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Original Article

COMPARATIVE STUDY OF SEMI-SOLID BASES OF NAPROXEN: PHARMACEUTICAL TECHNOLOGY ASPECTS

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ABSTRACT

Objective: The main objectives of the present investigation work included that the preparation of a suitable naproxen semi-solid dosage form by using different types of semi-solid bases (gel bases, ointment bases) for topical application for the effective treatment of muscle aches.

Methods: Different types of semi-solid bases (gel bases and ointment bases) were successfully prepared by the incorporation method to know the effect of semi-solid bases on drug release from topical semi-solid formulations. In all formulations, the drug was added by the levigation method. An evaluation study of prepared formulations, includes physical appearance, spreadability, extrudability, pH was conducted according to official methods.

Results: Percent drug release of all formulations was conducted by taking diffusion cells with cellophane membrane and results showed that gel-based formulations showed more drug release than ointment-based formulations. Carbopol gel base (F1) showed more drug release (98.76 %), simple ointment base formulation (F8) showed least drug release (25.11%). From the stability studies reports at various temperature and humidity conditions it is evident that all formulations are stable for one month. In all the formulations, the drug content was observed at 95.75%.

Conclusion: Finally concluded that the NXN topical dosage forms can be prepared by using gel-type bases preferably than ointment bases to release more drug from formulations.

Keywords: Semi-solid bases of NXN, Pharmaceutical technology aspects

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INTRODUCTION

Nonsteroidal anti-inflammatory medicines (NSAIDs) are among the most often prescribed medications for pain and inflammation relief. Although NSAIDs inhibit cyclooxygenase-2 at the site of inflammation, they also inhibit gastric mucous cyclooxygenase-1, which causes stomach injury. NSAIDs used topically have been demonstrated to be beneficial in treating acute and chronic soft tissue disorders in several investigations [1]. The therapeutic benefit of a topical NSAID gel over its oral equivalent can be attained while considerably lowering any potential systemic adverse effects.

Recent research has found considerable drug levels in deep tissues including fascia, muscle, and synovium, following topical administration, which is a desired property for relieving local symptoms with low doses while decreasing systemic adverse effects. The concentration obtained in the subcutaneous tissues by NSAID gels is adequate to produce a therapeutic advantage, according to Rhodes *et al.* [2]. Furthermore, because the plasma concentration acquired with topical administration is 1–10% of that obtained through oral therapy, the risk of potentially serious side effects is considerably reduced.

When examined *in vitro*, Naproxen is a non-selective cyclooxygenase-1/2 inhibitor, but when tested ex vivo, it is a somewhat preferred cyclooxygenase-2 inhibitor. Despite the fact that it is one of the best-tolerated traditional NSAIDs, gastropathy develops with long-term oral treatment. Alternative administration routes, on the other hand, should be examined to minimise systemic adverse effects and gastrointestinal issues that frequently emerge after prolonged oral treatment.

As a result, an enhanced NXN formula with a high degree of skin penetration might be beneficial in the treatment of not only locally inflamed skin tissues but also painful states of supporting body components such as bones, ligaments, joints, tendons, and muscles. The ointments, pastes, and creams are made up of the medicine suspended in a semi-solid base that is either hydrophobic or hydrophilic [3]. The bases are crucial in defining the drug release characteristics of the formulation. Creams are semi-solid emulsions, whereas ointments are hydrophobic, oleaginous-based dosage forms. Pastes have a thicker consistency than ointments because they include more solids. Lotions, suspensions of particles in aqueous solution, or emulsions are used for topical treatment in liquid form other than the solution.

MATERIALS AND METHODS

Naproxan (NXN) was obtained as gift samples from FDC limited Mumbai, India. Carbopol 940, sodium carboxy methyl cellulose (NaCMC), hydroxyl propyl methyl cellulose (HPMC), Polyethylene glycol (PEG 400), Triethanolamine was purchased from SD Fine chemicals, Hyderabad. Ointment base, Tween 80, Span 40 and glycerin were procured from the Loba Chemic Pvt. Ltd. Mumbai, India.

Analytical methods

Construction of calibration curve

The stock solution of NXN was serially diluted with same pH buffer to get drug concentration in the range of 5-25 µg/ml. The absorbance of the solutions was measured against 7.4 pH buffer as a blank at 271 nm by double beam UV-visible spectrophotometer (Model No. UV S.220V, 2401(PC), Shimadzu Corporation, Japan).

Preformulation study

The drug and used excipients were blended in a poly bag and passed through a 40 # sieve. Measure quantity of blend was placed in a glass vial and sealed with a rubber stopper.

The vials were stored at 40±2/75±5 % RH (Wadegati TM Labe Quip (P) Ltd., Model No. HTC-3003, Andheri (E), Mumbai, India). Physical observation of the blend was recorded at initial, 2 and 4 w for two months [4]. Physical characteristics (colour change) were checked on a regular basis. Any change in colour in a combination was used to exclude it out of the research.

Formulation methods

Formulation of NXN semisolid bases

The proportions as mentioned in table 1 are accurately weighed and compounding was done by the method of incorporation as per the previous study performed by Kameswararao *et al.* [4]. The stainless steel spatula and porcelain tile were used for levigation.

Table 1: Composition of NXN topical formulations

Ingredients	Weight % (w/v)										
	F1 (Carbopol gel base)	F2 (HPMC gel base)	F3 (Sodium CMC gel base)	F4 (PEG base)	F5 (Water miscible base)	F6 (Cold cream base)	F7 (Beller's Ointment base)	F8 (Simple ointment base)	F9 (Oleaginous base)	F10 absorption base	F11 Emulsifying ointment base
NXN	1	1	1	1	1	1	1	1	1	1	1
Carbopol 940	2	-	-	-							
HPMC	-	3	-	-							
Sod CMC	-	-	5	-							
PEG 4000	-	-	-	25							
PEG 400	-	-	-	75							
Triethanolamine	q. s	-	-	-							
Propyl hydroxybenzoate	0.05	-	-	-							
Methyl hydroxybenzoate	0.15	-	-	-							
Cetosteryl alcohol	-	-	-	-		10		85	83	90	50
White soft paraffin											
Liquid paraffin						45					20
Hard paraffin						7		3		3	
Wool fat									9		
Emulsifying wax											30
Yellow Bees Wax	-	-	-	-	2.5	5	1	2	2		
White bees-wax										2	
Tween-80	--	-	-	-	5.5						
Span-60	-	-	-	-	7.5						
Glycerin	-	-	24	-	-						
Borax						0.2					
Sod meta bisulfate							0.1				
SLS							2				
Prop Glycol							10				
Propyl Paraben	-	0.1	0.1	-	0.1	0.1	0.1				
Methyl Paraben	-	0.2	0.2	-	0.2	0.2	0.2				
Distilled water	97.8	q. s	q. s	-	q. s	q. s	q. s				

Carbopol gel base (F1)

Carbopol 940 was gently added with a little amount of distilled water as a medium and continually mixed to achieve a uniform carbopol dispersion. NXN, methyl hydroxy benzoate, and propylhydroxy benzoate were pre-dissolved in a tiny amount of water before being added to the carbopol dispersion. Water was used to modify the final volume, and triethanolamine was used to neutralise the pH [5]. This mixture was held overnight to ensure that the carbopol texture and appearance were homogeneous, and that any air bubbles were eradicated.

HPMC gel base (F2)

To prevent lumping, the weighed HPMC powder is disseminated and hydrated in a quantity of hot water (approximately one-third of the entire volume) heated above 90 °C with vigorous stirring. The remaining cold water (two-thirds of the total volume) is then added to complete solubilization by lowering the temperature of the dispersion. Before adding to the dispersion, NXN, methyl hydroxybenzoate, and propyl hydroxybenzoate are dissolved in water. HPMC becomes water-soluble when the temperature is dropped, resulting in greater viscosity ("hot/cold" approach).

Sodium CMC gel (F3)

The considered amount of propyl paraben and methyl paraben was dissolved in water (1/3 quantity of total volume) by heating. NXN was dissolved in a preservative solution and warm to about 70 °C. Sodium CMC was mixed with glycerin in a glass mortar. Drug solution with preservative was added to Sodium CMC-glycerin mixture. The resultant solution was mixed thoroughly with trituration until clear jelly was formed.

Macrogol gel (PEG; F4)

In a porcelain dish, the weighed quantity of PEG 4000 was melted. PEG 400 is continuously stirred into this melt. The melt was withdrawn from the heating mantle and continued to be stirred until it began to solidify. NXN was inserted when the temperature of the base was about room temperature. For levigation, a stainless steel spatula and porcelain tile were utilised.

Water miscible base (F5)

Cetostearyl alcohol, yellow bees wax, span 60 and propylparaben were weighed and melted together in a china dish on a water bath. Tween 80, methylparaben and NXN were dissolved in distilled water and heated in a separate beaker on a water bath. With continual stirring, the hot aqueous phase was introduced to the hot oily phase until the melt began to solidify.

Cold cream base (F6)

White bees wax, soft yellow paraffin, hard paraffin and Propylparaben were weighed and melted together in a china dish on a water bath. To this melt, liquid paraffin was added by continuous

stirring at 70 °C. Methylparaben and NXN were dissolved in distilled water and heated in a separate beaker on a water bath at 70 °C. With continual stirring, the hot aqueous phase was transferred to the hot oily phase until the melt congealed.

Beller's ointment base (F7)

Cetostearyl alcohol, yellow bees wax and propylparaben were weighed and melted together in a china dish on a water bath at 70 °C. Propylene glycol, sodium metabisulphite, methylparaben and NXN were dissolved in distilled water and heated in a separate beaker on a water bath at 70 °C. With continual stirring, the hot aqueous phase was transferred to the hot oily phase until the melt congealed.

Simple ointment base (F8)

Hard paraffin, bees wax, cetostearyl alcohol, and soft white paraffin were weighed and heated together in a porcelain dish. The melt was withdrawn from the heating mantle and continued to be stirred until it began to solidify. NXN was inserted when the temperature of the base was about room temperature. For levigation, a stainless steel spatula and porcelain tile were utilized.

Oleaginous base (F9)

The weighed quantity of yellow bees wax, soft white paraffin and wool fat was taken in a china dish and melted collected. The melt was withdrawn from the heating mantle and continued to be stirred until it began to solidify. NXN was inserted when the temperature of the base was about room temperature. For levigation, a stainless steel spatula and porcelain tile were utilised.

Paraffin ointment base (F10)

Weighed quantities of hard paraffin, white paraffin, white bees wax and cetostearyl alcohol are taken in a china dish and melted in a heating mantle, with continuous stirring. Stirring is continued until it becomes cold and in semi-solid consistency. NXN was inserted when the temperature of the base was about room temperature. Vigorous stirring was avoided, which may lead to excessive aeration.

Emulsifying ointment base (F11)

The Emulsifying wax, soft white paraffin and Liquid paraffin are exactly weighed as per the formula and taken in a China dish. China dish is placed in a water bath and heated until the whole components melt. The resultant mixture was continuously stirred until it becomes cold and allowed to congeal. After melting, mix the components until the ointment is completely cool, being careful not to induce localised cooling. NXN was inserted when the temperature of the base was about room temperature. After the ointment has thickened, vigorous stirring creates excessive aeration and should be avoided.

Evaluation of bases

The visual characteristics of preparations was virtually checked for colour, consistency, texture, and greasiness by Brookfield viscometer (Anatech India) pvt, Ltd, Mumbai, India) was used to determine the viscosity of prepared ointment by filling a wide mouth jar with a sufficient quantity of ointments gels and creams separately. The height of the ointments in the jar should be adequate to allow the spindle to be dipped. The spindle was set at 2.5 revolutions per minute. The formulations' viscosity was measured.

Spreadability

A formulation's medicinal efficacy is also determined by its spreading value. The two glass slides, each measuring 62.2 cm, were chosen. One of the slides was covered with the formulation whose spreadability was to be tested (500 mg). The formulation was sandwiched between the two slides after the second slide was put over the first [6]. The upper slide was given a 100 gramme weight so that the formulation between the two slides could be squeezed consistently to produce a thin coating. The weight was repositioned, and any extra formulation stuck to the slides was scraped away. The bottom slide was attached to the apparatus's board, while the higher slide was attached to a string on which a 20-gram force could be imparted using a simple pulley. The time it took for the upper slide to travel 6 cm and separate from the lower slide under the weight's direction was recorded. The experiment was done three times, with the average of the results calculated for each formulation.

Spreadability = ml/t

Where, m = weight tied to the upper slide (20 gm); l = length of glass slide (6 cm); t = time in seconds.

Extrudability, pH and drug content

The mixtures were poured into metal tubes that could be collapsed. The material was extruded by pressing the tubes, and the extrudability of the formulations was tested. A digital pH meter was used to determine the pH of all formulations (Ultra-Tech System, India). The pH of the semi-solid formulations was measured after the electrodes were completely immersed in them. Weighing 200 mg of the mixture and transferring it to a 100 ml volumetric flask. Formulation was dissolved in a suitable solvent (distilled water for NXN and acetate buffer pH 4.0) and the volume was made with up to 100 ml; after appropriate dilution and the solution absorbance was measured at 271 nm for NXN using UV visible spectrophotometer (Elico SL-164, Company, Hyderabad, India), and the amount of NXN present was calculated using the respective regression equations.

FT-IR study

IR spectroscopy of NXN and formulations was performed using a diffuse reflectance FTIR spectrophotometer (Shimadzu Corporation, Jappan). NXN and dry formulation samples were mixed uniformly and filled into the die cavity of the sample holder, and an IR spectrum was recorded using the diffuse reflectance FTIR spectrophotometer [7].

Differential scanning calorimetry (DSC)

A differential scanning calorimeter was used to record the DSC thermograms of the pure medication (NXN) and all formulations. An empty metal pan was utilised as a reference (DSC SDT Q600 V20.9 Build20, universal V4.5ATA instrument).

***In-vitro* diffusion study**

The NXN is freely soluble in water; hence distilled water was selected as the receptor medium for *in vitro* diffusion studies. Acetate buffer pH 4.0 was selected as the receptor medium for NXN for *in vitro* diffusion studies. The cellophane membrane 25 cm^2 was taken and washed in the consecutive water. It was formerly saturated in distilled water for 2 h, after which it is again rewashed in the running water so that the glycerin on it is removed; it is then soaked overnight in alcohol. On the next day, it is washed with water to remove the alcohol and was mounted on the diffusion cell for further diffusion studies. The *in vitro* diffusion of NXN from various dermatological preparations was investigated using a laboratory-fabricated cylindrical tube (3.6557 cm2 area and 100 mm height). The diffusion cell was firmly attached to one end of the tube, while the other was left exposed to the elements. On to the cellophane membrane was placed a weight of formulations equating to 25 mg of medication. The cell was inverted and slightly submerged in 20 ml of distilled water in a beaker as the receptor phase, and the system was kept at 37 1 oC for 6 h. The aliquots 2 ml of samples were withdrawn at the specific interval of time as shown in table up to 6 h. The media was stirred using magnetic Teflon-coated bead. 2 ml of sample was withdrawn with proper dilution in distilled water and the NXN content was estimated spectrophotometrically at 271 nm [8]. For each time period, the drug released was determined as the average of three such assessments. The cumulative drug release profile *in vitro* was determined, and the percentage drug release was approximated.

Dissolution profile modeling

Several model-dependent strategies for characterizing the kinetics of drug release from dosage forms have been published by various researchers. Curve fitting is used in all of the model-dependent approaches. To represent the observed data, various mathematical functions were applied. In practice, both linear and non-linear models are utilised for dissolution modeling. Zero order, Higuchi,

Hixon-Crowell, Quadratic, and polynomials are examples of linear models, whereas nonlinear models include First order, Weibull, KorsMeyer-Peppas, Logistic, and others. To characterise release processes and compare test and control groups, numerous linear and non-linear kinetic models have been developed.

Stability studies

In this study, chosen formulations were maintained for four weeks at four different temperatures: cold (4 °C), room temperature (25–30 °C), and accelerated temperature (45 °C), and any changes in physical properties and drug content were recorded. Visual appearance, spreadability, extrudability, pH, leakage, nature, drug content, and phase separation were all examined. The formulations were poured into aluminium collapsible tubes and kept for 4 w at 4, 27, and 45 °C.

RESULTS AND DISCUSSIONS

Calibration curve

Calibration curve of NXN in 7.4 pH phosphate buffer was plotted by preparing serial dilutions ranging from 5–25 µg. ml^{-1} and absorbance was checked at 271 nm against 7.4 pH phophate buffer as blank by using UV–VIS spectrophotometer. A good linearity with R^2 of 0.999 was observed.

Interaction studies outcome

The NXN was combined in various quantities with all of the excipients that would be utilised in our formulation in various ratios and stored at 40 degrees Celsius for four weeks. Physical qualities (colour change) were evaluated on a regular basis, and any combination that changed colour was discarded from the research.

Evaluation of semi-solid preparations

The compositions' physical appearance (table 2) was examined and contrasted visually and by physical application. The carbopol gel, (F1), the HPMC gel (F2) and sodium CMC gel formulations (F3) were translucent, yellowish glossy, smooth and non-greasy on application. PEG-based formulation (F4) was found to be opaque, off white and greasy on application. The water-miscible base and cold cream base formulation (F5 and F6) showed opaque nature, slight yellowish color and greasy on application. Beller's ointment base, Simple ointment base, oleaginous ointment base, Paraffin ointment base (absorption base) formulations (F7, F8, F9, and F10) showed opaque nature, creamy yellowish color and greasy on application. Emulsifying ointment base showed opaque, off white and greasy on application [9].

The gel formulations showed better spreadability than the ointments. Among the formulations, the F1 showed the maximum spreadability and the F7 showed the least spreadability (table 2). The gel and oleaginous base formulations showed excellent extrudability compared to other formulation [10, 11]. All the ointment formulations showed better extrudability when they were extruded from the metallic collapsible tubes. The pH of the formulations was found to be near to neutral range i.e. 6.22 to 7.81, which showed the suitability of the formulations for application on the skin, because skin pH lies in this range. From the drug content estimation all the formulations were found to contain 97.65% to 99.64% of the labeled amount of the NXN.

FT-IR study

To investigate any possible interactions between drug and the utilized polymer under investigation FT-IR spectrophotometer method was used. The IR spectra of pure drug (Dipyridamole) and its physical mixture were carried out by the FT-IR spectrophotometer.

Table 2: Physical appearance of the formulations

Bases	Appearance	Viscosity	Spreadability (gm. cm/sec)	Extrudability	pH	% Drug content
F1	Translucent, yellowish glossy, smooth and non-greasy on application	4227	18.2	+++	7.23	98.36
F2	Translucent, yellowish glossy, smooth and non-greasy on application	5633	14.6	+++	7.12	99.64
F3	Translucent, yellowish glossy, smooth and non-greasy on application	7268	15.8	+++	6.22	97.65
F4	Opaque, off white and greasy on application	1375	18.4	+	6.24	98.17
F5	Opaque, slight yellowish and greasy on application	1134	7.55	+	6.37	99.61
F6	Opaque, slight yellowish and greasy on application	6946	5.46	++	7.16	99.39
F7	Opaque, creamy yellow and greasy on application	4125	3.74	+	7.36	98.46
F8	Opaque, creamy yellow and greasy on application	9045	7.45	++	6.98	98.54
F9	Opaque, creamy yellow and greasy on application	1245	11.74	+++	7.81	99.48
F10	Opaque, creamy yellow and greasy on application	2415	12.57	+	6.57	99.33
F11	Opaque, off white and greasy on application	2596	13.14	+	6.76	98.36

+++Excellent,++Good,+Satisfactory

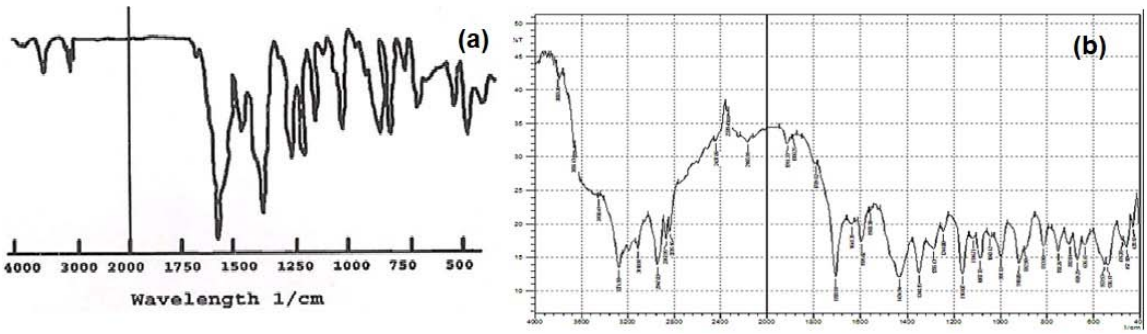

Fig. 1: FTIR spectrum of (a) NXN, and (b) F1

A sharp and a decrease in altered of peak at 1627.63 cm^{-1}, a peak between 1615-1495 and at 612.39 cm^{-1}, represents a double bond and the overlapping of functional groups of aliphatic and aromatic compounds. A strong band occurred at 2919.7 cm^{-1} as a result of sulphides of keratin molecules (fig. 1).

Thus, the FTIR analysis revealed the compatibility between the components of the NXN with mere association and/or conjugation of their groups [12]. The studied effect might be possible to connect all the components together in order to form a continuous scaffold.

DSC

The DSC curves of NXN and its corresponding F1 semi-solid preparation are shown in fig. 2. When guest molecules interacted with host molecules in carbopol, physiochemical parameters such as melting, boiling, and sublimation point were frequently affected. Entire elimination of endothermic peak corresponding to NXN in formulation (F1) of carbopol owing to release of water molecules or conversion to complete amorphous form or breakdown of crystalline into molten carrier [13]. A tiny broad peak about 210 °C in the F1 was seen with reduced intensity, which might correspond to NXN melting point displaced to a higher temperature. This suggested that the NXN crystallinity had decreased.

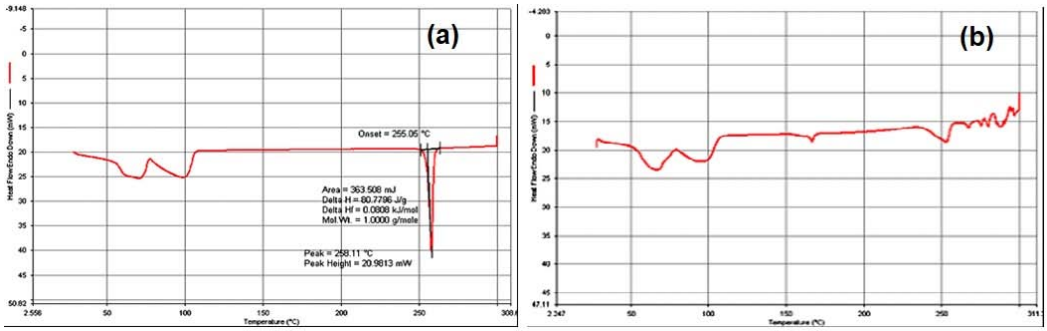

Fig. 2: DSC thermogram of (a) pure NXN, (b) F1

***In vitro*-drug release**

As shown in fig. 3, it is clearly evident that gel based formulations carbopal gel base (F1), HPMC gel base (F2), and PEG base (F4), water miscible base (F5) showed better drug release (>90 %) than the ointment based formulations. Formulations F6, F8 and F9 showed the least drug release (<40 %) among all formulations. The overall % Cumulative drug release from different formulations through the cellophane membrane in decreasing order is follows: F1>F5>F4>F2>F7>F3>F11>F10>F6>F9>F8.

Percent drug release of all formulations was conducted by taking diffusion cells with cellophane membrane and results showed that gel-based formulations showed more drug release than ointment-based formulations [14]. Carbopol gel base (F1) showed more drug release (98.76 %), and simple ointment base formulation (F8) showed least drug release (25.11%). From the stability studies reports at various temperature and humidity conditions, it is evident that all formulations are stable for one month. In all the formulations, the drug content was observed at 95.75%.

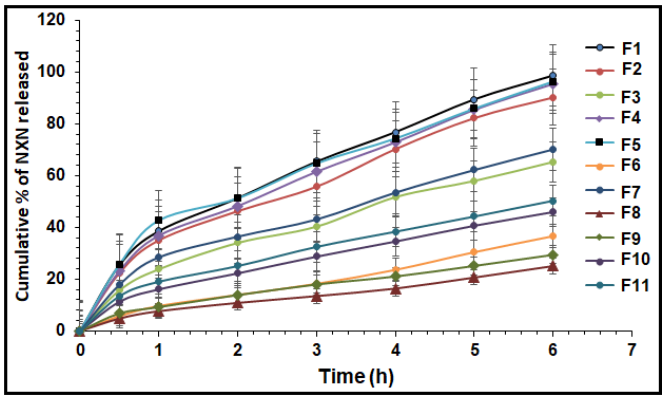

Fig. 3: *In vitro* release of NXN from various prepared semi-solid bases

Release kinetics

The mechanism of drug release was explored by subjecting the data to kinetic analysis by fitting to various mathematical equations and models, viz., zero order, first order, Higuchi and Peppas models (table 3). On the basis of higher regression values obtained, the semi-solid formulation followed zero-order kinetic and followed Higuchi pattern (R^2 = 0.9432 to 0.9923) [15].

Table 3: Correlation coefficients (R^2) values of different kinetic models

Bases	r^2				Peppas
	Zero order	First order	Higuchi	Peppas	(n)
F1	0.967±0.071	0.973±0.059	0.946±0.057	0.968±0.048	0.94±0.012
F2	0.946±0.023	0.933±0.044	0.934±0.073	0.924±0.027	0.83±0.015
F3	0.938±0.054	0.946±0.090	0.946±0.063	0.974±0.026	0.43±0.016
F4	0.972±0.075	0.981±0.075	0.976±0.072	0.926±0.065	0.57±0.023
F5	0.966±0.043	0.864±0.048	0.946±0.059	0.987±0.080	0.42±0.035
F6	0.915±0.065	0.985±0.058	0.992±0.061	0.994±0.087	0.34±0.031
F7	0.939±0.045	0.915±0.041	0.971±0.030	0.985±0.036	0.47±0.022
F8	0.984±0.057	0.946±0.059	0.934±0.031	0.983±0.012	0.84±0.024
F9	0.976±0.079	0.846±0.046	0.957±0.037	0.946±0.021	0.76±0.051
F10	0.938±0.048	0.956±0.033	0.994±0.024	0.926±0.057	0.83±0.061
F11	0.926±0.031	0.925±0.034	0.942±0.037	0.981±0.044	0.64±0.029

Effect on stability

Effect of different storage conditions on the stability of the selected formulations were conducted at room temperature (27°±1 °C), refrigerator temperature (4 °C) and oven temperature 45°±1 °C. All the formulations did not show any significant difference in visual appearance, pH, extrudability and spreadability. Phase separation or softening and leakage from tubes were not observed in any of the formulations after 4 w. In all the formulations, the drug content was above 95.75 % observed up to 4 w [16]. From the stability studies reports at various temperature and humidity conditions, it was evident that all formulations are stable for one month. In all the formulations, the drug content was observed at 95.75%.

CONCLUSION

In the present study, topical dosage forms of NXN with different types of semi-solid bases were prepared and evaluated to know the effect of semi-solid bases on drug release. The prepared topical formulations excipients were selected based on the reports of preformulation studies and all excipients are compatible with the drug. An evaluation study of prepared formulations, includes physical appearance, spreadability, extrudability, pH was conducted according to official methods and results were within limits. For the preparation of NXN semi-solid preparation, carbopol gel was ideal to release the medicament-controlled fashion with stability throughout.

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AUTHORS CONTRIBUTIONS

All the authors are contributed equally.

CONFLICTS OF INTERESTS

The authors declare that there are no conflicts of interest.

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