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IN SITU GEL -SUSTAINED NASAL DRUG DELIVERY

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ABSTRACT: *In situ* forming polymeric formulations are drug delivery systems that are in sol form before administration in the nasal cavity, but once administered, undergo gelation *in situ*, to form a gel. The formation of gel depends on factors like temperature modulation, pH change, presence of ions and ultra violet irradiation, from which the drug gets released in a sustained and controlled manner. In the recent years, nasal route has been identified as promising drug delivery route for systemic therapy. Mucoadhesive *in situ* gel formulations have demonstrated increase in the residence time in the nasal cavity as well enhancement of the permeation characteristics of the drug. The in situgel forming polymeric formulations offer several advantages like sustained and prolonged action in comparison to conventional drug delivery systems.

INTRODUCTION:

a) 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.

b) *In-Situ* Gel Delivery System: *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. [1-3]

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Advantages of *In-Situ* Gel Nasal Formulation:

- 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 actingdrug
- Improved patient compliance. [4-7]

Nasal Drug Delivery:

Intranasal route is considered for the drugs that are ineffective orally and are used chronically where rapid entry into the Circulation is desired

and they require small doses. The absorption of drugs from the nasal mucosa most probably takes place via the aqueous channels of the membrane. Therefore, as long as the drug is in the form of solution and the molecular size is small, the drug will be absorbed rapidly via the aqueous path of the membrane. The absorption from the nasal cavity decreases as the molecular size increases. Nasal mucociliary clearance is one of the most important limiting factors for nasal drug delivery. It severely limits the time allowed for drug absorption to occur. However, mucoadhesive preparations had been developed to increase the contact time between the dosage form and mucosal layers of nasal cavities.[8-13]

Nasal Anatomy and Physiology:

The nose is divided into two nasal cavities via the septum. The volume of nasal cavity is approximately 15 ml with a surface area of around 150 cm^2. **Fig. 1** shows the three distinct functional regions in the nose – the vestibular, respiratory, and olfactory [14]. Amongst these, the respiratory region is the most important for systemic drug delivery. The respiratory epithelium consists of basal cells, mucus containing goblet cells, ciliated columnar and non-ciliated columnar cell types as presented in **Fig. 2**. The cilia move in a wavelike fashion to transport particles to the pharynx area for ingestion [15]. Additionally, the cells in this region are covered by nearly 300 microvilli, providing a large surface area for absorption. Below the epithelium is the lamina propria, where blood vessels, nerves, serous glands, and mucus secretory glands may be found. [16, 17] The lamina propria also houses a dense network of capillaries, through which drug absorption takes place.

The nasal passage epithelium is covered by a mucus layer that is renewed every 10 to 15 min. [18] The pH of the mucosal secretions ranges from 5.5 to 6.5 in adults and 5.0 to 6.7 in children. [19] The mucus layer entraps particles, which are then cleared from the nasal cavity by the cilia. The mucus moves through the nose at an approximate rate of 5 to 6 mm/min resulting in particle clearance within the nose every 20 min. The nasal cavity also houses numerous enzymes.[20, 21] In humans, cytochrome P450 enzyme is forms have been identified and they are CYP1A, CYP2A and CYP2E. Other enzymes detected in the human nose include carboxylesterases and glutathione S-transeferases. [22-25]

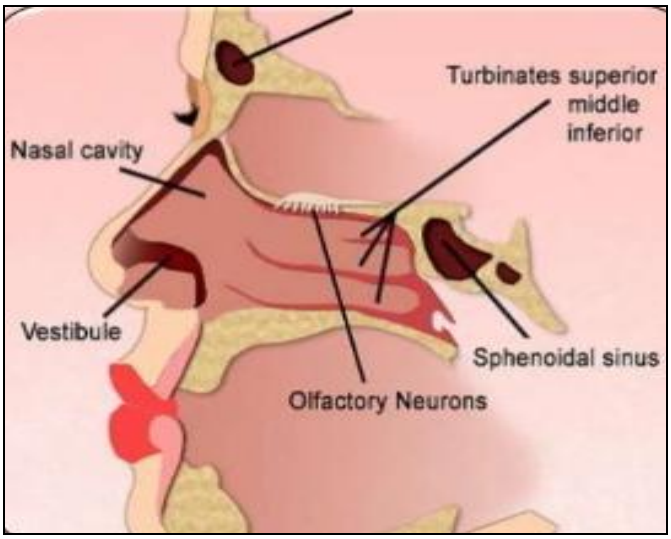

FIG.1: PARTS OF NASAL CAVITY CONSISTS OF NASAL VESTIBULE, INFERIOR TURBINATE, MIDDLE TURBINATE, SUPERIOR TURBINATE AND OLFACTORY NEURONS

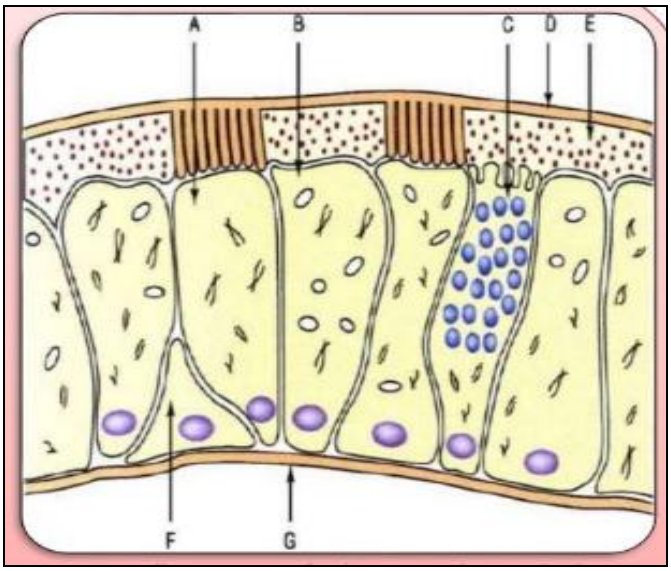

FIG.2: CELL TYPE OF THE NASAL EPITHELIUM SHOWING CILIATED CELL (A) NON CILIATED CELL (B) GOBLET CELLS (C) GEL MUCUS LAYER (D) SOL LAYER (E) BASAL CELL (F) BASEMENT MEMBRANE

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 transcellular or simple diffusion across the membrane, paracellular transport which occurs between cells and transcytosis which involves vesicle carriers 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 drugabsorption.[26-28]

a) 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 1000Daltons due to poor bioavailability.[29]

b) Second mechanism– also known as transcellular route which utilizes the lipoidal route for transport of lipophilic drugs.

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

E.g. chitosan a natural biopolymer from shell fish opens tight junctions between epithelial cells to facilitate transport.

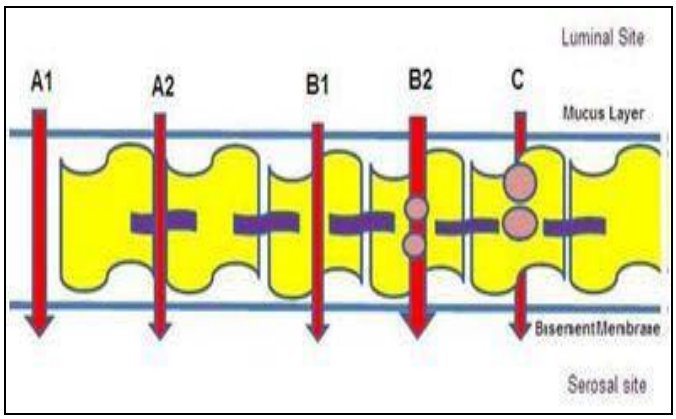

FIG.3: INTERCELLULAR SPACES, (A2) TIGHT JUNCTIONS, (B1) PASSIVE DIFFUSION, (B2) ACTIVE TRANSPORT, (C) TRANSCYTOSIS.

Barriers for Nasal Drug Delivery:

Low bioavailability:

Bioavailability of polar drugs is generally low; about 10% for low molecular weight drugs and not above 1% for peptides such as calcitonin and insulin. [30] The most important factor limiting the nasal absorption of polar drugs and especially large molecular weight polar drugs such as peptides and proteins is the low membrane permeability. Larger peptides and proteins are able to pass the nasal membrane using an endocytotic transport process but only in low amounts. [31]

Mucociliary clearance:

The drugs administered by nasal route are subject to fast clearance from the nasal cavity owing to mucociliary clearance. As a result of this, it leads to decreased transport of drugs across the nasal mucosa. This is especially the case, when the drug is not absorbed rapidly enough across the nasal mucosa. It has been shown that for both liquid and powder formulations, which are not bioadhesive, the half-life for clearance is of the order of 15 - 30 min. [32, 33] The use of bioadhesive excipients in the formulations is an approach to overcome the rapid mucociliary clearance. The clearance may also be reduced by depositing the formulation in the anterior and less ciliated part of the nasal cavity thus leading to improved absorption. [34, 35]

Enzymatic degradation:

Another contributing, but often less considered factor to the low bioavailability of peptides and proteins across the nasal mucosa is the possibility of an enzymatic degradation of the molecule in the lumen of the nasal cavity or during passage through the epithelial barrier. Both these sites contain exopeptidases such as mono and diamino peptidases that can cleave peptides at their N and C termini and endopeptidases such as serine and cysteine, which can attack internal peptide bonds.[36] The use of enzyme inhibitors and/or saturation of enzymes may be the approaches to overcome this barrier.

Factors that affect the rate and extent of absorption of drugs via the nasal route are as follows:

- 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.

Various approaches of *in-situ* gelation:

To cause sol to gel phase transition on the nasal surface the following type of systems are recognized:

i. pH Triggered system
ii. Temperature dependent system
iii. Ion activated system
iv. Induced photo polymerization gelation (UV Induced gelation) [37-42]

pH Triggered system:

All the pH sensitive polymer contain acidic or basic groups that either accept or release proton in response to in environmental pH. In the case of anionic groups swelling of gel increases as the external pH increases, but decrease if polymer contains cationic groups.

Temperature dependent system:

Temperature sensitive gels are classified into two type first negatively thermo sensitive and second positively thermo sensitive.CST is critical solution temperature at which temperature gelation occurs.

a) Negatively thermo sensitive:

Negative temperature sensitive gel had a lower critical solution temperature (LCST) and contract upon heating above the LCST.

b) Positively thermo sensitive:

Positive temperature sensitive gel had an upper critical solution temperature (UCST).

Ion activated system:

In situ formation is based on chemical reactions, following chemical reactions cause gelation, undergoes in situ gelling in the presence of mono- and divalent cations , including Ca^{2+} , Mg^{2+} , K^{+} and Na^{+}. Alginic acid undergoes gelation in presence of divalent/polyvalent cations.

Induced photo polymerization gelation:

Photo polymerization is commonly used for in situ formation of biomaterials. A solution of monomers or reactive micromere and initiator can be injected into a tissue site and application of electromagnetic radiation used to form gel. The photo reaction provides rapid polymerization rate at physiological temperature. The photo polymerization systems when introduced to the desired site via injection get photo cured in situ with the help of fiber optic cables and then release the drug for prolonged period of time.

Polymer used in *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. The potential use of PF-127 as an artificial skin has also been reported. Poloxamer 407 (PF-127) is a non ionic surfactant composed of polyoxyethylene 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.[43-46]

It has been considered for topical delivery of lidocaine, anti cancer agents and for the covering of burnt wounds. Its use in ophthalmic purpose was also studied using pilocarpine as model drug and PF-127 as vehicle. Finally it is also studied as a potential vehicle for injectables by both the intramuscular and subcutaneous routes. The aqueous solutions of Poloxamer are stable in the presence of acids, alkalis and metal ions. Commonly used Poloxamers include the 188(F-68 grade), 237(F-8grade), 338(F-108 grade) and

407(F-127grade) which are freely soluble in water. The flake form is designated as "F". Of all these PF-127 has a good solubilizing capacity, low toxicity and is considered as a good carrier for drug delivery systems. [47-50] PF-127 is more soluble in cold water than in hot water as a result of increased salvation and hydrogen bonding at low temperatures. These Poloxamers have the reversible property of being gel upon warming to room temperature and convert back to liquid when refrigerated (4-50C).[51]

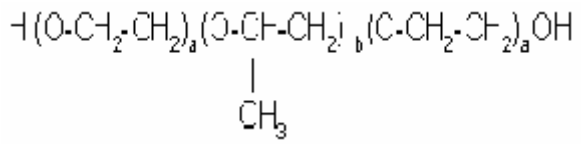

FIG.6: CHEMICAL STRUCTURE OF PLURONIC F-127 (A) ETHYLENE OXIDE PORTION (B) PROPYLENE OXIDE PORTION.

Hydroxypropyl methyl cellulose (HPMC) [52], Methylcellulose, Poly-(N isopropylacrylamide) [53-55] are the other thermo reversible polymers which can be used as a carrier in the delivery of various drugs. Following considerations must be kept in mind while selecting a thermo reversible polymer for nasal administration: [56]

- 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.[57]

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.[58-61]

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 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*. *In situ* gelling gellan formulation as vehicle for oral delivery of theophylline is reported.[62- 64]

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. The anionic character of this polymer is due to the presence of both glucuronic acid and pyruvic acid groups in the side chain.[65]

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 non toxicity. 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 mucoadhesive properties.[66, 67]

TABLE 1: SOME NASAL MUCOADHESIVE DELIVERY SYSTEMS

Drug	Mucoadhesive polymer	Dosage form
Metochlopramide hydrochloride	Poloxamer407/Polyethylene glycol	Gel
Metochlopramide hydrochloride	Carbopol 981	Solution, Gel, Powder

Evaluation of formulation:

- **Clarity:**

The clarity of in situ gel was examined by visually under dark background. [68]

- **pH of the gel:**

The normal range of nasal mucosal pH is 6.2 to 7.0 pH. The advisable pH of the nasal formulation is in the range of 5.5 to 7. For determining the pH of the formulation of nasal *in situ* gel, taken 1 ml quantity of each formulation transferred into a different beaker and diluted it with distilled water up to 25 ml and then pH of each formulation was determined by using pH meter (model no CL 54).

- **Drug content:**

1 ml of formulation was taken in 10 ml volumetric flask and then it was diluted with 10 ml of distilled water then volume adjusted to 10 ml, 1 ml from this solution again diluted with distilled water up to 10 ml. After this absorbance of prepared solution was measured at particular wavelength of the drug by using U.V visible spectrophotometer.

- **Viscosity measurement:**

Viscosity of nasal *in situ* gel was measured by using (cone and plate viscometer) programmable Brookfield dv2nd model viscometer .The viscometer was equipped with the temperature control unit and the sample were equilibrated for 10 min before the measurement. The viscosity of nasal *in situ* gel were recorded at various temperature from 4°c to 40 °c respectively against increasing the shear rate.

- **Measurement of gelation temperature:**

The gelation temperature was described by miller & Donovan technique. In this phase transition occurred from liquid phase to a gel phase. In this 2 ml *in situ* gel transferred to test tube and placed into water bath then the temperature of water bath increased slowly and constantly. Gel was allowed to equilibrate for 5 minute at each setting, then formulation was examined for gelation. When the meniscus would no longer move upon tilting to 90°, this is known as agelation temperature.

- **Determination of Mucoadhesive Strength:**

Mucoadhesive strength is known as the force to detach the *in situ* gel formulation from nasal mucosal tissue, for determining the mucoadhesive strength we use modified special chemical balance .A small section of nasal mucosa of goat was cut & tied or fixed on 2 glass vial with the help of rubber band or thread and stored it at 37°c ±2°c for 10 minute and then50mg of gel was placed on first vial and it placed below the height adjustable balance, while on another hand second vial was fixed in inverted position to the underside of the same balance after this height both vial were

adjusted and come in intimate contact for 5 minute to ensure the contact between nasal mucosal tissue and the *in situ* gel formulation. Then weight was put off on the other side of balance, until vials got detached, it expressed as the strength or stress in dyne/cm².

A. Stress is calculated by the formula:

$$\text{Detachment Stress (dyne/cm}^2) = M \times G \div A$$

Where

M = wt required for detachment of two vials in gm
G = acceleration due to gravity
A = Area of tissue exposed.

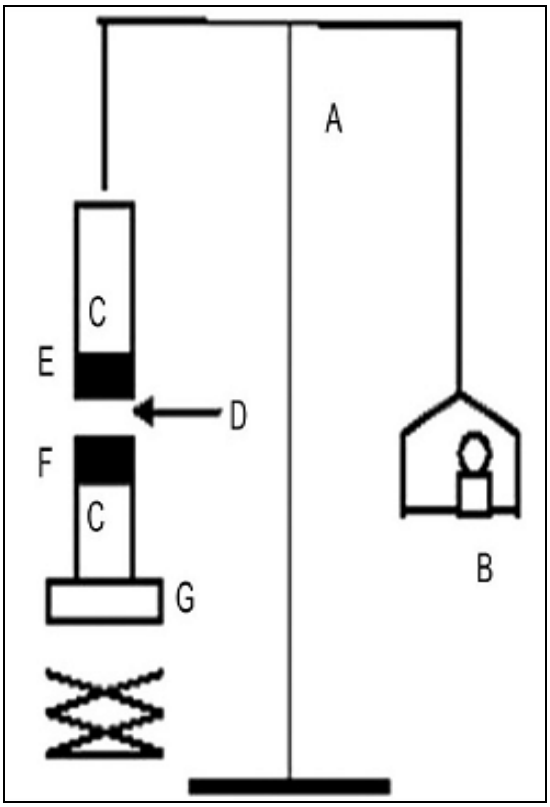

FIG.4: MODIFIED BALANCE, B WEIGHTS, C GLASS VIAL, E, F MEMBRANE, G HEIGHT ADJUSTABLE PAN.

- ***In vitro* diffusion study of *in situ* gel:**

Franz having capacity 2.4 diameter and 15 ml diffusion cell was used for in vitro diffusion study of in situ gel. Dialysis (.22µm pore size) or cellophane membrane (12000-18000 mol wt) with diffusion area .8cm² used.60 ml of phosphate buffer (6.4-6.6pH) was prepared and membrane was soaked with phosphate buffer (6.4- 6.6 pH), after this temperature was maintained at 37°C±0.5°C, after this phosphate buffer placed into the acceptor chamber and gel containing drug equivalent to 10 mg was placed in donor chamber, at predetermined time point, 1ml sample was withdrawn from acceptor chamber and then replaced the sample volume with equal amount of phosphate buffer after each sampling process, for a period of 300 minute, after each sampling, the samples were suitably diluted and measured spectrophotometrically at specific wavelength of drug. The concentration of drug was determined with the help of previous calibration curve.

- ***In vitro* Permeation Study of *In situ* Gel:**

To check permeation of drug and capacity of permeation enhancer which was added in formulation. Fresh nasal tissue section of goat obtains from slaughter house. Tissue was inserted in the diffusion cell. Gel containing drug equivalent to 10 mg was placed in donor chamber, at predetermined time point, 1ml sample was withdrawn from acceptor chamber and replacing the sampled volume with same amount of phosphate buffer, for a period of 300minute, after each sampling, the sample were suitably diluted and measured spectrophotometrically at specific wavelength of drug.

B. Permeability coefficient calculated from the slope of the graph:

$$P = \text{Slope} \times Vd \div s$$

Vd = volume of the donor solution
S = surface area of tissue
P = permeability coefficient.

D.S.C (Differential Scanning Calorimetry), X Ray Diffraction and FTIT (Fourier Transform Infra – Red Spectroscopy) Studies: used for drug and polymer interaction, compatibility and to check matrix formation [69-71].

CONCLUSION: Used of biodegradable, water soluble, thermo sensitive, pH sensitive polymer for the nasal *in situ* gel formulations can make them more acceptable and excellent drug delivery system. Exploitation of polymeric in situ gels for controlled release of various drugs, good stability and biocompatibility, bioavailability of drug characteristics make the nasal *in situ* gel dosage forms very reliable. Nasal *in situ* gel enhanced the nasal residence time due to its viscosity and

mucoadhesive strength. For optimum formulation can be achieved with better rheological properties, gelation time, gelation temperature, pH, mucoadhesive strength, and *in vitro* release and permeation studies.

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