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Formulation and Evaluation of Phenylephrine Nasal Gels

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Abstract

The primary objective of this study is to develop and evaluate phenylephrine nasal gels, aiming for stable blood levels with lower drug doses through consistent administration, avoiding first-pass hepatic metabolism. Compatibility among the drug, polymers, and lipids was confirmed using FTIR and DSC spectra. Phenylephrine nasal gels were formulated, and their clarity assessed. The gels (ONGF1-ONGF8) had pH values of 6.1-7.2, spreadability of 18.33-21.62 g/cm/sec, and viscosity of 934.2-966.2 centipoises. Drug concentration in these formulations varied from 85.52% to 98.88%, indicating acceptable medication content. Gel strength ranged from 64% to 95%. In-vitro drug release of phenylephrine showed 77% to 95% diffusion for ONGF1. The release kinetics followed first order, zero order, Higuchi model, and Korsemeyer-Peppas equations. Kinetic values for all formulations were tabulated. ONGF1 exhibited the most efficient release, with 95% of the drug released within 7 hours, demonstrating a diffusion mechanism followed by non-Fickian transport, adhering to both zero order and Korsemeyer-Peppas models.

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INTRODUCTION

The word "gels" is a general one that covers semisolid materials with a variety of properties, including rather stiff gelatin slabs, colloidal clay solutions, and specific greases. You can think of a gel as consisting of two interpenetrating phases: a fluid component and a gelling agent. Gels are semisolid substances that consist of either big organic molecules interspersed with liquid or suspensions of small inorganic particles. Within the gel in the first instance, inorganic particles like bentonite create a three-dimensional "house of cards" structure [1]. This is a real two-phase system since the inorganic particles are only scattered throughout the continuous phase and

are not soluble. Oversized organic molecules typically reside in solution as flexible chains that are randomly coiled. These molecules' random motion causes them to entangle with one another, whether they are manufactured or natural polymers. The interaction between the inorganic and organic colloidal phase units creates the "structural viscosity" that immobilises the liquid continuous phase [2]. As a result, gels have properties halfway between those of liquids and solids. Gels ought to have characteristics like To shield against microbial attack, it should have the right antimicrobial. Tacky topical gel is not what you want. Sterile ophthalmic gel is required. It ought to be affordable. Gel is used in the pharmaceutical and cosmetic industries for a variety of purposes, including as a vehicle for the delivery of oral medications as well as topical medications that are applied directly to the skin, mucous membranes, or eyes [3].

MATERIALS AND METHODS

Phenylephrine the gift sample is from Aurovindo Pharma LTD, Hyderabad, and other excipient's such as Hydroxy Propyl Methyl Cellulose is from Himedia Laboratories Pvt. Ltd. Mumbai, Carbopol is from Finar Chemicals Ltd, Ahmedabad, Methylparaben is from Central Drug House Pvt Ltd, New Delhi, and other polymers like Poloxamer 188, Ethanol, Phenyl mercuric nitrate is from S.D. Fine Chem. Ltd. Mumbai.

METHODS

Pre-Formulation Study

The physical, chemical, as well as mechanical properties of novel pharmaceutical substances must first be characterised by formulation scientists in order to develop stable, secure, and effective dosage forms. Preformulation is the term for this procedure. Ideally, preformulation should begin early in the process of discovery, allowing for the availability of relevant physical and chemical data to help in the selection of new chemical entities that enter the development process. The present study also takes into account potential interactions with different inert ingredients meant for use in the final dosage form [4].

FT-IR studies for drug and excipients compatibilities

The preformulation research was completed before the dosage forms were developed. IR spectrum investigations are primarily used to identify chemicals qualitatively, whether they are in their pure form or in combination with polymers and excipients. They also serve as a tool for determining the nature of chemical interactions [5]. I.R. is associated with covalent bonding, hence the spectra can provide intricate details about the composition of molecules. Comparisons between the compounds' spectra and the pure compound were done to prove this hypothesis [6].

Figure 1 Photography of FTIR spectro-photometer (BRUKER)

Differential Scanning Calorimetric

Distinctive Scanning To look into any changes in the drug's melting point after mixing it with the excipients, calorimetric analysis of both pure pharmaceuticals and the polymers utilised was conducted [7]. Distinctive Scanning With a sample weight of 3 mg, calorimeter curves were acquired using a differential scanning calorimeter with a heating rate of 10°C/min from 25° to 250°C in a nitrogen environment (20 mL/min).

Formulation of Phenylephrine Nasal Gels

Method of Formulation

The dispersion process was used to create phenylephrine nasal gels. 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 fully swell for 24 hours following complete dispersion. A predetermined

Table 1 Formulation data of Phenylephrine Nasal gels

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Phenylephrine (gms)	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Carbopol (gms)	2	2.5	3	3.0	3.0	3	2.5	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

amount of phenolphthalein and Poloxamer 188 were precisely weighed and added to this solution, along with a predetermined amount of phenolphthalein nitrate, which was then dissolved (Solution-B). With the aid of a high-speed magnetic stirrer operating at 500 rpm, solution A and B were completely mixed while being careful to prevent air from becoming trapped. Lastly, distilled water was added to create a uniform gel dispersion. The gel that was created had its pH adjusted to 6.8.

Figure 2 : Eight Formulation of Phenylephrine Nasal gels

Evaluation of Nasal Gels

The drug content, in vitro release tests, as well as physicochemical characteristics of the formulated gel were assessed [8].

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): +++.

Measurement of Ph

Using a digtal pH metre, the pH of the phenylephrine gel formulation was measured. 100ml of distilled water was used to dissolve 1 gramme of gel. Using a digital pH metre (Systronics Digital pH metre), the pH of each formulation was measured [9].

Spreadability

Glass plate apparatus, which was appropriately adjusted in the laboratory as well as employed for the investigation, was used to measure spreadability. Spreadability was evaluated based on the gel's "slip" and drag properties. The spread diameter of one gramme of gel between two glass plates was measured 48 hours after preparation to test the formulations' spreadability. After one minute, the mass of the upper plate was standardised to 125 grammes. To create a consistent gel layer between the slides and to release trapped air, a 1 kg weight was positioned on top of each slide for five minutes. The excess gel around the edges was scraped off. After then, an 80 gramme pull was applied to the top plate [10].

The formula below was used to calculate the spredability.

$$S = \frac{ML}{T}$$

Figure 3 Brookfield Viscometer

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 grammes apiece were employed [11]. Based on the gel's viscosity, spindle number 61 was chosen. It was revolved at 50 revolutions per minute, as well as dial readings were taken until two readings that were similar were obtained.

Drug content

By carefully weighing one gramme of gel as well as dissolving it in 6.8 pH phosphate buffer76, the drug concentration of the gel was ascertained. With an appropriate dilution, absorbance was measured at 245 nm using a UV visible spectrometer. The slope of a standard curve was used to calculate the drug content [12].

The following equation was used to determine the drug content.

Drug Content = Conversion factor × volume taken × concentration of drug

Gelling strength

The Carbopol & HPMC gel can be penetrated by setting the thermostat to 37°C in a 100 ml measuring cylinder filled with 50 gm of gel [13]. To measure the time in seconds, place the gadget at physiological temperature as well as apply pressure while lowering it five centimetres.

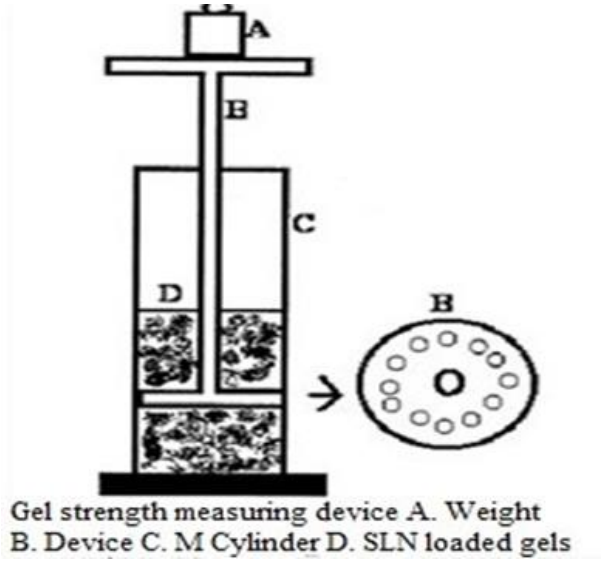

Figure 4 Measurement of Gel strength

In vitro diffusion studies

The produced gel was studied in vitro for diffusion using an egg membrane in a Franz diffusion cell. The receptor compartment was filled with 20 millilitres of phosphate buffer, and 5 grammes of phenylephrine gel was then evenly distributed across the membrane [14]. The donor compartment was kept in touch with a receptor compartment, and the temperature was kept at 37±0.5°C. At predetermined intervals, such as 1, 2, 3, 4, 5, 6 & 7 hours, the receptor's solution pipette out 5 ml of solution from the receptor compartment and immediately replace it with a fresh 2 ml phosphate buffer [15]. The following release order graphs show the in-vitro release profile results for each formulation:

Kinetic study the Release Order kinetics Mechanism

The in-vitro release profile results for each formulation were plotted using the following data treatment modes [16].

Zero order kinetics

Cumulative % of drug release vs. time (Zero-order).

$Qt = Qo + Ko\ t$

First order kinetics

Log Cumulative % drug retained vs. time (first-order).

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

Higuchi model

Cumulative percentage of drug release vs. Time squared (Higuchi Matrix Model).

$Q\ t = KH.\ t1/2$

Korsemeyer and Peppas Release model

Log drug release cumulative percentage V/s log time (Krosmeyer-Peppas Model).

$F = Mt / M = K.tn$

A linear plot of drug release against time will have an intercept equal to log K and a slope of n.

With n = 0.5, pure fickian diffusion is indicated.

The values of n = 0.5-1 or 0.45-0.89 suggest non-fickian diffusion. i.e., the spectrum of drug release and solvent penetration rates is shared.

Table 2 Physical Evaluation Method of Drug

Description	Method Evaluated	0th day	1st week	2nd week
Phenylephrine	Physical Evaluation	White Crystalline powder	White Crystalline Powder	White Crystalline powder

Table 3 Interpretation data of IR spectra Phenylephrine

IR absorption bands (cm-1)		Bond	Functional group
Observed peak	Characteristic peak		
3691.88	3000-3700	OH	
2360.95	2100-2660	C=C	Alkynes
2345.52	2100-2660	C=C	Alkynes
1452.45	1330-1540	NO_2	Nitro compounds
1413.87	1330-1540	NO_2	Nitro compounds
1377.22	1220-1540	NO_2	Nitro compounds
1315.50	600-1500	CH	Alkane
1155.40	600-1500	CH	Alkane
	1000-1300	CO	Alcohols
1116.82	600-1500	CH	Alkane
	1000-1300	CO	Alcohols

Zero order release is indicated by n = 0.89 or 1, and it can occur when drug diffusion is faster than the steady-state rate of solvent-induced relaxation.

RESULTS AND DISCUSSION

Preformulation Studies

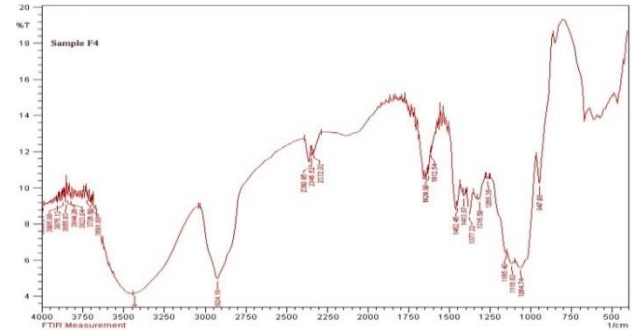

Figure 5 FTIR spectrum of Phenylephrine

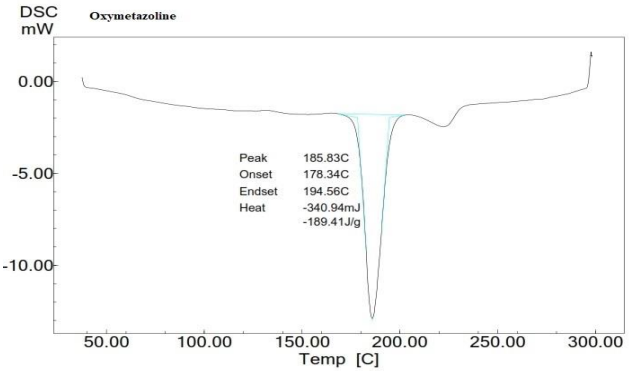

Figure 6 DSC curve of Phenylephrine

Differential Scanning Calorimetry

The Phenylephrine of endothermic peak was found to be 194.56°C.

Evaluation of Phenylephrine Nasal Gels

Clarity: Gels containing carbopol were observed to be translucent and dazzling. It was discovered that polxamer and HPMC gels were translucent and white viscous. Table 4 indicates that there were no particles present in any of the gels.

pH

All produced gel formulations (ONGF1-ONGF8) had pH values between 6.2 and 6.9, as indicated by table 4 as well as figure 7.

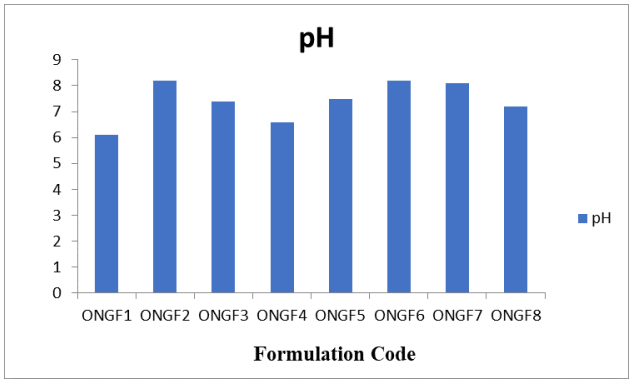

Figure 7 pH of Phenylephrine Nasal gels

Spreadability

The spreadability rating shows how easily a modest amount of shear can spread the gel. The gels' spreadability ranged from 19.51 to 33.91 g.cm/sec, as indicated by Table 4 and Figure 8.

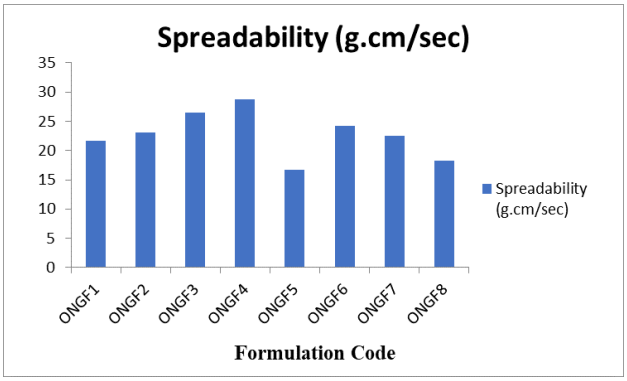

Figure 8 Spreadability of Phenylephrine Nasal gels

Viscosity measurement

Using a Brookfield viscometer, the viscosity of many formulations of phenylephrine gels was determined. All gel systems that were formulated had their rheological behaviour examined. Consistency in a gel system is determined by the ratio of the solid to liquid fraction, which creates the structure. As indicated in table 4 and figure 9, the viscosity of the different gel formulations was found to range from 8628 to 9622 centipoises.

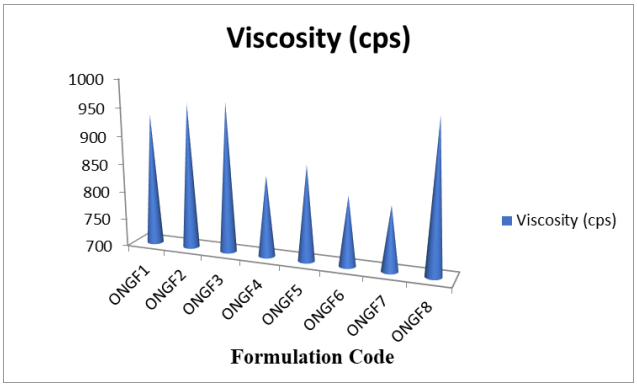

Figure 9 Viscosity of Phenylephrine Nasal gels

All manufactured gel formulations were found to have a drug concentration ranging from 78.53 to 98.56 percent. It was determined that the formulations' % medication content was acceptable. Methods used for gel compositions were therefore determined to be appropriate, as displayed in Figure 10 and Table 4.

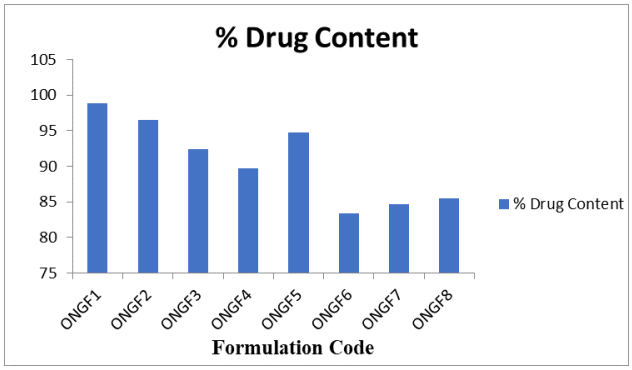

Figure 10 Drug Content of Phenylephrine Nasal gels

Gel strength

It was discovered that the gel strength of every manufactured gel formulation fell between 69 and 96%. 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 4 as well as figure 11.

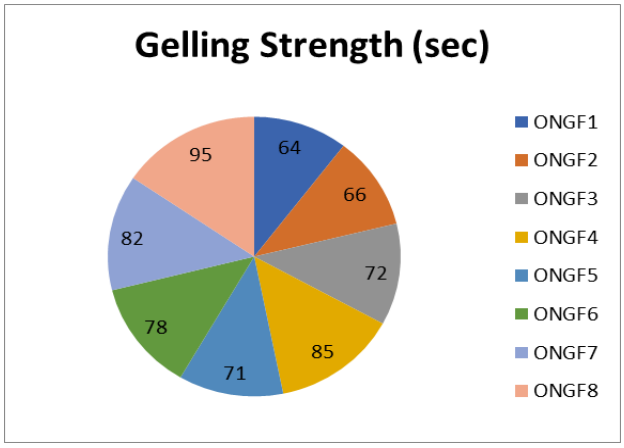

Figure 11 Gel strength of Phenylephrine Nasal gels

Figure 12 In vitro Franz's diffusion cell

Table 4 Evaluation parameters of Phenylephrine nasal gel

Formulation code	Clarity	pH	Spread ability(g.cm/sec)	Viscosity (cps)	% Drug Content	Gelling strength (sec)
ONGF1	+++	6.1	21.62	934.2	98.88	64±2
ONGF2	+	8.2	23.12	958.8	96.55	66±4
ONGF3	++	7.4	26.44	965.2	92.44	72±3
ONGF4	+	6.6	28.72	844.3	89.66	85±5
ONGF5	++	7.5	16.76	868.9	94.76	71±2
ONGF6	+	8.2	24.22	822.8	83.33	78±5
ONGF7	+	8.1	22.48	813.8	84.68	82±3
ONGF8	+	7.2	18.33	966.2	85.52	95±3

Table 5 In-vitro diffusion drug release of Phenylephrine of nasal gels

Time (Hrs)	Percentage amount of drug release							
	ONGF1	ONGF2	ONGF3	ONGF4	ONGF5	ONGF6	ONGF7	ONGF8
1	41 ± 0.2	47 ± 0.2	41 ± 0.5	31 ± 0.3	21 ± 0.3	22 ± 0.5	22 ± 0.2	22 ±0.3
2	42 ± 0.3	43 ± 0.5	43 ± 0.5	47 ± 0.6	33 ± 0.4	38 ± 0.5	36 ±0.4	27 ±0.5
3	48 ± 0.5	53 ± 0.3	57 ± 0.1	61 ± 0.2	45 ± 0.6	53 ± 0.7	48 ±0.5	37 ±0.7
4	55 ± 0.2	61 ± 0.2	68 ± 0.5	63 ± 0.3	55 ± 0.8	63 ± 0.7	54 ±0.7	45 ±0.4
5	76 ± 0.1	71 ± 0.5	77 ± 0.3	74 ± 0.5	71 ± 0.2	75 ± 0.8	62 ±0.3	57 ± 0.2
6	78 ± 0.5	82 ± 0.6	86 ± 0.6	82 ± 0.4	77 ± 0.3	81 ± 0.4	65 ±0.6	72 ± 0.8
7	94 ± 0.6	92 ± 0.7	93 ± 0.2	93 ± 0.2	81 ± 0.5	88 ± 0.2	77 ±0.4	83 ± 0.7
8	93 ± 0.4	91 ± 0.5	91 ± 0.3	92 ± 0.2	82 ± 0.4	87 ± 0.3	76±0.3	82 ± 0.6

Table 6 In-vitro drug release kinetics data for Formulation ONGF1

Zero order		First order		Higuchi's data		Korsmeyer-Peppas data	
Time (h)	% CDR	Time (h)	Log % CD Remaining	SQR Time	% CDR	Log Time	Log % CDR
0	0	0	2	1	0	0	0
1	41	1	1.75	1.72	41	0.46	1.61
2	42	2	1.74	3	42	0.59	1.62
3	46	3	1.71	2.22	46	0.68	1.66
4	55	4	1.63	2.43	55	0.76	1.73
5	77	5	1.33	2.63	77	0.76	1.73
6	78	6	1.31	2.81	78	0.84	1.88
7	94	7	0.68	2.81	951	0.91	1.90

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 to be as indicated in Table 5.

Kinetic Models Data Analysis

First order, zero order, Higuchi model, as well as Korsemeyer-Peppas drug release kinetic equations were fitted to the diffusion data. Every formulation (ONGF1, ONGF2, ONGF3, ONGF4, ONGF5, ONGF6, ONGF7, & ONGF8) had its kinetic values obtained and tabulated accordingly. The Higuchi, Zero order, First order, and Korsemeyer-Peppas models' 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 are plotted against these graphs.

Table 7 Drug Release Kinetics of Phenylephrine 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	
ONGF1	0.9055	11.475	0.8277	0.150	0.874	29.805	0.8968	0.822	Non-Fickian

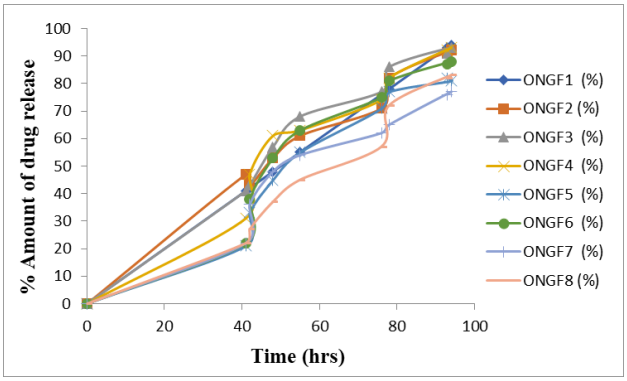

Figure 13 The profiles of formulations for in vitro drug release ONGF-1–ONGF8

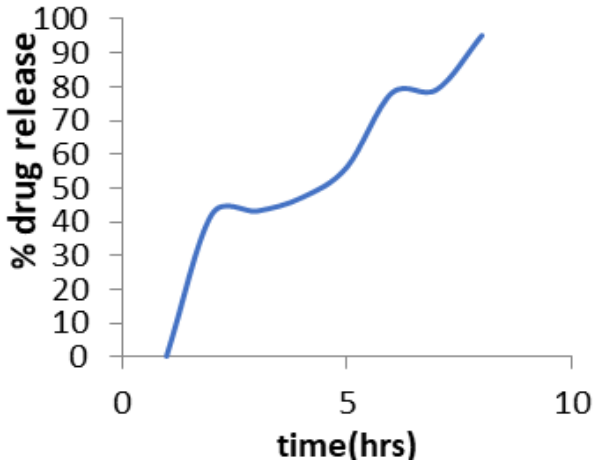

Figure 14 Zero order Plot for ONGF1 Formulation

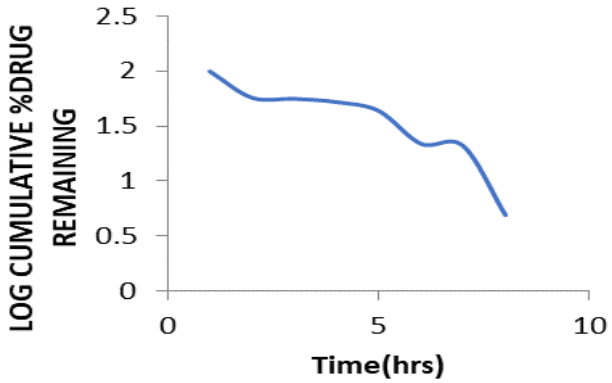

Figure 15 First order plot for ONGF1 Formulation

Korsemeyer-Peppas formulations for F1, F2, F3, F4, F5, F6, F7, and F8 were used; the correlation coefficients were R2=0.8968, 0.6042, 0.8592, 0.8095, 0.9721, 0.9706, 0.3191, and 0.2692, in that order. The ONGF1 formulation shows a diffusion release mechanism followed by non-fickian transport. It adheres to both the Zero order as well as Korsmeyer-Peppas models.

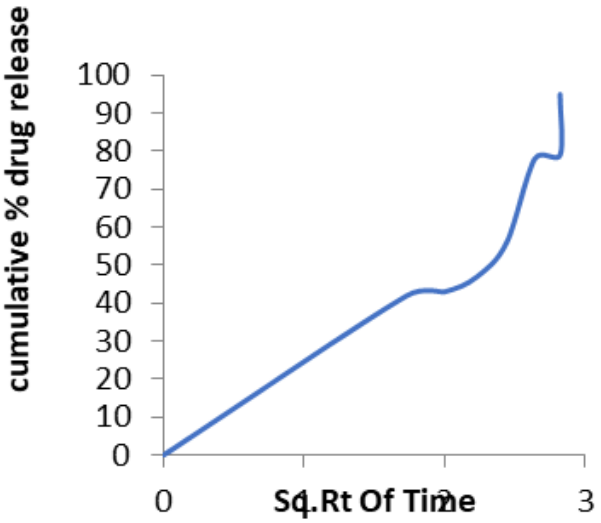

Figure 16 Higuchi plot for ONGF1 Formulation

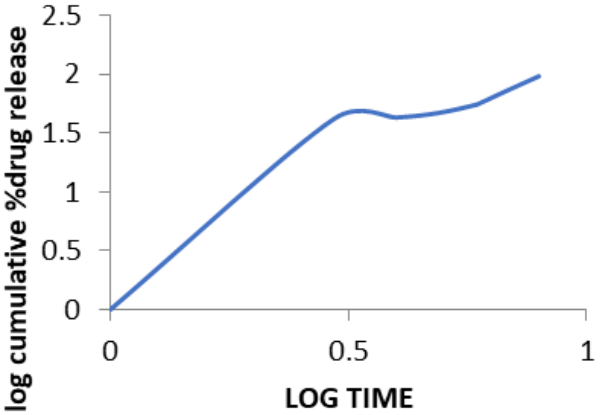

Figure 17 Korsmeyer-Peppas for ONGF1Formulation

CONCLUSION

The goal of the current study was to formulate and assess cold-pressed phenylephrine nasal gels.

There was no chemical interaction during the encapsulation process, according to the FTIR and DSC measurements. The transparency of the phenylephrine nasal gel evaluation using the clarity test will be ensured. All gel formulations that were produced (ONGF1-ONGF8) had PH values between 6.1 and 7.2. The gels' spread ability ranged from 21.62 to 18.33 g/cm/sec. The range of viscosity of several gel formulations was found to be between 934.2 as well as 966.2 centipoises. All prepared gel formulations were found to have a drug concentration ranging from 98.88 to 85.52%. It was determined that the formulations' % medication content was acceptable. It was discovered that the gel strength of every manufactured gel formulation ranged from 64 to 95%. 95% of the drug was released within 7 hours in the case of the delayed in-vitro release of phenylephrine. The ONGF 1 formulation is the best of the eight; it shows a diffusion release mechanism followed by non-fickian transport and follows both the Zero order as well as Korsemeyer-Peppas models.

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Conflict of Interest

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

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