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Preparation and Evaluation of Sumatriptan Succinate In-Situ Gels

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ABSTRACT

The ‘in situ gel’ system has emerged as one of the best novel drug delivery systems; it helps for the sustained and controlled release of drugs by its special characteristic feature of the ‘Sol to Gel’ transition. In this research work an attempt was made to formulate and evaluate *in-situ* gel for the intranasal delivery of Sumatriptan succinate (STS) for the effective treatment of migraines. Thermally gelling *in-situ* gel formulations for nasal administration were prepared by using polymers such as Polyvinyl Pyrolide (PVP K30), Poloxamer188 &Carbomer 940 in varying concentrations by using cold technique. The formulated *in-situ* gels were evaluated for clarity, pH, gelation temperature, and gel strength, viscosity, and drug content and *in-vitro* drug diffusion studies. The drug-polymer compatibility was determined by using FTIR studies. Further, the drug release data obtained from the formulations were fitted to various kinetic models such as zero order, first order and Higuchi matrix kinetic models. From these findings, it can be concluded that *in situ* nasal gels may be potential drug delivery systems for sumatriptan succinate to overcome first-pass metabolism and thereby to improve the bioavailability.

INTRODUCTION

The nasal route is an important mode of drug delivery, with a growing number of products available for administration through the route for systemic and local administration. In-situ gel is a new dosage form that has been applied in nasal drug delivery recently[1]. Compared with liquid nasal formulation nasal in-situ gels are instilled as low viscosity solution into the nasal cavity. Upon contact with the nasal mucosa, the polymer changes conformation producing a gel. So that it not only prolongs the contact time between the drug and the absorptive site in the nasal cavity, but also releases the drug slowly. Gel is the state between liquid and solid, which consists of physically cross-linked networks of long polymer molecules, with liquid molecules trapped within a three-dimensional polymeric network swollen by a solvent. Before administration, the *in-situ* gelling system is a liquid aqueous solution and it converts into gel at physiological conditions [2].

Prolonged and sustained release of the drug is reproducible, and in-situ gel is biocompatible, with magnificent stability and reliable quantities of medication, making it more accurate. There are various routes for in situ gel drug delivery, for, example, oral, ocular, vaginal, rectal, intravenous, intraperitoneal, etc. Gelation happens through crosslinking of the polymer chain, which can be attained through covalent bond formation (chemical crosslinking) or non-covalent bond formation (physical crosslinking). Different mechanisms exist which provoke the formation of in-situ gels, such as those based on physiologic stimuli (e.g. temperature modifications, pH-triggered systems), those based on physical changes in biomaterials (e.g. Solvent exchange and swelling), and those based on chemical reactions (e.g. UV radiation, ionic crosslinking and ion activated systems). In-situ gel formulation is executed for targeted delivery through the vaginal and rectal routes, and the nasal mucosa, circumventing the hepatic first-pass metabolism, which is important for the delivery of proteins and peptides that are usually administered via the intravenous route because of their susceptibility to the gastrointestinal protease [3].

Migraine is a neurological disorder, which is often characterized by recurrent attacks accompanied by primary symptoms, gastrointestinal, headache, neurologic, and sometimes aural symptoms [4,5]. Migraine is one of the most common disorders in the world [6]. It is the second most common cause of the short-period absence of non-manual workers [7]. Migraine has been treated by many drug formulations; however, accompanying limitations with drug delivery systems have proved a major obstacle. The nasal drug delivery system may be

affected by many factors; the capacity of the nasal cavity for the drug volume (<0.2 mL), anterior leakage, and mucociliary clearance [8-9].

Two types of drugs can be used for treating migraine; one of them is preventive and the other is abortive. Abortive drugs, including triptans (e.g. sumatriptan citrate), target serotonin receptor (5-HT receptor). Moreover, sumatriptan succinate (STS) inhibits calcitonin gene-related peptide. STS is administered in different routes such as oral, intranasal and subcutaneous (s.c) routes. However, its oral administration or intranasal application is limited because of low absolute bioavailability, pre-systemic breakdown, and incomplete absorption. Despite the absolute bioavailability of the parenteral formulation of STS being high (96%), its parenteral formulation is inconvenient. In this sense, intranasal formulations can be developed to overcome the reasons of low bioavailability of STS. High vascular mucous membranes of the nose facilitate rapid absorption of the un-metabolized drug to the central nervous system[10]. Recently, novel studies have been carried out to enhance bioavailability, such as solid dispersion, liposomes, chitosan microparticles, polymeric lipid-core nanocapsules, and lipid vesicle. The present study was aimed to develop in situ nasal gel containing sumatriptan with enhanced drug loading and Trans nasal permeation properties, which were achieved by improving drug solubility and permeability.

MATERIALS AND METHODS

MATERIALS

Sumatriptan Succinate was obtained as a gift sample from M/S Life Line Formulations., Vijayawada. Polyvinyl Pyrolide, Merck Ltd., Mumbai.Poloxamer and Carbomerwere procured from LobaChemie Pvt Ltd. Benzalkonium Chloride was procured from S.D Fine Chem. Ltd., Mumbai.

ESTIMATION OF SUMATRIPTAN SUCCINATE

Several methods have been reported for the estimation of sumatriptan succinate by spectrophotometric and chromatographic techniques. In the present study a simple, sensitive more accurate spectrophotometric method was used for the estimation of sumatriptan succinate. The absorbance values of sumatriptan were measured at a λ_{max} of 289 nm.

Preparation of standard stock solution:

100 mg of Sumatriptan Succinate was accurately weighed and dissolved in small amount of 7.4pH in 100 ml volumetric flask and then the volume was adjusted with water resultant solution giving the concentration of 1mg/ml ie.1000 µg/ml (stock –I solution). From this 10 ml solution was taken and then diluted up to 100 ml with the same solvent in a volumetric flask and then the concentration of this stock was 100µg/ml (II stock solution).

Determination of absorbance maxima (λmax):

The stock solution was further diluted this solution was then scanned at a wavelength of 200 to 400 nm against blank. The wavelength of maximum absorbance was found at 289 nm which is used for the preparation of the calibration curve.

Preparation of Calibration Curve:

100 mg Sumatriptan Succinate of was accurately weighed and dissolved in a small amount of 7.4pH in 100 ml volumetric flask and then the volume was adjusted with 7.4pH, the resultant solution gives the concentration of 1mg/ml ie.1000 µg/ml (stock –I solution). From this 10 ml solution was taken and then diluted up to 100 ml with the same solvent in a volumetric flask and then the concentration of this stock will be 100µg/ml (II stock solution). From this II stock solution, 2, 4,6,8 & 10ml solutions were pipetted and the volume was made to 100 ml using water as a solvent to get concentrations 2, 4,6,8 &10 respectively. The absorbance of these solutions was measured at 289nm. the standard calibration curve was obtained for data of concentration vs absorbance; standard calibration curve data reported in (Table no.1, Figure no.1).

Saturated Solubility Studies:

Saturated solubility studies of sumatriptan were performed in different dissolution media. 100 mg of sumatriptan was weighed and transferred into different conical flasks.10ml of different dissolution media were transferred into an individual conical flask and were closed appropriately. All the conical flasks were placed in the REMI incubator shaker. The shaker was allowed to operate at 50 rpm at 37º C ± 1º C for 24 hrs. The clear solution obtained by filtration was suitably diluted with appropriate dissolution media and the absorbance values were noted at 289 nm by using the corresponding dissolution media as blank solution**.**

Preformulation Studies:

The drug sumatriptan and polymer/excipient interaction studies were evaluated by checking the physical appearance, drug content and analytical methods.

Preparation of In-Situ Gels:

In situ gels were prepared by using cold technique. Briefly, poloxamer 188 and carbomer 940 were weighed in screw cap vials, containing a calculated amount of double distilled water with 0.002% w/v benzalkonium chloride, as preservative and was kept at 4°C until a clear solution was obtained. Then a blend of selected mixed solubilizers was added such that the concentration ranged from 15% w/w-25% w/w. Then the selected aqueous mixed solvent blend containing a specified amount of sumatriptan and Polyvinylpyrrolidone dissolve in few ml of distilled water and it was added to the above solution. The preparation was mixed thoroughly on magnetic stirrer with a magnetic bar in the beaker to make the homogeneous gel form and was stored at 4°C composition was given in table 2.

Evaluation studies of sumatriptan in- situ gels

Physico-chemical properties of Sumatriptan Succinate in situ nasal gel:

The in situ nasal gel was evaluated for physicochemical properties like pH, clarity, viscosity and drug content. The pH of the formulation was determined by using pH meter (Lab India) which should be comparable as that of nasal cavity pH (6.0−6.4). The clarity was observed against white and black backgrounds.

pH Determination:

pH of each formulation was measured using pH meter which was previously calibrated using standard buffers of pH 4, 7 & 9.

Clarity:

The developed formulations were inspected visually for clarity, colour in sol and gel form against white background and for any particulate matter if present.

Measurement of Gelation Temperature:

It was determined by using modified miller and Donovan techniques. A 2ml aliquot of the formulation was taken into test tubes which were placed in water bath at 4°C. The temperature of water bath was increased in the increment of 1°C. The samples were examined for gelation, which was said to have occurred when the meniscus would follow Non Newtonian flow upon Filling.

Rheological studies:

Determination of the developed domperidone in situ gel formulation was done using a Brookfield viscometer (LV D III model) using spindle number seven. Viscosity was determined at two temperatures, at room temperature i.e. 25±0.5°C and at transition temperature (body temperature) i.e. 37±0.5°C. Viscosity of the sample solution was measured over a range of 0.3 to 30 rpm speed. The hierarchy of speed was reversed from 30 to 0.3 rpm. The average of the two dial readings was used to calculate the viscosity. To evaluate viscosity change at cool conditions and at body temperature, rheological measurements were taken after increasing the temperature of nasal in situ gel to 37±0.5°C.

Drug Content Estimation:

1 ml formulation was taken in 10 ml volumetric flask and then diluted using 7.4pH. Again 1 ml quantity from this solution was taken and diluted with 10 ml of 7.4pH. Finally, the absorbance of the prepared solution was measured at 289 nm against blank reagent using UV visible spectrophotometer (Lab India 3200+). Finally, the concentration of the drug present in the formulation was computed with the help of a calibration curve.

In vitro drug release:

In Vitro drug release of formulated gels were carried out in two-chambered Franz diffusion cell at room temperature by using dialysis membrane-70 with molecular weight cut off 1200-1400KDa. The artificial membrane was soaked in phosphate buffer 7.4 for 2 hrs before maintaining on the diffusion cell. 20ml of Phosphate buffer 7.4 was placed in receptor compartment. The position of donor compartment was adjusted so that dialysis membrane just touches the diffusion medium. An aliquot of 2ml sample was withdrawn from receiver compartment at periodic time intervals of 30mins, 1, 2, 3, 4, 5 etc., and replace with same amount of fresh medium with drawn aliquots were suitably diluted and analyzed using UV

Spectrophotometer at 289nm for drug. The drug release profiles and values are shown in table 3 and figure 2.

RESULT AND DISCUSSION:

The spectrophotometric method used for the estimation of sumatriptan succinate in different dissolution media was found to be linear and reproducible. This method obeyed beer's law in the concentration range of 2-10µg/ml. The reproducibility of the method was tested by analyzing 6 separately weighed samples of sumatriptan. Thus, the method was found to be suitable for the estimation of sumatriptan in dissolution media. The calibration curve of sumatriptan in water was given in table 1 and shown as figure 1.

Table No 1: Calibration Data for the Estimation of sumatriptan succinate

Concentration (µg/ml)	Absorbance at 289nm (Mean±S.D)
2	0.1719 ± 0.1
4	0.3621±0.2
6	0.5404 ±0.1
8	0.7288 ±0.3
10	0.8955 ±0.4

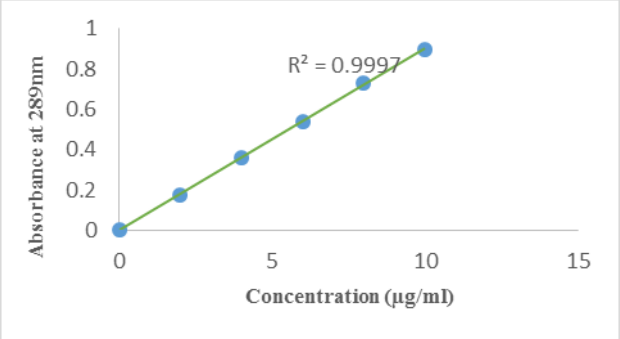

Figure 1: Calibration Curve of sumatriptan succinate

Sumatriptan Succinate belongs to class III of the biopharmaceutical classification of drugs having good solubility but low permeability and hence saturated solubility studies were performed. The solubility studies were carried out with different buffer media and along with different solubilizers. The solubilizers are used to enhance the nasal permeation of the drug.

The results of solubility studies indicated that drug showed maximum solubility in the pH 7.4 buffer media containing PVPK30 as a solubilizer.

All the formulations showed a clear appearance in the solution form. The gelling temperature of the prepared in situ nasal gels was carried out and found in the range of 34 to 35°C. The gelling point refers to the temperature when the meniscus of the formulation will not more upon slanting the test tubes, with gradual increase in the temperature. The prepared formulations are clear and transparent. The pH of the formulation ranged between 6.1 to 6.5. The pH of the dosage forms should be such that it should remain stable at that pH and at the same time it should not cause any irritation to the nasal mucosa after administration of dosage form. The pH of the formulations was determined using a precalibrated pH meter.

Table no 2: Composition of In Situ Gels of Sumatriptan Succinate

Ingredients	**SF1**	**SF 2**	**SF3**	**SF4**
Sumatriptan(mg)	10	10	10	10
PVP K30(mg)	3	3	3	3
Polaxomer 188	-	-	2.5	5
Carbomer 940	2.5	5	-	-
Preservative (0.002%)	q.s	q.s	q.s	q.s
Distilled water	q.s to 5ml	q.s to 5ml	q.s to 5ml	q.s to 5ml

Note: 1 part is equivalent to 10mg

Drug content is one of the most important attribute of dosage form because it plays prime role in the determination of the efficacy of the formulation and batch-to-batch uniformity thus makes a drug delivery system effective. The drug content of the prepared formulations was determined spectrophotometrically at 289nm and was found to be in the range of 95-99%.

All the formulations were subjected to diffusion studies using Franz diffusion cell in 7.4 pH buffer as diffusion medium. The drug release of the prepared formulations was shown in the table 3 & figure 2 & 3. The formulation SF4 showed maximum cumulative % drug release after 4hrs of drug diffusion studies when compared to other formulations.

Table no 3: In-vitro drug release studies of Sumatriptan succinate In- situ gel formulations

Time (hrs)	Cumulative % Drug Dissolved			
	SF1	SF2	SF3	SF4
1	22.50	32.94	37.7	49.75
2	38.25	45.23	47.55	57.25
3	89.41	90.2	62.03	71.25
4	-	-	91.25	96.05

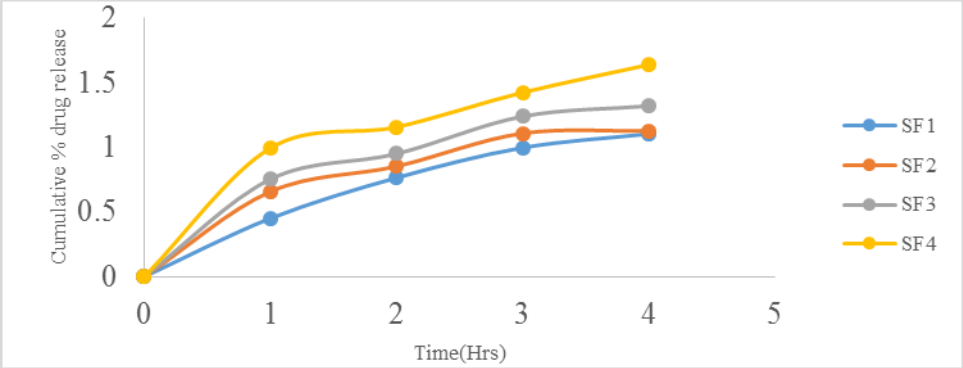

Figure 2: Dissolution profile curve of sumatriptan in-situ gel

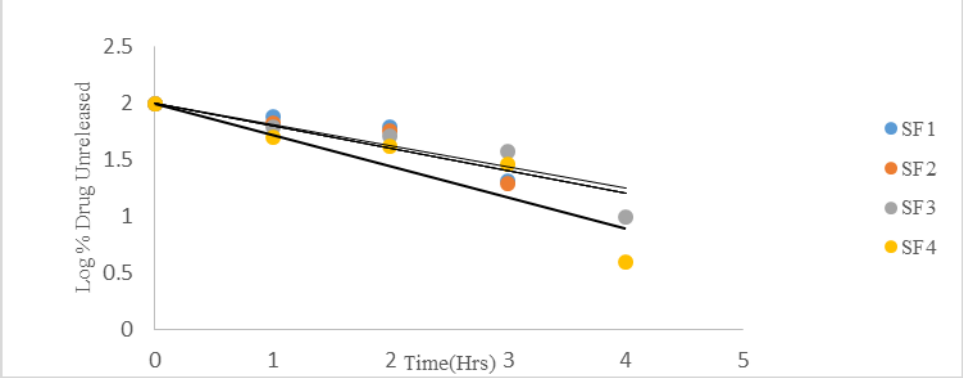

Figure 3: First-order plot for sumatriptan in-situ gel

Drug polymer interaction studies were performed by using FTIR spectroscopy to know the compatibility aspects of drug and polymers. The characteristic C-H band stretch of the carboxylic group was present in the spectrum which is stretching between 2800-3600 cm-1. N-H stretching at 3417.44 cm-1, alkane saturated peak at 2925.59 cm-1 and C=C at 1600.98 cm-1 were also observed in the obtained spectra. From the FT-IR spectra of pure drug and the combination spectra of drug with the polymers, it was observed that all the characteristic

peaks of drug are present in the combination spectra thereby indicating the compatibility of the drug with the polymers used and shown in figure 4.

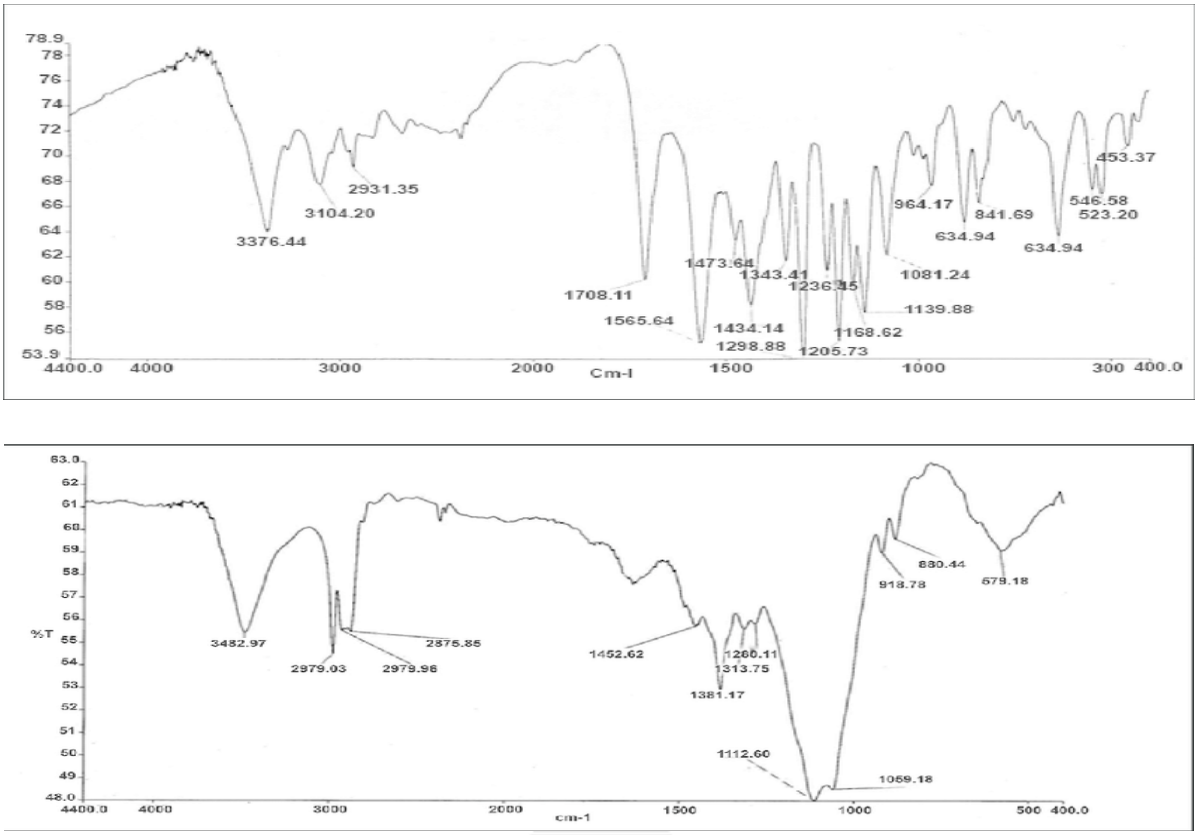

Figure 4: FTIR Spectrum of Sumatriptan succinate in-situ nasal gels (pure drug and optimised formulation)

CONCLUSION:

The project aimed to formulate the nasal in-situ gel. The nasal in-situ gels of Sumatriptan Succinate were successfully developed using poloxamer 188 and Carbomer by using cold method. The optimized concentration was proven to be a promising nasal delivery system for the antimigraine drug Sumatriptan, which would enhance nasal residence time owning to increase viscosity and mucoadhesive strength and further this type of delivery is a pleasant and painless alternative to another delivery system. Sustained and prolonged release of the drug, stability and biocompatibility characteristics make the in situ gel dosage forms exceptionally reliable. Use of biodegradable and water soluble polymers for the in situ gel formulations can make them more acceptable and excellent drug delivery systems.

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ABBREVIATIONS: Fourier Transform Infrared (FTIR), Pyrolide (PVP K30), Sumatriptan Succinate (STS), Subcutaneous (s.c)**,** UV (Ultra Visible), Kilo Daltons (KDa)

CONFLICT OF INTEREST:

The authors declare no conflict of interest.

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