

# Development and Evaluation of Nanocarrier-Loaded Nasal Gel for Enhanced Drug Delivery

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## ABSTRACT:

### Objective:

To develop and evaluate a nano-carrier-based nasal gel of *Benincasa hispida* fruit extract (EEBH) for enhanced nasal retention, controlled release, and improved neuroprotective efficacy.

### Methods:

Liposome- and nanocochleate-loaded nasal gels were prepared using Poloxamer 188 and Carbopol 934P and optimized via statistical design. Formulations (GF1–GF13) were assessed for physicochemical properties including pH, viscosity, gel strength, spreadability, and drug content. In vitro and ex vivo diffusion studies were conducted to evaluate drug release. Neuroprotective activity was studied in scopolamine-induced memory-impaired rats using behavioral models such as Morris Water Maze and Y-maze models. All formulations showed good clarity and stability. The optimized formulation (GF6) exhibited suitable pH (6.5), high viscosity (1124.2 cP), good gel strength (59 s), high spreadability (24.5 cm<sup>2</sup>/min), and drug content (94.19%). GF6 demonstrated sustained drug release (>95%) following zero-order kinetics. Behavioral studies showed significant improvement in learning and memory.

### Conclusion:

The developed nano-carrier nasal gel of *Benincasa hispida* showed improved drug delivery and significant neuroprotective effects, suggesting its potential as a promising natural therapy for neurodegenerative disorders.

**Keywords:** Nano-carrier; Nanocochleates; Thermosensitive nasal gel; *Benincasa hispida*; Poloxamer 188; Controlled drug release; Alzheimer's Disease

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## INTRODUCTION:

Nasal drug delivery has emerged as a promising and non-invasive route for both local and systemic therapy due to its rapid onset of action, high patient compliance, and avoidance of hepatic first-pass metabolism. In recent years, the nasal route has attracted significant attention for the delivery of drugs to the central nervous system (CNS) via the olfactory and trigeminal pathways, offering a potential alternative to invasive methods. However, the clinical effectiveness of conventional nasal formulations is often limited by poor drug permeability, rapid mucociliary clearance, enzymatic degradation, and short residence time within the nasal cavity [1,2].

To overcome these limitations, advanced drug delivery systems such as nano-carriers have been extensively explored. Nano-carrier-based systems can enhance drug solubility, protect labile drugs from degradation, prolong nasal residence time, and improve absorption

across the nasal epithelium. Among various nano-carriers, liposomes and nanocochleates have gained considerable interest due to their biocompatibility, structural versatility, and ability to encapsulate both hydrophilic and lipophilic compounds [3]. Liposomes are spherical vesicular systems composed of phospholipid bilayers that closely resemble biological membranes, making them suitable carriers for nasal administration. Their ability to improve drug permeation and reduce toxicity has been well documented. However, liposomes may suffer from stability issues such as drug leakage and fusion during storage [4,5].

Nanocochleates are a novel lipid-based delivery system derived from liposomes by the action of divalent cations, particularly calcium ions. Structurally, nanocochleates are rigid, spiral-shaped lipid assemblies without an internal aqueous phase, which confer enhanced physical and chemical stability

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compared to liposomes. The tightly packed lipid bilayers in nanocochleates provide protection to encapsulated drugs and allow sustained and controlled drug release. Due to these advantages, nanocochleates have emerged as a promising alternative to conventional vesicular systems for nasal and nose-to-brain drug delivery [6].

Incorporation of nano-carriers into a gel-based system further improves their suitability for nasal administration. Nasal gels offer prolonged residence time, reduced nasal drainage, and enhanced contact with the nasal mucosa. Mucoadhesive gels, in particular, can interact with the mucus layer and reduce mucociliary clearance, thereby improving drug absorption and therapeutic efficacy. The combination of nano-carriers with a gel matrix represents a synergistic approach to enhance drug stability, retention, and controlled release in the nasal cavity [7,8].

*Benincasa hispida* (Thunb.) Cogn., commonly known as winter melon or ash gourd, is a medicinal plant belonging to the family Cucurbitaceae and has been traditionally used in various systems of medicine for the treatment of neurological, inflammatory, and metabolic disorders. Phytochemical studies have revealed the presence of flavonoids, triterpenoids, sterols, and phenolic compounds in *Benincasa hispida*, which contribute to its antioxidant, anti-inflammatory, neuroprotective, anxiolytic, and antidepressant activities. Despite its promising pharmacological potential, the therapeutic application of *Benincasa hispida* is limited due to poor aqueous solubility, low bioavailability, and instability of its bioactive constituents [9,10].

Considering these challenges, the development of a nano-carrier-based nasal delivery system for *Benincasa hispida* represents a rational and innovative strategy. Encapsulation of the plant extract within liposomes and nanocochleates can enhance drug stability, improve absorption, and provide controlled release, while incorporation into a nasal gel can further improve residence time and patient acceptability [11]. Therefore, the present study focuses on the formulation and characterization of liposomes and nanocochleates loaded with *Benincasa hispida* extract and their incorporation into a nasal gel system for improved nasal drug delivery.

### MATERIALS AND METHODS:

*Benincasa hispida* extract, Poloxamer 188 and Carbopol 934P were sourced from Cosmo Chem Pvt. Ltd., Pune, and supplied by Solanki Enterprise, Pune.

Distilled and deionized water was used throughout the study. Phosphate buffer saline (PBS), dialysis membrane, methanol, and other analytical reagents used for in vitro evaluation were of analytical grade and procured from Cosmo Chem Pvt. Ltd., Pune and used without further purification.

### Preparation of Benincasa hispida nano-cochleate gel

1. The cold method was used for the development of the in nasal gel using thermosensitive polymers. The different concentrations of thermosensitive (i.e., poloxamer 188) were taken and dissolved in cold water ( $4 \pm 2$  °C) with continuous stirring (250 rpm, 2 h) to obtain the clear solution.
2. This solution was kept overnight in the quiescent state at  $4 \pm 2$  °C to affect the complete dissolution of the polymer. The obtained clear poloxamer 188 solution was then mixed with a fixed concentration of carbopol 934P (a mucoadhesive agent).
3. The optimized nanococheleate formulation was dispersed into a gelling solution and stored at 4 °C in the refrigerator for evaluation [12].

**Table 1: DOE suggested and Experimental batches**

Formula tion code	Drug loaded nanococh elate formulati on equivalen t weight	Poloxa mer 188	carbo pol 934P	Wat er
GF1	18.20	1	0.75	30ml
GF2	18.20	0.1	0.75	30ml
GF3	18.20	1	0.5	30ml
GF4	18.20	1	0.75	30ml
GF5	18.20	0.55	0.75	30ml
GF6	18.20	0.55	1	30ml
GF7	18.20	0.1	0.5	30ml

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GF8	18.20	0.55	0.5	30ml
GF9	18.20	0.1	1	30ml
GF10	18.20	0.55	0.5	30ml
GF11	18.20	0.55	1	30ml
GF12	18.20	0.1	0.75	30ml
GF13	18.20	1	1	30ml

### EVULATION OF NANO-COCHLEATE GEL:

#### Physical appearances

Physical appearance of the prepared gels were evaluated by visual perception [13].

#### pH Analysis

The pH of the nanocochelete formulation in gel was evaluated using a pH meter. The electrode was dipped into the formulation, equilibrated for 1 min, and the pH value was recorded [14].

#### Viscosity

The viscosity of the prepared nanocochelete formulation gel formulations was measured at 37 °C by a Brookfield viscomete using spindle S18 at speeds of 15 rpm [15].

#### Drug Content

The drug content for the Benicasa hispida. Extract loaded liposomal in all nanocochelete formulation in gel formulations was determined by dissolving 10mg of prepared gel in methanol and then centrifuging at 6000 rpm for 20 min, followed by filtering through a filter medium. The solution was then diluted using phosphate-buffered saline (PBS, pH 6.5) and analyzed by UV spectrophotometry at 252 nm [16].

#### Gelling Temperature

Gelling temperature was determined by visual examination. Briefly, 6 mL of the prepared nanocochelete loaded in nasal gel was transferred into a 25 mL beaker and stirred with a magnetic bead. The beaker was placed on the thermostatic water bath, and the temperature was increased from 18 °C to 40 °C with continuous rotation at 50 rpm. The gel was then observed visually until the bead stopped rotating. The temperature at which bead rotation stopped was considered the gelation temperature [17].

#### Gel Strength

A sample of 1gm of the gel was put in a 10ml graduated cylinder and placed in a thermostatically controlled water bath at 37°C for 30 minutes for gelation of the formulas. A mass of 3.5g was placed on

the surface of the gel. The gel strength was determined by the time in seconds required by the weight to penetrate 0.5cm deep into the gel [17]

#### Spreadability

Spreadability is the area traveled per unit time (cm<sup>2</sup>/min) by the gel formulation. Whatmann filter paper (0.45 μm) was used for determination of spreadability of solution formulations GF1 to GF13. A 1-ml graduated pipette with rubber bulb was clamped vertically to the stand in such a way that the tip of pipette was at 2 cm above the horizontal surface of round shape filter paper. A 0.1-ml gel formulation was dropped at center of filter paper. At fixed time interval, 20 s, the surface area covered by the formulation was measured [17].

#### In vitro Franz Diffusion study

Drug release was evaluated using a Franz diffusion cell fitted with a dialysis membrane (MWCO 12,000 Da). The gel (0.5 g) was placed in the donor compartment, while phosphate buffer pH 6.5 was used as the receptor medium, maintained at 37 °C and stirred at 100 rpm. Samples (5 ml) were withdrawn at predetermined time intervals and replaced with fresh medium to maintain sink conditions. The drug content was analyzed by UV spectrophotometry and cumulative drug release was calculated [18].

#### Ex vivo permeation study

Franz diffusion cell having surface area of 0.77 cm<sup>2</sup> and receptor volume of 5 ml was used for the ex vivo drug permeation through Sheep nasal mucosa. Phosphate buffer having pH 6.4 was transferred to the receptor compartment. The Sheep nasal mucosa was then fixed between receptor and donor compartments. The Sheep nasal mucosa was towards the receptor compartment. Then 0.5 g of the sample was introduced into the donor compartment. Franz diffusion cell's temperature was kept constant 37 °C by the surrounding jacket water. The magnetic stirrer was used to stir the medium at a speed of 100 rpm. The samples were collected at regular intervals i.e. 1, 2, 3, 4, 5 and 6 hr and fresh phosphate buffer in the same quantity was introduced into the receptor compartment to keep the volume constant. The spectrophotometer was used for the analysis of the drug amount in the samples at 252 nm .and phosphate buffer pH 6.4 was used as a blank [19].

#### Kinetic analysis of drug release-

To determine the drug release mechanism, in vitro release data of the optimized batch (GF6) were fitted to zero-order, first-order, and Higuchi models. Based on the highest determination coefficient (R<sup>2</sup>), the release from GF6 followed zero-order kinetics,

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indicating a controlled and constant drug release pattern.

### Evaluation of Alzheimer's study activity of Benincasa hispida fruit juice in experimental Animals

#### Experimental Animals and Study Design

Adult male Wistar albino rats ( $\approx 200$  g) were used in the study and housed in polypropylene cages under standard laboratory conditions (temperature 22–25 °C, relative humidity 50–60%, and 12 h light/dark cycle). Animals were fed a standard pellet diet with free access to water. All experimental procedures were approved by the Institutional Animal Ethics Committee (IAEC). Rats were acclimatized for 7 days prior to experimentation.

Animals were randomly divided into five groups (n = 6):

- Group I: Vehicle control (saline)
- Group II: Negative control (restraint stress)
- Group III: Benincasa hispida fruit juice extract (200 mg/kg)
- Group IV: Optimized gel formulation of Benincasa hispida (200 mg/kg)
- Group V: Standard drug, rivastigmine (0.5 mg/kg)

Except for the normal control group, all animals were subjected to restraint stress and scopolamine-induced memory impairment (1 mg/kg, i.p.) for 28 days. Treatments were administered orally once daily for 28 days.

#### Behavioral Assessment

Learning and memory were evaluated before and after treatment using standard behavioral models:

1. **Morris Water Maze (MWM):** Spatial learning and memory were evaluated by measuring escape latency during training trials and time spent in the target quadrant during the probe test.
2. **Y-Maze Spontaneous Alternation Test:** Spatial working memory was assessed based on the percentage of spontaneous alternations and total arm entries [20].

## RESULTS AND DISCUSSION:

### Physical appearances

All formulations (GF1–GF13) were clear, indicating uniform mixing and good formulation stability, suitable for nasal application.

### pH Analysis

Most formulations showed pH values within the acceptable nasal range (4.5–6.5). GF6 (pH 6.5) was the

most suitable formulation, while GF1, GF3, and GF8 were slightly acidic and GF13 was marginally alkaline.

### ANOVA for 2FI model

#### Response 1:

##### pH

The statistical model for pH was significant ( $F = 5.11$ ,  $p = 0.0338$ ), indicating a reliable relationship between formulation variables and pH. Poloxamer 188 (A), Carbopol 934P (B), and their interaction (AB) significantly influenced pH ( $p < 0.05$ ), while stirring speed (C) had no significant effect. The model showed good fit ( $R^2 = 0.8362$ , Adeq Precision = 7.26), confirming adequate signal and predictability. Overall, polymer concentration—especially the interaction between Poloxamer 188 and Carbopol 934P—was the key determinant of nasal gel pH.

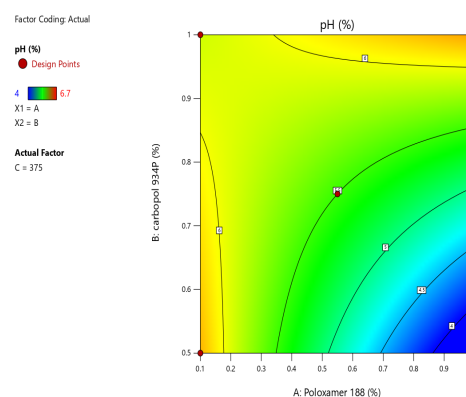
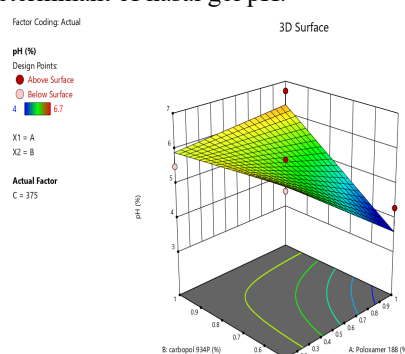


Figure 1: 3D Surface plot

Figure 2: Counter plot

#### Viscosity:

Viscosity of formulations ranged from 569.6 to 1124.2 cP. GF6 showed the highest viscosity, indicating better gel strength and nasal retention, while all formulations remained within a suitable range for nasal application.

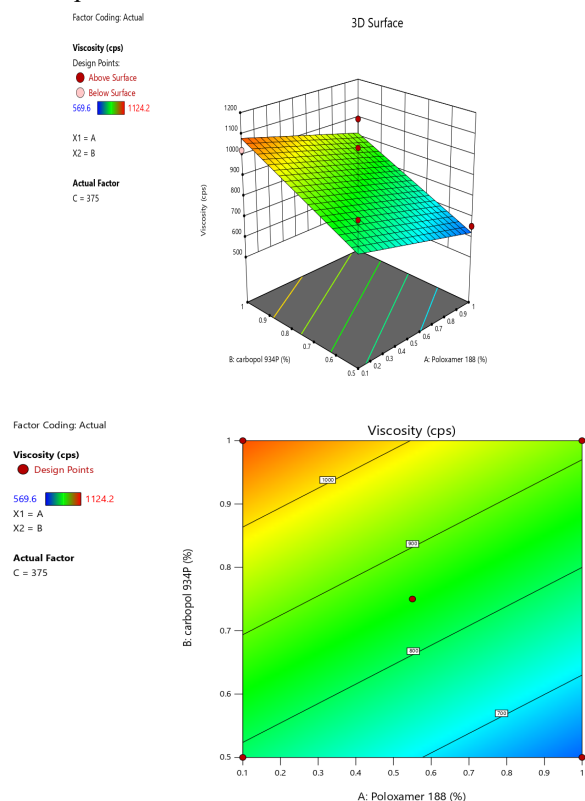
### ANOVA for Linear model

#### Response 2: Viscosity

The linear model for viscosity was statistically significant ( $F = 3.95$ ,  $p = 0.0474$ ), indicating that formulation variables influenced viscosity. Carbopol 934P (B) was the only significant factor ( $p = 0.0169$ ),

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showing a major positive effect on viscosity. Poloxamer 188 (A) and stirring speed (C) were not significant. The model showed moderate fit ( $R^2 = 0.5683$ ) with adequate signal (Adeq Precision = 5.79), confirming that viscosity was primarily governed by Carbopol 934P concentration.



**Figure 3: 3D Surface plot Counter plot**

### Drug Content

The drug content of formulations ranged from  $67.19 \pm 0.30\%$  to  $94.19 \pm 0.87\%$ . Most formulations showed acceptable and uniform drug content, with GF6 exhibiting the highest drug content, indicating good drug incorporation and content uniformity.

### Gelling Temperature

The gelling temperature of formulations ranged from 20–40 °C. Most formulations gelled near nasal physiological temperature, while GF6 showed the lowest gelling temperature (20–21 °C). Formulations gelling around 30–37 °C are considered most suitable for nasal application.

### Gel Strength

Gel strength values ranged from  $28 \pm 0.41$  to  $59 \pm 0.01$  s. GF6 exhibited the highest gel strength, indicating better gel integrity and nasal retention, while all formulations showed acceptable mechanical strength for nasal application.

### Spreadability

Spreadability values ranged from 5.6 to 24.5 cm<sup>2</sup>/min. GF6 showed the highest spreadability, indicating

better ease of application and uniform nasal spreading, while all formulations were within an acceptable range for nasal gels.

**Table 2: Evaluation Parameters of GF1- GF13**

Formulation code	Physical appearances	pH	viscosity	Drug content (%)	Gelling temperature (°C)	Gel Strength (S) Mean±std	Spr eability (cm 2/m in)
GF1	clear	4.2	569.6	82.2±0.14	24–26	36±0.02	22.5
GF2	clear	6.3	669.8	67.19±0.30	35–36	52±0.12	11.5
GF3	clear	4.3	654.9	85.6±0.06	26–28	42±0.45	6.8
GF4	clear	4.6	745.8	82.93±0.98	36–38	35±0.06	10.8
GF5	clear	5.7	1035.1	87.1±0.02	36–38	54±0.03	21.5
GF6	clear	6.5	1124.2	94.19±0.87	20–21	59±0.01	24.5
GF7	clear	6.1	932.5	90.97±0.93	40–41	30±0.65	7.8
GF8	clear	4	689.5	81.42±0.01	27–28	28±0.41	8.2
GF9	clear	5.5	1023.2	86.55±0.45	30–34	47±0.02	9.4
GF10	clear	5.4	668.2	88.34±0.69	24–28	55±0.36	11.7

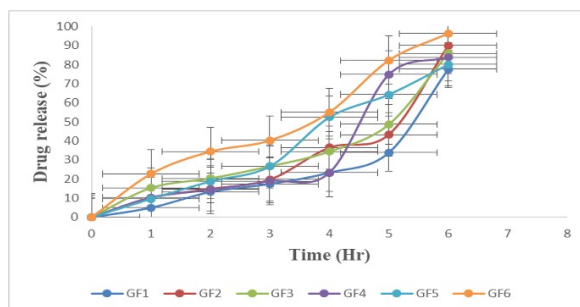
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GF1 1	clear	5 · 8	98 2.2	89. 78± 0.0 2	34- 36	49± 0.2 8	5.6
GF1 2	clear	6 · 4	98 7.2	90. 96± 0.0 1	35- 37	34± 0.0 9	6.8
GF1 3	clear	6 · 7	99 2.2	89. 21± 0.0 5	31- 32	38± 0.0 3	7.5

### In vitro Franz Diffusion study [8]

**Table 3: Drug release of GF1-GF6**

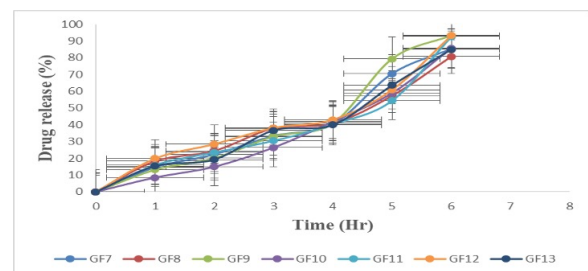
Time in (HR)	G F 1	G F 2	G F 3	G F 4	G F 5	G F 6
0	0	0	0	0	0	0
1	5.02 ± 0.02	10.2 7 ± 0.98	15.4 1 ± 0.87	10.3 6 ±0 .15	9.65 ± 0.01	22.7 6 ± 0.98
2	13.2 7 ± 0.78	14.8 6 ± 0.47	20.3 5 ± 0.63	14.4 3 ± 0.96	18.8 1 ± 0.96	34.4 3 ± 0.25
3	17.4 5 ± 0.06	19.8 1 ± 0.44	26.6 9 ± 0.45	18.9 1 ± 0.34	26.6 8 ± 0.55	40.2 6 ± 0.78
4	23.3 8 ± 0.45	36.5 1 ± 0.63	34.4 2 ± 0.75	23.3 5 ± 0.06	52.3 8 ± 0.72	55.0 0 ± 0.34
5	33.8 5 ± 0.58	43.3 4 ± 0.33	48.6 5 ± 0.96	74.7 3 ± 0.78	64.2 7 ± 0.14	82.1 9 ± 0.58
6	77.6 0 ± 0.12	89.9 3 ± 0.28	85.9 3 ± 0.48	83.7 4± 0.38	80.0 5 ± 0.96	96.3 4± 0.24



**Figure 5: Drug release of GF1-GF6**

**Table 4: Drug release of GF7-GF13**

Time in (HR)	GF 7	GF 8	GF 9	GF 10	GF 11	GF 12	GF 13
0	0	0	0	0	0	0	0
1	14. 62± 0.1 2	18. 25± 0.0 8	13. 16± 0.1 2	8.5 4±0 .03	15. 94± 0.9 6	19. 85± 0.9 9	15. 41± 0.9 9
2	22. 42± 0.3 6	24. 50± 0.0 6	20. 15± 0.8 7	14. 99± 0.0 4	23. 55± 0.4 8	28. 48± 0.7 9	19. 30± 0.6 3
3	33. 39± 0.0 2	37. 94± 0.4 78	33. 04± 0.0 2	26. 44± 0.0 1	30. 43± 0.3 9	38. 16± 0.0 6	36. 70± 0.7 8
4	40. 34± 0.0 9	40. 86± 0.3 2	40. 89± 0.9 6	41. 92± 0.3 8	40. 28± 0.0 4	43. 08± 0.0 1	39. 95± 0.0 2
5	70. 54± 0.1 4	57. 30± 0.6 5	79. 41± 0.0 2	58. 95± 0.0 3	54. 41± 0.0 6	60. 86± 0.8 7	63. 59± 0.0 4
6	85. 44± 0.3 6	80. 79± 0.0 2	93. 40± 0.4 4	85. 72± 0.8 5	92. 67± 0.0 8	93. 24± 0.3 6	85. 03± 0.0 3



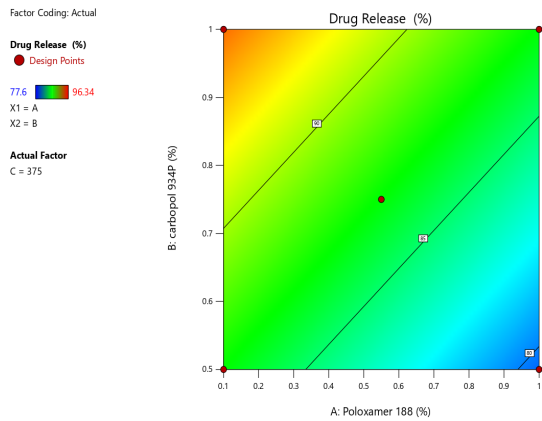
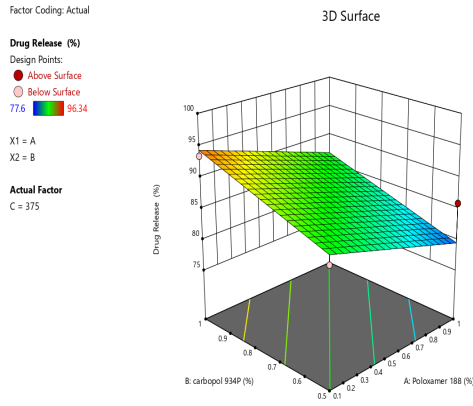
**Figure 6: Drug release of GF7-GF13**

### ANOVA for Linear model

#### Response 3: Drug Release

The linear model for drug release was statistically significant ( $F = 4.15$ ,  $p = 0.0419$ ). Poloxamer 188 (A) and Carbopol 934P (B) significantly influenced drug release ( $p < 0.05$ ), while stirring speed had no significant effect. The model showed acceptable predictability ( $R^2 = 0.5807$ , Adeq Precision = 6.17), indicating that polymer concentrations were the key factors governing drug release behavior.

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**Figure 7: 3D Surface plot**

**Figure 8: Counter plot**

## Ex vivo permeation study

**Table 5: Drug release of GF1-GF7**

Time in (H R)	GF 1	GF 2	GF 3	GF 4	GF 5	GF 6	GF 7
	0	0	0	0	0	0	0
1	8.5 8±0 .02 15	11. 94 ±0. 059	15. 18 ±0. 045	7.9 7±0 .00 45	18. 36 ±0. 012	19. 58± 0.0 148	11. 04± 0.0 09
2	13. 85± 0.0 63	14. 75 ±0. 012	19. 01 ±0. 062	11. 75± 0.0 02	28. 49 ±0. 006	34. 02± 0.0 08	15. 95± 0.0 23
3	24. 68± 0.0 489	22. 43 ±0. 019	32. 06 ±0. 005	20. 55± 0.0 06	39. 24 ±0. 021	40. 07± 0.0 06	22. 27± 0.0 18
4	36. 16± 0.0 25	39. 55 ±0. 082	54. 62 ±0. 009	37. 51± 0.0 03	43. 49 ±0. 003	56. 06± 0.0 42	40. 74± 0.0 24

5	66. 73± 0.2 145	64. 14 ±0. 013	81. 68 ±0. 048	71. 28± 0.0 021	72. 07 ±0. 049	85. 36± 0.0 02	70. 25± 0.0 28	
	6	80. 57± 0.6 523	87. 02 ±0. 009	90. 20 ±0. 024	86. 94± 0.0 96	84. 85 ±0. 002	95. 23± 0.0 14	83. 39± 0.0 023

**Table 6: Drug release of GF8-GF13**

Time in (H R)	GF 1	GF 2	GF 3	GF 4	GF 5	GF 6	GF 7
	0	0	0	0	0	0	0
1	8.5 8± 0.0 021	11. 94± 0.0 21	15. 18 ±0. 623	7.9 7± 0.0 89	18. 36± 0.0 24	19. 58± 0.0 021	11. 04± 0.0 42
2	13. 85 ±0. 256	14. 75± 0.0 59	19. 01 ±0. 049	11. 75 ±0. 065	28. 49± 0.0 96	34. 02± 0.0 049	15. 95± 0.0 63
3	24. 68 ±0. 148	22. 43± 0.0 23	32. 06 ±0. 036	20. 55 ±0. 028	39. 24± 0.0 482	40. 07± 0.0 65	22. 27± 0.0 02
4	36. 16 ±0. 236	39. 55± 0.0 021	54. 62 ±0. 048	37. 51 ±0. 005	43. 49± 0.0 23	56. 06± 0.0 12	40. 74± 0.0 89
5	66. 73 ±0. 005	64. 14± 0.0 03	81. 68 ±0. 003	71. 28 ±0. 062	72. 07± 0.0 484	85. 36± 0.0 592	70. 25± 0.0 752
6	80. 57 ±0. 089	87. 02± 0.1 98	90. 20 ±0. 042	86. 94 ±0. 017	84. 85± 0.0 032	95. 23± 0.0 48	83. 39± 0.6 23

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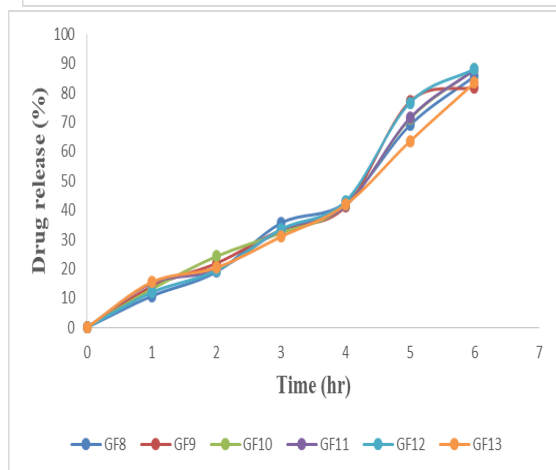
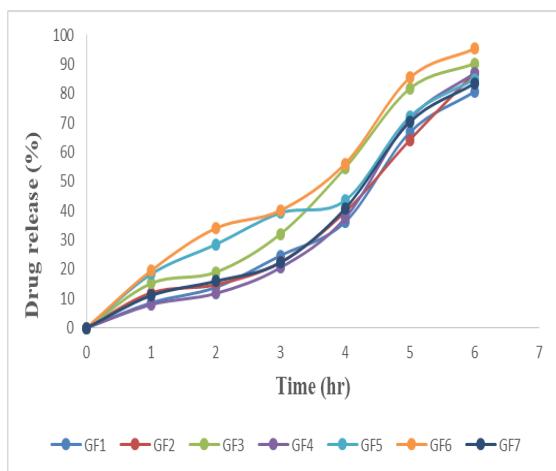


Figure 9: Drug release of GF1-GF7  
Figure 10: Drug release of GF8-GF13

### Kinetic analysis of drug release-

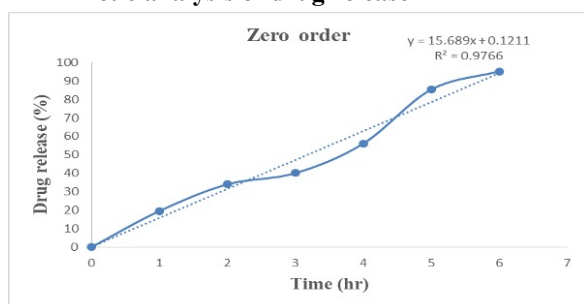


Figure 11: Zero order of GF6

Among the kinetic models evaluated for GF6, the zero-order model showed the highest  $R^2$  value (0.9766), indicating that drug release followed a controlled and constant release pattern, while first-order and Higuchi models showed comparatively lower correlation.

### 11. Estimation of Behavioural Study

#### 1) Morris Water Maze Apparatus

Table 7: Effect of EEBH on escape latency of rats in MWM apparatus

Sr No.	Groups	Escape Latency (sec)	Retention time (sec)
1.	Normal Control	10.5±1.29	62.75±1.78
2.	Negative control	80.25±1.72 @	21.69±1.82 @
3.	EEBH (200mg/kg)	59.14±1.83 **	33.5±2.32* *
4.	optimized batch gel formulation 200mg/kg	29.85±2.21 **	49.74±1.25 **
5.	Rivastigmine (0.5mg/kg)	12.25±1.78 **	54.25±1.71 **

#### 2) Y-Maze Spontaneous Alternation Test

Table 8: Effect of EEBH on spontaneous alternation behavior of rats in Y-maze apparatus

Sr. No.	Groups	Spontaneous Alternation (%) (0 day)	Spontaneous Alternation (%) (28 day)
1.	Normal control	68.42 ± 0.56	67.12 ± 0.64
2.	Negative control	67.85 ± 0.48ns	42.25 ± 1.52@
3.	EEBH (200 mg/kg)	68.12 ± 0.62ns	55.42 ± 0.47**
4.	optimized batch gel formulation 200mg/kg	69.02 ± 0.58ns	61.84 ± 0.52**
5.	Rivastigmine (0.5 mg/kg)	68.74 ± 0.44ns	66.28 ± 0.39**

The present study demonstrates the neuroprotective and cognitive-enhancing potential of Benincasa hispida fruit juice (EEBH) in a scopolamine-induced memory impairment model in rats. Behavioral assessments using the Morris Water Maze, and Y-maze revealed significant learning and memory deficits in the disease control group, which were effectively reversed by EEBH treatment. Both the fruit juice extract (200 mg/kg) and the optimized gel formulation (200 mg/kg) improved spatial memory, learning ability, and anxiety-related behavior, with the optimized gel formulation exhibiting superior efficacy comparable to rivastigmine. Overall, the study highlights the memory-enhancing, antioxidant, anti-inflammatory, and neuroprotective properties of

*Benincasa hispida*, particularly in its optimized gel formulation. These findings suggest that EEBH may serve as a promising natural therapeutic candidate for the management of cognitive disorders associated with cholinergic dysfunction, oxidative stress, and neuroinflammation, including Alzheimer's disease. Further mechanistic and clinical studies are warranted to establish its translational potential.

### SUMMARY:

The present work focused on the development and evaluation of a nano-carrier-based nasal gel system containing *Benincasa hispida* fruit juice extract (EEBH) to enhance nasal drug delivery and improve neuroprotective efficacy. Liposome- and nanocochleate-loaded nasal gels (GF1–GF13) were prepared using Poloxamer 188 and Carbopol 934P and evaluated for physicochemical, rheological, and release characteristics. All formulations were clear and stable, with acceptable pH, viscosity, gel strength, and spreadability suitable for nasal administration. Among them, GF6 emerged as the optimized formulation, exhibiting optimal pH (6.5), high viscosity, superior gel strength, maximum drug content, and controlled drug release following zero-order kinetics.

In vitro and ex vivo diffusion studies confirmed enhanced and sustained drug release from the optimized formulation. Statistical analysis revealed that polymer concentration significantly influenced pH, viscosity, and drug release behavior. The neuroprotective potential of EEBH and the optimized nasal gel was further evaluated in scopolamine-induced memory-impaired rats using behavioral study. The optimized gel formulation significantly improved learning, memory, and cognitive performance compared to the disease control and plain extract.

### CONCLUSION:

The findings of the present study demonstrate that *Benincasa hispida* fruit juice extract possesses significant neuroprotective and cognitive-enhancing properties. Formulation of EEBH into a nano-carrier-based nasal gel system markedly improved its stability, nasal residence time, and controlled release profile. The optimized formulation (GF6) effectively reversed scopolamine-induced cognitive deficits.

Overall, the study confirms that the nano-carrier-based nasal gel of *Benincasa hispida* is a promising, non-invasive therapeutic approach for the management of cognitive disorders associated with oxidative stress, neuroinflammation, and cholinergic dysfunction, such as Alzheimer's disease. Further mechanistic and

clinical investigations are warranted to explore its translational potential.

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