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Developing Novel Polymers and Nanomaterial for Transmucosal Naproxen Drug Delivery

Mudiga Anuradha[1], Dr. Duguta Tirumala[2], Gangadevi Shirisha[3], T Surekha[4]
[1, 2, 4]*OMEGA COLLEGE OF PHARMACY, India*
[3]*Vijaya College of Pharmacy, India*

Abstract: ***The development of novel polymers and nanomaterials for transmucoasal drug delivery holds immense promise for enhancing the bioavailability and therapeutic efficacy of various drugs. This study focuses on the design and fabrication of advanced polymeric matrices and nanomaterials for the transmucoasal delivery of naproxen, a widely used nonsteroidal anti-inflammatory drug (NSAID). Transmucoasal delivery systems are advantageous over traditional oral or parenteral routes, as they offer enhanced drug absorption, improved patient compliance, and reduced side effects. In this work, a variety of biocompatible and biodegradable polymers, along with nanomaterial-based carriers such as nanoparticles and nanogels, were synthesized and characterized for their suitability in naproxen delivery. The fabricated systems were evaluated for their mucoadhesive properties, controlled drug release profiles, and in vitro permeation through mucosal barriers. The results demonstrate significant improvements in naproxen absorption and sustained release, suggesting the potential of these novel polymeric and nanomaterial systems for effective transmucoasal drug delivery. These findings provide a foundation for future studies aimed at optimizing transmucoasal drug delivery systems for enhanced therapeutic outcomes.***

Keywords:

- ***Transmucoasal drug delivery***
- ***Naproxen***
- ***Polymers***
- ***Nanomaterials***
- ***Nanoparticles***
- ***Mucoadhesion***
- ***Drug release***
- ***Controlled release***
- ***Biodegradable polymers***
- ***Nanogels***
- ***Bioavailability***
- ***Anti-inflammatory drugs***
- ***Pharmaceutical delivery systems***

I. INTRODUCTION

A. TRANSMUCOSAL:

Introduction:

These ultra deformable vesicles possess elasticity that enables them to squeeze through pores significantly smaller (1/10th) than their own size. They are applied to the skin in a non-occluded manner and have demonstrated the ability to permeate the stratum corneum lipid lamellar regions due to skin hydration or osmotic force. Transmucosal, composed of a combination of phospholipids and surfactants (such as Sodium Cholate, Spans, and Tweens), control the flexibility of the vesicles by adjusting the ratio and total amount of surfactants that act as edge activators.

This drug carrier system stands out for its capacity to accommodate hydrophilic, lipophilic, and amphiphilic drugs. These highly deformable drug carriers autonomously penetrate intact skin, likely facilitated by the naturally occurring transcutaneous hydration gradient. The ability of Transmucosal to seek moisture (hydrotaxis) allows them to transport over 50% of the topically administered drug across the skin barrier.

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In a study by Nagasamy et al. (2014), various Transmucosal formulations were reviewed, leading to the conclusion that their ultra deformable nature allows them to pass through even extremely tiny pores (100nm). They possess the capability to transport a substantial quantity of drug per unit time across the skin. Moreover, they can accommodate larger molecules such as peptides and drugs, modifying them to achieve faster and more targeted action.

Transmucosalis a complex, highly adaptable, and stress-responsive aggregate that takes the form of an ultra-deformable vesicle with an aqueous core surrounded by a complex lipid bilayer. These vesicles are colloidal particles containing water, with their walls comprised of bilayers formed by amphiphilic molecules (lipids and surfactants).

In topical formulations, these vesicles serve as depots for sustained release of active compounds, while in transdermal formulations, they act as rate-limiting membrane barriers for modulating systemic absorption. Transmucosal consist of phospholipids and a surfactant mixture, and the flexibility of the vesicle is controlled by the ratio and total amount of surfactants. This unique drug carrier system has the ability to accommodate hydrophilic, lipophilic, and amphiphilic drugs. Additionally, Transmucosal have demonstrated the capability to permeate the stratum corneum by leveraging skin hydration or osmotic force, forming lipid lamellar regions. They can deform and pass through narrow constrictions, up to 5 to 10 times their own diameter, without measurable loss. Notably, Transmucosal can traverse even the tiniest pores (100mm) almost as effectively as water, despite their small size being 1500 times smaller.

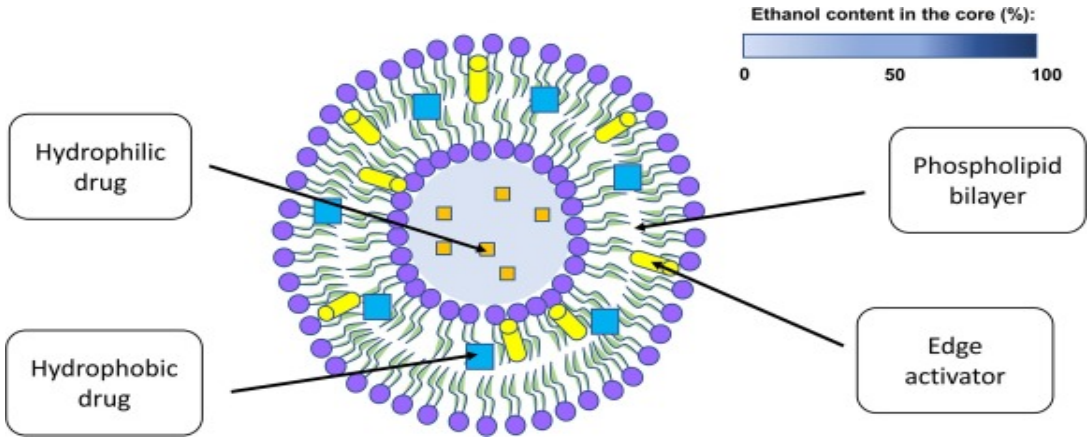


Figure No. 1: Structural representation of Transmucosal unit

Transmucosal exhibit the ability to transport a wide range of drugs, both low and high molecular weight, including analgesics, anesthetics, corticosteroids, sex hormones, anticancer drugs, insulin, gap junction protein, and albumin. These vesicles protect the encapsulated drug from metabolic degradation and function as a depot for gradual release. They can be utilized for systemic as well as topical drug delivery. The simplicity of the procedure and the absence of pharmaceutically unacceptable additives make scaling up the production process easy.

1) Distinctive characteristics of Transmucosal include:

The composition of hydrophobic and hydrophilic components enables them to accommodate drugs with varying solubilities.

Their remarkable deformability allows them to traverse narrow constrictions, up to five to ten times their own diameter, without significant loss. This flexibility facilitates their penetration into intact vesicles.

They possess the capacity to transport both low and high molecular weight drugs, such as analgesics, anesthetics, corticosteroids, sex hormones, anticancer drugs, insulin, gap junction protein, and albumin. Moreover, they are biocompatible and biodegradable due to their natural phospholipid composition.

They exhibit high entrapment efficiency, reaching approximately 90% for lipophilic drugs.

They safeguard the encapsulated drug from metabolic degradation.

They serve as a depot for controlled release of the drug.

They are suitable for systemic as well as topical drug delivery.

The simplicity of the procedure facilitates scalability without the need for lengthy processes or the use of pharmaceutically unacceptable additives.

Advantages of Transmucosalinclude:High entrapment efficiency, particularly for lipophilic drugs, achieving approximately 90%.

Capability to encapsulate both hydrophilic and lipophilic drugs.

Suitable carrier for a wide range of drugs, spanning low and high molecular weights, such as analgesics, corticosteroids, hormones, anticancer drugs, insulin, proteins, and more.
Ability to deform and pass through narrow constrictions, up to five to ten times their own diameter, without noticeable loss.
Applicability for both systemic and topical drug delivery.
Prevention of metabolic degradation of the encapsulated drug.
Biodegradable and free from toxins.

2) Limitations of Transmucosal are as follows:

Susceptibility to chemical instability, making them prone to oxidative degradation.
Higher formulation costs.

The composition of a Transmucosalinvolves two primary components. First, an amphipathic ingredient, such as phosphatidylcholine, self-assembles into a lipid bilayer within aqueous solvents, forming the basic lipid vesicle structure. Second, a bilayer softening component, like a biocompatible surfactant or an amphiphile drug, is added to enhance lipid bilayer flexibility and permeability. This results in the formation of a flexible and permeability-optimized Transmucosalvesicle that can adapt its shape to the surrounding environment by adjusting the local concentration of each bilayer component in response to local stress. Consequently, Transmucosal differ from conventional vesicles due to their "softer," more deformable, and adjustable artificial membrane.

3) Mechanism of Penetration of Transmucosa

penetrating the outermost skin layers, Transmucosal reach the deeper skin layer. They are often flushed out of the bloodstream. It offers access to all bodily tissues when applied correctly.

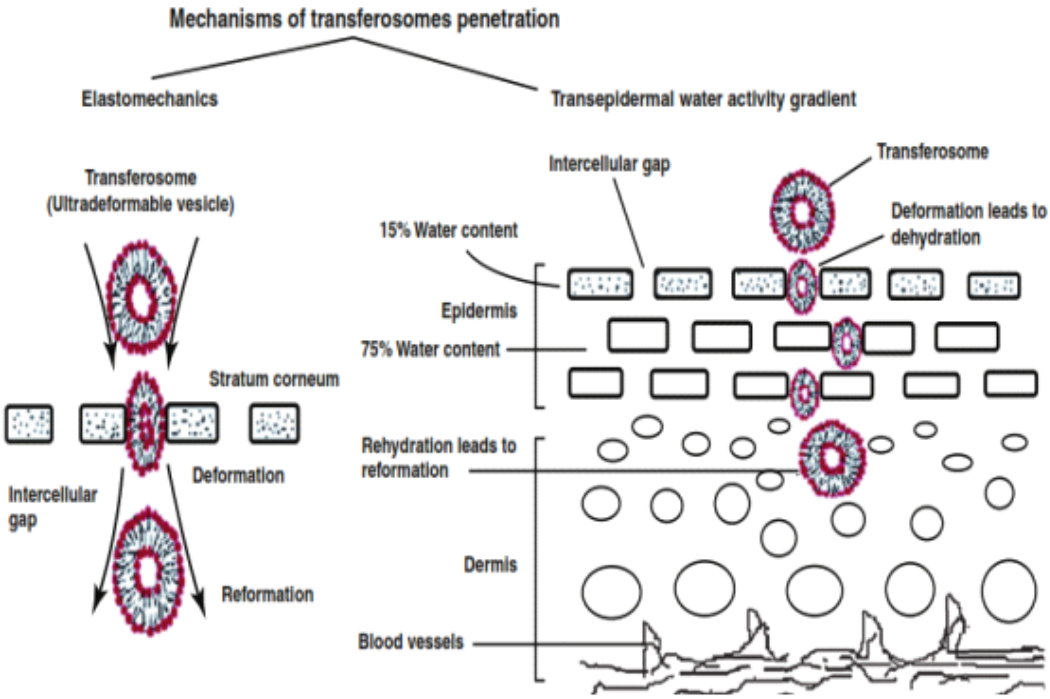


Figure 2: Penetration pathway of Transmucosal

The penetration mechanism involves the creation of an "osmotic gradient" due to water evaporation while applying Transmucosal to the skin's surface. The transport of these flexible vesicles is not dependent on concentration. The skin penetration barrier establishes an osmotic gradient, which prevents water loss through the skin and maintains a difference in water activity within the viable part of the epidermis. Despite being smaller than the pores in the stratum corneum, the elastic vesicles can pass through them. By following their own path, Transmucosal induce hydration, which expands the hydrophobic skin pores and allows for the controlled release of drugs that target specific organs.

Transmucosal act as penetration enhancers by disrupting intercellular lipids in the stratum, widening the skin pores, facilitating molecular interaction, and promoting system penetration across the skin.

4) Methods for preparing Transmucosal:

Vortexing-sonication method: In this approach, a mixture of lipids (phosphatidylcholine, edge activator, and the therapeutic agent) is vortexed in a phosphate buffer to form a milky suspension. After sonication, the suspension is extruded through poly-carbonate membranes.

Suspension homogenization process: Transmucosal are created by combining an ethanolic soybean phosphatidylcholine solution with an appropriate amount of an edge-active molecule like sodium cholate. This prepared suspension is then mixed with Triethanolamine-HCl buffer to determine the total lipid concentration. The resulting suspension undergoes two rounds of sonication, freezing, and thawing.

Modified handshaking process: This technique, known as "lipid film hydration," involves dissolving the drug, lecithin (PC), and edge activator in a 1:1 mixture of ethanol and chloroform. The organic solvent is evaporated by hand shaking above the lipid transition temperature (43°C). With rotation, a thin lipid film forms inside the flask, which is left overnight for complete evaporation of the solvent. The film is then hydrated with phosphate buffer (pH 7.4) for 15 minutes at the appropriate temperature.

Aqueous lipid suspension process: The drug-to-lipid ratio in the vehicles is set between 1/4 and 1/9, depending on the formulation type. This ratio ensures high flexibility of the vesicle membrane compared to standard phosphatidylcholine vesicles in the fluid phase. Soy phosphatidylcholine is used to create vesicles ranging from 100 to 200 nm in size with a size distribution standard deviation of approximately 30 percent. This formulation is achieved by suspending the lipids in an aqueous phase containing the drug.

Centrifugation process: In this method, phospholipids, surfactants, and the drug are dissolved in alcohol. The solvent is then removed through rotary evaporation under reduced pressure at 40°C. Vacuum is applied to eliminate any remaining traces of the solvent. The deposited lipid film is subsequently hydrated with the appropriate buffer through centrifugation at 60 rpm for 1 hour at room temperature. The resulting vesicles undergo a 2-hour swelling period at room temperature, followed by sonication at room temperature to obtain multilamellar lipid vesicles.

Thin film hydration technique is employed for the preparation of Transmucosal, involving three steps:

Dissolve phospholipids and surfactant in a volatile organic solvent to form a thin film from the mixture of vesicle-forming ingredients (chloroform-methanol). Evaporate the organic solvent using a rotary evaporator above the lipid transition temperature (room temperature for pure PC vesicles or 50°C for dipalmitoylphosphatidylThe lasOvernight, the final traces of solvent were sucked away.2.After 1 hour of spinning at 60 rpm at the appropriate temperature, a produced thin film is hydrated with buffer (pH 6.5). The resultant vesicles swelled for 2 hours at room temperature.

3. The generated vesicles were sonicated at ambient temperature or 500 degrees Celsius for 30 minutes with a bath sonicator or a probe sonicated at 40 degrees Celsius for 30 minutes to create tiny vesicles. The sonicated vesicles were homogenised ten times by manual extrusion through a sandwich of 200 and 100 nm polycarbonate membranes.

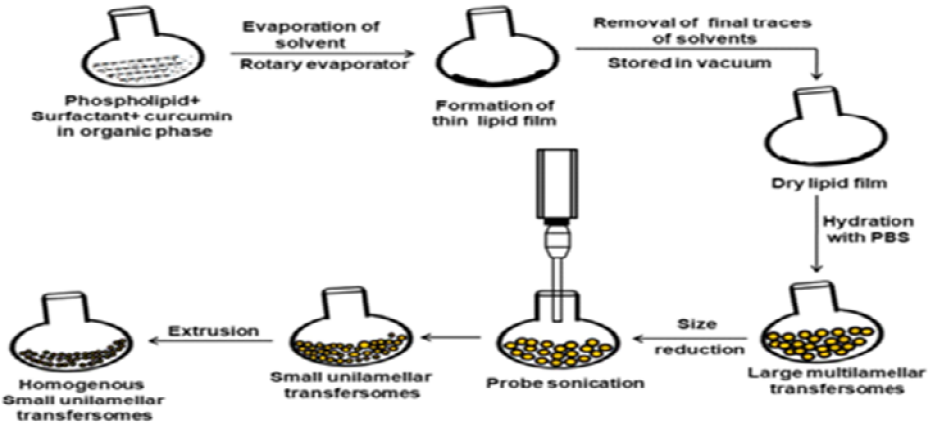


Figure 3: Modified hand shaking, lipid film hydration technique is also founded for the preparation of Transmucosal which comprised following steps:[127,128,129]

The drug, lecithin (PC), and edge activator were dissolved in an ethanol: 1:1 chloroform mixture. The organic solvent was removed by hand shaking above the lipid transition temperature (43°C). With rotation, a thin lipid film formed inside the flask wall. The thin film was then hydrated with phosphate buffer (pH 7.4) for 15 minutes at the appropriate temperature with gentle shaking.

5) Characterization of Transmucosal:

Transmucosal are classified in the same way as liposomes, niosomes, and micelles [36,37]. For Transmucosal, the following characterization parameters must be checked..

Entrapment efficiency, Drug content, Vesicle morphology, Vesicle size distribution and zeta potential, No. of vesicles per cubic mm, Confocal scanning laser microscopy study, Zeta potential, Polydispersibilityindex,Turbidity measurement, Surface charge and charge density, Penetration ability, Occlusion effect, Physical stability, In-vitro drug release

B. EMULGEL

Topical drug delivery involves applying a formulation containing medication to the skin for the treatment of a skin-related condition. This approach is utilized when other methods of drug administration, such as oral, sublingual, rectal, and parental routes, are unsuccessful or when there is a local skin infection like a fungal infection. Topical drug administration is a commonly used treatment approach for both localized and systemic conditions. In this delivery system, the drug is absorbed through the skin and reaches the targeted area to produce a therapeutic effect. The rate at which the drug is released from the topical preparation depends directly on the physiological characteristics of the carrier. The main advantage of using a topical delivery system is that it bypasses the first-pass metabolism. The term "microemulsion" is based on particle size, as the smaller drug particles can easily penetrate the skin and reach their intended site of action. The gel component of the microemulsion sustains the release of the drug over a prolonged period. Nowadays, various fungal infections have become a significant societal issue. Skin infections like Tinea capitis, Tinea pedis, and Tinea corporis can severely affect the skin. The use of techniques like emulgel can facilitate the drug's easy penetration into the skin and provide a rapid onset of action.

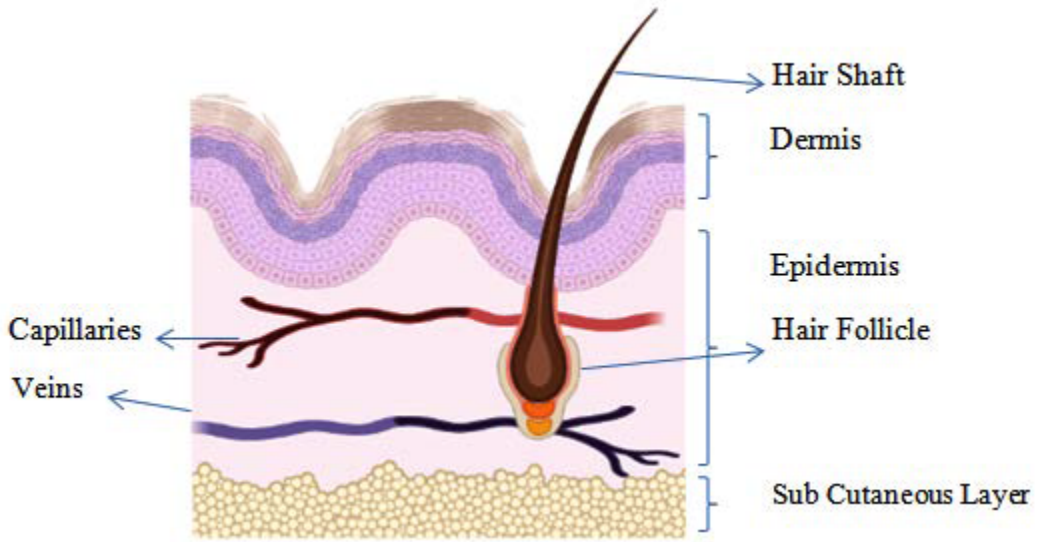


Figure No. 4: Structure of skin

1) Physiology of the Skin:

To develop topical dosage forms, it is crucial to have a fundamental understanding of the physiology and function of the skin. This is because the skin is treated using topical formulations. Human skin can be treated with microemulsion-based gels that have an appropriate viscosity for topical application (37, 38, 39).

2) Nanoemulgel:

Nanoemulsion refers to transparent or translucent oil-water dispersions that are thermodynamically stable due to the presence of surfactant and cosurfactant molecules. These nanoemulsions have globule sizes ranging from 1nm to 100nm. When the nanoemulsion is combined with a gel, it is called Nanoemulgel. Compared to traditional formulations like emulsions and gels, nanoemulsions facilitate higher transdermal permeation of many drugs.

In both in vivo and in vitro settings, nanoemulsions exhibit improved transdermal and dermal delivery properties. Their small globule size and high loading capacity enable the drug to penetrate the skin easily, resulting in a more rapid therapeutic effect.

3) Macroemulsion gel:

Emulgel refers to a gel containing emulsion droplets with particle sizes exceeding 400nm. While these macroemulsion droplets are physically invisible to the naked eye, they can be clearly seen under a microscope. Macroemulsions are thermodynamically unstable; however, the presence of surface-active agents helps stabilize them.

Table No. 1. : Classification of topical dosage form[40]

Liquid form	Solid form	Semisolid form
Syrup	Tablet	Emulgel
Solution	Capsule	Creams
Emulsion	Powder	Gel
Suspension	Dusting powder	Suppositories

4) Advantages of emulgel

- Hydrophobic drugs can be quickly incorporated into the gel base using water/oil/water emulsions.
- Improved stability and load capacity. 3. Simple and low-cost mechanism. 4. Avoid sonication. 5. Enhanced patient acceptability and appropriateness for self-medication. 6. Ability to easily discontinue medication41.

5) Disadvantages of emulgel

- The medication and/or excipients may cause skin irritation in those who have contact dermatitis.
- Some drugs have a poor skin permeability.
- Allergic responses are possible.
- Larger-particle-size medicines are difficult to absorb through the skin42.

The rationale of emulgel as topical drug delivery

The market offers a variety of semisolids and other preparations that can restore the skin's fundamental role or pharmacologically modify underlying tissue operations43. However, these formulations, including lotions, ointments, and creams, have certain drawbacks such as stickiness, low spreading coefficient, and stability issues. Transparent gels are the only type of formulation that has gained recognition in pharmaceutical and cosmetic preparations, mainly due to limitations associated with semisolid preparations44. Consequently, an emulsion-based solution is employed to overcome these limitations. Therefore, the hydrophobic component of the drug should be incorporated and delivered through gels. Emulgel, which combines drug/oil/water emulsions, can be used to integrate hydrophobic drugs. Since solubility poses a challenge, direct insertion of most drugs into gel bases is not feasible and can lead to issues with drug release. The emulgel system enables the incorporation of a hydrophobic drug into the oil phase, and then the oily globules can be easily dispersed into the aqueous phase, resulting in an oil/water emulsion. This emulsion can be blended into the gel base, potentially improving drug stability and release compared to simply incorporating the drug into the gel base45.

6) Emulgel Components:

- Oils: Mineral oil and soft or hard paraffin are commonly utilized as the oil phase in emulsions applied topically. For both oral and topical preparations, castor and mineral oils, known for their laxative effects, are commonly employed oils46, 47.
- Vehicles: Emulgel preparations use both oily and aqueous vehicles, allowing for the incorporation of hydrophobic and hydrophilic drugs. Examples of vehicles include alcohol, water, and other aqueous materials commonly used in aqueous phase emulsions48.
- Emulsifiers: An emulsifier is employed to enhance the emulsification of the preparation and improve its shelf-life stability. Examples of emulsifying agents include Tween 80, Span80, Tween 20, stearic acid, etc.49.
- Gelling agent: Gelling agents play a crucial role in preparing gels for various dosage forms and contribute to the consistency of the formulation. Examples of gelling agents include Carbopol 940, Carbopol 934, HPMC-2910, etc.50.
- pH adjusting agent: These agents are used to maintain the desired pH of the formulation. Examples include triethylamine, NaOH, etc.agent for changing the pH

These substances are employed to keep the formulation's pH stable. For instance, triethylamine, NaOH, and so forth.
Creating an emulgel
Step 1: Create a gel base
The gel base is made by dissolving a specified amount of polymer in DDW and mixing it at a reasonable speed with a magnetic stirrer. The pH is adjusted to 5-6.5 using Triethanolamine and NaOH51.
Step 2: Create an O/W or W/O type emulsion.
Using a magnetic stirrer, prepare Smix in the required ratio. Drop the Smix into the oil phase while continuously swirling, resulting in a clear emulsion52.
Step 3: Emulgel formulation
To make emulgel53, drop the prepared emulsion into the gel basis while continuously swirling with a homogenizer.

II. AIM AND OBJECTIVES

A. *Aim:*

To develop and optimize novel polymers and nanomaterials that enhance the efficiency and effectiveness of transmucosal delivery of naproxen.

B. *Objectives:*

- To estimate the compatibility between the drug and excipients
- To prepare the Transmucosal of Naproxen sodium by thin film hydration techniques using Soya PC and Tween 80.
- To perform the various characterization of Naproxen Transmucosal
- Best formulation is prepared as Gel by using Carbopol
- To perform the evaluation test for the Transmucosal

III. DRUG PROFILE

Structure

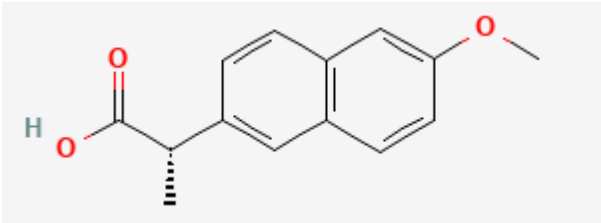


Fig-5 Structure of naproxen

Name of Drug : Naproxen[71-72]
Chemical Name : (2S)-2-(6-methoxynaphthalen-2-yl)propanoate
Formula :$C_{14}H_{13}NaO_3$
Molecular Weight : 230.26
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 No.2: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.

IV. EXCIPIENTS PROFILE

Carbopol 974 :[73]

1) Nonproprietary Names:

- BP: Carbomers
- PhEur: Carbomer
- USP-NF: Carbomer

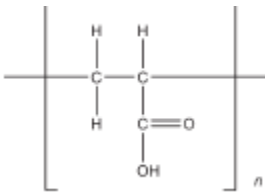
2) Synonyms :carboxypolymethylene; carbomers.

3) Chemical Name and CAS Registry Number :Carbomer [9003-01-4]

4) Empirical Formula :C5H10O2

5) Molecular Weight :86,000

6) Structural Formula :



7) Functional Category: Bioadhesive material, Stabilizing agent, Emulsifying agent, Tablet binder are all examples of CR agents.

8) Applications in Pharmaceutical Formulation or Technology:

Carbomers are used to modify the rheology of liquid or semisolid medicinal formulations. Among the formulations available for use in ophthalmic, rectal, topical, and vaginal preparations are creams, gels, lotions, and ointments. Carbomer polymers have also been investigated as peptide-containing enzyme inhibitors of intestinal proteases, as a bioadhesive for a cervical patch and intranasally administered microspheres, in magnetic granules for site-specific drug delivery to the oesophagus, and in oral mucoadhesive controlled drug delivery systems.

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9) Description:

Carbomers are white, 'fluffy,' acidic, hygroscopic granules with a faint scent.

TWEEN 80:

It is a nonionic surfactant and emulsifier used in food and cosmetics. This chemical is a water-soluble viscous yellow liquid.

Synonyms:Mantanx 80;Alkest TW 80;Polysorbate 80;PS 80

Structure:

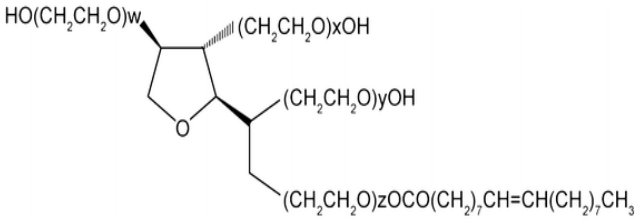


FIG-6 Structure of TWEEN 80

- Molecular formula: C64H124O26
- Molecular Weight:1,310 g/mol
- Properties :
- Appearance :Ambercoloutred liquid
- Density :1.06 g/cm3
- Boiling point : ≥ 100°C
- Solubility in water : 100ml/L
- Solubility in other solvents :Ethanol, cotton seed oil, corn oil, ethyl acetate, and methanol are all soluble in it.

SOY LECITHIN

Lecithin (Wikipedia. Org/wiki/lecithin) is a group of yellow-brownish fatty substance occurring in animal and plant tissues, and in egg yolk, composed of phosphoric acid, choline, fatty acids, glycerol, glycolipids, triglycerides, and phospholipids (e.g., Phosphatidylcholine, phosphatidylethanolamine and phosphatidylinositol). However, lecithin is occasionally used interchangeably with pure phosphatidylcholine, a phospholipid that constitutes the majority of its phosphatide portion. It can be separated either chemically (using hexane) or mechanically from egg yolk (in Greek lekithos) or from soy beans. Lecithin is utilised as a dietary supplement as well as for medicinal purposes.

Chemistry:

The lecithin employed in the study is made up of several phospholipids such as phosphatidylcholine, phosphatidyletanolamine, phosphatidyllinositol, and lysophophatidylcholine cholesterol. The basic phospholipids molecule structure is shown below.

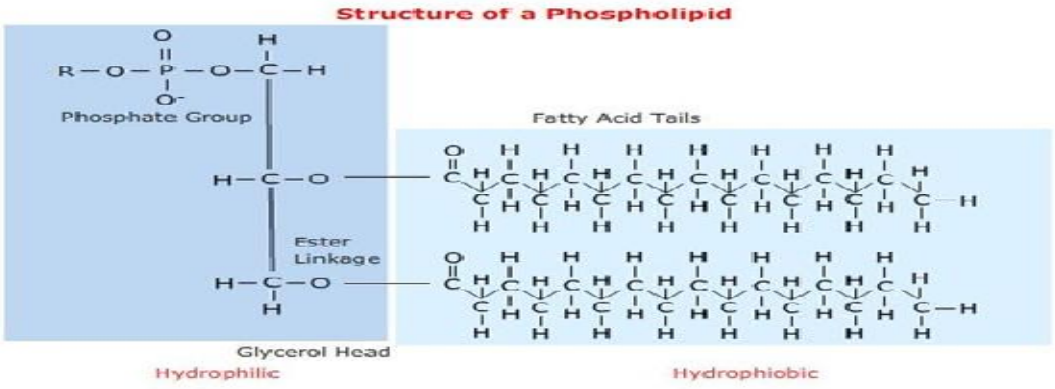


Figure No.7 . Structure of Phospholipids

Description:
Colour: Yellowish brown
Molecular Formula: C36H72NO8P
Molecular Weight: 677.93gm
Consistency: Agglomerates
Iodine value: 85-95
Peroxide value: n.m.t 3
Solubility:
Lecithin dissolves in both aqueous and organic solutions. As a result, it may be used as an emulsifier in the food business, and it can also form vesicles, therefore it is employed in the pharmaceutical sector. With both phases, it produces clear or faintly opalescent solutions.

V. PLAN OF WORK

1) Literature Survey
2) Selection of Drug and Excipients
3) Procurement of Drug and Excipients
4) Preformulation studies
- Construction of calibration curve
- Solubility studies
- FTIR Compatibility studies

5) Fabrication of Naproxen Transmucosal with Soya PC, tween 80 by using thin film hydration technique.
6) Characterization Naproxen Transmucosal
- Particle size
- Entrapment efficiency
- Zeta potential

7) Best formulation is prepared as gel with Carbopol
- Drug content
- pH
- Spreadability
- Viscosity measurement
- In Vitro drug release studies
- In Vitro drug release kinetics studies

VI. MATERIALS AND METHODS

Table No. 3: Materials used

Sl. No.	Materials	Manufacturer	Application
1.	Naproxen	Navakar Biochemical, Gujarat	API
2.	Carbopol	Loba Chemicals Pvt Ltd, Hyd	Gelling agent
3.	Phosphotidyl choline	Yarrow	Phospholipids
4.	Tween 80	Fisher Scientific, Mumbai	Surfactant

Table No. 4: Instruments and Equipment used

Sl. No.	Instruments/ equipment	Manufacturer
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

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VII. METHODOLOGY

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 aluminum 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 No. 5: 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

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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).

VIII. CHARACTERIZAITON OF TRANSMUCOSAL

1) Microscopic observation of prepared Transmucosal[75-83]

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.

2) Evaluation of Gels

pH determination: 50 grammes 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 and 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.

3) Release kinetics of the optimized formulations

- Drug Release Kinetics

The data from the in vitro release research was applied to various motor circumstances. Zero request (aggregate level of medication discharge versus time), first request (log total level of medication remaining versus time), Higuchi model (total level of medication discharge versus square base of time), and Korsmeyer-Peppas (log combined percent sedate delivery versus log of time) were the active models used. Relapse (r2) values were calculated for the direct bends obtained from relapse research.

Kinetic analysis: The grid frameworks were accounted for in order to follow the zero-request discharge rate and the Diffusion component for pharmaceutical arrival. The information obtained was fitted into the Zero request, First request, Higuchi lattice, and Peppa's model to break down the system for the delivery and delivery rate energy of the measurements structure. The best fit model was picked in this case based on the r Values obtained.

a. Kinetics of zero order: The following equation can be used to depict drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the medication slowly, provided that the area does not change and no equilibrium conditions are established.

$$Qt = Q0+K0t$$

Where Qt represents the quantity of drug dissolved in time t, Q0 represents the starting amount of drug in the solution, and Ko represents the zero order release constant.

To investigate first order release kinetics, the release rate data were fitted to the following equation.

Qt = log Q0 + k1t/2.303

Where Qt represents the quantity of drug released in time t, Qo represents the initial amount of drug in the solution, and K1 represents the first order release constant.

a. Higuchi model: Higuchi created many theoretical models to investigate the release of water-soluble and low-soluble medicines integrated in semisolids and/or solid matrices. For drug particles distributed in a uniform matrix acting as a diffusion medium, mathematical formulas were developed. And the formula is Qt = KH.t1/2.

Where Qt represents the quantity of medication released in time t and KH represents the Higuchi Dissolution constant.

a. The Korsmeyer and Peppa model: To investigate this concept, the following equation is fitted to the release rate data.

Mt/M = Ktn

Where Mt/M is the drug release percentage, K is the release constant, t is the release period, and n is the drug release diffusion exponent that depends on the geometry of the matrix dosage form.

Table No.6: Diffusion exponent and solute release mechanism for cylindrical shape Diffusion

Diffusion coefficient	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-fickian diffusion)
0.89	Case II transport
n>0.89	Super Case II transport

IX. RESULTS AND DISCUSSION

Identification of Drug:

Organoleptic Properties:

Color: White to off-white

State: Crystalline powder

Odour: odour less

Determination of Melting Point: Melting point of Naproxen was found to be 153 ºC.

Solubility Study:

Table No.7 The solubility of naproxen various solvents

S.No.	Name of solvent	Solubility	Parts of solvent required for 1 part of solute
1	pH 6.8 phosphate buffer	Freely soluble	From 1 to 10
2	Methanol	Freely soluble	From 1 to 10
3	Ethanol	Sparingly soluble	From 30 to 100
4	Water	Freely soluble	From 1 to 10

1) Pre-compressional Evaluations

- Calibration curve

The calibration curve of drug obeyed Beer Lambert's law in the concentration range of 0-10µg/ml (R^2 = 0.9982) at 331nm and the result is shown in table 4 and plot is shown in fig. 16.

Table No.8: Calibration curve of Naproxen in pH 6.8

Sl. No.	Concentration (µg/ml)	Absorbance at 322nm
1	2	0.099
2	4	0.227
3	6	0.400
4	8	0.612
5	10	0.722

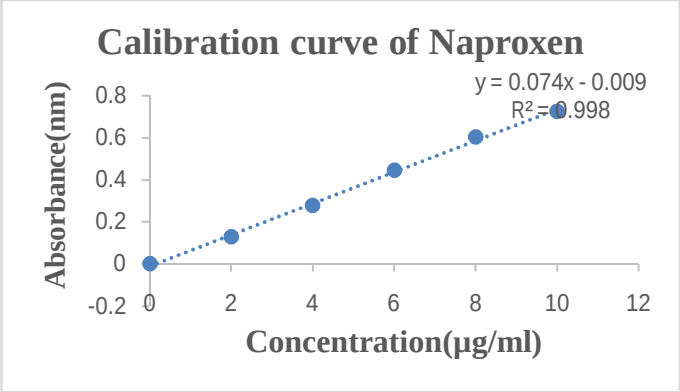


Figure No. 8: Standard calibration curve of Naproxen in Phosphate buffer pH 6.8

- Compatibility study by FTIR:

The existence of distinct functional groups was verified by the FTIR spectrum of Naproxen, as shown in Table and Figure. The various peaks produced from the IR spectra were also found to match the IR spectrum of naproxen published in approved reference books.

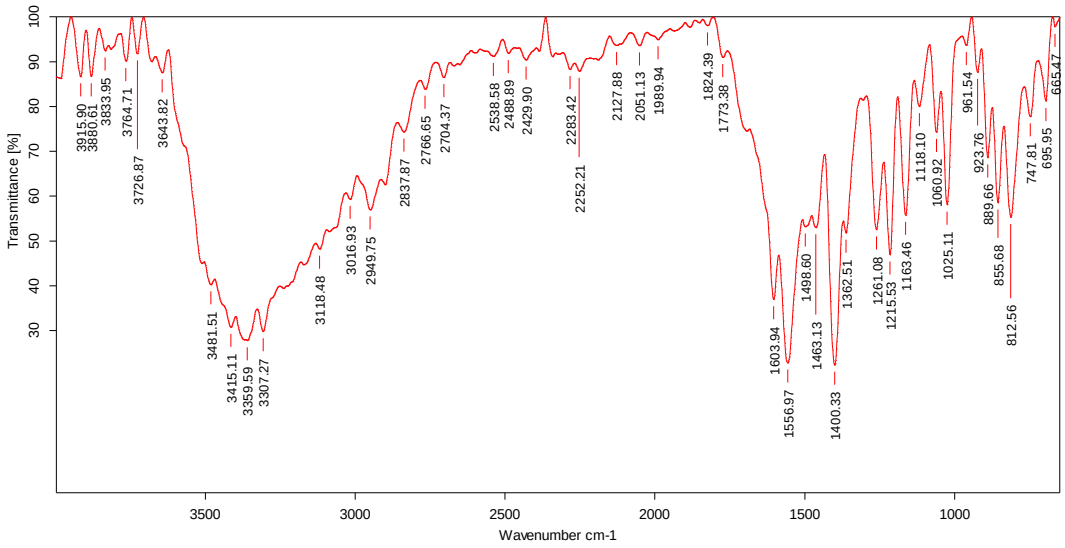


Figure No.9:FTIR spectrum of naproxen

Table No.9: IR Spectral Analysis ofnaproxen

FTIR range	Absorption	Group	Compound
1261.08	1275-1200	C-O stretching	Alkyl aryl ether
1603.94	1650-1566	C=C stretching	Conjugate alkene

2949.75	3000-2840	C-H stretching	Thiol
3359.59	3533-3267	C-H stretching	Alkyne
1382.51	1440-1395	O-H bending	Carboxylic acid

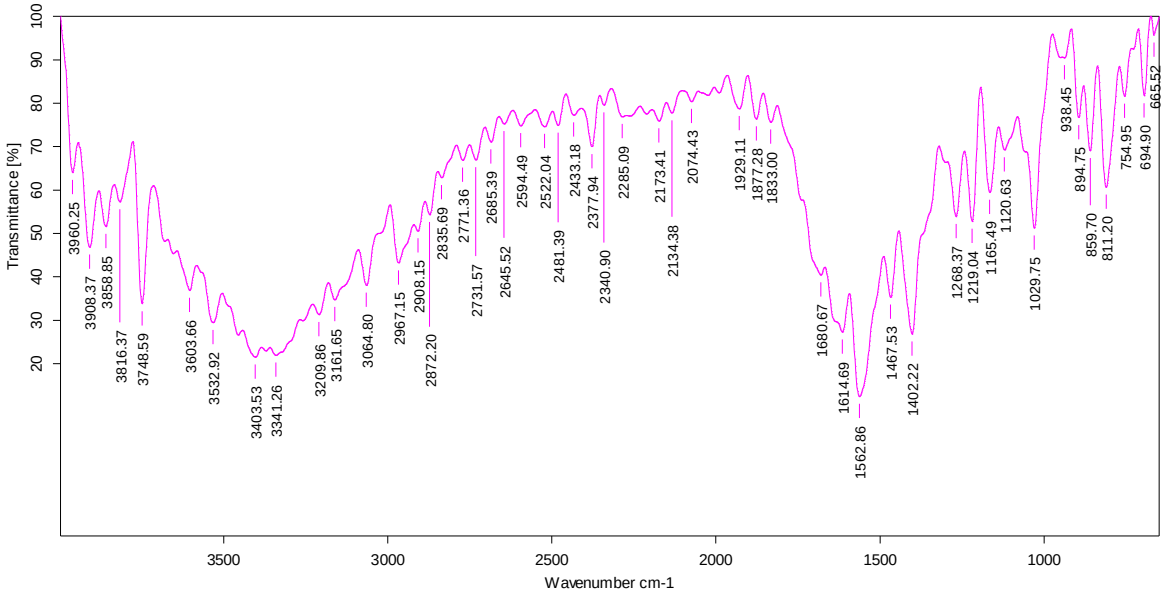


Figure No.10: FTIR spectrum of Naproxen with Tween 80

Table No.10: IR Spectral Analysis ofnaproxen with Tween 80

FTIR range	Absorption	Group	Compound
1268.37	1275-1200	C-O stretching	Alkyl aryl ether
1614.69	1650-1566	C=C stretching	Conjugate alkene
2967.15	3000-2840	C-H stretching	Thiol
3341.26	3533-3267	C-H stretching	Alkyne

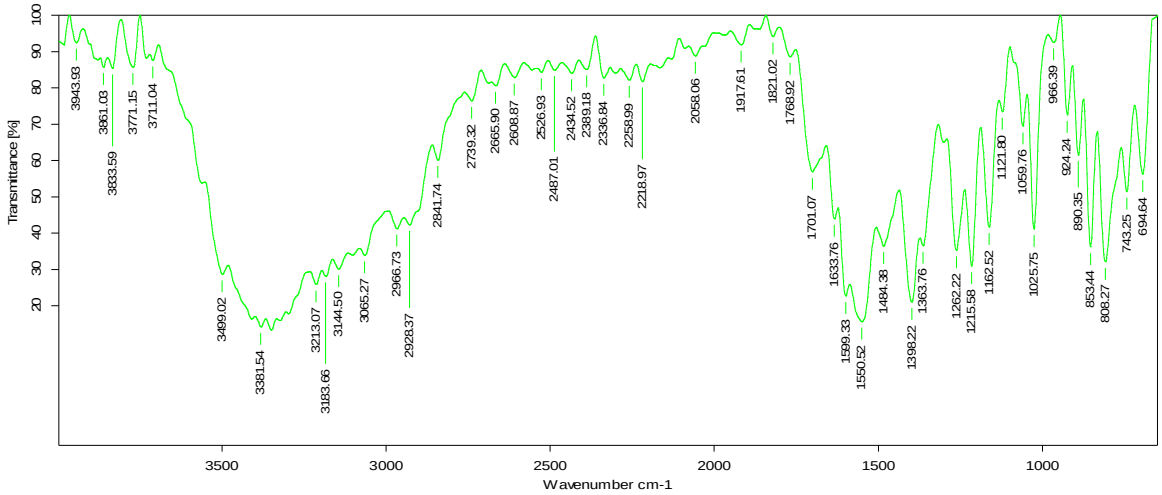


Figure No.11: FTIR spectrum of Naproxen with Phosphotidyl chlorine

Table No.11: IR Spectral Analysis ofnaproxen with Phosphotidyl chlorine

FTIR range	Absorption	Group	Compound
1262.22	1275-1200	C-O stretching	Alkyl aryl ether
1633.76	1650-1566	C=C stretching	Cyclic alkene
2928.37	3000-2840	C-H stretching	Thiol
3381.54	3533-3267	C-H stretching	Alkyne
1398.22	1440-1395	O-H bending	Carboxylic acid
1633.76	1650-1600	C=C stretching	Conjugate alkene

- Differential scanning calorimetry studies:

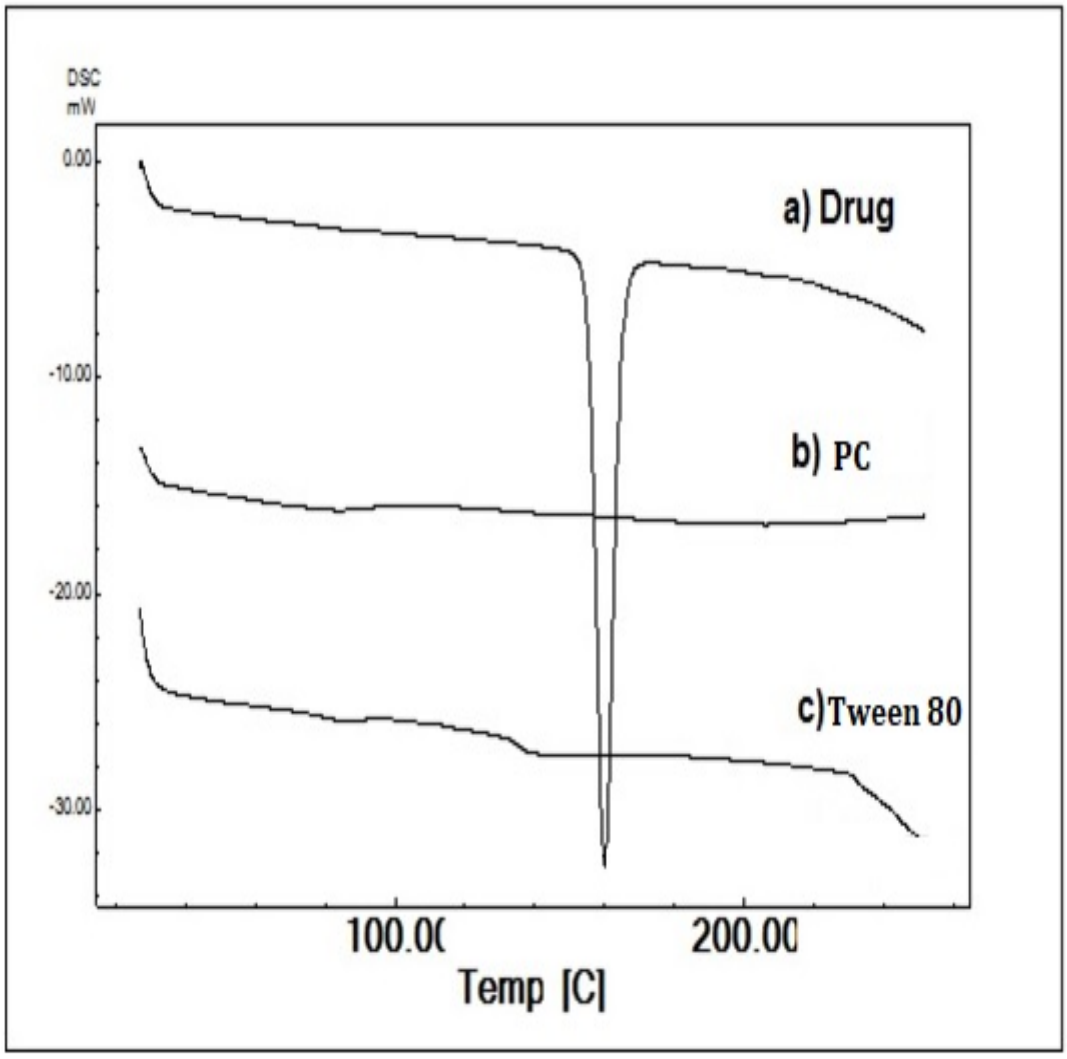


Figure No12: DSC thermograms of a) naproxen, b) PC and c) Tween 80

DSC was used to do thermal analysis on pure. Naproxen exhibited a pronounced endothermic peak at 161.12oC, which corresponded to the drug melting with a heat of fusion (H) of -990.12 mJ.

- 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).

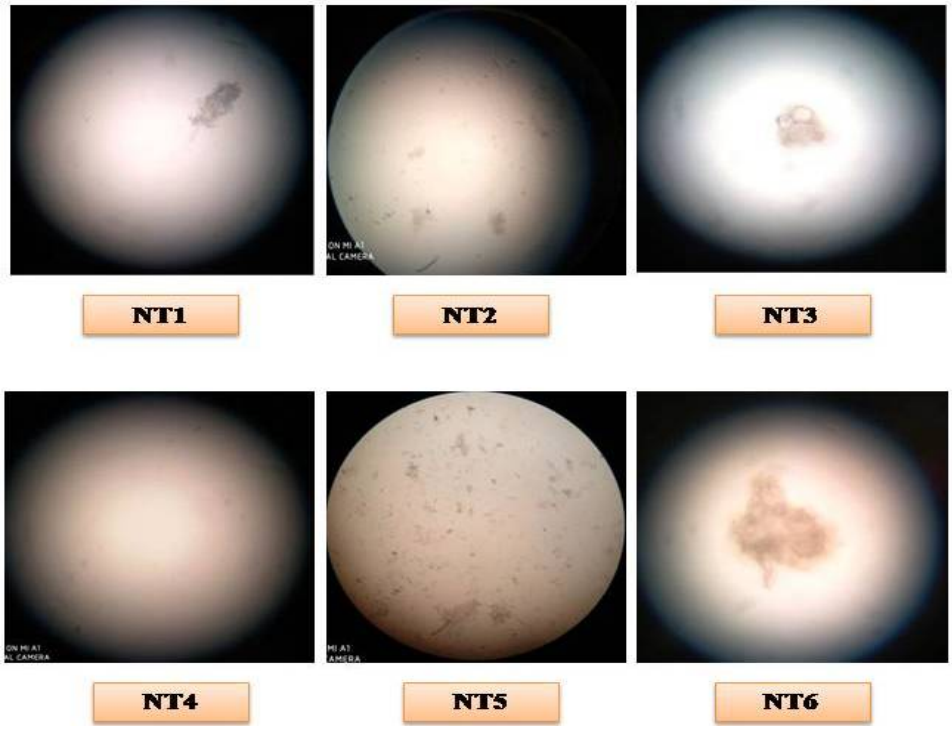


Figure No. 13: Microscopic observation of Transmucosal formulations

Evaluation of Vesicle size and Entrapment efficiency

The table comprises the vesicle size and entrapment efficiency values. The vesicle size of all Transmucosal ranged from 178.89 to 245.65 nm, with entrapment effectiveness ranging from 61.15 to 75.65%.

The results revealed that formulation NT2 Sleeted was optimised for further assessment because it has the lowest vesicle size and increases entrapment efficiency.

Table No. 12: Vesicle size (nm) & % EE of Naproxen of Transmucosal

S.No.	Formulation code	Vesicle size (nm)	Entrapment efficiency (%)
1	NT1	188.11±0.23	72.25±1.52
2	NT2	178.50±0.21	80.14±1.85
3	NT3	211.24±1.11	62.15±1.63
4	NT4	235.35±0.45	63.27±1.22
5	NT5	242.45±0.65	67.64±1.70
6	NT6	257.27±0.54	69.74±1.21

Table No. 13: Vesicle size (nm), % EE, Zetapotential of best Naproxen of Transmucosal

Formulation code	Vesicle size (nm)	Entrapment efficiency (%)	Zeta potential (mV)
NT2	178.50±0.21	80.14±1.85	-48.5

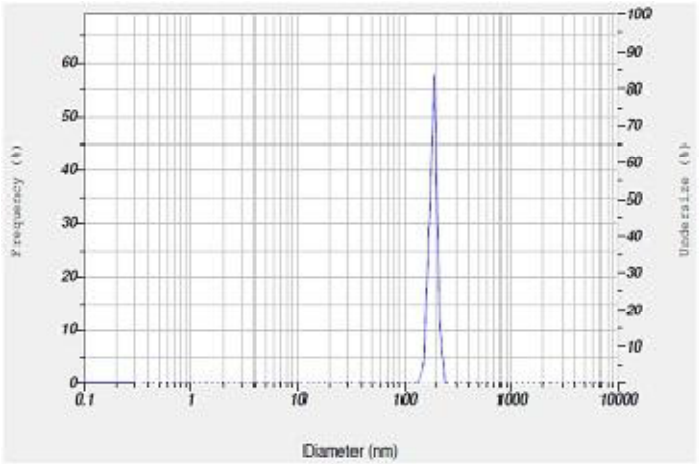


Figure 14: Vesicle Size of BestTransmucosal formulation NT2

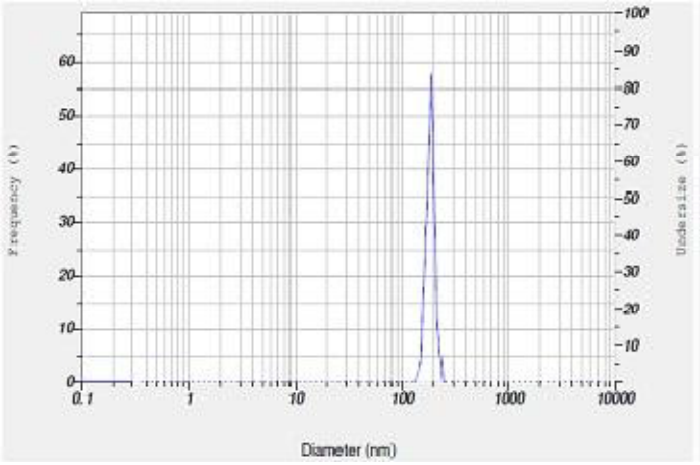


Figure 15: Zeta potential of BestTransmucosal formulation NT2

- Evaluation of Transmucosal:

Drug content is the most significant aspect in Transmucosalformulation, and the findings obtained are good. It was discovered to be 99.87, indicating that the formulation has a strong ability to contain the medication.

pH: The pH of a transdermal drug delivery system is critical, and the results of Transmucosal formulation reveal that all formulations are acceptable for skin distribution. The pH of the best Transmucosal gel formulation NT-2 was determined to be 6.99 0.14.

- Spreadability: To determine spreadability, a modified apparatus was employed. The spreadability of the gels was determined using slip and drag characteristics and was found to be 14.691.52 gms. cm. /sec.

Measurement of viscosity: The viscosity of gels was measured using a Brookfield viscometer DV-II model. A T-Bar spindle in conjunction with a helipath stand was utilised to accurately measure the viscosity.

The viscosity was calculated by averaging five observations made over a 60-second period. The optimised formulation's viscosity was determined to be 274822 cps.

Table 14: Results of Transmucosal gel formulations

Formulation Code	Drug content (%)	pH	Spreadability (Gm.cm/sec)	Viscosity
NT2	99.87	6.99 ± 0.14	14.69±1.52	2748±22

- In-Vitro drug release studies:

Table No. 15: In Vitro drug release studies NT2

Time in Hrs	% Cumulative drug release
0.5	21.32
1	42.23
2	49.48
4	71.65
6	77.97
8	90.67
10	97.69

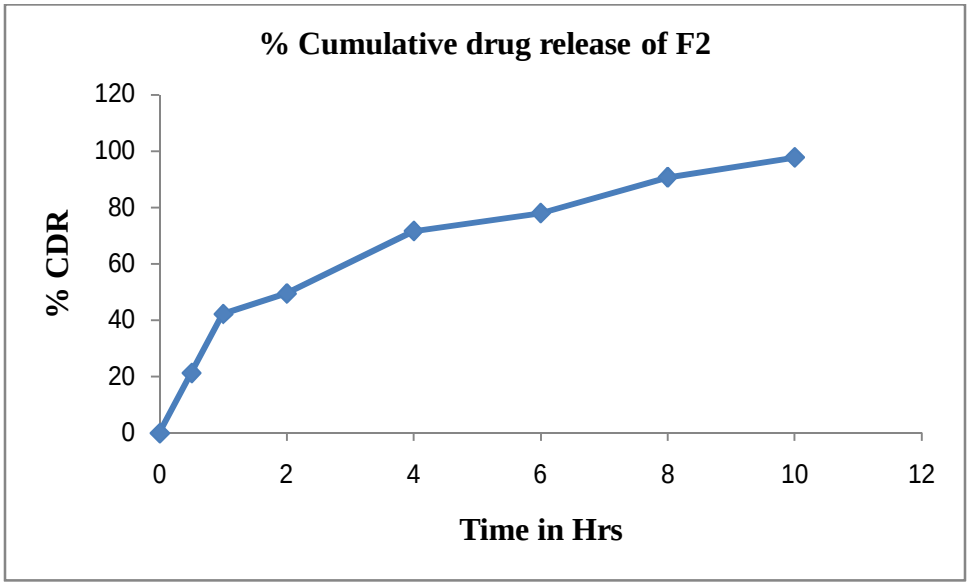


Figure No. 16: % CDR of formulation F2

- In Vitro drug release kinetics studies:

The results of the in vitro release investigation were utilised to fit into kinetic models. This was done to determine the mechanism of Naproxen medication release. In order to identify the release model, in vitro release data were evaluated using the simplified Higuchi model for zero order, first order, and diffusion controlled mechanisms. The choice of a mechanism was based on the coefficient of determination (r2) for the parameters tested, with the highest coefficient of determination favoured for the order of release selection. The kinetic characteristics of Naproxen Transmucosal are depicted in Table No. 8.9 – 8.13. Fig No. 8.7 – 8.10.

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Table No. 16: 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

- Zero order kinetics:

Table No. 17: Zero order kinetics of formulation NT2

Time in Hrs	% CDR
0	0
0.5	21.32
1	42.23
2	49.48
4	71.65
6	77.97
8	90.67
10	97.69

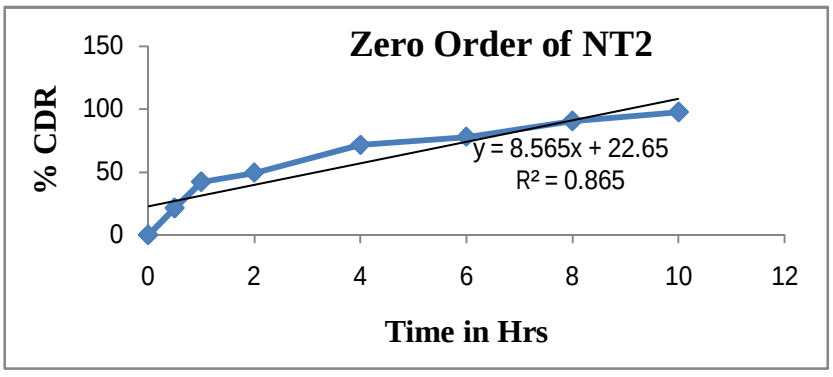


Figure No. 17: Zero order kinetics of formulation NT2

- First order kinetics:

Table No. 18: First order kinetics of formulation NT2

Time in Hrs	log% unCDR
0	2
0.5	1.9
1	1.76
2	1.7
4	1.45
6	1.34
8	0.97
10	0.36

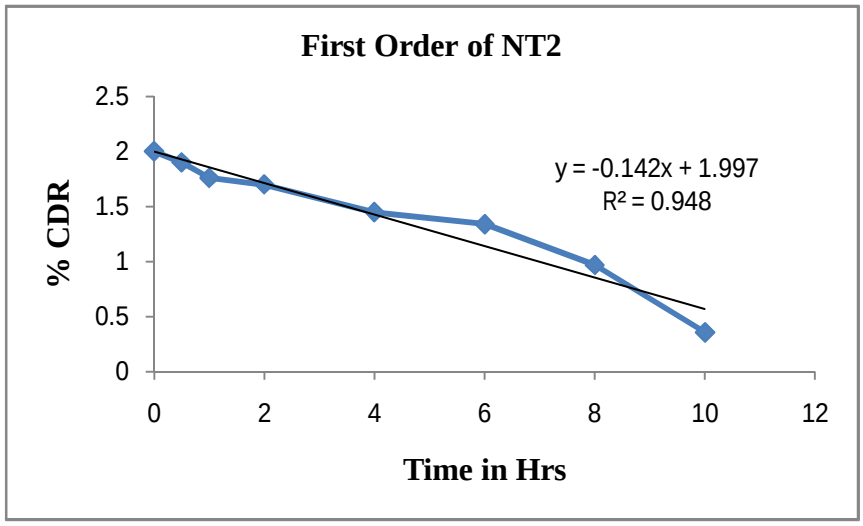


Figure No 18: First order kinetics of formulation NT2

- Higuchi equation:

Table No. 19: Higuchi kinetics of formulation NT2

Sqrt time	%CDR
0	0
0.71	21.32
1	42.23
1.41	49.48
2	71.65
2.45	77.97
2.83	90.67
3.16	97.69

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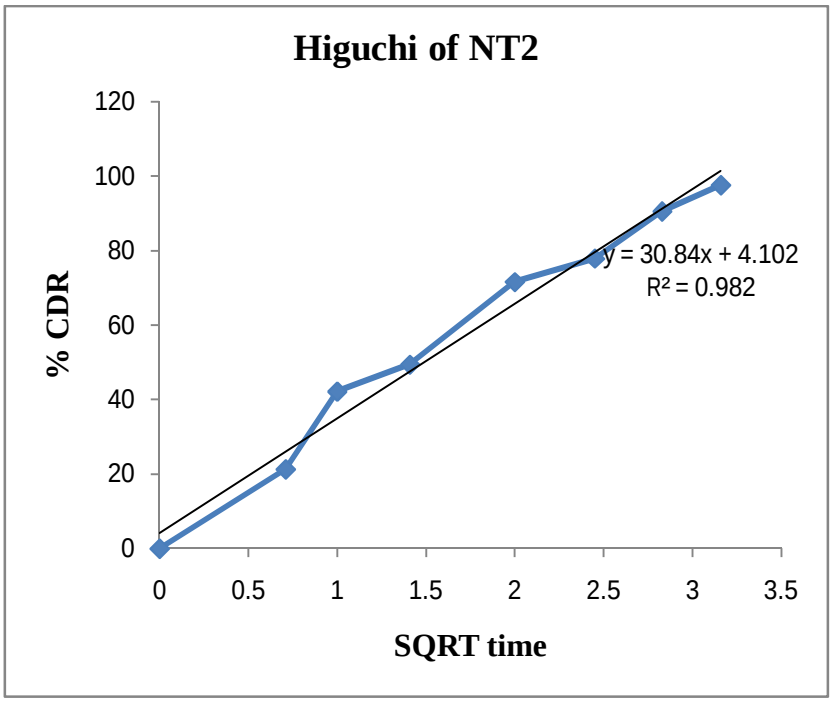


Figure No.19: Higuchi equation kinetics of formulation NT2

- Peppass equation:

Table No. 20: Peppas kinetics of formulation NT2

Log time	Log % CDR
0	0
-0.3	1.33
0	1.63
0.3	1.69
0.6	1.86
0.8	1.89
0.9	1.96
1	1.99

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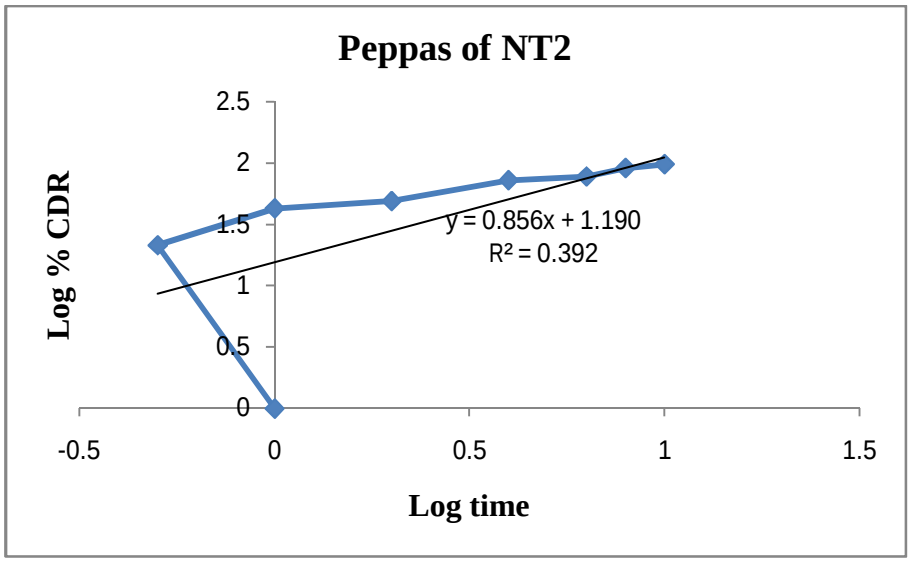


Figure No. 20: Higuchi equation kinetics of formulation NT2

Table No. 21*: Invitro*Drug releasekinetics 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

The curve fitting findings of the developed formulations' release rate profiles provided insight into the process of drug release. According to the data analysis, the drug release follows the Higuchi equation, as the greatest linearity of R2 achieved was close to one for the total produced Nanoparticles as plot between SQRT time vs percent cumulative drug releases.

X. SUMMMARY AND CONCLUSION

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.

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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

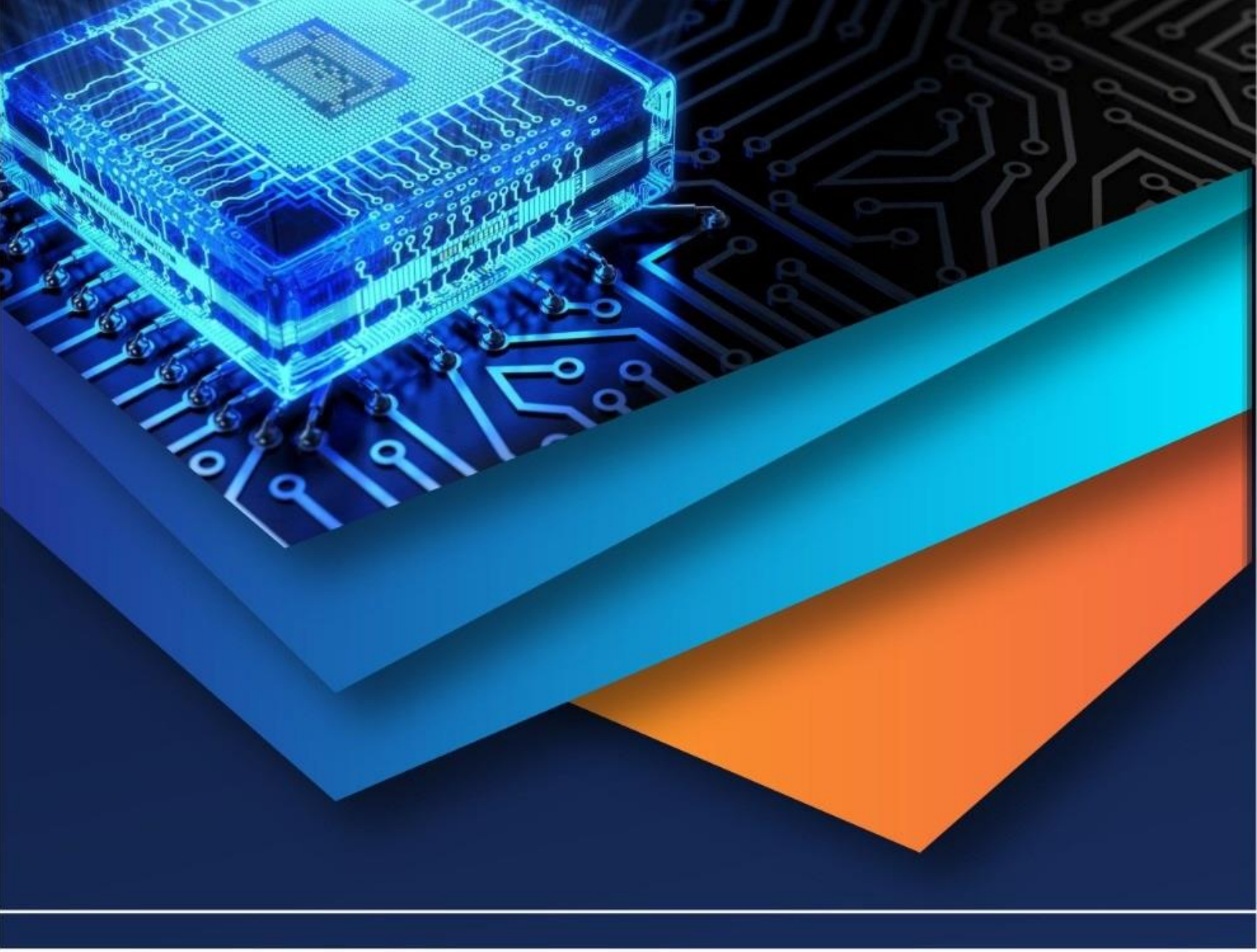
XI. CONCLUSION

From this study, it was concluded that the best formulation of NaproxenTransmucosal, 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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