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Formulation and Evaluation of thermal Induced intranasal *In-Situ* Gel of Sumatriptan Succinate

ABIKESH P K MAHAPATRA*[1], DR. ROHIT SARASWAT[2], DR. ANJAN K MAHAPATRA[3], RAVINDRA Y PATIL[4],DR. K.C. PANDA[5]

[1.] *Vergo Pharma Research Private Limited, Verna, Goa*
[2.] *OPJS University, School of Pharmacy, Churu, Rajasthan-331303*
[3.] *Royal College of Pharmacy and Health Sciences, Berhampur, Ganjam, Odisha-761001*
[4.] *National Institute of Pharmaceutical Education and Research (NIPER), S.A.S. Nagar. Sector 67, Mohali, Punjab-160062*
[5.] *Anwar-ul-Uloom College of Pharmacy, New Mallepally, Hyderabad*
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ABSTRACT: Sumatriptan is having high first pass metabolism leading to low bioavailability (absolute Bioavailability 14% in humans).So there is a need to improve the nasal bioavailability by improving nasal penetration because of long duration of retention. The prolonged residence of drug formulation in the nasal cavity is of utmost importance for intranasal drug delivery.The objective of this work was to improve the nasal bioavailability of antimigraine drug, Sumatriptan Succinate by increasing its nasal retention time as well as by means of nasal permeation.To improve the nasal retention time of Sumatriptan Succinate, it has been formulated as *In-situ* mucoadhesive gel by using blend of Poloxamer 407 and HPMC K4 M. The *In-vitro* tests performed for mucoadhesive strength and drug diffusion showed that nasal *In-situ* gelling formulations prepared were having good mucoadhesive strength with very good drug diffusion. The drug release mechanism gel matrices was found to be anomalous and following the Higuchi equation and the diffusion follows Fickian diffusion mechanism. The formulations were evaluated for physiochemical parameter like gelation temperature,viscosity, gel strength, drug content , FTIR and DSC. FTIR and DSC studies were carried out on pure drug as well as for all excipients used in the final formulation and exhibited no interaction.So, this study points to the potential of mucoadhesive In-situ nasal gel of Sumatriptan Succinate in terms of ease of administration, accuracy of dosing, prolonged nasal residence and improved nasal bioavailability.
KEY WORDS: Nasal drug delivery,Poloxamer 407, HPMC K4 M, Sumatriptan Succinate.

I. INTRODUCTION

Sumatriptan is one of the first used antimigraine drug which prevents migraine and has been used by oral and injectable administration. It is having high first pass metabolism leading to low bioavailability. So there is a need to improve the bioavailability by improving nasal penetration because of long duration of retention. It is a drug of 5-HT agonist and mainly used in migraine so as it is acting in CNS and is not able to cross the Blood Brain Barrier[1]. Therefore, for better action or activity it is required to cross the Blood Brain Barrier. Intranasal administration allows transport of drugs to the brain circumventing (bypassing) BBB as well as first pass metabolism. Nasal delivery has been paid attention as an alternative dosage form. The advantages of nasal route have been suggested as follows: rapid absorption, higher bioavailability allowing lower doses, avoidance of liver or gastrointestinal metabolism, avoidance of gastric irritation, non-invasive administration, ease of self-medication, improved patient compliance, and reduced risk of infectious disease transmission. The idea of mucoadhesive system came from the need to localize drug at a certain site in the body, often as the extent of drug absorption is limited due to the residence time of drug at the absorption site. Several mucosal routes have been investigated over the last decades as alternatives to oral and parenteral drug administration including nasal, buccal, rectal, ocular, pulmonary, and vaginal mucosa[2]. Their advantages are the easy accessibility and circumvention of the presystemic metabolism. Mucosal bioavailability can vary between almost 100% for low molecular weight hydrophobic drugs[3]. The *In-situ* forming hydrogels that exhibit mucoadhesive behaviour could be extremely useful in nasal drug delivery applications. Such gels would swell significantly when in contact with the mucosa and release the drug in a continuous fashion while adhering to the nasal mucosa. Several nasal gel compositions using hydroxypropyl methylcellulose or other gelling agents have been patented, e.g. for the delivery of erythropoietin[4], insulin with sodium glycocholate as absorption enhancer[5]. Use of pH responsive polymers such as polyvinylacetal diethylamino acetate (PVADEA[6], temperature responsive polymers such as PNIPAAm and ethyl (hydroxyethyl) cellulose[7, 8] and ion-responsive polymers such as pectin

are also reported in nasal drug delivery[9]. They offer the advantage of easy administration at low pH, low temperature or low ion content respectively but formation of a viscous gel after contact with the nasal mucosa. Poloxamer is a block copolymer that consists of polyethylene oxide (PEO) and polypropylene oxide (PPO) units, is known for exhibiting the phenomenon of reverse thermal gelation under a certain concentration and temperature [15,16]. There are several *In-situ* gelling system for nasal administration of an antimigraine drug Sumatriptan Succinate was performed using different thermal induced polymers[10-14]. In some of studies Sol-to-gel systems of Sumatriptan Succinate were prepared utilizing the phase transition properties of Poloxamer 188, sodium carboxy methyl cellulose as a viscosity enhancing agent and carbopol 934 P as mucoadhesive agent [17,18]. The objective of present work was to formulate and develop thermo sensitive *In-situ* gelling system for nasal administration of an antimigraine drug Sumatriptan Succinate, by different approaches using different thermal induced polymers.

II. EXPERIMENTAL

MATERIALS

Sumatriptan Succinate (Sun Pharmaceuticals Ltd, Baroda, India), Poloxamer 407(BASF India Ltd., Mumbai), Hydroxy Propyl Methyl Cellulose K4M (Dow chemicals,Mumbai), EDTA (Finar chemicals Ltd, Ahmadabad), Sodium Lauryl Sulphate(S.D.Fine-chemicals Ltd., Mumbai), Methyl Paraben (Lobachemie, Mumbai), Propylene glycol(Lobachemie, Mumbai),Sodium metabisulphites(Lobachemie, Mumbai).

METHODS

PREPARATION AND OPTIMIZATIONOF INTRANASAL I*N- SITU* GEL

The dose of Sumatriptan Succinate for preparation of *In-situ* gel was 200mg. This dose was fixed for preparation of the *In-situ* gel formulation and in this dose of the drug there is no interference found through out the study. The gels were Prepared on a weight basis using the cold method. The *In-situ* nasal gel was prepared by cold mmethod[19, 20.] The Poloxamer 407 was slowly added to cold water (5^0c) maintaining at constant stirring. All other excipients were added with continuous stirring. The dispersions were then stored in a refrigerator until clear solution was obtained. The HPMC K4M with different concentrations (1%, 1.5 %, 2% and 2.5%) were dissolved in distilled water and stirred for 1 hr. From the each prepared HPMC solution, 200mg of the Sumatriptan Succinate was added. Then the Poloxamer 407 solution was slowly added to that HPMC K4 M solution containing drug stirred for 1 hr. The composition of developed gel formulations was summarized in Table 1 and Table 2.

Table 1: Composition of developed thermo reversible In-situ gel of Sumatriptan Succinate using Poloxamer

Ingredients	Formulations						
	SP1	SP2	SP3	SP4	SP5	SP6	SP7
Sumatriptan Succinate (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Poloxamer 407 (%w/w)	18.0	20.0	20.0	20.0	25.0	25.0	25.0
Sodium Lauryl Sulphate(%w/v)	-	-	0.5	1.0	-	0.5	1.0
Propylene Glycol(% v/v)	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Methyl Paraben (%w/v)	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Sodium metabisulphites (%w/v)	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Distilled Water % upto(mL)	100	100	100	100	100	100	100

Table2: Composition of developed thermo reversible *In-situ* gel of Sumatriptan Succinate using combination of Poloxamer and HPMC K4M

Ingredients	Formulations			
	SP8	SP9	SP10	SP11
Sumatriptan Succinate (%)	0.2	0.2	0.2	0.2
Poloxamer 407 (%w/w)	18.0	18.0	18.0	18.0
Hydroxy Propyl Methyl Cellulose (HPMC K4M)(%w/v)	1.0	1.5	2.0	2.5
Sodium Lauryl Sulphate(%w/v)	1.0	1.0	1.0	1.0
Propylene Glycol(% v/v)	1.0	1.0	1.0	1.0
Methyl Paraben (%w/v)	0.01	0.01	0.01	0.01
Sodium metabisulphites(%w/v)	0.1	0.1	0.1	0.1
Distilled Water % upto(mL)	100	100	100	100

EVALUATION OF *IN-SITU* GEL

The Sumatriptan Succinate *In-situ* gels were examined for not only for appearance in terms of clarity, texture and consistency. But also for viscosity, pH, gelation time, gel strength, gelation temperature and drug content and *In-vitro* drug release study.

Appearance

Appearance is an important characteristic in gel formulations as it increases the patient acceptability. The appearance of *In-situ* gels in terms of clear or turbid was evaluated visually.

Texture evaluation

Texture of the *In-situ* gel in terms of stickiness and grittiness was evaluated by mildly rubbing the gel between two fingers.

Rheological measurement

Viscosity of all the batches of *In-situ* gels was measured using Brookfield DV-E viscometer. The gel was taken in a 100ml beaker and the viscosity was measured using spindle no 64 at the rotation speed 0.6 RPM at room temperature.

pH of the gels

The pH of the *In-situ* gel was measured using Labindia SAB 5000 digital pH meter at room temperature.

Gel strength[21]

The gel strength is important in finding the condition, which can delay the post nasal drip or anterior leakage. The gel strength was found to be affected by concentrations of gelling and bioadhesive polymers. Optimal *In-situ* gel must have suitable gel strength so as to be administered easily and can be retained at nasal mucosa without leakage after administration. Gel strength of the *In-situ* gel was measured by using ball (10 gm) placed in a 100 ml beaker containing *In-situ* gel and measured the time taken by the ball to penetrate 5 cm and it was determined in second. The gel strength was performed in triplicate.

Gelation Temperature[20, 21]

The gelation temperature was measured by using water bath maintained at 37 ± 5^0c temperature. The temperature at which it forms the gel is recorded as the gelation temperature. It was measured when temperature induced polymer was used for *In-situ* gel formulation. The significance of gelation temperature is that after easy instillation in to nasal cavity the liquid polymeric solutions should undergo rapid sol to gel transition by means of temperature induced gelation. Thus the *In-situ* formed gel should preserve its integrity without dissolving or eroding so as to localize the drug at absorption site for extended duration.

Drug content[22]

Five gram of *In-situ* gel was accurately weighed on an electronic balance and transferred to 100 ml volumetric flask. Then 100 ml of Phosphate buffer of pH 6.4 was added to dissolve the gel. From that, 1 ml of the sample was withdrawn and diluted up to 100 ml with Phosphate buffer of pH 6.4 Samples were analyzed spectrophotometrically at 281.50 nm after filtering the sample in the whatmann filter paper.

***In-vitro* diffusion studies**[23]

The rate of diffusion may be directly related to the efficacy of the *In-situ* gel formulation, as well as bioavailability differences between formulations. *In vitro* release studies of formulations were performed using the Franz diffusion cell with dialysis membrane. Phosphate buffer of pH 6.4 was used as diffusion media.

Mathematical treatment to *in vitro* release data[24]

To precisely know the drug release mechanisms from *In-situ* gelling systems, the *In vitro* release data of final formulation was treated with Zero order, First order, Higuchi's diffusion equation ($Q = kt^{1/2}$) and Korsmeyer- Peppas.For zero order the graph was plotted between Q_t Vs t and for first order the graph was plotted between log ($Q_o - Q_t$) Vs t .

For higuchi the graph was plotted between percentage cumulative drug release and square root of time .The drug transport mechanism of the same formulations was determined by using the Korsmeyer- Peppas exponential equation [log (M_t / M_∞) Vs log t]. Form the plot of log (M_t / M_∞); fraction of drug released at time't' versus log of time. The kinetic parameters 'n' and 'k' were also calculated.

III. RESULTS AND DISCUSSION

Scanning of Sumatriptan Succinate solution in pH 6.4 Phosphate buffer by UV Spectrophotometer showed the λ_{max} 281.5 nm. Linearity was observed in the range of 5 to 50 μg/ml with the R^2 value of 0.998. The

appearance of prepared gels were examined by visually. From the study it was observed that all formulations having clear appearance. The pH of the developed formulations was in between the range of 5.9 to 6.3. Texture of the *In-situ* gel in terms of stickiness and grittiness was evaluated by mildly rubbing the gel between two fingers. All the formulations were sticky and Non-greasy. The gelation temperature (The temperature at which the sol form converts into gel) for all formulations were determined and shown in Table 3 and Table 4. The results also clearly indicates that with increase in concentration of Poloxamer the gelation temperature decreases while in combination formulation of poloxamer and HPMC K4,with increase in concentration of HPMC K4 the gelation temperature increases. In the development of nasal *In-situ* gelling system, the gel strength is important in finding the condition, which can delay the post nasal drip or anterior leakage. The gel strength was found to be affected by concentrations of gelling and bioadhesive polymers. Optimal *In-situ* gel must have suitable gel strength so as to be administered easily and can be retained at nasal mucosa without leakage after administration.

The gel strength for all formulations were determined and shown in Table 3 and Table 4. The results also clearly indicates that with increase in concentration of Poloxamer the gel strength increases while in combination formulation of poloxamer and HPMC K4,with increase in concentration of HPMC K4 the gel strength also increases.

From the viscosity study on formulations shows increase in viscosity at 37°C. This indicated the temperature induced gel structure formulation of Poloxamer. The results were reported in Table 3 and Table 4, and showed that viscosity resulted at physiological temperature at 0.6 RPM by using spindle no 64 of rotating type Brook field viscometer. The drug content of all formulations were ranging from 97.30% to 100.04%.

Table 3: Evaluation parameters of formulations with poloxamer

TEST PARAMETERS	RESULTS						
	SP1	SP2	SP3	SP4	SP5	SP6	SP7
Appearance	Clear	Clear	Clear	Clear	Clear	Clear	Clear
Texture	Sticky, Non greasy	Sticky, Non greasy	Sticky, Non greasy	Sticky, Non greasy	Sticky, Non greasy	Sticky, Non greasy	Sticky, Non greasy
pH	6.1	6.2	6.1	6.3	6.0	5.9	6.0
Gelation Temperature (^{0}c)	31	27	27	28	22	24	22
Drug Content (%w/w)	98± 1.67	99.76± 0.43	98.13± 1.34	98.26± 1.48	97.55±2.15	97.30± 0.77	97.63± 1.68
Gel Strength (sec)	40± 1.01	60±0.36	61± 0.38	61± 0.39	90± 0.87	92± 0.37	96± 0.86
Viscosity (CPS)	548617	752135	752135	752135	924156	915421	924165

Table 4: Evaluation parameters of formulations with combination of Poloxamer and HPMC K4

TEST PARAMETERS	RESULTS			
	SP8	SP9	SP10	SP11
Appearance	Clear	Clear	Clear	Clear
Texture	Sticky, Non greasy	Sticky, Non greasy	Sticky, Non greasy	Sticky, Non greasy
pH	6.3	6.1	5.9	6.0
Gelation Temperature (^{0}c)	32	34	36	42
Drug Content(%w/w)	99.07± 0.16	98.13± 1.66	99.26± 1.32	100.04± 0.66
Gel Strength(sec)	48± 0.31	52± 1.47	64± 0.53	83± 0.40
Viscosity (CPS)	562157	664860	745469	772854

***IN –VITRO* DIFFUSION STUDIES**

In vitro release studies of formulations were performed using the Franz diffusion cell with dialysis membrane by using Phosphate buffer of pH 6.4 as diffusion media.

The initial rates of drug release were very rapid due to incomplete gel formation, but as the time progresses the release rate decreases due to complete gel formation. With increase in concentration of poloxamer the release rates were found to decrease gradually. The *In-vitro* study was also carried to check the effect of penetration enhancer on the release of Sumatriptan Succinate. Thus, studies were planned with or without SLS as a penetration enhancer. It was observed that the release was much slower, without any penetration enhancer i.e. SLS. It may be due to poor penetration of the polymer i.e. poloxamer in the nasal mucosa. So, further the study was carried out by using different concentration of SLS as a penetration enhancer.

The consistency and viscosity of SP1 and SP8 formulations (Refer Table No.3 and 4) were not proper, so both formulations were excluded from the study. The use of penetration enhancer was tried with 20% w/w and 25 %w/w of poloxamer.

From the study it was observed that SLS at a concentration of 1 % shows very good release. The study reveals that the formulation SP4 (contains Poloxamer 20% and SLS 1%) shows a good release upto 96.69% at about 8 hour. But, the formulation SP7 shows release 71.11% at about 8 hour study. The decrease in release form SP7 formulation may be due to high viscosity of formulation.

By observing the *In-vitro* release study and all other evaluation parameter the formulation SP4 considered as a good formulation.

The release profiles exhibited an inflection point, which indicated the gel formation in the donor compartment of diffusion cell. During gel formation, a portion of drug might be loaded in to the gel matrix, thus the cross linking of polymer reduces the drug release rate.

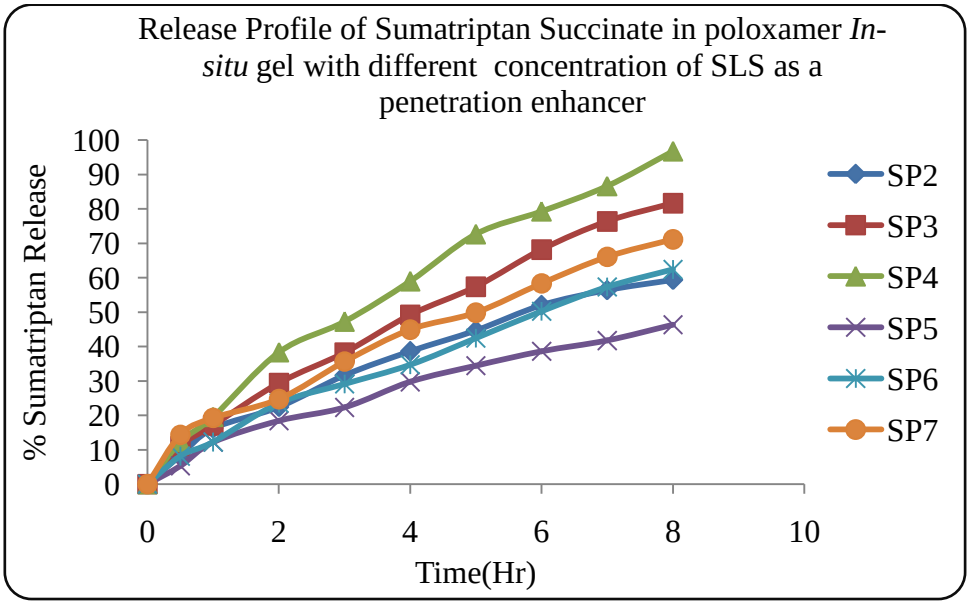
The initial rapid release of Sumatriptan Succinate was may be due to formation of pre hydrated matrix containing water filled pores due to presence of aqueous vehicle. The results showed that the formed gels had the ability to extend the release of Sumatriptan Succinate for the duration of about 8hr.

In-vitro release study indicated that the release of drug varied according to the concentration of polymers. The results further showed that the amount of the drug released i.e. very first in first 2 hr and then gradually decreased gradually the increasing polymer concentration and this pattern continued till the entire duration of study.

Table 5:*In-vitro* diffusion studies of formulations from SP2– SP7

Sl No.	Time(hrs)	Cumulative Percentage Drug Released					
		SP2	SP3	SP4	SP5	SP6	SP7
1	0	0	0	0	0	0	0
2	0.5	8.37	11.11	12.32	5.32	8.16	14.33
3	1	16.23	17.10	19.55	12.19	12.24	19.24
4	2	22.45	29.43	38.36	18.46	23.56	24.72
5	3	31.62	38.26	47.21	22.28	29.11	35.62
6	4	38.55	49.15	58.93	29.73	34.68	44.89
7	5	44.68	57.36	72.61	34.45	42.44	49.82
8	6	51.95	68.12	79.23	38.61	50.22	58.31
9	7	56.38	76.33	86.62	41.72	57.32	66.03
10	8	59.32	81.62	96.69	46.32	62.36	71.11
11	9	61.98	80.06	93.87	65.33	69.41	51.14

Fig 1: Graphical presentation of *In-vitro* diffusion studies of formulations from SP 1 – SP 7

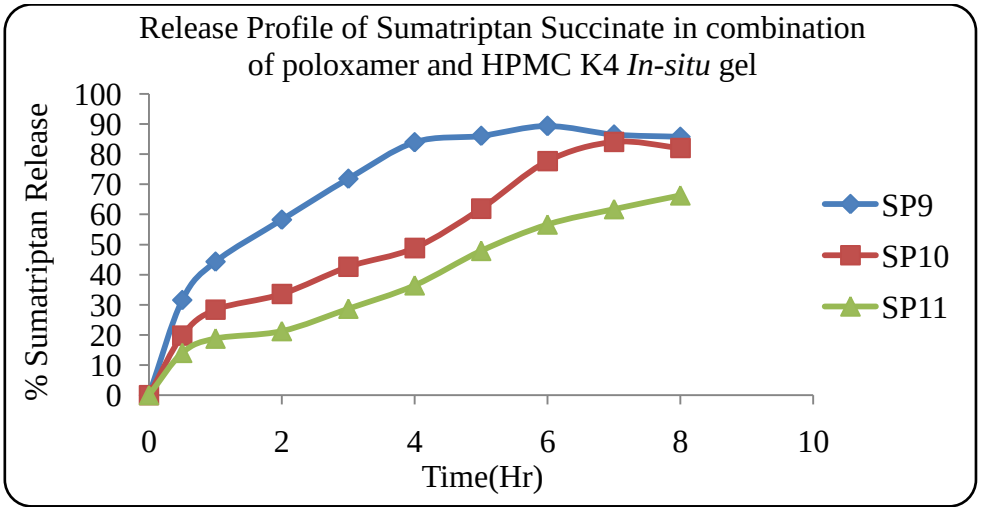


The *In-vitro* release study of formulation SP9-SP11 reveals that the formulation SP10 (contains HPMC K4 M 2% w/w) shows a good release upto 82.09% at 8 hour. However, the formulation SP9 shows a maximum of 89.36% Sumatriptan Succinate at 6 hour study. Formulation SP11 releases 66.32% drug at 8 hour study. The decrease in release form formulation SP10 and SP11 may be due to increase in concentration of HPMC K4 which resulted high viscosity of formulation.

Table 6:*In-vitro* diffusion studies of formulations from SP9 – SP11

Sl No.	Time(hrs)	Cumulative Percentage Drug Released		
		SP9	SP10	SP11
1	0	0	0	0
2	0.5	31.56	19.77	14.03
3	1	44.31	28.34	18.73
4	2	58.25	33.59	21.27
5	3	71.90	42.63	28.66
6	4	84.00	48.85	36.44
7	5	86.12	61.92	47.89
8	6	89.36	77.71	56.63
9	7	86.56	84.08	61.75
10	8	85.78	82.09	66.32
11	9	85.11	81.74	68.42

Fig 2: Graphical presentation *In-vitro* diffusion studies of formulations from SP 8 – SP 11



By observing comparative *In-vitro* release study and all other evaluation parameters, from all the studied formulation (SP1-SP11) the formulation SP4 considered as the optimized formulation.

MATHEMATICAL TREATMENT TO *IN-VITRO* RELEASE DATA

Mathematical treatments were performed for the final formulation SP4 to know the kinetics of drug release mechanism. The drug release mechanism from these types of the gel matrices was found to be anomalous and following the Higuchi equation and the diffusion follows Fickian diffusion mechanism.

The detail of the release plot of SP4 formulations was given below.

Figure 3: Zero order, First order, Higuchi and Korsemeyer Peppas plots of Sumatriptan Succinate for formulation SP4

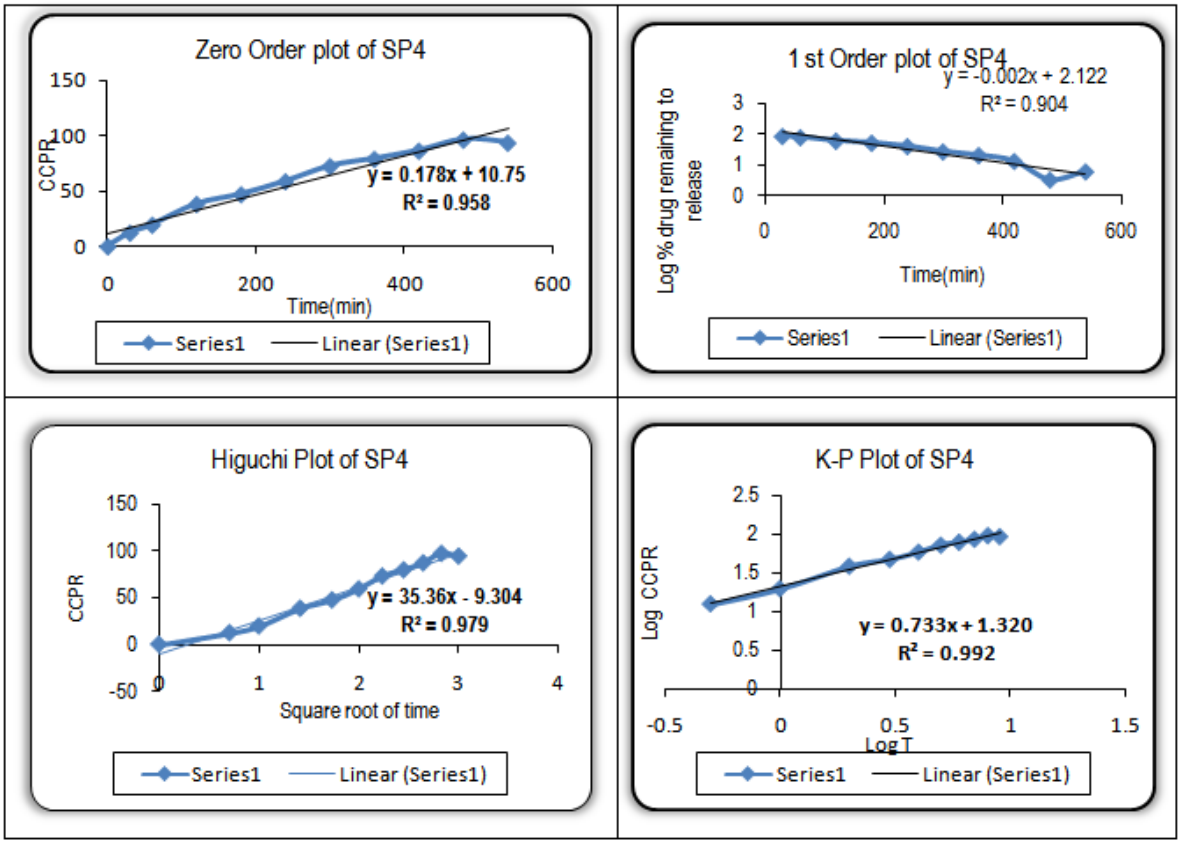


Table 7: Drug release kinetics data from optimized *In-situ* gel formulations of Sumatriptan Succinate

Zero order		First order		Higuchi model		Korsemeyer-Peppas model	
r^2	k_0	r^2	k_1	r^2	k_h	r^2	n
0.958	0.178	0.904	- 0.002	0.979	35.36	0.992	0.733

Note: Where, r2 is the correlation coefficient, and k0, k1, kh and k are the release rate constants of the Zero order, First order, Higuchi model and 'n' is the release exponent of Korsemeyer-Peppas model.

DRUG-POLYMER COMPATIBILITY STUDY

FTIR and DSC studies were carried out on pure drug as well as for all excipients used in the final formulation and exhibited no interaction.

The detail of the interaction study (FTIR and DSC) plot of SP4 formulations was given below

Fig 4: FTIR of Sumatriptan Succinate

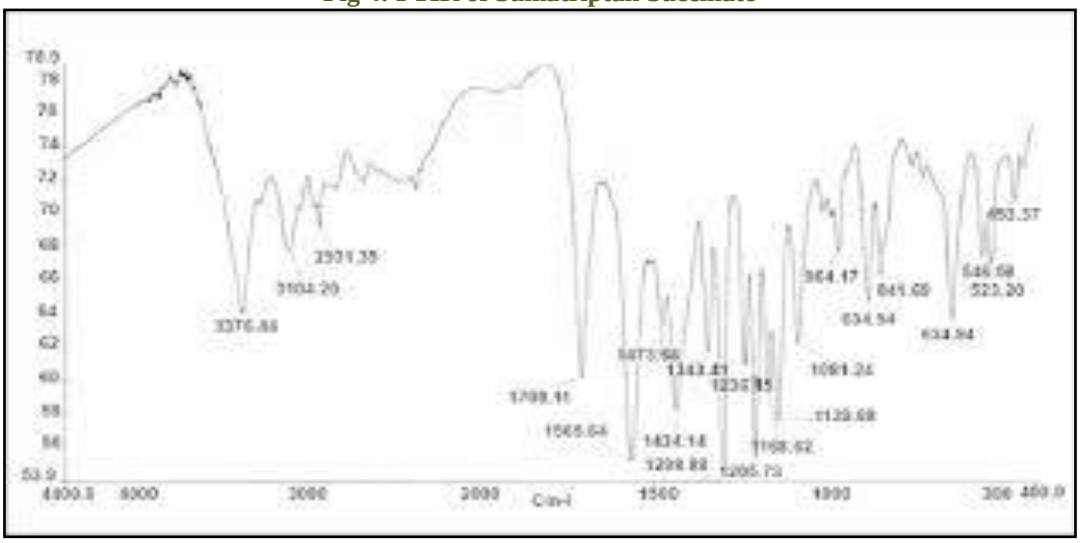


Fig 5: FTIR spectrum of Poloxamer 407

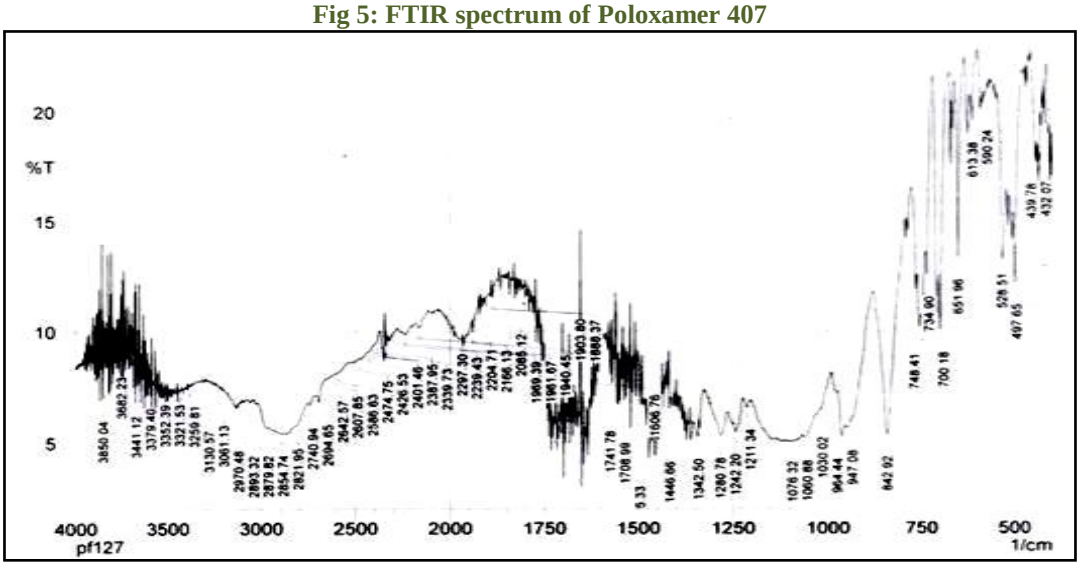


Fig 6: FTIR spectrum of HPMC K4 M

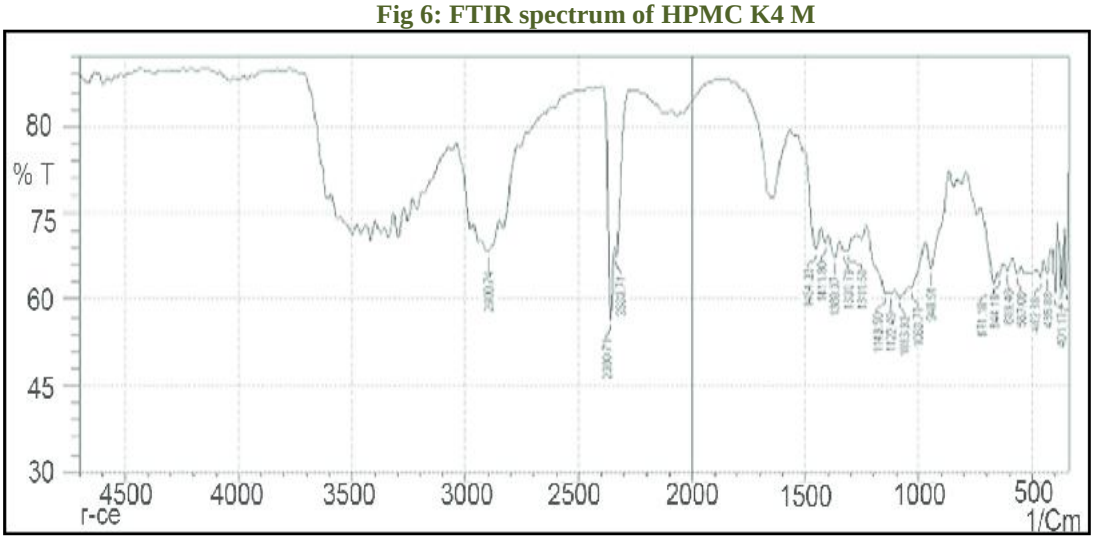


Fig 7: FTIR spectrum of Formulation SP4

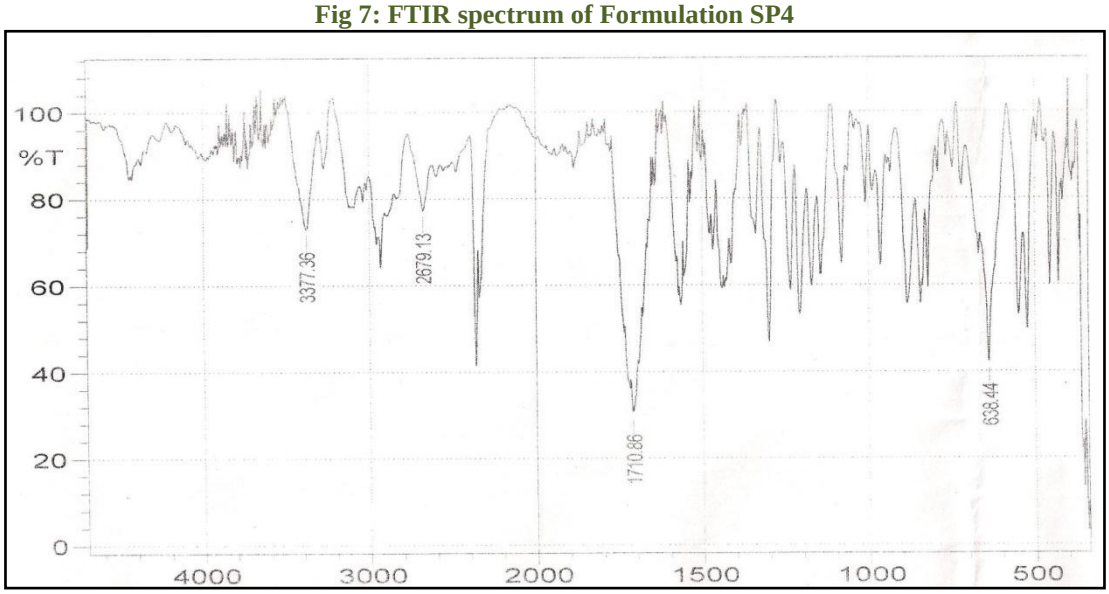


Fig 8: DSC thermogram of Sumatriptan Succinate

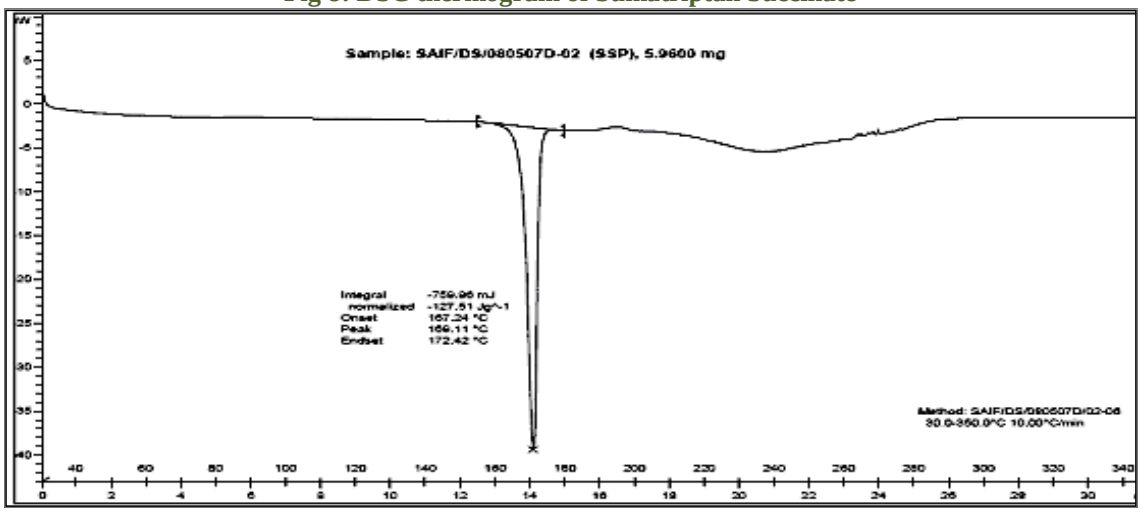
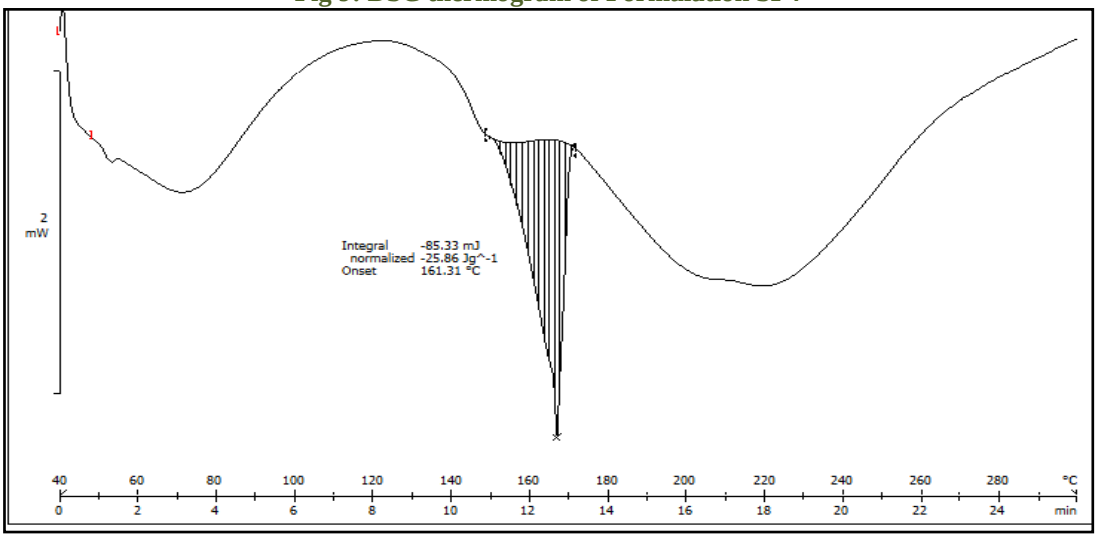


Fig 9: DSC thermogram of Formulation SP4



IV. CONCLUSION

Sumatriptan Succinate is a 5-HT agonist and mainly used in treatment of migraine, was successfully formulated in thermo-responsive *In-situ* nasal gel by using alone Poloxamer 407, also with combination of Poloxamer 407 and HPMC K4 M in different ratios. From the study conducted, it was found that the formulation SP4 was substantially stable and was able to release the drugin sustained manner. The methodology adopted for preparation of *In-situ* gel solution was very simple and cost effective. It is a newer approach to easy instillation by nasal route, improve the residence time, bioavailability and prolong drug release. These *In-situ* gelling systems would be definitely useful for migraine in combating the severe pain induced due to migraine and also to overcome the disadvantages of conventional Sumatriptan Succinate tablet dosage form.

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COMPETING INTERESTS DISCLAIMER

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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