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IN-SITU NASAL GEL A PANACEA FORMULATION FOR NASAL DRUG DELIVERY

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ABSTRACT

In-situ Nasal gel are novel formulation intended to provide desired pharmacological effect on specific site and on predetermined rate which make this pharmaceutical formulation a good formulation .Nasal route is also more permeable to compounds than gastro intestinal tract. There were many absorption mechanism were established to predict the mechanism of drug absorption from the in-situ nasal gel formulation but only two mechanism have been mostly applicable such as paracellular process and transcellular process of absorption of drug. Generally there are two methods of preparation, one is cold method and second is hot method. This in situ gel formulation can be evaluated by determining Clarity, Texture Analysis, Viscosity, drug content ,pH, gel strength, Sol-gel transition temperature and gelling time, Accelerated stability study, Interaction study, In vitro drug release studies and Ex Vivo drug release .this review shows the multi-dimensional importance of in situ nasal gel .

KEYWORDS: In-Situ, Paracellular, Permeable, Formulation, Drug Release.

INTRODUCTION

Pharmaceutical formulation have been used to serve human kind for ages and various attempts of harness of these well designed and fabricated formulation have been made to get therapeutic benefit. Some formulations like gel and in-situ gel are among such formulations. Gel: A semisolid dosage form, which is to be found between liquid and solid phase. The hard element involves molecules which prevent from moving the liquid phase.

IN–SITU GEL DELIVERY SYSTEM

It is the course of gel formulation at the site of process after the formulation has been applied. In this process liquid depends upon the solution of drug formulation and changed into semi solid mucoadhesive key depot.[1-2]

NASAL DRUG DELIVERY

In Ayurveda system of medicine the intranasal therapy is accepted form of treatment. It is also called “NASAYA KARMA”. Nasal route has improved systemic bioavailability and it achieves fast and higher level of drug absorption as compared to oral. Nasal route is good because it is more permeable to compounds than gastro intestinal tract due to insufficiency of pancreatic and gastric enzymatic activity, neutral pH of nasal mucus.[3-4]

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

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Bio-adhesive polymers help to keep the dosage form more longer time onto nasal mucosa. There are some natural and synthetic polymers which under go for SOL- Gel transition by changing pH or temperature.[5]

A delivery system in which solution is changed in to the gel (sol gel) by changing temperature can keep longer onto mucosal epithelium. This type of system is turned as in-situ gelling drug delivery. Ropinirole, Midazolam are best example of In-situ nasal thermoresponsive gel drug delivery system. The noninvasiveness and self-administration nature also attracts the formulation and it helps scientists to deliver peptide and protein components.[6-7]

NASAL GELS

These are high viscosity thickened solutions or suspensions. The deposition of gel depends on the mode of administration due to its viscosity. The formulation has poor spreading capacities without special application techniques it only occurs a narrow distribution area in the nasal cavity, where it is placed directly. The first nasal gel containing vitamin B12 for systemic medication has entered in the market. [8]

MECHANISM OF NASAL ABSORPTION

The first step in absorption of drug from the nasal cavity is passage through the mucus. Small, unchanged drug easily pass through this layer but large charge particles of drugs are difficult to pass. The principle protein mucin, it has the affinity to bind to the solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes (i.e. temperature, pH etc.). So, many absorption mechanism were established earlier but only two mechanism have been mostly used such as: [9]

FIRST MECHANISM

It is an aqueous route of transport, it is slow and inactive. It is known as paracellular process. (Transport of substances across an epithelium by passing through the intercellular space) There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. Drugs having molecular weight better than 1000 Daltons shows poor bioavailability.

SECOND MECHANISM

It involves lipid route of transport. It is known as the transcellular process. (Transportation of solutes by a cell through a cell)It is liable for the transport of lipophilic drugs that show a rate dependence on their lipophillicity. Drug molecules also cross cell membranes by an active transport route via carrier-mediated mean.[10]

FACTORS THAT AFFECT THE RATE AND EXTENT OF ABSORPTION OF DRUGS VIA THE NASAL ROUTE ARE

- Ciliary movement: Ciliary movement is responsible for the retention of formulation at the site of action. If higher is the ciliary movement lesser is the retention.
- Vascularity of the nose: Higher is vascularity better is the absorption.
- The rate of nasal secretion: If the secretion rate is high the retention is very less.
- Metabolism of drugs in nasal cavity: Higher is the metabolism lesser is the action. If the drug is not a pro drug.
- Diseases affecting nasal mucosa membrane: all the diseases causing asymmetric, somehow diseases reduces the absorption of drug.
- Volume that can be delivered into nasal cavity is restricted 25-200μl^{-1}

ADVANTAGES

- Degradation of drug in gastro intestinal tract is absent.
- Absorption is speedily.
- Self-administration can be possible.

- Fast onset of action.
- It bypasses the first- pass metabolism.
- Nasal bioavailability is good for small drug molecules.
- Unstable drugs in G.I.T fluid are administered by nasal route.
- For large molecules bioavailability can be amended by absorption enhancers or other.
- Drugs which shows poor absorbed orally can be delivered by nasal route.
- As compared with parenteral route, it is a convenient and long term therapy is possible.
- Polar compounds can be administered by this route of delivery. [11-12]

DISADVANTAGE

- Rapid removal of dose from the site of absorption is difficult once drug is to be administered.
- Bioavailability is effected in cold and allergies.[13]
- As compared to gastro intestinal tract nasal cavity offers small absorption area.
- Frequently use of nasal route leads to mucosal damage.[14]

PROPERTIES OF NASAL IN-SITU GEL

- Nasal in-situ gel should possess low viscous.
- It has long residence time.
- In nasal cavity, it allows the reproducible administration and have free flowing.
- In nasal cavity it follows shear force with phase transition mechanism.[15]

PREPARATION METHOD OF IN-SITU GEL

Generally there are two methods of preparation, one is cold method and second is hot method. Cold method involves slow addition of polymers, drug, and additives in cold water. In this, small quantity of water dissolves various concentration ranges of polymers separately at cold conditions. The quantity of polymers which are used as gelling and viscosity enhancing agents was dissolved in that. Later drug, water soluble polymer and parabens were incorporated and stirred until clear solution is obtained. Finally make up the volume with distilled water and kept overnight at 4-10ºC. The in-situ gel formulation having satisfactory gelation temperature and was selected as optimized formulation.[12]

EVALUATION OF NASAL IN-SITU GEL

1. **CLARITY**: The clarity may be determined by visual inspection under the black and white back ground.[16]
2. **TEXTURE ANALYSIS:** In this constancy, firmness and cohesiveness of formulation may be determined by using texture analyzer which mainly denotes the syringe ability of Solution so formulation can be simple and easy administrated in-vivo.[4]
3. **VISCOSITY:** Either in solution or in gel the viscosity properties of formulation was determined by using different viscometer like Brookfield viscometer and Cone and Plate viscometer. The viscosity of these formulations should be patient compliance.[4-17]
4. **DRUG CONTENT:** Drug content was determined by dissolving 1ml of formulation and adjust to 10ml in volumetric flask and then dilute with 10ml of distilled water, 1ml from diluted formulation, again diluted with distilled water up to 10ml. After this by using U.V visible spectroscopy take an absorbance of prepared solution at a particular wavelength.[3]
5. **PH OF THE GEL:** All the batches were determined by digital pH meter and it is found to have a satisfactory pH so no irritation to be expected.[12]
6. **GEL STRENGTH:** Gel strength was measured by various methods: 1) On the surface of performed gel dropping of iron ball is used. This distance travelled by ball for specific period of time was measured.[12] 2) A definite amount of gel is prepared in beaker and from

the solution form, by depending on the mechanism of the gelling agent used and evaluated by Rheometer. In beaker the gel is raised at certain rates and pushing a probe slowly through the gel. On the below gel surface the function of deepness of immersion of the probe can be measured by changes in the load on the probe.[18]

7. **SOL-GEL TRANSITION TEMPERATURE AND GELLING TIME**: In in-situ gel, the sol-gel pH, and transition temperature should be determined. Gelling time means the time which is required for the first detection of gelation at body temperature.[19]
8. **ACCELERATED STABILITY STUDY:** Formulation is replaced in a yellowish-brown colored vials and seal with aluminum foil for the short term accelerated stability as per ICH state guidelines.[4]
9. **DRUG POLYMER INTERACTION STUDY AND THERMAL ANALYSIS**: With the help of Fourier Transform Infrared (FTIR) spectroscopy drug polymer interaction studies may be determined and the interacting forces can be evaluated by employing KBr pellet method.
10. **INTERACTION STUDY**: Differential scanning calorimeter (DSC) conducted to observe if there are any change in thermo gram as compared with pure active ingredients used for gelation.[12]
11. **STABILITY STUDY**: Stability study of formulation was performed under storage condition (refrigeration condition) and formulation was stored in cool, dry, clean, moisture proof bottles and keep away from light.[12]
12. **IN VITRO DRUG RELEASE STUDIES:** This studies was carried out by Franz diffusion and Plastic dialysis cell. In Franz diffusion cell membrane was used. Diffusion cell was filled with phosphate buffer and the constant temperature was maintained.[12]
13. **EX VIVO DRUG RELEASE:** It is carried out of only optimized batch by using nasal mucosa of goat.[12]

CONCLUSION

Through this review nasal in-situ gel is the best possible formulation and is proven to be a promising nasal drug delivery system. It would enhance nasal residence time owing to increased viscosity and bioavailability strength. And have excellent gelation time, gelation temperature and suitable prolonged drug release could possibly be advantageous in terms of increase bioavailability.[12]

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