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Preformulation Studies Of Risperidone: Initial Step Towards Development Of Immediate Drug Release System

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ABSTRACT:

Introduction: Pre-formulation studies are the initial step in the development of dosage forms of any drug substance. It confirms that there are no significant barriers to the compound's development as a marketed drug. **Objective:** The main objective of this research work was to conduct a pre-formulation analysis of risperidone an antipsychotic medicine in order to produce a stable, robust including therapeutically effective system. **Methods:** Risperidone was analyzed to determine its flow characteristic by angle of repose, carr's index, bulk density, tapped density etc. Solubility was also determined in various pH-varying solvents and its purity was determined by FTIR and absorption maxima. Standard calibration curve was developed to aid in further analytical research studies. At last drug-excipients compatibility studies were performed. **Results:** Risperidone has good flow and compressibility properties (BD 0.562 g/ml, TD 0.714 g/ml, Angle of Repose (ɵ) 24.68, Carr's index 12.39%, Hauser's ratio 1.12). Solubility of drug was found to decrease with increase in pH. The purity of drug was confirmed by infrared spectrum which showed characteristics peaks and by UV spectroscopy which exhibited maxima at 280 nm. The standard curve obtained was linear with correlation coefficient (R2 =0.997) and equation y = 0.026 +0.0028. There were no drug excipient interactions which was clear as no visual changes in drug samples were observed with respect to discoloration, liquefaction and odor. **Conclusion:** The powder blend under consideration was pure Risperidone which had good flow property suggesting use of granulation technique during tablet manufacturing and it was stable with selected excipient at reported ratio at 40oC / 75 % RH for 4 weeks.

KEY WORDS: Pre-formulation, risperidone, excipients, flow property, FTIR

INTRODUCTION:

After synthesis and development of a promising new API, it requires transformation to appropriate dosage form in order to show better and desirable effect at appropriate site.[1]Immediate release system is a novel drug delivery system which disintegrates and dissolves quickly to release the drug content. [2] The basic approach used in development of these tablets is the use of superdisintegrants like carboxy methyl cellulose (Croscarmellose), Cross linked Poly-vinyl pyrrolidone or crospovidone (Polyplasdone), Sodium starch glycolate (Primogel, Explotab) etc. [3] Research for development of a new drug is a complex, long and very expensive process and the success rate is low during the process. [4] To minimize this it is essential, to understand the physicochemical properties of drug content or biological compounds that are candidates for development into final products. Therefore, pre-formulation study is an approach for generation of pharmaceutical formulation which utilizes expertise and application of biochemistry, medicinal chemistry, toxicology and analytical chemistry. [5]

Pre-formulation is the study of the physical and chemical nature of the drug prior to compounding process. Pre-formulation study is the first step in the development of dosage forms of any drug substance. [1, 6] Pre-formulation studies act an important criterion to understand the potential pharmaco-kinetics of a drug substance in humans as well as in animals and the opportunities and limitations for process change as the product is scaled up in production. [6, 7]

These studies are performed after the completion of pre clinical / clinical trial and before starting actual formulation and development of dosage form. These studies designed to determine the effect of physicochemical characteristics of drug substances and excipients on formulation properties of dosage form, method of manufacture and pharmacokinetic–biopharmaceutical properties of the resulting product. [6, 8] Pre-formulation studies utilize to analyze compatibility of drug with all excipients. [9] It helps researcher to choose appropriate form of a drug substance to enhance bioavailability.[10]

Risperidone is a novel antipsychotic with dopaminergic and serotonergic effects. It has been characterized as atypical, but shares some of the extrapyramidal side effect profile of the earlier antipsychotics, particularly at higher doses. [11, 12] The main pharmacological activities of risperidone include serotonin 5-HT2 receptor blockade and dopamine D2 antagonism. [13]

Objective of this work was to perform pre-formulation study of risperidone in order to develop a stable, robust as well as the therapeutically effective and safe immediate release dosage form of Risperidone.

In order to achieve this objective characterization of risperidone was done by calculate Bulk Density, Tapped Density, Carr's Index and Hausner's Ratio. [14] Solubility of drug in various solvents of having different pH was determined. Infrared spectrum was done to determine purity of drug and UV Spectra was developed which will help in further analytical studies. [15] Loss on Drying (LOD) was carried out to calculate assay compensation. Finally drug-excipients compatibility studies were carried out to determine drug – excipient interactions. [16]

Principal Areas of Pre-formulation:

Organoleptic properties: [9, 10]

- **Color:** A small quantity of drug was taken in butter paper and viewed in well-illuminated place.
- **Taste and odour:** Very less quantity of drug was used to get taste with the help of tongue as well as smelled to get the odor

Melting point: Melting point was determined by capillary fusion method. [17]

Partition coefficient ($P_{o/w}$): The partition coefficient of Drug was determined in n-octanol/distilled water at room temperature (25± 2ºC). [18]

$$P_{o/w} = (C_{octanol} / C_{aqueous})$$

Characterization of Risperidone: [19, 20]

The drug substance was characterized for following parameters.

Bulk Density: A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume, Vo, to the nearest graduated unit. Calculate the bulk density, in gm per ml, by the formula.

Bulk density = Bulk Mass/ Bulk Volume

Tapped Density:

Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped and volume readings are taken until little further volume changes observed. The mechanical tapping is achieved by raising the cylinder and allowing it to drop under its own weight a specific distance. Cylinder dropping distance: 14± 2 mm at a normal rate of 300 drops / minute. Unless otherwise specified, tap the cylinder 500 times initially and measure the tapped volume, Va, to the nearest graduated unit. Repeat the tapping an additional 750 times and measure the tapped volume, Vb, to the nearest graduated unit. If the difference between the two volumes is less than 2%, Vb is the final tapped volume, Vf. Repeat in increments of 1250 taps, as needed, unit the difference between succeeding measurements is less than 2%. Calculate the tapped density, in gm per ml, by the formula:

$$\text{Tapped Density} = \frac{m}{Vf}$$

Measurement of Powder Compressibility Index:

Particle–Particle interactions affect bulking properties and powder flow. Comparing bulk and tapped densities will give us a measure of the relative importance of these interactions in a given powder. [10] Compressibility Index was calculated by the following formula:

CI (%) = (Tapped density– Bulk density) X 100 / Tapped density

Hausner's Ratio (H):

Hausner Ratio is measure of the propensity of a powder to be compressed. As the difference between the bulk and tapped density increases flow property decreases. This difference is reflected in Hausner Ratio. Hausner Ratio was calculated by the following formula: [21]

Hausner's ratio = Tapped Density / Bulk density

Determination of Solubility:

It is an essential and extensively utilized pre-formulation parameter. [22] The solubility of drug risperidone was determined as per BCS classification system. [23] The solubility was checked in 250 ml different medium and water. The solubility of risperidon in different solvents like water, 0.1N HCl, and phosphate buffer pH 6.8 was determined by using standard procedure.

Infrared spectrum:

The infrared spectrum of Risperidon pure drug and with excipients was carried out using potassium bromide disk method. The samples were prepared on KBr-press and over wave number range of 4000 to 400cm $^{-1}$ it was scanned.

Differential Scanning Calorimetry: Samples were prepared by placing 5 mg of the drug substance into an aluminium pan, which covered and crimped for analysis. Samples were desiccated over calcium chloride for 24 hours prior to assay in an effort to remove surface absorbed water. Thermograph was analysed qualitatively by examining both the peak temperature and the endothermic transition contour. The nitrogen flow rate was 20ml/min and the heating rate was 5°C/min over the range of 40 to 2500C.

UV Spectral Analysis: [24]

An accurately weighed amount (10mg) of Risperidon was transferred to 100 ml volumetric flask. The drug was dissolved in methanol and volume was made up to 100 ml with the same solvent (Methanol) to obtain a stock solution of 100mg/ml. From the standard stock solution, 1 ml was taken out in 10 ml volumetric flask and volume was made up to 10 ml with PBS pH 7.5. The resulting solution containing 10mg/ml was scanned over complete UV range (i.e. 200–400 nm)[19] using Shimadzu UV–Visible spectrophotometer for determination of λ max of the Risperidon. This stock solution was diluted with PBS pH 7.5 to give concentrations in the range of 5µg /ml-40µg /ml. Absorbance of these samples at varying concentrations were determined and data was used to plot calibration curve.

Drug: excipients compatibility study:

The study was designed with different ratio for drug and excipients as per their functionality. The weighed amount of API was mixed well with a proposed proportion of individual excipients (Table 5). Blend was filled and sealed in 5 ml glass vials. Vials were subjected to 40°C ± 2°C/75% ± 5% RH and 25°C 60% RH for 4 weeks conditions. The initial samples were analyzed immediately and used as control[25]. The samples were observed for physical changes[26] like discoloration, liquefaction.

RESULTS AND DISCUSSION:

Physiochemical Characterization of Risperidon:

The physicochemical properties of the powder blend affect the quality of tablet formulated. The drug **Risperidon**, selected for present study was identified using different procedure reported in the literature viz. melting point determination, partition coefficient determination, determination of absorption maxima (λ_{max}), FTIR spectroscopy and drug excipient interaction studies.

Organoleptic properties indicated that the drug is amorphous in nature, white in color and have no odor. The melting point was recorded at 170 ºC. The partition coefficient value log P was found to be 3.5±0.2. The observations are recorded in table 1.

Table 1 Results of Physiochemical properties of the Risperidone

Characters	Inference
Color	white or almost white powder
Odor	odorless
Nature	Amorphous powder
Melting Point	170 ºC
Partition Coefficient	3.5±0.2

Characterization of Risperidone:

There are many formulations and process variables involved in mixing step and all these can affect the characteristics of blend produced. Physical parameters such as bulk density, tapped density, Carr's index and Hausner's ratio of risperidone were determined as per method described in material method.

Table No.2: Physical properties of Risperidone drug

Parameters	Observed Value
Bulk density (g/mL)	0.562
Tapped density (g/mL)	0.714
Angle of Repose (ɵ)	24.68
Carr's index (%)	12.39
Hausner's ratio	1.12

Powder blends have superdisintegrants for immediate release tablets were showed Angle of repose 24.68, Carr's index less than 15.2 and Hausner ratio less than 1.18. Results indicate that powder blends has good flow properties.

The results of the table also indicate that the granules ready for compression showing fair to good Carr's Index, Hausner's ratio and flow ability.

Solubility Study:

The solubility of **Risperidon** in different solvents like water, 0.1N HCl, and phosphate buffer pH 6.8 was determined by using standard procedure. The observations are given in Table 3.

Table 3 Solubility Profile of Risperidon in different solvent

Sr. No.	Medium	Solubility (mg/ml)
1	Water	Insoluble
2	0.1 N Hydrochloric acid	Soluble
3	pH 4.5 Acetate buffer	Insoluble
4	pH 6.8 Phosphate buffer	Insoluble
5	Methanol	Soluble
6	Methylene chloride	Freely Soluble

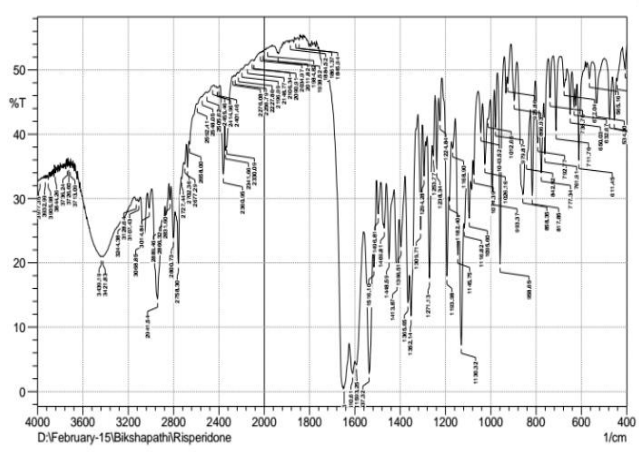
Fourier Transform infrared (FTIR) spectral studies:

While comparing the obtained FTIR spectra with the official spectra given in Indian Pharmacopoeia (2010), no differences were witnessed in the absorption peak pattern, which indicated the purity of the drug.

Among the various bands obtained in the spectra of **Risperidon**, only important ones were identified. An IR band was obtained at 2092.4.2 which can be assigned to C=N stretch, 3023 assigned to stretching of aromatic C-H group, 2938.9 assigned to stretching of aliphatic C-H group, 1693.9 assigned to C=O stretch. Table 4

Table 4: Interpretation of FTIR spectra of Risperidone

Stretching type	Spectra range cm^{-1}	Observed peak cm^{-1}
C=N	2250-2100	2092.4
C=0	1725-1700	1693.9
C-H aromatic	3030	3023
C-H aliphatic	3000-2850	2938.9



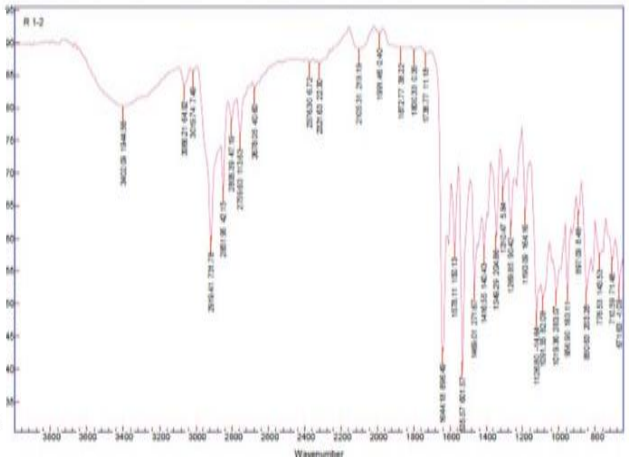
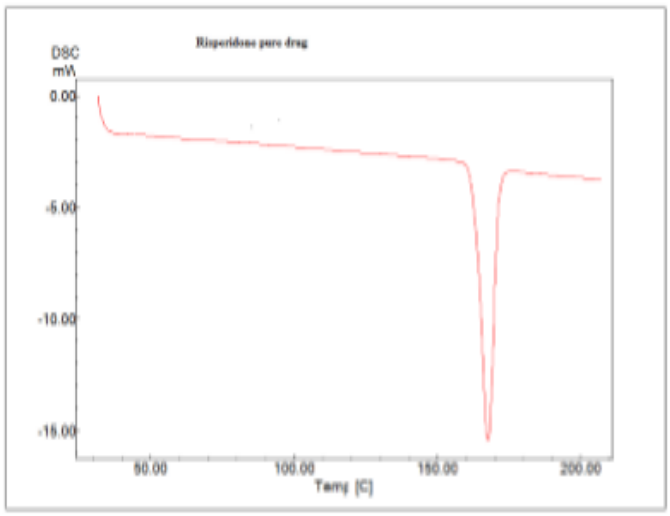


Fig. 1 Official FTIR Spectra of Pure Risperidone **Fig.2 Observed FTIR spectra of Risperidone**

Differential Scanning Calorimetry:

Differential scanning calorimetry (DSC) curves for Risperidon was recorded. Melting point was recorded as 168.2ºC which was almost similar to the value obtained through capillary fusion method. The thermograph is shown in fig. 3A and 3B



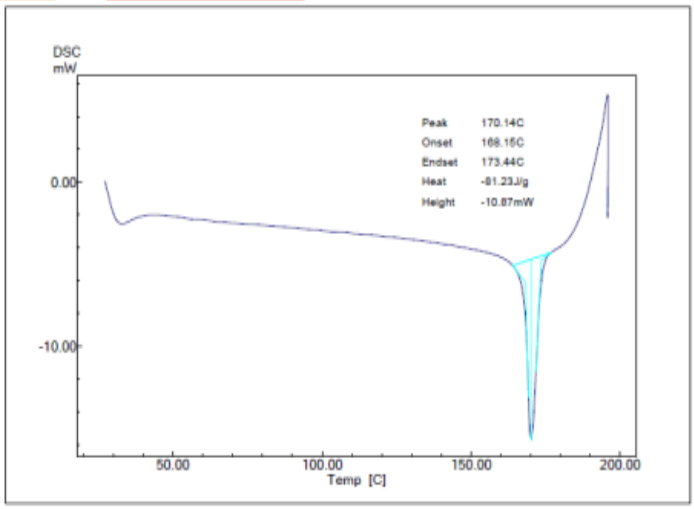


Fig 3A DSC Thermograph of Pure Risperidon **Fig 3B DSC of Risperidone and Mixture of Excipients**

Spectrophotometric Analysis of Risperidon:

Ultraviolet absorption in the range 200 nm to 400 nm of a solution of known concentration in Phosphate Buffer pH 6.8 was measured. The absorption maxima (λmax) of drug in this solution was found to be 280 nm (Fig. 7.4) which is in the close vicinity of maxima (280 nm in Phosphate Buffer pH 6.8) reported in literatures and official monographs. The prepared stock solution was analyzed spectrophotometrically at 280 nm to develop the calibration curve.

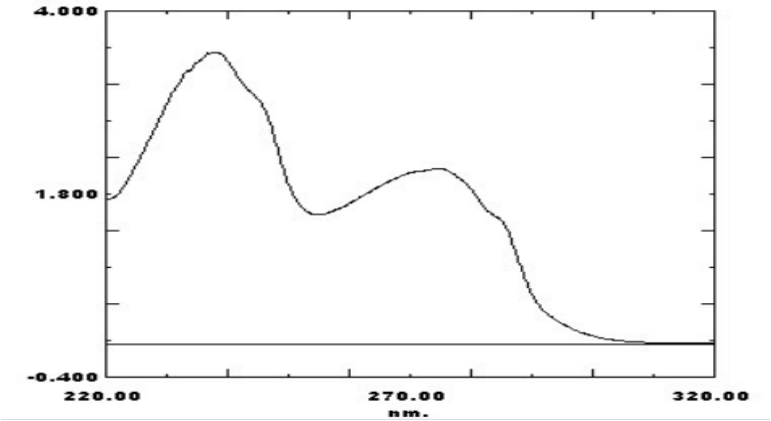


Fig.4: UV scanning of Risperidon (λ_{max}) at 280nm

Table 5: Calibration curve data of Risperidone in Phosphate Buffer pH 6.8

S.No	Concentration (µg/ml)	Absorbance(280nm) Phosphate buffer pH 6.8
1	5	0.175
2	10	0.314
3	20	0.58
4	30	0. 81
5	40	1.099

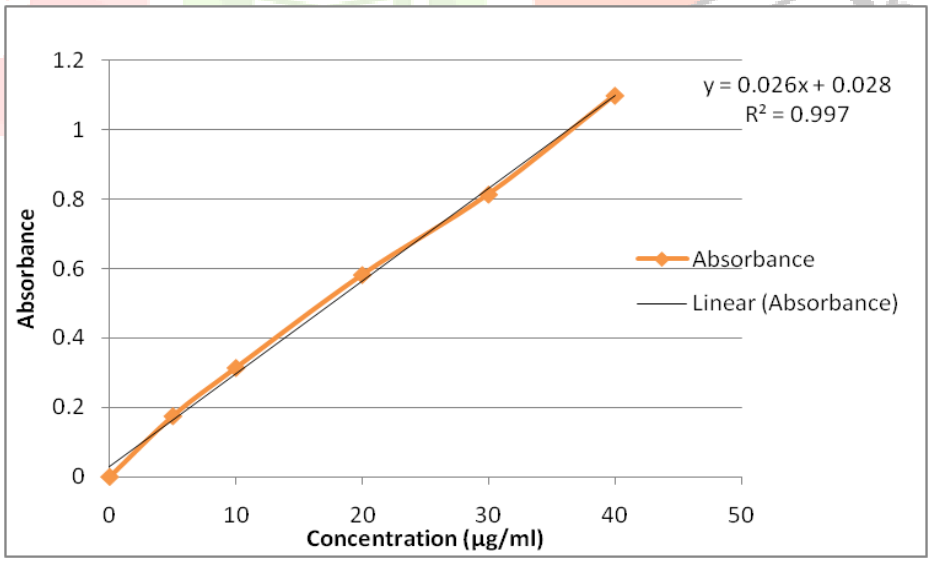


Fig. 5 Standard calibration curve of Risperidone in Phosphate buffer at pH 6.8 at 280nm

Drug-Excipients Compatibility Study:

The different formulation excipients, Risperidone, and their physical mixtures were found to be stable under selected storage conditions for one month, as there was no change in their physical characteristics.

Table 6: Observations of Drug-Excipient Interaction Studies

S. No	Drug-Excipients Combination	Initial Physical State	Observation at Different Storage Conditions				
			25˚C		40˚C		
			Duration (weeks)				
			2	4	2	4	
1	Risperidone Drug Pure	WP*	NCC	NCC	NCC	NCC	Compatible
2	Drug +PEG6000	WP	NCC	NCC	NCC	NCC	Compatible
3	Drug + Povidone (PVPK30)	WP	NCC	NCC	NCC	NCC	Compatible
4	Drug + Sodium Starch Glycolate	WP	NCC	NCC	NCC	NCC	Compatible
5	Drug + Crospovidone	WP	NCC	NCC	NCC	NCC	Compatible
6	Drug + Mannitol + Mg Stearate+Talc+Avicel PH102+Lactose	WP	NCC	NCC	NCC	NCC	Compatible
7	DRUG +PEG6000+Mannitol+Mg Stearate+Talc+Avicel PH102+Lactose	WP	NCC	NCC	NCC	NCC	Compatible
8	DRUG +PVPK30+Mannitol+MagnesiumStearate+Talc+Avicel PH102+Lactose	WP	NCC	NCC	NCC	NCC	Compatible

CONCLUSION:

In the present work, the preformulation study of antipsychotic risperidone drug was done. Pre-formulation analysis is most important phase in developing safe, effective and stable dosage form. Outcomes of these studies have great impact on further development of final dosage form. The organoleptic feature complies with Indian Pharmacopeia. Physical characteristics studies found that drug has good flow and compressibility properties. Solubility of drug was found to increase with increase in pH. The purity of drug was confirmed by infrared spectrum which showed characteristics peaks and by UV spectroscopy which exhibited maxima at 280 nm. The standard curve obtained was linear with correlation coefficient (R2 =0.997) and equation y = 0.026x +0.0028. The potential excipients Povidone, Sodium Starch Glycolate, Crospovidone, Lactose, Mannitol, Mg Stearate and talc which we are intending to use in formulating immediate release drug delivery system were found to be

compatible with drug risperidone when subjected to different temperature and humidity condition. This study shows a satisfactory result for all characterization and on the basis of this study we concluded that the drug was suitable for choice of formulation.

CONFLICT OF INTEREST:

No conflicts of interest are mentioned by the researchers. The composition and writing of the document are the sole responsibility of the writer.

REFERENCES:

1. Patel P. Preformulation Studies: An Integral Part of Formulation Design. Pharmaceutical Formulation Design, 2018: 1-5

2. Bhowmik D, Singh A, Gautam D. Immediate release drug delivery system-A novel drug delivery system. Journal of Pharmaceutical and Biological Sciences, 2016; 4(6): 197-202

3. Rohit P, Jagtap VA, Patil AV, Sarode S. A Review on Role of Novel Superdisintegrants in Pharmacy. European Journal of Pharmaceutical and Medical Research, 2015; 2(3): 390-400

4. Mohs RC, Greig NH. Drug discovery and development: Role of basic biological research. Alzheimers Dement (NY), 2017;3(4):651-657

5. Hughes JP, Rees S, Kalindjian SB, Philpott KL. Principles of early drug discovery. Br J Pharmacol. 2011 Mar; 162(6):1239-49

6. Trevor M. Preformulation Studies , in Pharmaceutical Formulation: The Science and Technology of Dosage Forms, 2018: 1-41

7. Bachhav AA, Ahire SA, Jadhav AG. Preformulation Study of Piroxicam. International Journal of Pharmaceutical Sciences and Research. 2019; 10(2): 811-818

8. Shah SM, Jain AS, Kaushik R, Nagarsenker MS, Nerurkar MJ. Preclinical formulations: insight, strategies, and practical considerations. AAPS Pharm Sci Tech., 2014; 15(5):1307-23

9. Desu PK, Vaishnavi G, Divya K and Lakshmi U. An overview on preformulation studies. Indo American Journal of Pharmaceutical Sciences. 2015; 2(10): 1399-1407

10. Nandgude TD and Bhise KS. Characterization of drug and polymers for development of colon specific drug delivery system. Asian J Biomed Pharm Sci., 2011; 1: 17-21.

11. Farah A. Atypicality of atypical antipsychotics. Prim Care Companion J Clin Psychiatry., 2005;7(6):268-74

12. Mauri MC, Paletta S, Maffini M, Colasanti A, Dragogna F. Clinical pharmacology of atypical antipsychotics: an update. Excli J. 2014; 13(13):1163-91

13. Megens AA, Awouters FH, Schotte A, Meert TF, Dugovic C, Niemegeers CJ, Leysen JE. Survey on the pharmacodynamics of the new antipsychotic risperidone. Psychopharmacology (Berl)., 1994; 114(1):9-23

14. Rakhi BS, Mobin AT, Mansoor AK. Comparative Evaluation of Flow for Pharmaceutical Powders and Granules. AAPS Pharm Sci Tech., 2008; 9: 250-258.

15. Wani M, Jagdale S, Khanna P. Formulation and Evaluation of Ophthalmic In-Situ Gel using Moxifloxacin Coated Silver Nanoparticles. Research Journal of Pharm. and Tech., 2020; 13(8): 3623-3630.

16. More S, Nandgude T, Poddar S. Vesicles as a tool for enhanced topical drug delivery. Asian J Pharm., 2016; 10: 196-209.

17. Mealey D, Svard M, Rasmuson AC. Thermodynamics of risperidone and solubility in pure organic solvents. Fluid Phase Equilibria, 2014; 375:73–79

18. Dubey SK, Singhvi G, Tyagi A. Spectrophotometric Determination of pKa and Log P of Risperidone. J App Pharm Sci, 2017; 7 (11): 155-158.

19. Ammar HO, Ghorab MM, Mahmaud AA. Formulation of risperidone in floating microparticles to alleviate its extrapyramidal side effects. Future Journal of Pharm Sciences, 2016; 2(2): 43-59

20. Ramu B. Formulation and Evaluation of Risperidone Fast Disintegrating Tablets by Using Co- processed Superdisintegrants. The Pharmaceutical and Chemical Journal, 2016; (334):334-342

21. Sopanrao MS, Nandgude T, Poddar S. Formulation and Optimization of Lansoprazole Pellets Using Factorial Design Prepared by Extrusion-Spheronization Technique Using Carboxymethyl Tamarind Kernel Powder. Recent patents on drug delivery & formulation, 2017; 11(1): 54-66.

22. Manohar Kengar, Rohit Howal, Dattatray Aundhakar, Amit Nikam and Priyajit Hasabe. Physico-chemical Properties of Solid Drugs: A Review. Asian J. Pharm. Tech., 2019; 9(1): 53-59.

23. Prashant R, Rakesh M, Tanaji N and Sushilkumar P. Solubility and dissolution enhancement of albendazole by spherical crystallization. Asian journal of biomedical and pharmaceutical sciences, 2016; 6(52): 09-14.

24. Karkhanis VV, Captain AD and Patel PH. Development and Validation of UV Spectrophotometric method for estimation of Glipizide in Bulk and Pharmaceutical Dosage Forms. Int J Pharm Sci Res., 2013; 4(5): 1865-1867.