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"Formulation and Evaluation of In -Situ Gel of Donepezil for Nasal Drug Delivery"

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I. INTRODUCTION

Oralroute is most convient route of drug administration. Due to failure of adequate absorption through GIT lead to researcher to find alternatives route of drug delivery. To overcome these problems researchers developed parental route of drug administration.

Now days, researches also selected nasal mucosa as another route for drug administration targeted drug delivery is concentrated on the medication in the tissues of which reducing the relative concentration of medication in the remaining in the tissues of which reducing the relativeconcentration of medication in remaining tissue.

Intranasal delivery mainly offers potentially an alternative variable for various drug delivery. Suitable for the local and systemic delivery of diverse therapeutic compounds. It is effective in the treatment of local, systematic and CNS site.

After tremendous literatures survey.

It can be concluded that nasal drug delivery is convenient for drugs with following criteria:-

1.It is ineffective orally.
2.It can be used chronically.
3.Small dose is preferable.
4.Quick entry to the general circulation is desirable.

The Oral administration of protein and peptide drug is not probable because they are considerably degraded in the gastrointestinal tract or considerably metabolized by the first-pass effect in the liver. Intranasal drug delivery offers a hopeful alternative route for administration of such drugs. Many advanced and useful approaches to the CNS delivery of drugs have emerged in recent years. Intranasal drug delivery is one of the focused delivery options for brain targeting as brain and nose compartments are connected to each other via olfactory/trigeminal route via peripheral circulation.

Direct nose to brain transport results into rapid and/or higher uptake in the brain. which provides asubstitute option of self-medication? Synthesis of additional lipophilic analogues, enzyme inhibitors, permeation enhancers, colloidal, bio adhesive and novel drug delivery systems like microemulsion, liposomes and nanoparticles could help in eliminating certain pharmaceutical challenges like low bioavailability, local irritation and toxicity upon long term handling. With all its inherent advantages intranasal route has been indicated as the most promising approach for delivery of drugs to the brain/CNS.

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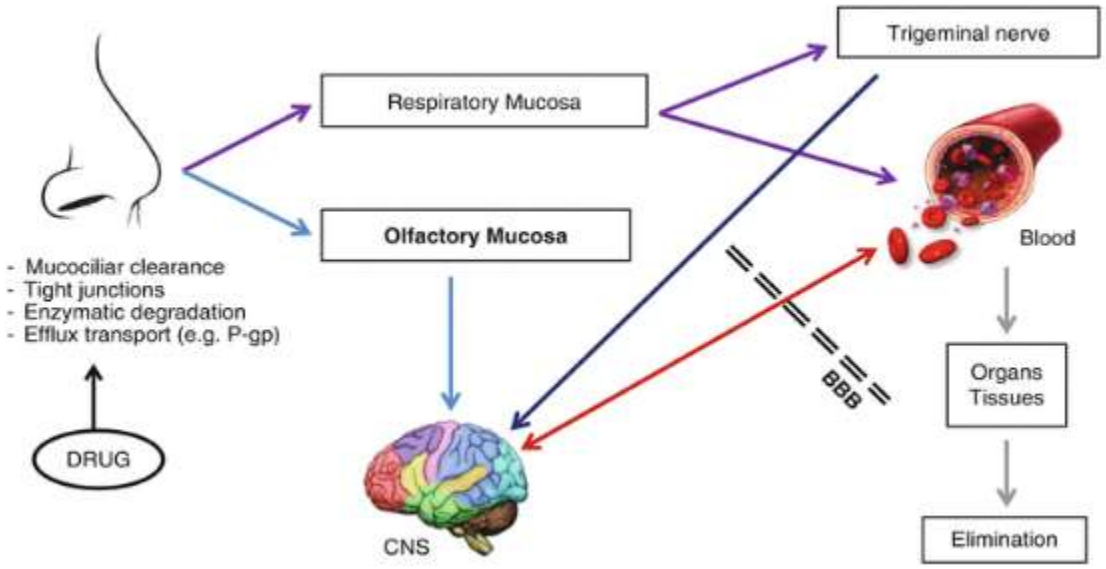

Figure 1.: Schematic illustration of the respiratory mucosa and the probable pathways involved in the transport of drugs from nose to systemic blood stream. Factors that influence systematic absorption of nasal drugs are also represents.

Pathways	Molecules
Nasal mucosa → olfactory epithelium (sensory nerve cells) → blood stream	Albumen
Nasal mucosa → olfactory nerve fiber	Amino-acid
Nasopharyngeal epithelium → cervical lymphatic vessel → blood vessel	Rabbit virulent type 3 streptococcus bacteria (pneumococci)
Nasal mucosa → CSF and serum	3,4-dihydroxyphenethylamine, estradiol
Nasal membrane → olfactory dendrites → central nervous system → olfactory mucosa (supporting cells) → submucosal blood vascular system	Norethisterone, progestogen
Nasal membrane → peripheral circulation and CSF → central nervous system	Norethisterone
Nasal mucosa → peripheral and the cranial nerves → central nervous system	Herpes virus encephalitis (HSV)

Table1: Nose -to-brain transport of drug molecules and possible pathways: -

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ADVANTAGES OF NASAL DRUG DELIVERY: -

- Easy to administration, non-invasive, rapid and comfortable.
- Easy accessibility to blood capillaries.
- Avoid side effects like nausea and vomiting which is normally seen after oral administration.
- Avoids destruction in the gastrointestinal tract.
- Convenient for the patients, when compared with long term therapy of parenteral Medication
- It is more useful for those drugs which possessing poor stability in GIT.
- Fluids are given by nasal route.
- It avoids metabolism by the gastrointestinal tract;
- It can avoid irritation of the gastrointestinal membrane;
- It reduces risk of overdose;"
- It reduced risk of infectious disease transmission:
- It easy to self-medication; It's an needle-free drug application without the necessity of trained personnel facilitates.
- It improves patient compliance;
- It can be a beneficial adjunct product to an existing product:
- As we know every product have advantages but it also has some drawbacks.

THE DRAWBACKS OF NASAL DRUG DELIVERY INCLUDE

- There will be chances of nasal irritation
- Some drug may undergo metabolic degradation in the nasal cavity.
- It is less suitable for chronically administered drugs.
- Several use of nasal route may result into the mucosal damage.
- It requires high volume of dose 25-200ml depending on aqueous solubility of drug.
- There is chance of some side effects and irreversible damage of the cilia on the nasal mucosa, from the substance and constituents added in the dosage from.
- Mucociliary clearance reduces the residence time of drug
- It is not applicable to all drugs:
- It having insufficient absorption due to lack of adequate aqueous solubility;
- It requires high volume of dose (25-200 ml) depending on aqueous solubility of drug: There will be chances of nasal irritation;
- Some drugs may undergo metabolic degradation in the nasal cavity;It is less suitable for chronically administered drugs;
- Drugs requiring sustained blood levels should not be considered for nasal delivery as there is no conventional way of formulating sustained release type of nasal dosage forms.
- There will be a chance of mechanical loss of the dosage form into the other sections of the respiratory tract like lungs due to the improper methods of administration.
- There are chances of some side effects and irreversible damage of the cilia on the nasal mucosa, from the substance and constituents added in the dosage form.
- Nasal congestion due to cold or allergies may interfere with this method delivery. Several use of nasal route may result into the mucosal damage.

ANATOMY AND PHYSIOLOGY NOSE

It is essential to have a clear understanding of the anatomy and physiology of the nose and how it relates to the characteristics of the delivery system used.

Inhumansand otheranimalspecies,the major functions of the nasal cavity are breathing andolfaction.

It also affordsan important protective activity once. it filters, heat and humidifiestheinhaled air before reaching the lowest airways.

The human nasal cavity has a total volume of 15-20ml and a total surface area of approximately 150cm.

The noseisseparated intwo nasal cavities bythe septum. The volume of each cavity is about 7.5ml and has a surface area around 75cm pH of the mucosal secretions ranges from 5.0 to 6.7 in children and 5.5 to 6.5 in adults.

The nasal passage epithelium is covered by a mucus layer that is renewed every 10 to 15 min from thenose,mucus moves at a rate of 5 to 6 mm/min resulting in particle clearance within the nose every 20 min.

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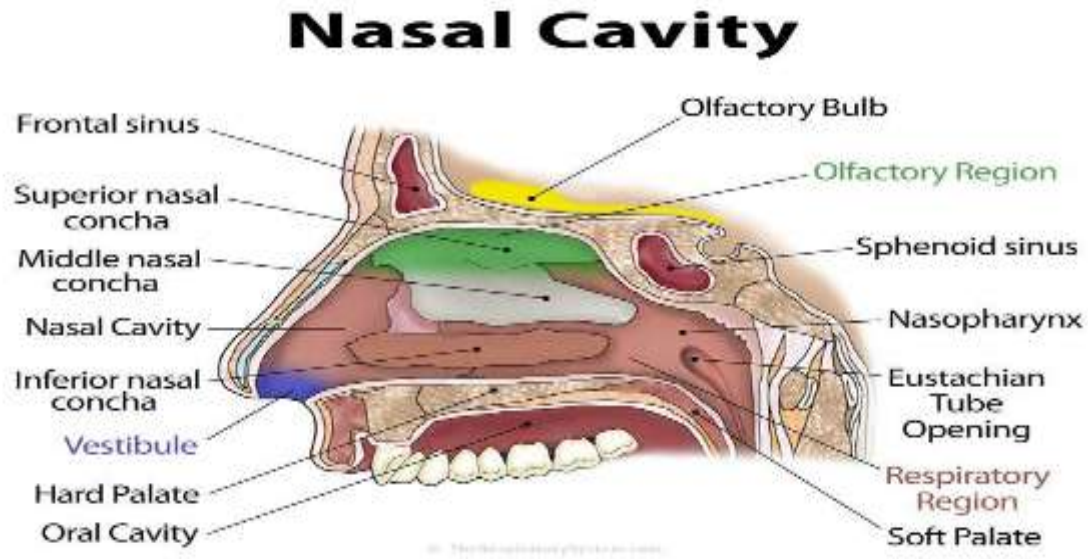

Figure2: anatomy and histology of human nasal cavity

Three regions can be distinguished in each part

1. Respiratory region:

The nasal respiratory region is the largest part of the nasal cavity, also called conchae. The respiratory region is the most important for systemic drug delivery. The respiratory epithelium is composed of four types of cells, namely, non-ciliated and ciliated columnar cells, basal cells and goblet cells.

The respiratory region containsthree nasal turbinates: -
1.superior,
2.middle,
3.inferior

Which project from the lateral wall of each of the nasal cavity.
For systemic drug delivery,nasal respiratory mucosa is considered the most important.

2.Vestibular region:

Most anterior part of the nasal cavity is nasal vestibule, just inside the nostrils, and presents an area about 0.6 cm this nasal portion is covered by a stratified squamous and keratinized epithelium with sebaceous glands is responsible for filtering out the airborne particles. It is considered to be less important in the three regions concerning drug absorption.

Figure 3: vestibular region of human nasal cavity

3.Olfactory region:

The olfactory region is located in the roof of the nasal cavity and extends a short way down the septum and lateral wall itis of about 10 cm2 in surface area and it plays a vital role in the transportation of drugs to the brain and the CSF.

When the drug is administered by the nasal route, it can enter into the brain by three different paths.

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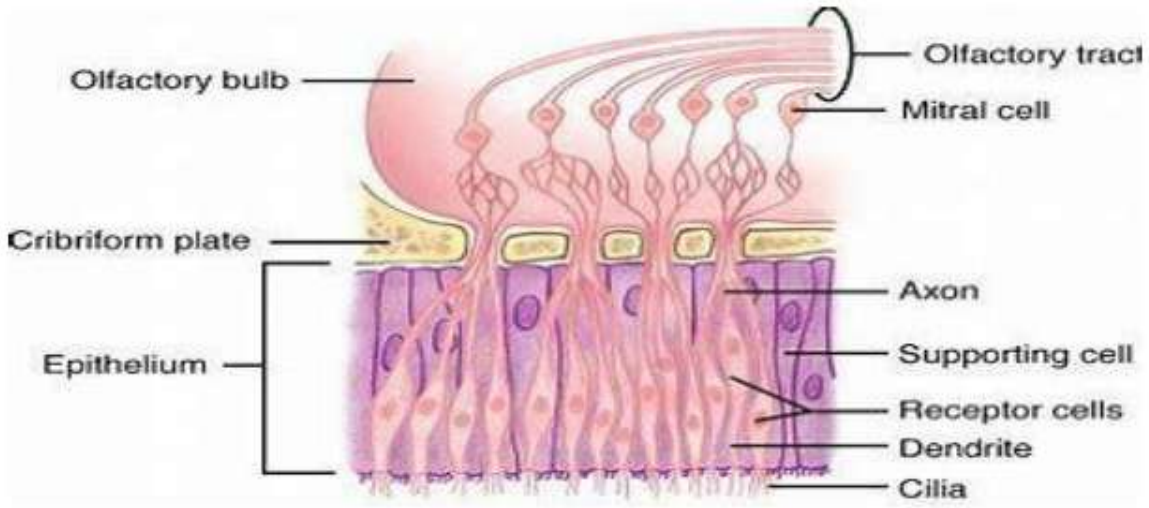

Figure 4: olfactory region of human nasal cavity

The first one is thesystemic path, by this route thedrug is absorbed intothe systemic circulation and subsequently reaches the brain by crossing BBB[especially lipophilic drug].

The other pathways are the olfactory region and the trigeminal neural pathway by which the drug is directly transported from the nasal cavity to CNS [cerebrospinal fluid and brain tissue]. There is a different mechanism by which the drugs across the olfactory membrane reach CNS.

The first mechanism involves a direct transfer of the drug to primaryneurons of the olfactory epitheliaand transport to the olfactory bulb by intracellularaxonal transport with subsequent possible distribution into more distant brain tissues. The second mechanismdependsonthedrug permeation across the olfactory sustentacular epithelial cells, either by transcellular orparacellularmechanisms followed by uptake into CNS. Thelast one employs pinocytosis by olfactory neurons.

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PHYSIOLOGY OF NASAL MUCOSA

A. Effect of deposition on absorption:

Deposition of the formulation in anterior portion in the nasal cavity, it provides a longer residence time. The anterior portion of the nasal cavity is an area having low permeability and posterior portion of the nasal cavityhaving high drug permeability and ithavingshorter residence time.

B. Nasal blood flow:

Nasal mucosal membrane is very rich in vasculature.Itplays an important role in the thermal regulation and humidification of the inhaled air. Blood flow and absorption of drug is depending upon vasodilation and vasoconstriction of blood vessel.

C. Mucociliary clearance (MCC):

It is a one of theself defensemechanisms of the respiratory tract. Its function is to filtrate foreign particles, which get attached to mucus layer by draining them into the nasopharynx. These are cleared by the GI Tract (Gastro-intestinal tract).

Therefore,Mucociliaryclearance (MCC) alters the residence time of the drug which administered through nasal route by altering the drug absorption. In physiological conditions, 3-5 mm/min is the rate of mucus transportation and 15-25 min is the reported as the transit time in human nasal cavity. If decrease in the MCC, then it will be increase in the residence time of the therapeutics in nasal mucosa. It result into increased permeation.

D. Enzymatic activity and its effect:

So many enzymes that are present in the nasal mucosa, affect the stability of drugs. For example, proteins and peptides are subjected to degradation by proteases and aminopeptidase at the mucosal membrane. The level of aminopeptidase presents much lower than that in the Gil Tract. Peptides also forms complex with Immunoglobulin (Igs) in nasal cavity leading to an increase in the molecular weight and it leads to a reduction of permeability. E Pathological condition and its effect: Intranasalpathologies (allergic rhinitis, infections and previous nasal surgery)maybe affect the nasal mucociliary transport process and/or capacity for nasal absorption. During the common cold, the efficiency of an intranasal medication is often compromised. Innasal clearance is goes to reduce in insulin dependent diabetes. Nasal pathology can also change to mucosal pH and it leads to impinge on absorption.

F. Nasal secretions:

Nasal secretion changes from person to person and it depends on the person-to-person health condition. Viscosity and rate of nasal secretion mainly affects the bioavailability nasal secretion. The production of mucus is about 1.5-20 ml per day. The change in rate of nasal secretion is increased, so decrease in drugsbioavailability. Drug permeability affected by viscosity of nasal secreation through nasal mucosa. The viscous surface layer will inhibit the ciliary beating if the sol layer of mucus is too thin and if the sol layer is too thick, mucociliary clearance is impairedwhich in turn affects the drug permeation by altering the contact time with the mucosa. A drug needs to be solubilized in the nasal secretions before it permeates, Physicochemical characteristics of drug are required for dissolution in nasal secretions.

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G. pH of the nasal cavity:

Drug permeation is usually greater at a nasal pH that is lower than the drug's pk, because under these conditions the penetrant molecules exist as unionized species. Normally, the pH of the nasal cavity varies between 5.5 6.5 in adults and 5.5-7.0 in infants. Depending on the nature of the drug, a change in the pH of the mucus affects the ionizations which in turn, can increase or decrease the drug permeation 9

NASAL DRUG ABSORPTION

Transport route of nasal absorption.
1.paracellular route
2.transcellular route
3.transcellular passive diffusion.

MECHANISM OF DRUG ABSORPTION

Some mechanism of drug absorption through nasal cavity are highlighted below:

Aqueous route of transport is inolved in frist mechanism of drug absorption which known as paracellular route paracellular route is very slow and also passive. intranasal absorption and molecular weight of water soluble compound having an inverse log-log correlation in both.poor bioavailability was showed in drug with a molecular weight greater than 1000 daltons.

Second mechanism involved in transportthrough a lipoidal route is also called as the transcellular process.it is responsible for the transport of lipophilic drug which show a rate dependency on their lipophilicity.Drug can across cell membrances by an active transport route through carrier-mediated means or transport through the opening of tight junctions.

FACTORS AFFECTING NASAL DRUG ABSORPTION.

Systemic bioavailability of nasally administered drugs can be affect by many factors.

Physicochemical properties of the drugs and the characteristics of other ingredient of delivery system has affects drug absorption. Theseplays important role for most of the drugs in order to reach therapeutically effective blood levels after administration in nasal cavity.

FACTORS AFFECTING NASAL DRUG ABSORPTION ARE AS FALLOW:

1.PHYSICOCHEMICAL PROPERTIES OF DRUG

A. Chemical from
B. Polymorphism of drug
C. Molecular weight of drug
D. Particle size of drug
E. Solubility and dissolution rate of drug
F. Lipophilicity.

A) Molecular weight

Fisher et al. concluded that the permeation of drugs less than 300 Da is not significantly influenced by the physicochemical properties of the drug (like molecular weight, size, formulation pH, and pKa of molecule).As molecular weight increases, nasal absorption of drug increases (Fisher et al. 1992).

B)polymorphism

Polymorphism affects the rate of drug dissolution, solubility, and absorption through biological membranes (Garg et al. 2013).

C)Solubility & dissolution rate

Both are important factors in determining nasal absorption of drugs from powders and suspensions. In the nasal cavity, the deposited particles need to be dissolved priorto absorption. No absorption takes place if particles remain in the nasal cavity. The mucosa in nasal cavity is insufficient for dissolution of drug particles, when compared to gastrointestinal fluid available in the case of oral drug delivery (Goyal et al. 2013a).

D)Lipophilicity

On increasing lipophilicity, the permeation of the compound through the nasal mucosa increases because of high lipophilicity, though it has some hydrophilic character.

Lipophilic compounds easily cross biological membranes through the transcellular route, since they are fit to partition into the lipid (bilayer) of the cell membrane and diffuse into and traverse the cell in the cell cytoplasm. Systemic bioavailability is decreased due to the hydrophilic nature of many drugs (Goyal et al. 2013b)

2.NASAL EFFECT: -

- Membrane permeability
- Environmental PH
- Mucociliaryclearance(MCC)
- Cold,rhinitis(Allergies)
-

3.DELIVERY EFFECT: -

- Formulation (concentration,PH,osmolarity)
- Delivery effects of drug.
- Distribution of drugs and deposition

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- Effect of formulation on Mucociliary clearance(Mcc)
- Poisonous effect on ciliary function and epithelial membranes.

PHARMACOKINETICS OF NASAL ABSORPTION

Factors affect the pharmacokinetic parameters following intranasal administrationare: -

1.PHYSIOLOGY –RELATED

- Mucus flow speed
- Infection presence
- Environmental conditions.

2.DOSAGE FROM RELATED

- active drugs concentration
- physicochemical properties of api
- formulations density and viscosity properties
- dosage from ph and toxicity
- excipients used in dosage from

3.Administration related

- Droplet size
- Deposition size
- mechanical damage into esophagus
- mechanical damage into other regions in the nose
- mechanical damage anteriorly from nose

Approaches for improving availability in Nasal administration:

Various strategies used to improve availability of the drug in the nasal mucosa. Include; -

1. To progress the residence time of nasal
2. To improve nasal absorption
3. To amend drug structure to change physicochemical properties

Various Dosage Forms used in Nasal Drug Delivery;

There are several dosages form available in market through intranasal cavity. Theselection of dosage form is totally depending on compliance,proposedindication, mainlydrug being used and marketing preference.

Various dosage forms used in Nasal drug delivery are as follows:

There are multiple of intranasal formulation available in market such as: -

A. Nasal spray
B. Nasal Drops
C. Nasal suspension
D. Nasal powder
E. Nasal Gel
F. Nasal Insert

are used to deliver the drug into the target site that is brain Among these formulations, in situ gelling systems are widely used for brain targeting.

DIFFERENT DOSAGE FORMS PROVIDED BY THE NASAL ROUTE

A) **Nasal sprays:**

Nasal sprays can be made from both solutions and suspensions.

A nasal spray can give a precise amount from 25 to 250 pL due to the availability of metered dose pumps and actuators. The size and shape (for suspension) of the particles. The medication and viscosity of the formulation influence the pump and actuator selectionassembly. Nasal spray formulations were far better absorbed than powder versions formulations. The highest concentration of ketorolac trimethamine was found in a nasal spray formulation absorption with a 91 percent absolute bioavailability.

B) Nasal drops: -

Nasal drops are one of the most straightforward and practical nasal administration technologies available. The lack of dosing is the biggest downside of this approach as a result,nasal drops may not be appropriate for prescription use.

Nasal drops have been reported to deposit more human serum albumin in the nostril Nasal sprays and metered dose nebulizers are less effective. Drugs having a molecular structure. When mass is less than 1000 Dalton, nasal bioavailability's are acceptable.

C)Nasal Suspension:

Nasal suspensions are made by suspending micronized drugs in a liquid diluent or carrier that is suitable for application to the nasal mucosa. In comparison to death solution preparation, suspension form preparation resulted in greater insulin uptake and blood glucose decrease. 159,160

D)Powders:

Compared to liquid formulations, powder dosage forms of medicines for nasal delivery have various advantages. The chemical stability of the medicine is improved in powder form because no preservative is required in the formulation, and greater doses of drugs can be administered. Powder form is appropriate for a variety of nonpeptide medicines and peptide drugs.

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A dry powder vaccine formulation with whole inactivated influenza virus (WITV) and a mucoadhesive component for nasal delivery was developed. Lyophlizationwas used to create powders that included W1IV and either lactose or treehouse. Tire lyophilized cake was reduced to sizes suited for nasal administration using a micro-ball mill. Alsoinvestigated were particle size analysis, powder flow characteristics, bulk and tapped densities, and static angle of repose.

E) Nasal inserts: -

Are a revolutionary, innovative, bioadhesive, solid dosage form for extended systemic medication delivery via the nasal route.

The dosage form's principle is to imbibe nasal fluid from the mucosa after injection and form a nasal gel to prevent the sense of a foreign body This gel sticks to the nose. Due to its bio-adhesivecharacteristics,

It also serves as a release controller. This allows for long-term medication delivery.

Because of gel dissolution andThere is no need to withdraw the insert from the mucociliary removal towards the nasopharynx.mechanically after the medicine has been depleted Nasal inserts that gelled in place were used, there is no need to remove it mechanically.

As a result, in situ gelling nasal inserts were made by lyophilizing aqueous solutions containing medication, carrier polymer, and additional excipients as needed.

The sponge-like structure of in situ gelling nasal inserts is a key factor in ensuring quick hydration and gelation of the inserts on the nasal mucosa.

When compared to other solid dosageforms, such as tablets, rapid water uptake by capillary forces ensures rapid gelation and thereby reduces the foreign body impression.

Initial research was conducted to discover the polymers that form sponges during freeze-drying.

The characteristics of in situ gelling nasal implants made from various polymers were also studied. Water penetration, polymer chain relaxation, insert swelling and spreading, and water-soluble drug dissolution are all factors in medication release from nasal inserts.interactions between the medication and the carrier, and drug diffusion through the polymer insert.

Generally, nasal inserts are prepared by lyophilization technique.

A lyophilization process for a pharmaceutical unit dosage form was developed which comprised a container closed with an impermeable membrane pierced with one or more holes through which the material in the container can be lyophilized.

The hole or holes in the membrane have to be sufficiently large to allow water vapor to escape but small to ensure that the material is kept within the container.

The technique offers a novel convenient means of lyophilizing nonsterile products in their primary pack and increases the potential for die development of lyophilizedformulations for non-parenteralapplications.

Nasal absorption can be used for the delivery of nicotine in anti-smoking.

E) Gels: -

Nasal gels are high viscosity thickened solutions or suspensions.

In Latin, in situ means ‘in position’ or ‘in its original place’. For the past 30 years, greater attention has been directed towards the development of controlled and sustained drug delivery systems.

A vast amount of research has been carried outin designing polymeric systems such as in situ gels. In situ gel formation of drug delivery systems can be defined as a liquid Formulation generating a solid or semisolid depot after administration.

In situ activatedgel, forming Systems are those which are when exposed to physiological conditions that will shift to a gel phase.

This new concept of manufacturing a gel in situwas suggested forthe first time in the early 1980s. Gelation occurs via the cross-linking ofpolymer chains that can be achieved by covalent bond of cross-linking or Non-covalent bond formation (physical cross-linking).

The routes of administration for in situ gel could be oral, ocular, rectal, vaginal, injectable and intra-peritoneal.

Gelis that the state which exists in between liquid and solid, which consists of physicallycross-linked networks of long polymer molecules,with liquid molecules trapped within a three-dimensional polymeric network swollen by a solvent.

A gel is a state between liquid and solid, which consists of physically cross-linked networks of long polymer molecules. Before administration, the in-situ gelling system is a liquid aqueous

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solution and it changes into a gel at the physiological condition.
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.

This system is a liquid aqueous solution before the administration and a gel at physiological conditions.

Prolonged and sustained release of the drug is reproducible, and the 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.

In situ gel is a new dosage form that hasbeen applied in nasal drug delivery recently. Compared with other liquid nasal formulations, nasal in situ gels are administered as low viscosity solutions into the nasal cavity, and upon contact with the nasal mucosa, the polymer changes conformation producing a gel, soit cannot only prolong the contact time between the drug and also the absorptive sites within the cavity but also release drug slowly and continuously, hence,it's especiallyuseful for those drugs used chronically.

The phase transition can be induced by a shift in pH, a shift in temperature or by the presence of cations.

- The advantages and disadvantages of nasal gel include: -
- The reduction of post-nasal drip due to high viscosity.
- The reduction of taste impact due to reduce swallowing.
- The reduction of anterior leakage of die formulation.
- The reduction of irritation by using soothing/emollient excipients and target delivery to mucosa for better absorption.

METHODS OF FORMULATION: -
1.Cold method
2.Hot method

OTHER METHODS OF PREPARATION
A. Solution polymerization
B. Suspension polymerization
C. Chemically cross-linked hydrogels.
D. polymerization by irradiation.
E. Physically cross-linked hydrogels.

1. COLD METHOD: -

In this approach, the drug is mixed with a suitable amount of double distilled water and maintained in the refrigerator overnight at 4°C.

The in situ gelling polymers are then progressively added while stirring. The dispersion is kept in the refrigerator until it forms a clear solution, and then the volume is adjusted with distilled water. This approach is employed when a gelling polymer such use as poloxamer, natural polymer.

Because the solubility of the polypropylene oxide chain of poloxamer reduces at high temperatures, resulting in precipitation or salting-out of a polymer, the polymeric dispersion of poloxamer is in solution at lower temperatures and converts into a gel at higher nasal temperatures. Similarly, polymer requires a low temperature to stay a solution at room temperature, and its hydrophobicity increases as the temperature rises.

2. HOT METHOD: -
When gallant gum or pectin is employed as a gelling polymer, this approach is used.

Gallant chains dissolve in water at high temperatures and assume a random-coil shape with great segmental mobility, while remaining as a solution at lower temperatures.

In the presence of ions such as K+ or Ca2+, a phase shift occurs on a cooling gallant gum solution. Similarly, pectin's de-methylation demands a high temperature, which aids in the production of a solution or dissolving of pectin.

IMPORTANCE OF IN SITU GELLING SYSTEM

The major importance is that the possibility of administering accurate and reproducible quantities compared to already formed gel. It increases the exposure time of drugs with that of mucus at the site of absorption and has better bioavailability, increases patient compliance.

PRINCIPLE OF IN SITU GELLING SYSTEM

The principle of insitu gelling system is of solid nasal formulations are that the nasal

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formulations absorb thenasal fluid after administration and form a gel within the cavity. The foreign body sensation can avoid by the formation of nasal gel within the cavity. Due to bio adhesivenature, the gel adheres to the nasal mucosa. It acts as a release controllingmatrix and thus acts as a sustained drugdelivery system.

PROPERTIES OF NASAL IN-SITU GEL

 It should have a long residence time.
 It should be low viscous.
 Free flowing allows for reproducible administration to the nasal cavity.
 The nasal in-situ gel follows the phase transition mechanism and shear forces in nasal cavity wall.

RATIONALE / OBJECTIVES: -

AIM OF PRESENT WORK: -

Aim of the present work is to develop novel, patient compliance and stable in-situ gel of donepezil,by using safe excipient for treatment of Alzheimer disease such a condition of dementia.

Study how certain drugs, polymers concentration and formulation excipients influences the gelation temperature of poloxamer gel.

- To exploit different ways of controlling the release of drug from the gels by using different polymers or different thermo-reversible systems of pluronic.
- To optimize the formulations on the basis of gelation temperature,bio-adhesion,gel strength, invitro diffusion, viscosity, stability, ease of administration, safety etc.
- To check the in vivo performance of the optimized formulation.
- To formulate a nasal patch (Nasal insert) system so as to have increase in nasal residence time.
- To synthesize a muco-adhesive polymer suitable for nasal drug delivery.

OBJECTIVES: -

1.Isolate the natural mucilage from natural polymer.
2.Evalution and characterization of mucilage from natural polymer.
3.Preformulation studies
4.Calibration of standard curve
5.FT-IR compatibility study
6.Solubility studies

II. LITERATURE REVIEW: -

PLAN OF WORK: -

STEP 1

1. Literature survey.
2. Raw material selection and procurement
   - Drug
   - Excipients
   - Preformulation studies

A) ANALYSIS OF DRUG
- Organoleptic properties
- Melting point
- DSC
- Solubility
- UV-VIS spectroscopy
- Preparation of calibration curve
- Determination of max

B)ANALYSIS OF POLYMER.
- Isolation of natural polymer.
- Evolution and characterization of natural polymer.
- Calibration of standard curve
- FT-IR compatibility studies
- Solubility studies

C)DRUG POLYMER INTERACTION STUDIES
- FTIR of drug-polymer
- FTIR of drug polymer –excipients
- DSC of drug – polymer
- DSC of drug –polymer-excipients

STEP 2: -
- Preparation of in situ Gel of Donepezil for nasal drug delivery
- Characterization of in situ Gel.
- pH of Formulation.
- Measurement of Gelation Temperature.
- Drug Content Estimation.
- Viscosity measurements.
- Gel strength determination.
- In vitro Diffusion study.

DRUG AND POLYMER PROFILE: -

IDEAL DRUG CANDIDATE FOR NASAL DRUG DELIVERY: -

1.The drug should not produce any irritation to the nasal mucosa.
2.The drug should not cause any side effect.
3.The drug should not contain any toxic metabolites.
4.The drug should be free from any offensive odor.
5.A dose of the drug should be less than 25 mg.

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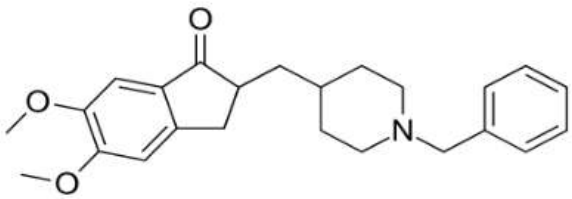
6.The drug should poses appropriate nasal absorption property.
7.Suitable clinical rationale for a nasal dosage form.
8.Suitably stable characteristics.

Donepezil-

- Synonyms: Donepezil
- IUPAC Name:2-[(1-benzylpiperidin-4-yl) methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one
- Molecular formula:C24H29NO3
- Boiling point:527.9
- Molar mass: 379.5 g/mole
- Solubility: freely soluble in chloroform, soluble in water, slightly soluble in ethanol.
- Melting point :223-227
- Category: cholinesterase inhibitor.
- structure



- 2-[(1-benzylpiperidin-4-yl) methyl]-5,6-dimethoxy-2,3-dihydroinden-1-o

MECHANISM OF ACTION

DP was one of acetylcholinesterase inhibitors, it was widely used in the treatment of mild to moderate Alzheimer disease(AD)
In AD reduced levels of acetylcholine in brain.
cholinesterase inhibitors block the action of enzyme cholinesterase which is responsible for breaking down acetylcholine.

It improves mental function (such as memory, attention, the ability to interact with others, speak, think clearly, and perform regular daily activities) by increasing the amount of a certain naturally occurring substance in the brain.

Signs of Severe Alzheimer's Disease

People with severe Alzheimer's cannot communicate and are completely dependent on others for their care. Near the end, the person may be in bed most or all of the time as the body shuts down.

Their symptoms often include:

- Inability to communicate
- Weight loss
- Seizures
- Skin infections
- Difficulty swallowing
- Groaning, moaning, or grunting
- Increased sleeping
- Loss of bowel and bladder control.

A common cause of death for people with Alzheimer's disease is aspiration pneumonia.

This type of pneumonia develops when a person cannot swallow properly and takes food or liquids into the lungs instead of air. There is currently no cure for Alzheimer's, though there are medicines that can treat the symptoms of the disease.
Their are various Cholinergic activators which treat the disease.

1.Donepezil
2. Rivastigmine
3.Galantamine

Benefits of cholinesterase inhibitors

In patients of AD, the level of acetylcholine is reduced and cholinergic neurotransmission has been obstructed. The cholinesterase inhibitors improve the cholinergic transmission by inhibiting the metabolism of acetylcholine from cholinesterase enzymes. The cholinesterase inhibitors are available for the management of AD:

Donepezil (Aricept®), is cerebroselective and reversible acetylcholinesterase (AChE) inhibitor used in treatment of all levels of Alzheimer's disease. Donepezil HCl improves cognitive as well as non-cognitive functions and improves the Ach level in the cerebral cortex and hippocampal region. Donepezil HCl has a long half-life of 70 h and so can be administered once daily at bedtime.

The initial dose of donepezil is 5mg at bedtime for four to six weeks. In moderate stage of

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the disease, this dose can be increased up to 10 mg at bedtime

POLYMER PROFILE
POLYMERUSEDIN-SITUT GEL:
1.NATURAL POLYMER

These polymers are obtained from different sources like Protein, Carbohydrate and chemically modified Carbohydrates

- Protein: Albumin, Gelatin, Collagen
- Carbohydrate: Starch, Agarose, Carrageenan
- Chemically Modified Carbohydrate: Polyacrylic Dexron, Poly acryl Starch
  - The polymers and their degradation products should not be poisonous or absorbable through the gastrointestinal tract.
  - It must stick immediately to moist tissue and be site-specific.
  - It must not cause irritation to the mucous membranes.
  - Both locally and systemically, it should have a large safety margin.
  - The polymer value should not be excessively high in order for the manufactured dosage form to stay competitive.

A. CHIA SEED

- chia seed (Salvia his panica L.) is an annual herbaceous plant belonging to the Lamiaceae family, is native to Mexico and Australia. Chia seeds provide a great source of ω-3 and ω-6 fatty acids, proteins of high biological value, soluble and insoluble fibers, antioxidants, vitamins and minerals.
- Mucilage: Mucilage is a long chain Polysaccharide substance extracted as a viscus or of gelatinous solution from plant part (roots, seed, leaves etc.) That are hydrophilic, being able to attract bind with volume of water that far exceeds the mass of the mucilage. They are biocompatible and nontoxic in nature.
- Pharmaceutical use: Tablet binders, disintegrant, emulsifying and suspending agents in biphasic liquid dosage form. Gelling agents, stabilizing agents, thickening agents, film forming agents in transdermal andperiodontal films, buccal tablet, sustaining agents in matrix tablets and coating agents in microcapsules including those used for portions delivery.

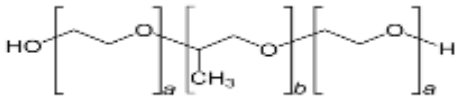
2. POLOXOMER 407

poloxamer 407 (Pluronics F127) has excellent thermo-sensitive gelling properties, low toxicity, excellent water solubility, good drug release characteristics and compatibility with other excipients.

Poloxamer 407 is a non-ionic hydrophilic surfactant that belongs to the poloxamer family of copolymers.

Poloxamer 407 is a three-block copolymer with a corehydrophobic block in the middle ordered by two hydrophilic blocks of polypropylene glycol

Structure :-



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IUPAC name: -
Oxirane, methyl-, polymer withoxirane

SYNONYMS: -
- Pluronic F-127
- Synperonic PE/F-127
- Kolliphor P 407
- Poloxalene

Chemicalformula

C572H1146O259
Molar mass
12,600 g/mol
CAS Number 691397-13-4 (https://commonchemistry.cas.org/detail?cas_rn=691397-13-4)
This particularcompound is also known by the BASF trade name Pluronic F-12or by the Croda trade name Synperonic PE/F 127.
BASF alsooffers a pharmaceutical grade, under trade name Kolliphor 407.

APPLICATIONS:-

The majority of poloxamer 407's common applications are connected to its surfactant characteristics.
It's extensively used in cosmetics to dissolve greasy components in water, for example. It's also in multi-purpose contact lens cleaning solutions, where it's used to help remove lipid deposits from the lenses. Some mouthwashes include it as well.A study is now underway to see if poloxamer 407 can be used to align damaged blood arteries before surgically gluing them together.
Poloxamer 407 can also be employed in aqueous media because of its thermo gelling characteristics.
The FDA has approved Poloxamer 407 as an excipient in a variety ofpharmaceutical dosage forms.

EXCIPIENT PROFILE: -
Polyethylene glycol (PEG)
Description

Polyethylene glycol (PEG) is used for many purposes such as industrial manufacturing processes to the medicine. Polyethylene glycol (PEG) is mainly based on number of laxatives such as macrogol-containing products, such as Movicol and polyethylene glycol 3350, or Soft Lax, Miral.AX, Clearl.AX, Osmolax or Glycol ax.

Irrigation of the bowel with polyethylene glycol and electrolytes is included in bowel preparation therapy, normally indicated before a colonoscopy to ensure adequate visualization of the bowel. Therapeutic classification is as an Osmotic Laxative that works by drawing water into the lumen of the intestinal tract. Shown to decrease consistency and increase weight of stool in constipated patients at low doses.

Synonyms
- Macrogol
- Macrogol 3350
- Macrogol 4000
- Macrogol 6000
- PEG400
- polyethylene glycol 3350
- polyethylene glycol 4000
- polyethylene glycol 6000

CAS number -25322-68-3

Pharmacodynamics

Polyethylene glycol (PEG)use in gastroenterology is its inverse relation between molecular mass and intestinal absorbability, with practically no intestinal absorption at molecular masses exceeding 3000, its lack of intestinal enzymatic degradation or bacterial metabolism, and its water binding capacity.

Mechanism of action.

Polyethylene glycol (PEG) functions as Osmotic agent which causing excess water to be retained in the stool and it stimulating a bowel movement.

Absorption
Polyethylene glycol (PEG) are poorly absorbed after oral administration due tohigh and intermediate molecular weight.

Metabolism
Lack of intestinal enzymatic degradation (bacterial metabolism).

METHYL PARABEN
DISTILLED WATER

MATERIAL AND EQUIPMENT
List of drug and excipient:
The chemicals and equipment used for various experiments are enlisted as follows:

1.DONEPEZIL(API)
- Batch no :
- Mfg. date

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- Exp. date
- colour
- Mfg. .by
- Quantity

2.POLYMER

I. Natural polymer

- Batch no :
- Mfg.date
- Exp. date
- colour
- Mfg. .by
- Quantity

II. Poloxamer 407

- Batch no :
- Mfg.date
- Exp. date
- colour
- Mfg. .by
- Quantity

3.EXCIPIENTS

A. PEG400

- Batch no :
- Mfg.date
- Exp. date
- colour
- Mfg. .by
- Quantity

B. DISTILLED WATER

EQUIPMENTS: -

Name of equipment's and manufactures: -

Sr. No	Instrument name	Make/suppliers	Model
1	Laboratory centrifuge	Remi	C-24
2	Magnetic stirrer with hot plate	Eltek	MS 205
3	Refrigerator	SAMSUNG	-----
4	Lab stirrer	Remi	JDR 3030
5	Uv-visible double beam spectrophotometer	Shimadzu	Shimadzu UV-1800
6	FTIR	Bruker	Bruker Alpha-2
7	Diffusion cell apparatus	DBK	EDC-06
8	DSC	Metler	Star SEW 9.01
9	Digital analytical balance	Shimadzu	Shimadzu
10	Digital pH meter	Chemiline technologies	CL120
11	Brookfield digital viscometer	Brookfiled engineering laboratory,US	RVDV-2+Pro

REAGENTS

A. Methanol
B. Distilled Water
C. Buffer Solution
D. Ethanol

Reagents were available from institute laboratory which were of analytical grade.

Experimental work

Characterization of donepezil

Determination of physical constants

Description

The sample of donepezil was examined for its physical appearance and colour and it reported.

Determination of melting point of donepezil:

Melting point of donepezil can be done by using (ThieletubeLaboratoryglassware)conventional method designed to contain and heat an oil bath, care is taken to maintain uniform heating.

Spectral Analysis of Donepezil:

UV-visible spectrophotometry:

Lymdamax determination of Donepezil

Accurately weighed10.0 mg of Cinnarizine was transferred to dried 100 ml of volumetric flask and dissolve it by using methanol.

Make up the final volume with methanol and stock solution is prepared. Stock solution is further diluted to get the solution of 2,4,6,8,10,12 µg/ml.

All the solutions were scanned in the range of 200 to 400 nm using methanol as blank solution and its Amax was recorded.

Preparation of calibration curve of donepezil:

Accurately weighed 10.0 mg of donepezil were dissolved in volumetric flask of methanol to give stock solution of 100 ug/ml.

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This stock solution was diluted by using methanol to prepare solutions of2,4,6,8,10,12and20µg/ml range of solutions.
spectrophotometrically at previous reported Amax value 313 nm. were recorded

INFRARED SPECTROSCOPY
Infrared absorption spectrum determination of Donepezil:
IR absorption spectrum of Donepezil was recorded by keeping sample on ATR assembly and scanned from4000-400cm and IR spectrum was recorded using FTIR SPECTROPHOTOMETER (ALPHA-II Bruker)
Solubility analysis of donepezil

Solubility of drug was measured in distilled water.
3 ml of distilled water was taken in each glass vials of 5 ml capacity. The small amount of drug was added with some increase in proportion, stirring until saturation level is exists.
The given solution is filtered by through 0.45-micron membrane filter paper and then diluted to take absorbance at 313 nm.

Differential scanning calorimetry:
Donepezilwas assessed by carrying out thermal analysis. The sample were heatedfrom 25% to 250 c at the rate of 10 "c/min.
The purging of nitrogen gas during theexperiment can be done to keep the inert atmosphere at the rate of 40 ml/min. Thesmall number of samples are transferred and heated in crimped aluminum pan.

EXCIPIENTS CHARACTERIZATION:
Appearance, odour and colour of excipients: Excipients appearance, odour and colour were examined.

ISOLATION OF NATURAL CHIA SEED POLYMER

The seeds of Salvia his panica were soaked in water for overnight (seed-solvent ratio was 1:20),

Boiled for half an hour and mixed on magnetic stirrer for 1 hour so that the mucilage releases completely into water. The resulting mixture was centrifuged at 5000rpm for 50 min, after which three different layers were formed.

Only the gel layer was collected and dried in a hot air oven at 50°C. The product was grounded, passed through the sieve no. 80 and then stored at room temperature

Characterization of natural chia seed polymer

- Colour: off white
- Odor: odorless
- Taste: tasteless
- Appearance: flaky appearance
- Solubility: soluble in water

FORMULATION AND EVALUATION OF IN-SITU GELFOR NASAL DRUG DELIVERY SYSTEM
Screening of excipients:
Solubilitystudy:
The solubility of donepezil was determined in various oils,surfactants and co surfactants.
Donepezilwas added in 2 ml of each of selected oil, surfactant, co surfactants taken in 5ml of glass vials having stopper and mix it.

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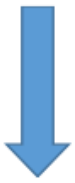
The sample were kept at 25°C for 24 Hours and then equilibrated samples are centrifuged at 3000rpm. for 15 mins.
They are then filtered through 0.45-micron filter diluted with methanolandabsorbance of given solutions were noted using UV-spectrophotometer and the concentrationDonepezil of was calculated in respective oils, surfactant and co-surfactant

FORMULATION OF IN-SITU GEL
COLD METHOD: -
Take a beaker and the in-situ gelling polymers are then progressively added in distilled water while stirring.
Sonicate it for 15 min.

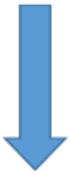


The dispersion is kept in the refrigerator at 4C until it forms a clear solution. This approach is employed when a gelling polymer such use as poloxamer, natural polymer.

Because the solubility of the polypropylene oxide chain of poloxamer reduces at high temperatures, resulting in precipitation or salting-out of a polymer, the polymeric dispersion of poloxamer is in solution at lower temperatures and converts into a gel at higher nasal temperatures. Similarly, polymer requires a lowtemperature to stay a solution at room temperature, and its hydrophobicity increases as the temperature

Take another beaker

The drug is mixed with a suitable amount of propylene glycol 400and maintained in the cool place by continuous stirring



Afterword's added the suitable amount of natural chia seed polymer and the preservative for the stability of a in-situ gel

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COMPOSITION OF IN-SITU GEL

Sr no.	Ingredients	F1	F2	F3	F4
1	DONEPEZIL				
2	NATURAL POLYMER				
3	POLOXAMER407				
4	METHYL PARABEN				
5	DISTILLED WATER				

- Donepezil (API): -
- Natural polymer: -
- Poloxamer 407: -
- Methyl paraben: -
- Distilled water: -

EVALUATION OF IN-SITU GEL

1.Drug Polymer Interaction Studies:

Fourier Transform Infrared Spectroscopy was used to determine the purity of the drug sample and interaction of the drug with the polymers

Infrared spectra of drug and polymers, alone and in mixture were taken. Then it was investigated for possible interaction between polymer and drug and compared with the standard IR spectra of the pure drug.

2.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.

3.pH of gel:

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

4.Measurement of Gelation Temperature:

It was determined by using modified Miller and Donovan technique. A 2 ml aliquot of gel was taken into the test tubes which were placed in water bath at 4 ºC inside an insulating chamber. The temperature of water bath was increased in the increment of 1ºC. The samples were examined for gelation, which was said to have occurred when the meniscus would follow non-Newtonian flow upon tilting.

5.Drug Content Estimation

Take 0.2 g of gel dissolve in distilled water sonicate the solution and make up the volume up to 100ml

Then take a 1ml solution and diluted with 10 ml distilled water. Finally, absorbance of prepared solution was measured at 313.0 nm by using uv visible spectrophotometer.

6.Gel Strength:

A sample of 50 g of nasal gel was taken in 100 ml graduated cylinder and gelled in thermostatically controlled water bath at 37 ºC. Weight of 35 g was placed onto the gelled solution. The gel strength, which is an indication for the viscosity of the nasal gel at physiological temperature, was determined as time in sec required by the weight to penetrate 5 cm into gel.

7.Viscosity:

The rheological studies were carried out using the Brookfield viscometer. The gel formulation under study was placed in the sample holder and then suitable spindle was selected and inserted perpendicular into the sample.

8.Diffusion study:

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