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Formulation and evaluation of naphazoline hydrochloride nasal gels

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Abstract

This study focuses on the formulation and evaluation of naphazoline hydrochloride nasal gels to bypass first-pass liver metabolism, ensuring consistent drug levels with reduced doses. Compatibility of lipids, polymers, and the drug was confirmed via FTIR and DSC analyses. Nasal gels were formulated using carbopol, poloxamer, and hydroxypropyl methylcellulose (HPMC). Gels containing carbopol were clear and sparkling, while those with HPMC appeared white and viscous. The formulations (NNGF1-NNGF8) had pH values between 6.7 and 6.9, spreadability ranging from 22.98 to 25.36 g.cm/sec, and viscosities between 939 and 941 centipoises. Drug content varied from 83.46% to 97.32%, which was deemed acceptable. Gel strengths ranged from 64% to 95%. The in-vitro release studies showed sustained drug release, with 95% of the drug released within seven hours. Among the eight formulations, NNGF1 exhibited the best performance, indicating a diffusion-controlled release mechanism with non-Fickian transport. The drug release followed both Zero-order and Korsmeyer-Peppas models.

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INTRODUCTION

Two interpenetrating phases—the gelling agent and a fluid component—can be thought of as making up a gel. Semisolid gels are either giant organic molecules interspersed with liquid or suspensions of small inorganic particles. Consequently, gels have properties that lie halfway between those of liquids and solids [1]. Regarding systemic impact, oral administration is the most often utilized. The oral bioavailability of certain medications results in less-than-ideal systemic effects, which has prompted researchers to look for more efficient ways to deliver these treatments systemically [2]. Commonly, nasal cavity conditions are treated locally, including rhinitis, migraines, colds,

discomfort, and congestion. It has been demonstrated in recent years that multiple drugs have improved systemic absorption when taken by nasal route. The nasal approach uses a variety of formulations, such as nasal gels, sprays, powders, etc. The primary method of administration to produce a quicker and higher amount of medication absorption is the trans-mucosal route of drug delivery, which refers to the mucosal lining of the nasal, rectal, vaginal, ocular, and oral cavities. This can be attributed to the anatomy and physiology of the nose passage, which includes a wide surface area, high total blood flow, a porous endothelium membrane, avoidance of first-pass metabolism, and easy accessibility [3]. Because the olfactory receptor cells are in direct contact with the central nervous system, nasal medication delivery also offers access to the brain that avoids the blood-brain barrier. Due to its high surface area and low proteolytic activity, the nasal route is appealing for vaccine distribution. In addition, compared to parenteral manufacturing, it lowers production costs and increases patient compliance. Owing to their excellent permeability, only tiny molecular-weight medicines are shown to be better absorbed through the nasal route [4].

MATERIALS AND METHODS:

Materials:

Naphazoline hydrochloride is a gift sample from Aurobindo Pharma LTD, Hyderabad, and other polymer mixtures such as Hydroxy Propyl Methyl Cellulose, Carbopol, Methylparaben, Poloxamer 188, Ethanol, and Phenyl mercuric nitrate.

Methods:

Pre-Formulation Study:

Compatibility Study:

FT-IR analyses to determine the compatibility of drugs and excipients: The formulation research was completed before the dosage forms were developed. I.R. spectrum investigations are primarily used to qualitatively identify chemicals in their pure form or in combination with polymers and excipients. They also serve as a tool for determining the nature of chemical interactions. I.R. is associated with covalent bonding; hence, the spectra can provide intricate details about the composition of molecules. This point was established by drawing similarities between the components' spectra and the pure compound [5].

Figure 1 Photography of FTIR spectrophotometer (BRUKER) Differential

Differential Scanning Calorimetric:

Distinctive Scanning To look into any changes in the drug's melting point after mixing it with the excipients, a calorimetric analysis of both pure pharmaceuticals and the polymers employed was conducted. Distinctive Scanning With a sample weight of 3 mg, the differential scanning calorimeter was used to acquire calorimeter curves at a heating rate of 10°C/min from 25° to 250°C in a nitrogen environment (20 mL/min) [6].

Formulation of Naphazoline hydrochloride Nasal Gels

Method of Formulation : Nasal gels containing naphazoline hydrochloride were made using the dispersion process. This approach involved dissolving weighed amounts of polymers, such as HPMC K100 and Carbopol 934, in a known volume of distilled water (Solution-A). The polymer solution was allowed to swell for 24 hours after complete dispersion. A precise amount of dissolved Poloxamer 188 and Naphazoline hydrochloride were added to this solution, together with a predetermined amount of dissolved phenyl mercuric nitrate (Solution-B) [7].

Using a high-speed magnetic stirrer set at 500 rpm, solutions A and B were thoroughly mixed while being careful not to trap any air. Distilled water was added to a uniform dispersion. After formation, the gel's pH was brought to 6.8.

Table 1 Formulation data of Naphazoline hydrochloride Nasal gels

Formulations Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Oxymetazoli ne (gms)	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Carbopol (gms)	2	2.0	3	3.0	3.0	3	2.0	2
HPMC (gms)	3.0	3	2.0	2	2	2.0	3	3.0
Poloxamer (gms)	1.0	2	2.0	3	1.0	2	2.0	3
Methyl Paraben (%)	2	2	2	2	2	2	2	2
Distilled water (ml)	100	100	100	100	100	100	100	100

Figure 2 Eight Formulation of Naphazoline hydrochloride Nasal gels

Evaluation of Nasal Gel:

The drug content, in vitro release tests, and physical-chemical characteristics of the formulated gel were assessed.

Clarity:

Visual inspection against a black and white background was used to assess the clarity of each formulation, and the results were scored as follows: turbid: +, clear: ++, and very clear (glassy): +++ [8].

Measurement of Ph:

The pH of the Naphazoline hydrochloride gel formulation was ascertained using a digital pH meter. 100ml of distilled water was used to dissolve 1 gram of gel. Using a digital pH meter (Systronics Digital pH meter), the pH of each formulation was measured [9].

Spreadability:

The Glass plate apparatus, employed for the investigation and appropriately adapted in the lab, was used to measure spreadability. The "slip" and drag properties of the gel were used to gauge spreadability. The following formula was used to determine the spreadability [10].

$S = M/T$

Viscosity:

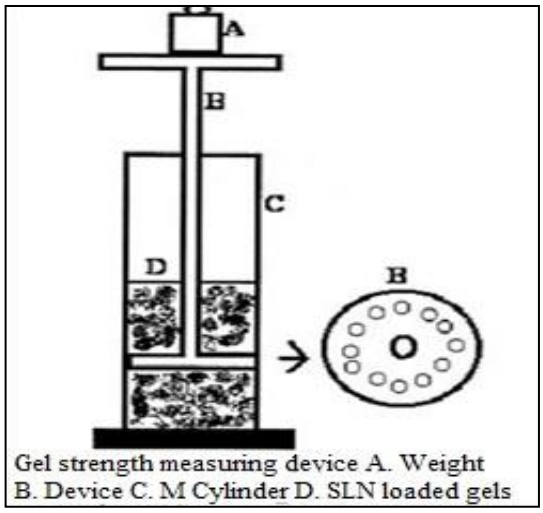
A brook field viscometer (DV II +) was used to measure the viscosity of each gel. Initially, the spindle was submerged in the gel until the spindle's notch made contact with the gel's surface. In the investigation, formulation gels of 100 grams apiece were employed. Based on the gel's viscosity, spindle number 61 was chosen. It revolved at 50 revolutions per minute, and dial readings were taken until two similar readings were obtained [11].

Figure 3 Brookfield Viscometer

Drug content:

The drug concentration of the gel was ascertained by dissolving a precisely weighed one-gram gel in a 6.8 pH phosphate buffer. Absorbance was measured using a UV-visible spectrometer at 250 nm following an appropriate dilution. The standard curve's slope was used to calculate the drug content. The following formula was used to calculate the drug content [12].

Drug content is calculated using the formula (concentration x volume taken) x conversion factor.



Gel strength measuring device A. Weight B. Device C. M Cylinder D. SLN loaded gels

Figure 4 Measurement of Gel strength

Gelling strength:

A thermostat permits penetrating the Carbopol and HPMC gel in a 100 ml measuring cylinder containing 50 grams of gel at 37oC. At physiological temperature, pressure is applied to the device sink at a depth of 5cm to measure time in seconds [13].

In vitro diffusion studies:

In vitro, diffusion of prepared gel was performed in a Franz diffusion cell via an egg membrane. 20 ml of phosphate buffer was used as the receptor compartment, and 5 gm of Naphazoline hydrochloride gel was evenly distributed on the membrane. The donor and receptor compartments were kept in contact, with a temperature of 37±0.50C. Pipette 5 ml of solution from the receptor compartment at predetermined time intervals (1, 2, 3, 4, 5, 6, and 7 hours) and immediately replace with fresh 2 ml phosphate buffer. The results of the in-vitro release profile obtained for all formulations were shown in Release order kinetics as follows [14],

Release Order Kinetics

Zero-order kinetics:

The following equation can depict drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the medication slowly, provided that the area remains constant and no equilibrium conditions are established [15].

$Qt = Qo + Ko\ t$

First-order kinetics:

To investigate the first-order release kinetics, the release rate data

$Log\ Qt = log\ Qo + K\ t / 2.303$

Higuchi model:

Higuchi created many theoretical models to investigate the release of water-soluble and low-soluble medicines embedded in semisolids and/or solid matrices. Mathematical formulas were obtained for drug particles scattered in a uniform matrix acting as the diffusion medium; the equation is

$Q\ t = K.H.\ t1/2$

Korsemeyer and Peppas Release model:

The release rate data is fitted to the following equation to investigate this model.

$F = Mt / M = K.tn$

RESULTS AND DISCUSSION:

Preformulation Studies

Compatibility studies:

FTIR spectral analysis was used to characterize the drug and polymers for any physical or chemical changes to the drug's properties. The results showed no interference in the functional groups since the principle peaks of Naphazoline hydrochloride remained unchanged in the spectra of the drug-polymer mixture.

Table 2 FTIR spectrum of drug and polymer mixtures

Functional Groups	Naphazoline hydrochloride	Carbopol	Poloxamer	HPMC	Mixture
C=C (Alkynes)	2360.95	1608.69	2438.10	3174.94	3244.38
NO_2 (Nitro Compounds)	1452.45	1552.75	1514.86	2692.72	2249.07
CH (Alkane)	1155.40	3084.28	3138.29	2852.81	2171.92
CO (Alcohols)	1116.82	1639.55	1542.56	1629.90	1643.62

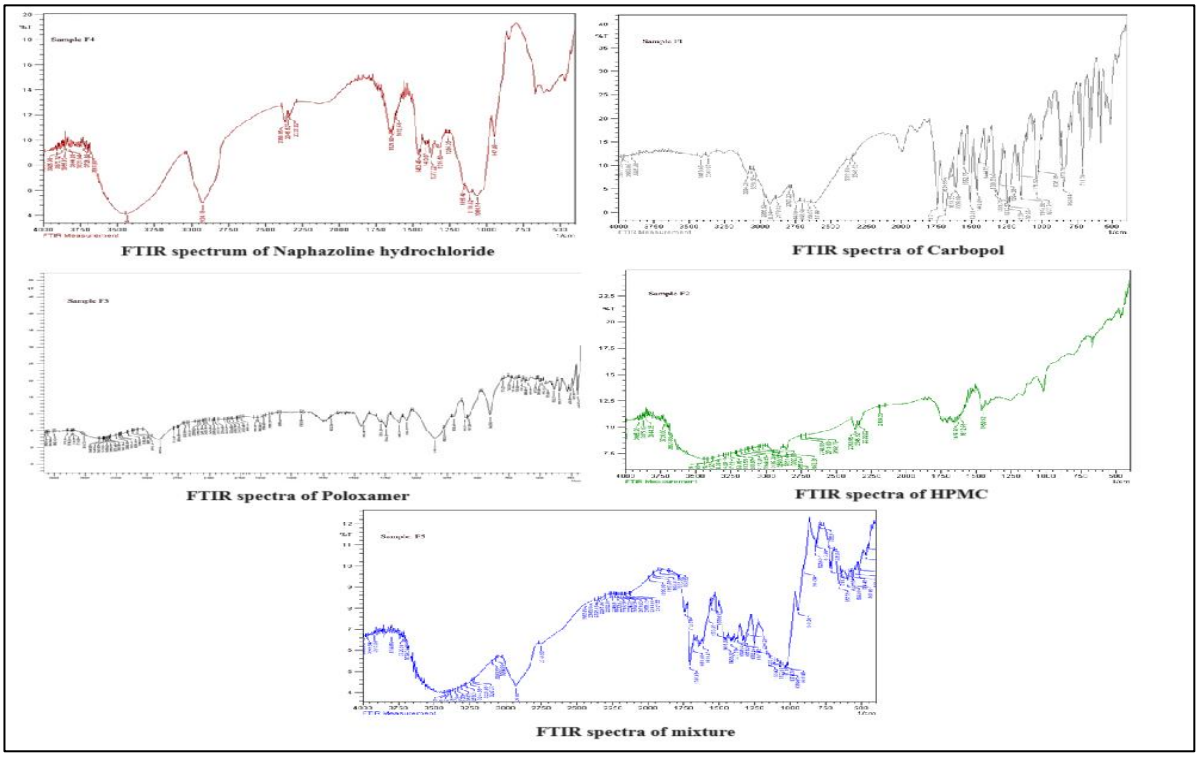


Figure 5 FTIR spectrums of drug and Polymer mixtures

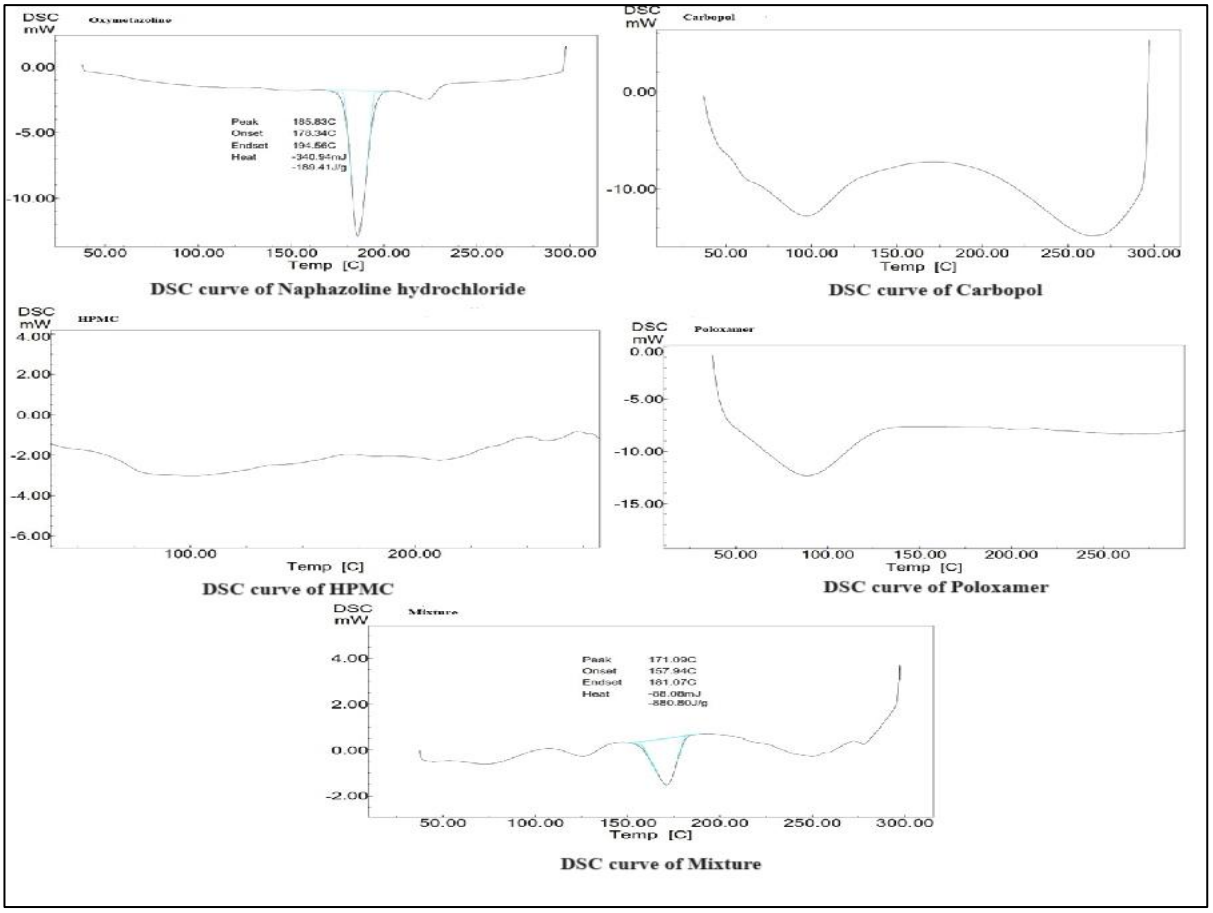


Figure 6 DSC curve of drug and polymer Mixtures

Differential Scanning Calorimetry:

Naphazoline hydrochloride's endothermic peak was discovered to be 194.56°C. The Carbopol endothermic peak was found to be 250oC. The HPMC's endothermic peak was determined to be 99oC. The Poloxamer endothermic peak was discovered to be 95oC. The mixture of the endothermic peak was found to be 95oC. There is no interaction between pure drugs, polymers, and lipids. As indicated in **Figure 6**.

Evaluation of Naphazoline hydrochloride NasalGels:

Clarity: Gels containing carbopol were observed to be transparent and dazzling. It was discovered that poloxamer and Hydroxy Propyl Methylcellulose gels were translucent and white viscous. It indicates that no particles were present in any of the gels. **pH:** All produced gel formulations (NNGF1-NNGF8) had pH values between 6.2 and 6.9, as indicated by **Table 3** and **Figure 7**.

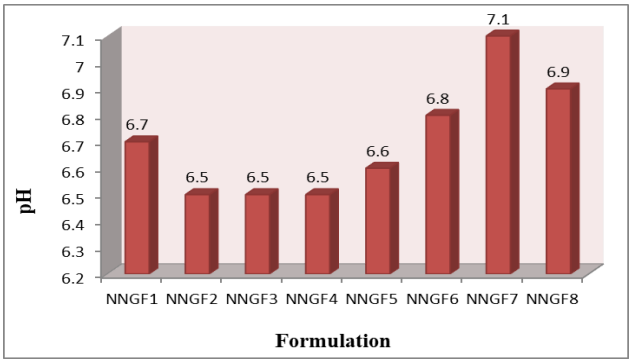


Figure 7 pH of Naphazoline hydrochloride Nasal gels

Spreadability: The spreadability rating shows how easily a modest amount of shear can spread the gel. The gels' spreadability ranged from 22.98 to 25.36 g/cm/sec, as shown in **Table 3** & **Figure 8**.

Viscosity measurement: A Brookfield viscometer was used to determine the viscosity of several formulations of Naphazoline hydrochloride gels. Every formed gel system's rheological behavior was examined. The ratio of the solid fraction—which creates the structure—to the liquid portion determines the consistency of a gel system. **Table 3** and **Figure 9** illustrate the range of values for viscosity of different designed gels, which were determined to be 941 to 939 centipoises.

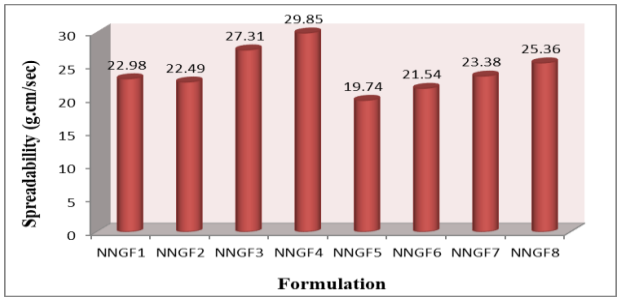


Figure 8 Spreadability of Naphazoline hydrochloride Nasal gels

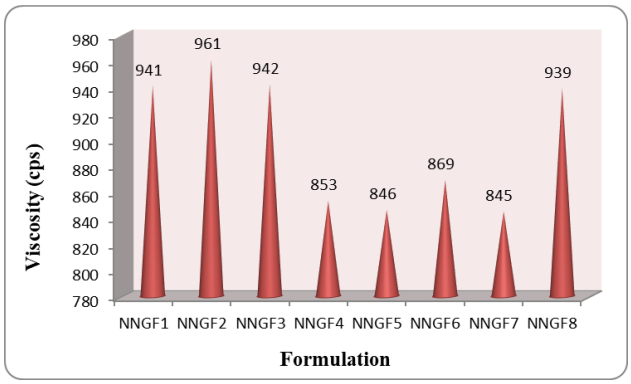


Figure 9 Viscosity of Naphazoline hydrochloride Nasal gels

Drug content: It was discovered that the drug content ranged from 97.32% to 83.46% in all manufactured gel formulations. The formulations' % medication content was judged to be acceptable. As a result, techniques used for gel compositions were determined to be appropriate, according to **Table 3** and **Figure 10**.

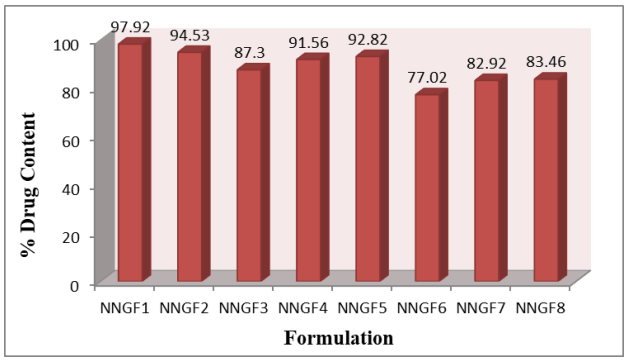


Figure 10 Drug Content of Naphazoline hydrochloride Nasal gels

Gel strength: All prepared gel compositions were found to have gel strengths ranging from 64 to 95%. The formulations' % medication content was

Table 3 Evaluation parameters of Naphazoline hydrochloride nasal gel

Formulation code	pH	Spreadability (g.cm/sec)	Viscosity(cps)	%Drug Content	Gelling strength(sec)
NNGF1	6.7	22.98	941.2	97.92	64±1
NNGF2	6.5	22.49	961.6	94.53	68±4
NNGF3	6.5	27.31	942.2	87.30	69±3
NNGF4	6.5	29.85	853.1	91.56	81±5
NNGF5	6.6	19.74	846.9	92.82	67±2
NNGF6	6.8	21.54	869.8	77.02	74±5
NNGF7	7.1	23.38	845.8	82.92	78±3
NNGF8	6.9	25.36	939..2	83.46	95±3

Table 4 Naphazoline hydrochloride in-vitro diffusion drug release from nasal gel

Time(Hrs)	% amount of drug release							
	NNGF1 (%)	NNGF2 (%)	NNGF3 (%)	NNGF4 (%)	NNGF5 (%)	NNGF6 (%)	NNGF7 (%)	NNGF8 (%)
1	42 ± 0.1	48 ± 0.3	40 ± 0.6	32 ±0.4	20 ±0.2	21 ±0.4	22±0.2	19 ±0.1
2	43 ± 0.4	44 ± 0.6	44 ±0.4	48 ±0.7	34 ± 0.5	37 ±0.6	36 ±0.4	28 ±0.4
3	47 ± 0.6	52 ± 0.4	58 ±0.2	62 ±0.1	46 ± 0.7	54 ±0.7	48 ±0.5	38 ±0.6
4	56 ± 0.3	62 ± 0.1	69 ±0.6	64 ±0.2	56 ± 0.6	64 ±0.8	54 ±0.7	46 ±0.5
5	78 ± 0.2	72 ± 0.6	78 ±0.2	75 ±0.6	72 ±0.1	76 ±0.9	62 ±0.3	58±0.3
6	79 ± 0.6	83 ± 0.7	87 ±0.7	83 ± 0.3	76 ± 0.2	82±0.3	65 ±0.6	71 ±0.7
7	95 ± 0.7	93 ± 0.8	94 ±0.3	94 ± 0.1	82 ±0.4	89±0.1	77 ±0.4	84± 0.8

judged to be acceptable. As a result, techniques used for gel compositions were determined to be appropriate. According to **Table 3** and **Figure 11**.

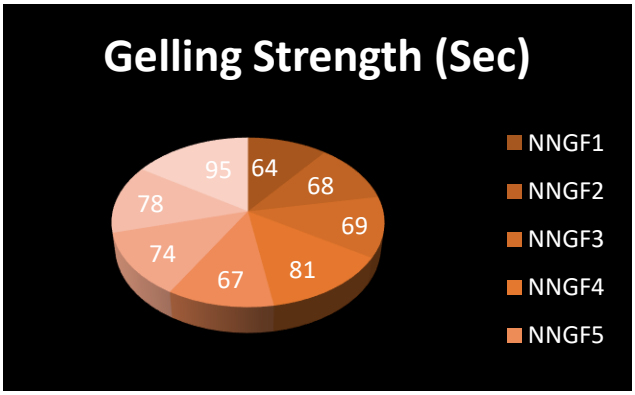


Figure 11 Gel strength of Naphazoline hydrochloride Nasal gels

***In vitro* drug diffusion studies:** The Franz diffusion cell was used as the diffusion test device for in vitro drug release investigations. According to these release investigations, the release sequence was discovered, as indicated in **Table 4**.

Kinetic Models Data Analysis: Diffusion data fitted to first order, zero order, Higuchi model, and Korsemeyer-Peppas drug release kinetic equations. All of the formulations—NNGF1, NNGF2, NNGF3, NNGF4, NNGF5, NNGF6, NNGF7, and NNGF8—had their kinetic values tabulated, correspondingly. Graphs are plotted against cumulative drug release percentage versus time (hours), log cumulative drug remaining percentage versus time (hours), cumulative drug release percentage versus square root of time, and log cumulative drug release percentage versus log time for the Zero order, First order, Higuchi model, and Korsemeyer-Peppas models.

Figure 12 In vitro Franz's diffusion cell

Korsemeyer-Peppas formulations for NNGF1, NNGF2, NNGF3, NNGF4, NNGF5, NNGF6, NNGF7,

Table 5 Drug Release Kinetics of Naphazoline hydrochloride Nasal Gels

Order Of Process	Zero order		First Order		Higuchi		Korse Meyer Peppass		Mechanism
	R^2	slope	R^2	slope	R^2	slope	R^2	N	
NNGF1	0.9056	11.476	0.8278	0.151	0.875	29.806	0.8969	0.823	Non-Fickian
NNGF2	0.9025	1.1449	0.4821	0.0664	0.7269	39.64	0.6042	0.943	Zero-order
NNGF3	0.9262	1.272	0.893	0.0838	0.9215	41.404	0.8592	0.852	Non-Fickian
NNGF4	0.939	1.386	0.6231	0.0779	0.7635	41.716	0.8095	0.756	Non-Fickian
NNGF5	0.9648	0.1224	0.971	0.0963	0.9409	47.483	0.9721	0.865	Non-Fickian
NNGF6	0.9659	0.1607	0.9804	0.1131	0.454	34.502	0.9706	0.831	Non-Fickian
NNGF7	0.9319	0.201	0.0158	0.0173	0.0103	5.7846	0.3191	0.975	Zero-order
NNGF8	0.9029	0.2005	0.1054	0.0235	0.0129	4.2484	0.2692	0.853	Non-Fickian

and NNGF8 were used; the correlation coefficients were R2=0.8969, 0.6042, 0.8592, 0.8095, 0.9721, 0.9706, 0.3191, and 0.2692, in that order. The NNGF1 formulation denotes a diffusion release mechanism followed by non-fiction transport and follows both the Zero order and Korsmeyer-Peppas models.

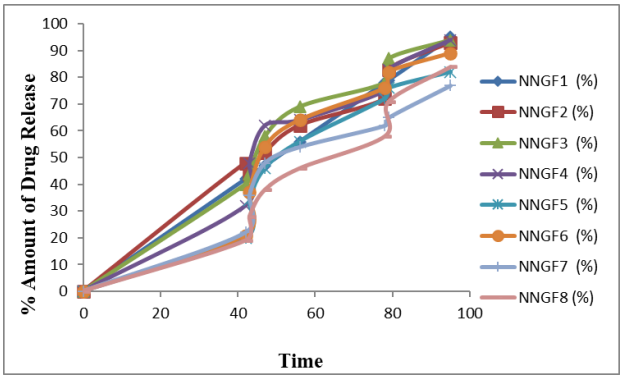


Figure 13 *In-vitro* drug release Profiles of Formulations NNGF1-NNGF8

CONCLUSION

It was determined that the formulations' % drug content was acceptable. All prepared gel compositions were found to have gel strengths ranging from 64 to 95%. Naphazoline hydrochloride was released in vitro with a prolonged half-life of 7 hours, with 95% of the substance released. The NNGF 1 formulation is the best of the eight; it implies a diffusion release mechanism followed by non-fiction transport and follows both the Zero order and Korsemeyer-Peppas models.

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Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

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