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Formulation and evaluation of oxymetazoline hydrochloride nasal gels

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ABSTRACT

The main intend of the implement sniff out formulate and evaluate oxymetazoline nasal gels. To achieve more persistent blood levels with decrease dosage of medicine by extended drug evidence and by passing hepatic initially cross metabolism and body including inferable disgrace. The FTIR & DSC spectra there is not any discrepancein the seam clean medicine, polymers & lipids. The Carbopol consisting of reinforce precail eventual scintillating moreover transparent Poloxamer, Hydroxy Propyl Methyl cellulose gels crop up prospective lucent as a consequence frosted slimy. The pH value of all developed formulations of gels (ONGF1-ONGF8) was in the range of 6.2 to 6.9. Spreadability of gels was in the range 19.51 - 33.91 g.cm/sec, The Viscosity of various formulated gels was found in range of 8628 to 9622 centipoises. The percentage drug content of all prepared gel formulations were found to be in the range of 78.53 to 98.56 %. The gel strength of all prepared formulations of gels was found to be in the range of 69 to 96 %. In-vitro diffusion drug release of Oxymetazoline Hydrochloride of nasal gels ONGF1 shows the 95% drug release. The release order kinetics shows all the formulations ONGF1 to ONGF8 formulations were followed Korsemeyer-Peppas with correlation coefficient R^2=0.8969 & 0.2692 respectively. ONGF1 formulation follows both Zero order and Korsmeyer-Peppas models, it indicates diffusion release mechanism followed by non-fickian transport.

Keywords: Nasal, Gels, Oxymetazoline, *In-vitro* diffusion, Carbopol.

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INTRODUCTION

Oxymetazoline hydrochloride (6-tert-Butyl-3-(4,5-dihydro-1H-imidazol-2-ylmethyl)-2,4-dimethylphenol hydrochloride) is an imidazoline derivative sympathomimetic amine. Oxymetazoline is a vasoconstrictor that acts directly on nasal membranes and has been available as a over the counter intranasal drug in the United States for more than 40 years [1]. It is approved for the relief of nasal congestion as a result of common colds and allergic rhinitis. The main aim of the present work is to formulate and evaluate oxymetazoline nasal gels. To achieve more constant blood levels with lower dosage of drugs by continuous drug input and by passing hepatic first pass metabolism and consequent degradation [2]. To reduce the frequency of dose dumping and increase the residence time. The intranasal administration of drugs has long been used for the treatment of rhinitis and nasal congestion. Intranasal administration can overcome the side effects that happen in the gastrointestinal tract and the hepatic first-pass effect [3]. Furthermore, drugs are absorbed better, because of the abundant blood and lymphatic capillaries under the nasal mucosa. Since these properties, intranasal administration can effectively enhance the bioavailability of drugs. Intranasal administration has been stated to reach comparable blood concentrations as intravenous administration [4]. Most of the commercially available nasal preparations are now sprays. The scavenging effect of nasal cilia leads to a very short drug residence time on the human nasal mucosal surface (only 15–30 min), which affects the clinical efficacy to some extent. The term gel represents a physical state with properties intermediate between those of solid and liquids. However, it is often wrongly used to describe any fluid system that exhibits some degree of rigidity [5]. Nasal drug delivery also provides a way to the brain that circumvents the blood-brain barrier because the olfactory receptor cells are in contact with central nervous system directly. The first step involved is absorption of drug in the nasal cavity is crossing the mucus membrane. Because small, uncharged particles can pass through the mucus easily. But charged large molecule does not easily passes through the mucus membrane. Mucin is the protein present in the mucus layer, which binds with the solutes that delays the diffusion and structural changes in the mucus layer also possible because of environmental changes [6].

MATERIALS

Oxymetazoline hydrochloride were gifted sample from Kotra Pharma (M) Sdn Bhd. Poloxamer 188 were purchased S.D. Fine Chem. Ltd. Mumbai. Hydroxypropylmethyl cellulose procured from Sigma Aldrich USA Carbopol procured from Finar Chemicals Ltd, Ahmedabad. All the chemicals were used as HPLC grade.

METHODOLOGY

FT-IR studies for drug and excipients compatibilities: Prior to the development of the dosage forms the preformulation study was carried out [7]. IR spectral studies lies more in the qualitative identification of substances either in pure form or in combination with polymers and excipients and acts as a tool in establishment of chemical interaction. Since I.R. is related to covalent bonds, the spectra can provide detailed information about the structure of molecular compounds. In order to establish this point, comparisons were made between the spectrum of the substances and the pure compound.

Differential Scanning Calorimetric: Differential Scanning Calorimetric of pure drugs and polymers used were studied to investigate any changes in melting points of the drug after combining it with the excipients [8]. Differential Scanning Calorimeter curves were obtained by at a heating rate of 10°C/min from 25°-250°C in nitrogen atmosphere (20 mL/min) with a sample weight of 3mg.

Formulation of Oxymetazoline Hydrochloride Nasal Gels

Oxymetazoline Hydrochloride Nasal Gels was prepared by Dispersion method. In this method weighed quantities of polymers such as HPMC K100, Carbopol 934 was dissolved in known quantity of distilled water (Solution-A).After complete dispersion the polymer solution was kept it aside for 24hrs for complete the swelling [9]. Accurately weighed amount of Oxymetazoline Hydrochloride, Poloxamer 188 was dissolved in a specified quantity to this solution; specified quantity of Phenylmercuric nitrate was added and dissolved (Solution-B). Solution A and B were mixed thoroughly with the help of high speed magnetic stirrer (500rpm) taking precautions that air did not entrap. Finally distilled water was added to obtain a homogenous dispersion of gel. The pH of the formed gel was adjusted to pH 6.8.

Table 1: Formulation data of Oxymetazoline Hydrochloride Nasal gels

Ingredients	ONGF1	ONGF2	ONGF3	ONGF4	ONGF5	ONGF6	ONGF7	ONGF8
Oxymetazoline (gms)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Carbopol (gms)	1	1.5	2	2.5	2.5	2	1.5	1
HPMC (gms)	2.5	2	1.5	1	1	1.5	2	2.5
Poloxamer (gms)	0.5	1	1.5	2	0.5	1	1.5	2
Methyl Paraben (%)	1	1	1	1	1	1	1	1
Distilled water (ml)	100	100	100	100	100	100	100	100

Evaluation of oxymetazoline nasal gels: Formulated gel was evaluated for their clarity, pH, Spreadability, viscosity, drug content, Gel strength and *in-vitro* release studies.

Clarity: The clarity of various formulations [10] was determined by visual inspection under black and white background and it was graded as follows; turbid: +, clear: ++, very clear (glassy): +++.

Measurement of pH: The pH of oxymetazoline gel formulation was determined by using digital pH meter 1gram of gel was dissolved in 100ml of distilled water [11]. The pH of all formulation was determined by using digital pH meter.

Spreadability: It was determined by glass plate apparatus which was suitably modified in the laboratory and used for the study. Spreadability was measured on the basis of 'slip' and drag characteristics of gel. Spreadability of the formulations was determined 48 hrs after preparation, by measuring the spreading diameter of 1gm of gel between two glass plates after 1 min. the mass of upper plate was standardized at 125g. A 1kg weight was placed on the top of two slides for 5min to expel air and to provide a uniform film of gel between the slides. Excess of gel was scrapped off from the edges [12]. The top plate was then subjected to pull of 80 gm.

The spredability was measured by using the following formula

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

Where,

S = Spreadability

M = Weight tide to upper slide

L = Length moved on the glass slide

T = Time taken to separate the slide completely from each other

Viscosity: The viscosity of all gels was measured using a brook field viscometer (DV II +). First, the spindle was dipped into the gel till the notch on the spindle touched the gel surface.100 gm each of formulation gels was used in the study [13]. The spindle no. 61 was selected based on the viscosity of the gel, this spindle was rotated at 50 rpm, and dial reading was recorded until 2 consecutive similar readings were obtained.

Drug content: Drug content of gel was determined by dissolving accurately weighed 1 gm gel in 6.8 pH Phosphate buffer [14]. After suitable dilution absorbance was recorded using UV visible spectrometer at 245 nm. Drug content was determined using slope of standard curve. The drug content was determined by using following equation

Drug content = (concentration× volume taken) × conversion factor

Gelling strength: In 100 ml measuring cylinder containing 50 gm of gel at thermostat at 37°C, it allows to penetrate into the Carbopol & HPMC gel. At physiological temperature while applying pressure on the device sink at 5cm down, to measure the time in seconds [15].

***In vitro* diffusion studies:** The in vitro diffusion study of prepared gel was carried out in Franz diffusion cell using

through an egg membrane. 20 ml of phosphate buffer was taken in as receptor compartment, then 5 gm Oxymetazoline gel was spreaded uniformly on the membrane [16]. The donor compartment was kept in contact with a receptor compartment and the temperature was maintained at 37±0.5^{0}C. The solution on the receptor pipette out 5 ml of solution from the receptor compartment at specified time intervals like 1, 2, 3, 4, 5, 6 & 7hrs and immediately replaced with the fresh 2 ml phosphate buffer. The results of *in-vitro* release profile obtained for all formulations were plotted in Release order kinetics as follows:

Kinetic study the Release Order kinetics Mechanism: The results of *in-vitro* release profile obtained for all formulations were plotted in modes [17] of data treatment as follows:

- Cumulative percent drug release V/s. Time (Zero-order).
- Cumulative percent drug release V/s. Square root of Time (Higuchi Matrix Model).
- Log Cumulative percent drug retained V/s. Time (First-order).
- Log Cumulative percent drug release in V/s. log Time (Krosmeyer-Peppas Model).

Zero order kinetics: Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, assuming that the area does not change and no equilibrium conditions are obtained can be represented by the following equation [18] .

$$Q_t = Q_o + K_o t$$

Where,

Q_t = Cumulative amount of drug release at time t,

Q_o = Initial amount of drug in the solution

K_o = zero order release constant

t = Time in hours

First order kinetics: To study the first order release kinetics the release rate data were fitted to following equation [18].

$$\text{Log } Q_t = \log Q_o + K\, t / 2.303$$

Where,

Q_t= Cumulative amount of drug released at time t,

Q_o = Initial amount of drug in the solution and

K= First order release constant.

Higuchi model: Higuchi developed several theoretical models to study the release of water-soluble and low soluble drugs incorporated in semisolids and or solid matrices [19]. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media, the equation is

$$Q_t = K_H . t_{1/2}$$

Where,

Q_t = Cumulative amount of drug release at time t

K_H = Higuchi dissolution constant

t = Time in hours

Korsemeyer and Peppas Release model: To study this model the release rate data are fitted to the following equation [20].

$$F = M_t / M = K.t^n$$

Where,

F = Fraction of drug released at time't'

M_t = Amount of drug released at time't'

M = Total amount of drug in dosage form

K = Kinetic release constant

t = Time in hours and

n = Diffusion exponent for the drug release that is dependent on the shape of the matrix dosage form.

A plot of log drug release verses log time will be linear with slope of n and intercept gives the value of log K.

- n = 0.5 indicating pure fickian diffusion.
- n = 0.5-1 or 0.45-0.89 indicating non fickian diffusion ie, the rate of solvent penetration and drug release are in the same range.
- n = 0.89 or 1 indicate zero order release which can be achieved when drug diffusion is rapid compared to the constant rate of solvent induced relaxation.

RESULTS AND DISCUSSION

Compatibility studies

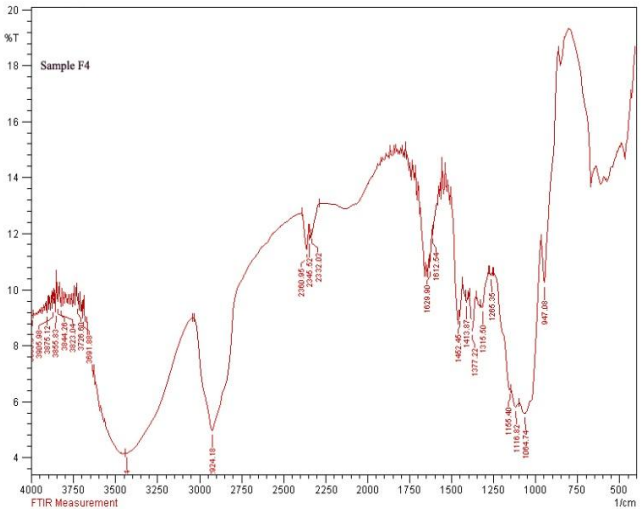

Figure 1: FTIR spectrum of Oxymetazoline Hydrochloride

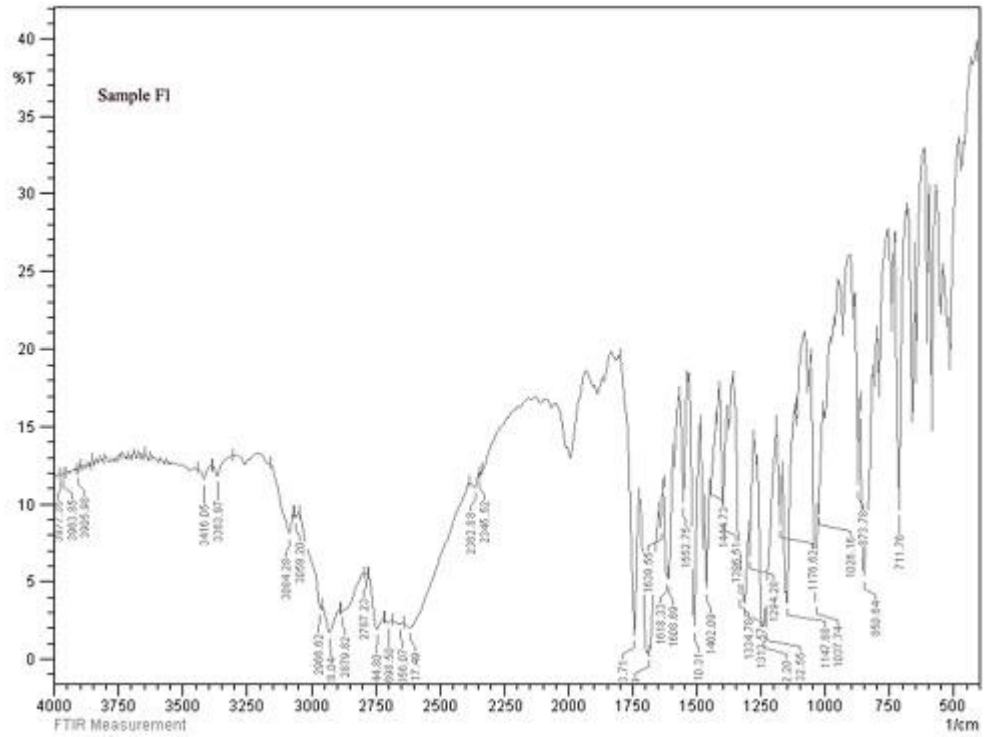

Figure 2: FTIR spectra of Carbopol

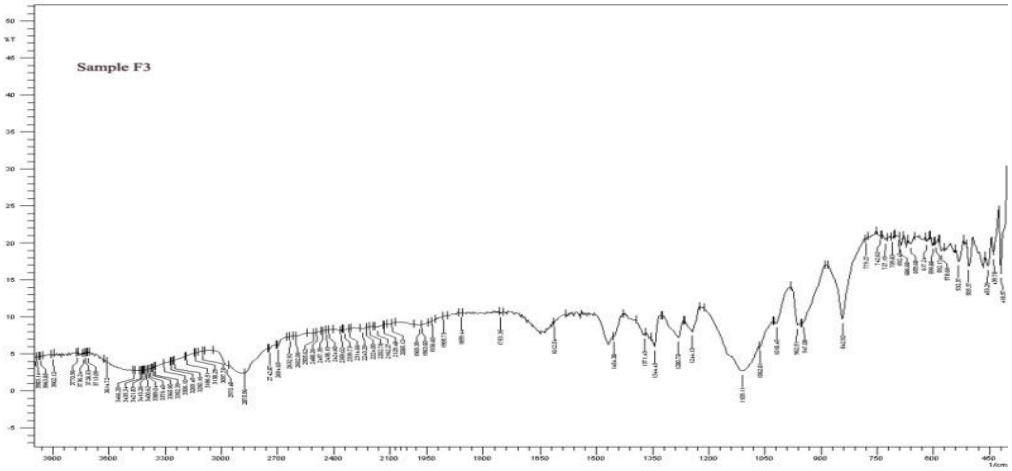

Figure 3: FTIR spectra of Poloxamer 188

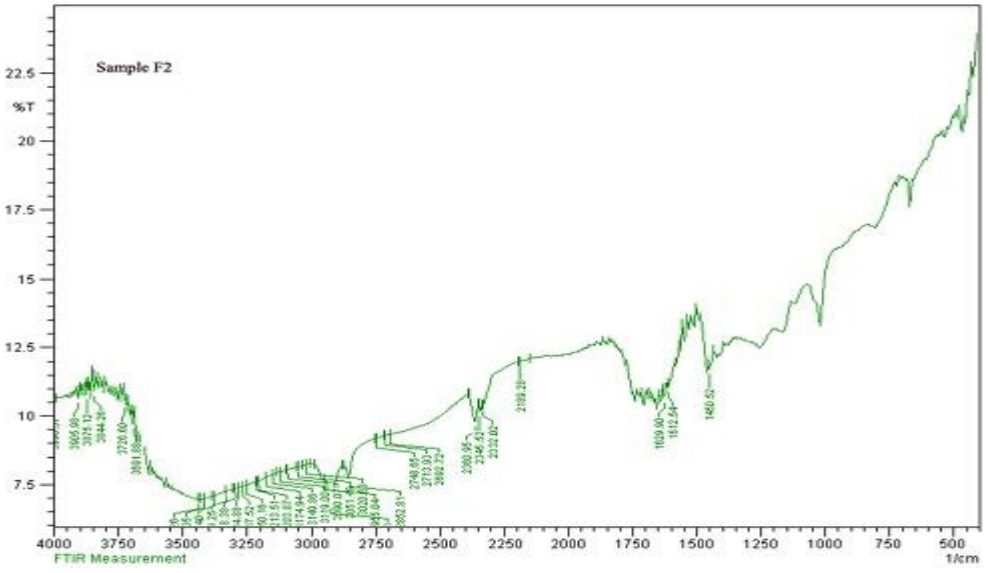

Figure 4: FTIR spectra of HPMC

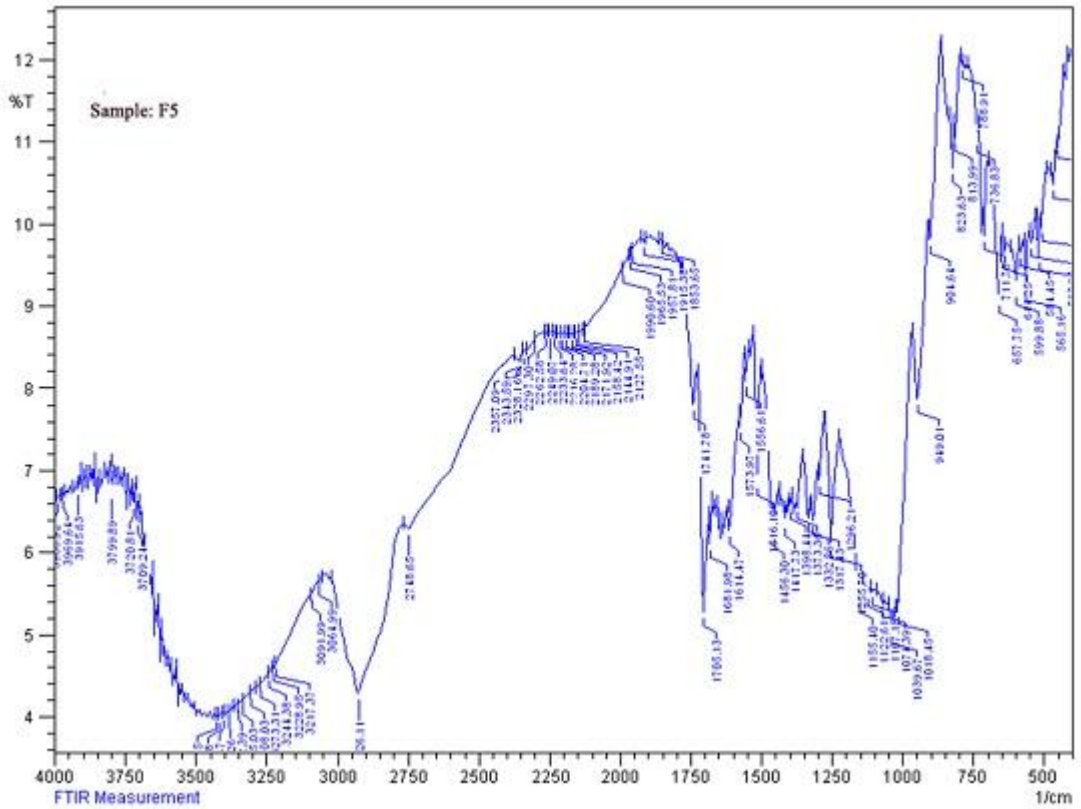

Figure 5: FTIR spectra of mixture

The drug and polymers were characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From the results, it was concluded that there was no interference in the functional groups as the principle peaks of the Oxymetazoline Hydrochloride were found to be unaltered in the spectra of the drug-polymer mixture.

Table 2: FTIR spectrum of observed and characteristic peak of Drug, Lipids, Excipients & Mixture of compounds

FTIR Spectrum	IR absorption bands (cm-1)		Bond	Functional group
	Observed peak	Characteristic peak		
Oxymetazoline Hydrochloride	2360.95	2100-2660	C=C	Alkynes
	2345.52	2100-2660	C=C	Alkynes
	1413.87	1330-1540	NO_2	Nitro compounds
	1377.22	1220-1540	NO_2	Nitro compounds
Carbopol	3363.97	3310-3500	NH	2˚amines
	3084.28	3010-3095	CH	Alkene
	2966.62	2500-3000	OH	Hydrogen bonded acids
Poloxamer 188	3602.09	3580-3650	OH	Alcohols
	3614.72	3580-3650	OH	Alcohols
	2359.02	2100-2660	C=C	Alkynes
	2339.73	2100-2660	C=C	Alkynes
	2243.29	2240-2275	C=N	Iso cyanide
Hydroxy Propyl Methyl cellulose	3174.94	3000-3300	CH	Alkynes
	3149.86	3000-3300	CH	Alkynes
	3051.49	3000-3300	CH	Alkynes
	3020.63	3000-3300	CH	Alkynes
	1629.90	1620-1680	C=C	Alkynes
Mixture	3244.38	3010-3300	C≡H	Alkynes
	2249.07	2100-2660	C=C	Alkynes
	2171.92	2100-2660	C=C	Alkynes
	2158.42	2100-2660	C=C	Alkynes

Differential Scanning Calorimetry:

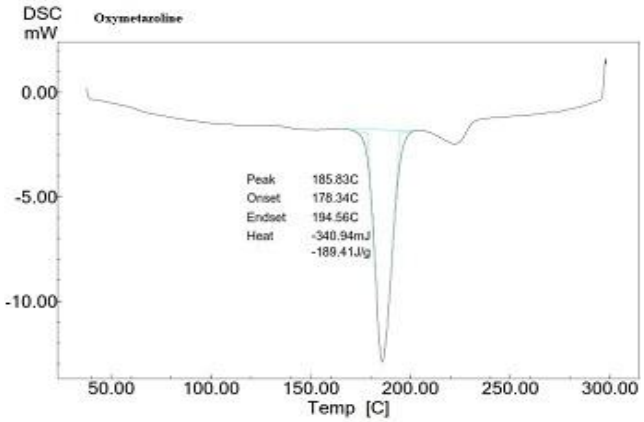

Figure 6: DSC curve of Oxymetazoline

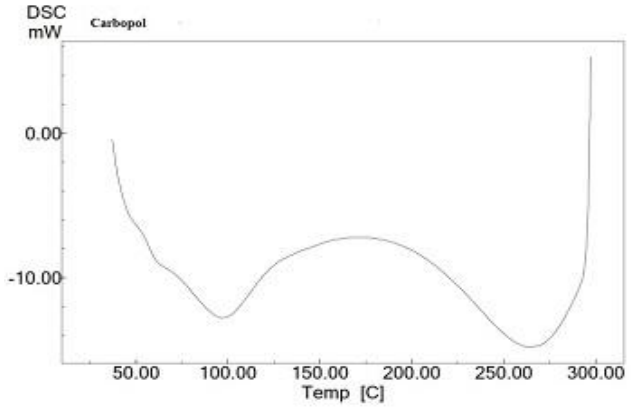

Figure 7: DSC curve of Carbopol

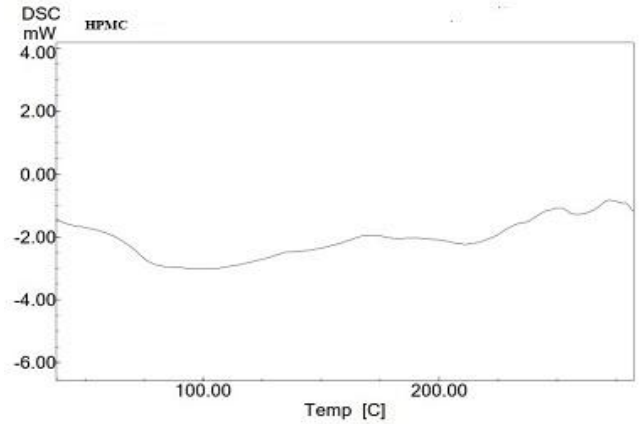

Figure 8: DSC curve of HPMC

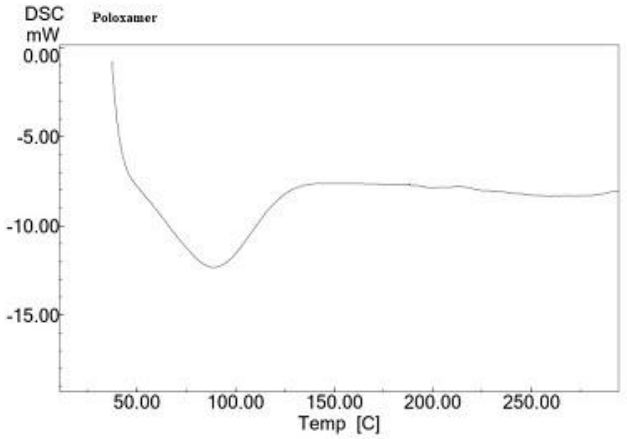

Figure 9: DSC curve of Poloxamer

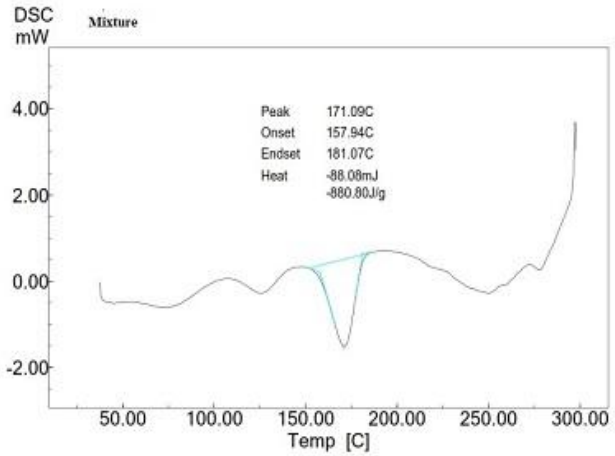

Figure 10: DSC curve of Mixture

The oxymetazoline hydrochloride of endothermic peak was found to be 194.56°C. The Carbopol of endothermic peak was found to be 250°C. The HPMC the endothermic peak was found to be 99°C. The Poloxamer of endothermic peak was found to be 95°C. The Mixture of endothermic peak was found to be 95°C. There is no interaction between pure drug, polymer & lipids. As shown in figure 6 to 10.

Evaluation of oxymetazoline hydrochloride nasalgels:

Clarity: Carbopol containing gels were found to be sparkling and transparent Poloxamer, Hydroxy Propyl Methyl cellulose gels were found to be translucent and white viscous. All gels were free from presence of particles as shown in Table 3.

pH: The pH value of all developed formulations of gels (ONGF1-ONGF8) were in the range of 6.2 to 6.9 as shown in Table 3.

Spreadability: The value of spreadability indicates that the gel is easily spreadable by small amount of shear. Spreadability of gels was in the range 19.51 - 33.91 g.cm/sec, as shown in Table 3.

Viscosity measurement: The viscosity of various formulated Oxymetazoline Hydrochloride gels was measured using a Brookfield viscometer. The rheological behavior of all formulated gels systems was studied. In gel system, consistency depends on the ratio of solid fraction, which produces the structure to liquid fraction. Viscosity of various formulated gels was found in range of 8628 to 9622 centipoises as shown in Table 3.

Drug content: The percentage drug content of all prepared gel formulations were found to be in the range of 78.53 to 98.56 %. The percentage drug content of formulations was found satisfactory. Hence methods adopted for gels formulations were found suitable. As shown in Table 3.

Gel strength: The gel strength of all prepared formulations of gels was found to be in the range of 69 to 96 %. The percentage drug content of formulations was found satisfactory. Hence methods adopted for gels formulations were found suitable. As shown in Table 3.

Table 3: Evaluation parameters of Oxymetazoline nasal gel

Formulation code	Clarity	pH	Spreadability (g.cm/sec)	Viscosity (cps)	% Drug Content	Gelling strength (sec)
ONGF1	+++	6.9	21.99	943.2	98.92	65±1
ONGF2	+	6.8	21.50	962.6	95.53	69±4
ONGF3	++	6.7	26.30	944.2	88.30	70±3
ONGF4	+	6.7	28.86	855.1	91.56	82±5
ONGF5	++	6.8	18.75	848.9	93.82	68±2
ONGF6	+	6.7	20.55	871.8	78.02	73±5
ONGF7	+	7.1	22.39	847.8	83.92	79±3
ONGF8	+	6.9	18.07	942..2	82.46	96±3

***In vitro* drug diffusion studies:** *In vitro* drug release studies were carried out on diffusion test apparatus Franz diffusion cell. These release studies revealed that, the order of release was found as shown in table 4 & figure 11.

Table 4: In-vitro diffusion drug release of Oxymetazoline Hydrochloride of nasal gels

Time (Hrs)	Percentage amount of drug release							
	ONGF1 (%)	ONGF2 (%)	ONGF3 (%)	ONGF4 (%)	ONGF5 (%)	ONGF6 (%)	ONGF7 (%)	ONGF8 (%)
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

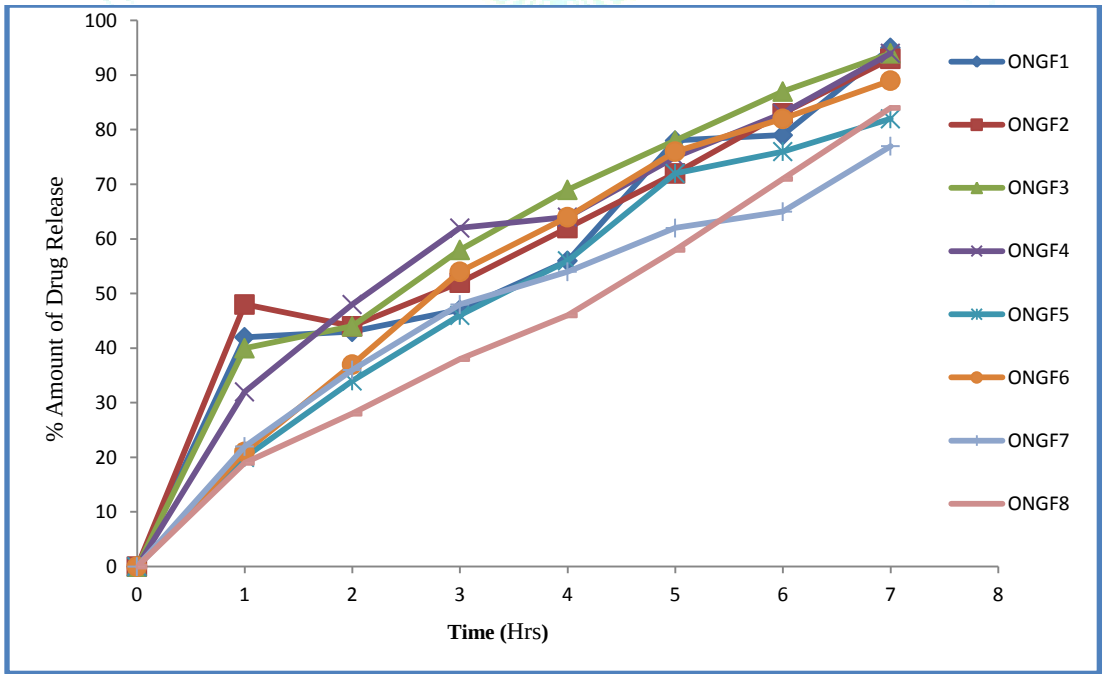

Figure 11: *In-vitro* drug release Profiles of Formulations ONGF1-ONGF8

Kinetic models data analysis: The results of diffusion data fitted to various drug release kinetic equations like Zero order, First order, Higuchi model and Korsemeyer-Peppas. The kinetic values obtained for all formulations ONGF1, ONGF2, ONGF3, ONGF4, ONGF5, ONGF6, ONGF7 & ONGF8were tabulated respectively, Graphs are Plotted for Zero order, First order, Higuchi model and Korsemeyer-Peppas against cumulative % drug release Vs Time (Hrs), Log cumulative % drug remaining Vs Time (Hrs), cumulative % drug release Vs Square root of Time, Log cumulative % drug release Vs Log Time.

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	42	1	1.76	1.73	42	0.47	1.62
2	43	2	1.75	2	43	0.60	1.63
3	47	3	1.72	2.23	47	0.69	1.67
4	56	4	1.64	2.44	56	0.77	1.74
5	78	5	1.34	2.64	78	0.77	1.74
6	79	6	1.32	2.82	79	0.85	1.89
7	95	7	0.69	2.82	950	0.90	1.89

Table 7: Drug Release Kinetics of Oxymetazoline 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	0.9056	11.476	0.8278	0.151	0.875	29.806	0.8969	0.823	Non-Fickian
ONGF2	0.9025	1.1449	0.4821	0.0664	0.7269	39.64	0.6042	0.943	Zeroorder
ONGF3	0.9262	1.272	0.893	0.0838	0.9215	41.404	0.8592	0.852	Non-Fickian
ONGF4	0.939	1.386	0.6231	0.0779	0.7635	41.716	0.8095	0.756	Non-Fickian
ONGF5	0.9648	0.1224	0.971	0.0963	0.9409	47.483	0.9721	0.865	Non-Fickian
ONGF6	0.9659	0.1607	0.9804	0.1131	0.454	34.502	0.9706	0.831	Non-Fickian
ONGF7	0.9319	0.201	0.0158	0.0173	0.0103	5.7846	0.3191	0.975	Zero-order
ONGF8	0.9029	0.2005	0.1054	0.0235	0.0129	4.2484	0.2692	0.853	Non-Fickian

ONGF1, ONGF2, ONGF3, ONGF4, ONGF5, ONGF6, ONGF7 &ONGF8 formulations were followed Korsemeyer-Peppas with correlation coefficient R^2=0.8969, 0.6042, 0.8592, 0.8095, 0.9721, 0.9706, 0.3191& 0.2692 respectively. ONGF1 formulation follows both Zero order and Korsmeyer-Peppas models, it indicates diffusion release mechanism followed by non-fickian transport.

CONCLUSION

The present work was carried out to Formulate and evaluate oxymetazoline hydrochloride nasal gels was prepared by cold method. The FTIR & DSC studies confirmed that there is no chemical interaction took place during encapsulation process. The Evaluation of Oxymetazoline Hydrochloride Nasal Gels performed with the clarity test will be transparent. pH value of all developed formulations of gels (ONGF1-ONGF8) was in the range of 6.2 to 6.9. Spread ability of gels was in the range 19.51 - 33.91 g.cm/sec. Viscosity of various formulated gels was found in range of 8628 to 9622 centipoises. The percentage drug content of all prepared gel formulations were found to be in the range of 78.53 to 98.56 %. The percentage drug content of formulations was found satisfactory. The gel strength of all prepared formulations of gels was found to be in the range of 69 to 96 %. The *In-vitro* release of oxymetazoline HCl was prolonged release of drug ranges from 95 % of released within 7 hour. Among the eight formulations the best formulation is ONGF 1 formulation follows both Zero order and Korsemeyer-Peppas models, It indicates diffusion release mechanism followed by non-fickian transport.

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