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Formulation and evaluation of brain targeting drug loaded in-situ gelling systems through intranasal administration for schizophrenia

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ABSTRACT

In the present study an attempt was made to formulate and evaluate nasal in situ gel of Risperidone for Schizophrenia by ion activation method. It is a complex, chronic mental health disorder characterized by an array of symptoms, including delusions, hallucinations, disorganized speech. The preformulation studies for the drugs included API characterization, solubility, melting point, drug and excipient compatibility study was carried out. To develop nose to brain drug delivery through olfactory nerves. In ion activated method, various formulations (F1-F9) were developed using excipients in various concentration of gelrite and HPMC E50 LV. Formulations were evaluated for various physicochemical parameters like appearance, clarity, pH, gelation time, viscosity, in-vitro diffusion studies, sterility studies, isotonicity, drug content and stability studies. As the concentration of the polymer increases properties like gel strength, viscosity found to increasing but whereas the percentage of cumulative drug release from the formulation was decreased. F5 was selected as best formulation because of its good gelling capacity and optimum viscosity. Drug content was found to be 96.45 ± 0.20%. It showed 92.3% in vitro drug release for 12h. The F5 formulation follows First order kinetic which is depend on the concentration of the polymers and follows non fickian mechanism of drug release. Stability studies were carried out for F5 formulations as per ICH guidelines for a period of 30 days and the stability was confirmed as there were no significant changes observed in physicochemical parameters.

Keywords: Risperidone, In-situ gel, Intranasal, schizophrenia.

INTRODUCTION

Nasal drug delivery has been recognized as potential route from ancient days and nowadays it becomes an important tool in the treatment of various disorders. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal drug delivery has been practiced for thousands of years have been given a new lease of life. It is useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides. [1] In humans and other animal species the major functions of the nasal cavity are breathing and olfaction. It also affords an important protective activity once it filters, heat and humidity by the inhaled air before reaching the lowest – airways. Risperidone is a second-generation antipsychotic, marks a significant progress in the treatment of schizophrenia. Risperidone is a D2 antagonist and is included in the drug class of antipsychotics. Despite high levels of D2 receptor occupancy, moderate-dose risperidone treatment (4-6 mg/day) poses a somewhat lower EPS risk than treatment. with some FGAs. The affinity of risperidone for D2 receptors is approximately 50- fold greater than that of clozapine and approximately 20-50 % that of haloperidol. Risperidone is characterized by a very high affinity for 5-HT2A receptors, and a moderately high affinity for D2, H1, and alpha 1 and alpha 2 adrenergic receptors. In vitro, the affinity of risperidone for 5-HT2A receptors is roughly 10- to 20-fold greater than for D2 receptors[2]. The purpose of this research work was to formulate and evaluate Risperidone nasal in-situ gel using different polymers Gelrite, HPMC E50LV by ion activation method, used for the treatment of Schizophrenia in order to enhance bioavailability as well as to sustain the drug release for prolonged period of time and to improve patient compliance.

MATERIALS AND METHODS

Material

Risperidone was collected as gift sample from Micro Labs Limited, Bangalore. Gelrite were obtained from Sigma aldrich, Bangalore. HPMC E50 LV was obtained from Yarrow Chem Products, Mumbai. All chemicals and solvents used were of analytical grade.

Preformulation Studies

Solubility: The solubility of the selected drug was determined in methanol, water, 0.1N HCL, and SNF pH 6.4 using the standard method.

Melting point: Fine powder of Risperidone was filled in a glass capillary tube (previously sealed at one end) and attached to a thermometer with a rubber band, was immersed in the Thiel's tube containing liquid Paraffin. Heating was commenced. The melting temperature was determined.

Estimation of Risperidone: A Spectrophoto- metric method based on the measurement of extinction at 280 nm in simulated nasal fluid pH 6.4 was used for the estimation of Risperidone.

Fourier Transform Infrared Radiation (FTIR): The FTIR spectroscopy studies were carried out for pure drug alone and along with excipients to check the compatibility between drug and Gelrite,HPMC E50 LV which are used to formulate Nasal in-situ gel. The drug spectrum peaks were compared with the drug and polymer mixture spectrum peaks. The instrument from Tensor 27 was used for the study using the KBr pellets method. The major sharp and significant peaks (functional groups) of the drug and drug-polymer mixture was noted.

Method of preparation of Risperidone Nasal in-situ gel:

Gelrite was dissolved in deionised water and heated up to 85°C for 15 min. The solution was cooled by continuous stirring in open air. Sodium Propyl Paraben and drug solution were added to the above polymer solution. The volume was made up to 100 ml with deionised water followed by suitable filtration by using filter paper (0.2 mm). The prepared formulations were terminally sterilized by autoclaving at 121°C and 15 Psi for 20 min [3-5]. Five such formulations were formulated and the formulation chart of in-situ gel systems by ion activated method is shown in table: 1

EVALUATION OF RISPERIDONE NASAL IN-SITU GEL

Physical Examination

The prepared gel formulation was inspected visually for their colour, odour, appearance, clarity (visually). [6,7,8]

Determination of pH

The pH of gels was determined using a calibrated pH meter. The readings were taken for average of 3 samples.

Rheological Studies

Rheological study was carried out by Brookfield viscometer by selecting suitable spindle and at 0.3, 0.6, 1.5, 3, 6, 12, 30, 60rpm. Preparation was kept in 30ml beaker which was set up to spindle groove was dipped avoiding trapping of air bubbles. Spindle was selected by trial- and-error method.

Gelation Time

The time which is taken by the formulation for transition of liquid phase to gel. The test was carried out by taking 2ml of liquid in test tube and kept it in water bath. The time taken for transition was recorded.

Gelling capacity

Gelling capacity test was carried out to find optimum viscosity, which is the main criteria for sol to gel transition. A drop of prepared formulation was added to 2 ml of simulated nasal fluid. Gelling capacity was observed.

Sterility Studies

Tests for sterility were performed for fungi, aerobic and anaerobic bacteria by using fluid thioglycollate media and soya casein digest media.

Isotonicity

Isotonicity is an important characteristic of the nasal drug delivery system. Isotonicity has to be maintained to prevent tissue damage. Formulations are mixed with few drops of blood and observed under microscope at 45x magnification and compared with standard marketed nasal formulation. The shape of blood cell is compared with standard marketed nasal formulation as per IP.

In-Vitro Diffusion Studies

In vitro release study of in situ gel formulations are carried out by using Franz diffusion cell of 200 ml capacity. The formulation is placed in donor compartment and 200 ml of freshly prepared simulated nasal fluid of pH 6.5 was placed in receptor compartment. Between receptor and donor compartment, cellophane membrane previously soaked overnight in the dissolution medium is placed. The whole assembly is placed on thermostatically controlled magnetic stirrer. The temperature of the medium is maintained at 37ºc± 0.5ºc. 1ml sample is withdrawn at predetermined time interval of 1hr for 12hrs. The sample volume of fresh medium is replaced

with SNF. The withdrawn samples are suitably diluted & analyzed by UV spectrophotometer using reagent blank. After performing suitable dilution samples were analyzed spectrophotometrically at 280 nm. The drug content is calculated using an equation generated from standard calibration curve. [9]

Kinetics of drug release

To study the release kinetics of in-vitro drug release, data obtained from the in-vitro release study were plotted in various kinetic models: Zero-order as % drug released Vs time, First order as log % drug retained Vs time, Higuchi as % drug released Vs √time, Korsmeyer-Peppas as log % drug released Vs log time. By comparing the r2-values obtained, the best-fit model was selected.

Stability studies

The optimized nasal in-situ gel formulae was sealed in 5ml clear glass vials and stored at 40 ± 2ºC and 75±5%RH. After 0, 30 days, Samples were periodically taken and evaluated for physiochemical parameter, drug content and in vitro release using the same procedure mentioned previously. [9]

RESULTS AND DISCUSSION

Code / mg	F1	F2	F3	F4	F9	F5	F6	F7	F8	F9
Resperidone	300	300	300	300	300	300	300	300	300	300
Gelrite	250	250	250	500	750	500	500	750	750	750
HPMC K100M	300	400	500	300	500	400	500	300	400	500
Calcium chloride	160	160	160	160	160	160	160	160	160	160
Sodium citrate	170	170	170	170	170	170	170	170	170	170
Sodium propyl paraben	0.02 %	0.02 %	0.02 %	0.02 %	0.02 %	0.02 %	0.02 %	0.02 %	0.02 %	0.02 %

Table 1: Formulation of ion activated Risperidone nasal in-situ gel

DRUG	Risperidone
NATURE	Solid
COLOUR	White
ODOUR	Odourless

Table 2 : Description about drug

SOLVENTS	AMOUNT OF DRUG	INFERENCE
Methanol	**150mg/ml**	Freely soluble
Ethanol	**150mg/ml**	Freely soluble
Dimethylformamide	**190mg/ml**	Freely soluble
0.1N Hcl	**>1000mg/ml**	Very soluble
Water	**0.5mg/ml**	Insoluble
Simulated nasal fluid	**10mg/ml**	Soluble

Table 3: Solubility profile of Risperidone

SL.NO	ACTUAL MELTING POINT (^{O}C)	OBSERVED MELTING POINT (^{O}C)
1.	Melts at170ºC	170ºC
2.		167ºC
3.		168ºC
	Average Melting Point	169ºC

Table 4: Melting point of Risperidone

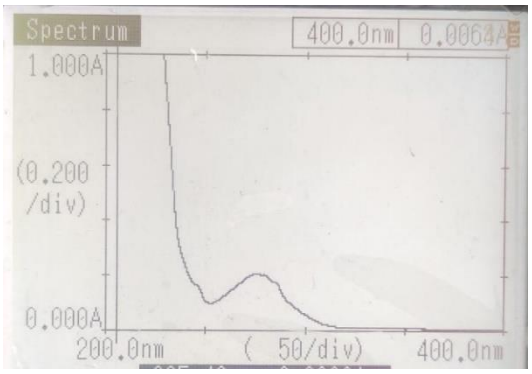

Fig1:λmax of Risperidone in Methanol

Fig2: λmax of Risperidone in SNF

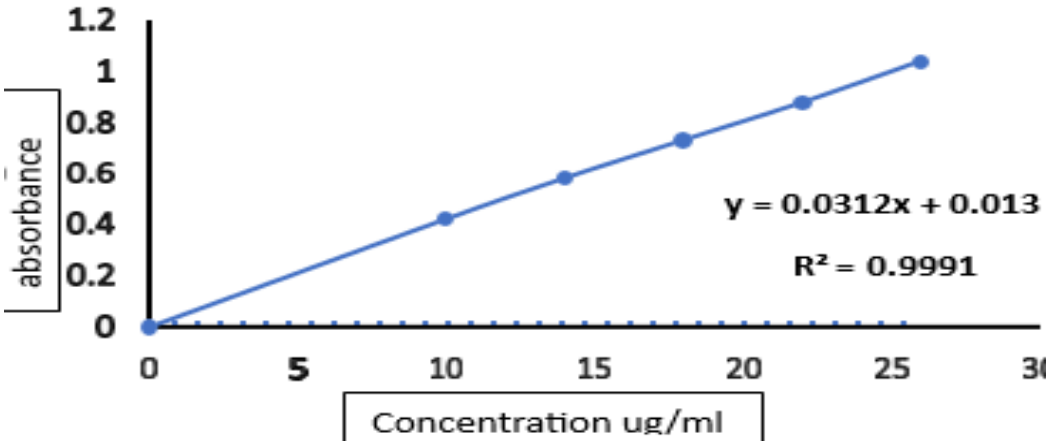

Figure 3: Standard Calibration Curve of Risperidone in Methanol

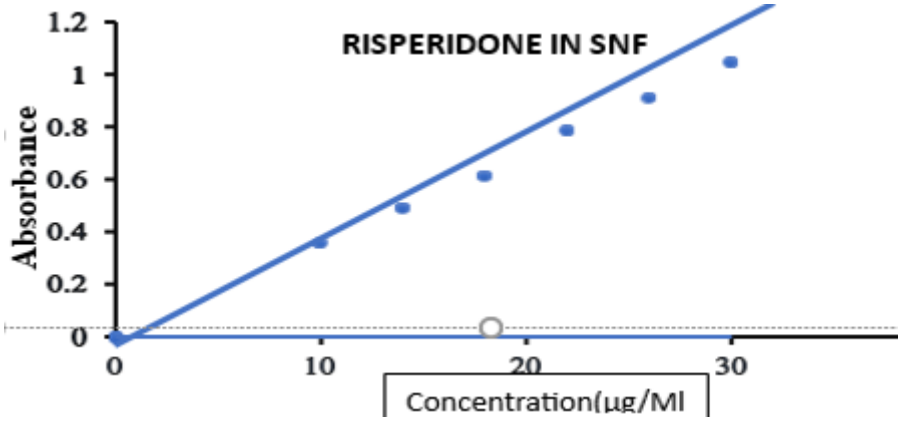

Figure 4: Standard Calibration Curve of Risperidone in SNF

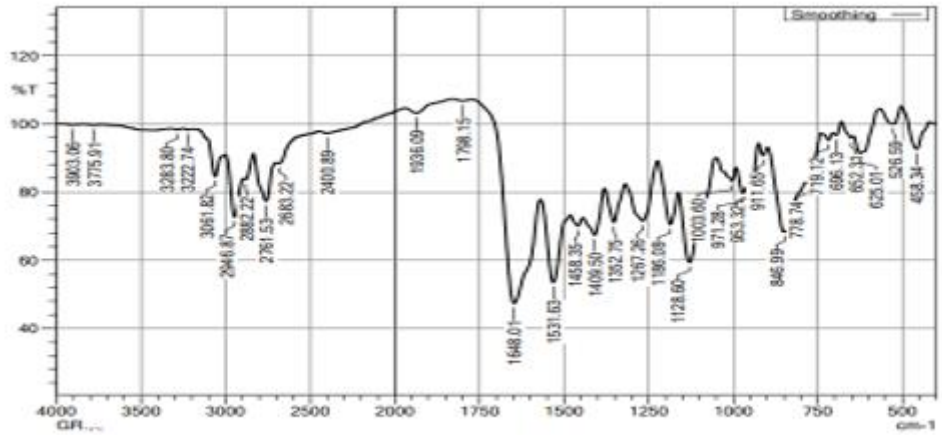

Figure 5: *FT-IR* Spectra of RISPERIDONE

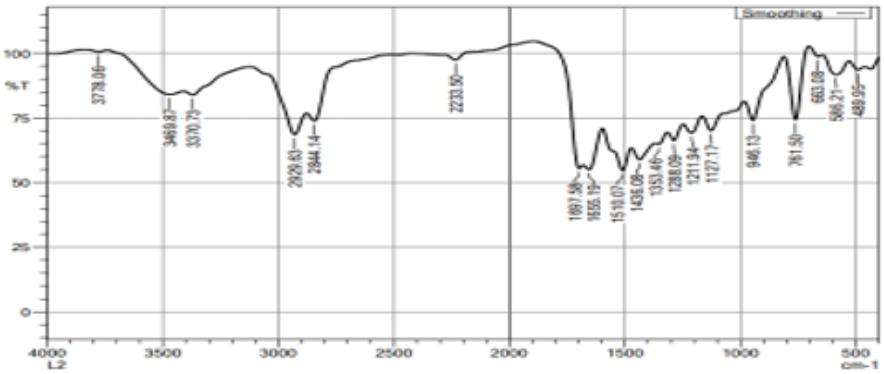

Figure 6: *FT-IR* Spectra of HPMC E50 LV

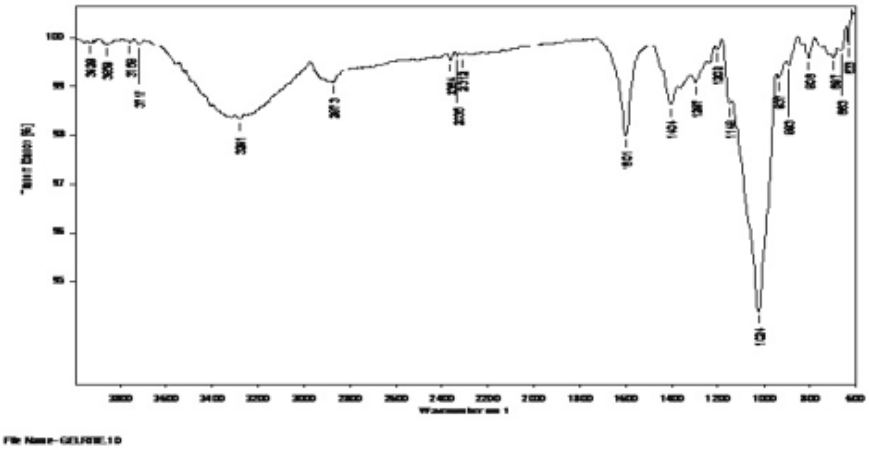

Figure 7: *FT-IR* Spectra of Gelrite

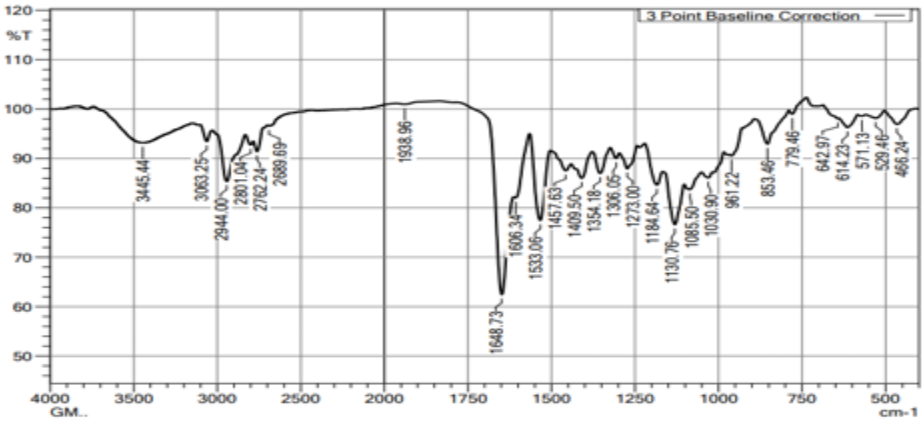

Figure 8: *FT-IR* Spectra of Risperidone + Gelrite + HPMC E50 LV

Formulation code	Appearance	Clarity	pH
F1	Transparent	Clear	6.28
F2	Transparent	Clear	6.17
F3	Transparent	Clear	6.08
F4	Transparent	Clear	6.24
F5	Transparent	Clear	6.54
F6	Transparent	Clear	6.20
F7	Transparent	Clear	6.02
F8	Transparent	Clear	6.13
F9	Transparent	Clear	6.08

Table 5: Physical appearance & clarity (F1-F9)

Formulation code	Gelation time (sec)	Gelling capacity	% DRUG CONTENT
F1	63	+	95.66
F2	61	+	96.95
F3	60	++	98.97
F4	61	+++	96.57
F5	58	+++	98.45
F6	56	+++	99.49
F7	58	+++	101.20
F8	53	+++	1011.86
F9	52	+++	101.35

Table 6: Gelation time, Gelationcapacity and % Drug Content of *in situ* gelling formulation (F1-F9)

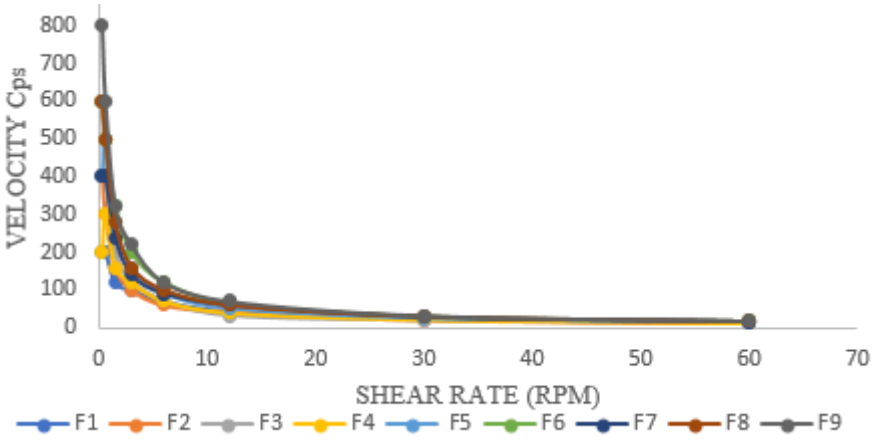

Figure9: Rheological studies of F1-F9 in-situ gel formulations (before gel)

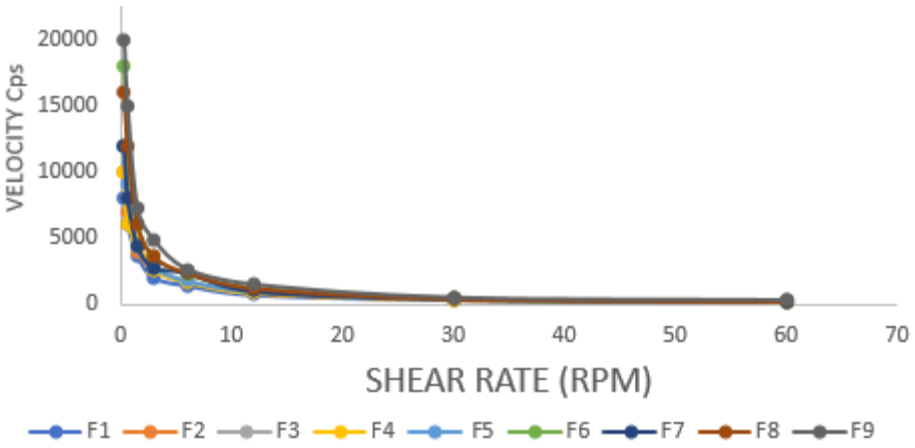

Figure9: Rheological studies of F1-F9 in-situ gel formulations (after gel)

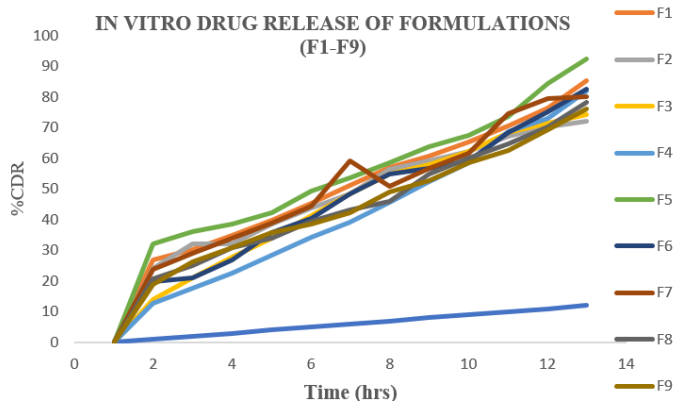

Figure 10: In -vitro drug release of formulations

Sterility Tests	Results Obtained																				
	(-) ve control							Test-F5							(+) ve control						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Test for aerobic bacteria	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+
Test for anaerobic bacteria	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+
Test for Fungi	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+	+	+	+	+

Table 7: Observations of sterility testing for F5 formulation

*** (-)** sign suggests negative results (No growth of microorganisms)

**** (+)** sign suggests positive results (Formation of colonies of microorganisms)

Isotonicity studies

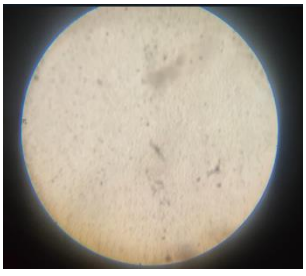

Figure 11: Blood cells with marketed nasal formulations as standard

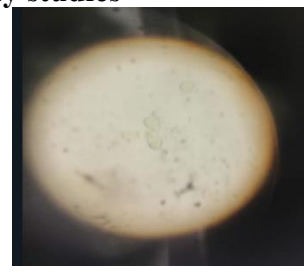

Figure 12: Blood cells with formulation F5

DISCUSSION

Nine formulations of Risperidone in situ gelling systems were prepared by using various concentrations of Gelrite and HPMC E50 LV in different ratio as per formula given in Table 1. All the formulations had fixed drug concentration of 300mg Risperidone. The formulations from F1 to F9 were transparent and the formulations clarity was found to be translucent. The pH of all the formulations was within the acceptable range (6.02 to 6.54) and hence would not cause any irritation upon administration. The drug content of all the formulations was in range. (95.66 to 101.86). Except for the formulations F1, F2, F3 all the formulations gelled instantaneously with a translucent matrix on addition to the STF. All the formulations exhibited pseudo-plastic rheology and a decrease in the viscosity with increased angular velocity. The results indicated that the formulation F5 showed better sustaining effect amongst all formulations. This may be due to the presence of higher concentration of Gelrite and HPMC in the formulation F5. All the prepared formulation was fitted in zero order release, first order release, higuchi model and korsemeyer peppas model based on the in vitro drug release data. The in vitro drug release showed highest regression value for the First order kinetics which is depend on the concentration of polymers, because the value of r2 was greater in this model. The data obtained from Korsmeyer-Peppas plot; the value of 'n' was found to be >0.5 which indicates that the mechanism of drug release was non fickian. So, the results obtained from the release kinetics indicate that the drug release from the nasal in situ gel occurs by non fickian mechanism for drug release which follows First order kinetic model. The formulation passed the sterility test as there was no appearance of turbidity and hence no evidence of microbial growth. The overall results of the sterility test showed that, the prepared nasal formulation was sterile. The best Gelling capacity, the best in vitro drug diffusion profile was achieved by formulation F5 which shows 92.3% drug release up to 12 hrs and it has optimum viscosity range without producing any injury to nose.

CONCLSION

In the present work, an in-situ gel of Risperidone was formulated successfully which when instilled into nasal fluid the sol becomes gels, thereby it provides increased contact time, so that it improves the bioavailability results in better therapeutic effects. The nine formulations were prepared by using Gelrite and HPMC E50 LV by ion activated method. In this F5 showed good results in the evaluation tests as pH, appearance, clarity, gelation time, in vitro studies. The developed in situ gelling system may be the alternative to conventional nasal drops as it may provide better patient compliance through easy and decreased frequency of administration

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REFERENCES

1. Lacro JP, Dunn LB, Dolder CR, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. The Journal of clinical psychiatry. 2002 Oct 1;63(10):15489.

2. Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: overview and treatment options. Pharmacy and Therapeutics. 2014 Sep;39(9):638.

3.Y. D. Sanzgiri, S. Maschi, V. Crescenzi, L. Calligaro, E. M. Topp and V. J. Stella. Gellan-based systems for ophthalmic sustained delivery of methyl prednisolone. J. Contr. Rel. 1993;26 :195– 201.

4. Raymond C Rowe, Paul J Sheskey and Marian E Quinn. Handbook of Pharmaceutical Excipients. 6th ed. London: Pharmaceutical press and the American pharmacists association; 2009; p:326-29,110-14, 506-9.

5. Madan M, Bajaj A, Lewis S, Udupa N and Baig JA. Insitu forming polymeric drug delivery systems. Indian J. Pharm. Sci. 2009; 71(3): 242-51.

6. Elad D, Wolf M, Keck T. Air-conditioning in the human nasal cavity. Respiratory physiology & neurobiology. 2008 Nov 30;163(1-3):121-7.

7. Ramya D. D, Abhirami M, Brindha R, Gomathi S, Vedhahari B.N. In-Situ gelling system potential tool for improving therapeutic effects of drugs. Int J Pharm Pharm Sci.2013; 5(3): 27- 30.

8. Khairnar P.S, WalkeP.S, NarkhedeM.R, Nehete J.Y. Formulation and in-vitro evaluation of thermoreversible Rizatriptan benzoate nasal gel. Int J Pharm Pharm Sci. 2011;3(4):250- 256.

9. A.Geethalakshmi,Roopakarki, Sajal Kumar Jha, D.P. Venkatesh and B.Nikunj. Sustained Ocular Delivery of Brimonidine Tartrate using Ion Activated In Situ Gelling System. Current Drug Delivery, 2012; 9,197- 204.