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Tolerability and Consistency of Effect of Zolmitriptan Nasal Spray in a Long-Term Migraine Treatment Trial

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ABSTRACT
Migraine is an episodic brain disorder that affects 15% of general population. It is one of the very common referral to neurology clinic, highly disabling, costly and difficult to treat. Two types of treatment are available of which one is the treatment of acute attack. Another is for prophylaxis. Non specific treatment for acute attack includes aspirin, paracetamol, naproxen, ibuprofen, tolfenamic acid with or without antiemetic agents. Many patients suffer from 2 or more migraine attacks per month. Taking non specific analgesic more than 10 days per month can also produce drug induced headache. Moreover such drugs can also produce gastrointestinal (GI) intolerance. Specific treatments for migraine include ergotamine and triptans. Ergatoamine is known to have higher incidence of nausea than triptans, however, its overuse can produce dreadful headache besides various vascular problems. Triptans are very effective in acute migraine attack. Their pharmacokinetic features are excellent. There are very few studies depicting efficacy, tolerability and side effects of zolmitriptan in acute migraine attack.

I. INTRODUCTION :-

Migraine: Migraine is a common headache disorder which significantly affects about 15% of females and 6% of males. It is a neurobiological syndrome which is mainly characterized by a unilateral throbbing headache (Abrahmet al., 2006). Other major symptoms include nausea, vomiting, and sensitivity to light. During the migraine attack, blood vessels of the brain get dilated due to a decrease in the level of the vasoconstrictor known as 5-hydroxytryptamine (5-HT) which causes intense headaches (Villalon et al., 2003). Migraine is a primary headache disorder characterized by recurrent headaches that are moderate to severe. Typically, the headaches affect one half of the head, are pulsating in nature, and last from two to 72 hours. Associated symptoms may include nausea, vomiting, and sensitivity to light, sound, or smell (Roger et al., 2009) .The pain is generally made worse by physical activity. Up to one-third of people have an aura: typically a short period of visual disturbance which signals that the headache will soon occur (Roger et al., 2009) Occasionally, an aura can occur with little or no headache following it (Phillips and William et al., 2003).

Pathophysiology of migraine:

The exact pathophysiology of migraine is unknown. The prevailing theory is that a trigger (such as fatigue, stress, or certain foods) sets off a wave of brief neuronal activation, followed by a more sustained neuronal inhibition known as Cortical Spreading Depression (CSD). The exact mechanism responsible for the disorder is not known, but the head pain is related to dilatation of extra cranial blood vessels, which may be the result of chemical changes that cause spasms of intracranial vessels. The prodromes are thought to be related to constriction of the arterioles

(Terry et al., 1993). This neurovascular disorder related to dysfunctions in brainstem centers which regulate vascular tone and pain sensation. In the pathophysiology of migraine, both central and peripheral mechanism, as well as nerves and vessels are involved (Listos et al., 2013).

- ❖ Spreading depression in the cortex
- ❖ Release of Potassium
- ❖ Release of glutamate
- ❖ Pain Syndrome
- ❖ Trigeminal nucleus activated
- ❖ Calcitonin gene – related peptide (CGRP) released by trigeminal nerve
- ❖ CGRP release causes vasodilation
- ❖ Plasma protein extravasation
- ❖ causes sterile inflammation in the dura matter

Treatment of migraine:

These drugs are taken at the onset of migraine symptoms or auras to relieve a headache or reduce its severity. Taking any of these drugs

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too often can lead to a rebound headache, headaches that arise from overuse of medication, which then necessitate additional medication. If you need to use acute migraine drugs more than nine times per month, talk to your doctor about possible preventive treatments.

Painkillers: Some over-the-counter painkillers are commonly used for migraine, but many are only available in prescription strength. Aside from acetaminophen, an analgesic that only relieves pain, these drugs are non-steroidal, anti-inflammatory drugs (NSAIDs), which relieve pain and reduce inflammation:

- Acetaminophen (Excedrin, Tylenol)
- Aspirin
- Diclofenac (Cataflam)
- Ibuprofen (Advil, Motrin)
- Ketorolac (Toradol)
- Naproxen (Aleve)

Many over-the-counter drugs marketed specifically for migraine or headaches in general combine one or more of the drugs above with a small amount of caffeine, which can make them work more quickly and effectively, especially for mild migraine headaches.

Possible side effects of long-term NSAID use include:

- Heart attack
- Stroke
- Kidney damage
- Stomach ulcers

Triptans: Triptans are a newer class of drug that increases serotonin levels in your brain, reducing inflammation and constricting blood vessels, effectively ending a migraine. Triptans are available as pills, nasal sprays, injections, and tablets that dissolve under your tongue, and work quickly to stop a migraine. Some triptans are:

- Almotriptan (Axert)
- Eletriptan (Relpax)
- Frovatriptan (Frova)
- Naratriptan (Amerge)
- Nizatriptan (Maxalt, Maxalt-MLT)
- Sumatriptan (Imitrex)
- Sumatriptan and naproxen (Treximet
- Zolmitriptan (Zomig)

Nasal: The drug is administered as snuff or spray or nebulized solution in the nose; where the drug penetrates the nasal mucous membrane to reach the blood.

Advantages:

- The drug can avoid digestive juices and liver.
- Drugs are readily absorbed from this route.

Disadvantages:

- Irritant drugs cannot be administered through this route.
- E.g. Posterior pituitary powder and desmopressin are applied as snuff.

Parenteral: (Par- beyond, enteral- intestinal) Routes of drug administration other than oral route are known as parenteral route. This refers to administration by injection which takes

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drug directly into the tissue fluid or blood without having to cross the intestinal mucosa and subsequently liver.

Advantages:

- ❖ Absorption is faster and surer, hence drug can be administered rapidly and in accurate dose in time of emergencies.
- ❖ Gastric irritation and vomiting are not provoked
- ❖ It can be employed in unconscious, uncooperative or vomiting patients.
- ❖ There are no chances of interference by food or digestive juices.
- ❖ Liver is bypassed.

Disadvantages:

- ❖ The preparation has to be sterilized and is costlier.
- ❖ The injection may be painful.
- ❖ Self-medication is difficult - another trained person is required to give the injection.
- ❖ Abcess and inflammation at the site of injection may take place.

Mechanism of nasal absorption:

The first step in the absorption of drugs from the nasal cavity is the passage through the mucus. Small unchanged particles easily pass through this layer while large charged particles find it more difficult to cross. The primary protein present in mucus is mucin which has a tendency to bind to solutes which in turn hinder diffusion. Also structural changes due to environmental changes like pH, temperature, etc are also possible. The passage of drug through the mucus has been explained by several mechanisms such as trans cellular or simple diffusion across the membrane, paracellular transport which occurs between cells and transcytosis which involves vesicle carrier's cellular transport out of which two are considered important. Potential metabolisms before reaching the systemic circulation and limited residence time in the nasal cavity are the major obstacles for drug absorption.

Nasal drug delivery is one of the challenging endeavors facing the pharmaceutical scientist today. Nasal administration is significantly effective in case of oral administration of drug gives an undesirable side effect. From the pharmacokinetic standpoint, intranasal administration avoids first-pass metabolism and retards incomplete absorption in the gastrointestinal tract which leads to improve the bioavailability (Kushwaha et al., 2011).

First mechanism: Also known as paracellular transport this utilizes the aqueous route of transport and is slow and passive. This route is not suitable for the drugs having
molecular weight greater than 1000 Daltons due to poor bioavailability.

Second mechanism: Also known as trans cellular route which utilizes the lipoidal route for transport of lipophilic drugs.

Drugs also cross cell membranes by an active transport route via carrier mediated or transport through the opening of tight junctions.

Factors affecting absorption of drugs via nasal route:

- ❖ The rate of nasal secretion.
- ❖ Ciliary movement.
- ❖ Vascularity of the nose.
- ❖ Metabolism of drugs in the nasal cavity.
- ❖ Volume that can be delivered into nasal cavity is restricted 25 to 200 µl.
- ❖ Diseases affecting nasal mucous membrane.

Gel: Gel is the state which exists between solid and liquid phase. The solid component comprises a three dimensional network of inter-linked molecules which immobilizes the liquid phase.

A fast-acting transdermal gel using a proprietary formulation of the nonsteroidal anti- inflammatory drug (NSAID) ketoprofen (Topofen, Achelios Therapeutics) reduced pain severity in patients with severe migraine with and without aura compared with placebo and had few adverse effects.

In Situ Gel Delivery System:

It is a drug delivery system which is in a solution form before the administration in the body but it converts in to a gel form after the administration. There are various routs such as oral, ocular, intravenous, intraperitoneal etc.

In situ gelation is a process of gel formation at the site of action after the formulation has been applied at the site. In situ gel phenomenon based upon liquid solution of drug formulation and converted into semi-solid mucoadhesive key depot. It permits the drug must be delivered in a
liquid form or solution form.

In situ gelling systems can be classified as ion-activated systems (e.g. gellan gum and sodium alginate), temperature-dependent systems (e.g. Pluronics, Tetronics and polymethacrylates) and pH-triggered systems (e.g. Carbopol and cellulose acetate phthalate). The principal advantage of in situ gels is that they can be easily administered

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with accurate and reproducible dose compared to that of ordinary gels, have an advantage over ordinary gels that they can be easily instilled in liquid form and are capable of prolonging the residence time of the formulation on the surface of the nasal cavity due to gelling (Noha et al., 2007) (Nirmal et al.,2010).

Advantages:

- Increased residence time of drug in nasal cavity.
- Decreased frequency of drug administration.
- Results in rapid absorption and onset of effect.
- Avoids degradation of drug in gastrointestinal tract resulting from acidic or enzymatic degradation.
- Low dose required.
- Minimized local and systemic side effects.
- Improved bio-ability of drug.
- Direct transport into systemic circulation and CNS, is possible.
- Offers lower risk of overdose of CNS acting drug
- Improved patient compliance.

Properties of Nasal In-Situ Gel:

It should be low viscous.

It should be free flowing to allow for reproducible administration to the nasal cavity, as droplet mist or as a spray.

Nasal in–situ gel should have long residence time.

The nasal in–situ gel follows phase transition mechanism and to stand with the shear forces in the nasal cavity.

Polymer used in situ gel drug delivery system:

For achieving better drug product effectiveness, reliability we select appropriate polymer for the formulation. Material that show sol to gel transition in aqueous solution used in in situ gelation. Some example of polymers are capable of in situ gelation such as poloxamer, pluronics, various copopolymers such as PEO-PLLA and PEG-PLGA-PEG. Pectin, gelrite, cellulose acetophalate latex, gellan gum, alginate, matrigel, carbopol, chitin. The gel formation is induced by temperature change poloxamer, cellulose acetophalate latex, carbopol gelation induced by pH change.

Pluronics or Poloxamers:

These are a class of thermo reversible gels that have the capacity to make, break and modify the bonds responsible for holding the network together. There are different classes of Pluronics (pluronic F-127, F-188 etc.).Their thermo reversible property make them useful as a carrier for most routes of administration including oral, topical, intranasal, vaginal, rectal, ocular and parenteral routes.

PREFORMULATION STUDY OF DURG

Physical appearance: White crystalline powder.

Solubility study:

Solubility of Zolmitriptan was checked qualitatively in methanol, ethanol, phosphate buffer (pH 6.8) and Distilled water. The drug zolmitriptan was found to be freely soluble in phosphatebuffer (pH 6.8) and distilled water, and slightly insoluble in methanol and insoluble in ether or ethanol.

Table : Solubility of zolmitriptan in different solvents

S. No.	Solvents	Solubility
1.	Phosphate buffer (pH 6.4)	Soluble
2.	Distilled water	Soluble
3.	Methanol	Slightly insoluble
4.	Ethanol	Insoluble
5.	Ether	Insoluble

Melting point: It is one of the parameters for the purity of drugs. In case of pure chemicals, melting points are very sharp and constant. Melting point of zolmitriptan was measured in a programmable melting point apparatus that was found to be 138-142°C with decomposition.

Partition coefficient: The partition coefficient of the zolmitriptan in water and n-octanol was found to be 1.6.

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Table: Result of Melting Point and Partition Coefficient

S. No.	Drug	Melting Point (°C)	Partition Coefficient
1.	Zolmitriptan	138-142	1.6

FT-IR study: Identification and authentication of drug sample was done by infrared spectroscopy. The principal group of infrared spectroscopy showed that the drug sample was authentic

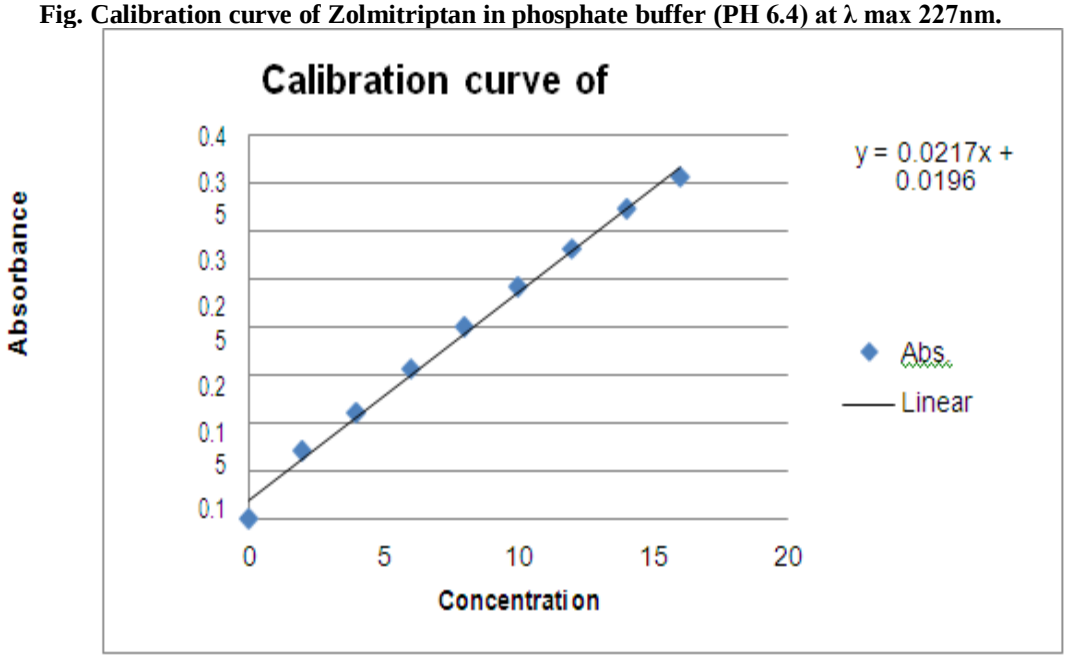
Fig. IR spectrum of Zolmitriptan

Table : Characteristic IR absorption bands of zolmitriptan

S. No.	Wave Number (cm^{-1})	Characteristic Abs.
1.	3411.11	N-H Stretching
2.	1420.41	C-H Stretching
3.	1703.98	C=O Stretching
4.	1320.11	C-N Stretching
5.	910.05	Aromatic ring

Standard curve & ƛ max determination: Standard calibration curve was plotted for Zolmitriptan linearity of graph show that the drug follow the **Lambert Beer's law.**
Zolmitriptan sloution was scanned in U.V range of 200-800 nm using u.v visible spectrophotometer to obtain the ƛ max. while identifing in U.V spectroscopy it show maximum wavelength ƛ max 227 nm.

Fig. Calibration curve of Zolmitriptan in phosphate buffer (PH 6.4) at λ max 227nm.



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EVALUATION OF PLACEBO OPTIMIZED FORMULATION

Various parameters like effect of HPMC and effect of Xanthan gum were used to optimize pH value, viscosity and gelling capacity.

Effect of HPMC:

In order to investigate the effect of HPMC on formulation of F1-F5, (0.10, 0.20, 0.30, 0.40, 0.50 %) five concentration were used. Increase in the concentration of HPMC was observed an increase of the viscosity, because HPMC polymer are used for muco-adhesive or viscosity enhances properties of formulation. And also changes in the pH value and also increase of the gelling capacity. Best result was found in formulation F2 having concentration of HPMC 0.20%, pH value 5.82 and viscosity 2.9 and gelling capacity (+ +) show in table no.8.2.

Effect of Xanthan gum:

In order to investigate the effect of xanthan gum on formulation of F6-F10, (0.10, 0.20, 0.30, 0.40, 0.50 %) five concentration were used. Increase in the concentration of xanthan gum was observed an increase of the viscosity, because Xanthan gum polymer are used for thegelation and viscosity enhances properties of formulation. And changes in the pH value and also increase of the gelling capacity. Best result was found in formulation F8 having concentration of xanthan gum 0.30%, pH value 5.82 and viscosity 2.9 and gelling capacity (+ +) show in tableno.8.3.

Effect of PEG 4000:

In order to investigate the effect of PEG 4000 on formulation of F11-F15, (1.0, 2.0, 3.0, 4.0, 5.0 %) five concentration were used. PEG 4000 polymer are used as a surfactant and co-solvent so that increase in the concentration of PEG 4000 was observed decrease of the viscosity, changes in the pH value and also changes of the gelling capacity. Best result was found in formulation F12 having concentration of PEG 4000 2.0%, pH value 5.82 and viscosity 2.9 and gelling capacity (+ +) show in table no.8.4.

DRUG LOADED IN SITU GEL FORMULATION CHARACTERIZATION

Clarity:

Clarity of one of the most important feature of in situ gel. The in situ gel formulation were evaluated for clarity by visual observation against a black or white background.

pH value:

The pH of in situ gel formulation was found to be 5.72, which in desirable nasal (4.50-6.50)pH range.

Viscosity:

Viscosity values obtained for in situ gel formulation was 3.1 using Brookfield viscometer. Formulation (FA-01) containing sumatriptan succinate 2.5% and xanthan gum 0.30% w/v and HPMC 0.20% w/v or PEG 4000 2.0% exhibited optimum viscosity.

Gelling capacity:

The gelling capacity of prepared formulations presented in Table 10.5.

Table: Coding for gelling capacity

S. No	Observation	Coding
1.	No gelation	-
2.	Gelation occurred in few min & remained for few hours	+
3.	Gelation immediate, remained for few hours	+ +
4.	Gelation immediate, and for extended period	+ + +
5.	Very stiff gel	+ + + +

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Table : Result of different parameters

Formulation code	Clarity	pH value	Viscosity (cps)	Gelling Capacity
FA-01	Clear	5.72	3.1	+ +

Spreadability:
It is very important for in situ gel to have suitable spreadability to administer easily and tospread easily on nasal mucosa without leakage after administration. Formulation (FA-01) shows (18.462±0.102cm^2/min) maximum spreadability due to more surface area covered by in situ gel after placing on filter paper.

Gel strength:
Gel strength of the formulation was found to be 7.2 g/s.

Drug content:
The final formulations reflected fairly uniform drug content ensuring adequacy in the method of preparation of the in situ gel. Drug content was found to be within the range of 80-99%.

Table: Result of Gel Strength, Drug Content

Formulation Code	Gel strength (g/s)	Spreadability (cm^2/min)	Drug Content %
FA-01	7.2	18.462±0.102	89.33

In vitro drug release study:
For the estimation of in vitro drug release study was performed in situ gel loaded with drug. The cumulative percentage drug release for model drug (Zolmitriptan) were carried out over a period of 8 hrs.

Table: Drug Release for optimized formulation

Sr. No	Time (T) mint	% Cumulative drug release
1.	0	0
2.	30	12.60
3.	60	25.07
4.	120	35.04
5.	180	45.07
6.	240	53.07
7.	300	64.06
8.	360	74.02
9.	420	84.95

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Data treatment:

The release of drug from in situ gel complicated. It involves drug diffusion, interface movement and various interaction. The release rate process is describe simply by comparing the correction coefficient value of lines collected from the graphical presentation of different mathematical models. In order to determine the mechanism of drug release from the drug loaded in situ gel, the data were treated using following mathematical models.

1. Cumulative percentage of drug release versus time (Zero order)
2. Log percentage of drug unreleased versus time (First order)
3. Cumulative percentage of drug release versus square root of time (Higuchi squareroot law)
4. Log of cumulative percentage of drug release versus log time (Koresmeyer's Peppas model)

The release data was plotted according to the following equations,

- Zero order: $M = M0 - K0t$
- First order: $LogC = Log\ Q0 + Kt/2.303$
- Higuchi square root law: $Q = Kt^n$
- Koresmeyer'sPeppas model: $Mt/M\infty = Kt^n$

Where M, C and Q is amount of drug released at time t, M0, and C0 is the total amount of drug & K0, K and k are corresponding rate constants. In case of Koresmeyer'sPeppas model, Mt/M∞ is the fractional drug release at time t, k is constant incorporating the properties of macromolecular polymeric system and the drug, n is a kinetic constant which is used to characterize the transport mechanism.

Table: Cumulative % drug release and log cumulative % drug release profile of in situ gel

S. No.	Time (T) Hours	Root T	Log T	Cumulative % drug release of in situ gel		Log Cumulative % drug release of in situ gel	
				Release	Remaining	Release	Remaining
1.	0	00	00	0	100	0	100
2.	1	1	0	4.85	95.15	0.68	1.97
3.	2	1.41	0.30	9.00	91.00	0.95	1.95
4.	3	1.73	0.48	17.38	82.62	1.24	1.91
5.	4	2	0.60	29.08	70.92	1.46	1.85
6.	5	2.24	0.70	44.41	55.59	1.64	1.74
7.	6	2.45	0.78	52.63	47.37	1.72	1.67
8.	7	2.65	0.85	69.80	30.2	1.84	1.48
9.	8	2.83	0.90	83.93	16.07	1.92	1.20

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Fig: Zero order plot of optimized formulation withdrug

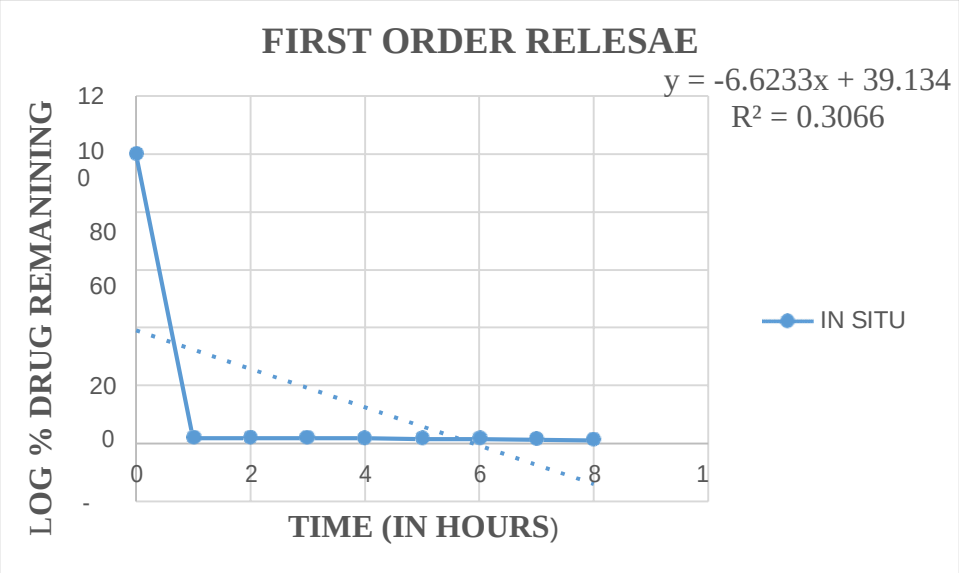

Fig: First order plot of optimized formulation withdrug

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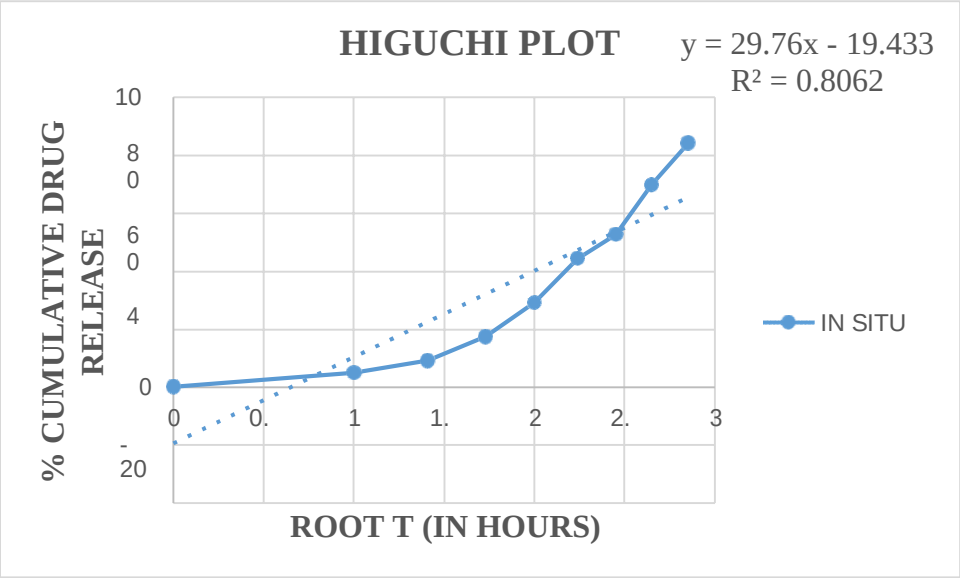

Fig: Higuchi diffusion plot of optimized formulation with drug

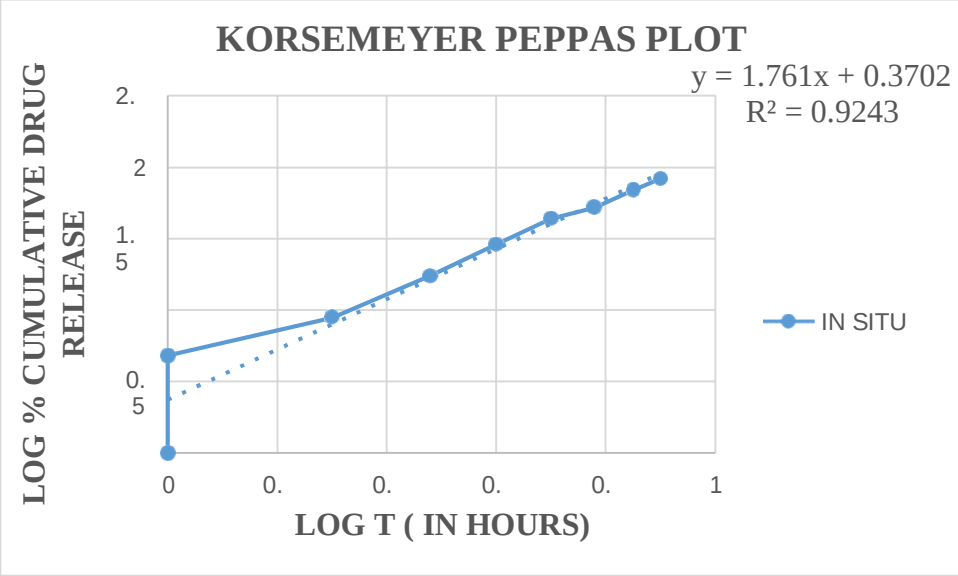

Fig: Korsemeyer's peppas plot of optimized formulation with drug

Release data showed that maximum drug release was as 83.93 % in 8 hours. The release rate is describe simply by comparing the correction coefficient value of lines collected from the graphical presentation of different models. The correction coefficient value of different mathematical models of in situ gel data is given below.

Table: r^2 value of optimized formulation

CORRELATION COEFFICIENT

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S. NO	KINETICS MODELS	IN SITU GEL
1.	**Zero order plot**	**0.9682**
2.	First order plot	0.3066
3.	Higuchi plot	0.8031
4.	Korsemeyer's plot	0.9243

From the correlation coefficient value of different mathematical models, obtained data show that in situ gel loaded with drug (sumatriptan) follow the Zero order plot because its r^2 value is0.9682 which was very near to unity it mean drug release follow the zero order model, in which the drug release occurs by diffusion process from the in situ gel, so it was selected as best fit model.
an artificial skin has also been reported. Poloxamer 407 (PF-127) is a non-ionic surfactant composed of polyoxypropylene copolymers in a concentration ranging from 20-30%. These polymers are produced by condensation of ethylene oxide and propylene oxide. These are white, waxy, free flowing granules that are practically odorless and tasteless. Reverse thermal gelation and low toxicity have been the basis of research into the use of PF-127 as a possible drug delivery system in man.

Following considerations while selecting a thermo reversible polymer for nasal administration:

- Quick transition from liquid to solid upon temperature change: this keeps the gel to stay at the site.
- Prevent the wastage of dosage form from the applied site.
- Solid- to- gel state reversible property of polymer may be adjusted from temporary to permanent by changing its chemical composition.
- Increase drug concentration at the site of deposition

Carbopol:

They are very high molecular weight polymers of acrylic acid and are used mainly in liquid or semi-solid pharmaceutical formulations such as gels, suspensions and emulsions, as a thickening and viscosity agent in order to modify the flow characteristics. They are also used for mucoadhesive properties and a relevant amount of work has been done on the bioadhesive potential of carbopol polymers. Carbopol are used in formulations for ophthalmic, rectal, buccal, nasal, intestinal, vaginal and topical preparations. Carbopol gels are prepared by the dispersion of polymers in water. In which it swellsupto1000 times the original volume (BF Good rich hand book) and neutralizes the system. It permits the ionization of the carboxylic groups and as a result strong gel forms.

Chitosan:

Chitosan is a biodegradable, thermo sensitive, poly cationic polymer obtained by alkaline deacetylation of chitin, a natural component of shrimp and crab shell. Chitosan is a biocompatible pH dependent cationic polymer, which remains dissolved in aqueous solutions up to a pH of 6.2. Neutralization of chitosan aqueous solution to a pH exceeding 6.2 leads to the formation of a hydrated gel like precipitate. The pH gelling cationic polysaccharides solution are transformed into thermally sensitive pH dependent gel forming aqueous solutions, without any chemical modification or cross linking by addition of polyol salts bearing a single anionic head such as glycerol, sorbitol, fructose or glucose phosphate salts to chitosan aqueous solution.

Gellan gum:

Gellan gum (commercially available as Gelrite TM or Kelcogel TM) is an anionic deacetylated exocellular polysaccharide secreted by Pseudomonas elodea with at etrasaccharide repeating unit of one α-L-rhamnose, one β-D-glucuronic acid and two β-D-glucuronic acid residues. It has the tendency of gelation which is temperature dependent or cations induced. This gelation involves the formation of double helical junction zones followed by aggregation of the double helical segments to form a three-dimensional network by complexation with cations and hydrogen bonding with water. The formulation

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consisted of gellan solution with calcium chloride and sodium citrate complex. When administered orally, the calcium ions are released in acidic environment of stomach leading to gelation of gellan thus forming a gel in situ.

Xanthan gum:

Xanthan gum is a high molecular weight extra cellular polysaccharide produced by the fermentation of the gram-negative bacterium Xanthomonas campestris. The primary structure of this naturally produced cellulose derivative contains a cellulosic backbone (β- D-glucoseresidues) and a trisaccharide side chain of β-D-mannose-β-D-glucuronicacid- α- D - mannose attached with alternate glucose residues of the main chain.

Alginic acid:

It is a linear block copolymer polysaccharide consisting of β-D-mannuronic acid and α-L- glucuronic acid residues joined by 1, 4-glycosidic linkages. The proportion of each block and the arrangement of blocks along the molecule vary depending on the algal source. Dilute aqueous solutions of alginates form firm gels on addition of di and trivalent metal ions by a cooperative process involving consecutive glucuronic residues in the α-L glucuronic acid blocks of the alginate chain. Alginic acid can be chosen as a vehicle for ophthalmic formulations, since it exhibits favorable biological properties such as biodegrade ability and nontoxicity. A prolonged precorneal residence of formulations containing alginic acid was looked for, not only based on its ability to gel in the eye, but also because of its mucoadhesiveproperties.

HPMC:

Hypromellose (INN), short for hydroxypropyl methylcellulose (HPMC), is a semisynthetic, inert, viscoelastic polymer used as eye drops, as well as an excipient and controlled-delivery component in oral medicaments, found in a variety of commercial products.(Silva & Olver et al 2005).

As a food additives, hypromellose is an emulsifier, thickening and suspending agent, and an alternative to animal gelatin.Its Codex Alimentarius code (Enumber) is E464.Hypromellose is a solid, and is a slightly off-white to beige powder in appearance and may be formed into granules. The compound forms colloidswhen dissolved in water. This non-toxic ingredient is combustible and can react vigorously with oxidising agents.

Hypromellose in an aqueous solution, unlike methylcellulose, exhibits a thermal gelation property. That is, when the solution heats up to a critical temperature, the solution congeals into a non-flowable but semi-flexible mass. Typically, this critical (congealing) temperature is inversely related to both the solution concentration of HPMC and the concentration of the methoxy group within the HPMC molecule (which in turn depends on both the degree of substitution of the methoxy group and the molar substitution. That is, the higher the concentration of the methoxy group, the lower the critical temperature. The inflexibility/viscosity of the resulting mass, however, is directly related to the concentration of the methoxy group (the higher the concentration, the more viscous or less flexible the resulting mass is) (Williams, Sykora & Mahaguna et al 2001).

1.10.8 PEG 4000:

Polyethylene glycol (PEG) is a polyether compound with many applications from industrial manufacturing to medicine. PEG is also known as polyethylene oxide (PEO) or polyoxyethylene (POE), depending on its molecular weight. The structure of PEG is commonly expressed as H-($O-CH_2-CH_2$)$_n$−OH.(Kahovec & Hatada, et al 2002)

PEG is generally considered biologically inert and safe. However, studies of clinical safety are generally based on adults, not children. The FDA has been asked to investigate the possible effects of PEG in laxatives for children.Also, a minority of people are allergic to it. Allergy to PEG is usually discovered after a person has been diagnosed with an allergy to an increasing number of seemingly unrelated products, including processed foods, cosmetics, drugs, and other substances that contain PEG or were manufactured with PEG.When PEG is chemically attached to therapeutic molecules (such as protein drugs or nanoparticles), it can sometimes be immunogenic, stimulating an anti-PEG antibody response in some patients. This effect has only been shown for a few of the many available PEGylated therapeutics, but it has significant effects on clinical outcomes of affected patients. Other than these few instances where patients have anti-PEG immune responses, it is generally considered to be a safe component of drug formulations.(Banville et al, 2017).

PEG is the basis of a number of laxatives. Whole bowel irrigation with polyethylene glycol and added electrolytes is used for bowel preparation before surgery or

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colonoscopy. PEG is also used as an excipient in many pharmaceutical products. When attached to various protein medications, polyethylene glycol allows a slowed clearance of the carried protein from the blood.

II. SUMMARY AND CONCLUSION

The aim of the research was to prepare and characterize nasal in situ gels comprising of drug zolmitriptan in order to enhance the absorption and bioavailability of zolmitriptan through nasal route of administration. The solubility studies of zolmitriptan was checked qualitatively in different polar and non-polar solvents. The zolmitriptan was found to be freely soluble in distilled water and phosphate buffer (pH 6.4) and slightly soluble in ethanol.

Optimization of the formulation was done by varying the concentration of HPMC, concentration of xanthan gum, concentration of PEG 4000 and the response were recorded in terms of pH value, viscosity and gelling capacity, which was determine by using digital pH meter and brookfield viscometer and gelling capacity was observed visibly in black or white background. Different formulations of various composition were prepared for optimization among which F2 and F8 and F12 show best response. Based on the optimized parameters drug loaded formulation was prepared. The drug loaded formulation (FA-01) was characterized for clarity, pH value, viscosity,
% drug content and results showed that pH value was 5.72 and viscosity was 3.1 cps and % drug content was 89.33% respectively.
The in vitro drug release study of in situ gel for the estimation of drug release and cumulative percentage release of model drug (zolmitriptan) for in situ gel formulation carried out over a period of 8 hours. Release data show that maximum drug release was obtained as 83.93 % in 8 hours, while the burst release was found as 17.38 % in 4 hours.
From the correlation coefficient value of different mathematical models, obtained data show that in situ gel loaded with drug (zolmitriptan) follow the Zero order equation because its r^2 value is 0.9682 which was very near to unity it mean drug release follow the Zero order model, in which the drug release occurs by diffusion process from the in situ gel, so it was selected as best fit model.

Future scope

In conclusion, zolmitriptan based novel in situ gels can be developed to overcome the first-pass metabolism and enhance the subsequent low bioavailability of the drug and to bring about complete absorption from the nasal mucosae. In vitro studies have shown that in situ gels act as potential drug delivery system for zolmitriptan, with better stability and release profile. However, future in vivo studies are warranted to confirm these results.

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