Available online on 15.07.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

Formulation and Evaluation of Nasal In-situ Gel of Sumatriptan Succinate for the Treatment of Migraine

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ABSTRACT

In situ gelling systems are better and formulation of time since they have multiple advantages over conventional drug delivery system includes better bioavailability, retention on the desired site and patient compliance. Nasal drug delivery is a better option to deliver drug across Blood brain barrier and in this research work an attempt was made to prepare in-situ temperature triggered nasal gel of Sumatriptan Succinate for the treatment of Migraine. For the preparation of best insitu gel Poloxamer 188 in different concentration was used to formulate insitu gel along with HPMC K4M .The optimized formulation was chosen after evaluating the prepared gel for pH, Viscosity, Gel strength and mucoadhesive strength then final optimized formulation was subjected for texture analysis, in vitro drug release and Differential Scanning Calorimetery and drug release data was also evaluated for Release kinetic of formulation .Formulation batch F5 was selected as best formulation batch because it exhibited best result among all the prepared formulation and proved as promising temperature triggered formulation of in-situ gel.

Keywords: Nasal In-situ Gel, Sumatriptan Succinate, Migraine

Article Info: Received 13 May 2019; Review Completed 25 June 2019; Accepted 29 June 2019; Available online 15 July 2019

Cite this article as:

Aabid PK, Ashwani M, Formulation and Evaluation of Nasal In-situ Gel of Sumatriptan Succinate for the Treatment of Migraine , Journal of Drug Delivery and Therapeutics. 2019; 9(4):389-394 **http://dx.doi.org/10.22270/jddt.v9i4.3184**

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1. INTRODUCTION

In Ayurveda system of medicine the intranasal therapy is accepted form of treatment. It is also called "NASAYA KARMA". Nasal route has improved systemic bioavailability and it achieves fast and higher level of drug absorption as compared to oral. Nasal route is good because it is more permeable to compounds than gastro intestinal tract due to insufficiency of pancreatic and gastric enzymatic activity, neutral pH of nasal mucus. [1]

In nasal drug delivery formulation, gel formulation is very famous in pharmaceutical researchers. Gel formulation can keep on any application area more longer time than solution due to the imparted viscosity.

A delivery system in which solution is changed in to the gel (sol-gel) by changing temperature can keep longer onto mucosal epithelium. This type of system is turned as *in-situ* gelling drug delivery. Ropinirole, Midazolam are best example of *In-situ* nasal thermo-responsive gel drug delivery system. The noninvasiveness and self-administration nature also attracts the formulation and it helps scientists to deliver peptide and protein components. [2-3]

The first step in absorption of drug from the nasal cavity is passage through the mucus. Small, unchanged drug easily pass through this layer. So many absorption mechanism were established earlier but only two mechanism have been mostly used such as [4]

First mechanism It is an aqueous route of transport, it is slow and inactive. It is known as paracellular process. (transport of substances across an epithelium by passing through the intercellular space)Drugs having molecular weight greater than 1000 Daltons shows poor bioavailability.

Second Mechanism It involves lipid route of transport. It is known as the transcellular process. Transportation of solutes by a cell through a cell. It is liable for the transport of lipophilic drugs that show a rate dependence on their lipophillicity. Drug molecules also cross cell membranes by an active transport route via carrier-mediated mean. [5]

There are dismal statistics that indicate that migraines are quite common. 25-30% of women and 15-20% of men occasionally get migraines. It is of two major types-Classical migraine (migraine with aura) - headache is preceded by visual or other neurological symptoms. Common migraine (migraine without aura) - it is not accompanied any visual symptoms.[6-7]

Sumatriptan Succinate is an effective drug in the treatment of Migraine patients. Sumatriptan Succinate is a selective 5HT-

receptor agonist structurally similar to Serotonin. The specific receptor subtype (5-HT $_{1D}$ and 5-HT $_{1B}$) it activates, are present on the cranial arteries and veins. Acting as an agonist at these receptors, Sumatriptan reduces the vascular inflammation associated with migraine. [8]

Administration of conventional tablets of Sumatriptan Succinate has been reported to exhibit very low bioavailability, presystemic metabolism, and incomplete absorption from stomach as well as irritation caused at the site of injection. For a good therapeutic response and improve patience compliance. It was the objective of the study to develop a dosage form "Nasal *in-situ* Gel" of the drug Sumatriptan Succinate using polymers like Poloxamer, HPMC, which will avoid the metabolism of the drug in GIT and may increase the bioavailability by increasing concentration of drug at a site of action. A research article on development of immediate release liquid fill formulations for soft gels of Sumatriptan Succinate and mentioned the HPMC is best gelling agent with this drug as compared to pectin [9-10] In order to improve rate of absorption and thereby its bioavailability. Therefore it was assumed that the application of drug in the form of *in-situ* nasal gel will be effective.

In the present study nasal *in-situ* gel formulation was prepared over conventional tablet or other formulations, as it has several advantages like convenient and long term therapy is possible, degradation of drug in GIT is absent and may increase the bioavailability by increasing the concentration of drug at a site of action.

2. MATERIAL AND METHODS

Sumatriptan succinate was a gift sample from Nosch Laboratory Pvt. Ltd. Hyderabad. HPMC K4M, Poloxamer 188 and Glycerin were purchased from Central Drug House and all other chemicals are of analytical grade.

3 Preparation of nasal *in-situ* gel by temperature triggered method.

Nasal *in-situ* gel was prepared using cold method involving addition of polymers and additives in cold water with continuous agitation. The formed mixture was stored overnight at 4-10ºC. Polymer (poloxamer 188 in concentration 4, 6, 8, 12, 14% w/v) at cold condition was dissolved in water. The quantity of mucoadhesive polymer HPMC K4M (0.5% w/v) and glycerin (0.5% w/v) were mixed with one by one with continuous agitation. The formed mixture was stored overnight at freezing condition.

Table no 1: Composition of formulation batches [71]

Composition (%w/v)	F1	F2	F3	F4	F5
Sumatriptan Succinate	10	10	10	10	10
Poloxamer 188	4	6	8	12	14
HPMC K4M	0.5	0.5	0.5	0.5	0.5
Glycerin	0.5	0.5	0.5	0.5	0.5
Distilled water	qs	qs	qs	qs	qs

3.1Evaluation of Insitu Gel

Physical appearance and clarity test: The prepared formulations are visually examined of any foreign particles present.

3.1.1 pH of gel: pH of human nasal mucosa is found to be in the range of 5-6.5. But it can tolerate about 4-7.5. pH of prepared formulations should be within the range of nasal mucosa which can tolerate in order to reduce nasal irritation. pH of all formulations is mentioned in table 2. The result indicates that in all formulations pH is found to be within the tolerable. They are in the range of 6.1-6.5

Table no 2: Evaluation of pH

Formulations	pH
F1	6.1
F2	6.1
F3	6.3
F4	6.5
F5	6.5

3.1.2 Rheological studies: Viscosity of the nasal *in-situ* gel is an important factor in determining the residence time of drug in nasal cavity. Viscosity was determined by using Brooke field Viscometer DV II + Pro model in spindle no T95. The viscosity was measured using 25 mg of gel in 100ml beaker. The T95 bar spindle was fixed and suspended so that spindle does not touch the bottom of the beaker. T95 spindle was used for determining the viscosity. Factors like temperature (before and after gelation), shear force and sample size was maintained during this process. The T bar spindle was moved up and down giving viscosities at number of points. The rotation speed was 50 and 100 rpm to study the effect of shear on viscosity. The average of the three readings was used to calculate viscosity in cps.

The viscosities of the formulations before and after gel formulation are mentioned below in table no 3 and 4.

Table no3: Rheological studies of nasal *in-situ* gel before gelation

Shear rate (rpm)	Viscosity(cps)				
	F1	**F2**	**F3**	**F4**	**F5**
50	422	480	663	887	851
100	285	320	426	710	349

Table no 4: Rheological studies of nasal *in-situ* gel after gelation

Shear rate (rpm)	Viscosity(cps)				
	F1	**F2**	**F3**	**F4**	**F5**
50	513	645	1110	755	2073
100	336	543	825	1075	702

3.1.3 Measurement of gel strength: It is very important that the nasal *in-situ* gel formulation must have suitable gel strength. The gel strength of nasal gel formulation at 37ºC

±1, increased as the concentration of Poloxamer 188 and HPMC K4M increased.

3.1.4 Measurement of gel temperature: The gelation temperature was described by Miller and Donovan technique. In this technique phase transition occurred from liquid phase to a gel phase. In this 2 ml *in-situ* gel transferred to test tube and placed into water bath then the temperature of water bath increased slowly and constantly. Gel was allowed to equilibrate for 5 minutes at each setting, then the formulation was examined for gelation. When the meniscus would no longer move upon tilting to 90ºC, this is known as gelation temperature.

3.1.5 Mucoadhesive strength: Mucoadhesive strength is known as the force to detach the *in-situ* gel formulation from nasal mucosa tissue, for determining the mucoadhesive strength we use modified special balance. A small section of nasal mucosa of goat was cut and tied on 2 glass vials with the help of thread and stored it at 37ºC ±2ºC for 10 minute and then 50mg of gel was placed on first vial and placed below the height adjustable balance. While on another hand second vial was fixed in inverted position to the underside of the same balance after this height both vial were adjusted and come in intimate contact for 5 minute to ensure the contact between nasal mucosal tissue and the *in-situ* gel formulation. Then weight was put off on the other side of balance, until vials got detached, it expressed as the strength or stress in weight.

Table no 5: Mucoadhesive strength of nasal *in-situ* gel

Formulations	Time (sec)	Weight (gm)
F1	35	05
F2	36	07
F3	40	7.6
F4	47	8
F5	58	10.4

3.1.6 *In-vitro* drug release studies: The *in-vitro* drug release studies of the prepared *in-situ* gel (F5) were carried out in French diffusion cell. French diffusion membrane was used as diffusion membrane. Diffusion cell was filled with phosphate buffer pH7.4; diffusion membrane was mounted on cell. The temperature was maintained at 34-37ºC. At predetermined time points, 5 ml sample was withdrawn from receptor compartment, replaced the sample volume with phosphate buffer pH 7.4, after each sampling for a period of 360 minute. The sample withdrawn were filtered and analyzed for drug content by using phosphate buffer as blank by UV spectroscopy at 228 nm.

Table no 6: *In-vitro* drug release studies

Time (hrs)	% Cumulative drug release
1	0.555
2	0.765
3	0.995
4	1.185
5	1.435
6	1.645

Table no. 7: Regression co-efficient (r^2) values of different kinetic models for formulation F5

Release kinetic Model	**Regression value (r^2)**
Zero order	0.931
First order	0.880
Higuchi	0.880
Peppas	0.880

3.1.7 Differential Scanning Calorimetry:

Instrument version: Perkin Elmer Jade DSC

Load temperature: 30ºC

High temperature: 330ºC

Rate of heat flow: 10ºC/min

DSC was used for thermal of drug, mixture and excipients. Individual sample of Sumatriptan Succinate (2.367 mg) was weighed and scanned in the temperature range of -27 -305º at the heating rate of 5ºC/min under an atmospheric condition of dry nitrogen. Thermogram obtained of all sample. A formulated nasal *in-situ* gel was also subjected to this procedure. 3.612 mg of sample powder of *in-situ* gel was weighted and processed for the above method for DSC. Thermogram was shown in graph no 5. F3 sample was also analyzed which is shown in Fig no -2

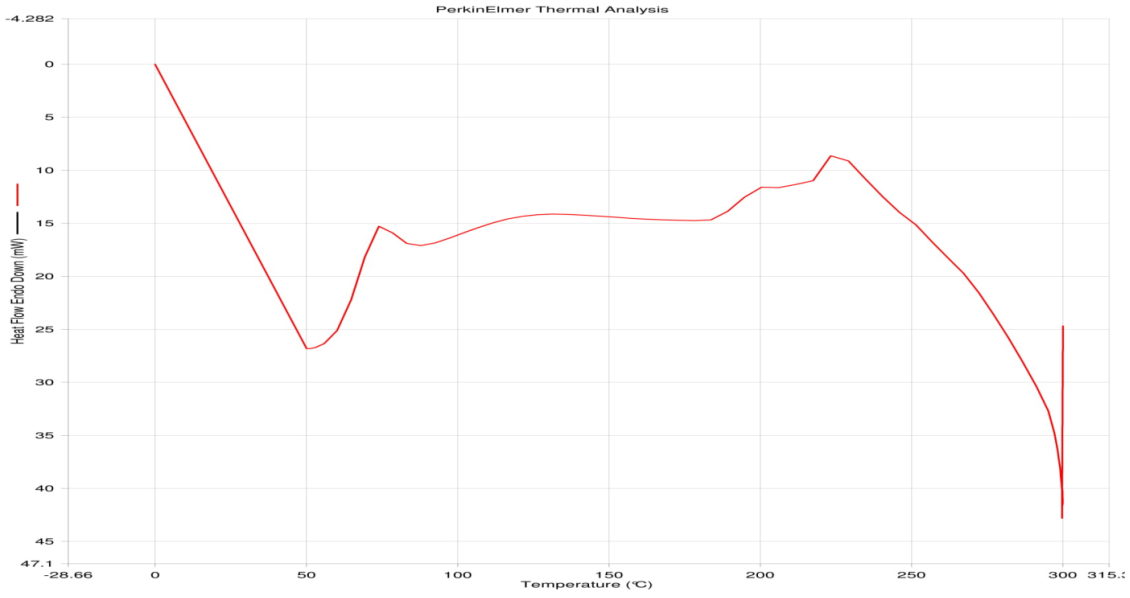

Fig no.2: DSC thermogram of the Formulation

In the thermogram of formulation glass temperature of polymer is visible between 50- 60°C and one more endotherm between 160-200°C shows melting point of drug into the thermogram though the intensity of peak is very less which shows the significant interaction between drug and polymer.

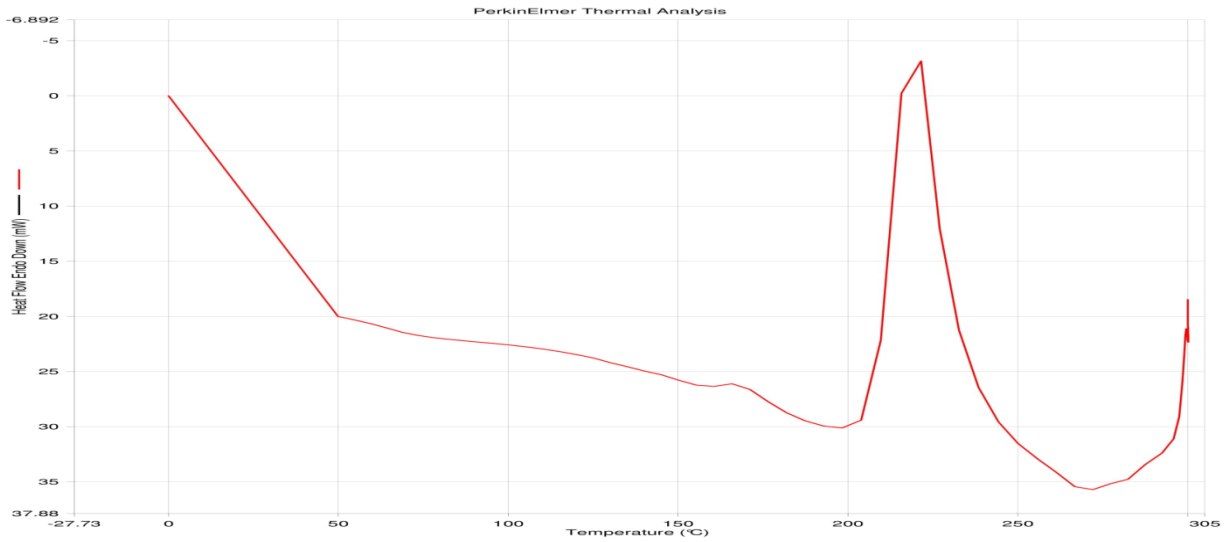

Fig no-3: DSC thermogram of pure drug

The thermogram of drug, an endotherm peak was observed between 169-190°C which is reported as melting point of the drug. One more endotherm peak was observed at 155°-160C which is due to the evaporation of the bond bond water into drug molecule.

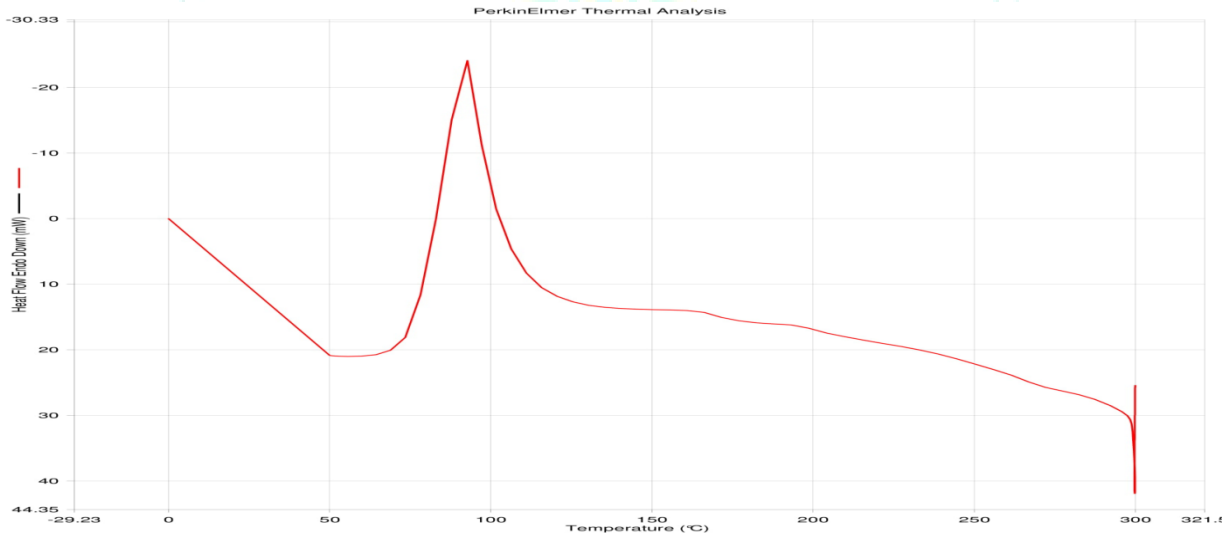

Fig no-4: DSC thermogram of HPMC K4M polymer

In this thermogram of polymer one endothermic peak was obtained at 50-55°C it should be glass transition of polymer and a sharp exothermic peak was obtained at 90°C which is revealed property of crystallization and freezing point of polymer.

3.1.8 Texture Analysis: Texture analysis is a primary concerned with measurement of mechanical properties of nasal *in-situ* gel. The analyses of texture or rheological properties are an assessment of a particle characteristic, such as adhesiveness, Hardness, elasticity. Contrary to verbal description- sticky, tacky, gummy texture analysis made these rheological characteristics quantifiable and therefore comparable.

Texture analysis of optimal gel was performed by using TA. In which pre- test speed was 0.05 mm/sec and post-test speed was 10.0mm/sec. The force applied was 500 gm. it was preformation 400 test run and a curve is obtained as a result of mucoadhesive force of optimized gel was 6.8 kg

Parameters fixed for Mucoadhesive test-

Sequence Title: Adhesive Test ,Test Mode: Tension ,Pre-Test Speed: 0.5 mm/sec ,Test Speed: 0.5 mm/sec ,Post-Test Speed: 10.0 mm/sec ,T.A. Variable No: 5: 500 ,Applied Force: 500.0 g ,Return Distance: 10.0 mm ,T.A. Variable No: 8: 0.0 %, Trigger Type: Auto ,Trigger Force: 5.0 g ,Probe: A/MUC; Mucoadhesion

TEST RIG:

GEL F5 AFTER HEATING, Points per second: 400 Test Run Mucoadhesive Overlay Curve:

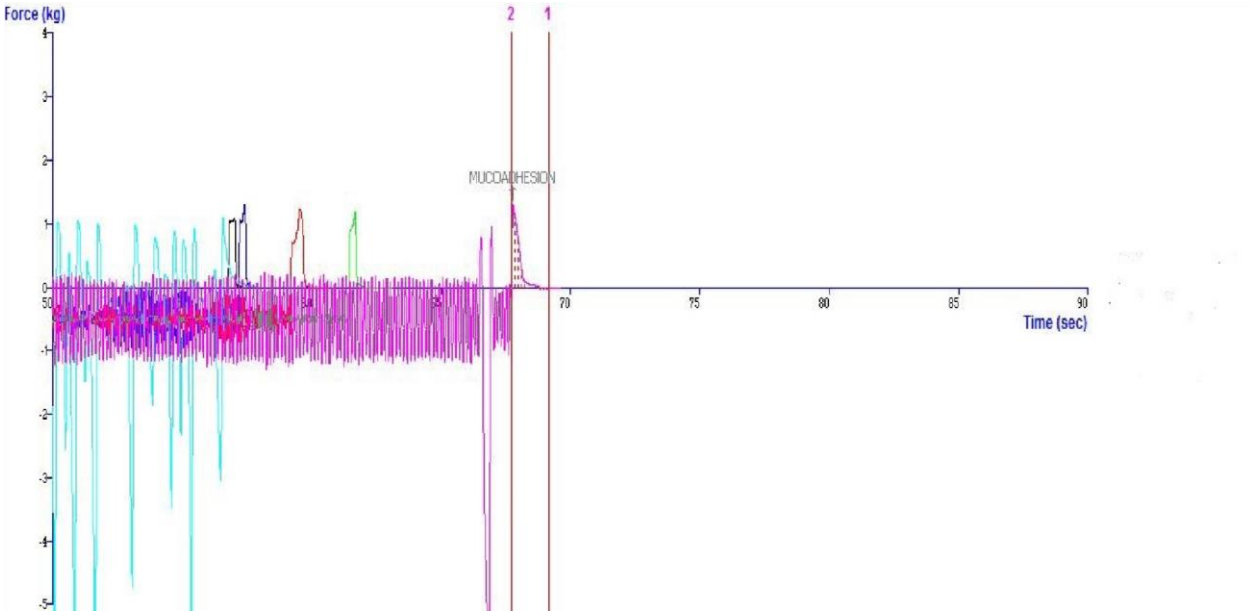

Fig no. 5: Result Avg Mucoadhesive force for 06 repetitive gel sample F5

Table no 8: Texture analysis report of *in-situ* nasal gel (after heating)

Sample number	Batch	Mucoadhesive force (kg)
1	Gel Sample F5-1	1.117
2	Gel Sample F5-2	1.153
3	Gel Sample F5-3	1.319
4	Gel Sample F5-4	1.311
5	Gel Sample F5-5	1.253
6	Gel Sample F5-6	1.196
	AVERAGE("BATCH")	1.231
	STDEV("BATCH")	0.073
	STDEV("BATCH") / AVERAGE("BATCH") * 100	6.892

4 RESULTS AND DISCUSSION

4.1 Identification of Sumatriptan Succinate by DSC

4.1 Differential Scanning Calorimetry

The thermogram of drug showed endotherm between 160-200°C shows melting point of drug into the thermo gram though the intensity of peak is very less.

4.2 Visual appearance and clarity

The prepared formulations are clear and transparent. The pH of the formulations was found to be in the range of 6.1-6.5 as shown in the table no. 2.

4.3 Rheological Studies

The viscosity of the formulations before and after gelation was evaluated using Brook Field Viscometer (DV II + Pro Model). The results obtained are shown in table no. 3 and 4.The result showed that viscosity of all formulations decreased as the shear rate increased, which indicates that the character of pseudoplastic fluid. The results revealed

4.4. Gelling temperature

Gelling temperature of all the formulations was between 34-42ºC.

4.5. Mucoadhesive strength

Mucoadhesive strength was best in all samples but F5 sample have more mucoadhessive strength

4.6. *In-vitro* drug release

The optimized formulation F5 was subjected to *in-vitro* drug release. The release study of prepared formulation was carried out up to 6 hrs. The result showed that formulation F5 showed 1.645% cumulative drug release which is greater than other. And its drug release was studied using different kinetic models. From the release study of F5, release kinetics was studied using zero order, First order, Higuchi release and Korsemeyer peppas kinetic model. The regression value of each of these release kinetics were calculated and compared. The data revealed that the release pattern of formulation best fitted for Zero order release kinetics as shown in table no. 7. In-vitro drug release study showed that the 1.645% was obtained for F5 in 6 hrs.

4.7 **Differential Scanning Calorimetry:** The thermogram of drug an endothermic peak was obtained. In the thermo gram of formulation glass temperature of polymer is visible between 50- 60°C and one more endotherm between 160-200°C shows melting point of drug into the thermo gram

though the intensity of peak is very less which shows the significant interaction between drug and polymer.

4.8 **Texture Analysis:** Texture analysis report revealed that the after heating and conversion of sol to gel Mucoadhesive force (kg**)** obtained was 1.231 kg after 06 repetitive Gel sample F5.

CONCLUSION:

The aim of the project was to formulate the nasal in-situ gel. The nasal in-situ gels of Sumatriptan Succinate were successfully developed using poloxamer 188 and HPMC K4M by using cold method. The optimized concentration was proven to be promising nasal delivery system for anti-migraine drug Sumariptan Succinate, which would enhance nasal residence time owning to increase viscosity and mucoadhesive strength. Further this type of delivery is pleasant and pain less alternative to other delivery system.

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