

Research Article



Zolmitriptan Nasal *In-situ* Gel Using *Sterculia Foetida* Linn Gum As Natural Mucoadhesive Polymer

N. G. Mahakalkar*, K. P. Upadhye

Department of Pharmaceutics, Priyadarshni J. L. C. College of Pharmacy, Hingna Road, Nagpur, Maharashtra, India.

*Corresponding author's E-mail: mahakalkarng18@gmail.com

Accepted on: 29-07-2013; Finalized on: 30-09-2013.

ABSTRACT

A new *in-situ* mucoadhesive nasal gel formulation has been developed using a natural mucoadhesive polymer obtained from bark of *Sterculia foetida* Linn. The mucoadhesive strength and viscosity of this natural mucoadhesive polymer was found to be higher in comparison to the synthetic polymers, namely HPMC and carbopol 934 which are conventionally used for a similar purpose. Nasal mucosa has been considered as a potential administration route to achieve faster and higher level of drug absorption because it is permeable to more compounds than the gastrointestinal tract due to lack of pancreatic, gastric enzymatic activity and neutral pH of the nasal mucus, less dilution by gastrointestinal contents, relatively large surface area available for absorption, the highly vascularized epithelial layer and avoidance of first pass effects thus improve bioavailability of drug and as a safe and sustained release nasal delivery System to control migraine. Migraine is a recurrent incapacitating neurovascular disorder characterized by attacks of debilitating pain associated with photophobia, phonophobia, nausea and vomiting. In the present study nasal *in-situ* gel is prepared for treatment of migraine using zolmitriptan drug. The *in-situ* gelation was achieved by the use of pluronic F127 which exhibit thermoreversible gelation property. The purpose of the present work was to prepare *in-situ* nasal gel of zolmitriptan by cold technique for improved drug residence time in nasal cavity and characterized by gelation temperature, permeation studies, pH, drug content, rheological studies, gel strength, drug polymer interaction, and stability study.

Keywords: *In-situ* gel, Mucoadhesive, Nasal delivery, Zolmitriptan.

INTRODUCTION

Nasal drug delivery has been recognized as potential route from ancient days and nowadays it becomes an important tool in the treatment of various disorders. In recent years many drugs have been shown to achieve better systemic bioavailability through nasal route than by oral administration. Nasal drug delivery which has been practiced for thousands of years has been given a new lease of life. It is a useful delivery method for drugs that are active in low doses and show no minimal oral bioavailability such as proteins and peptides.¹

Environment sensitive gel is a new dosage form which has been applied in nasal drug delivery recently. Compared to liquid nasal formulations, nasal *in situ* gels are instilled as low viscosity solutions into nasal cavity, and upon contact with the nasal mucosa, the polymer changes the conformation producing a gel, so it cannot only prolong the contact time between the drug and the absorptive sites in the nasal cavity, but also release the drug slowly and continuously.^{2,3}

To improve the nasal absorption of drug, it is necessary to increase the nasal residence time. One method to lengthen nasal residence time has been to include a bioadhesive in the formulation. Natural gums are used as versatile excipients in pharmaceutical formulations. These natural polymers are beneficial for human beings as compared to synthetic polymer. Therefore natural gums are preferred due to their safety, economy, natural origin, free from side effect, low cost, renewable sources, public

acceptance and patient compliance, environment friendly and easily available.^{4,5}

Considering the importance of natural polymers the present research work is undertaken to study the natural gum from *Sterculia foetida* Linn. SFG is obtained from dried gummy exudates of stem bark of *Sterculia foetida* of the family Sterculiaceae. Therefore the aim of this work is to explore the *Sterculia foetida* Gum as mucoadhesive polymer and pharmaceutical aid for nasal *in-situ* gel formulation.⁶⁻⁸

Poloxamer 407 (PF-127) is a nonionic surfactant composed of polyoxyethylene-polyoxypropylene copolymers. Poloxamers or pluronics are triblock copolymers which form micelles at low concentration and clear, thermoreversible gel at high concentrations. The concentrated solutions are transformed from low viscosity transparent solutions to solid gel on heating to body temperature.^{1,9,10}

Migraine is a neurological syndrome characterized by altered bodily perceptions, headaches, and nausea.¹¹ Zolmitriptan, 4S-4-((3-[2-(dimethylamino) ethyl]-1H-indol-5-yl)methyl)-1, 3-oxazolidin -2-one, is a second – generation triptan prescribed for patients with migraine attacks, with or without an aura, and cluster headaches. It has a selective action on serotonin (5HT_{1B/1D}) receptors and is very effective in reducing migraine symptoms, including pain, nausea, and photo-or phonophobia. The absolute bioavailability of zolmitriptan is up to 40% for both oral and nasal dosage forms. The faster clearance of



the drug from the nasal cavity could explain the low bioavailability for nasal formulation.^{12,13}

In our present work, study was focused to develop an ideal nasal in situ gelling system using a potent and effective anti-migraine as a model drug, *Sterculia foetida* Gum as an mucoadhesive polymer and poloxamer-407 as an thermoreversible polymer by cold method.

MATERIALS AND METHODS

Materials

Zolmitriptan was obtained as a gift sample from Cipla Ltd., Patalganga, Poloxamer (BASF, Mumbai), Carbopol 940 (Vagh Brother's, Nagpur), benzalkonium chloride (Premier Intermediates Pvt. Ltd., Mumbai), Sodium bisulfate (Imperial Oilfield Chemicals Pvt. Ltd., Gujarat), sorbitol used were of AR grade.

Methods

Preformulation Studies

Physicochemical properties of drug

Determination of solubility of Zolmitriptan

The solubility of zolmitriptan was tested in various solvents such as distilled water, ethyl alcohol, phosphate buffer, propanol and acetone. Solubility experiments were conducted in triplets.

Melting point determination

The melting point of drug was determined by taking a small amount of drug in capillary tube closed at one end and placed in melting point apparatus and the temperature at which drug melts was recorded. This was performed in triplets and average value noted.

Analytical method used in the determination of zolmitriptan

The UV-Spectrophotometer method was developed for the analysis of the drug using double beam Shimadzu 1601 Spectrophotometer.

Determination of λ_{max}

Zolmitriptan was dissolved in phosphate buffer and further diluted with the same. A solution of concentration of 5mcg/ml was prepared and scanned for maximum absorbance in double beam UV-Spectrophotometer in range 200-400nm, phosphate buffer pH 5 as a blank. The λ_{max} of the drug was found to be 229.4nm.¹³

Preparation of Standard curve for Zolmitriptan

The standard stock solution was prepared by dissolving zolmitriptan in phosphate buffer pH 5 to make final concentration of 100 μ g/ml. Different aliquots were taken from stock solution and diluted with phosphate buffer pH 5 separately to prepare series of concentrations from 1-5 μ g/ml. Absorbance was measured at 229.4 nm against phosphate buffer pH 5 as blank. The calibration curve was prepared by plotting absorbance versus concentration (μ g/ml) of zolmitriptan shown in figure 1.¹⁴

Identification and Authentication of plant material

The gum of *Sterculia foetida* (Sterculiaceae) was procured from the vendor Mr. Wagh brothers, Nagpur. The gum was authenticated and approved macroscopically and microscopically evaluation by Senior Taxonomist Dr. Vinayak Naik, Nicholas Piramal Mumbai. The above gum was used for research work.

Purification of Gum

Sterculia foetida gum (SFG) powder was purified by dissolving the dry SFG powder into water, centrifuging out the water-insoluble impurities, and precipitating the remaining part into ethanol. The concentration of SFG used in purification was typically about 0.1% -0.5% solution by using standard laboratory centrifuges. Dissolution of SFG was typically performed by stirring the powder in water at 25^o C for 4-6 hours. Dissolution could be facilitated by heating the solution to 60^oC for 1 hour while the solution was stirred. Precipitation was performed by adding the centrifuged SFG solution to 95% ethanol. The wet, precipitated SFG was dried in a vacuum oven at 40^oC for several hours. The dry, purified SFG was then milled to powder by the use of a small electric grinder. The milled powder was sieved using a sieve shaker for 10 min to yield a particles having 125 μ m (#120 mesh). The coarse powder, larger than this particle size was milled again and the sieving was repeated.¹⁵

Physiological properties of SFG

Determination of Moisture (Loss on Drying)

Weighed about 10 grams of SFG powder and placed in a tarred evaporating dish, which was then dried in an oven at 105^oC for 5 hrs. It was then cooled in desiccators and weighed. The process of drying, cooling and weighing was repeated after every one hour until the difference between two consecutive weighing corresponded to not more than 0.25%.^{16,17}

Solubility

All solubility determinations were carried out at the room temperature in small test tubes with a small amount of SFG in the various solvents with vigorous shaking. The solubility tests were determined in ether, chloroform, ethyl acetate, ethanol, water, 5% hydrochloric acid, 5% sodium hydroxide, conc. sulphuric acid.

Density

Sample of 50g of SFG powder was evaluated for density in triplicate. For density determination, the powder sample was poured into a 100 ml graduated cylinder using a large funnel and the volume occupied was measured. The sample weight was then divided by the bulk volume to obtain the bulk density. The unit for density is g/ml.

Viscosity and pH measurement

The viscosity of 1% w/v *Sterculia foetida* gum (SFG) in aqueous dispersion was measured using Brookfield viscometer at 10-100 rpm. pH of 1% w/v *Sterculia foetida*



gum (SFG) aqueous dispersion was measured using pH meter.^{18,19}

Swelling Index

About 1g of SFG powder was taken in 100ml of measuring cylinder. Measure the initial volume of SFG in measuring cylinder. Make volume upto 100ml with water. Then occasionally shaken for 1hr and stand for 24hrs, then measured the final volume occupied by the swollen gum.^{16,17}

$$\text{Swelling index} = (Wt - Wo / Wo) \times 100$$

Where, Wt = final volume occupied by the swollen gum,

Wo = initial volume occupied by the gum

Drug-Excipients Interaction study

There is always possibility of drug-excipients interaction of any formulation due to their intimate contact. The technique employed in this study to know drug-excipients interaction is FTIR study and Differential Scanning Calorimetry technique.

FTIR Spectroscopy

IR Spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. Infra-red spectra of pure drug ZMT and formulation were scanned by using FTIR 8400S Shimadzu-1700 by KBr pellets method.^{20,21}

Differential Scanning Calorimetry (DSC)

The Differential Scanning Calorimetry (DSC) thermogram of pure ZMT and physical mixtures of the drug was recorded by using the differential scanning calorimeter

equipped with the computerized data station. All samples were weighed and heated in a closed pierced aluminium pan at a scanning rate of 10°C/min between 40 and 220°C and 40ml/min of nitrogen flow.²²

Formulation of Zolmitriptan Gel

In present work cold method was preferred for the preparation of thermoreversible mucoadhesive nasal gel. Aqueous zolmitriptan nasal gel using different concentration of pluronic F-127 and mucoadhesive polymer and various formulation additives a shown in Table 1 were prepared by cold method described by **Schomolka** (et al.) Optimization of their concentration was done on the basis of gelation temperature. At those respective concentrations they get converted to gel at nasal temperature. Briefly, the method involved slow addition of polymer, drug and other additive in cold water with continuous agitation. The formed mixtures were stored overnight at 4°C.^{12,23}

Procedure

For preparation of gel, accurately weighed thermoreversible polymers Pluronic F127 (PF127) were solubilized in cold water with continuous stirring using magnetic stirrer and were stored overnight at 4°C until clear solution obtained. Also the (SFG) mucoadhesive polymer was separately soaked overnight for proper solubilisation and swelling. Now natural mucoadhesive polymer and other excipients were slowly added to the thermoreversible solution with continuous agitation to form formulation. The formed mixtures were stored overnight at 4°C until clear solution obtained.

Table 1: Composition of nasal formulation containing bioadhesive polymer

Ingredients (In %)	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈	F ₉	F ₁₀	F ₁₁
PF-127	16	16	16	18	18	18	20	20	20	20	20
SFG	0.14	0.16	0.18	0.14	0.16	0.18	0.14	0.16	0.18	0.20	0.22
Drug	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sorbitol	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Na-bisulfite	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Benzalkonium chloride	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Dist. Water (Qs) in ml	10	10	10	10	10	10	10	10	10	10	10

Evaluation of nasal gel

Determination of visual appearance and clarity

Gel formulations were visually inspected for clarity, color homogeneity, presence of particles and fibers.

Determination of pH of gel

pH of the each formulation was determined by using pH meter at room temperature. The pH meter was first calibrated using solutions of pH 4 and pH 7.²⁴

Determination of gelation studies

Gelation temperature was assessed using a modification of Miller and Donovan technique¹. A 2 ml aliquot of gel was transferred to test tubes, immersed in a water bath at 4°C. The temperature of water bath was increased in increments of 1°C. The samples were then examined for gelation, which was said to have occurred when the meniscus would no longer move upon tilting through 90°C.²⁵

Viscosity measurement

Viscosity determination of the prepared *in situ* gels as well as sols was carried out on Brookfield digital



viscometer. Developed *in situ* gelled formulations were transferred into the beaker; temperature was maintained at 37 ± 0.5 °C for all the formulations throughout the experiment. The viscosity was measured at different rpm with Spindle No. B96. The viscosity measurements were carried out in triplicate and average readings were taken for calculation.^{26,27}

Drug content uniformity⁵³

Nasal gels of Zolmitriptan were assayed by spectrophotometric analysis. Each formulation (1 ml) was taken in a 100 ml volumetric flask diluted with phosphate buffer (PBS) pH 5 and was shaken to dissolve the drug in PBS pH 5. The solution was filtered through Whatman filter paper and the filtrate was further diluted if necessary with PBS pH 5. Drug content was determined using at 229.4nm on UV\ visible spectrophotometer, Shimadzu UV 1601.²⁸

Determination of Mucoadhesive Strength

The mucoadhesive strength was determined by using the modified method. The mucoadhesive potential of each formulation was determined by measuring a force required to detach the formulation from nasal mucosal tissue. A section of sheep nasal mucosa was fixed on each of two glass slides using thread as shown in Fig.5.1. 50mg of gel was placed on first slide and this slide placed below the height adjustable pan. While another slide with mucosal section was fixed in inverted position to the underside of the same pan. Both the slides with gel formulation between them held in contact with each other, for 2 min to ensure intimate contact between them. Then weight was kept rising in second pan until slides get detached from each other. The mucoadhesive force expressed as the detachment stress in dyne/cm² was determined from the minimal weight that detached the mucosal tissue from surface of each formulation.^{25,29}

$$\text{Mucoadhesive Strength (dyne/cm}^2\text{)} = \text{mg/A,}$$

Where, m = weight required for detachment in gram,

g = Acceleration due to gravity (980cm/s²),

A = Area of mucosa exposed

The nasal mucosa was changed for each measurement

Measurement of gel strength

Formulated gels were placed in the test tubes and gelled in a thermostat at 37°C. The apparatus for measuring gel strength (Weight: 27gm.) was then placed onto the Poloxamer gel. The time taken by the apparatus to sink to a depth of 5 cm through the prepared gel was measured for each formulation.^{25,29}

Drug release studies

In vitro permeation studies using diffusion cell

The *in vitro* permeation studied was conducted using cellophane membrane. The cellophane membrane was mounted in between the donor and the receptor

compartment of the diffusion cell. The position of the donor compartment was adjusted so that the mucosa just touches the permeation medium. Formulation equivalent to contain 25 mg of drug was taken in the donor compartment which was in contact with the mucosal surface of the membrane, while the receptor compartment was filled with 30 ml of phosphate buffer pH 5 and its temperature was maintained at 37 °C. The content of the receptor compartment was stirred using a magnetic stirrer. An aliquot of 5 ml was withdrawn from the receptor compartment at suitable time intervals and replaced with the same volume of fresh medium. These samples were analyzed spectrophotometrically at 229.4nm.^{28,30}

Ex vivo permeation studies using diffusion cell

The *ex vivo* permeation studied was conducted using ship nasal mucosal membrane. The ship nasal mucosal membrane was mounted in between the donor and the receptor compartment of the diffusion cell. The position of the donor compartment was adjusted so that the mucosa just touches the permeation medium. Formulation equivalent to contain 25 mg of drug was taken in the donor compartment which was in contact with the mucosal surface of the membrane, while the receptor compartment was filled with 30 ml of phosphate buffer pH 5 and its temperature was maintained at 37 °C. The content of the receptor compartment was stirred using a magnetic stirrer. An aliquot of 5 ml was withdrawn from the receptor compartment at suitable time intervals and replaced with the same volume of fresh medium. These samples were analyzed spectrophotometrically at 229.4nm.^{27,30}

Accelerated Stability study

The stability test under the actual condition of storage i.e. refrigeration condition. Gels were stored in clean, dry, airtight moisture proof bottles, kept away from light. At various time intervals of 15, 30, 45 and 60 days end, samples were collected and evaluated for drug content, pH, viscosity and clarity.²⁶

To assess long term stability of the prepared gelling systems at 40 °C/75% relative humidity (RH) in the stability chamber for 2 months. The samples were withdrawn at different time intervals and observed for physical characteristics, drug content and *in vitro* drug release characteristics.^{31,32}

RESULTS AND DISCUSSION

Physiochemical Characterization of Drugs

Solubility studies

From the solubility studies, zolmitriptan was found to be freely soluble in ethanol, methanol and practically in soluble in water.

Melting Point

Melting point of zolmitriptan was found to be in the range of 150- 155°C as reported in literature, thus indicating



purity of the drug sample. Any impurity, if present, will cause variation in the melting point of a given drug substance.

Standard Calibration curve for Zolmitriptan

The standard curve of zolmitriptan was prepared in phosphate buffer pH 5, at λ_{max} of 229.4nm. The value of regression coefficient was found to be 0.9986, which showed linear relationship between concentration and absorbance. The regression equation generated was $y=0.062x$. The standard calibration curve obeyed Beer's law at given concentration range of 1 $\mu\text{g/ml}$ to 5 $\mu\text{g/ml}$.

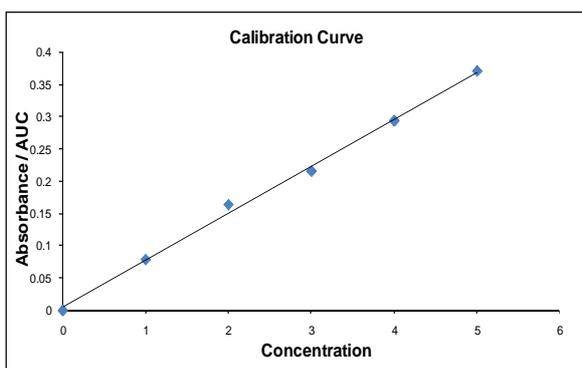


Figure 1: Standard curve of Zolmitriptan in phosphate buffer pH 5

Table 2: Physiological characterization of *Sterculia foetida* gum

Physical evaluation	Results
Loss on drying	0.1586 %w/w
Solubility	Soluble in- water form colloidal solution, 5% HCL, Sparingly soluble in 5% NaOH, conc. H ₂ SO ₄ . Insoluble in- ether, chloroform, ethyl acetate, ethanol.
pH (1% w/v)	4.65 % w/w
Melting point	222-228°C (decomposes)
Density	0.6097g/ml
Swelling Index (%)	83.13 \pm 0.3164
Viscosity (at 100rpm)	2952 centipoise

Characterization of *Sterculia foetida* gum

This SFG powdered material was subjected for evaluation of following physiological parameters. The value of these parameters was found to be loss on drying was 0.1586 % w/w, pH- 4.65, density - 0.6097. Solubility were found to be soluble in- water to form colloidal solution, sparingly soluble in 5 % HCl, 5 % NaOH & completely soluble in conc. H₂SO₄. Insoluble in ether, chloroform, ethyl acetate, ethanol. *Sterculia foetida* gum was showed very good Swelling index i.e. 83.13 %.

The FT-IR spectra of pure ZMT showed characteristics peaks at 1408 cm^{-1} indicates C=C stretching vibration, 2878 cm^{-1} indicates C-H stretching vibration, 1739 cm^{-1} indicates C=O stretching vibration and the peak at 3352 cm^{-1} indicates N-H bond which is depicted in figure (Fig. 2).

Similarly, IR spectra of pure ZMT and its physical mixtures (Fig. 3) did not show any significant difference from those obtained from their physical mixture. These obtained results indicate that there was no positive evidence for the interaction between ZMT and excipients used.

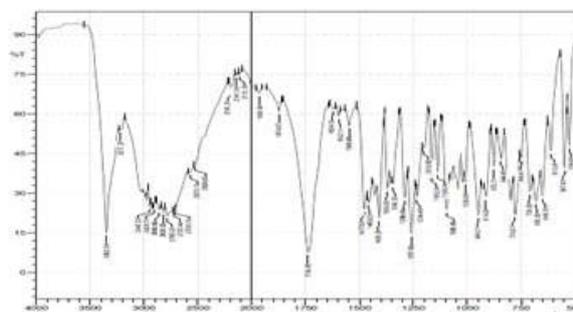


Figure 2: FT-IR spectra of pure zolmitriptan

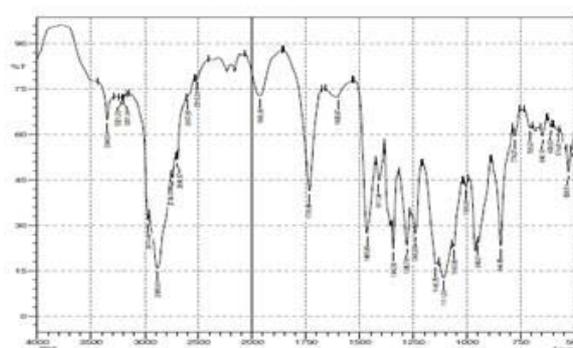


Figure 3: FT-IR spectra of mixture

Differential Scanning Calorimetry (DSC)

DSC curves obtained for pure Zolmitriptan and physical mixture of pure drug. Pure powdered Zolmitriptan showed melting endotherm at 153.07°C, while physical mixture of drug and excipients showed the melting peak of the drug at 154.42°C which indicates that all ingredients are compatible with each other.

Evaluation of nasal gel³¹

Determination of visual appearance and clarity

Clarity of all the formulations was found to be satisfactory.

pH of mucoadhesive nasal gels

The pH of the formulations was found to be satisfactory and was in the range of 4.5-5.5.

Determination of gelation temperature of gels

Table 3 shows the gelling capacity of formulations from F₇-F₁₁. F₉ formulations showed instantaneous gelation when contacted with simulated nasal fluid. However, the nature of the gel formed depended on the concentration of polymers used. The nasal gel formulation F₉ showing most satisfactory gelation temperature (30°C – 40°C).

Drug content uniformity determination

Table 3 shows the percent drug content for formulations F₇ to F₁₁. The drug content was found to be in acceptable

range for all the formulations. Percent drug content of formulations F₇, F₈, F₉, F₁₀ and F₁₁ was found to be 91.80%, 98.33%, 99.19%, 97.03% and 94.09% respectively. This indicate that process employed to prepare gels in this study was capable of producing gels with uniform drug content and minimal gel variability.

Determination of Mucoadhesive Force

Mucoadhesive force of developed thermoreversible mucoadhesive nasal gel was determined using sheep

nasal mucosa and was measured by modified bioadhesive force device. The mucoadhesive force was found to be in the range of 45.3 to 72.4 dynes/cm² as shown in table 3.

Measurement of gel strength

Mucoadhesive strength of developed thermoreversible mucoadhesive nasal gel was determined using sheep nasal mucosa and was measured by modified bioadhesive strength device. The mucoadhesive time was found to be in the range of 20.33-123 seconds as shown in table 3.

Table 3: Physical evaluation of *in-situ* gels

Code	pH	Gelation temperature(°C)	Drug content	Mucoadhesive force (dynes/cm ²)	Gel Strength (sec.)
F ₇	4.65 ± 0.015	62	91.80 ± 0.010	45.3 ± 1.38	20.33 ± 1.52
F ₈	5.08 ± 0.025	43	94.33 ± 0.010	47.9 ± 2.08	30.66 ± 1.53
F ₉	5.14 ± 0.025	38	99.19 ± 0.016	59.7 ± 0.24	40.33 ± 1.52
F ₁₀	4.71 ± 0.020	24	97.03 ± 0.013	60.3 ± 1.03	73.66 ± 2.08
F ₁₁	5.10 ± 0.015	18	94.09 ± 0.012	72.4 ± 1.21	123 ± 1.73

Viscosity measurements of nasal gel formulations

The formulated thermoreversible mucoadhesive nasal gel had viscosity ranging from 500 to 25000cps, which was measured by using Brookfeild viscometer at 10 to 100 rpm using spindle no.B-96 at room temperature. This showed that the viscosity of gels increase with the SFG content. Formulations were shear thinning and an increase in shear stress was observed with increase in angular velocity (pseudoplastic rheology).

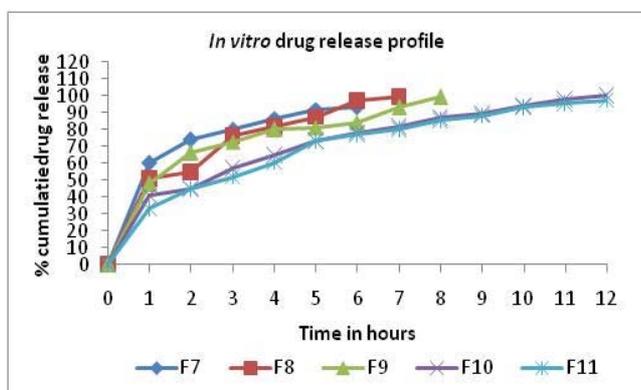


Figure 4: Comparative *in vitro* release profile of different thermoreversible mucoadhesive nasal gels

Drug release studies

In vitro permeation studies using diffusion cell

From the results it observed that the release of zolmitriptan was not only affected by PF-127 concentration but also by the concentration of bioadhesive polymer SFG used. So, all the bioadhesive polymers retarded the drug release from nasal gel. According to the release data, it was possible to modulate the release of zolmitriptan by adjusting the concentration of the polymer to obtain a sustained drug release profile for 8 hrs.

It was found that cumulative percent drug release was 99.24% for F₉ formulation after 8 hours. The *in vitro* release data indicated that the formulation F₉ showed better sustained effect than other four formulations in 8 hrs.

The drug is released in a sustained manner over a period of time and F₈, F₁₀, F₁₁ shows zero order drug release and F₇, F₉ shows first order drug release for all formulations. Thought the zero order drug release is best for sustained release formulation but F₉ formulation was selected as optimized formulation because it shows gelation at required temperature.

Ex vivo drug release permeation study of F₉ formulation:

The *ex vivo* study was done on optimized batch i.e. F₉ selected on basis of results of all evaluation parameters. Among them gelation temperature and diffusion data was important. The *ex vivo* permeation studied was conducted using sheep nasal mucosal membrane and phosphate buffer pH 5 as an *ex vivo* study fluid in the receptor compartment of a Franz diffusion cell.

It was showed promising drug release from sheep nasal mucosa. From data it showed 99.46 % drug release in 8 hrs.

Accelerated Stability Study

Accelerated Stability studies were carried out of the most satisfactory formulations for two months to assess their long term stability. At various time intervals of 15, 30, 45 and 60 days end, samples were collected and evaluated for drug content, pH, viscosity and clarity. From the stability studies it was confirmed that *in situ* gelling formulations of zolmitriptan remained stable at ambient temperature (40°C) and 75% relative humidity.

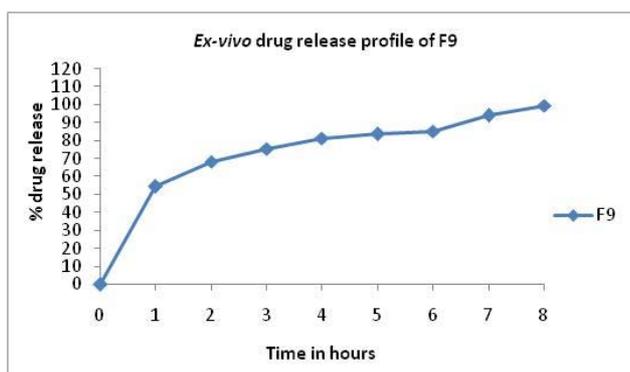


Figure 5: Ex-vivo drug release profile of F₉ formulation

CONCLUSION

It can be concluded that *sterculia foetida* gum can be successfully used as a mucoadhesive natural polymer in developed thermoreversible mucoadhesive nasal gel of zolmitriptan. It is also beneficial for the treatment or management of migraine for long period of time by sustaining the drug release. Improved bioadhesion by using *sterculia foetida* gum enhances nasal residence time owing to increased viscosity of gel in the nose which may be advantageous to protect the drug from draining out and it also exhibits a permeation enhancing effect thus increase bioavailability of drug. As concentration of *sterculia foetida* gum is increases, the bioadhesive force, gel strength and sustained release effect on the drug increases.

REFERENCES

- Khairnar PS, Walke PS, Narkhede MR, Nehete JY, Formulation and In-Vitro Evaluation of Thermoreversible Rizatriptan Benzoate Nasal Gel, International Journal Of Pharmacy And Pharmaceutical Sciences, 3(4), 2011, 250-256.
- Swamy NG, Abbas Z, Mucoadhesive In Situ Gels As Nasal Drug Delivery Systems: An Overview, Asian Journal of Pharmaceutical Sciences, 7(3), 2012, 168-180.
- Kant A, Reddy S, Shankraiah MM, Venkatesh JS, Nagesh C, In Situ Gelling System – An Overview, Pharmacologyonline, 2, 2011, 28-44.
- Abbas Z, Sachin, Swamy NGN, Mucoadhesive Polymers: Drug Carriers for Improved Nasal Drug Delivery, Indian Journal of Novel Drug Delivery, 4(1), 2012, 2-16.
- Jani GK, Shah DP, Prajapati VD, Jain VC, Gums and Mucilages: Versatile Excipients for Pharmaceutical Formulations, Asian Journal of Pharmaceutica Sciences, 4, 2009, 309-323.
- Chivate AA, Poddar SS, Abdul S, Savant G, Evaluation of Sterculia Foetida Gum As Controlled Release Excipient, American Association of Pharmaceutical Scientists, 9(1), 2008, 197-204.
- Avachat AM, Dash RR, Shrotriya SN, Recent Investigations Of Plant Based Natural Gums, Mucilages And Resins In Novel Drug Delivery Systems, Indian Journal of Pharmaceutical Education And Research, 45(1), 2011, 86-99.
- Sujitha B, Krishnamoorthy B, Muthukumaran M, A Role of Natural Polymers Used In Formulation Of Pharmaceutical Dosage Forms: A Review, International Journal of Pharmacy & Technology, 4(4), 2013, 2347-2362.
- Patel HR, Patel RP, Patel MM, Poloxamers: A Pharmaceutical Excipients with Therapeutic Behaviors, International Journal of Pharmtech Research, 1(2), 2009, 299-303.
- Cafaggi S, E Russo E, Caviglioli G, Parodi B, Stefani R, Sillo G, Leardi R, Bignardi G, Poloxamer 407 As A Solubilising Agent For Tolfenamic Acid And As A Base For A Gel Formulation, European Journal of Pharmaceutical Sciences, 35, 2008, 19-29.
- Arulmozhi DK, Veeranjanyulu A, Bodhankar SL, Migraine: Current Concepts And Emerging Therapies, Vascular Pharmacology, 43, 2005, 176-187.
- Kolsure PK, Raj Kapoor B, Development of Zolmitriptan Gel For Nasal Administration, Asian Journal of Pharmaceutical And Clinical Research, 5(3), 2012, 88-94.
- Raza A, Ansari TM, Niazi SB, A Novel Spectrophotometric Method For The Determination Of Zolmitriptan In Pharmaceutical Formulations, Journal Of The Chinese Chemical Society, 54, 2007, 1413-1417.
- Humaira S, Raghavendra Rao NG, Munde MR, Validated UV Spectroscopic Method For Estimation Of Zolmitriptan From Tablet Formulations, International Journal Of Biomedical And Advance Research, 1(3), 2010, 82-87.
- Prajapati PA, Poddar SS, Patel MM, Patel BK, Ophthalmic Minitablet With Natural Polymer: *Sterculia foetida* Gum, Scholar Research Library, 2 (1), 2010, 467-474.
- Nayak RK, Patil SR, Patil MB, Bhat M, Evaluation Of Disintegrating Properties Of *Mangifera Indica* Gum, RGUHS Journal Of Pharmaceutical Sciences, 1(1), 2011, 11-21.
- Nayak RK, Narayana Swammy VB, Senthil A, Mahalaxmi R, An In-Vitro Evaluation Of *Mangifera Indica* Gum As A Potential Excipients For Oral Controlled Released Matrix Tablet, Pharmacologyonline, 2, 2011, 360-391.
- Paul OA, Physicochemical Properties and Rheological Behaviour of *Ficus glumosa* Gum in Aqueous Solution, International Journal of Modern Chemistry, 2(3), 2012, 84-99.
- Prasannaraju Y, Asuntha G, Satyanadam S, Ramana Murthy KV, A Study on Physical Characterization of Hupu Gum, a Natural Polysaccharide for Pharmaceutical use, JITPS, 2 (6), 2011, 174-183.
- Mandlik SK, Adhikari S, Ranpise NS, Formulation And In-Vitro Characterization Of Chitosan Biodegradable Nanoparticles Of Zolmitriptan For Migraine Treatment, International Journal of Comprehensive Pharmacy, 1(5), 2013, 1-5.
- Sherman Hsu CP, Handbook of Instrumental Techniques for Analytical Chemistry, Infrared Spectroscopy, 15, 247-283.
- Ohannesian L, Anthony JS, Drugs and the Pharmaceutical Sciences, Handbook of Pharmaceutical Analysis, 117, 1-10.
- Kumari A, Sharma N, Sharma PK, Goyal N, Rheological Evaluation of Thermoreversible And Mucoadhesive Nasal

- Gels Of Zolmitriptan, European Review For Medical And Pharmacological Sciences, 16, 2012, 1022-1027.
24. Kumar MV, Aravindram AS, Rohitash K, Gowda DV, Parjanya K, Formulation And Evaluation Of *In-Situ* Gel Of Bromhexine Hydrochloride For Nasal Delivery, Pelagia Research Library, 3(6), 2012, 699-707.
25. Patel M, Thakkar H, Kasture PV, Preparation and Evaluation Of Thermoreversible Formulations Of Flunarizine Hydrochloride For Nasal Delivery, International Journal Of Pharmacy And Pharmaceutical Sciences, 2(4), 2010, 116-120.
26. Chaudhari P, Ajab A, Malpure P, Kolsure P, Sanap D, Development and In Vitro Evaluation of Thermoreversible Nasal Gel Formulations of Rizatriptan Benzoate, Indian Journal of Pharmaceutical Education & Research, 43(1), 2009, 55-62.
27. Jaiswal J, Anantvar SP, Narkhede MR, Gore SV, Mehta K, Formulation And Evaluation Of Thermoreversible *In-Situ* Nasal Gel Of Metoprolol Succinate, International Journal Of Pharmacy And Pharmaceutical Sciences, 4(3), 2012, 96-102.
28. Athare AB, Rohamare P, Mahale N, Chaudhary S, Formulation and Evaluation Of Eletriptan Hydrobromide Thermoreversibal Nasal In-Situ Gel, International Journal of Pharmaceutical Research And Development, 4(4), 2012, 267-275.
29. Shah RA, Mehta MR, Patel DM, Patel CN, Design And Evaluation Of Ph Dependant Mucoadhesive In Situ Gel of Sodium Cromoglycate For Nasal Delivery, International Journal Of Advances In Pharmaceutical Research, 2(3), 2011, 64-77.
30. Mahajan H, Shaikh H, Gattani S, Nerkar P, *In-situ* gelling system based on thiolated gellum gum a new carrier for nasal administration of dimenhydrinate, International Journal Of Pharmaceutical Sciences And Nanotechnology, 2(2), 2009, 544-550.
31. Uttarwar S, Formulation And Development Of *In Situ* Gelling System For Nasal Administration For An Antiemetic Drug Ondansetron Hydrochloride By Using Pluronic 127P And Pluronic 68, International Journal Of Research In Pharmaceutical And Biomedical Sciences, 3 (3), 2012, 1103-1118.
32. Parmar V, Lumbhania N, Design And Evaluation Of Ph-triggered Metoclopramide Hydrochloride Mucoadhesive In Situ Nasal Gelling System, International Journal Of Pharmaceutical Research & Development, 4(7), 2012, 79-91.

Source of Support: Nil, Conflict of Interest: None.

