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Research Article

DESIGN AND DEVELOPMENT OF A WEEKLY SHOT OF INJECTABLE *IN-SITU* GEL FOR AN ANTIPSYCHOTIC DRUG IN THE TREATMENT OF SCHIZOPHRENIA

Santhi Priya. Nagam, Geetha. Achanta*, Naveena, Mandava,

Pooja.Chalimadugu, Sai Lakshmi Jyothirmai. Kala, Rama Rao. Nadendla

Department of Pharmaceutics, Chalapathi Institute of Pharmaceutical Sciences, Lam, Guntur, Andhra Pradesh, India.

ABSTRACT

Injectable *insitu* forming depots comprise a specific class of polymeric delivery system that posess the advantages of straight forward even for sensitive molecules and ease of application as a liquid, which solidifies after application by phase separation. The paper introduces a novel type of injection temperature sensitive polymer based on *insitu* gel for IM delivery of Ziprasidone mesylate into systemic circulation. The drug has 100%bioavailability when administered through intra muscular route.and has less oral bioavailability when administered through the other routes inorder to increase the bioavailabilty it has been formulated in the form of injectable gel. The thermogelling polymer with different concentrations has been used for formation of *insitu* gel of Ziprasidone mesylate with polymer and propylene glycol as plasticizer and glutaraldehyde as cross linking agent for sustained release. The FTIR studies confirm the absence of interaction between dru g and polymer. The developed formulation were evaluated for various parameters like surface gelation temperature, drug content, spreadability, viscosity, *invitro* drug release studies. Among all the developed formulations F6 was found to be the best in terms of cumulative percent drug release of 98.6% along with zero order kinetics mechanism and the release of the drug lasts for seven days and fulfilled many requirements of once a week delivery system .

Keywords: Ziprasidone mesylate, chitosan, propylene glycol, glutaraldehyde.

INTRODUCTION

The aim of current psychotic therapy is to formulate and evaluate the *insitu* forming mainly temperature induced and gelling injectables of Ziprasidone mesylate which is an antipsychotic agent indicated primarily for treatment of schizophrenia ,in order to render it target specific in nature and to maintain its high concentration and the target site for an extended time .the use of biodegradable polymer can lengthen the residence time and enhance bioavailability of drug that delivers into systemic circulation.

Sustain release drug delivery systems provide several advantages over the regular formulations such as better patient comfort and compliance, prolonged drug delivery, decreased dosing frequency, minimum side effects. The *insitu* gel system is a special class of polymeric sustained release system that is manufactured as a liquid and solidifies after administration.

The intramuscular administration of a formulation could be considered as alternative for the commercially available drug into systemic circulation. This will avoid the drug peroral first pass effect, enhance the drug bioavailability, and is expected to achieve better patient comfort and complaints due to decreased drug dosing frequency.

The development of injectable drug delivery system has received considerable attention over the past few years. The reason to receive attention is advantages of new injectable drug delivery system. These advantages are ease of application, site specific action, prolonged drug release, decreased drug dose and better patient compliance and comfort. Modified

Release injectable delivery systems such as microspheres, liposomes, gels, suspensions, *insitu* forming implants, lipophilic solutions, solid lipid Nano particles and drug eluting stents.

In recent years, development of *insitu* gel systems has received a considerable attention as polymeric drug delivery Systems. The importance of *insitu* forming matrix systems is related to several advantages such as, for instance, easy application, use of non toxic carriers, simple and economical elaboration, prolonged residence time and controlled drug release. Moreover these systems avoid painful surgical procedures to insert solid implants. The *insitu* forming gel systems are designed such that they are fluid prior to injection. Once injected the formulation response to a change in a environment to give a high viscosity or a solid depot at the injection site. The most studied thermosenstive and bio degradable polymer is used for the preparation of gels.

The chitosan has favorable biological properties such as biodegradability and bio compatibility which has attracted a lot of attention in the pharmaceutical and medical fields and an attractive material for multiple applications .Blending of chitosan with other polymers and cross linking are both convenient and effective methods of improving the physical and mechanical properties of chitosan for practical applications.

MATERIALS AND METHODS

Ziprasidone mesylate has been obtained as a gift sample from hetero labs. Chitosan was obtained from Sdfcl, Mumbai .all the other chemicals used in the work are of analytical value.

PREFORMULATION STUDIES

Drug solubility studies

The solubility of ziprasidone mesylate was performed in a variety of solvents . Drug (100mg)was added to 10 ml of various solvents .The dispersions was shaken in a thermostatically controlled water bath shaker at 37±0.5^{0}C until equilibrium(48 h) is achieved. Afterward, samples were withdrawn, filtered through a 0.45 micro meter membrane filter and suitably diluted . Concentration of the gel was found using a uv-visible spectrophotometer at 282nm.

Fourier transform infrared spectroscopy (FT-IR)

FTIR spectra of a pure drug, chitosan and physical mixture (ZM+chitosan) were obtained by using KBr pellet method (applying 6000kg/cm^2).spectral measurements were obtained by powder diffuse reflectance on a FTIR spectro photometer. Each spectrum was recorded in the frequency range of 4000-450^{cm-1}.

Preparation of *insitu* gels

The present study 6 batches of ziprasidone mesylate cross linked *insitu* gels was prepared by using natural biodegradable polymer ,chitosan in variable concentrations of polymer solutions (0.5,1,1.5,2,2.5,3%)were prepared by dissolving chitosan in 1% dilute acetic acid into a glass vial .the vial was placed in a continuous shaker over night at room temperature to completely dissolve the polymer. Then 10% v/v propylene glycol as plasticizer was added into the polymer solution and mixed together.1%w/w of drug ziprasidone mesylate was added to the drug free formulation. All formulations were clear , homogeneous solutions at room temperature. The mixture was stirred for 30 minutes at room temperature until it became increasingly viscous. The viscous solutions were left at room temperature to remove bubbles.

Characterization of Injectable *in situ* Gels

Clarity

The clarity of formulated solution was determined under dark and light background by visual inspection by using clarity testing apparatus.

In-vitro Gelling Capacity

In-vitro gelling study of final optimized formulation was determined in phosphate buffer saline (P.B.S . P^H 7.4), desired amount of each optimized formulation was injected in beaker contain P.B. S 7.4 using 21-guage needle and gelling capacity was recorded for each formulations.

Rheology

This is an important parameter for insitu gels to be evaluated. The rheological properties of the polymeric formulations, are determined with Brook field viscometer.

Estimation of drug uniformity

Formulations containing 1mg drug was taken in 10ml volumetric flask, dissolved in PBS 7.4, made up the volume to 10ml with PBS 7.4 and the solution was filtered. Absorbance values were measured with suitable dilutions at 282 nm. Concentration of drug was calculated from the standard calibration curve prepared in buffer 7.4.

Syringe ability Study

Take a disposable syringe, fill the desirable amount of formulation in it, and then pass the

formulation through 21 –gauge needle. The formulations that passed easily from the needle pass the syringe ability test.

Texture analysis

The firmness, consistency and cohesiveness of formulation were assessed using texture analyzer, which mainly indicates the syringe ability of sol. So the formulation can be easily, administered, *in-vivo*. Higher values of adhesiveness of gels are needed to maintain an intimate contact with surface like tissues.

***In-vitro* dissolution study**

In-vitro release profile was studied using USP apparatus II at37 ± 1^0C with a rotating speed of 100 rpm in dissolution media namely,PBS p^H 7.4.During the study, 5 ml of aliquots were removed at predetermined time intervals (0.5,1,2,4,6,8,10 and 24 hrs) from the dissolution medium and replaced with fresh buffer to ensure sink condition and drug content can be determined by spectrophotometrically at 282 nm.

***In-vitro* diffusion studies**

In vitro diffusion was determined by Franz diffusion cell. In Franz diffusion cell, cellophane membrane was sandwiched securely between donor and receptor compartment with the epidermis site facing the donor department .The receptor compartment is filled with buffer solution, which is continuously stirred and thermostated at 37^0C + or – 1^0C throughout the experiment Before starting the experiment the donor cell was sealed with paraffin film and covered with aluminum foil to prevent exposure to light. At predetermined time interval (0.5,1,2,4,6,8,10, and 24 hr.)5ml of aliquots are withdrawn and are replaced with an equal volumes of fresh buffer to ensure sink condition and drug content can be determined spectrophotometrically. Higuchi s equation ($Q=Kt^{1/2}$) and Korsmeyer–peppas equation are used to know precisely the mechanism of drug release from the injectable *insitu* gels.

Accelerated stability study

The parenteral formulations in amber colored vials were used for a short- term accelerated stability studies by storing at 40 ± 2^0C and 75±5% RH as per modified ICH guidelines. Samples were periodically evaluated for appearance, p^H, and drug content during the study period.

RESULTS AND DISCUSSION

Fourier transform infrared spectroscopy

The FTIR spectra of ziprasidone mesylate, chitosan and physical mixture of ziprasidone mesylate and chitosan, and optimized formulation of injectable are shown in fig -1.From this it is clear that there is no interaction between ziprasidone mesylate and polymers.

Appearance, clarity, Drug content

The appearance of all formulations were transparent and clear in color. Terminal sterilization by autoclaving had no effect on the formulations. The drug content of optimized (F6-F11) formulations was within the range of 96.30 % to 98.90%showed the uniform distribution of drug in the injectable formulations.

Gelling study

The viscosity and gelling capacity place a important role for *insitu* gelling system .the formulation should have a optimum viscosity such that it may be easy to administered by injection as a liquid which undergo sol-to-gel transition.

Rheological Studies

Rheological studies of final formulations

Rheological studies of the final formulations were done using Brookfield viscometer at a different rpm (20, 40, 60 ,80rpm)and then plotting the rheogram(viscosity/angular velocity),the flow behavior of solution was assessed. The rheogram showed the pseudo plastic behavior of the sol, with no yield value. Hence syringe ability of the sol will follow pseudo plastic behavior. viscosity of different formulation was recorded in table.

Rheological studies of insitu gel

The *insitu* gel prepared from final formulations(F1-F11) was studied for its rheological profile using Brookfield viscometer at different rpm(20,40,60,80rpm) Then plotting the rheogram between (viscosity/angular velocity),gel shows its pseudo plastic behavior, as with increase in shear rate there is no linear reduction in viscosity of the gel.

***In-vitro* dissolution study**

Invitro dissolution study of final 6 formulations (F6-F11) in PBS 7.4, was conducted in USP dissolution apparatus-2 and the result of *invitro* dissolution study tabulated in table and the mathematical models for the dissolution data of final formulation tabulated in table.7.

In-vitro diffusion study

Diffusion study of final formulation (F6,F7,F8,F9,F10,F11) was conducted in PBS 7.4 and the results of *invitro* diffusion release study are tabulated in table and release kinetics (mathematical model) were tabulated

in table. The *invitro* release (dissolution and diffusion) showed that formulation F6 has given least cumulative drug release in24 hrs. (58.0 and 53.21% respectively), thus it is best formulation capable of sustaining the release of drug. From the table 6 and 7 all the values of release rate exponent (n) of Korsmeyer-peppas release model were within the range of (0.5-1.0) 0.543-0.727 in PBS (P^H 7.4). Therefore, it can be concluded that drug release in PBS(p^H7.4)were mainly following Anomalous Transport which corresponds to diffusion, erosion and swelling mechanism or mixed order kinetics.

Texture Analysis of Insitu Gel

Consistency of the formulated gel was assessed using texture analyzer. The peak or maximum force is taken as a measurement of firmness-the higher the value the firmer is the sample. The area of the curve upto this point is taken as a measurement of consistency – the higher the area the thicker the consistency of the sample. The maximum negative force is taken as an indication of the cohesiveness of the sample-the more negative the value the more cohesive is the sample. The area of the negative region of the curve is referred as the work of cohesion-the higher the area the more resistant to withdrawal the sample is .which is an indication of the cohesiveness and also consistency \ viscosity of the sample the firmness, consistency and cohesiveness of formulation are assessed using texture analyzer, which mainly indicates the syringeability of sol so the formulation can be easily administered in-vivo. Higher values of adhesiveness of gels are needed to maintain an intimate contact with surface like tissues. The graphs obtain from texture analyzer have been shown in various figures given below. Firmness cohesiveness and consistency were measured using texture analyzer. The *in situ* gel prepared from formulation F6 was most firm, cohesive and has a higher consistency than other formulations. This finding is in accordance with the finding of *invitro* diffusion studies, where F6 have shown controlled release.further,F6 formulation shows matrix release indicating a controlled but slow release of formulation.

Stability studies

The formulationF6-F11 were kept at different storage conditions. The control samples were kept at 2-8^{0}C and test samples were kept at ambient temperature and at 40^{0}C the drug content of the gel was determined spectrophotometrically at 7 days. The drug content of the formulation at 0 days was taken as 100.00%.The sol is also assessed for transparency, clarity and for any physical preparation. From the results it has been observed that the formulation showed no change in appearance, clarity and in drug content**.**

CONCLUSION

From the study, it can be concluded that the temperature sensitive injectable *insitu* gel can be used to achieve sustained drug release. Because of its sustained release profile water soluble nature, physical stability and good spreadability. The gel formed insitu afforded sustained drug release over a period of 7 days. The IM drug release of ziprasidone mesylate since it would probably eliminate side effects and renders it target specific nature and to maintain its high concentration at the target site for an extended time . All the gels are formulated had gelation temperature well below body temperature thus they readily became gels, making them ideally suited to function as drug depot. Through the research work we have successfully assessed the resultant solutions for their physical stability. Thus the developed dosage form was found easy to administer, simple, comfortable , with increased patient compliance.

Table 1: Compositions of *insitu* gels
Formulation Table

FORMULATION CODE	CONCENTRATION OF DRUG	CONCENTRATION OF CHITOSAN	CONCENTRATION OF PLASTICIZER	CONCENTRATION OF GLUTARALDEHYDE
F1	0.2	0	0.5	1%
F2	0.2	0.1	0.45	1%
F3	0.2	0.2	0.4	1%
F4	0.2	0.3	0.35	1%
F5	02	0.4	0.3	1%
F6	0.2	0.5	0.25	1%
F7	0.2	0.6	0.2	1%
F8	0.2	0.7	0.15	1%
F9	02	0.8	0.1	1%
F10	02	0.9	0.05	1%
F11	0.2	1.0	0	1%

Table 2: Interpretation of FTIR Spectra

Polymer+Drug	Drug peak	Polymer peak	Conclusion
Drug +chitosan(1 :1)	3971.35,3667.28,3180.46,621.91,416.61	3980.82,3943.76,3759.57,3509.36,683.45,416.53	No Interaction

Table 3: Evaluation of injectable *insitu* gels

Formulation code	Appearance	Clarity	P^H ±S.D*.	Gelling capacity	Drug content +.S.D*.
F1	Transparent	Clear	3.18±0.02	++	Rejected formulation
F2	Transparent	Clear	4.86±0.03	++	Rejected Formulation
F3	Transparent	Clear	5.11±0.05	+	Rejected formulation
F4	Transparent	Clear	6.19±0.05	+	Rejected formulation
F5	Transparent	Clear	6.93±0.01	+	Rejected formulation
F6	Transparent	Clear	6.81±0.02	+++	98.8±0.002
F7	Transparent	Clear	6.63±0.03	+++	98.9±0.001
F8	Transparent	Clear	6.42±0.04	+++	96.3±0.001
F9	Transparent	Clear	6.38±0.03	+++	97.6±0.003
F10	Transparent	Clear	6.29±001	+++	98.6±0.002
F11	Transparent	Clear	6.19±0.01	+++	98.5±0003

+ = Gels slowly and dissolves
++ = Gelation immediate and remains for few hours
+++ = Gelation immediate and remains for an extended period.

Table 4: Viscosity range final formulation

Formulation code	Viscosity at RPM 20	Viscosity at RPM 40	Viscosity at RPM 60	Viscosity at RPM 80
F1-F11	1012-2015	453-1312	240-860	117-521

Table 5: Viscosity range of *insitu* gels

Formulation code	Viscosity at RPM20	Viscosity at RPM40	Viscosity at RPM 60	Viscosity at RPM 80
F1-F11	2017-3021	1014-2029	411-1022	314-517

Table 6: Percent cumulative release of ziprasidone mesylate

Time (Hrs)	F6	F7	F8	F9	F10	F11
0	0	0	0	0	0	0
0.5	4.6±0.18	4.2±0.16	7.6±0.54	8.92±0.13	6.82±0.21	5.85±0.69
1	9.8±0.24	15.12±0.34	9.48±0.55	15.3±0.26	16.71±0.25	16.13±0.23
2	19.6±0.34	18.64±0.33	21.97±0.99	23.7±0.67	27.99±0.24	28.19±0.32
4	27.2±0.14	26.56±0.55	28.96±0.52	34.1±0.32	32.18±0.58	36.27±0.69
6	34.8±0.23	33.2±0.66	32.45±0.66	38.2±0.56	34.6±0.69	38.69±0.67
8	37±0.18	44±0.12	36±0.89	45.9±0.78	45.5±0.33	42.6±0.56
10	43±0.22	46.1±0.66	48.5±0.74	49.2±0.63	53.4±0.59	52.1±0.22
24	56±0.11	64±0.66	57.1±0.89	63.2±0.60	62.4±0.52	65.4±0.64

Table 6(a): Mathematical models for the dissolution data of final formulation

S.NO	Formulation code	Zero order r^2	First order r^2	Higuchi r^2	Korsemeyer and peppas
1	F6	0.848	0.933	0.970	0.663
2	F7	0.828	0.923	0.966	0.682
3	F8	0.866	0.946	0.980	0.566
4	F9	0.828	0.923	0.964	0.546
5	F10	0.830	0.922	0.965	0.549
6	F11	0.800	0.901	0.951	0,543

Table 7: % cumulative release of ziprasidone mesylate

Time (hrs)	F6	F7	F8	F9	F10	F11
0	0.0	0.0	0.0	0.0	0.0	0.0
0.5	3.97±0.23	3.39±0.17	5.85±0.38	6.8±0.89	8.57±0.62	5.48±0.56
1	7.91±0.43	9.8±0.69	8.73±0.31	12.42±0.73	12.4±0.13	12.28±0.54
2	16.82±0.52	12.27±0.37	18.47±0.16	18.3±0.45	14.04±0.65	22±0.34
4	24.8±0.79	26.52±0.99	24.3±0.56	29.88±0.46	27.66±0.72	36.47±0.49
6	28.8±0.48	33.4±0.56	27.12±0.61	35.69±0.57	34.38±0.9	37.23±0.46
8	36.7±0.34	36.23±0.4	32.98±0.37	39.42±1.2	38.04±1.2	42.95±0.38
10	39.6±0.79	47.13±0.43	36.8±0.91	47.71±0.79	46.71±0.97	47.66±0.43
24	56.21±0.66	54.40±0.23	57.20±0.76	62.35±0.55	63.89±0.55	55.95±0.78

Table 7 (a): Mathematical models for the diffusion data of final formulation

S.NO	Formulation code	Zero order r^2	First order r^2	Higuchi r^2	Korsmeyer and peppas n
1	F6	0.750	0.824	0.935	0.720
2	F7	0.839	0.908	0.970	0.734
3	F8	0.900	0.954	0.982	0.647
4	F9	0.949	0.922	0.983	0.626
5	F10	0.765	0.931	0.980	0.528
6	F11	0.847	0.910	0.952	0.687

Table 8: Texture analysis of *insitu* gel

S.NO	Formulation code	Mean max.+ve force firmness	Mean +ve area consistency	Mean max.-ve force cohesiveness
1	F6	119.80	1099.40	-95.80
2	F7	98.32	931.24	-85.45
3	F8	80.23	733.22	-63.11
4	F9	79.63	723.41	-65.26
5	F10	80.42	718.41	-66.44
6	F11	78.33	769.45	-69.45

Table 9: Results of stability studies

Formulation code	Storage condition	Transparency and clarity	0 day	7 days	15 days	21days	30 days
F6	4^0C RT 40^0C	Transparent and clear	97.9	97.72 95.98 93.46	98.63 95.63 93.93	97.33 94.56 93.46	98.52 94.44 93.65
F7	4^0 C RT 40^0C	Transparent and clear	98.7	97.85 96.94 94.26	97.52 96.81 95.98	97.58 96.38 94.66	95.81 96.70 92.59
F8	4^0C RT 40^0C	Transparent and clear	95.8	96.30 94.58 95.31	96.95 93.51 94.73	95.47 93.14 93.69	95.66 92.93 92.56
F9	4^0C RT 40^0C	Transparent and clear	98.6	98.50 97.97 96.36	96.97 96.94 95.91	95.94 95.87 93.89	94.89 93.81 92.75
F10	4^0C RT 40^0C	Transparent and clear	97.6	97.50 96.98 94.81	96.97 95.95 93.99	95.94 94.86 92.58	93.92 93.75 90.49
F11	4^0C RT 40^0C	Transparent and clear	98.5	98.39 97.98 96.51	97.97 96.91 95.98	96.94 95.85 93.78	94.84 93.79 90.61

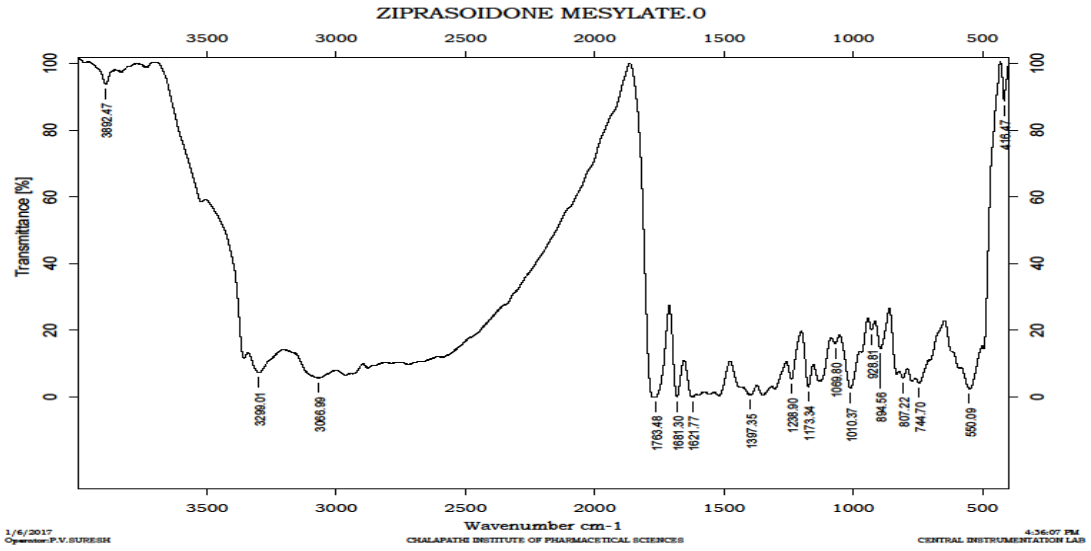

Fig. 1: FT-IR of ziprasidonemesylate

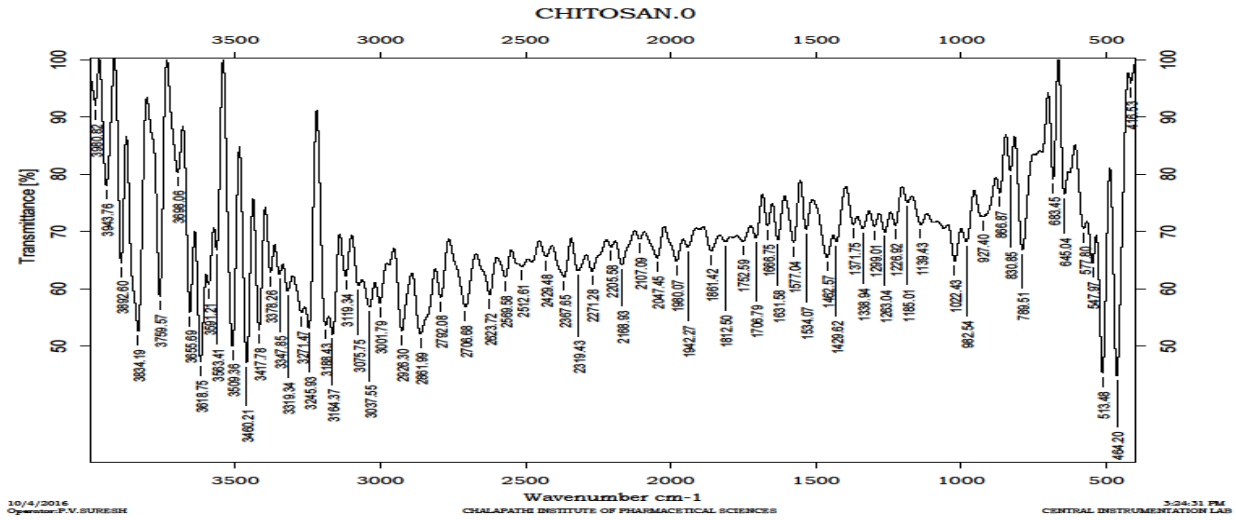

Fig. 2: FT-IR of chitosan

Fig. 3: Clarity testing of injectable *insitu* gel forming systems

Fig. 4: Invitro gelling capacity of all formulations

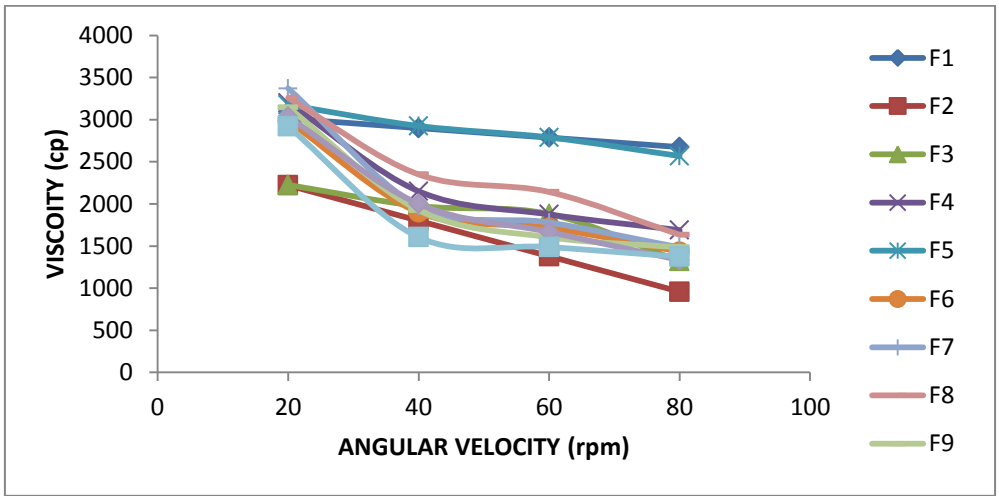

Fig. 5: Rheological profile of gel using Brookield Viscometer

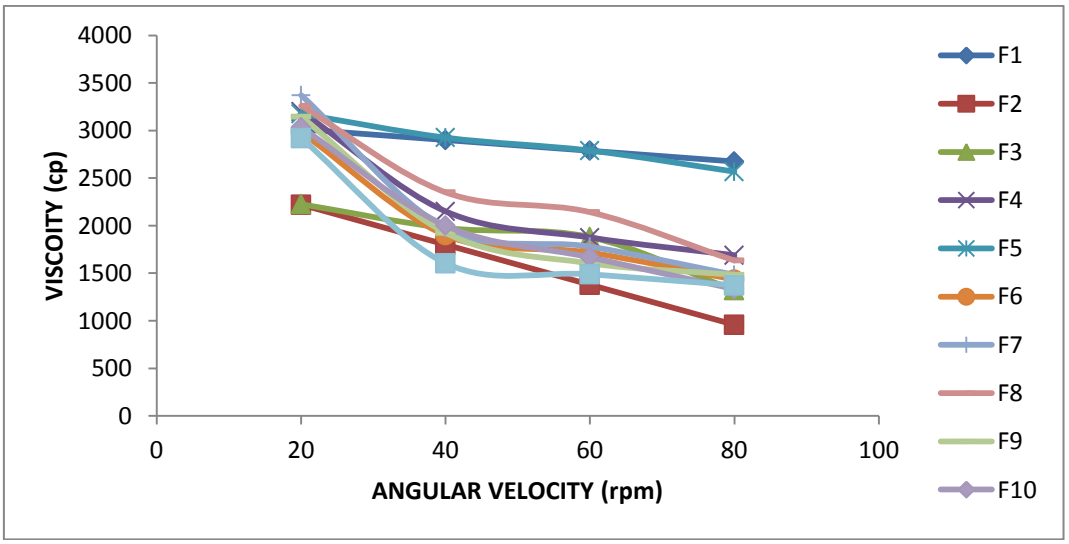

Fig. 6: Rheological profile of sol using Brookfield viscometer

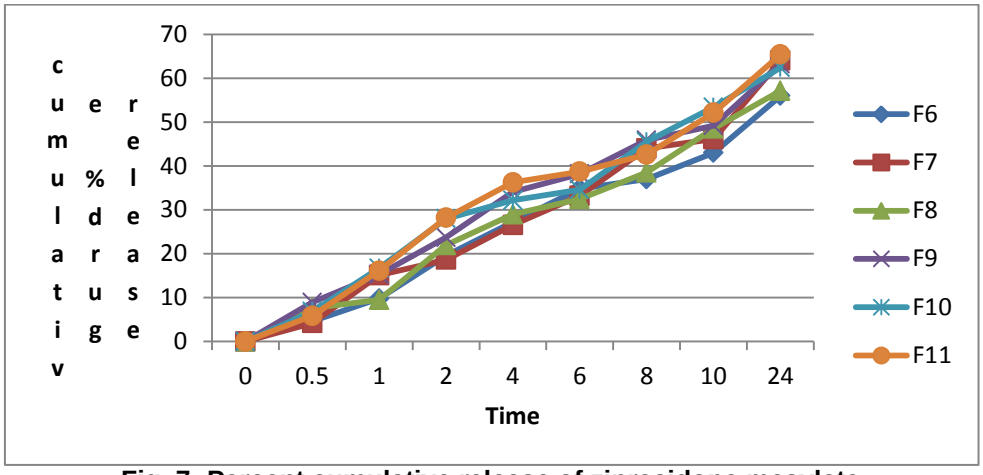

Fig. 7: Percent cumulative release of ziprasidone mesylate

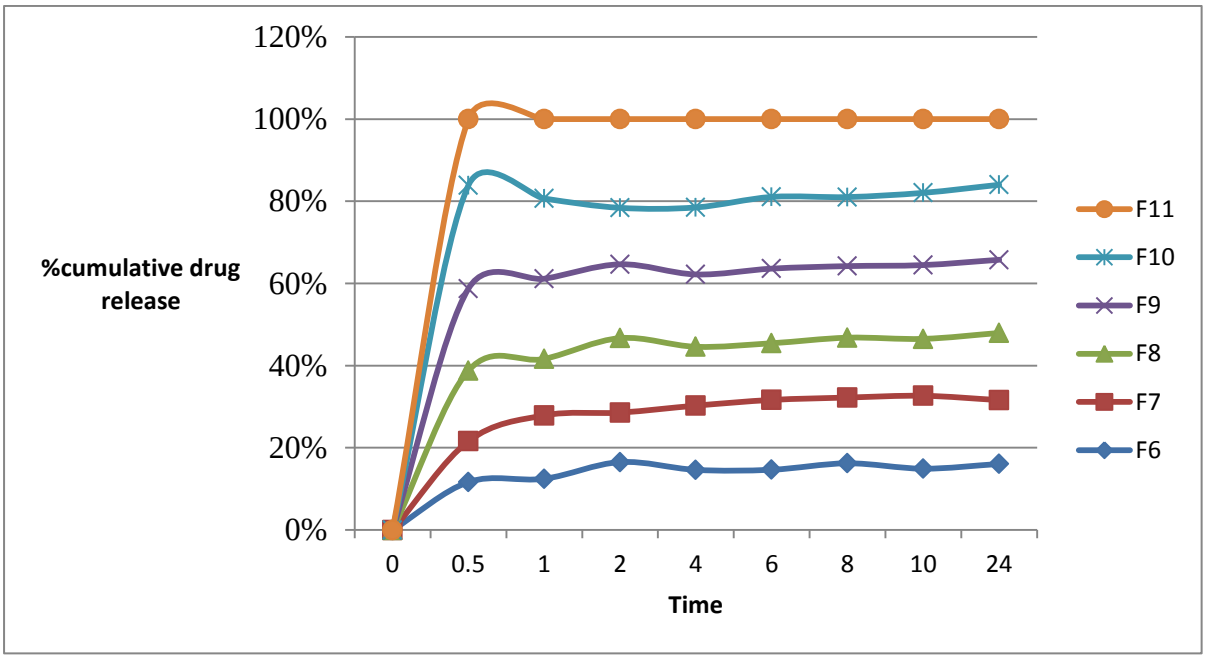

Fig. 8: % cumulative release of ziprasidone mesylate

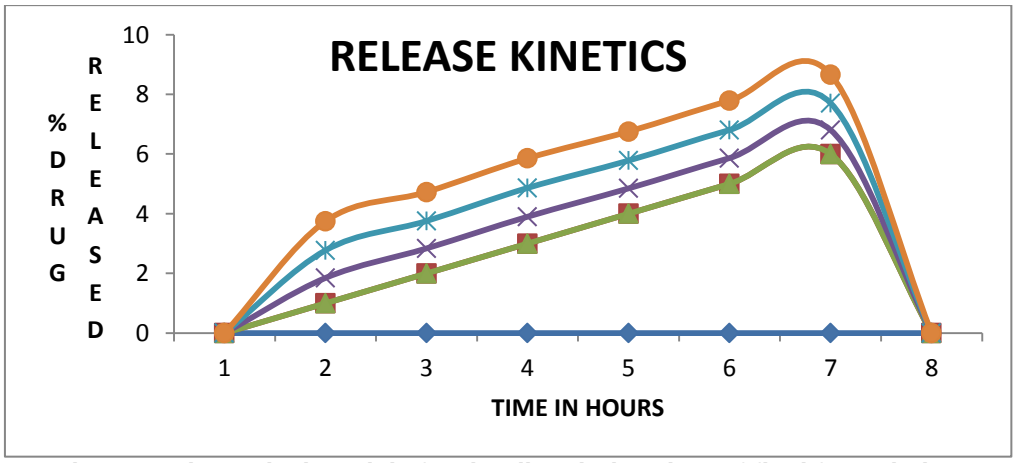

Fig. 9: Mathematical models for the dissolution data of final formulation

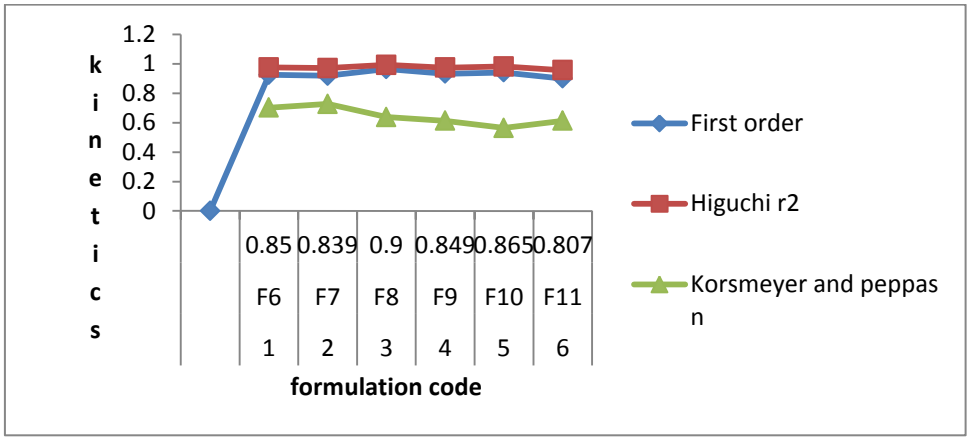

Fig. 10: Mathematical models for the diffusion data of final formulation

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