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FORMULATION AND EVALUATION OF NASAL INSITU-GEL OF ELETRIPTAN FOR THE TREATMENT OF MIGRAINE

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ABSTRACT

Nasal in situ gel based formulations are those which upon administration get converted into gel by various mechanism like pH , Temperature & other factor. Eletriptan is BCS class 1 drug with lesser aqueous solubility which is used for Migrane. Existing market formulation include tablet for the same with less than 50 percentage bioavailability because of cytochrome induction and first pass metabolism. Mainly cause for failure of the formulation to achieve desired bioavailability and therapeutic action is because of first pass metabolism and cytochrome induction which can be avoided by nasal delivery. Polaxomer 407 and Carbopol 934 used to formulate the nasal in situ gel of Eletriptan by cold method of preparation. While polyethylene glycol400 increase the solubility of drug in polaxomer along with increasing the permeation through nasal membrane. Hence by formulating nasal in situ gel of Eletriptan we can avoid FTM and get brain targeted drug delivery for the migrane.

KEYWORDS: *Nasal in-situ gel, Eletriptan, Migraine, cytochrome induction, first pass metabolism, brain targeted drug delivery.*

INTRODUCTION [1,2,3]

Migraine is a nervous system disorder that causes severe headache, brain dysfunction, aura, and sometimes neurological symptoms. to contribute to its development. 3. A new class of selective serotonin (5-hydroxytryptamine [5-HT]) receptor agonists called triptans can activate 5-HT1B and 5-HT1D (5-HT1B/1D) receptors in many people with migraine. It has been shown to improve quality of life. Migraine symptoms are throbbing pain on one side of the brain and moderate to severe headaches.

Many patients also report light and sound sensitivity, dizziness and nausea. Approximately one in five men and one in five women suffer from migraines, making them painful. They usually begin after the person reaches adulthood. It has a range of anti-inflammatory effects on brain chemistry and neuronal activity in all migraine sufferers. These actions affect blood flow to the brain. Migraine is characterized by throbbing pain that usually affects one side of the brain more than the other. You may also experience symptoms

Gel is the space between the liquid and solid phase. The component consists of a three-dimensional central network of molecules that carries the liquid phase. In Situ Gel Delivery Systems In situ gelation is the process of forming a gel at the site of action after formulation when activated at the site of action. The semi-solid muco-adhesive ring is produced by the in situ gel effect, which is essentially the liquid of the medicinal product. This allows the drug to be administered in solution or liquid form

Drugs that are not safe to take orally are usually given intranasally in low doses and quickly mix into the bloodstream. Most drugs enter the body through the membranous water in the nasal mucosa. Therefore, the drug molecule is absorbed even if it is small and in solution. As the molecular size increases, nasal absorption decreases. Nasal mucociliary clearance is one of the less important parameters for nasal delivery. This greatly reduces the time it takes for the medication to be absorbed. Mucoadhesive formulations are designed to increase the time the formulation is in contact with the nasal mucosa.

PREFORMULATION STUDIES OF DRUG (ELETRIPTAN)

Sr. No	Parameters	Result
1.	**Organoleptic Properties** i. Color ii. Odor iii. Nature	 Colorless Odorless Amorphous
2.	**Solubility** i. Water ii. PEG 400 iii. Ethanol	 Partially soluble Soluble Insoluble
3.	Melting point	168-170°C
4.	FTIR	

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5.	**UV Spectrophotometer (Calibration curve)** i. **Water** ii. **pH Buffer 6.8** iii. **Ethanol**	**Absorbance maxima** **221nm** **223nm** **222nm**

Table No. 1 Preformulation studies of drug (Eletriptan)

FTIR OF A DRUG

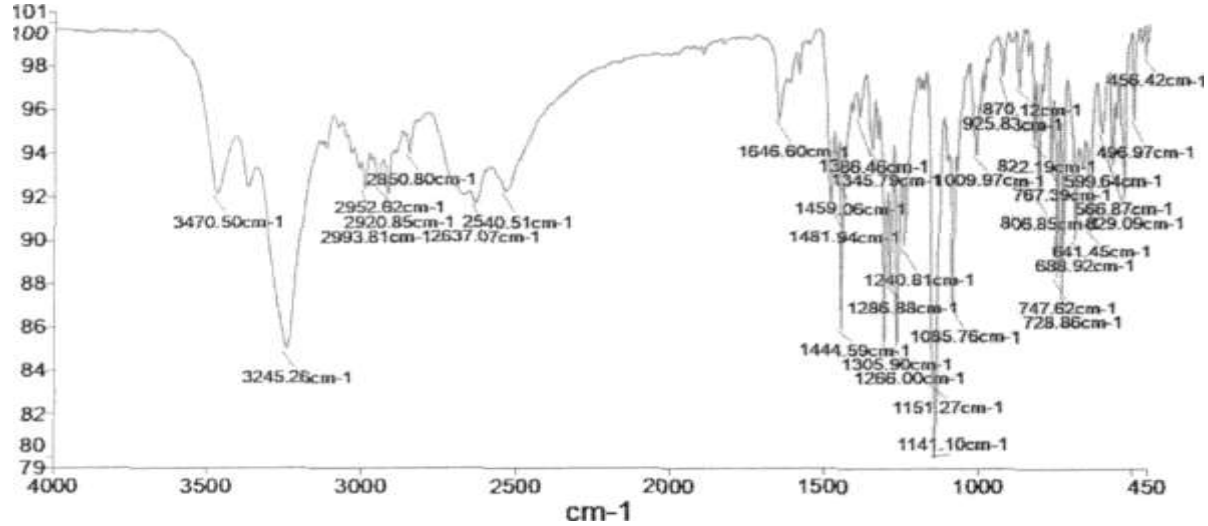

Figure No.1 FTIR of a drug

CALIBRATION CURVE OF A DRUG

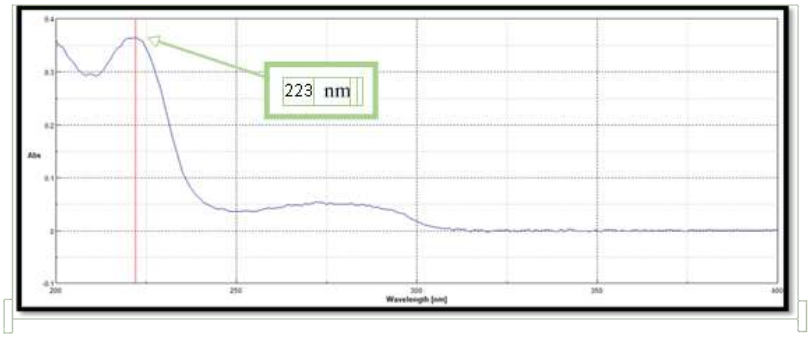

Figure No.2 Wavelength of Drug in ethanol

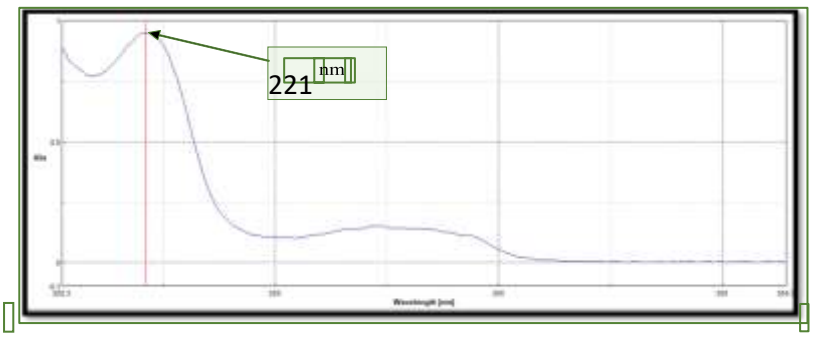

Figure No.3 Wavelength of Drug in water

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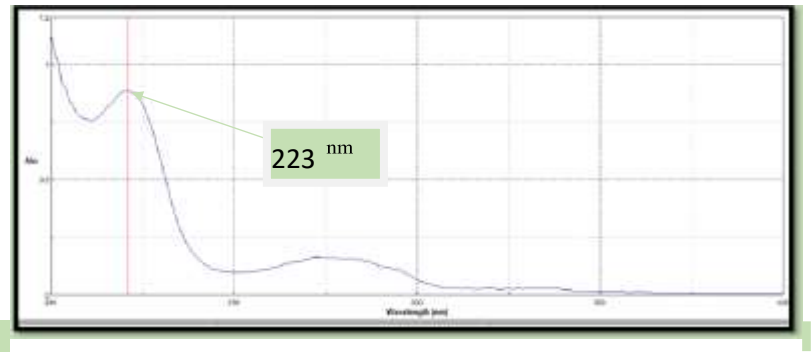

Figure No.4 Wavelength of Drug in PBS6.8

MATERIAL AND METHOD

Reagents required : Eletriptan, Polaxomer 407, Carbopol 934P, PEG 400, Benzyl alkolium chloride.

Instrumentation required : Weighing Balance, Hot plate, Mechanical Stirrer, Magnetic Stirrer, pH Meter, Incubator.

PROCEDURE [22]

The purpose of drug in situ gel formation is to provide a solution to the patient's identity as water drops that gel immediately after temperature changes when applied to the nasal mucosa. Preliminary experiments were performed to determine the temperature of the thermosensitive polymer (Polaxomer 407) at different concentrations of 15% and 25% w/v. It was found that at low polymer concentrations (15-16% w/v) phase change did not occur until the temperature reached 40°C. At a concentration of 17% (w/v), viscosity was found to increase from 38°C onwards. However, phase change occurs at 40°C. However, gelation occurs when the polymer concentration is increased from 18% to 25% (w/v).

The temperature decreases with increasing polymer pressure. 18% to 22% (w/v) of poloxamers were found at temperatures suitable for nasal use. Therefore, concentrations in the first group of eletriptan nasal in situ gel were found. Since the maximum drug concentration that could be added to clarify the in situ gel was 0.2% (w/v), the content of the starting drug was adjusted based on the solubility data. Since PEG 400 and PEG 6000 are more soluble, heavy weight (15 wt% each) was also included in the formulation. According to the data, three different amounts of polymer (0.1%, 0.3% and 0.5% w/v) were added to the samples. development.The final formulation also contained benzyl alcohol chloride, a known preservative, to prevent microbial development.

FORMULATION DEVELOPMENT OF NASAL INSITU-GEL [22]

INGREDIENT	FORMULATION						
	AA	AB	AE	AF	AG	AH	AI
Eletriptan	0.2	0.2	0.2	0.2	0.2	**0.2**	0.2
PEG 400	3	3	3	3	3	**3**	3
Polaxomer 407	16	16	-	18	18	**18**	-
Carbopol 934	0.1	0.3	0.1	0.3	0.5	**0.1**	0.3
HPMCK4M	-	-	0.4	-	-	**-**	0.4
Benzyl Alkonium Chloride	0.05	0.05	0.05	0.05	0.05	**0.05**	0.05
Distilled Water	Upto 10	Upto 10	Upto 10	Upto 10	Upto 10	**Upto 10**	Upto 10

Table No.2 Formulation developments of nasal insitu gel

EVALUATION PARAMETER OF FORMULATION [25,26,27]

1. **Sharpness**
   Sharpness can be evaluated visually on a black and white background.
2. **Viscosity**
   Viscosity and rheological properties of polymeric formulations can be measured in solution or in gels formed from tissue products media using a variety of viscometers such as Brookfield, cone and plate viscometers. Patient compliance should be taken into account in the viscosity of the formulations.
3. **Contents of the medicine**
   Place one milliliter of the preparation in the measuring bottle, adjust to ten milliliters, and then dilute with ten milliliters of distilled water. Then dilute 1 ml of this solution again with 10 ml of pure water. Finally, the absorbance of the solution at a specific wavelength is measured using UV-visible spectroscopy.
4. **Gelling ability**
   You can use the remote control to measure this parameter. Under the action of the gelling agent, a certain amount of gel in the form of sol is formed in the beaker. It is important to push the probe slowly into the gel because the beaker containing the gel will rise at a noticeable rate. The depth at which the probe is immersed at the bottom of the gel can be used to calculate the change in probe loading.

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5. **Gel time and pH of sol-gel transition**
   Sol-gel transition pits must be available for in situ gel formation systems. Gel time is the time it takes for the gel test to first detect gelation.
6. **Examination of Drug-Polymer Interactions Using Fourier Transform Infrared (FTIR) Spectroscopy Interaction and Thermal Analysis**
   The KBr technique can be used to measure the types of interactions that occur during gelation. The percentage of water in the hydrogel can be determined using a thermogravimetric analysis (TGA) of the formation of the polymer layer. Use differential scanning calorimetry (DSC) to examine whether temperature changes when comparing pure components used for gelation.
7. **Isotonicity Evaluation:**
   An important aspect of nasal and eye formulations is isotonicity. Maintain isotonicity to prevent tissue damage. Isotonicity testing showed that all nasal formulations had good release, gelling properties and appropriate dispersion. Mix with a few drops of blood, examine under a microscope at 45x magnification, and compare with commercial standards.
8. **Sterility Test**
   Sterility test complies with IP 1996 rules. To detect fungal growth, the sample must be treated in thioglycolic acid liquid between 300-350 °C for at least the same period.
9. **In vitro drug release**
   Plastic dialysis cells were used to study drug release from in situ drugs for oral or ocular administration. The transmitter and receiver are the two half cells that make up the battery. The two halves of the cell are separated by a cellulose membrane. The left form of the formulation is placed in the feeding chamber. After that, the finished cells were placed in the oven and shaken horizontally. Occasionally, the receptor may be removed entirely and replaced with new media. Analytical receptor media is used to study the release of drugs from these receptors. Then, water at the appropriate temperature is placed in the shaking bath. Remove and examine active samples.
10. **Stability Test**
    The optimized milk was subjected to a 1-month stability study at 27°C / 80% RH.

RESULT AND DISCUSSION

Sr No.	Evaluation Parameters	Result
1.	Clarity	Clear
2.	Viscosity	Sol-245 Gel-980
3.	Drug content	Absorbance at 227nm
4.	Gelling Capacity	
5.	Gelation Time and pH	5.20sec and 7.12
6.	FTIR	Compatible
7.	Isotonicity	Isotonic solution
8.	Sterility Testing	No growth of microorganisms
9.	In-Vitro drug release	Within 8 hr 94% of drug in released

Table No. 3 Result and Discussion of nasal in-situ gel

CONCLUSION

The aim of this study was to develop and evaluate Eletriptan nasal gel, a polymer-filled nasal gel for the treatment of migraine. The bioavailability and first pass metabolism of elatriptan are low. Once administered, it is not subject to first pass metabolism or cytochrome enzymatic cleavage. It can be concluded that nasal administration of eletriptan is beneficial in terms of increasing bioavailability and providing faster therapeutic results with less drug. Nasal inhalation may increase bioavailability. FTIR analysis was performed and no chemical or physical interaction was found between the drug and the additive. Once administered, the drug turns into a gel and acts directly on the brain without first going through metabolism, increasing bioavailability and allowing for a rapid onset of lower doses. It also increases patient compliance. They are also portable and wearable. They are very easy to manage. For this reason, nasal in situ gels are very popular in the pharmaceutical industry.

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