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Enhancing the Solubility and Dissolution of Ketoprofen by Recrystallization Method

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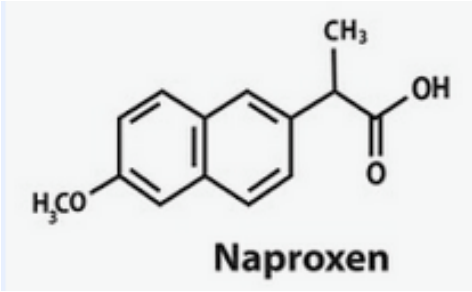
ABSTRACT
The preliminary study characterized Naproxen as a white, crystalline, odorless powder with high solubility in ethanol, methanol, and phosphate buffer (pH 7.4), while it showed limited solubility in water and 0.1N HCl. The melting point (153°C) was within the standard range. FTIR analysis of the physical mixture revealed no interaction between Naproxen and phosphatidylcholine, confirming their compatibility and supporting vesicular drug delivery formulation. Six formulations varying in soya-phosphatidylcholine, Tween 80, and drug content were prepared and evaluated. Formulation NT2 demonstrated the smallest vesicle size and the highest encapsulation efficiency, making it suitable for further studies. The optimized formulation was incorporated into a gel base and assessed for pH (6.99 ± 0.14), spreadability (14.69 ± 1.52g.cm/sec), viscosity (2748 ± 22 cps), drug content (99.87%), and in vitro drug diffusion. No significant changes were observed in physical appearance, particle size, or drug content during the evaluation. The study concluded that the formulated Naproxen transmucosal gel exhibited high encapsulation efficiency, small particle size, and effective skin barrier penetration, indicating its potential to enhance drug release and bioavailability in transdermal delivery.

Keywords: Naproxen, vesicular drug delivery, phosphatidylcholine, Tween 80, transmucosal gel, FTIR compatibility

INTRODUCTION

Name of Drug : Naproxen
Chemical Name: (2S)-2-(6-methoxynaphthalen-2-yl) propanoate
Formula : $C_{14}H_{13}NaO_3$
Molecular Weight : 230.26
Structure :



Category : Analgesic/NSAID
Description : Solid, White to off-white crystalline powder
Odor : Practically odorless
Solubility : 15.9 mg/L (at 25 degrees Celsius), Slightly soluble in ether; soluble in methanol, chloroform, and acetic acid. 25 parts ethanol (96%), 20 parts methanol, 15 parts chloroform, and 40 parts ether are soluble. It is almost insoluble in water but easily soluble in alcohol.
Accession Number : DBSALT000949
Log P : 3.18
Mechanism of action: `
Reduces inflammation, discomfort, and fever, most likely via inhibiting cyclooxygenase activity and prostaglandin formation. Naproxen is a well-known non-selective NSAID that may be used as an analgesic, anti-inflammatory, and antipyretic. The pharmacological effect of naproxen, like that of other NSAIDs, can be linked to the inhibition of cyclo-oxygenase, which lowers prostaglandin production in many tissues and fluids, including synovial fluid, stomach mucosa, and blood. Although naproxen is an efficient painkiller, it might have unanticipated negative consequences for the patient. Naproxen, for example, can impair blood pressure management. A research discovered that using naproxen caused a rise in blood pressure, however not as severe as taking ibuprofen.
Contraindications: Allergy to aspirin, iodides or any NSAID.

Table 1: Pharmacokinetic characters of the drug

Pharmacokinetic characters	Naproxen
Oral bioavailability (%)	Higher than 80%
Plasma protein binding (%)	>99%
Volume of distribution (L/Kg)	0.16L/kg
Elimination $t^{1/2}$ (hr)	12-17 hours.
Routes of administration	In both immediate and ER tablets or suspension forms, or topically

Interactions
Anticoagulants: Because of lower plasma protein binding, anticoagulants may have a stronger impact. May increase the likelihood of stomach erosion and bleeding. Lithium: Lithium clearance may be reduced. Methotrexate: May cause methotrexate levels to rise.

MATERIALS AND METHODS

Table 2: Materials used

S.No.	Materials	Manufacturer
1.	Naproxen	Navakar Biochemical, Gujarat
2.	Carbopol	Loba Chemicals Pvt Ltd, Hyd
3.	Phosphotidyl choline	Yarrow
4.	Tween 80	Fisher Scientific, Mumbai

Table 3: List equipment's used

S.No	Name of the Equipment	Suppliers
1	Digital Balance	Infra, India
2	Fourier Transmission infrared radiation (FTIR)	Shimadzu IR-470 (Tokyo, Japan)
3	Dissolution Apparatus	Lab India
4	UV Visible Spectro Photometer	Shimadzu, Japan

Drug Identification: The physical and chemical characteristics of the drug were evaluated in preliminary tests.

Organoleptic qualities: Descriptive terminology was used to record the drug's organoleptic features, such as physical condition, colour, scent, and so on. It aids in drug identification.

Melting point determination: This is the most basic technique of identifying the medication. The melting point of naproxen was calculated using a laboratory melting point device and the method described in the Indian Pharmacopoeia 2007.

To fulfil regulatory criteria, the solubility of naproxen in several solvents was evaluated using a micropipette. The solubility of the medication was determined using various descriptive language from the Indian Pharmacopoeia, 2007. Table 1 shows the Indian Pharmacopoeia's broad definition of solubility.

Calibration curve

Stock solution preparation

Naproxen standard stock solution was made by dissolving correctly weighed 10 mg of medication in phosphate buffer pH 6.8 in 100 ml volumetric flasks to provide a concentration of 100 g/ml.

Creating standard dilutions

Five volumetric flasks of 50 mL were used. Aliquots of 1 ml, 2 ml, 4 ml, 6 ml, and 8 ml were obtained from the stock solution and diluted to achieve concentrations of 2 g/ml, 4 g/ml, 8 g/ml, 12 g/ml, and 16 g/ml, respectively. It was then tested using a UV visible spectrometer at 331 nm.

Drug-polymer Compatibility studies: [74]

Infrared spectroscopy was utilised to explore any potential interactions between the medication and the Excipients. The IR spectrums of pure drug, polymer, and physical combination of drug and polymer were collected, analysed, and compared. Shimadzu IR-470 spectrophotometer was used to capture the IR spectra. The samples were made as potassium bromide discs squeezed less than 6 tonnes of pressure. The scanning range was more than 4000-400 cm-1.

Differential Scanning Calorimetry (DSC)

A Perkin-Elmer Differential Scanning calorimeter with a display and a Computerised Thermal Analysis System and printer was utilised. Standard medium was used to calibrate the device. Samples weighing 5-10 mg were weighed and hermetically sealed in flat bottomed alumininum pans. These samples were cooked in a nitrogen environment (50 ml/min.) at a continuous heating rate of 200 degrees Celsius per minute, with almina as the reference standard. DSC can offer a rough notion of the possibility of interaction merely by comparing the curves related to the specific excipient.

PREPARATION OF TRANSMUCOSAL [75-83]

Tween 80 (95:05, 90:10, 85:15, 80:20, and 85:15) and Naproxen (250mg) were dissolved in alcohol. The solution was then placed in a flask with a circular bottom. Shaking was used to disintegrate them. The thin film was then created by maintaining it at 400 degrees Celsius in the rotator vacuum evaporator. Under hoover, the last traces of solvent are eliminated. Rotation at 60 rpm for 1 hour at room temperature hydrates the deposited lipid layer with the suitable buffer. At normal temperature, the resultant vesicles swell for 2 hours. At room temperature, the multilamellar lipid vesicles (MLV) are sonicated. The Transmucosal was created by hydrating the thin film with phosphate buffer saline.

Table 4: Formulation code and variable used in preparation of Transmucosal

S.No.	Formulation code	PC:T (mg)	Drug (mg)
1	NT1	95:05	250
2	NT2	90:10	250
3	NT3	85:15	250
4	NT4	80:20	250
5	NT5	75:25	250
6	NT6	70:30	250

Preparation of Topical Transmucosal Formulation:

Transmucosal were mixed in a 1:1 ratio with carbopol-934 (1%) gel basis. The carbopol-934 (1%) gel basis was made by soaking it for 30 minutes and then continuously swirling it with water. The consistency of 1% carbopol-934 gel base is satisfactory (it gels).

Characterization of Transmucosal

Microscopic observation of prepared Transmucosal

The shape of the created Transmucosal formulation was observed using an optical microscope (cippon, Japan) with a camera attachment (Minolta). Vesicle size estimation: The particle size analyzer (Malvern Master Sizer, Malvern Instruments Ltd., Malvern, UK) was used to determine the size of the vesicles. Entrapment effectiveness: The concentration of unentrapped free drug in aqueous medium was used to calculate entrapment efficiency. In the Ependorf tubes, 1 ml of the drug-loaded Transmucosal dispersion was deposited and centrifuged at 10,000 rpm for 30 minutes. At the bottom of the tubes, the Transmucosal and encapsulated medication were separated. As a control, plain Transmucosal without Naproxen were centrifuged in the same manner. The UV absorbance of the supernatant at 331 nm was measured to estimate the free drug content.

Evaluation of Gels

pH determination: 50gr of gel formulation were weighed and transferred to a 10 ml beaker before being tested with a digital pH metre. To treat skin infections, the pH of the topical gel formulation should be between 3& 9. Spreadability was determined using a modified equipment that was recommended. The slip and drag properties of the gels were used to calculate spreadability. The modified apparatus was made of two glass slides, the bottom of which was fastened to a wooden plate and the top of which was attached to a balance via a hook. The spreadability was calculated using the

formula: S=ml/t, where S is the spreadability, m is the weight in the pan attached to the higher slide, t is the time required to move a certain distance, and l is the distance travelled. The mass, length, and't' were kept constant for practical purposes. The spreadability of each formulation was measured in triplicate, and the average values are provided.84

Medicinal content:

100 cc of ethyl alcohol was combined with 1 gramme of the produced gel. After filtering the stock solution, aliquots of various concentrations were produced using appropriate dilutions, and absorbance was measured at 331 nm. The drug content was determined using a linear regression analysis of the calibration curve.

In-vitro diffusion research:

A drug release investigation in vitro was carried out utilising a redesigned Franz diffusion cell. Between the receptor and donor compartments, a dialysis membrane (Hi Media, Molecular weight 5000 Daltons) was put. The donor compartment was filled with Naproxen Transmucosal, while the receptor compartment was filled with phosphate buffer, pH 7.4 (24 ml). Throughout the experiment, the diffusion cells were kept at 370.5°C with stirring at 50 rpm. At various time intervals, 5 ml aliquots were removed from the receiver compartment via the side tube and analysed for drug content using a UV Visible spectrophotometer.

RESULTS AND DISCUSSION

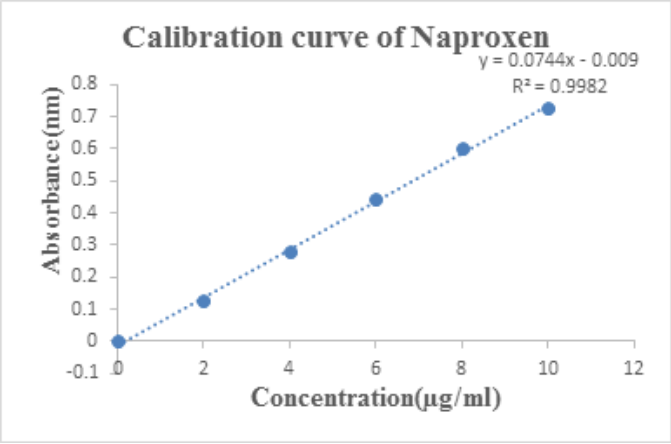


Fig.1: Standard calibration curve of Naproxen in Phosphate buffer pH 6.8

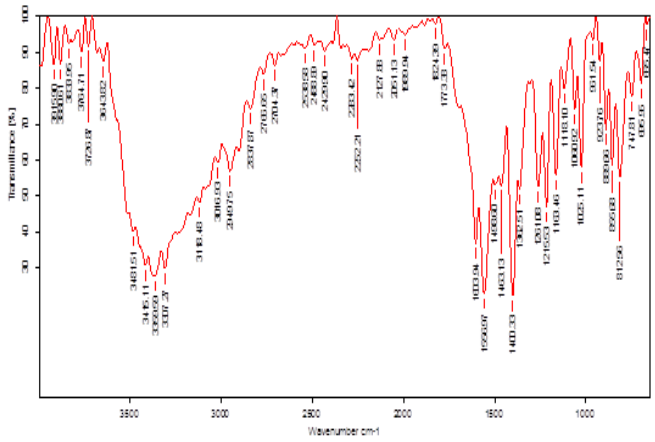


Fig.2: FTIR spectrum of naproxen

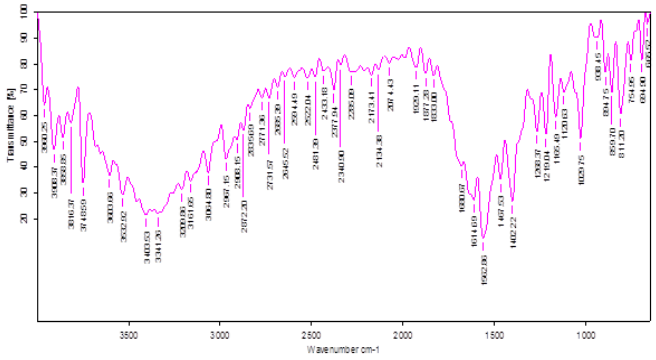


Fig.3: FTIR spectrum of Naproxen with Tween 80

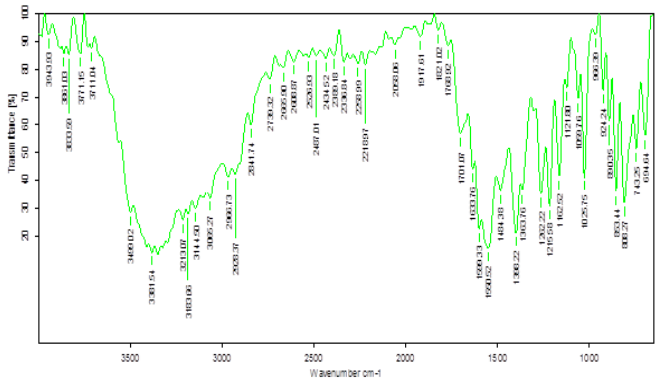


Fig.4: FTIR spectrum of Naproxen with Phosphotidyl chlorine

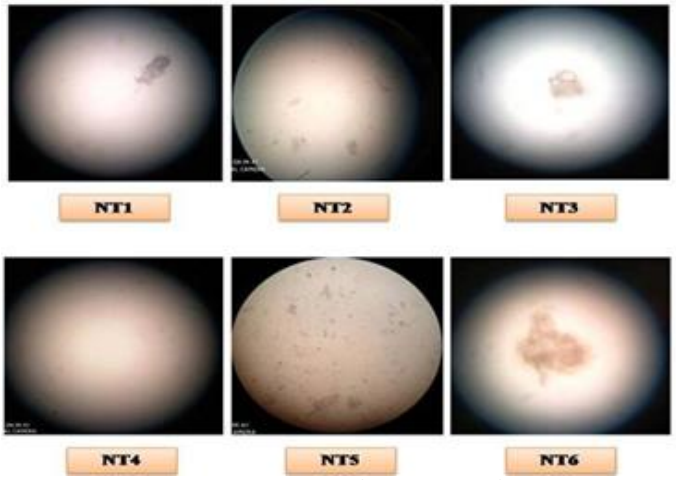


Fig.5: Microscopic observation of Transmucosal formulations

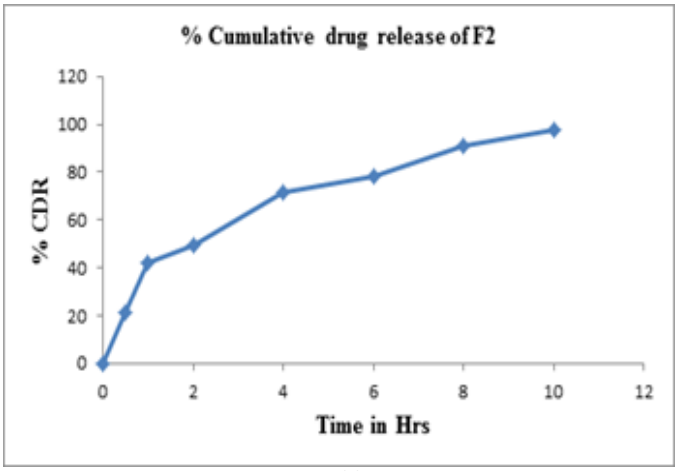


Fig.6: % CDR of formulation F2

Table 5: In Vitro drug release kinetic studies formulation NT2

Time in Hrs	Sqrt time	Log time	% CDR	Un CDR	log% unCDR	Log % CDR
0	0	0	0	100	2	0
0.5	0.71	-0.3	21.32	78.68	1.90	1.33
1	1.00	0.0	42.23	57.77	1.76	1.63
2	1.41	0.3	49.48	50.52	1.70	1.69
4	2.00	0.6	71.65	28.35	1.45	1.86
6	2.45	0.8	77.97	22.03	1.34	1.89
8	2.83	0.9	90.67	9.33	0.97	1.96
10	10	3.16	1.0	97.69	2.31	0.36

Table 6*: In vitro* Drug release kinetics of Naproxen Transmucosal

Formulation code	Zero order		First order		Higuchi model		Korsmeyer-peppas		Release Mechanism transport
	Slope	R^2	Slope	R^2	Slope	R^2	n	R^2	
NT2	8.565	0.865	-0.142	0.948	30.84	0.982	0.856	0.392	Anomalous (non-Fickian) diffusion

Discussion

The preliminary study indicated that Naproxen is a white, crystalline, odorless powder. It has high solubility in Ethanol and Methanol, and is soluble in Phosphate Buffer 7.4. It is slightly soluble in water and 0.1 N HCL. The melting point ranged from 153°C, which is within the standard value range of 152-154°C. Based on the FTIR data of the physical mixture, it is evident that the drug's functionalities, including peak intensities, remained unchanged. This suggests that there was no reaction between the drug and PC during the process, leading to the formation of reactant products. Therefore, there is no interaction between them, which supports the formulation of a vesicular drug delivery system. The FTIR study confirms compatibility between the drug and Excipient.
A total of six formulations were prepared, varying the amount of Soya-phosphatidylcholine, Tween 80, and the drug. These formulations were evaluated for vesicle size and entrapment efficiency. Among them, Formulation NT2 exhibited the smallest vesicle size and an increase in entrapment efficiency, making it the best formulation for further evaluation.

The best batch of Transmucosal was incorporated into a gel base and evaluated for pH, spreadability, viscosity measurement, drug content, and in-vitro diffusion study. The drug content is crucial in Transmucosal formulation, and the obtained data was satisfactory. The drug content was found to be 99.87%, indicating the formulation's good capacity to retain the drug. In transdermal drug delivery systems, pH plays an important role. The results of the Transmucosal formulation demonstrated that all the formulations are suitable for skin delivery. The pH value of the prepared Transmucosal gels was determined to be 6.99±0.14.

A modified apparatus was utilized to measure spreadability based on the slip and drag characteristics of the gels. The measured spreadability ranged from 14.69±1.52 gms.cm/sec. Optimum spreadability is desired, as very high or very low values make it difficult to apply the gel to the desired site. The selection of the spindle was determined through trial and error, starting from T91 spindle. Spindles were added incrementally based on the % torque and error. The goal was to achieve a viscometer dial or display reading (% torque) between 10 and 100, as the relative measurement error improves as the reading approaches 100. Spindle T95 was identified as suitable for measuring the viscosity of all the gels. The Helipath T-Bar spindles were rotated up and down in the sample to obtain variable viscosities at programmed points over time. Five readings taken within 60 seconds were averaged to determine viscosity. The viscosity of the optimized formulation was found to be 2748±22 cps. No significant variation was observed in the physical appearance, average particle size, and % drug content of the Transmucosal

CONCLUSION

From this study, it was concluded that the best formulation of Naproxen Transmucosal, with high EE% and small particle size. Also, the fabrication of Naproxen as Transmucosal has the ability to defeat the barrier properties of the skin and enhance the drug release.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL: Not applicable

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AI TOOL DECLARATION

The authors declare that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

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