release systems are only a few examples.

For the treatment of schizophrenia, a variety of oral atypical antipsychotics are available. Noncompliance limits their benefits due to their limited availability as oral medications alone. As a result, the development of an effective long-acting injectable atypical drug with few side effects and high treatment compliance would be a significant contribution to long-term schizophrenia care [1]. Risperidone (RSP) is an atypical antipsychotic medication with a high antagonistic effect on the serotonin 5-HT2 and dopamineD2 receptors [2,3]. This medication is known for its ability to treat both positive and negative symptoms of schizophrenia [4]. Furthermore, it has less negative effects than traditional antipsychotics, including extrapyramidal side effects [5]. RSP provides signs of a curve linear dose–response association for oral medication spanning the range 1–16 mg/day, with maximum antipsychotic action apparently occurring at dosages of 4–8 mg/day, according to some authors [5,6].Risperidone which was an atypical antipsychotic (dopaminergic antagonist) was the drug that effectively improves such symptoms, it has fewer side effects and it has moderate tendencies to cause weight gain. When compared to other atypical antipsychotic. Extended release mini tablet formulation was needed for Risperidone because there is a less risk of dose dumping, less inter and intra subject variability ,high degree of dispersion in the digestive tract minimizing the risk of high local drug interactions. The basic approach was to select rate controlling polymers and formulate extended release mini tablets.

MATERIALS AND METHODS

Materials: Risperidone was obtained from SUN pharma, Mumbai. HPMC was gift sample from ASTRA-ZENECA, Bangalore. Lactose, Magnesium stearate and Colloidal silicon dioxide (talc) were procured from Karnataka fine chemicals, Bangalore. All other reagents and solvents used were of analytical grade.

Methods: Weighed quantities of ingredients were triturated to fine powder individually in a mortar & pestle and passed through sieve no.40.

Preparation of extended release mini tablets- by direct compression method

Extended release mini tablets were prepared using risperidone, HPMCK100M,HPMCK15M, lactose , Aerosil , magnesiumstearate .Variable concentration of Drug:polymer ratio and other excipients were weighed and mixed as per formulation batches.The powder blends were lubricated with Aerosil and magnesium stearate and passed through sieve no.60 and then directly compressed using mini punches and then filled into capsules.

TABLE:1.Formulation variables for Risperidone mini-tablets:

S.no	Trial Ingredients	F1	F2	F3	F4	F5	F6
1	Risperidone(gm)	4	4	4	4	4	4
2	HPMCK100M(gm)	50	37.5	75	-	-	75
3	HPMCK15M	-	-	-	75	100	-
4	Lactose (gm)	25	50	25	25	25	50
5	Aerosil(gm)	1	1	1	1	1	1
6	Magnesium Stearate (gm)	0.5	0.5	0.5	0.5	0.5	0.5
	Total (gm)	80.5	93	105.5	105.5	130.5	130.5

EVALUATION OF EXTENDED RELEASE RISPERIDONE MINI TABLETS

Angle of repose[7], bulk density and tapped density [8], Carr's index[9], and Hausner's ratio[10] were used to characterize the flow properties of blends before compression. Tablet examination can be broken down into physical and chemical factors. Physical appearance, tablet size and thickness, average tablet weight, hardness test, and chemical parameters such as content homogeneity and in-vitro drug release are all factors to consider.

Physical evaluation

Two tablets from each formulation were randomly selected and organoleptic properties such as color, odour, taste and shape were evaluated. Thickness and diameter of ten tablets were measured using vernier calipers. The prepared mini tablets were evaluated for weight variation[10] using 20 tablets, hardness[10] (Monsanto tester), and friability[10] using 10 tablets (Roche friabilator)[10].

Drug content estimation

The drug content in each formulation was determined by triturating 10 tablets and powder equivalent to 50 mg was added in 0.1N HCl followed by stirring. The solution was filtered through a 0.45 µ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 280 nm using 0.1NHCl as blank [9].

In-Vitro drug release (Dissolution test)

Release of the drug *in vitro*, was determined by estimating the dissolution profile. *In-vitro* drug release study was carried out using USP apparatus II at $37^0C \pm 0.5^0C$ for 12hrs, at 50rpm.0.1N HCL (pH 1.2) was used as dissolution medium for the first 2hrs, followed by pH 6.8 phosphate buffer for further 10hrs .10 ml of sample was withdrawn after every hour and was replaced with an equal volume of fresh dissolution medium to maintain the equilibrium. Collected are analysed by U.V spectrophotometer at 280nm.

Parameters for dissolution test

Apparatus : USP 1 (Basket apparatus) Revolution per minute : 100rpm
Dissolution medium : 6.8 phosphate buffer
Temperature : 37 ± 0.5^0C
Dissolution time : 20hrs Sample quantity with drawn
10ml Sample time interval : 1hr

The prepared tablets of all the formulations wereevaluated for precompression parameters like angle of repose, bulk density, tapped density and compressibility index and physical characters like tablet hardness, friability, weight variation, content uniformity, *in vitro* drug release. The main aim was to control the release of drug up to 20 hrs.

Physical characters of Risperidone were found as

Table 2: Physical Characters of Risperidone:

S.No.	Characters	Inference
1.	Nature	Amorphous powder
2.	Colour	White
3.	Odour	Odourless
5.	Melting point	170^oC
6.	Solubility- In Water In 1N HCl In 0.1N HCl In Methanol In Methylene chloride	 Insoluble soluble soluble soluble Freely soluble
7.	Loss on drying	0.5% w/w (Not more than 1.0%, determined on 1 g by drying in an oven at 105^0C)

On the basis of the above tests, it was confirmed that the drug sample of Risperidone was an authentic one.

Preparation of Risperidone calibration curvein Phosphate buffer pH 6.8 at 280nm

Calibration curve was drawn in Phosphate buffer (pH 6.8), which follows beer's Lambert law.Assay was performed to analyse the percentage purity and was found to be 101%w/w pure.The standard curve of Risperidone was obtained by taking the absorbance at 280nm,the values are shown in the table below and it shows that the values complies the Beer's law. The standard curve of the Risperidone is plotted by taking concentration on the x-axis and absorbance on the y- axis.

Table: 3. Risperidone calibration curve

S.no	Concentration µg/ml	Absorbance (280nm)
1	5	0.1781
2	10	0.3121
3	20	0.5737
4	30	0.8091
5	40	1.0998

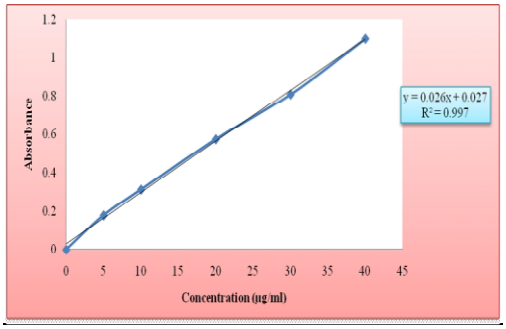


Fig:1 Calibration curve of Risperidone in Phosphate pH 6.8 buffer at 280nm:

Table:4.Drug-excipient compatibility ratios:

Drug-Excipients Combination	D:E Ratio	Initial	40°c 75% RH(1month)	60°c(1 month)
API alone	-	White to half white	NCC	NCC
API+HPMCK100M	1:10	White to half white	NCC	NCC
API+HPMCK15M	1:10	White to half white	NCC	NCC
API+ lactose	1:10	White to half white	NCC	NCC
API+Mg stearate	1:5	White to half white	NCC	NCC
API+ Aerosil	1:5	White to half white	NCC	NCC

There was no interaction between drug and polymers, drug and excipients. So the selected excipients were found to be compatible with Risperidone. Powder blend for mini tablets showed Angle of repose $24^0$65' -$28^0$68' less than 35, Carr's index less than 15.5 and Hausner's ratio less than 1.18 indicates good flow properties of the powder blend.

Preformulation parameters

The Risperidone powder blend was evaluated for bulk density, tapped density, angle of repose,Carr's ratio and Hausner's ratio. The results are shown in the table 4respectively.

Table: 5. Preformulation parameters of powder blend:

Formulation Code	Bulk density(g/ml)	Tapped density(g/ml)	Angle of repose°	Carr's index (%)	Hausner's ratio
F1	0.526	0.612	26.76	14.0	1.16
F2	0.662	0.763	27.54	13.23	1.15
F3	0.695	0.823	24.65	15.5	1.18
F4	0.782	0.869	28.68	11.0	1.11
F5	0.560	0.631	24.68	11.25	1.12
F6	0.628	0.714	25.16	14.27	1.17

Table: 6. Parameters of Risperidone mini tablets:

S.No	Parameters	F1	F2	F3	F4	F5	F6
1	Average weight of tablets(mg)	80.2	92.1	104.8	104.5	129.2	129.6
2	Thickness(mm)	3.94	3.92	3.93	3.91	3.90	3.94
3	Hardness(kg/cm^2)	3.58	3.52	3.47	3.32	3.20	3.38
4	Average Uniformity of content (%)	99	98.5	99.2	98.3	99.1	98.4

Table: 7.*In -vitro* release data ofRisperidone mini tablets:

Time(hrs)	Cumulative %drug release					
	F1	F2	F3	F4	F5	F6
1	15	25	10	21	12	15
2	21	36	15	30	24	22
4	27	45	20	42	32	30
6	35	54	30	53	43	36
8	42	68	37	65	51	45
10	55	82	50	80	60	58
12	70	-	66	92	73	74
16	85	-	80	-	88	87
20	90	-	86	-	94	94

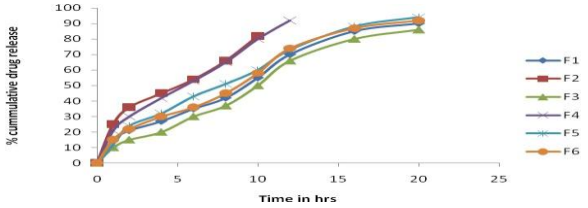


Fig: 2. In–vitro drugrelease data of Risperidone mini tablets:

Kinetics Study

Zero order equation ……. Q = K0t
First order equation..... In (100- Q) = InQ-K1t
Korsmeyer and Peppas equation.....Q = Kp tn

Where Q, is the percent of the drug release at time "t" and K0 and Kt are the constants of the equations. Kp is the constant incorporating structural and geometric characteristic of the release device, Ks is a constant incorporating the surface volume relation and "n" is the release exponent indicative of mechanism of release.The dissolution data were examined for models of first order, zero order, Higuchi, Korsmeyer-Peppas.

Table:7. Kinetic models of optimized batch:

Release kinetics	Correlation Coefficient(R^2)
Zero order equation	0.970
First order equation	0.586
Higuchi(diffusion)co-efficient	0.95
Korsmeyer Peppas equation	0.718

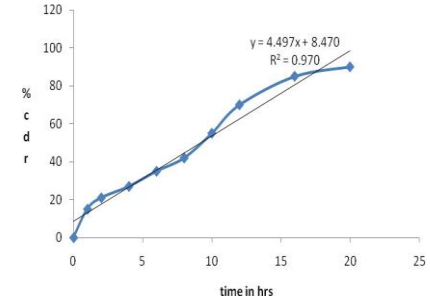


Fig:3 Zero order plot of optimized F1.

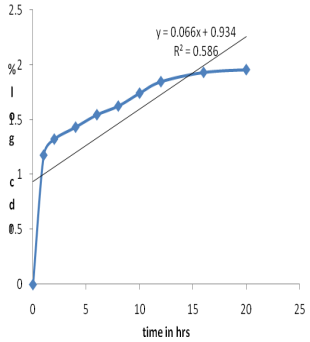
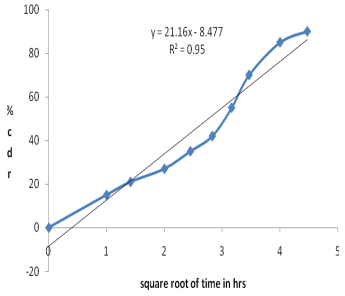


Fig: 4 First order plot of optimized F1



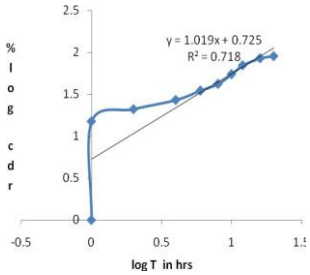


Fig: 5. Higuchi (diffusion)co-efficient plot of optimized F1. Fig:6. Korsmeyer Peppas plot of optimized F1.

SUMMARY AND CONCLUSION

Mini tablets are small tablets with a diameter of 2.5mm or less that are packed into capsules or compacted into larger tablets on occasion. Immediate release, delayed release, and/or controlled release are all possible combinations of distinct micro tablets. It's also conceivable to combine tiny tablets of multiple pharmaceuticals to treat concurrent diseases or combinations of treatments to improve overall therapeutic outcomes, all while giving varying release rates for each drug according on the ailment. The purpose of this study was to develop Risperidone micro tablets put inside firm gelatin capsules for use in the treatment of psychosis. Risperidone preformulation experiments were carried out, as well as drug–polymer compatibility tests using FT-IR spectra analysis. All six formulations had good flow Carr's index, Hausner's ratio, and angle of repose within the limit, according to the precompression parameters. Risperidone is made utilizing a variety of polymers, including HPMCK100M and HPMCK15M, as well as fillers including lactose and other excipients. Six formulations (F1,F2,F3,F4,F5, and F6) were carried out and evaluated.

Overall, the formulation thickness ranges from 3.90 to 3.94mm, with the optimal batch having a hardness of 3.18kg/cm2. The optimized formulation had no variance in hardness, indicating that powder blending was homogeneous. F1, F2, F3, F6 trials were done with K100M polymer and F4,F5 with K15M polymer using an optimal amount of lactose. The best batch among them is F1 since it had 90% release, could continue its activity until the 20th hour, and is extremely cost effective. The optimal Risperidone formulation was chosen, the capsule was filled, and all of the tests were completed in accordance with the I.P.

To summarize, Risperidone is reported to be highly bioavailable, and an ER mumps has been developed to minimize repetitive multiple dosage. The overall results showed that Risperidone with formulation no.1 were considered as the optimized formulation and filled within the hard gelatin capsules of size "1".

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