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## An Overview: Mucoadhesive Nasal In-Situ Gel as Nasal Drug Delivery System

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Mucoadhesive in-situ gel; Nasal in-situ gel; Nasal residence time; Intranasal delivery; Sustained nasal drug delivery

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**Abstract:** In-situ forming polymeric gel formulations are drug delivery systems that are in solution form before administration in the nasal cavity, but once administered, undergo gelation to form a gel enhancing the flexibility of administration. The gel formation depends on factors like temperature modulation, pH change, presence of ions, and ultraviolet irradiation, from which the drug gets released in a sustained and controlled manner. In recent years, the nasal route has been identified as a promising alternative drug delivery route for systemic therapy. Various nasal formulations show less residence time while Mucoadhesive in situ gel formulations have demonstrated an increase in the residence time in the nasal cavity as well enhancement of the permeation characteristics of the drug will reduce the dosage frequency and it enhance patient compliance. With a brief introduction to nasal drug delivery, in this paper, the use of novel mucoadhesive in situ gels for the intranasal delivery of drugs is reviewed along with methods available for evaluating in situ gels.

## 1. Introduction

### 1.1 Nasal Delivery

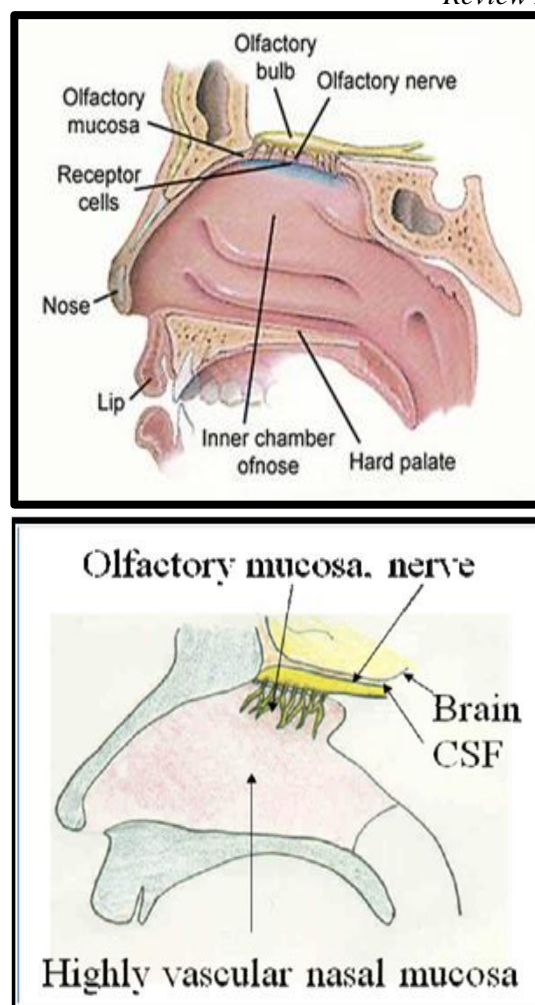
#### 1.1.1 Anatomy and Physiology of Nose

The nasal cavity is divided into two halves by the nasal septum and extends posterior to the nasopharynx, while the most anterior part of the nasal cavity, the nasal vestibule, opens to the face through the nostril. Breathing and olfaction are the major functions of human nose. But it also functioned as filtration and humidification of inhaled air before reaching in lowest airway. The nasal cavity has a mucus layer and hairs, those

helpful in the filtration of particles trapped in inhaled air. Additionally, the metabolism of endogenous substances, and mucociliary clearance also function of the nose. The human nasal cavity has a total volume of about 16-19ml and a total surface area of about 180cm<sup>2</sup> and is divided into two nasal cavities via septum. The volume of each cavity is approximately 7.5ml having surfaced around 75cm<sup>2</sup>.<sup>1</sup>

### Three Regions Can Be Distinguished in Each Part

- i. **The Respiratory Region:** - The respiratory region is the largest having the highest degree of vascularity and is mainly responsible for systemic drug absorption. The respiratory epithelium is composed of four types of cells namely non-ciliated, ciliated columnar cells, basal cells and goblet cells. These cells facilitate active transport processes such as exchange of water and ions between cells and motility of cilia. They may also serve to prevent drying of nasal mucosa.
- ii. **Olfactory Region:** - It is about 10cm<sup>2</sup> in surface area and it plays a vital role in transportation of drugs to the brain and CSF. The olfactory region is located on the roof of the nasal cavities, just below the cerebral form plate of the ethmoid bone, which separates the nasal cavities from the cranial cavity. The olfactory tissue is often yellow in colour, in contrast to surrounding pink tissue. The olfactory epithelial layer predominantly contains three cell types: - The olfactory neural cells, the subtentacular cells and the basal cells.
- iii. **The Vestibular Region:** - It is anterior part of nasal cavity. Surface area is 0.6cm. Nasal portion is covered by a stratified squamous keratinized epithelial with sebaceous gland. It is located at the opening of nasal passages and is responsible for filtering out the air borne particles. Drug absorption is very difficult in this region but is afforded high resistance against toxic environment. It is considered to be the least important of the three regions with regards to drug absorption.<sup>2</sup>



**Figure 1:** Representation of Olfactory Bulb

#### 1.1.3 Mechanism of Drug Permeation/Absorption by Nasal Route

The absorbed drugs from the nasal cavity must pass through the mucus layer. It is the first step in absorption. Small, unchanged drugs easily pass through this layer but large, charged drugs are difficult to cross it. The principle protein of the mucus is mucin which has the tendency to bind to the solutes, hindering diffusion. Additionally, structural changes in the mucus layer are possible as a result of environmental changes.<sup>3</sup>

#### 1.1.4 The Two Mechanisms Are as Follows

- i. **First Mechanism:** -It involves an aqueous route of transport, which is also

known as Para cellular route but slow and passive. There is an inverse log-log correlation between intranasal absorption and the molecular weight of water-soluble compounds. The molecular weight greater than 1000 Daltons show poor bioavailability.

- ii. **Second Mechanism:** - It involves transport through a lipoidal route known as the Trans cellular process. It is responsible for the transport of lipophilic drugs that show a rate dependency on their lipophilicity. Drugs can also cross cell membranes by an active transport route via carrier-mediated means or transport through the opening of tight junctions. For example chitosan, a natural biopolymer from shell fish opening of tight junctions between epithelial cells to facilitate drug transport.<sup>4,5</sup>

#### 1.1.5 Factors Affecting Nasal Drug Delivery System

Factors influencing absorption are related to nasal physiology; physic chemical Characteristics of drugs and formulation aspects.

##### 1.1.5.1 Biological Factors

- a. Structural Features
- b. Biochemical Changes
- c. Physiological Factors
- d. Blood Flow
- e. Nasal Secretions
- f. pH of the Nasal Cavity
- g. Mucociliary Clearance And Ciliary Beat Frequency
- h. Pathological Conditions
- i. Environmental Conditions
- j. Temperature
- k. Humidity

##### Physicochemical Properties of Drugs

- a. Molecular Weight
- b. Size

- c. Solubility
- d. Lipophilicity
- e. PKa and Partition Coefficient.

##### Physicochemical Properties of Formulation

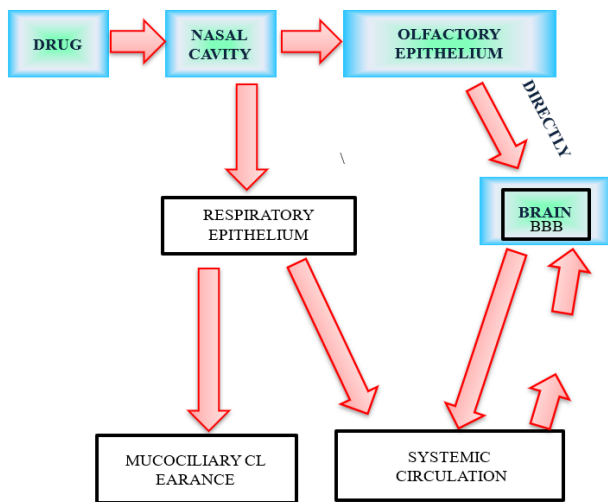
- a. Dosage Form.
- b. Viscosity.
- c. pH and Mucosal Irritancy.
- d. Osmolarity.
- e. Volume Of Solution Applied.

##### Device Related Factors

- a. Particle Size of the Droplet.
- b. Size and Pattern of Disposition.<sup>3</sup>

##### Intranasal Route for Brain Targeting

Blood brain barrier limits the entry of drugs and this makes the CNS treatment ineffective. Nose to brain drug delivery can revolutionize the treatment of brain disorders. The olfactory region, next to respiratory region is the foremost site from where drug can be absorbed directly into the brain by different mechanisms including trans cellular, Para cellular, olfactory (front of the brain) and trigeminal(back of the brain) neural pathways. The nerve cells of the olfactory epithelium project into the olfactory bulb of the brain, which provide a direct connection between brain and external environment. Intranasal delivery avoids gut and liver first pass metabolism so the drugs which get metabolised in GIT can be easily given by this route. The major challenges to this delivery are to achieve maximum absorption by efficiently targeting and retaining the formulation in the olfactory region. Drug can be targeted with the help of nanostructured lipid carrier, pressurized olfactory device, mucoadhesive micro emulsions. Intranasal delivery seems to be the most promising application form to improve CNS disorders including brain injuries. The following schematic representation shows route from nasal cavity to brain:-<sup>1,6-9</sup>



**Figure 2:** Route to brain from nasal cavity

### Delivery System Based Approaches for Intranasal Drug Delivery

#### i. Nasal Spray

Both solution and suspension formulations can be formulated into nasal sprays. The nasal spray can deliver 25-200 $\mu$ m due to availability of metered nasal pumps. The particle size and morphology (for suspensions) of the drug and viscosity of the formulation determine the choice of pump and actuator assembly.

#### ii. Nasal Drops

Nasal drops are one of the most simple and convenient systems developed for nasal delivery. Dose precision in nasal drops is not accurate which is major disadvantage of this system, and hence cannot be used for prescription products. It has been reported that nasal drops deposit human serum albumin in the nostrils more efficiently than nasal sprays.

#### iii. Nasal Gels

Nasal gels are high-viscosity thickened solutions or suspensions. There are many advantages of a nasal gel, which includes the reduction of post-nasal drip due to high viscosity, reduction of taste impact due to reduced swallowing, reduction of anterior leakage of the formulation,

reduction of irritation by using soothing/emollient excipients and target to mucosa for better absorption. So, this system can be considered convenient for nasal delivery.

#### iv. Nasal Powder

Nasal powders may be developed if solution and suspension dosage forms cannot be developed e.g., due to lack of drug stability. The advantages to the nasal powder dosage form are the absence of preservative and superior stability of the formulation. However, the suitability of the powder formulation is dependent on the solubility, particles size, aerodynamic properties and nasal irritancy of the active drug and /or excipients.

#### v. Liposomes

Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartments and wherein drugs and other substances can be included. Liposomal drug delivery systems present various advantages such as the effective encapsulation of small and large molecules with a wide range of hydrophilicity and PKa values. In fact, they have been found to enhance nasal absorption of peptides such as insulin and calcitonin by increasing their membrane penetration. This has been attributed to the increasing nasal retention of peptides. Protection of the entrapped peptides from enzymatic degradation and mucosal membrane disruption. The results demonstrated that this formulation was effective and that its mucoadhesive property is a viable option for a sustained release of insulin. Moreover, liposomal drug delivery systems were also reported as useful for influenza vaccine and non-peptide drugs such as nifedipine.

#### vi. Nanoparticles:

Nanoparticles may offer several advantages due to their small size, but



only the smallest nanoparticles penetrate the mucosal membrane by Para cellular route and in a limited quantity because the tight junctions are in the order of 3.9-8.4 Å. Controversial results are found when using nanoparticles in intranasal drug delivery.

**vii. Intranasal Microemulsion:**

Intranasal micro emulsion is one of the focused delivery options for non-invasive drug delivery to systemic circulation. It has been reported that micro emulsion formulations of clonazepam incorporated with mucoadhesive agents exhibited faster onset of action followed by prolonged duration of action in the treatment of status epileptics.

**viii. Intranasal Microspheres:**

Microsphere technology has been widely applied in designing formulations for nasal drug delivery. Microspheres are usually based on mucoadhesive polymers (chitosan, alginate), which present advantages for intranasal drug delivery. Furthermore, microspheres may also protect the drug from enzymatic metabolism and sustain drug release, prolonging its effect.<sup>9</sup>

**Application of Nasal Delivery**

Intranasal administration confers a simple, economic, convenient and non-invasive route for rapid drug delivery to systemic circulation

- i. Treatment of epilepsy and schizophrenia
- ii. Treatment of migraine
- iii. As an antidepressant
- iv. Treatment of angina pectoris and neurological deficit
- v. Treatment of amnesia
- vi. Intranasal delivery of peptides
- vii. Intranasal delivery of vaccine
- viii. Intranasal delivery of analgesics<sup>3</sup>

**In-Situ Gel & In-Situ Gelling System**

- **Gel-** Gel is the state which exists between solid and liquid phase. The solid component comprises a three-dimensional network of interlinked molecules which immobilizes the liquid phase.
- **In-Situ 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.

In-Situ gelation is a process of gel formation at the site of application after the composition or formulation has been applied to the site. In the field of human and animal medicine, the sites, topical application sites, surgical sites and other agents are brought into contact with tissues or body fluids. As a drug delivery agent, the in-situ gel has an advantage related to the gel being formed in-situ providing sustained release of the drug. At the same time, it permits the drug to be delivered in liquid form. This new concept of production a gel in-situ was suggested first time in early 1980s. In-situ means a Latin word at the place. Both natural and synthetic polymers are used for production of in-situ gels. In-situ gel forming drug delivery systems are principle, capable of releasing drug in sustained manner maintaining relatively plasma profiles.<sup>10</sup>

**Principle of In-Situ Gel**

Formulation of in-situ gel systems involves the use of gelling agent which can form a stable sol/suspension system to contain the dispersed drug and other excipients. The gelling of this sol/suspension is to be achieved in gastric environment, triggered by ionic complexation due to change in pH. The formulation adopted is a gellan gum or sodium alginate solution containing calcium chloride and sodium citrate, which

complexes the free calcium ions and releases them only in the acidic environment of the stomach. Gellan gum acts as gelling agent and can produce textures in the final product that vary from hard, non-elastic, brittle gels to fluid gels. The free calcium ions get entrapped in polymeric chains of gellan gum thereby causing cross linking of polymer chains to form matrix structure. This gelation involves the formation of double helical junction zones followed by re-aggregation of double helical Segments to form a three dimensional network by complexation with cations and hydrogen bonding with water.<sup>10</sup>

#### Importance of In-Situ Gelling System

- The possibilities of administering accurate and reproducible quantities compared to already formed gel.
- In-situ forming polymeric delivery system such as ease of administration and reduced frequency of administration improved patient compliance and comfort.
- Poor bioavailability and therapeutic response exhibited by conventional ophthalmic solution due to rapid precorneal elimination of drug may be overcome by use of gel system that are installed as drops into eye and undergoes a sol-gel transition from instilled dose.
- Liquid dosage form that can sustain drug release and remain in contact with cornea of eye for extended period of time is ideal.
- Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects.<sup>11</sup>

#### Advantages of In-Situ Gelling System

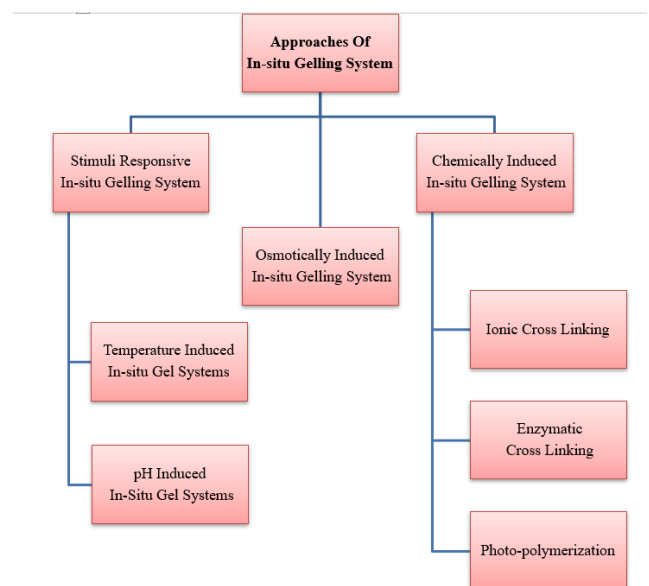
- Increased residence time of drug in nasal cavity.
- Decreased frequency of drug administration.
- Results in rapid absorption and onset of action.

- Avoid degradation of drug in gastrointestinal tract resulting from acidic or enzymatic degradation.
- Low dose required.
- Minimized local and systemic circulation and CNS possible.
- Offers lower risk of overdose of CNS acting drugs<sup>(12)</sup>

#### Properties of Nasal In-Situ Gel

- It should be low viscous.
- It should be free flowing to allow for reproducible administration to the nasal cavity, as droplet mist or as spray.
- Nasal in-situ gel should have long residence time.
- The nasal in-situ gel follows phase transition mechanism and to stand with shear forces in the nasal cavity wall.<sup>13</sup>

#### Approaches of In-Situ Gelling System



**Figure 3:** Approaches of In-Situ Gelling System<sup>14</sup>

*pH Induced In-Situ Gel Systems*

In situ gel based on physiologic stimuli is formation of gel induced by pH changes. All the pH-sensitive polymers contain pendant acidic or basic groups that either accept or release protons in response to changes in environmental pH. The polymers with a large number of ionizable groups are known as polyelectrolytes. Swelling of hydrogel increases as the external pH increases in the case of weakly acidic (anionic) groups, but decreases if polymer contains weakly basic (cationic) groups. The majority of anionic pH-sensitive polymers are based on PAA (Carbopol®, Carbomer) or its derivatives. Likewise, polyvinyl (Acetaldiethylamino Acetate) solutions with a low viscosity at pH 4 form hydrogel at neutral pH condition. Mixtures of poly(methacrylic acid) (PMA) and polyethylene glycol (PEG) also have been used as a pH sensitive system to achieve gelation.<sup>12, 15</sup>

*Temperature Dependent System*

Temperature sensitive gels are classified into two types 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).<sup>16, 17</sup>

In situ gel formation based on chemical reactions  
Chemical reactions that results *in situ* gelation may involve precipitation of inorganic solids from supersaturated ionic solutions, enzymatic processes, and photo-initiated processes.

*Ionic Cross Linking*

Polymers may undergo phase transition in presence of various ions. Some of the polysaccharides fall into the class of ion-sensitive

ones. While k-carrageenan forms rigid, brittle gels in replacement of small amount of K+, i-carrageenan forms elastic gels mainly in the presence of Ca<sup>2+</sup>. Gellan gum available commercially as Gelrite® is an anionic polysaccharide that undergoes *in situ* gelling in the presence of mono- and divalent cations, including Ca<sup>2+</sup>, Mg<sup>2+</sup>, K<sup>+</sup> and Na<sup>+</sup>. Gelation of the low-methoxypectins can be caused by divalent cations, especially Ca<sup>2+</sup>. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations eg. Ca<sup>2+</sup> due to the interaction with guluronic acid block in alginate chains.

*Photo-polymerization*

Photo-polymerisation is commonly used for *in situ* gel formation of biomaterials. A solution of monomers or reactive macromers and initiator can be injected into a tissue site and the application of electromagnetic radiation used to form gel. Acrylate or similar polymerizable functional groups are typically used as the polymerizable groups on the individual monomers and macromeres because they rapidly undergo photo-polymerisation in the presence of suitable photo initiator.<sup>18-20</sup>

Polymers used for the preparation of In-Situ Gelling System

**Table 1:** Polymers Used In the Preparation of In-Situ Gel<sup>3</sup>

Polyme r	Ori gin	Ch arg e	Solub ility	Mucoadhesive Capacity
• <b>pH sensitive Polymer</b>				
carbome r	Syn theti c	Ani oni c	Insolu ble	+++
Polyacr ylic Acid	Nat ural	Ani oni c	Insolu ble	+++
Cellulos e acetate phthalat e	Syn theti c	No n- ion ic	Insolu ble	++

• Temperature Sensitive Polymer				
Poloxo mer	Syn theti c	No n ion ic	Solubl e	++
Methyl Cellulos e	Nat ural	No n ion ic	Solubl e	+
Chitosa n	Nat ural	Cat ion ic	Solubl e	++
Hydrox ypropyl methyl cellulos e	Nat ural	No n ion ic	Solubl e	+
• Ion Sensitive Polymers				
Xanthan gum	Nat ural	Ani oni c	Insolu ble	+
Gellan gum(gel rite)	Nat ural	Ani oni c	Solubl e	++
Sodium alginate	Nat ural	Cat ion ic	Insolu ble	++

**Table 2:** Summary of the reported studies investigated as nasal mucoadhesive in situ gels<sup>21-38</sup>

Polymer	Gelling agent	Drug
Pluronic F 127	Polyethylene glycol	Vitamin B12 <sup>21</sup>
	Polyethylene glycol 400	Melatonin <sup>21</sup>
	Polyethylene glycol 15000	
	Carbopol 934P	Sumatriptan Succinate
	Carbopol 974P	Sumatriptan Succinate <sup>22</sup>
	Sodium carboxy methylcellulos e	Chlorpheniramin e maleate <sup>23</sup>

	Hydroxypropyl methylcellulos e	
	Carbopol 934P	Radix Bupleuri <sup>24</sup>
Pluronic 407	Chitosan Polyethylene glycol 4000	Fexofenadine hydrochloride <sup>25</sup>
Pluronic F68	Xanthan gum	Rizatriptan benzoate <sup>26</sup>
Pluronic F127	Locust bean gum	
Poloxame r	Hydroxypropyl methylcellulos e Xanthan gum	Pheniramine <sup>27</sup>
Carbopol 934P	Hydroxypropyl methylcellulos e	Diltiazem hydrochloride <sup>28</sup>
	Hydroxypropyl methylcellulos e Mucilage of Dellinia indica L.	Oxytocin <sup>29</sup>
Carbopol 934P	Hydroxypropyl methylcellulos e	Salbutamol Sulphate <sup>30</sup>
	Hydroxypropyl methylcellulos e	Salbutamol cromoglycate <sup>31</sup>
	Hydroxypropyl methylcellulos e	Midazolam <sup>32</sup>



	Mucilage of Ficus carica L.	
Chitosan	Hydroxypropyl methylcellulose	Ropinirole <sup>33</sup>
Pectin Chitosan	Hydroxypropyl methylcellulose	Ketorolac tromethamine <sup>34</sup>
Gellan gum	-	Scopolamine hydro bromide <sup>35</sup>
Gellan gum	-	Mometasone furoate <sup>36</sup>
		Dimenhydrinate <sup>37</sup>
Carbopol 934P	-	Metoclopramide Hydrochloride <sup>38</sup>

### Evaluation Parameters of Nasal In-Situ Gels

#### Clarity

The clarity may be determined by visual inspection under the black and white background.

#### Viscosity

The viscosity and rheological properties of the polymeric formulations, either in solution or in gel made with artificial tissue fluid and may be determined with different viscometer like Brookfield viscometer, cone and plate viscometer. The viscosity of these formulations should be such that it should be patient compliance.

#### Texture Analysis

The firmness, consistency and cohesiveness of formulation may be determined using texture analyser which mainly indicates the syringe ability of sol so the formulation can easily administer in-vivo.

#### Drug Content

Take 1ml of formulation and adjust to 10ml in volumetric flask and then dilute with 10ml of distilled water, 1ml from this solution again diluted with distilled water up to 10ml. after this take absorbance of prepared solution at a particular wavelength of the drug by using U.V visible spectroscopy.

#### Gel Strength

This parameter may be evaluated using a rheometer. Depending on the mechanism of the gelling agent used a specified amount of gel is prepared in beaker, from the sol form. This gel containing beaker is raised at certain rate, so pushing a probe slowly through the gel. The changes in the load on the probe can be measured as a function of depth of immersion of the probe below gel surface.



**Figure 4:** Mechanism of Determination of Gelling Strength

#### Sol-Gel Transition pH and Gelling Time

For in-situ gel forming systems, the sol-gel transition pH should be determined. Gelling time is the time required for the first detection of gelation of in-situ gelling system.

#### Drug Polymer Interaction Study and Thermal Analysis

Interaction study may be determined with Fourier transform infrared (FTIR) spectroscopy. During gelation process, the nature of the interacting forces can be evaluated using the technique by employing KBr pellet method. Thermo

gravimetric analysis (TGA) can be conducted for in-situ forming polymeric system to quantitate the percentage of water in hydro gel. Differential scanning calorimeter (DSC) conducted to observe if there are any changes in thermo gram as compared with pure active ingredients used for gelation.

#### Gelling capacity

Mix in-situ gel with simulated tear fluid (in the proportion of 25:7 i.e. application volume 25 $\mu$ l and volume of tear fluid in eye is 7  $\mu$ l) to find out gelling capacity of ophthalmic product. The gelation may be assessed visually by noting the time for and time taken for dissolution of the formed gel.



**Figure 5:** Measurement Of Gelling Capacity

#### Isotonicity Evaluation

Isotonicity is important characteristics of nasal and ophthalmic preparation. Isotonicity is maintained to prevent tissue damage or irritation of eye. All nasal preparation are subjected to isotonicity testing, science they exhibited good release characteristics and gelling capacity and the required velocity. Formulation mixed with few drops of blood and observed under microscope at 45x magnification and compared with standard marketed formulation.

#### Sterility Testing

Sterility testing is carried out as per the IP 1996. Incubate the formulation for not less than 14days at 300°-350°C in the fluid thioglycolate medium to find the growth of bacteria and at 200°-250°C

in soyabean casein digest medium to find the growth of fungi in formulation.

#### Accelerated Stability Studies

Formulation is replaced in amber-colored vials and sealed with aluminium foil for the short term accelerated stability at 40°±20°C and 75±5% RH as per ICH state guidelines.

#### In Vitro Drug Release Studies

For in-situ formulations to be administered by oral, ocular, the drug release studies are carried out by using the plastic dialysis cell. The cell is made up of two half cells, donor compartment and a receptor compartment. Both half cells are separated with the help of cellulose membrane. The sol form of the formulation is placed in the donor compartment. The assembled cell is then shaken horizontally in an incubator. The total volume of the receptor solution can be removed at intervals and replaced with the fresh media. This receptor solution is analysed for the drug release using analytical receptor media and placed on a shaker water bath at required temperature and oscillations rate. Samples are withdrawn periodically and analysed.

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