RESEARCH ARTICLE

Formulation and *In-vitro* Evaluation of Thermosensitive Ciprofloxacin HCL *In-situ* Gel for Local Nasal Infection

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ABSTRACT

Objective: A major concern about multi-site targeting is whether or not the nasal cavity is a viable route for delivering a broad range of medicines, from tiny molecules to biological macromolecules. Ciprofloxacin hydrochloride is a crystalline powder that is almost colorless. Slightly soluble in water with amphoteric properties in the form of a pKa of 6.09 for carboxylic acid and 8.8 for nitrogen on the piperazinyl ring, and the drug is 2.5% and has a pH of 3 to 4. *In situ* gel is a polymer solution in liquid form when applied to the mucosa. Once the solution is applied to the mucosa, it is transformed into a semisolid gel phase.

Methods: Seven were developed for various parameters for assessment.

Results: At physiological temperature, the gelation time for F1 and F5 was not achievable with gelation time for F3 and F4. With F3 and F7, a more tightly packed gel structure was found with the organization in a lattice pattern. Formulations containing Pluronics and chitosan demonstrated greater strength than formulations with chitosan/ethylcellulose or chitosan/chitosan ratio, which had the ethylcellulose/chitosan ratio as well as other factors in common. The interaction of chitosan with Pluronics may result in a greater molecular weight of hydrophobic molecules. It was discovered that the formulations' medication release percentage was 71 to 91% in the first eight hours. After seven hours, the total percentage of medication permeated through the sheep nasal membrane was 78%.

Conclusion: The improved formulation consisted of F3 and F7, both of which were safe for regular nasal administration, with the additional benefit of possessing required mucoadhesive strength and a temperature of 34°C for phase transition.

Keywords: Ciprofloxacin HCL, *In-situ* gel, Nasal, Pluronics, Thermosensitive.

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INTRODUCTION

An attractive method of multi-site targeting for delivering different medicines, including peptides, proteins, and vaccines, has been given to the nasal cavity.[1] Topical use of medicines to treat local illnesses affecting the nasal and paranasal sinuses, such as allergic or infectious rhinitis, is more advantageous via the nasal route.[2] Nasal mucosa can be used to safely and effectively transport low-bioavailability drugs across the systemic blood-brain barrier and into the bloodstream; the highly vascularized nasal epithelium has been employed to rapidly transport drugs that pass through the first-pass metabolism and gastric digestion of drugs after oral administration.[3] Although some therapeutic compounds cannot cross the blood-brain barrier (BBB) after being administered by other means, the nasal route bypasses this restriction and enables the delivery of such agents to the brain.[4] Drugs go directly from the nasal cavity to the brain through the olfactory neuroepithelium. Mucociliary clearance, which takes place in the nasal cavity, plays a significant role in how quickly drugs are absorbed into the body.[5] This process plays a significant role in quickly eliminating the medication from the nasal cavity, resulting in the drug's elimination sooner. It also delays the onset of local nasal illnesses and systemic circulation or brain by slowing the speed of absorption. To slow the fast clearance of medicines when given as aqueous solutions.[6]

A viscosity-enhancing method has been suggested in which the formulation incorporates viscosity-enhancing ingredients.[2] Formulations placed directly in the nasal cavity work well as an alternative to nasal liquid formulations, such as drops. These low-viscosity liquids are called "polymer solutions," and upon contact with the nasal mucosa, polymers will go into a gel.[7]

Different physical or chemical stimuli, such as temperature, pH, and ionic strength, may cause the sol-gel transition. Additionally, *in vivo* creation of a polymeric network increases the amount of time that the formulation has contact with the targeted area of absorption and extends the time the active component is delivered.[8]

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In-situ gelling methods offer benefits, they are beneficial for medication administration topical to the nasal cavity. The mucociliary clearance action is impeded, and locally active medicines cannot permeate the nasal mucosa to affect systemic absorption. To quickly disseminate throughout the circulatory system.[9]

Because of the high vascularity and permeability of the nasal mucosa, drugs are given to patients faster than they otherwise would be, which may be particularly helpful in treating severe nausea and vomiting associated with cancer treatment or migraine.[10]

There has been special interest in systemic medication delivery in patient compliance because it promotes compliance. It causes no discomfort, which enables the patient to self-medicate. More importantly, because nausea and vomiting are causes of stomach dysmotility, then nasogastric dosing ensures precise and constant medication dosage.[1]

The gel formed *in situ* is called *in situ* gel if applied to the mucosa, transformed into a semisolid gel phase under physiologic circumstances. There are two ways to gel anything. Depending on the temperature, pH, and the number of ions in the solution, it may be done by using energy or using a solvent.[11]

Pluronic triblock polymers are non-ionic, water-soluble polymers that have been utilized as medicinal excipients in formulations.[12]

Polar hydrophilic molecules having amphiphilic, surfactant, and membrane-binding properties depending on the temperature, Pluronics go through a gelling phase.[13]

Poloxamer is an example of a biocompatible polymer that belongs to the same category as Pluronics. Poloxamer is being studied for many other purposes in nasal preparations such as nasal, topical, rectal, vaginal, and intrauterine.[14]

Ciprofloxacin hydrochloride is a white, almost odorless crystalline powder. Solubility in water: 4.2 ppm Solubility in dehydrated alcohol: 17 ppm Solubility in acetone: 1.5 ppm Solubility in dichloromethane: 4.4 ppm Solubility in ethyl acetate: 10 ppm Solubility in methyl alcohol: 5 ppm Solubility in water: 2.5% At a slightly basic pH (7.4), where the medication is in zwitterionic form.[15]

Ciprofloxacin hydrochloride solution was photodegraded. The reaction rate increased when the pH decreased to about 3 to 4, and buffer type did not affect the initial concentration of the medication.[16]

The two most significant degradation products produced in acidic solutions were acid chlorides and hydrochloric acid. Nevertheless, when in solution, at pH 6 or above, many additional degradational products were found, which underwent secondary degradation after being exposed to light for an extended period. This means that the hospital's staff should shield ciprofloxacin and the liquid pharmaceutical formulation from light while being stored and handled. The biopharmaceutical categorization system categorizes ciprofloxacin as a drug with lower solubility and permeability, making it ineffective when administered orally.[17] Fluoroquinolones are synthetic bactericidal antibiotics that inhibit DNA gyrase (topoisomerase II) as their major mode of action. It is important to limit DNA synthesis and protein binding and penetration into a bacterial cell to reach this conclusion.[18]

MATERIALS AND METHODS

Materials

Ciprofloxacin hydrochloride (Samara Drug Industry, Iraq), Poloxamer 407 and 188 (HIMEDIA Laboratories, India), ethylcellulose (Sigma Chemical Co., USA), chitosan (Sigma Aldrich CO, USA), Tragacanth (HIMEDIA Laboratories, India), NaCl (Fluka ChemikaBioChemika, Switzerland), Benzalkonium Chloride (SigmaAldrichCO, USA),

Disodium Hydrogen Orthophosphate and Potassium Dihydrogen Orthophosphate (Sd fine-Chem limited, Mumbai, India).

Methods

Thermo-reversible Gel Preparation

The formulations were produced according to a cold technique, using the weight ratio of the mixture. Formulations made with mucoadhesive polymers chitosan and methylcellulose, including the P407 and P188 were medicated *in-situ* gelling formulations. Benzalkonium chloride and polymers were mixed with distilled water at room temperature in the indicated quantity. To delay the polymerization process, the dispersions were chilled. After this, the poloxamers were added, and the system was allowed to hydrate at 4°C as shown in Table 1. In this example, 0.1N Acetic Acid was used to dissolve the chitosan.[19]

Visual Appearance, Clarity, and pH of the *In-situ* Gel

Visual examination under the black and white background determines the clarity and color of the prepared solutions. The

Table 1: Preparation of different formulas of ciprofloxacin mucoadhesive *in situ* nasal gel (F1-F7)

Ingredients	*F1*	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*
Ciprofloxacin HCL (mg)	250	250	250	250	250	250	250
Poloxamer 407 (mg)	200	150	100	50	-	100	100
Poloxamer 188 (mg)	-	50	100	150	200	100	100
Chitosan (mg)	30	30	30	30	30	10	70
Ethyl cellulose (mg)	50	50	50	50	50	70	10
NaCl (mg)	0.9	0.9	0.9	0.9	0.9	0.9	0.9
Benzalkonium Chloride (mg)	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Distilled Water (mL)	100	100	100	100	100	100	100

formulation's pH was measured by immersing the pH meter's electrode in the formulation for one minute. Triplicate tests were conducted.[20]

Drug Content

Measuring drug content by HPLC was used to verify uniformity. To make the gel formulation, one hundred milliliters of a phosphate buffer solution with a pH of 6.8 was added to a volumetric flask and the mixture was filtered. In this instance, the solution was diluted with pH 6.8 phosphate buffer to a volume of 10 mL. Then, the absorbance was measured. Following the USP Pharmacopeia instructions, the assay was determined using the HPLC technique detailed below: Column size is 4 mm × 25 cm, and the product L1 is included in the packaging. phosphoric acid was first adjusted to a pH of three plus or minus 0.1 with triethylamine, then filtered and degassed in a 0.025 M mixture (87:13). The ambient temperature was around 30°C. Flow rate: 1.5 mL/minute. The system detects UV light at 278 nanometers. Generally, a solution is prepared by precisely weighing the amount of USP Ciprofloxacin HCl, then dissolving it in water to provide a concentration of 0.3 mg/mL. Ciprofloxacin was added to a 500 mL volumetric flask, about 400 mL of water was added, and the mixture was sonicated for about 20 minutes. The volume was then diluted to the appropriate level with the water, and the diluted solution was mixed. Next, a carefully measured volume of this solution was diluted with water to make a solution containing 0.25 mg of ciprofloxacin per milliliter.[21]

Gelation Temperature and Time Determination

A modified "visual tube inversion method" was used to find the gelation temperatures of formulations. Approximately 4 g of thermo-sensitive gel was added to each vial, and the mixture was then put into a thermostatic water bath and gradually heated to 37ºC over one minute. This was followed by an equilibration period of five minutes. Tiling the vials to the horizontal position to see the gel surfaces was done; each vial was then examined to determine its gelation temperature in 30 seconds. Each step was done three times. The described technique was used to determine the gelation time. Magnetically swirled 10 mL of the formulation was placed in a glass beaker and slowly heated up to a maximum of 80°C. The gelation time was the point at which the magnetic bead had stopped spinning. Triplicate measurements were performed.[22]

Study of Viscosity

In-situ gelling compositions were examined using a digital viscometer for rheological characteristics. Measurements were taken at 35.0 ± 0.1°C with a spindle speed of 100 rpm to get an output that ranges from 35.1 to 35.0.[23] Using a power-law constitutive equation, the viscosity (η) was found and fitted to the shear rate (γ) in S^{-1} and the flow index (n^{-1}). The viscosity index (m) was calculated, and it was adjusted to be equal to the shear rate in S^{-1} using the equation $\eta = m\,\gamma\,n^{-1}$. For any number of elements equal to one, the result is Newtonian behavior, as represented by a cylinder or a sphere, but if n is less than one, it means shear-thinning flow, and the more n is, the thinner the formulation.[24]

Gelling Strength

To assess the gel strength, a 25 g formulation was placed in a 100 mL beaker and the whole mixture was brought to a boil in a controlled temperature water bath at 34ºC. It took 35 g of weight to go 5 cm through the gel.[22]

Determination of Mucoadhesive Strength

The mucoadhesive potential was calculated using a modified pan balance to determine the force needed to remove each formulation from sheep nasal mucosal tissue. Following the sacrifice of the sheep, a sheep's nose was harvested from the butcher in around 15 minutes. This was done cautiously so as not to harm the nasal mucosal area of the sheep. To quickly ensure that the mucosal side was completely encased inside the glass vials, a rubber band was wrapped around each glass vial. After five minutes at a temperature of 34°C, the vials were connected to the equipment. The two vials were fastened on both the sides of a height-adjustable pan. Then they were allowed to raise and lower according to the weight of the vials. Adjusting the height of the second vial increased the physical contact between the first and second vials, resulting in uniform concentrations of each formulation in the nasal mucosa. Once the tissue had been made to come into touch with the sample for 2 minutes, it was confirmed that the intimate contact between tissue and sample had been achieved. Until the vials broke free from one other, the weight was increased on the pan on the opposite (right) side.[25]

The minimal weight needed for tissue separation is defined as the adhesive force, computed using the equation, and given as the formulation's bioadhesive force.

Detachment stress (Dyes/cm^2) = mg/A … Equation 1

Since gravity (980 cm/s^2) produces an acceleration of 980 cm/s^2, and the minimum weight needed for separating two vials in grams (g) is m, the area of tissue exposed in cm^2 is A. Every measurement was taken from the fresh nasal mucosa.[25]

Study of the Drug *In-vitro* Diffusion

The Franz diffusion cell dialysis membrane (Molecular weight 12,000–14,000 kDa) was used to conduct in-vitro diffusion experiments that used the gel as the receptor medium for four hours before usage. The F1 through F7 formulations were lined up sequentially in the donor chamber. 15 mL of phosphate buffer 6.8 with a magnetic stirrer at 34°C was used to prepare the receiver compartment, then kept at 100 rpm at that temperature during the experiment. A 1 mL aliquot was first taken to sample from the receptor compartment, and then a fresh 1-mL aliquot was added to the compartment every time a predetermined time interval elapsed until 8 hours. This period ran once an hour on the hour from 8 am to 8 pm. The spectrophotometer (Carry UV, Varian, Australia) was used to measure the samples. These were run on a phosphate buffer (pH 6.8) to create a blank, following which they were diluted and used in future measurements. A calibration curve was utilized to quantify the quantity of

ciprofloxacin dispersed.[20] After running several mathematical models, i.e., first-order, Higuchi model, and Korsmeyer-Peppas model, the results collected were then used to decipher the improved gel formulation's drug release mechanism and release rate kinetics new mathematical models. A model that shows the highest correlation was chosen by comparing R^2 values. To learn more about release kinetics, DDSolver was used.[26]

Ex-vivo Permeation Experiments (after Perfusion)

For the permeation experiments, the recently excised sheep nasal mucosa was obtained from the nearby butcher. Nasal mucosa (prepared by washing in saline and distilled water) was placed in the Franz diffusion cell (temperature maintained at 34 ± 0.5°C). The gel formulation was put on the mucosal surface of the donor chamber, with the formulation remaining within the chamber itself. While the medium was mixed using a magnetic stirrer, phosphate buffer saline (PBS) pH 6.8 was introduced to the receiver compartment. To begin, aliquots of 1-mL were taken from the receiver compartment every 30 minutes until the time designated, after which they were refilled with drug-free buffer for 7 hours. There were 60, 120, 180 minutes until the timer reached 420 minutes (7 hours). The materials were spectrophotometrically examined at 277 nm after filtering and dilution.[20,25]

Analysis of Statistical Data

A one-way analysis of variance (ANOVA) test was performed to see whether the various formulation outcomes differed. At ($\alpha = 0.05$), lower significance was signified by "statistically significant" results while higher significance was signified by "statistically insignificant."[27]

RESULTS AND DISCUSSION

Clarity, pH, and Visual Appearance of the *In-situ* Gel

In preparing the various prepared formulations, the researchers examined the finished products for color, clarity, and pH. The solution was clear to turbid opalescent dispersions and was maintained liquid at pH levels between 6 and 7, as shown in Table 2

Drug Content

Ciprofloxacin has the approval of the scientific community as the preferred analytical technique for a quantitative determination as raw material and nasal drops. 99% of the specified quantity; a value conforms with the USP's (98–102) claim.

Calculation of Gelation Temperature and Time

The physiological temperature of the nasal mucosa is 32°C–35°C. This product may be readily changed into a gel after it has been introduced into the nasal passage. At low temperatures, aqueous solutions have a hydration layer on top of the pluronic molecules. At higher temperatures, the bonds that cause aquaphobia (fear of water) break apart, releasing their solvent components, which causes hydrophobic interactions between the amide poly-oxypropylene domains to create a gel. The gel-like substance produced has micellar properties and was found in different configurations, for example, spherical, cylindrical, etc. First, the liquid micellar phase transforms into the cubic phase, then the hexagonal structure appears, and finally, the structure becomes completely cubic in temperature. As the concentration of the polymer rose, the gelation temperature increased. Lowering the gelation temperature may contribute to the larger micellar volume and number.[28]

A hydrophobic association is believed to have been formed as a consequence of increased chain friction and tangling. Because F1 and F5 could not gel at physiological temperatures, they could not deliver the requested time,[29] as shown in Table 3.

The gelation temperature may be modulated by varying the pluronic grade to obtain the required range. With F3 and F7, a more tightly packed gel structure was found with the organization in a lattice pattern. There is a significant increase in gelation temperature with chitosan. When pluronic gels are positioned densely and coated with chitosan, they increase in gelation temperature.[30]

Determination of Viscosity

Viscosity is a measure of a fluid's resistance to flow. When dealing with a system with a lot of internal friction, the higher the friction, the more power is required to create shear. K and n were the two dimensionless variables used in the process. This shows a Newtonian behavior when n is equal to one, but it indicates shear-thinning flow when n is less than one. Because the value of (n) is smaller, the formulation thins more during shearing. All formulations (F1–F7) had flow indices (n) close to 0.7 ($n > 0.5$) at 34°C,[25] as shown in Figure 1

Analyzing a Newtonian flow index (K) revealed that nasal administration was simple and uncomplicated.

Viscosity increased with increased temperature. To see whether sol/gel transition occurred, the rise in viscosity indicated that it occurred at body temperature. The gel's temperature-viscosity

Table 2: Determintion of pH and appearance of ciprofloxacin mucoadhesive *in situ* nasal gel (F1-F7)

Formula	*pH*	*Appearance*	*Clarity*
F1	6.7	White thin dispersion	Clear
F2	6.9	Turbid-white dispersion	Clear
F3	6.5	White thick dispersion	Clear
F4	6.5	Turbid-white dispersion	Clear
F5	6.2	White dispersion	Clear
F6	6.3	Opaque pourable dispersion	Clear
F7	6.2	Very thick gel	Clear

Table 3: Gelation temp. and gelation time for ciprofloxacin mucoadhesive *in situ* nasal gel (F1-F7)

Formula	*Gelation temp.*	*Gelation time (Sec) (mean ± SD)*
F1	33 ± 1°C	82 ± 3.1 Sec
F2	33 ± 1°C	72 ± 3.7 Sec
F3	32 ± 1°C	67 ± 1.8 Sec
F4	34 ± 1°C	74 ± 3.2 Sec
F5	33 ± 1°C	77 ± 2.5 Sec
F6	34 ± 1°C	70 ± 1.5 Sec
F7	35 ± 1°C	65 ± 2.4 Sec

Table 4: Gelling strength for *in situ* gel formulations (F1-F7)

Formula	*Gelling strength (Seconds) (mean ± SD)*
F1	70 ± 1.527 Sec
F2	74 ± 1.527 Sec
F3	92 ± 1.17 Sec
F4	74 ± 0.97 Sec
F5	65 ± 2.27 Sec
F6	66 ± 1.37 Sec
F7	115 ± 2.17 Sec

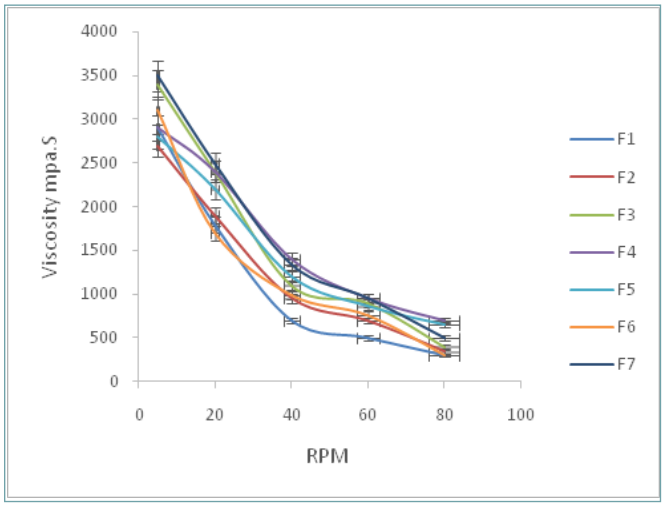

Figure 1: Viscosity for formulations F1–F7 at 34°C

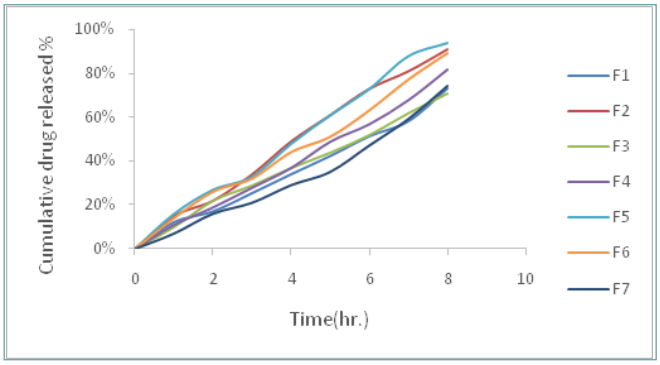

Figure 2: Comparative *in-vitro* diffusion profiles of formulations (F1-F7), in phosphate buffer pH 6.8 at 34 ± 1°C

curve showed newtonian behavior at low temperatures. Non-Newtonian behavior is signified by a sudden rise in viscosity around the gelation temperature. In agreement with pseudoplastic rheology, the viscosity of gels decreases as the shear rate increases.[20]

Gel Strength

The degree of stiffness of the gel is evaluated at the nasal mucosa's natural temperature of 34 ± 1°C. *In-situ* gel compositions were tested for their gel strength. As the ethylene oxide/propylene oxide ratio of pluronic 188 increased, the gel strength of formulations increased. The Pluronics and chitosan Formulations containing more Pluronic than the other formulas demonstrated a higher overall strength when compared to F6, which had a

Table 5: Mucoadhesive strength for *in situ* gel formulation (F1-F7)

Formula	*Mucoadhesive strength (Dynes/cm^2) (mean ± SD)*
F1	3200.05 ± 0.577
F2	3100.40 ± 0.517
F3	3900.6 ± 0.697
F4	2900.4 ± 1.17
F5	3100.7 ± 0.807
F6	2800.6 ± 0.657
F7	3850.95 ± 0.907

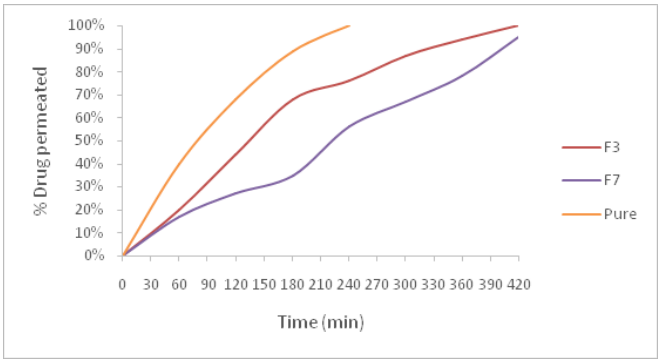

Figure 3: Cumulative drug permeation of formulation F3, F7, and pure ciprofloxacin HCL

higher ratio of ethylcellulose to chitosan as shown in Table 4. This could be because Pluronics cause the ethylcellulose to link together, increasing the molecular weight of hydrophobic molecules.[31]

Determination of Mucoadhesive Strength

An important physicochemical parameter for maintaining mucoadhesive retention time is the mucoadhesion strength. Mucoadhesion is determined by various factors, including polymer's concentration, excipients utilized in the dosage form, degree of hydration, polymer's molecular weight, and chain length.[32] Formulations may vary according to the ratio of polymers employed, and mucoadhesion characteristics may vary. The formula F3 and F7 produced more strength than the other formulas as shown in Table 5, this may be due to using two copolymers (as well as chitosan and mucoadhesive properties) in combination with the hydrating effect of mucin glycoprotein chains on polymeric chains, which ultimately leads to increased hydration.[33]

Study of the Drug *In-vitro* Diffusion

Ciprofloxacin HCL released and diffused from the formulations influences the drug delivery systems and directly influences the therapeutic effect. *In vitro* drug release studies must be performed to predict *in vivo* action accurately. The first phase of the Ciprofloxacin release from these gels exhibited a burst effect. Gelation proceeded, with the medication leaving at a slower rate as the reaction progressed. Matrix diffusion kinetics exhibits biphasic patterns of release. The formation of gels was shown to maintain the medication for eight hours (duration of the study). It was discovered

that the formulations' medication release percentage was 71% to 91% in the first eight hours as shown in Figure 2. It was shown that when combining pluronic surfactants, the drug release rate decreased, resulting in a greater resistant behavior and an increase in the creation of denser gels.[34] It was also observed that when the quantity of chitosan (F7) increased, the drug release rate was decreased, resulting in a denser gel that traps micelles. The findings mentioned above suggest that the structure of gel drug release functioned as a barrier. increased viscosity and prolonged drug release may be caused by the increase in the size of the micelle, which results in greater viscosity. To discover the mechanism of drug release, the study used some different kinetic models to match the release data. Higuchi provided the optimum formulations for all of the study's formulations, showing that diffusion regulated release mechanism. All formulations' diffusion exponent (n) values were less than 0.5, meaning the fictional drug release mechanism was most likely used.[26]

The research was done using living tissue (*Ex-vivo* permeation studies) as results shown in Figure 3.

After seven hours, the total percentage of medication permeated through the sheep nasal membrane was 78%. In the absence of polymers such as pluronic and chitosan, the medication could not exit the gel matrix, resulting in a delayed release. If you choose the slower release, you will get the benefits for a longer time and reduce the dosage interval.[25]

CONCLUSION

Rheological, gelation, and release characteristics *in vitro* were all desired attributes for mucoadhesive *in situ* gels. This treatment is safe for the nasal mucosa. The primary advantage of the *in-situ* gel is that it has a fluid-like consistency before being applied to the nasal mucosa. This attribute is particularly advantageous for patients because it is crucial for accurate dosage and the absence of the bitter taste of the antiemetic medication. In addition to oral and intravenous delivery, *in situ* gelling may be an additional route for intravenous and nasal administration. Ciprofloxacin *in-situ* intranasal gel formulation worked and was viable for delivery through intranasal spray with an extended drug residence duration in the nasal passage. Because the gel's thermo-reversible nature simplified administration and handling, mucoadhesive features increased nasal residence time, the gel's thermo-reversible nature helped administration and handling, and mucoadhesive characteristics increased nasal residence time. A formulation that was well-tailored to the specific characteristics of the intended application included ingredients F3 and F7 and having enough mucoadhesive strength and the appropriate phase transition temperature (34°C). The developed thermosensitive gel technology, as it seems, can administer ciprofloxacin HCl into the nose safely and effectively for treating localized nasal infections.

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