International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.9, pp 195-211, 2017

Formulation Development and Evaluation of In-Situ Nasal Gel of Ziprasidone Hydrochloride

R. B. Saudagar[1]*, Mita M. Kulkarni[2]

[1]*Department of Pharmaceutical Chemistry, R.G.Sapkal College of Pharmacy,Anjaneri.Nashik-422213,
[2]Department of Quality Assurance Techniques, R.G. Sapkal College of Pharmacy, Anjaneri,Nashik-422213, Maharashtra ,India.

Abstract : The present study was aimed to develop a Mucoadhesive in-situ gel of Ziprasidone Hydrochloride for improved bioavailability by avoiding the hepatic first pass metabolism and patient compliance. Ziprasidone Hydrochloride was incorporated into the blends of thermoreversible polymer poloxamer 407 and Mucoadhesive polymer HPMC K4M in the form of in-situ nasal gel by cold technique to reduce the muciliary clearance, and there by it will increase the contact of formulation with nasal mucosa and hence improving drug absorption. The prepared gels were characterized by, pH, drug content, gel strength, mucoadhesive strength permeation studies, drug release, stability study etc. pH of all the formulations were found to be within the range between 4.5-6.5 and the nasal mucosa can tolerate the above mentioned pH of the formulations. The drug content of all formulations was found to be 90.88 to 98.34%. Tests also revealed that as the level of HPMC K4M increases mucoadhesive strength also increase. Viscosity measurement of the formulations at room temperature & 37°C shows that there was increase in viscosity with increase in the temperature and it was found that all formulations were in liquid state at room temperature and were converted into gel at nasal physiological temperature. The optimized formulation showed a drug release of 97.07 % in 8 hour. The study indicate that the formulation was effective in providing in-vitro release of drug and the mucoadhesive formulation.
Keywords : Ziprasidone Hydrochloride, HPMC K4M, Poloxamer407, In-situ Gelling system.

Introduction

The most commonly used route of administration for systemic effect is oral administration. But for some drug the systemic effect was not in desirable condition due to oral bioavailability and promoted for search of more effective route for systemic delivery .Usually the nasal cavity is used for the treatment for the local diseases like rhinitis, migraine, cold, nasal congestion and CNS disorder. In recent years it has been proved that many drugs achieved better systemic bioavailability through nasal route. Nasal mucosa is major route of administration to achieve faster and higher level of drug absorption [1][2]. This is due to the anatomy and physiology of nasal passage that is porous endothelial membrane, large surface area, high total blood flow, the avoidance of first pass metabolism and readily accessibility [3]. In-situ is latin term which means 'In its original place or in position'. In-situ gel is a type of dosage form in which the medicament isin solution form before administration into the body, after administration it undergo gelation to form a gel.[4]Nasal drug delivery also provides a way to brain that circumvents the blood-brain barrier because the olfactory receptor cells are in contact with central nervous system directly [5]Ziprasidone hydrochloride is a antipcychotic agent used to

treating the schizophrenia. Ziprasidone hydrochloride is well absorbed from gastrointestinal tract after 8 hours. Ziprasidone hydrochloride undergo hepatic first pass metabolized by aldehyde oxidase and by cytocrome P450 isoenzymeCYP3A4 .Ziprasidone hydrochloride is5-{2[4(1,2-Benzisothiazole-3-yl)-1- piprazinyl]}-6-chloro-2 indolinone[6].It is lipophilic lipid soluble; it is soluble in methanol, phosphate buffer 6.8 and it is insoluble in water. It has absolute Bioavailability 59 % and it is undergo extensively hepatic first pass metabolized after oral administration with only small amount excreted in the urine (less than 1%) or feces (less than4%) as unchanged drug. Approximately 20% of the dose is excreted in the urine, with approximately 66% being eliminated in the feces. Ziprasidone hydrochloride is aacidic and its pKa value is 13.18, which satisfies the criterion for selection of drug. The Log(p) (Partiation Coefficient) value for Ziprasidone hydrochloride is about 3.8.The halp life of Ziprasidone hydrochloride is 4 hours. The dose of Ziprasidone hydrochloride is 20 mg twice a day and is used to treat the schizophrenia[6][7]. Schizophrenia is a chronic disabling illness, caused by abnormal amounts of certain neurotransmitters in the brain.[8]Poloxamers class of thermoreversible gels that have the capacity to make, break and modify the bonds responsible for holding the network together. Their thermoreversible property make them useful as a carrier for most routes of administration including oral, topical, intranasal, vaginal, rectal, ocular and parenteral routes. Reverse thermal gelation and low toxicity have been the basis of research into the use of Pluronics as a possible drug delivery system in man.[9]

Materials and Methods

Materials

Ziprasidone hydrochloride was obtained as a gift sample from Wockhedt Research center, Aurangabad Poloxamer-407 was obtained as a gift sample from Signet chemicals and BASF chemical company, NaviMumbai. Benzalkonium chloride and propylene glycol was procured from, Research-Lab Fine Chem. Industry Mumbai, India. All other chemicals were of research grade. The formulations were prepared by cold method. The drug containing Propylene glycol, Temperature sensitive polymer and mucoadhesive polymers were hydrated separately in calculated amount of distilled water at room temperature and cooled and stored at 4^{o}C. Both polymeric solutions was mixed slowly on ice bath, preservative was added slowly with continuous stirring in polymer solution. Both solutions (drug and polymer) were mixed with each other by gentle stirring. The final dispersion was then stored in a refrigerator until clear solution was obtained. Different formulation of gel were prepared by using ingredients mentioned in (Table no.2). In this formulation concentration of poloxamer 407 was ranged between 14 to 18 %, concentration of HPMC K4M in between 0.1 to 0.2%. Drug was dissolved in mixture of Propylene glycol both the polymers were hydrated separately. Kept solutions at room temperature over night. Preservative was added in polymeric solution. Mixing of drug and polymeric solution was done at cold condition

Physicochemical Studies

Drug Solubility Study[10]

Ziprasidone hydrochlorideis soluble in Methanol, phosphate buffer 6.8 and it is insoluble in water. The solubility of Ziprasidone hydrochloride in variety of solvents was carried out. The amount of 10mg Ziprasidone hydrochloride was added to 10 ml various solvents. The dispersions were shaken in thermostatically controlled water bath shaker at 37±0.5ºC until equilibrium. Afterwards samples were withdrawn diluted with a solvent. Drug concentration was analyzed and the absorbance of solution was measured by using UV-Visible Spectrophotometer.

Determination of λ_{max} in phosphate buffer pH 6.8

The UV spectrum of ziprasidone Hydrochloride was obtained using Ultra violet shimadzu 1800.Accurately weighed 10 mg of the drug was dissolved in sufficient quantity of phosphate buffer pH 6.8 and volume made up to 10 ml. The stock solution was diluted to obtain a concentration of 100 µg/ml. 6 ml of aliquot was withdrawn and volume was made up to 10 ml using phosphate buffer pH 6.8 to obtain the concentration of 60 µg/ml. The resultant solution was scanned from 200 to 400 nm and the spectrum was recorded to obtain the value of maximum wavelength.

Determination of λ_{max} in Methanol[11]

The UV spectrum of Ziprasidone Hydrochloride was obtained using Ultra violate Shimadzu 1800.Accurately weighed 10 mg of the drug was dissolved in sufficient quantity of Methanol and volume made up to 10 ml. The stock solution was diluted to obtain a concentration of 100 µg/ml. 8 ml of aliquot was withdrawn and volume was made up to 10 ml using methanol to obtain the concentration of 80 µg/ml. The resultant solution was scanned from 200 to 400 nm and the spectrum was recorded to obtain the value of maximum wavelength.

Fourier Transform Infrared Spectroscopy[12]

IR spectrum of pure Ziprasidone hydrochloride and physical mixture (1:1) of pure drug and polymer was analyzed in (BRUKAR) spectrophotometer. Physical mixtures of drug and polymer sample were kept for 1 month at 40 ^{0}C.The infrared absorption spectrum of Ziprasidone hydrochloride and their physical mixture with polymer are recorded the wave number

Preformulation Studies

Preformulation is the first step in designing or development of rational dosage forms of drug. Preformulation studies are to be doing for dosage forms to optimizing the delivery of drug through determination of physicochemical properties of the new compound that may affect the development or performances of stability, safety and efficiency of dosage forms. Preformulation studies gives complete information needed to define the nature of drug substance.

Formulation and Optimization

3^2factorial was applied to the formulation that showed the satisfactory gelation temperature and in-vitro drug release, to see the effect of varying concentration of variables Poloxamer-407 (X1) and HPMC K4M (X2) on various responses i.e. Viscosity, in-vitro diffusion study, mucoadhesive strength.

Variables in optimization study

Table no.1 Variables in optimization study

Variables	Factors
Independent	
X1	Poloxamer 407
X2	HPMC K4M
Dependent	
Y1	In-vitro drug release
Y2	Mucoadhesive strength
Y3	Viscosity

Table no.2 Composition of formulation batches as per 3^2 factorial design

Formulation code / Ingredient ↓	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ziprasidone Hydrochloride (%w/v)	5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9	5.9
Poloxamer– 407 (%w/v)	14	16	18	14	16	18	14	16	18
HMMC K4M (%w/v)	0.1	0.1	0.1	0.15	0.15	0.15	0.2	0.2	0.2
Propylene Glycol (%w/v)	5	5	5	5	5	5	5	5	5

Benzalkonium Chloride (%w/v)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Triethanolamine	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Purified water (ml)	100	100	100	100	100	100	100	100	100

The independent variables in formulation are Poloxamer-407 and HPMC K4M. These were used as Temperature Dependent polymer and also for mucoadhesive to the nasal mucosa to keep the formulation at site of administration also the polymers have either effect on parameters like gel strength, mucoadhesive strength, drug content, viscosity, In-vitro drug release and vitro permeation.

Evaluation of In-Situ Nasal Gel of Formulation[1][13][14][15]

Physical parameter

Clarity

The formulations were visually checked for the clarity.

pH

pH of each formulation was determined by using Digital pH meter (Sistronic Digital pH meter 335). This was previously calibrated by pH 4 and pH 7. The pH values were recorded immediately after preparation.

Rheological study

Viscosity

The rheological properties of gels were determined by the Brookfield viscometer; type DV-II + PRO using spindle LV-3 (63) .Viscosity of the formulations were taken at room temperature and the 37^0C with varying shear rate.

Measurement of Gelling capacity

The gelling capacities of formulations were determined by placing 1 drop of the prepared formulations into a vial containing 2 mL of SNF freshly prepared. Gelation was assessed visually and noting the time for gelation and the time taken for the gel formed to dissolve.

Measurement of the gel strength

A sample of 25 mL of the gel was put in a 50 ml graduated cylinder. A weight of 14.33 g was placed on the gel surface. The gel strength, which is an indication for the nasal gel at physiological temperature, was determined by the time in seconds required by the weight to penetrate 5 cm into the gel. All measurements were performed in triplicate (n=3). The apparatus used for measuring gel strength at room temperature and at 37ºC is shown in Fig.

Figure No. 1Gel strength Measuring Device

Mucoadhesive Strength

"Detachment Stress is the force required to detach the two surfaces of mucosa when a formulation/gel is placed in between them". The detachment stress was measured by using a modified analytical balance.

In vitro mucoadhesion studies were conducted using modified mucoadhesion test assembly described by Gupta et.al

i) Fabrication of equipment:

The equipment was fabricated by us in the laboratory as shown in figure 3. A double beam physical balance was taken, both the pans were removed. The left pan was replaced with a brass wire, to which was hanged a teflon disc (A), also locally fabricated. The dimensions are 2 cm height and include an expanded cap of diameter 3.8 cm and thickness 2 cm. Another teflon disc of 2 cm height and 1.5 cm diameter was placed right below the suspended disc upon the base of the balance. The right pan (C) was replaced with a lighter pan so that, the left pan weighs 5.25 gm more than the right pan. The lower polypropylene block was intended to hold the mucosal tissue (D) of goat nasal mucosa and to be placed in a beaker containing simulated nasal solution pH 6.7 (E).

ii) Measurement of adhesion force:

The following procedure was used for all the test formulations using the above equipment. The nasal mucosa was removed from refrigerator and allowed to attain equilibrium with ambient conditions in the laboratory. The goat nasal mucosa was carefully excised, without removing connective and adipose tissue and washed with simulated nasal solution. The tissue was stored in fresh simulated nasal solution. Immediately afterwards the membrane was placed over the surface of lower teflon cylinder (B) and secured. This assembly was placed into beaker containing simulated nasal solution pH 6.7 at 37 ± 2°C.From each batch, some quantity of gel was taken and applied on the lower surface of the upper teflon cylinder. The beaker containing mucosal tissue secured upon lower cylinder (B), was manipulated over the base of the balance so that, the mucosal tissue is exactly below the upper cylinder (A). The exposed part of the gel was wetted with a drop of simulated nasal solution, and then a weight of 10 gms was placed above the expanded cap, left for 10 minutes. After which the

gel binds with mucin. The weight was removed. Then slowly and gradually weights were added on the right side pan till the gel separates from the mucosal surface/ membrane.

The weight required for complete detachment is noted (W1) (W1-5.25G)) gives force required for detachment expressed in weight in grams. Procedure was repeated for two more times. Average was computed and recorded.

iii) Calibration of test equipment:

Initially, a gel from the same batch was taken ten times and individual force required for complete detachment was noted and S. D. was calculated.

iv) Force of adhesion(N) = (bioadhesive strength/1000) × 9.81
Bond strength (N/m^2) = force of adhesion (N)/surface area of disk (m^2)

Figure No. 2 Modified balance for Mucoadhesive study
A: Modified balance, B: Weighing pan, C: Weight D: Gel, E: Nasal mucosa F:polypropylenecylinder.x

Drug Content

1 ml of solution was taken in 10 ml volumetric flask then it was diluted with 10 ml of methanol. Aliquot 1 ml from this solution was diluted up to 10 ml methanol again 1 ml aliquot diluted 10 ml of methanol to get the final concentration. The absorbance of prepared solution was measured at 317 nm by using UV visible spectrophotometer.

In-vitro Drug Release Study

In-vitro release study of the formulated in-situ gel was carried out by using diffusion cell through egg membrane as a biological membrane. Diffusion cell with inner diameter 1.4cm was used for the study. The formulation 1 ml were placed in donor compartment and Freshly prepared 100 ml simulated nasal electrolyte solution (sodium chloride 0.745gm, potassium chloride 0.129 gm, calcium chloride dehydrated 0.005gm, distilled water q.s. 100ml) in receptor compartment. Egg membranes were mounted in between donor and receptor compartment. The position of the donor compartment was adjusted so that egg membrane just touches the diffusion medium. The whole assembly was placed on the thermostatically controlled magnetic stirrer. The temperature of the medium was maintained at 37°C ± 0.5°C. 2ml of sample is withdrawn from receiver

compartment after 30 min, 1, 2, 3, 4, 5, 6, 7 & 8 hrs and same volume of fresh medium is replaced. The withdrawn samples was diluted to 10ml in a volumetric flask with Methanol and analyzed by UV spectrophotometer at 317 nm.

Figure No.3.:Laboratory designed diffusion cell.
A- Test tube containing formulation. B- Egg membrane. C-beaker containing simulated nasal solution. D- Magnetic stirrer.

In-vitro permeation study

Natural membranes are utilized to determine in vitro permeation study to mimic the in vivo permeation patterns. In this experiment goat nasal mucosa was utilized because the respiratory area of goat is large and it is easy to get. Fresh mucosal tissue was removed from the nasal cavity of goat. The tissue was placed on the diffusion cell with permeation area 0.786cm^2. The acceptor chamber of the diffusion cell (laboratory designed) with a volume capacity 100ml was filled with simulated nasal fluid (SNF) contained accurately 7.45mg/ml NaCl, 1.29mg/ml KCl and 0.32mg/ml $CaCl_2 \cdot 2H_2O$. 0.5 (10mg equivalent) ml of formulation was placed in donor compartment .At predetermined time intervals of 30 min, 1,2,3,4,5,6,7,and 8 hrs 1ml of sample was withdrawn from the acceptor compartment replacing the sample removed with simulated nasal fluid after each sampling for period of 8 hrs .Then samples were specifically diluted and absorbance was noted at 317 nm. Permeability coefficient (p) was calculated by the following formula.

$P = (dQ/dt) / (C_0 \times A)$

Where, dQ/dt is the flux or permeability rate (mg/h), C_0 is the initial concentration in the donor compartment, and A is the effective surface area of nasal mucosa.

Stability studies

Test conditions for stability study are shown in (Table no.3).

Table No. 3 Test conditions for stability study

Test Conditions	
Duration of study:	3 months
Temperature conditions:	Room temperature $40^0C \pm 2^0C$
Relative humidity conditions:	75± 5%
Frequency of testing the samples:	30 days

The formulations were evaluated mainly for their physical characteristics at the predetermined intervals of 30 days like appearance/clarity, pH, viscosity and drug content

Result and Discussion

Physical parameter

Clarity

On careful visual inspection against dark and white background, all the prepared nasal gel formulations were found to be free from any suspended particulate matter. All the formulations were found to be clear. The prepared formulations are as shown in Figure 4.

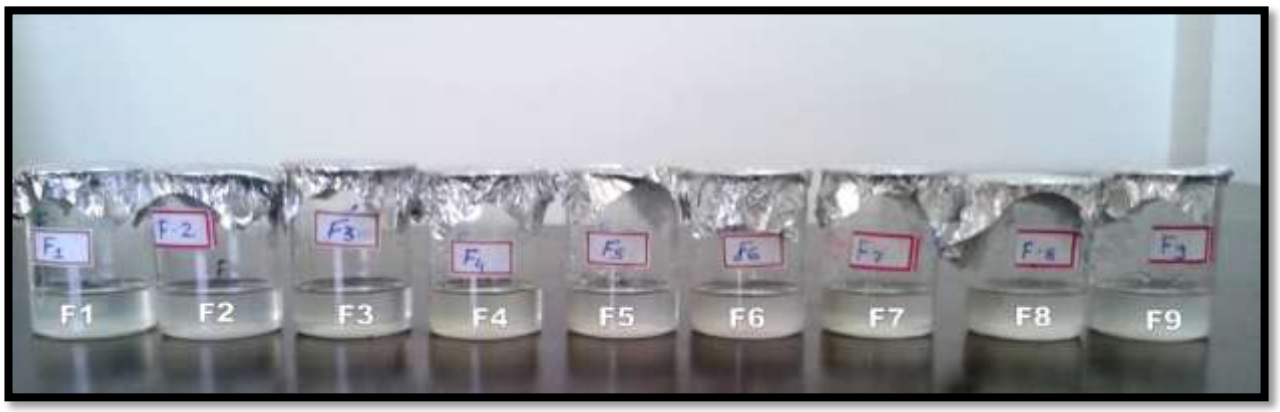

Figure 4: Prepared Formulation Batches

pH

The pH of all the formulations from F1 to F9was found to be in the range of 5.7 to 6.2 pH values of formulations shown in (Table.no.4)

TableNo.4 : pH values of formulations

Sr. No	Formulation code	Observed pH (±S.D.)
1	F1	5.7 ± 0.14
2	F2	6.1 ± 0.023
3	F3	6.2 ± 0.040
4	F4	6.2± 0.070
5	F5	6.2 ± 0.041
6	F6	6.1 ± 0.108
7	F7	5.8 ± 0.07
8	F8	6.2 ± 0.073
9	F9	6.1 ± 0.070

Ideally, the nasal solutions should passes pH in the range of 4.5-6.5, so as to minimize discomfort or irritation due to acidic pH and microbial growth due to basic pH.

Rheological study

Viscosity

The viscosity of formulations at room temperature and 37°C are shown in Table no.5 and6 respectively.

The Viscosity profile of formulations at room temperature and at 37°C is shown in Fig.5and6 respectively**.**

Table No.5 Viscosity of formulations at room temperature

Rpm	Viscosity (cp) at Room Temperature								
	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	283.1	280.6	355.5	295.6	383.9	459.6	321.9	461.0	522.8
10	271.9	275.1	349.2	271.7	379.1	425.5	303.9	457.9	498.7
15	249.6	254.9	333.4	253.9	361.8	397.1	296.9	439.2	475.2
20	238.7	238.2	310.8	242.5	359.2	375.1	285.7	427.4	468.8
25	231.9	238.9	304.4	236.2	346.1	356.9	251.3	418.6	457.2
30	215.3	209.2	298.9	227.7	321.3	338.1	238.4	396.9	429.9

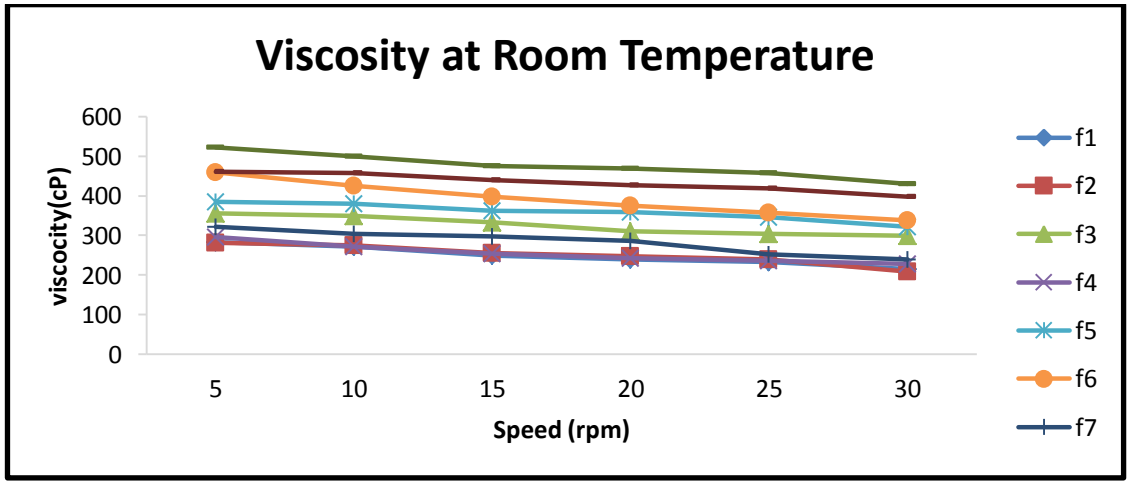

Figure 5 : Viscosity profile of formulations at room temperature

Table No. 6 . Viscosity of formulations at 37°C

Rpm	Viscosity (cp) at 37°C								
	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	338.3	398.9	498.1	358.6	491.8	574.1	416.9	518.9	599.8
10	319.1	392.2	488.6	336.2	470.6	528.8	408.8	489.1	578.2
15	302.8	385.9	477.3	320.9	433.1	503.7	382.1	450.3	557.9
20	292.6	367.2	471.8	301.3	373.2	492.3	361.9	421.6	540.7
25	280.4	343.1	451.2	296.1	348.6	472.9	334.2	401.3	525.1
30	256.9	268.9	360.5	267.9	320.3	428.5	291.1	378.2	424.9

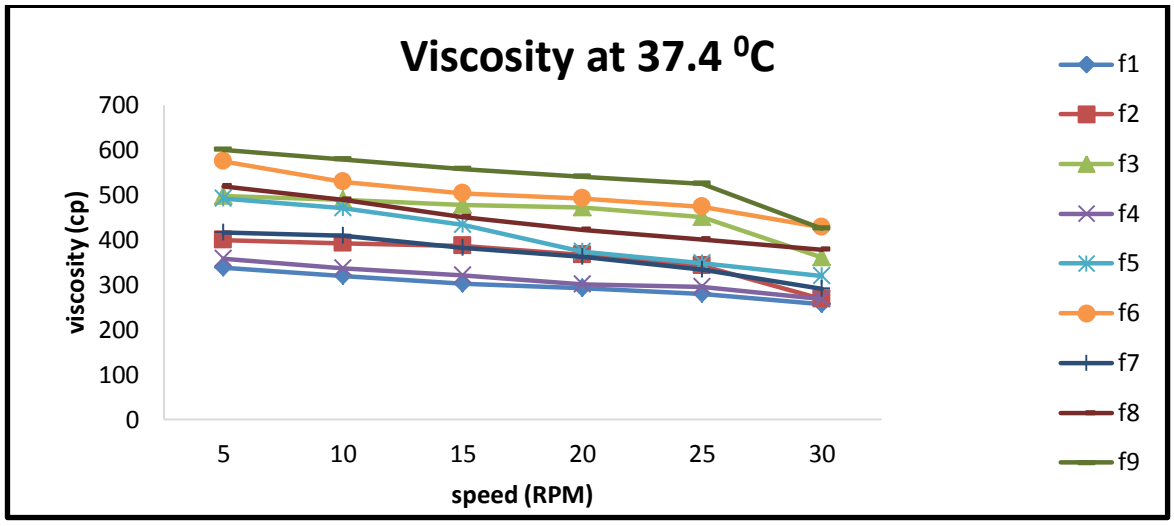

Figure 6 : Viscosity profile of formulations at 37°C

Viscosity v/s rpm plots for all formulations shows decrease in viscosity as shear rate (rpm) was increased. Which indicate that gel has the pseudo plastic flow.As temperature was increased the increase in viscosity was observed because of temperature sensitive polymer (poloxamer 407) was used in the formulation. Concentration of poloxamer 407 was a major factor affecting viscosity of formulations.

Measurement of Gelling capacity

The gelling capacity of Nasal Gel are shown in (Table no.7)

Table No 7 .Gelling capacity of Nasal formulation

Formulation Code	Gelling Capacity
F1	+
F2	+
F3	++
F4	+
F5	++
F6	+++
F7	++
F8	++
F9	+++

(+: Gel formed after a few minutes, dissolves rapidly, ++: Immediate gelation, remains for few hours, +++: Immediate gelation, remains for extended period.)

The two main prerequisites of phase transition system are viscosity and gelling capacity (speed and extent of gelation). Moreover, the flow behavior of the formulation is an important parameter involved in utilization and in vivo performance as if it is too viscous it will lead to difficult instillation; on the contrary, if viscosity is too low it will increase drainage. From visual and manual inspection we found that all formulation coded in Table no. 30 underwent transition into gel phase upon contact with SNF. However, it is clear that the nature of the gel formed was depended upon the polymer concentration. F1, F2 and F4 formed weak gel that dissolved rapidly. The flow of F3, F5, F7 and F8 was immediate gelation which remains for few hours. F6 and F9 forms immediate gelation and remains for extended period of time. F6 and F9 had a satisfactory attributes of gelling capacity and consistency.

Measurement of the Gel Strength

The gel strength of Nasal formulation at room temperature and 37°C are shown in Table no.8 and 9 respectively.

Table No.8 Gel strength of formulations at room temperature

Sr. No	Formulation code	Gel strength (sec)(±S.D.)
1	F1	0.58±0.005
2	F2	0.61 ± 0.012
3	F3	0.84 ±0.012
4	F4	0.79 ± 0.005
5	F5	0.77 ± 0.012
6	F6	0.98 ± 0.007
7	F7	0.72 ± 0.008
8	F8	1.26 ± 0.04
9	F9	2.01 ± 0.0067

Table No.9 Gel strength of formulations at 37ºC

Sr. No	Formulation code	Gel strength (sec)(±S.D.)
1	F1	0.626 ± 0.010
2	F2	0.87 ± 0.007
3	F3	1.38 ± 0.526
4	F4	0.96 ± 0.012
5	F5	0.88 ± 0.007
6	F6	2.03 ± 0.012
7	F7	0.77 ± 0.014
8	F8	2.07± 0.012
9	F9	2.40± 0.002

The gel strength was found to be affected by concentrations of gelling agent, mucoadhesive polymers and also by the temperature. Optimal mucoadhesive gel must have suitable gel strength so as to be administered easily and can be retained at Nasal region without leakage after administration. Gel strength of all formulations showed comparable results as that of viscosity results.

Mucoadhesive strength

The detachment stress of formulation is shown in Table 10.

Table No.10 Mucoadhesive strength of formulations

Formulation code	Detachment stress/Mucoadhesivestreangth (gm) (±S.D.)	Detachment Force/ Bond streangth (N) (±S.D)
F1	0.046 ± 0.005	0.0025 ±0.005
F2	0.047 ± 0.0007	0.0025±0.005
F3	0.052 ± 0.0008	0.0029 ±0.0005
F4	0.057 ± 0.05	0.0031 ±0.005
F5	0.062 ± 0.0005	0.0034 ±0.005
F6	0.063 ± 0.0007	0.0036 ±0.005
F7	0.072 ± 0.0007	0.0040 ±0.005
F8	0.075 ± 0.0007	0.0041 ± 0.005
F9	0.077 ± 0.0007	0.0039 ±0.0005

Mucoadhesive force means the force with which gels bind to nasal mucosa. Greater mucoadhesion is indicative of prolonged residence time of a gel and thus prevents its drainage from nasal cavity. The mucoadhesion force increased significantly as the concentration of mucoadhesion polymers increased. The Detachment Stress was determined for nasal gels. Results of this test indicate that the variable Poloxamer-407 and and HPMC K4M both are having effect on mucoadhesive strength. It shows that mucoadhesive force was increased with the increasing concentration of the Poloxamer-407 and HPMC K4M

Drug content

The Drug content of formulations is shown in Table no.11

Table 11: Percent drug content of nasal gel

Formulation Code	Drug content (%) (±S.D.)
F1	90.88± 0.12
F2	96.44± 0.17
F3	97.56± 0.16
F4	94.85± 0.065
F5	93.63± 0.172
F6	96.07± 0.113
F7	95.49± 0.13
F8	96.65± 0.17
F9	98.34± 0.12

The percentage drug content of all prepared nasal formulations was found to be in the range of 90-98 %. Therefore uniformity of content was maintained in all formulation.

In-vitro drug release study

The In-vitro drug release study of formulation is shown in Table 12.

Table No. 12 Cumulative drug release of formulations

Cumulative Drug Release (%) (±S.D.)									
Time in (Hrs.)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
30 min	10.20± 0.14	10.3± 0.07	2.31± 0.06	25.73± 0.06	8.97± 0.003	9.71± 0.07	9.71± 0.002	28.4± 0.06	19.89± 0.09
1	24.73± 0.10	22.36± 0.01	5.72± 0.06	26.08± 0.06	32.32± 0.06	15.58± 0.05	17.09± 0.06	29.87± 0.005	32.18± 0.14
2	31.4± 0.03	34.08± 0.06	19.63± 0.12	39.56± 0.06	35.35± 0.07	35.27± 0.08	28.30± 0.06	34.21± 0.06	42.92± 0.05
3	57.02± 0.06	39.99± 0.06	19.9± 0.04	52.09± 0.6	55.56± 0.06	56.21± 0.08	44.13± 0.063	47.15± 0.12	62.61± 0.03
4	59.38± 0.036	48.72± 0.04	32.18± 0.03	53.62± 0.01	64.28± 0.54	62.79± 0.03	42.88± 0.059	55.15± 0.06	69.29± 0.09
5	61.93± 0.047	54.86± 0.08	49.04± 0.03	53.39± 0.12	70.96± 0.04	78.67± 0.03	46.09± 0.10	58.46± 0.10	71.03± 0.19
6	64.52± 0.05	70.10± 0.06	61.37± 0.02	64.46± 0.02	78.81± 0.06	79.16± 0.01	50.80± 0.03	74.61± 0.005	90.24± 0.24

7	67.44± 0.08	75.27± 0.06	74.01± 0.08	71.37± 0.058	79.98± 0.06	88.83± 0.01	67.26± 0.06	83.44± 0.29	94.43± 0.06
8	70.10± 0.11	79.25± 0.08	88.45± 0.06	77.68± 0.11	83.38± 0.007	94.37± 0.02	81.22± 0.03	83.95± 0.40	97.07± 0.16

Out of nine formulations maximum release after 8 hrs was found for F9 formulation. This indicates release of 97.07 % drug available for antipcychotic activity of the drug. F9 formulation showed steady state release up to 8hrs which also indicates that this formulation would show better contact with biological membrane.In-vitro drug release profile of formulations shown in (Figure 7)

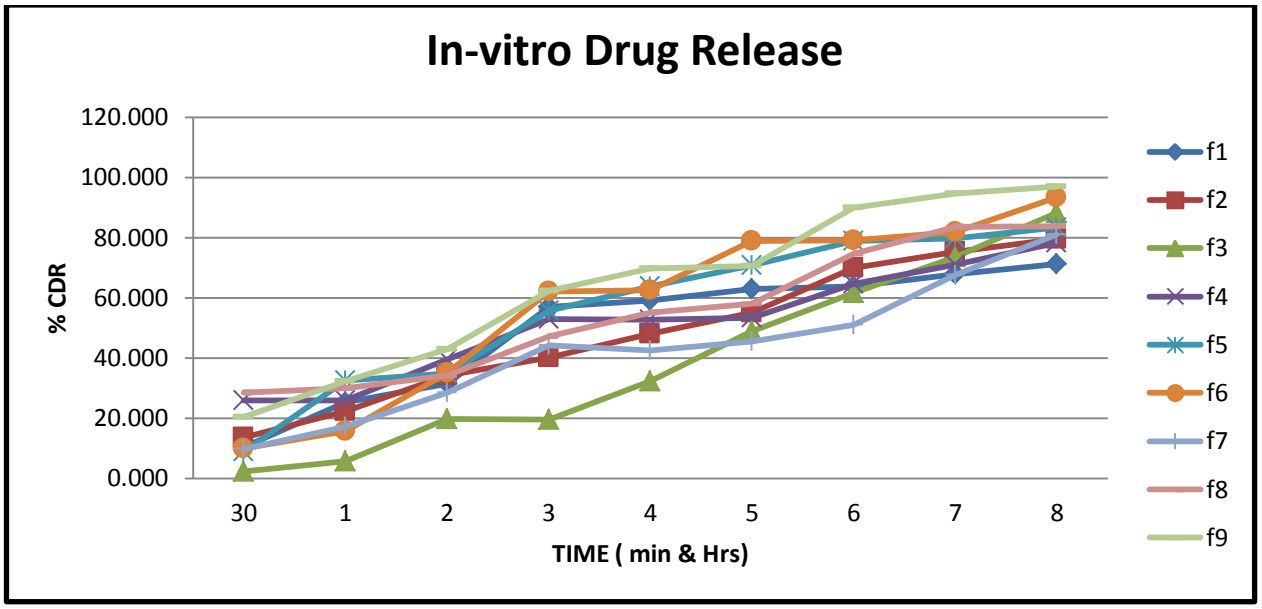

Figure 7: In-vitro drug release profile of formulations

Optimization

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels, respectively. The percentage of Poloxamer 407 (X1) and HPMC K4M (X2) were selected as independent variables and the dependent variable was % drug release, viscosity.The data obtained were treated using Design expert version 7.1.6 software and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to study the interaction of Poloxamer-407 (X1) and HPMC K4M (X2) on dependent variable. Table-3.Shows ANOVA for the dependent variable % drug release and viscosity. The values of X1 and X2 were found to be significant at $p < 0.05$, hence confirmed the significant effect of both the variables on the selected responses.From this data optimum concentration of Poloxamer -407 18n%w/v and HPMC K4M 0.2%w/v was found.

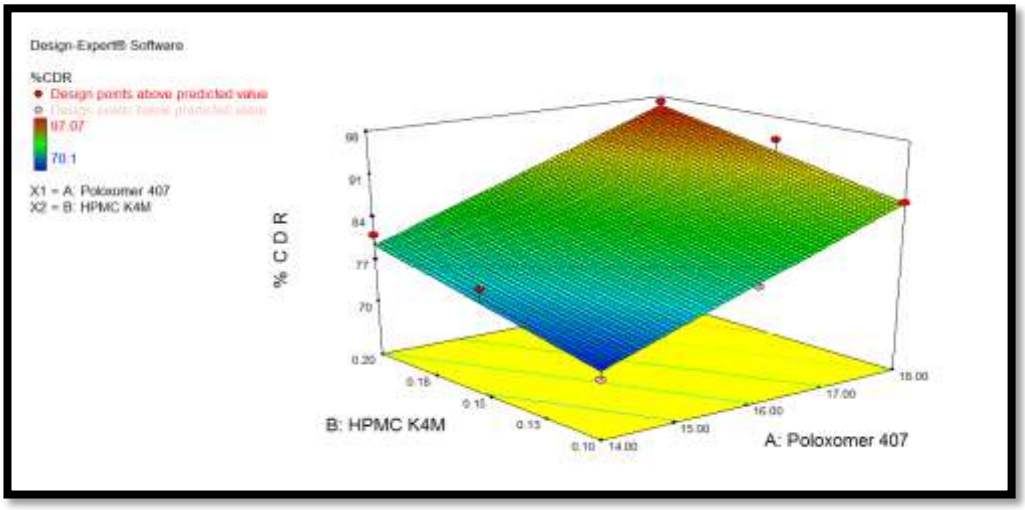

Figure No. 8 :Surface Response Plot Showing Effect of Poloxamer 407 and HPMC K4M on Drug Release

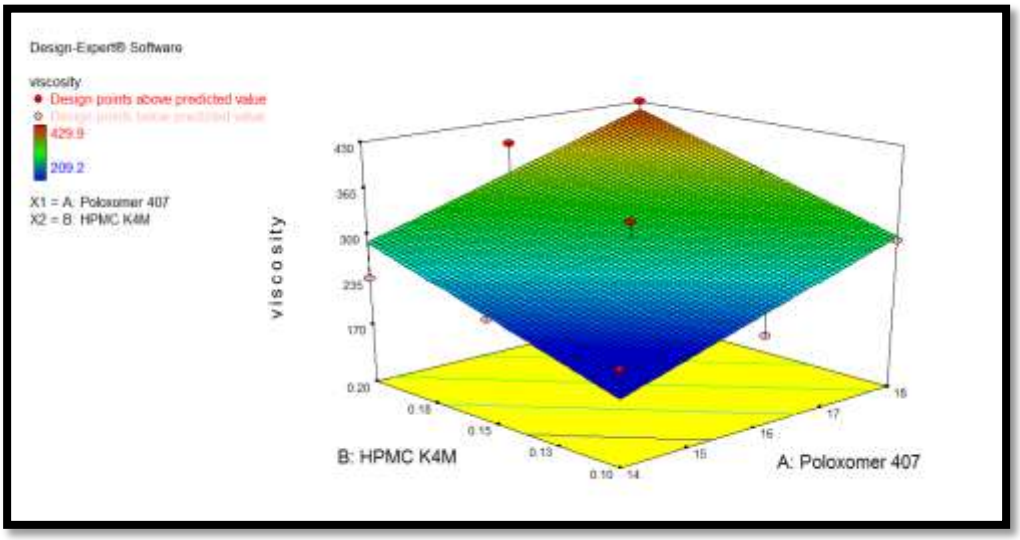

Figure No.9Surface Response Plot Showing Effect of Poloxamer 407 and HPMC K4M on Viscosity at Room Temparature

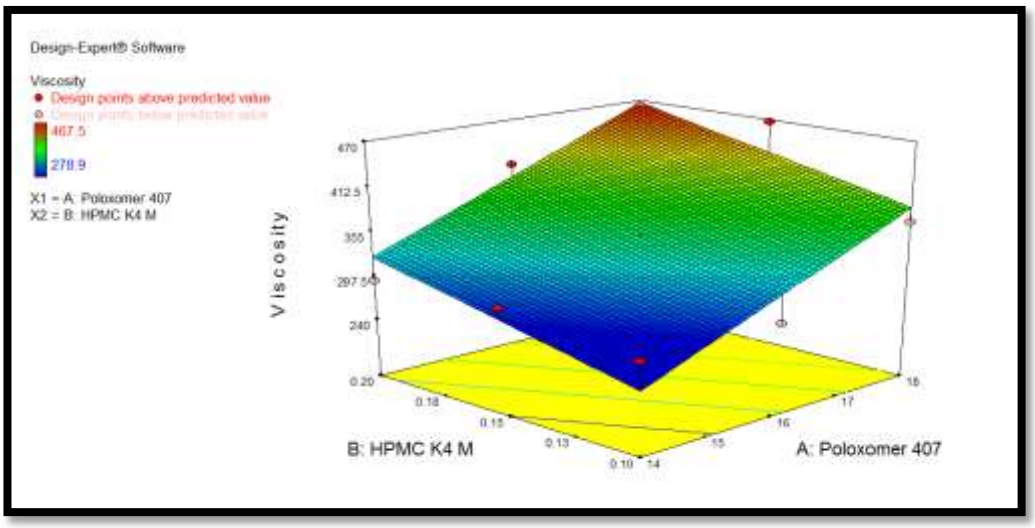

Figure No. 10Surface Response Plot Showing Effect of Poloxamer 407 and HPMC K4M on Viscosity at 37˚C Temperature

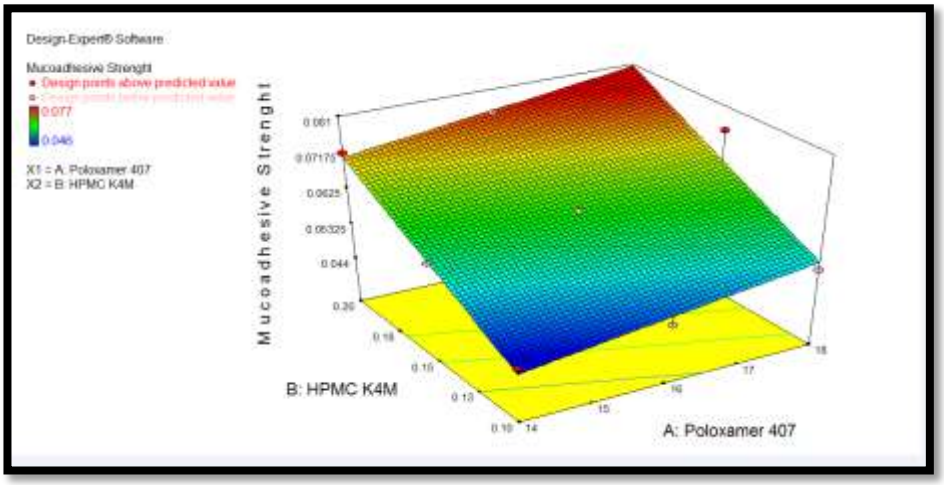

Figure No. 11: Surface response plot showing effect of Poloxamer 407 and HPMC K4M on Mucoadhesive strength.

In-vitro permeation study

The In-vitro permeation study of formulation F9 is shown in (Table-13).In-vitro permeation study was performed for the optimized batch using goat nasal mucosa. The percent drug permeated after 8 hr was found to be 98.96 % from nasal gel formulation. This suggests that this formulation can act as controlled release for treating the schizophrenia.

Table No.13: In-Vitro permeation study for optimized batch F9

Sr.no.	Time(hrs)	Cumulative drug permeation(±S.D.)
1	0.5	26.15 ± 0.15
2	1	34.67 ± 0.007
3	2	39.77 ± 0.02
4	3	58.07 ± 0.007
5	4	60.52 ± 0.015
6	5	61.92 ± 0.015
7	6	74.8 ± 0.07
8	7	76.97 ± 0.05
9	8	98.96 ± 0.014

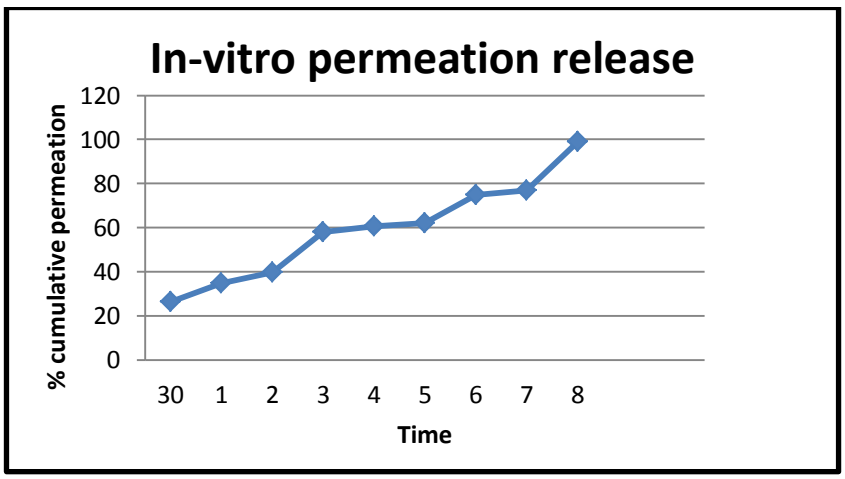

Figure No.12 Permeation rate of optimized formulation

Stability Test

Formulation at room temperature was found to be stable upto 3 month. There is no change in drug content, visual appearance, pH and viscosity. All formulation stored at elevated temperature found to be unchanged.

Conclusion:

Ziprasidone hydrochloride 5.9 % Temperature sensitive *in-situ* nasal gel formulation fulfills all necessary parameters required for nasal use. This optimized formulation having improved viscosity and better mucoadhesive property may improve the bioavailability of nasal administration of Ziprasidone hydrochloride in gel form and can be alternative to the conventionally administered oral formulation. Also, the common problem of food interaction, hepatic first pass metabolism seen with oral administration can be overcome by the use of the novel dosage form developed in this study.

References

1. SaudagarR.B.,MoreP.K., Formulation Development and Evaluation of Nasal In-situ Gel of Fosinopril Sodium, International Journal of Universal Pharmacy and Biosciences, volume 4(4),July-August 2015,Page No.63-89
2. Patil D.R., Saudagar R .B. A Review on Gel As a Nasal Drug Delivery System, World Journal of Pharmaceutical Sciences, volume 2(6),Page No.4831-4861
3. Bajpai V. *,In-Situ Gel Nasal Drug Delivery System- A Review, International Jouranal of Pharma Sciences, volume 4(3),2014,Page No.577-580
4. Karpagavali L. et al, An Outlook on In-Situ Mucoadhesive Gel for Nasal Delivery, International Journal of Pharmacy and Pharmaceutical Research, volume 4(1),2015,Page No.113-128
5. Sharma P.*Singh G.,A Review on Nasal Drug Delivery System For Brain Targeting, International journal of Institutional Pharmacy and Life Sciences,volume 6(3),May-June 2016,Page No.203-2015
6. Moffat.A. et al ,Clarke's Analysis of Drugs & Poisons ,3rdeddition, volume-II, Published By Pharma Press. 2011, Page No.1414
7. Sweetman S.C. Martindale-The complete Drug Reference,35theddition volume-I ., Pharmaceutical Press, London, Chicago, 2007, Page no.932-933
8. M. Ratnaparkhi , G. Mohanta, A Typical Antipsychotic : A Review International Journal of Drug Development and Research,vol 2(4),octo-dec 2010, page no.876-885
9. Raymond C.R, Paul J.S, Sian C.O., Handbook of Pharmaceutical Excipents,5theddition, Pharmaceutical Press,2006, Page no.506-509
10. Jadhav K,S.,ErandeB.,Solubility Enhancement and Formulstion of Fast Dissolving Tablet of Ziparasidone Hydrochloride, International Journal of Research in Pharmacy and Chemistry, volume 6(4), Page No.675-683
11. Mahale M.V*,Todkari V.B et al, U.V.Spectrophotometric Method Development for Quantitative Estimation of Ziprasidone Hydrochloride, International Journal of Pharmaceutical Archive, volume 2(5),2013,Page No.92-94
12. Pavia D.L, Lampman G.M, Kriz GS, Vyvyan JR, "Spectroscopy". Infrared Spectroscopy, Cengage Learning 2007:26-107.
13. Prajapati N.B, and Goyal A ,Thermoreversible Mucoadhesive Insitu gel: Review ,International Journal of Innovative Drug Discovery vol. 3/issue 2/2013/67-84
14. Jadhav A.J, Gondkar S.B, SaudagarR.B, Fornulation and Evaluation of pH DependantZolmitriptan in-Situ Nasal Gel,American Journal of Pharmtech Research,volume 4(6),2014,Page No.311-326
15. More B.A.,MeneR.H,etal,A Review on In-Situ Nasal Gel Drug Delivery System, International Journal of Pharmaceutical sciences Review and Research, volume 33(1),July-August 2015, Page No.199-207
16. The United State Pharmacopeia- The National Formulary. 31st ed. Vol I, II, III. The Official Compendia of Standards. Asian edition. 2008.
17. The United State Pharmacopeia- The National Formulary. 31st ed. Vol I, II, III. The Official Compendia of Standards. Asian edition. 2008.
18. Y. R. Sharma, Elementary Organic Spectroscopy, Principles and Chemical Applications, S. Chand Publication. 2010

19. Parekh H.B, JivaniR,Jivani N.P ,Novel In-situ Polymeric Drug Delivery System: A Review, Journal of Drug Delivery and Therapeutics 2012/VOL 2/ Issue 5,136-145
20. ChristophB , Katja S.Z ,Christian S, Nasal Drug Delivery in Humans.
21. Panchal D.R,PatilU.L, Bhimani B.V, Daslaniya D. J,Patel G.V ,Nasal In-Situ Gel: A Novel Drug Delivery System ,International Journal For Pharmaceutical Research Scholars Vol-1(2)-2012, Page No.457-472
22. Devi R., Abhirami M, Brindha R.et al ,In-situ gelling System- Potential tool for Improving Therapeutic Effects of Drugs ,International Journal of Pharmacy and Pharmaceutical Sciences 2013,vol.5(3), Page No.27-30
23. Goel A, Sharma M.S, SharmaA, AroraH.J, Pharmacokinetic data and solubility profile of antihypertensive drugs: Review ,International Journal of Pharma Professional's Research, July 2010 vol. 1(1),Page No. 41-53

*****