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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF EXTENDED RELEASE MINI TABLETS OF RISPERIDONE

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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 formulated with different concentration of polymers like HPMCK100M, HPMCK15M, filler like lactose and with other excipients. A total number of 6 formulations (F1,F2,F3,F4,F5 and F6)were carried and evaluated. In all the formulations thickness varies between 3.90-3.94mm and the hardness of the optimized batch was found to be 3.18kg/cm^2.No variation in the hardness was found in the optimized formulation that showed powder blending was uniform. Among 6 formulations, F1, F2, F3 and F6 trials were done using K100M polymer and F4, F5 with K15M polymer using optimized quantity of lactose, best batch among those is F1 because it had 90% drug release and it could sustain its action until 20thhr, and is very economical.

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

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INTRODUCTION

Despite tremendous advancement in drug delivery, oral route remains the preferred route for the administration of therapeutic agents, low cost of therapy and ease of administration leads to higher levels of patient compliance. Conventional oral dosage forms such as tablets, capsules provide specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Various approaches have been worked out to improve the drug release over an extended period of time with administration of single oral dose and without showing any fluctuations in plasma drug profile.

Eg. Sustained release systems, Extended drug release and Controlled release systems etc.

Several oral atypical antipsychotics are available for the management of schizophrenia. Due to their limited availability as oral agents only, their benefits are limited by noncompliance. Therefore, the development of an effective long-acting injectable atypical agent with limited adverse effects and with excellent treatment compliance would make an important contribution to the long-term management of schizophrenia [1]. Risperidone (RSP) is one of there presentative atypical antipsychotic drugs which have a potent antagonist effect on serotonin 5-HT2 and dopamineD2 receptors [2,3]. This drug is characterized by its effective ness against both positive and negative symptoms of schizophrenia [4]. Furthermore, it produces fewer side effects, including extra pyramidal side effects, than conventional antipsychotic drugs [5].

Some authors reported that RSP shows evidence of a curve linear dose–response relationship over the range 1–16 mg/day for oral therapy, with maximum antipsychotic activity apparently occurring at dosages of 4–8 mg/day [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 ,magnesium stearate .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

The flow properties of blends (before compression) were characterized in terms of Angle of repose[7], Bulk density and tapped density [8], Carr's index[9] and Hausner's ratio[10] and evaluation of tablets can be divided into physical and chemical parameters. Physical appearance, Tablet size and thickness, Average weight of tablets, Hardness test, and chemical parameters like content uniformity and in-vitro drug release.

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°C
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

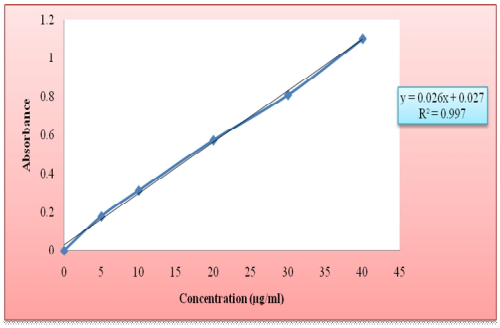

Fig:1 Calibration curve of Risperidone in Phosphate pH 6.8 buffer at 280nm:

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

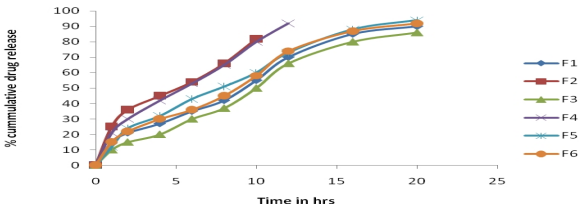

Fig: 2. In–vitro drugrelease data ofRisperidone mini tablets:

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

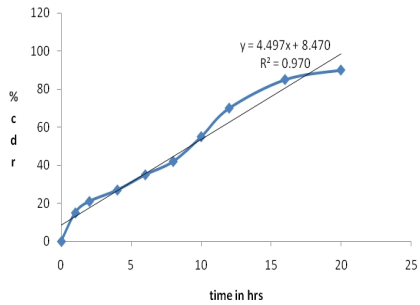

Fig:3 Zero order plot of optimized F1.

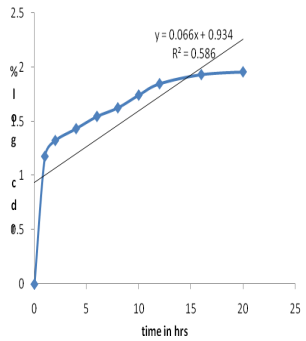

Fig: 4 First order plot of optimized F1

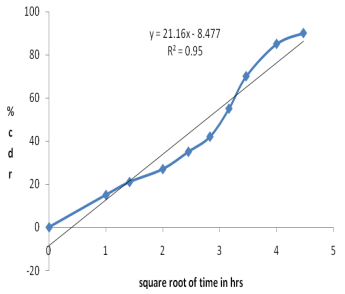

Fig: 5. Higuchi (diffusion)co-efficient plot of optimized F1.

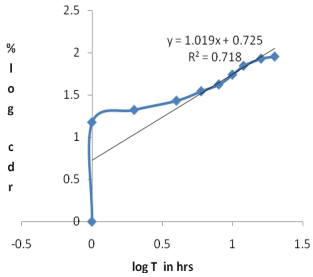

Fig:6. Korsmeyer Peppas plot of optimized F1.

SUMMARY AND CONCLUSION

Mini tablets are small tablets with diameter equal or less than 2.5mm that are filled into a capsule, or occasionally compressed into larger tablets. Combinations of different mini tablets may include immediate release, delayed release and/or controlled release. It is also possible to incorporate

mini tablets of different drugs to treat concurrent diseases or combinations of drugs to improve over all therapeutic outcomes, while delivering distinct release rates of each according to disease requirements. 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 formulated with different concentration of polymers like HPMCK100M,HPMCK15M, filler like lactose and with other excipients. A total number of 6 formulations (F1,F2,F3,F4,F5 and F6)were carried and evaluated.

In all the formulation thickness varies between 3.90-3.94mm and the hardness of the optimized batch was found to be 3.18kg/cm^2.No variation in the hardness was found in the optimized formulation that showed powder blending was uniform. Among 6 formulations done, F1, F2, F3, F6 trials were done using K100M polymer and F4,F5 with K15M polymer using optimized quantity of lactose, best batch among those is F1 because it had 90% release and it could sustain its action until 20th hr and is very economical. The optimized formulation of Risperidone was selected, filled in the capsule and all the evaluation were carried out according to the I.P.

In conclusion Risperidone is reported to be highly bio-available, and to avoid repeated multiple dosing, an ER mumps is been designed. 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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