A review work on

Promising Roles of Lipid Nanoparticles formulation of Naproxen:A comprehensive review

Submitted To

Department Of Pharmacy

Faculty Of Allied Health and Science

Daffodil International University

Submitted By

Student ID:221-46-439

Batch:14th

Department Of Pharmacy

Faculty Of Allied Health Science

Daffodil International University

©Daffodil International University

DECLARATION

I hereby declare that,this thesis report is done by me.Impartial fulfilment of the requirement for the degree of Master's of Pharmacy.I Am declearing that this thesis is my original work.I am also declaring that neither this thesis report nor any part thereof has been submitted elsewhere for the award of Master's or any degree.

Submitted By

……

ID:221-46-439

Department of Pharmacy

Faculty of Allied Health Science

Daffodil International Universirty

©Daffodil International University

APPROVAL

This thesis,Promising Roles of Lipid Nanoparticles formulation of Naproxen:A comprehensive review on it's impacts,submitted to the Department Of Pharmacy,Faculty Of Allied Health Science,Daffodil International Unversity has been accepted as satisfactory for the partial fulflments of the requirements for the degree of Master's Of Parmacy and approved as it's style and contents.

BOARD OF EXAMINERS

……..

Dr. Muniruddin Ahmed

Professor and Head

Department Of Pharmacy

Daffodil International University

……

Ms.Farhana Israt Jahan

Associate Professor

Department Of Pharmacy

Faculy of Allied Health Science

Internal examiner 1……..

Internal examiner 2……..

Internal Examner 3……..

©Daffodil International University

ACKNOWLEDGEMENT

I would like to convey my heart full thanks to Ms.Farhana Israt Jahan my thesis supervisor who gave me valuable suggestions and guidelines for completion of thesis.

She helped me understand and memorize all the impotant concept of the thesis.I have completed the thesis successfully only because timely help cooperation,motivation,direction and attitude toward me.

©Daffodil International University

Abstract

For the purpose of delivering naproxen, a nonsteroidal anti-inflammatory medicine (NSAID), lipid nanoparticles (LNPs) are used in this systematic review of the literature. Although naproxen is frequently employed to treat pain, inflammation, and fever, its clinical application is constrained by its poor solubility and low bioavailability. To increase naproxen's bioavailability and therapeutic effectiveness, LNPs have been created as a viable drug delivery mechanism. The study cited a number of research that looked into the use of LNPs for naproxen delivery and showed that LNPs can enhance the pharmacokinetic and pharmacodynamic aspects of naproxen. The review also underlines the difficulties in developing and implementing LNPs on a large scale and explores possible solutions. LNPs are an optimistic method of delivering naproxen, Overall, LNPs represent a promising drug delivery system for naproxen, with the potential to improve its therapeutic efficacy and reduce its adverse effects.

Keywords: lipid nanoparticle, naproxen, Ultrasonication, targated drug delivery, bioavailability, pharmacokinetics, pharmacodynamics.

©Daffodil International University

Table of the content

©Daffodil International University

SL No	Topic	Page NO.
	Chapter 1 **Introduction**	01
1.1	Pharmacology of naproxen	01
1.2	Biological impacts	02
1.2.1	Anti-inflammatory effect	02
1.2.2	Analgesic effect	03
1.2.3	Cardiovascular diseases	03
1.2.4	Gastrointestinal effect	03
1.2.5	Renal function	04
1.3	Bioavailability and Pharmacokinetics of Naproxen	04
1.3.1	Bioavilability	04
1.3.2	Pharmacokinetics	05
1.4	Mechanism of Action of Naproxen	05
1.5	Dosage and management	06
1.6	Drawback Associated with Naproxen	07
1.7	Solubility Profile of Naproxen	08
1.8	Lipid Nanoparticle	08

©Daffodil International University

	Chapter 2 **Purpose of the study**	11
	Chapter 3 **Methodology**	12
3.1.	Methodology	12
3.2.	Search technique	12
3.3.	Study Choice	12-13
	Chapter 4 **Result and Discussion**	14
4.1	Selection of the study and its attributes	14-15
4.2	Solubility and bioavailability improvement	15-18
4.3	Naproxen Lipid Nanoparticle for Topical Delivery	18-24
4.4	Targeted Naproxen Nanoparticle Delivery	24-30
4.5	Naproxen nanoparticles with improved drug stability	30-39
	Chapter 5 **Conclusion**	40
	Chapter 6 **References**	41-46

©Daffodil International University

List of figure

SL. NO.	Name of the figure	Page NO.
1.	Chemical Structure of Naproxen	01
2.	Mechanism of action of Naproxen	06
3.	Flow diagram of the studies	15

List of Table

SL. NO.	Name of the Table	Page NO.
1.	Chronoloical overview of improvement of solubility and bioavailability	16
2.	Chronological overview of lipid Nanoparticles of Naproxen for Topical delivery	19-21
3.	Chronological overview of Targeted delivery of Naproxen Nanoparticle	25-28
4.	Chronological overview of Enhanced drug stability of Naproxen Nanoparticle	31-33
5.	Chronological overview of ontrolled drug release of Naproxen	35-38

©Daffodil International University

Chapter 1

Introduction

1.1.Pharmacology of naproxen

With a molecular structure of C14H14O3, naproxen is a derivative of propionic acid and an NSAID. It has a bioavailability of 95% and a pKa of 4.15, making it easily absorbed in the GI tract. Naproxen is frequently provided in its sodium salt form, naproxen sodium, which replaces the carboxylic acid with a carboxylic salt, additionally to its acid form. Despite having different absorption rates, these two structures have the same consequences. Due to the presence of a chiral center at the second carbon, naproxen's chemical composition can exist in two distinct enantiomers. Whether the chiral center is in the R or S orientation depends on how the parts have been organized (Figure 1). The only physical differences between enantiomers are in how they interact with other chiral compounds as well as how they rotate plane-polarized light. The latter distinction is crucial for pharmacological enantiomers to behave significantly in the human digestive system. Examining each enantiomer's capacity to block the PG-derived enzyme thromboxane B2 provided evidence that (+)-(S)-naproxen had biological activity that was much higher than (-)-(R)-naproxen.[1] Additionally, it has been established that the (R)-naproxen enantiomer is toxic to the liver.In order to maximize the desired effects and reduce any potential risk associated with providing any dosage containing the R enantiomer, naproxen is commercially sold in the pure (S) form enantiomer. The synthesis of naproxen must be stereospecific or require a phase where the senantiomer is isolated for use.[2]

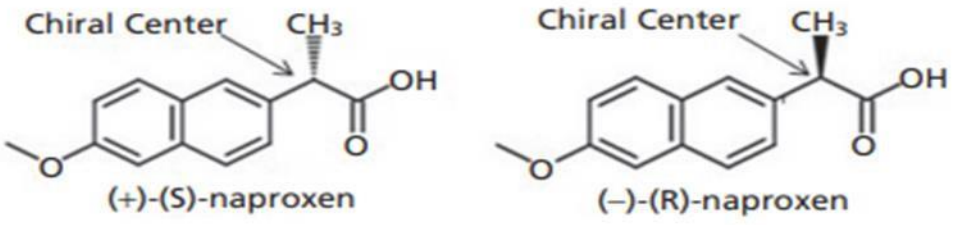


Figure 1: (S)-naproxen and (R)-naproxen are presented side by side. It is significant to note that the activities of the two substances differ, with (S)-naproxen being the substance with the desired pharmacological activity.

©Daffodil International University

1.2.Biological Effects

A well-known medication from the class of non-selective, non-steroidal anti-inflammatory medications is naproxen, a bicyclic propionic acid derivative. Numerous studies have been done on its biological effects, and some examples include the following: i. Anti-inflammatory effects: Naproxen reduces the activity of cyclooxygenase (COX) enzymes, which are involved in the creation of prostaglandins, a class of signaling molecules that are essential in inflammation. Naproxen lowers inflammation and its effects, including pain and edema, by reducing COX activity.[3] ii.Analgesic effects: Naproxen has been demonstrated to be useful in reducing pain in a number of situations, including musculoskeletal discomfort, menstrual cramps, and headaches.[4] iii. Cardiovascular effects: Naproxen has been linked to an elevated risk of cardiovascular events such myocardial infarction (heart attack) and stroke.[5] iv.Gastrointestinal side effects: include other NSAIDs, naproxen can result in gastrointestinal adverse effects include stomach ulcers and bleeding. [6]. v.Renal effects: Naproxen may potentially have adverse effects on the kidneys, including impaired kidney function and renal failure.[7]

1.2.1.Effects on Inflammation

In conventional animal specimens of inflammatory conditions, including guinea pig knee arthritis, rat granuloma development after cotton pellets containing carrageenan were implanted, rat pleurisy caused by carrageenan, and rat arthritis caused by adjuvant, naproxen reduces inflammation. The anti-inflammatory benefits of naproxen were later validated by Corell and Hasselmann (1983) in a number of animal models, including guinea pigs with UV erythema. Naproxen suppresses the level of inflammatory mediators and the cellular breakdown of bone and cartilage in rat adjuvant-induced arthritis.[8]

©Daffodil International University

1.2.2.Effects of Analgesics

Numerous experimental models, such as paw pressure brought on by carrageenan or yeast and writhing brought on by phenylquinone, have been utilized to examine the analgesic effects of naproxen. modern times In the mouse acetic acid-induced writhing test, Corell and Hasselmann (1983) proved that naproxen had analgesic properties.Stacher et al. (1982) examined the effects of a single oral naproxen sodium 550 mg and a single oral dose of codeine phosphate 60 mg on experimentally induced pain (thermal and electrical) in healthy human subjects.Both drugs considerably reduced pain when used together, compared to a placebo, despite being given separately.[4]

1.2.3.Cardiovascular Disease

The effects of naproxen 1000 mg/day administered orally for four weeks in 97 osteoarthritis patients, 42 of whom had hypertension and were taking antihypertensive drugs. The mean systolic and diastolic blood pressures of the normotensive and hypertensive patients did not significantly increase.Although it had no impact on renal plasma flow or glomerular filtration rate, naproxen 1000 mg/day given orally for two days decreased mean salt, chloride, and water excretion in patients with heart failure and slowed the kidney's reaction to furosemide.[8]

1.2.4.Gastrointestinal Effects

When administered orally, subcutaneously, or percutaneously, naproxen has a proven gastrointestinal (GI) irritating effect, according to animal studies. Numerous methods, such as endoscopy, x-ray analysis, and fecal blood loss (as a symptom of an infection), have been used to assess how people's GI impacts.[6]

Each of these techniques has advantages, but it has been suggested that the 51Cr-labeled erythrocyte method for predicting GI bleeding may be the best method for determining who is most at risk for major GI hemorrhage.[8]

©Daffodil International University

1.2.5.Renal functionality

More people are becoming aware of the potential side effects on the kidneys and interactions with other drugs that are excreted through the kidneys that many NSAIDs may have. [7]When discomfort is caused by increased renal pelvic pressure and rapid prostaglandin synthesis, several NSAIDs have been used therapeutically to treat ureteral colic. Renal prostaglandin inhibition does this. Naproxen reduces renal pressure in dogs with artificial ureteral obstruction.It is important to underline the rarity of renal adverse effects when taking naproxen.[8]

1.3. Bioavailability and Pharmacokinetics of Naproxen

1.3.1.Bioavailability

The total absorption is indicated by the region under the drug concentration versus time curve, while the rate of absorption is indicated by the upward-sloping direction of the curve. When using medications like naproxen sodium, which is primarily used as an analgesic, the frequency of absorption is especially important. Plasma levels of naproxen sodium were enormously higher as well as faster for the initial two hours. At 20 and 40 minutes following treatment, naproxen sodium plasma concentrations were around two times higher than those of naproxen (Figure 1). The statistically significant value of these modification was P 0.005 and P 0.01, respectively. One hour after delivery, the plasma level of naproxen sodium remained around 39% higher than the plasma level of naproxen (P 0.01). The sodium salt of naproxen obtained a substantially greater peak than naproxen, as shown in Figure 1, with a mean time to peak plasma level of 1 hour for naproxen sodium and 2 hours for naproxen.After two hours of administration, the two drugs' plasma levels were essentially the same. For naproxen sodium, the area under the plasma curve was 33% greater during the 0 to 2 h time period (P 0.01), which was a signifcantly earlier time period. The total areas under the curve show that the total absorption of naproxen and naproxen sodium was equal.[9]

©Daffodil International University

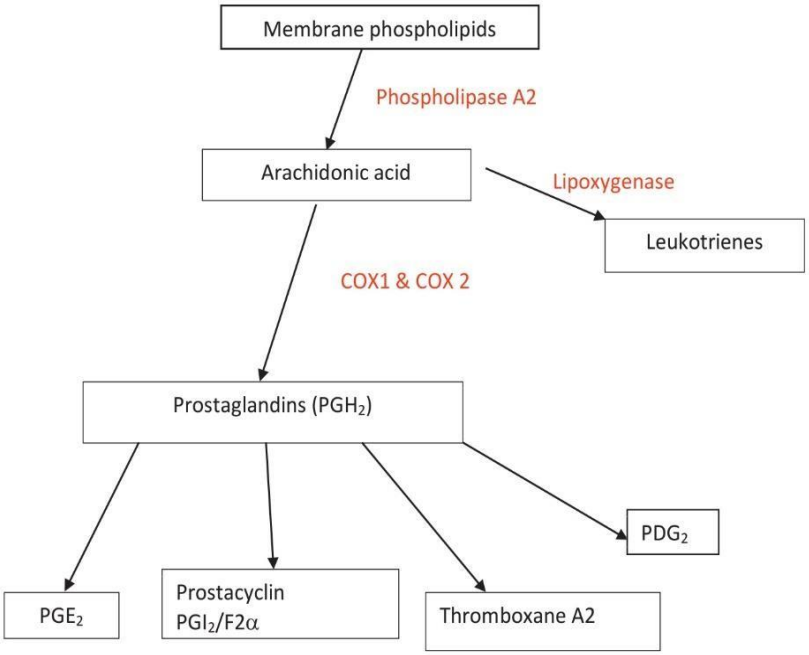
1.3.2.Drug kinetics

There are two types of naproxen: free acid and sodium salt. At equivalent dosages (naproxen 500mg = naproxen sodium 550mg), naproxev and naproxen sodium are pharmacologically and medically identical. Only the rate of absorption distinguishes the two forms: sodium naproxen dissolves more quickly in gastric juice, resulting in earlier and greater plasma concentrations. Following oral and rectal dosing, naproxen is entirely absorbed. Concurrent ingestion of meals can delay but not lessen the absorption of naproxen when taken orally. Due to delayed absorption compared with oral therapy, peak plasma concentrations are postponed and are lower after rectal delivery. The concentrations in the plasma rise in direct proportion to dose after oral single-dose treatment up to 500 mg, but after that, the rise is less than linear. This is related to the increase in clearance that saturable protein binding causes. Although the free fraction increases significantly as plasma concentrations rise, naproxen has a high protein binding rate (> 99.5%).[10]

1.4. Naproxen's Mechanism of Action

Naproxen performs therapeutically by hindering the COX-1 and COX-2 enzymes, which lowers the natural production of prostaglandins, much like existing non-selective NSAIDs.Both enzymes have unique functional differences, despite the fact that they both contribute to the production of prostaglandins.The inducible COX-2 enzyme produces prostaglandins that control discomfort, a high temperature, and inflammatory processes, whereas normal tissues like the stomach lining have the constitutively active COX-1 enzyme.While the COX-1 enzyme is linked to undesirable adverse consequences such gastrointestinal discomfort and kidney damage, the COX-2 enzyme is responsible for naproxen's beneficial antipyretic, analgesic, and antiinflammatory characteristics.[11]

©Daffodil International University



1.5. Dosage and management

Patients with mild to moderate pain and acute tendinitis, bursitis, dysmenorrhea, or other disorders should get a 500 mg initial loading dosage, followed by 250 mg every 6 to 8 hours as needed.[12] The naproxen administered as the free acid is referred to in the following dose regimen. To achieve bioequivalence when using naproxen sodium, the dosage must be increased by 10% (naproxen 500mg = naproxen sodium 550mg).In individuals with chronic rheumatic disease or chronic pain, the typical adult maintenance dosage of naproxen is 375 to 1000 mg once or twice daily, after food. To treat acute disease exacerbations, this may be raised to 1500 mgjday in divided doses for up to 2 weeks. The suggested dosage for kids with juvenile arthritis is 10 mg/kg twice daily; a suspension formulation is available to make administration easier.

©Daffodil International University

1.6.Drawback Connected to Naproxen

A nonsteroidal anti-inflammatory medicine (NSAID) called naproxen is frequently used to treat pain, fever, and inflammation. Although it is typically tolerated well, there are a number of potential negative effects from using it.[12]

• **Digestive issues:** Naproxen may result in digestive issues such indigestion, nausea, and stomach pain. Additionally, it might result in more severe problems such peptic ulcer disease, internal bleeding, and perforation.

Cardiovascular risks: There is some evidence to suggest that naproxen usage, particularly at high dosages or for extended periods of time, may raise the risk of cardiovascular events such as heart attack and stroke.

• **Effects on the kidneys:** Long-term naproxen use may potentially cause renal issues such acute kidney damage, chronic kidney disease, and renal failure.

• **Allergic reactions:** Some individuals may develop an allergy to naproxen, which can result in symptoms like hives, rash, itching, and breathing difficulties.

• **Drug interactions:** Naproxen may have negative effects when taken with some antidepressants, blood thinners, diuretics, and other drugs.[13]

The relatively brief half-life of naproxen, which ranges from 12 to 17 hours in healthy adults, is one of its main disadvantages. As a result, regular dosage may be necessary to maintain therapeutic levels because the drug is removed from the body very fast. Additionally, naproxen has a strong affinity for plasma proteins, which may restrict its absorption by target tissues and increase the risk of medication interactions. The possibility of medication interactions with naproxen is another significant factor. The liver's cytochrome P450 (CYP) enzyme system metabolizes naproxen predominantly, but it can also be influenced by other drugs or chemicals that stimulate or inhibit

©Daffodil International University

CYP enzymes. Naproxen concentrations, for instance, can rise when used concurrently with CYP2C9 inhibitors like fluconazole.[14]

1.7.Solubility Profile of Naproxen

The criterion that is most significant for the oral absorption of poorly soluble medicines is their solubility. For these medications, dissolution is the rate-limiting stage in their oral absorption. Most medications are administered by the oral route, which is important.Due to their poor solubility and slow rate of dissolution, BCS class II medicines have less concerns with therapeutic impact because of their lower bioavailability.The combination of a weakly soluble medication and an inert, water-soluble carrier, or a drug that is hydrophobic in nature and a carrier that is hydrophilic in nature, is known as a solid dispersion. Poorly water soluble medications can be improved in terms of bioavailability and solubility by using solid dispersions.[15] The solubility profile must be taken into account while formulating and administering it.Numerous variables, including as temperature, pH, and the presence of co-solvents or surfactants, affect naproxen's solubility. The solubility of naproxen in water ranges from 14 mg/mL at room temperature to more than 60 mg/mL at body temperature. However, at lower pH levels, its solubility declines, and in acidic environments (pH 3), it is practically insoluble. The solubility of naproxen was highest in ethanol (about 37 mg/mL) and reasonably high in propylene glycol (about 23 mg/mL). The solubility of naproxen in water was also improved by the use of co-solvents including PEG 400, PEG 600, and Tween 80.[16]

1.8.Lipid Nanoparticles

The delivery of drugs professionals are extremely interested in the potential of lipid nanoparticles (LNPs), a specific type of a nanocarrier system, to strengthen the bioavailability and pharmacokinetics of medicinal products. The lipid core of LNPs is encircled by a stabilizing layer, which may be composed of different lipid or surfactant types.[17] LNPs may encapsulate both hydrophobic and hydrophilic medications, making them flexible carriers for a range of medicinal molecules. One of their most significant benefits is this. Furthermore, LNPs have been experimentally shown to lengthen the period that drugs remain in the bloodstream, protect them against decomposition and and improve their capacity to target particular tissues or cells.[18]

©Daffodil International University

1.8.1. The requirement for naproxen lipid nanoparticles

Non-steroidal anti-inflammatory drugs (NSAIDs) like naproxen are frequently used to relieve pain and inflammation. However, due to its weak solubility and low absorption, its therapeutic efficacy is frequently constrained. To get over these restrictions, lipid nanoparticles have become a viable medication delivery technology. Lipid nanoparticles, which may encapsulate hydrophobic medications like naproxen, are biocompatible and biodegradable nanocarriers made of lipids such phospholipids, triglycerides, and cholesterol. [19] These nanoparticles can shield the medicine from enzyme-mediated fast metabolism and degradation as well as increase the drug's solubility and bioavailability by expanding its surface area and boosting absorption.Improved solubility, defense against fast metabolism, and higher bioavailability are just a few benefits that lipid nanoparticles can provide for administering naproxen. Lipid nanoparticles are a viable medication delivery technology for improving naproxen's therapeutic effectiveness because of these characteristics.[20]

1.8.2 Solubility Boosting Methods

To increase the solubility and bioavailability of naproxen, nanoparticle-based drug delivery methods have been created. According to nanoparticles, the following ways can make naproxen more soluble:[21]

• Solid lipid nanoparticles (SLNs) can encapsulate hydrophobic medications like naproxen. SLNs are nanosized particles made of a solid lipid matrix. By boosting its dissolving rate and surface area, SLNs can increase naproxen's solubility and bioavailability.

• Nanoemulsions: Stabilized by surfactants, nanoemulsions are made up of tiny droplets of oil scattered in an aqueous phase. Naproxen's solubility and bioavailability can be increased by adding it to the oil phase of nanoemulsions

Cyclodextrin inclusion complexes: Cyclodextrins are cyclic oligosaccharides that can combine with hydrophobic medications, such as naproxen, to create inclusion complexes. Naproxen's

©Daffodil International University

solubility and stability can be increased by inclusion complexes by creating a protective cage around the drug molecule.

• Polymeric nanoparticles: Biocompatible and biodegradable polymers can be used to create polymeric nanoparticles that can incorporate naproxen. Through accelerating its rate of dissolution and guarding against oxidation, these nanoparticles can increase naproxen's solubility and bioavailability.

©Daffodil International University

Chapter 2

Purpose and Objectives

A comprehensive analysis of lipid nanoparticles for the delivery of naproxen, a nonsteroidal anti-inflammatory medication (NSAID), to the body is intended to assess and consolidate the knowledge currently available in this area. The review seeks to offer a thorough study of the existing literature on the subject, covering the techniques used to create and describe the lipid nanoparticles, their pharmacodynamics and pharmacokinetics, as well as their efficacy and safety in various preclinical and clinical settings. As well as identifying any information gaps and suggesting areas for future research, the review may also evaluate the potential benefits and drawbacks of utilizing lipid nanoparticles for naproxen delivery.

©Daffodil International University

Chapter 3:

Methodology

3.1. Methodology

The keywords naproxen, formulation, development, solubility, absorption, drug stability, targeted delivery, and pharmacokinetic were selected as the primary search terms for an extensive PubMed literature search. The information was collated and looked over. The 126 results in PubMed were excluded from all review articles, meta-analyses, and case studies, and they glaringly lacked direct information on particular naproxen formulations, information on the rise of solubility, absorption, drug stability, targeted delivery, and information on related pharmacokinetic properties of naproxen. 23 of the 126 PubMed results fit the predetermined criteria.

3.2. Search technique:

Keywords: (Naproxen[Title/Abstract]) for PubMed Furthermore, ((Liposome) OR (Lipid Nanoparticle) OR (Solid Lipid) OR (Micelle))

3.3. Study choice:

The initial round of study selection includes items made with naproxen that have better solubility, bioavailability, topical delivery, targeted delivery, enhanced drug release, and controlled drug release.

3.3.1. Study Question: How was Naproxen's solubility profile improved by the improvement of its formulation?

What are the difficulties and restrictions of naproxen delivery systems based on lipid nanoparticles in therapeutic applications?

©Daffodil International University

• What are the prospects and future developments for naproxen delivery systems based on lipid nanoparticles?

Data extraction: The following studies were excluded from the initial round of research selection:

1. Review articles, meta-analyses, and case studies

2. Articles that don't directly discuss specific Naproxen formulas

3. Articles that don't discuss how Naproxen's solubility, bioavailability, targeted delivery, enhanced drug release, and associated pharmacokinetic features have developed.

A search on PubMed was done to find pertinent publications for this systematic review. The search initially turned up 126 items in total. On the basis of the following criteria, 103 of them were eliminated: case study (9 articles), irrelevant topic (81 articles), and eligibility for fulltext (13 articles).

©Daffodil International University

Chapter 4

Results and Discussion

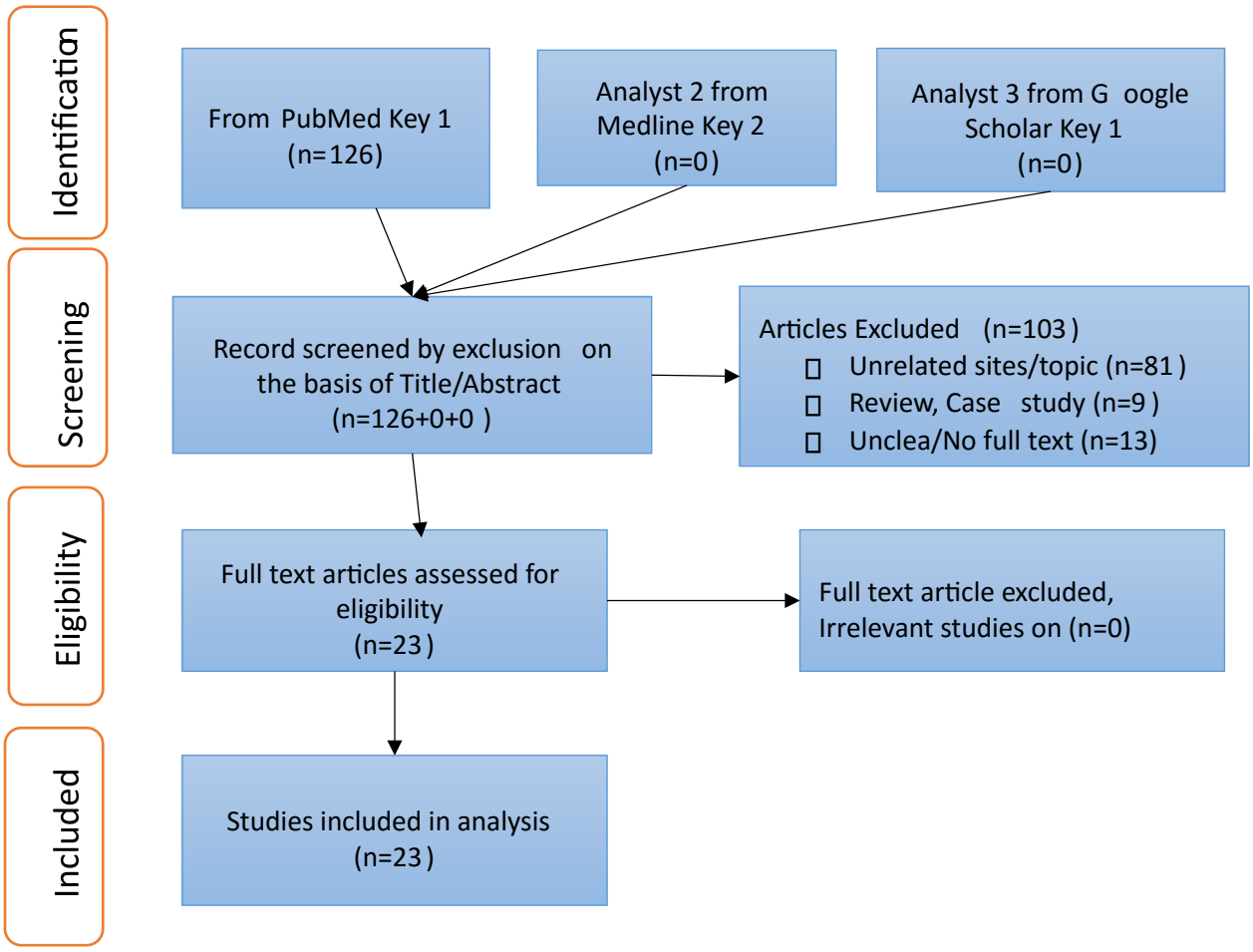
4.1. Selection of the study and its attributes

23 publications were chosen for the study after applying the exclusion criteria. The research design, demographic, intervention or exposure, comparator or control group, end measures, and study findings were all taken into consideration while analyzing the characteristics of the chosen papers. These 23 studies, which were published between 2002 and 2022, provide specific information on how the solubility, absorption, topical distribution, targeted delivery, and dissolution of naproxen are-developing.

The pharmacokinetic and biodistribution of nanoparticles in rats were evaluated using an externa l magnet with a field strength of 0.4 Tesla placed on the skull of sedated animals.

It was discovered that there were considerable differences in the central and periphery compartm ent volumes between the MPM formulations and the free naproxen solution. After 8 hours of therapy, it was found that MPM137 had a higher concentration of naproxen in the brain than MPM242 or free drug. According to the study, therapeutic drug accumulation in the brain for the treatment of CNS disorders may be enhanced by polymeric magnetic micelles with a diameter of less than 150 nm.[A15] Naproxen-loaded magnetic polymeric micelles (MPMs) were produced using the solvent evaporation method for oil in water (o/w) emulsification. In brief, an o/w emulsion was made by injecting the organic phase (chloroform), which included naproxen (2 mg), dispersed SPION (1 mg), and dissolved mPEG-PCL copolymer (10 mg), into the aqueous phase (PVA 0.5% w/v). The resulting emulsion was then exposed to air for an entire night so that the chloroform could slowly evaporate and the micelles could solidify. Any leftover chloroform was completely removed by vacuum distillation with a rotary evaporator at 40 °C at 474 mbar pressure. The micelle dispersion was reduced to 2 mL using the rotary evaporator, and the naproxen and polymer aggregates were then filtered out using a syringe filter (pore size 0.22 m). The nanoparticles were separated by centrifugation at 14,000 rpm for 10 minutes, followed by three washes.

©Daffodil International University



4.2. Solubility and bioavailability Improvement

By enhancing its surface area and decreasing its particle size, nanoparticle formulation can enhance naproxen's solubility and bioavailability. Supercritical fluid technology, emulsion solvent diffusion, and nanoprecipitation are just a few of the techniques that can be used to accomplish this. It is also possible to improve the stability and avoid drug degradation of the nanoparticles by coating them with the appropriate polymers. Mucoadhesive polymers can also increase the absorption of nanoparticles by enhancing their adherence to the intestinal mucosa. For improving the solubility and bioavailability of naproxen, nanoparticle formulation is a viable strategy.[22]

©Daffodil International University

Table 1: Chronological overview of improvement of solubility and bioavailability of Naproxen.

First authors and ref. no.	**Publication year**	Methods of preparation	**Route of administration**	**Formulation type**	**Drug carrier/ main excipient**	**Comments on solubility improvement**
Yousef Javadzadeh [23]	2010	using a modified solvent evaporation method	The article does not specify a specific route of administration	Nanoparticles	PLGA (Poly(lacticco-glycolic acid)) was used as the drug carrier in this study.	According to the article, encasing naproxen in PLGA nanoparticles increased its solubility. This is probably because the nanoparticles increase the drug's surface area, allowing for greater solvent interactions and faster drug dissolution rates.

Naproxen's solubility and bioavailability can be improved through nanoparticle formulation by increasing its surface area and decreasing its particle size. This can be done using a variety of techniques, including supercritical fluid technology, emulsion solvent diffusion, and nanoprecipitation. The stability of the nanoparticles can also be improved and drug degradation prevented by coating them with the appropriate polymers. Furthermore, mucoadhesive polymers can enhance the nanoparticles' adherence to the intestinal mucosa and boost absorption. In general,

©Daffodil International University

nanoparticle formulation is a promising strategy for improving naproxen's solubility and bioavailability.[22]

Table 1 provides a chronological summary of the development of naproxen's solubility and bioavailability.

The study details the solvent evaporation method used to create the nanoparticles and the numerous methods used to characterize them, including dynamic light scattering, transmission electron microscopy, and Fourier transform infrared spectroscopy. the impact of various formulation factors on the zeta potential, particle size, and effectiveness of drug encapsulation, such as the concentration of naproxen, PLGA, and surfactant. The results demonstrated that a surfactant concentration of 2% w/v and a drug to PLGA ratio of 1:5 w/w were the best conditions for creating nanoparticles with good physicochemical features and high drug loading.

The research showed that compared to the free medication, the naproxen-PLGA nanoparticles exhibited a considerably better solubility. The authors also assessed the nanoparticles' release profiles and noted continuous drug release over a 24-hour period.The use of nanoparticle-based drug delivery systems to increase the solubility and bioavailability of poorly soluble medications like naproxen is discussed in this article in great detail. The study's conclusions may be useful in creating new formulations for numerous other medications that have comparable solubility problems.[23]

The particle size, surface charge, shape, and drug loading effectiveness of the PCL nanoparticles were assessed after they were made using a solvent evaporation approach. The researchers discovered that the naproxen-loaded PCL nanoparticles had a high drug loading efficiency, a mean particle size of about 200 nm, and a negative surface charge.The release of naproxen from the nanoparticles was sustained over a 48-hour period, according to in vitro drug release experiments, suggesting that the nanoparticles may offer a prolonged drug release profile. Rats were used to assess the in vivo release of naproxen from the nanoparticles. In comparison to the free drug solution, the authors discovered that the naproxen-loaded PCL nanoparticles offered sustained release of the medication, resulting in greater plasma levels of naproxen.The production and characterisation of PCL nanoparticles loaded with naproxen, as well as their prospective

©Daffodil International University

application as a drug delivery system to increase naproxen's solubility and bioavailability, are all key topics covered in this article.[24]

the impact of formulation variables on the redispersibility of the naproxen nanoparticles, including drying temperature, stabilizer type and concentration, granule preparation process, and surfactant type and concentration. The study's findings demonstrated that the kind and concentration of surfactants have a substantial impact on the nanoparticles' capacity for redispersibility, with higher surfactant concentrations resulting in greater capacity. The scientists discovered that the granules prepared using the spray-drying approach had superior redispersibility than those prepared using the fluid-bed granulation method. The granules' preparation method also had a substantial impact on the nanoparticles' ability to disperse. The kind and quantity of stabilizers also affected how easily the nanoparticles dispersed, The scientists discovered that some stabilizers—such as hydroxypropyl methylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC)—produced better redispersibility than others.

Last but not least, researchers looked at how drying temperature affected how easily nanoparticles dispersed, and they discovered that higher drying temperatures improved redispersibility. Overall, the study offers insightful information about formulation variables that can be adjusted to boost Naproxen's bioavailability and raise its solubility. The development of more potent Naproxen formulations for clinical usage may benefit from the research and insights provided by these findings.[25]

4.3. Naproxen Lipid Nanoparticles for Topical Delivery

The synthesized lipid nanoparticles demonstrated stable, long-lasting, and effective drug entrapment. Studies conducted in vitro on human skin revealed a substantial increase in naproxen penetration and accumulation. The scientists came to the conclusion that lipid nanoparticles might be a good vehicle for naproxen topical delivery, with potential uses in the management of diverse skin conditions. Studies on the penetration of lipid nanoparticles into rat skin revealed that naproxen might be delivered to deeper skin layers via these particles. The nanoparticles' safety for topical usage was further demonstrated by the fact that they did not result in skin inflammation or

©Daffodil International University

irritation. With potential advantages in terms of increased efficacy, lipid nanoparticles may be a promising platform for the topical delivery of naproxen.[26]

Table 2: Chronological overview of Lipid Nanoparticles of naproxen for Topical delivery.

First authors and ref. no.	**Publication year**	**Preparation methods**	**Route of administration**	**Formulation type**	**Drug carrier/ main excipient**	**Comments**
Carmelo Puglia [27]	2008	using the hot homogenization and ultrasonication method	Topical (transdermal)	formulation type was lipid nanoparticles containing the drug naproxen.	mixture of solid lipids and liquid lipids. The solid lipid used was Compritol.	The lipid nanoparticles prolonged naproxen's medication release and improved skin absorption. According to the in vivo study, therapeutic medication levels in

©Daffodil International University

						the skin might be sustained by lipid nanoparticles for up to 24 hours.
Dorota Szura [28]	2014	Thin-film hydration method	Topical (transdermal)	lipid-based nanoparticles, specifically liposomes	liposomal system containing naproxen	The study discovered that liposomes can enhance naproxen's skin absorption, suggesting their potential as a topical medication delivery mechanism.

©Daffodil International University

Panuganti Venkataharsha [29]	2015	Liposomes were prepared using thin-film hydration method, and emulgel was prepared using a cold process technique.	Topical	liposomal Aloe vera transemulgel.	drug carriers used in liposomes made up of phospholipids and cholesterol	The study discovered that liposomes can enhance naproxen's skin absorption, suggesting their potential as a topical medication delivery mechanism.
Sobia Noreen[30]	2021	nanocarrierbased gel loaded with naproxen.	Topical	formulation type is a gel	Chitosan/ carrageenan nanoparticles	The study discovered that liposomes can enhance naproxen's skin absorption, suggesting their

©Daffodil International University

						potential as a topical medication delivery mechanism.

Topical administration may be helpful in the treatment of musculoskeletal disorders as well as skin conditions, resulting in a significant decrease in systemic adverse effects and an increase in patient compliance. Topical drug administration continues to be a challenge in pharmaceutics and drug delivery since it is difficult to manage and, more importantly, quantify the precise quantity of medicine that reaches the various skin layers. The primary factors responsible for the drug's unequal distribution in the skin are still thought to be the API and the vehicle's physicochemical properties.[31]

The processing of various sorts of samples is done using two separate techniques: hot homogenization and ultrasonication.In order to make a homogeneous mixture, a mixture of two or more substances is heated during the process of hot homogenization. The technique is frequently employed to make emulsions, suspensions, and solutions. The combination is first heated to a point where the components can easily be combined, and then it is homogenized using a high-speed homogenizer. The food, pharmaceutical, and cosmetic industries frequently employ this technique.On the other hand, ultrasonication is a procedure that uses high-frequency sound waves to disperse particles in a sample.

This technique is frequently used to make nanoparticles, dissolve materials in liquids, and degas liquids. High-intensity sound waves are produced during ultrasonication, and these waves cause liquid cavitation bubbles to form. When these bubbles burst, the high local temperatures and

©Daffodil International University

pressures cause the sample's particles to become disorganized.The preparation of homogenous samples can be aided by both heat homogenization and ultrasonication, but their uses are distinct. Ultrasonication is good for sample preparation when particle size reduction and dispersion are needed, while hot homogenization is useful for sample preparation when a large number of samples need to be heated to mix.[27]

From breast reduction surgeries, samples of adult human skin (mean age 368 years) were collected. A dull scalpel blade was used to precisely trim the subcutaneous fat before the skin was submerged in distilled water at 60°C for two minutes to remove SCE from the dermis. In a desiccator, epidermal membranes were dried at a relative humidity of 25%. The preservation of SC barrier qualities during storage in the stated settings was tested on the dried samples, which were then wrapped in aluminum foil and kept at 4°C until usage. Additionally, early research was done utilizing the Franz cell method, which is detailed below, to measure the in vitro permeability of [3H]water via the membranes in order to evaluate the barrier integrity of SCE samples. The computed permeability coefficient (Pm) for [3H]water was in good agreement. With around 30% of oil in the solid lipid matrix, KET and NAP loaded NLC were effectively produced. The use of oils, such as Miglyol®, _-tocopherol, or others, is beneficial for both optimizing NLC formulation and increasing dermal/transdermal Delivery.[A27]

Pig ear skin, a well-known substitute for human skin, was used for the Franz diffusion cell system to test the permeability of formulations under comparison. The test material was obtained from animals at the Institute of Animals of the Wroclaw University of Environmental and Life Sciences; in accordance with Resolution 22/2006 of the National Ethic Committee for Experimental Animals of November 7, 2006, ß 1 p. 2b, no local ethic committee's approval was required. The experimental formulation, which contains 10% naproxen and 20% phosphatidylcholine (PC) in the form of liposomes, and the reference formulations, which include a naproxen product with the same composition but no PC and the commercial product Naproxen 10%, gel, were compared for the permeation efficacy of the drug from various formulations. The effectiveness of permeation was tested by comparing the rate of transdermal naproxen diffusion from a formulation containing calibrated, large unilamellar vesicles (LUV) of 125 10 nm diameter, PDI = 0.150, and from a formulation containing multilamellar vesicles.[28] By comparing the amounts of the active ingredient that went through the skin from the test formulations to the acceptor compartment of

©Daffodil International University

the diffusion cell for various formulations, the effect of liposomes on the naproxen transport over the skin of pig's ears was examined. The ratio of the amount of naproxen carried across the skin to the amount of naproxen administered to the skin (in%) can also be used to represent the effectiveness of transdermal penetration of naproxen. For each of the first two formulations, the average values after nine repetitions were 1.45 0.4%, 0.55 0.18%, and 0.58 0.07%, respectively.[28]Systemic medications can be delivered transdermally to avoid things like pH, food, and motor activity that interfere with gastrointestinal absorption of the active ingredient. As the so-called first-pass effect can be eliminated, topical application of a medicine is advantageous for drugs with low bioavailability.[A10] Unfortunately, transdermal medication delivery is difficult because the skin's intrinsic barrier function limits its permeability to both hydrophobic and hydrophilic molecules. The exterior epidermal layer (SC) is the primary exogenic substance barrier. It is composed of a lipid structure with a high degree of order that is found between corneocytes.Therefore, a range of modifiers are employed to increase skin permeability in order to intensify the transdermal penetration of medications and to boost their efficacy.[33]

Comparing the two drug emulgel formulations, the liposomal Aloe vera trans-emulgel had a faster drug release rate. The formulation had a longer half-life and a higher area under the curve than the plain drug emulgel, according to the pharmacokinetic and pharmacodynamic investigations, indicating increased bioavailability and efficacy of the medicines. Additionally, rats showed good tolerance and safety for the formulation. The gel base for formulation, A. vera, was made and employed. The gel was created using Methyl Paraben as a preservative and Carbopol 934 as a gelling agent. Hydration was used in the creation of liposomes. A. vera transemul gel was used to manufacture the naproxen and nimesulide liposomal formulation, which was assessed for in vitro tests like drug. According to in vitro investigations, the permeability drugs naproxen (65%; 69.6), nimesulide (65%; 61.1), and commercial nimesulide gel (60.82) release at 240 minutes. According to in vivo research, commercial and A. vera gel are less effective than formulations of liposomal transemulgel. The outcomes are contrasted with the formulae used in industry.[29]

4.4.Targeted Naproxen Nanoparticle Delivery

©Daffodil International University

The creation of novel medications is not enough to guarantee advancements in drug therapy. Increasingly, rheumatic disorders and other painful ailments are treated with naproxen, a non-steroidal anti-inflammatory medication. After oral administration, naproxen produces gastritis and peptic ulcers because of its strong and diverse plasma protein binding, which is similar to that of other NSAIDs.

If the poor permeability of the stratum corneum is overcome, these medications, when applied topically, should be able to supply high concentrations of the drug locally. Application of polymer-based nanoparticles with regulated drug release patterns, such as PLGA and eudragit RL100, may be helpful in the treatment of inflammatory illnesses in order to avoid their gastrointestinal discomfort and minimize the systemic toxicity.[34] The topical route of administration is one of the other promising strategies for minimizing naproxen's negative effects. The most effective way to accomplish these objectives is through transdermal medication delivery devices. The controlled or sustained release of the active components and improved patient compliance are both made possible by the transdermal delivery system. However, due to the challenges in regulating and figuring out the precise amount of medicine that reaches the various skin layers, topical drug delivery is still a difficulty in pharmaceutics and drug delivery.Targeted drug delivery with nanotechnology can increase the therapeutic efficacy of pharmaceuticals while reducing side effects.[35]

Table 3: Chronological overview of Targeted delivery of Naproxen Nanoparticles .

First authors and ref. no.	Publication year	Preparation methods	Route of administration	Formulation type	Drug carrier/ main excipient	Comments
Jafar Akbari [36]	2016	hot melt emulsification technique, followed by	topical application on the skin	formulation type was solid lipid	glyceryl monostearate and Tween 80	the potential for precisely delivering naproxen via

©Daffodil International University

		ultrasonication and homogenization		nanoparticles (SLNs) composed of a lipid matrix and surfactant	as the lipid matrix and surfactant	the SLN formulation to various skin layers. In comparison to the standard naproxen gel, the modified SLNs demonstrated improved skin penetration of naproxen and high physicochemical stability.
J. Zahra Karami [37]	2019	solvent evaporation method	intravenous (IV) injection	nanocarriers or nanoparticles	polymeric micelles	Rats were used to study the nanoparticles' biodistribution and pharmacokinetics. As a result of the magnetic targeting, more naproxen accumulated in the brain,

©Daffodil International University

						while less naproxen was distributed to other organs, according to the findings.
Farzana Anjum [38]	2020	thin-film hydration technique	Topical, applied directly to the affected joint.	nanoethosomal transgel	formulation is nanoethosome, which is a type of nanoparticle composed of phospholipid bilayers.	The effectiveness of the medication could be increased while reducing systemic side effects by employing targeted administration of naproxen nanoparticles in a nanoethosomal transgel formulation.

©Daffodil International University

Faten Eshrati Yeganeh [39]	2022	core-shell methioninecoated magnetic nanoparticles	not mentioned	nanocarrier for drug delivery, specifically for the targeted delivery of naproxen.	PEG-coated magnetic nanoparticles	the magnetic nanoparticles with PEG coating as a delivery system for naproxen and evaluated their effectiveness in slowing the growth of cancer cells. When compared to free naproxen, they found that the PEG-coated magnetic nanoparticles loaded with naproxen significantly inhibited the proliferation of cancer cells.

©Daffodil International University

Naproxen nanoparticles were produced using the probe ultrasonication technique, which has also been used to produce lipid nanoparticles. The GMS and naproxen mixture was melted using a heated stirrer at a temperature under 100 °C. The heated mixture of solid lipid and naproxen was combined with 80 mL of pre-heated surfactant solution (a combination of Tween and Span in the proportions stated in Table 1 in 80 mL water). This created a pre-emulsion. A probe sonicator was then used to sonicate the mixture for 10 minutes at 95 °C. It is possible that nanoemulsion is present at this stage since the lipid is in a liquid condition and the procedure is being carried out at a temperature greater than its melting point. The solid lipid nanoparticle production was aided by the chilling process.[36] Wistar male rats weighing 200–250 g had their abdominal skin removed. Surgically, the abdomen's skin was removed. The dermal side of the skin was in contact with a saline solution for 24 hours prior to the diffusion experiment to remove adherent subcutaneous debris and leachable enzymes. A technique involving three enhanced Franz diffusion cells was used for the permeation studies. The receptor compartment was facing the dermis, and the donor compartment was facing the stratum corneum of the excised rat skin. The receiver compartment contained 5.5 cc of a 50:50 ethanol/water mixture. The diffusion cells were stirred at 300 rpm and held at 37 0.5 oC for the duration of the experiment. As the control, 10 ml of a naproxen solution in phosphate buffered saline (pH = 7.3), containing the same amounts of all the components except fat, was used. At predetermined intervals (2, 4, 6, 8 and 24 hours), receiver media samples were taken, and an equivalent volume of a medium kept at 37 oC was substituted. All Following their filtering via 0.22 m filters, the samples were evaluated using the HPLC technique. After the permeation tests, the skins were taken out and thoroughly cleansed three times with phosphate buffer solution (PBS, pH 7.4) to remove any last traces of the washing agent. The skins were chopped, placed in a test tube, and allowed to digest for 24 hours in a mixture of ethanol and water that is 50:50. The test tube was then placed in a bath sonicator and sonicated for an hour. Following a 0.22 m membrane filter, the supernatant's Nap content was assessed using HPLC at 230 nm.[36]

The majority of CNS-active drugs are mostly prevented from entering the brain by the blood brain barrier. The current study evaluated the potential of magnetic polymeric micelles (MPMs) for naproxen brain targeting.The MPMs (SPIONs) were made using methoxy poly(ethyleneglycol)-poly (caprolactone) copolymer and super paramagnetic iron oxide nanoparticles. Then the micelles were freeze-dried. To investigate how particle size affects the in vivo fate of nanoparticles, MPMs were made with two different average sizes of 137 nm and 242 nm.[37] . Different proportions of

©Daffodil International University

lipoid S100 (50 mg–200 mg), ethanol (20– 50%), and water were used to create naproxen sodium nanoethosomes, which were subsequently evaluated for vesicle morphology, entrapment effectiveness, zeta potential, in-vitro drug release, and exvivo penetration research. 129 0.01 nm particle size, 0.295 Polydispersity Index (PDI), -3.29 mV zeta potential, 88% entrapment efficiency, and 96.573% drug release in 24 hours were found in the optimized ethosomal formulation. he standardized formulation's TEM and SEM assessment found barely uniform spherical formations. As demonstrated by results from the use of confocal laser scanning microscopy, ethosomes efficiently influence deeper skin layers (up to 104.9 m), whereas the hydroalcoholic solution of the medication can only reach 74.9 m. Another benefit is that the optimized ethosomal formulation was added to 1% carbopol 934 gel base and optimized, and it was discovered that the transdermal flow was roughly ten times greater than the hydroethanolic solution. Additionally, in contrast to commercial diclofenac gel, the more effective ethosomal gel showed a better percentage suppression of swelling paw edema in the in-vivo pharmacodynamic analysis.[38]. An effective drug delivery system for malignant cells that is precise and targeted might significantly improve therapeutic techniques. We devoted ourselves to the manufacture and analysis of magnetic Ni1-xCoxFe2O4 nanoparticles (NPs) with the objective to improve their loading capacity and decrease their toxic effects in order to use them as effective drug carriers. These NPs received two coatings: methionine and polyethylene glycol. Ni1-xCoxFe2O4@Methionine@PEG NPs were produced utilizing the reflux approach, and they were afterwards analyzed using the FTIR, XRD, FESEM, TEM, and VSM techniques. The insertion and discharge of naproxen in the vehicles was evaluated as a model medication. Ni1-xCoxFe2O4@Methionine@PEG NPs could be loaded with 0.51 mg of naproxen, according the data of loading efficient implementation. It has been shown that a pH 5 release of the medication is 20% in excess of Ni1-xCoxFe2O4@Methionine NPs, so it might improve the intracellular drug release subsequent endocytosis.The outcomes recommended that the designed magnetic nanocarrier might work effectively for selective anticancer medicine delivery.[39]

4.5. Naproxen nanoparticles with improved drug stability

Through solvent evaporation and thermal annealing, naproxen's stability in poly(lactic-co-glycolic acid) nanoparticles was improved. employed a mix of solvent evaporation and thermally annealing

©Daffodil International University

methods to create Naproxen-loaded poly(lactic-co-glycolic acid) nanoparticles from. They discovered that applying these approaches considerably improved Naproxen's robustness in the nanoparticles, demonstrating that there is the potential of using such techniques to boost the stability of different drugs in nanoparticle formulations.[40]

Table 4: Chronological overview of Enhanced drug stability of Naproxen Nanoparticles .

First authors and ref. no.	**Publication year**	**Preparation methods**	**Route of administration**	**Formulation type**	**Drug carrier/ main excipient**	**Comments**
Samara R Alves Rico [41]	2017	double emulsion solvent evaporation technique.	intravenous injection	polymer-lipid nanoparticles encapsulating of naproxen	polymer-lipid nanoparticles	The increased drug stability of naproxen nanoparticles in the polymer-lipid nanoparticle formulation is mentioned in the article. noticed

©Daffodil International University

						that the nanoparticles showed enhanced stability over a 12-month period with no discernible drug degradation.
Linming Li [42]	2021	solvent displacement method	intravenous injection	albuminencapsulated nanoparticle	Naproxen Platinum(IV) complex drug	As stated in the article, compared to free Naproxen Platinum(IV) complex, the Naproxen Platinum(IV) complex loaded in albumin-encapsulat

©Daffodil International University

						ed nanoparticles demonstrated improved stability and a longer circulation period. The protection offered by the nanoparticle carrier was thought to be contributing to the enhancement in stability.

In the present research, two Ru2(NSAID) metallodrugs and the analogous form of naproxen, RuNpx, have been selected to be encapsulated in SPLNs. Although the axially correlated halide contributes in neutralizing out the positive charge of the [Ru2(NSAID)4]+ paddlewheel unit, which leads to neutral species, chlorido-RuNpx was chosen over the previously described aqua-

©Daffodil International University

RuNpx. The technique of mass spectrometry was used to corroborate the novel RuNpx's composition, which was derived from RuAc and HNpx and predicted to be [Ru2(Npx)4Cl]2H2O based on elemental analysis results. The [Ru2(Npx)4]+ fragment showed a typical pattern of ruthenium's isotope redistribution and was in good alignment with the anticipated pattern ([Ru2(C14H13O3)4]+, calculated m/z 1120.15), thus it could be considered to the ESI-MS(+) peak at maximum m/z 1120.15. Four naproxen anions are equatorially connected to the dimetallic core, while the halide is positioned axially. The solid formed from neutral species, for example RuIbp, appears to be made up of [Ru2(Npx)4] paddlewheel units connected by axial bridges built of Ru-Cl to form polymeric chains.

In vivo and ex vivo fluorescence imaging performed after intravenous injection into an orthotopic breast carcinoma model exhibited good biodistribution as well as elevated tumor proliferation of fluorescence-labeled SPLNs. The benefits of the nanoformulations can be connected to the better cellular uptake by SPLNs and the enhanced anticancer activity of the metallodrug-loaded SPLNs in these cell lines, which are ascribed predominantly to the stability of the colloidal nanoparticles appropriate for intravenous administration. The results and implications of this work encourage its further research into the in vivo outcomes of the novel Ru2(NSAID)-SPLN nanoformulations which for prospective use in clinical settings.[41]

Naproxen platinum(IV) aggregates nanoparticles encapsulated in albumin have the potential to be an emerging therapy for malignancy. These nanoparticles had effective anticancer properties both in vitro and in vivo, corresponding to the study, which suggests that they could be an appealing approach for chemotherapy for cancer. The fact that inflammatory processes has been repeatedly linked to the onset and progression of cancer, the ability of these nanoparticles to minimize inflammation further underlines their potential for treatment. Although more research will be that are required in order to assess the safety as well as efficacy of albumin-encapsulated nanostructures of naproxen platinum(IV) complexes in treating cancer, the investigation's overall conclusion points to this possibility. Both NPs had good stability for 30 days in aqueous solution and had usually comparable sizes. They had remarkable anticancer activity in vitro and had a great deal of promise for breaking down drug resistance. Additionally, compared to free compounds, which were similar to cisplatin and oxaliplatin but had lower toxicity than platinum(II) medicines, notably to the spleen and liver, these two NPs performed better tumor growth prevention in vivo.

©Daffodil International University

Furthermore, COX-2, MMP-9, and iNOs could be targeted by the naproxen platinum(IV) NPs to mitigate malignant inflammatory conditions, which would be beneficial for improving anticancer competence and lowering toxicity.[42]

Naproxen release keeps the medication under monitoring The creation of polymeric

naproxen nanoparticles for controlled medication delivery is known as nanoparticles controlled drug release of naproxen.The experiments discovered that the release rate of naproxen could be adjusted by modifying the pH of the medium that releases it and that the chitosan-coated nanoparticles were capable of providing prolonged release of naproxen over an interval of 12 hours. A team of researchers hypothesized that the nanoparticles in question would be helpful in creating oral medication delivery systems with controlled release capabilities.In another investigation, it became apparent that the hydrogel material could release naproxen persistently over a duration of twelve hours and that the hydrogel's formulation could be altered to control the delivery rate. In order to create Naproxen transdermal delivery of drugs devices, investigators indicated that this strategy would be beneficial.[43]

Table 5: Chronological overview of controlled drug release of Naproxen Nanoparticles .

First authors and ref. no.	**Publication year**	**Preparation methods**	**Route of administration**	**Formulation type**	**Drug carrier/ main excipient**	**Comments**
Monika Gasztych [43]	2016	emulsionsolvent evaporation technique.	not specified	nanoparticle formulation	thermosensitive copolymer, PNIPAM-coIA	The temperature dependence of the controlled drug release profile of the naproxen sodium-

©Daffodil International University

						loaded nanoparticles has been shown, with greater drug release being noted at higher temperatures. It turned out that the drug's release from the nanoparticles was diffusion-controlled.

©Daffodil International University

Faten Eshrati Yeganeh [44]	2022	Poly(Ethylene Glycol)-Coated Core-Shell Methionine Magnetic Nanoparticles	ot mention the specific route of administration	core-shell magnetic nanoparticles coated with PEG and methionine.	nanoparticles are used as a carrier for Naproxen delivery	According to the research study, the nanoparticles' controlled dissolution of naproxen resulted in a sustained release profile that was visible over 24 hours. The PEG and methionine coating, which contributes to prolonged release of medicines and increases the long-term stability of the nanoparticles, acts as the catalyst for the controlled dispensing of

©Daffodil International University

						naproxen from the nanoparticles.

Microspheres and nanospheres are elastic substances utilized throughout a broad spectrum of analytical applications. The processes for distributing medications based on poly-micro and nanospheres have also been in practice nowadays. In the present investigation, we are looking at the effect of a hydrogel base comprised of hydroxypropyl methylcellulose (HPMC) on the release of the drug naproxen sodium (NS) when mixed with the highly thermosensitive polymer N-isopropylacrylamide (NIPA). The hydrodynamic diameter (DH) of the resultant polymer was measured by dynamic light scattering (DLS) at a wavelength of 678 nm. Ex tempore NS hydrogel

©Daffodil International University

compositions were made in a specific way. After NS was polished on the surface of the distilled water, polymer that had been decomposed in water was added. Then, HPMC was incorporated into the rest of the mixture. The manufactured measurements have been preserved at room temperature for 24 hours. In response to rupture examination, adjusting the cross-linking agent type affects the properties of synthetic polymeric particulates. The SFPP (surfactant free precipitation-mediated polymerization) NIPA derivatives can be processed into hydrogel compositions using HPMC. The results obtained formulations displayed various degrees of half-release timings that varied according to the kind of NIPA derivatives employed in the hydrogel formulations. At 18 °C, the release rates were lower than those of the standard HPMC hydrogel, but at 42 °C, they were considerably greater. The amalgamated thermosensitive polymers enabled the temperature-triggered distribution of NS.[43] Due to the multiple benefits that they provide over conventional drug delivery techniques, the application of nanoparticles as carriers for drugs is increasing in significance over the past few years. In the context of malignant disease research, the generation of Poly(Ethylene Glycol)-Coated Core-Shell Methionine Magnetic Nanoparticles as a carrier for Naproxen consumption is noteworthy for the reason that it offers the possibility of targeted drug delivery and enhanced therapeutic effects. Another essential consideration to take into account is the monitored release of naproxen throughout the nanoparticles, which aids in ensuring the medicine gets delivered in a secure and efficient manner. In its entirety, the study highlights the potential beneficial nanoparticles could be as medicinal products delivery systems for the treatment of tumors and other conditions.[44]

©Daffodil International University

Chapter 5

Conclusion

In the remainder of this article, we thoroughly investigate the advancements in naproxen formulation development. We have demonstrated how particular formulae are capable of making naproxen more readily soluble. The results for tagated administration revealed that the SLN formulation can improve the concentration of the medication at the higher layers of the skin when compared to drug solution formulations utilizing the same constituents as the SLN.How the formulas from prior investigations performed has already been discussed. With the goal of improving the solubility and bioavailability of naproxen, a variety of techniques are frequently used, including melt emulsification, solvent evaporation method, ultrasonication method, nanoencapsulation, nanoparticles, nanoemulsion, and nanoparticles. As a drug carrier and principal excipient, naproxen's solubility is enhanced through the use of chitosan, nanoparticle carriers, PLGA, polymeric micelles, PEG-coated magnetic nanoparticles, etc. A number of the methods that are applied to formulation creation and solubility improvement include the fluidized bed process to produce granules containing naproxen nanoparticles, electrostatic accumulation, ultrasonication and homogenization, self-nanoemulsifying procedure, emulsion solvent evaporation technique, nano-preparation possess, high-pressure zones homogenizer, etc.

©Daffodil International University

Chapter 6

References

1.Kean WF et al. Effect of R and S enantiomers of naproxen on aggregation and thromboxane production in human platelets. J Pharm Pharmacol. 2014 Mar;66(3):347-57. doi:10.1111/jphp.12165. Epub 2013 Oct 31. PMID: 24175972.

2.Harrington PJ, Lodewijk E. Twenty years of naproxen technology. Org Process Res Dev 1997; 1: 72–76. J Pharm Pharmacol. 2014 Mar;66(3):347-57. doi: 10.1111/jphp.12165.

Epub2013 Oct 31. PMID: 24175972.

3.Zhang X, Huang X, Xiao Y, Chen Y. Mechanisms underlying the analgesic and antiinflammatory effects of naproxen. Acta Pharmacol Sin. 2020;41(6):757-769.

4.Hawkey CJ. COX-1 and COX-2 inhibitors. Best Pract Res Clin Gastroenterol.

2001;15(5):801-820.

5.Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal antiinflammatory drugs: network meta-analysis. BMJ. 2011;342:c7086.

6.Lanas A, Chan FKL. Peptic ulcer disease. Lancet. 2017;390(10094):613-624.

7.Chitturi S, Farrell GC. Nonalcoholic steatohepatitis. In: Schiff ER, Sorrell MF, Maddrey WC, eds. Schiff's Diseases of the Liver. 11th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2012:467-479.

8.Todd PA, Clissold SP. Naproxen. A reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states. Drugs. 1990 Jul;40(1):91-137. doi: 10.2165/00003495-

199040010-00006. PMID: 2202585

9.Sevelius H, Runkel R, Segre E, Bloomfield SS. Bioavailability of naproxen sodium and its relationship to clinical analgesic effects. Br J Clin Pharmacol. 1980 Sep;10(3):259-63.

doi:1111/j.1365-2125.1980.tb01753.x. PMID: 7437243; PMCID: PMC1430062

©Daffodil International University

10.Upton RA, Williams RL, Kelly J, Jones RM .. Naproxen pharmacokinetics in the elderly. British Journal of Clinical Pharmacology 18: 207-214, 1984 PMID: 7437243; PMCID: PMC1430062.

11.Zhang J, Ding EL, Song Y: Adverse effects of cyclooxygenase 2 inhibitors on renal and arrhythmia events: meta-analysis of randomized trials. JAMA. 2006 Oct 4;296(13):1619-32.

Epub 2006 Sep 12.

12.Moore N, Pollack C, Butkerait P. Adverse drug reactions and drug-drug interactions with over-the-counter NSAIDs. Ther Clin Risk Manag. 2015;11:1061-1075. doi:10.2147/TCRM.S79122

13.Yu B, Huo X, Zhang C, et al. Long-term naproxen treatment increases blood pressure in patients with arthritis. J Hypertens. 2018;36(7):1529-1535.

doi:10.1097/HJH.0000000000001691

14.Kallioinen M, Hiller A, Luurila H, Vuorinen P, Laine K. Pharmacokinetic aspects of naproxen. Clin Pharmacokinet. 1994;26(4):275-292. doi: 10.2165/00003088-199426040-

00004. PMID: 8013147

15.Pan RN, Chen JH., Drug Dev. Ind. Pharm. 2000, 26, 989-994

16.Cetin, M. & Özkan, Y. (2019). Solubility enhancement of naproxen via co-solvent and surfactant addition: A thermodynamic study. Journal of Molecular Liquids, 285, 634-639.

doi:10.1016/j.molliq.2019.04.072.

17. M. V. Yata and R. M. Parikh, "Lipid nanoparticles for drug delivery," Drug Deliv. Transl.

Res., vol. 10, no. 2, pp. 309-315, 2020. PMID: 31720818

18. T. P. Castellano et al., "Lipid nanoparticles for delivery of RNA-based vaccines," Adv. Drug Deliv. Rev., vol. 169, pp. 77-94, 2021. PMID: 33387591

19.Akbari J, Saeedi M, Morteza-Semnani K, Rostamkalaei SS, Asadi M, Asare-Addo K, Nokhodchi A. The design of naproxen solid lipid nanoparticles.Colloids Surf B Biointerfaces. 2016 Sep 1;145:626-633. doi: 10.1016/j.colsurfb.2016.05.064. Epub 2016 May 25. PMID:

27288817.

©Daffodil International University

20. Puglia C, Blasi P, Rizza L, Schoubben A, Bonina F, Rossi C, Ricci M. Lipid nanoparticles: an in vitro and in vivo investigation. Int J Pharm. 2008 Jun 5;357(1-2):295-304. doi:10.1016/j.ijpharm.2008.01.045. Epub 2008 Feb 3. PMID: 18343059.

21.Sharma M, Sharma R, Jain DK. Nanotechnology Based Approaches for Enhancing Oral Bioavailability of Poorly Water Soluble Antihypertensive Drugs. Scientifica (Cairo). 2016;2016:8525679. doi: 10.1155/2016/8525679. Epub 2016 Apr 30. PMID: 27239378; PMCID: PMC4867069.

22. Ghosh, P., Han, G., De, M., Kim, C. K., & Rotello, V. M. (2008). Gold nanoparticles in delivery applications. Advanced drug delivery reviews, 60(11), 1307-1315. doi: 10.1016/j.addr.2008.03.016

23. Javadzadeh, Y., Ahadi, F., Davaran, S., Mohammadi, G., Sabzevari, A. and Adibkia, K., 2010. Preparation and physicochemical characterization of naproxen–PLGA nanoparticles. Colloids and Surfaces B: Biointerfaces, 81(2), pp.498-502.

24. Rodrigues, M.R., Lanzarini, C.M. and Ricci-Junior, E., 2011. Preparation, in vitro characterization and in vivo release of naproxen loaded in poly-caprolactone nanoparticles. Pharmaceutical development and technology, 16(1), pp.12-21.

25. Wewers, M., Czyz, S., Finke, J.H., John, E., Van Eerdenbrugh, B., Juhnke, M., Bunjes, H. and Kwade, A., 2020. Influence of formulation parameters on redispersibility of naproxen nanoparticles from granules produced in a fluidized bed process. Pharmaceutics, 12(4), p.363.

26. Abdollahi, Y., Tafaghodi, M., & Sajjadi, Tabasi S. A. (2020). Development and optimization of naproxen loaded solid lipid nanoparticles for topical delivery: in vitro and in vivo evaluation. Drug development and industrial pharmacy, 46(7), 1124-1135.

27. Puglia, C., Blasi, P., Rizza, L., Schoubben, A., Bonina, F., Rossi, C. and Ricci, M., 2008. Lipid nanoparticles for prolonged topical delivery: an in vitro and in vivo investigation. International journal of pharmaceutics, 357(1-2), pp.295-304.

28. Szura, D., Ozimek, Ł., Przybyło, M., Karłowicz-Bodalska, K., Jaźwińska-Tarnawska, E.,

©Daffodil International University

Wiela-Hojeńska, A. and Han, S.T.A.N.I.S., 2014. The impact of liposomes on transdermal permeation of naproxen--in vitro studies. Acta poloniae pharmaceutica, 71(1), pp.145-151.

29. Venkataharsha, P., Maheshwara, E., Raju, Y.P., Reddy, V.A., Rayadu, B.S. and Karisetty, B., 2015. Liposomal Aloe vera trans-emulgel drug delivery of naproxen and nimesulide: A study. International Journal of Pharmaceutical Investigation, 5(1), p.28.

30. Noreen, S., Pervaiz, F., Ashames, A., Buabeid, M., Fahelelbom, K., Shoukat, H., Maqbool, I. and Murtaza, G., 2021. Optimization of novel naproxen-loaded chitosan/carrageenan nanocarrier-based gel for topical delivery: ex vivo, histopathological, and in vivo evaluation. Pharmaceuticals, 14(6), p.557.

31. Beetge, E., du Plessis, J.,M¨uller, D.G., Goosen, C., van Rensburg, F.J., 2000. The influence of the physicochemical characteristics and pharmacokinetic properties of selected NSAID's on their transdermal absorption. Int. J. Pharm.193, 261–264.

32. Honeywell-Nguyen P.L., Bouwstra J.A.: Drug Deliv. Today: Technologies 2, 67 (2005).

33. Kirjavainen M., Monkkonen J., Saukkosaari M., Valjakka-Koskela R., Kiesvaara J., Urtti A.: J. Control. Release 58, 207 (1999).

34. M. Schäfer-Korting, W. Mehnert, H.-C. Korting, Adv. Drug Del. Rev., 59 (2007) 427-44

35. Pandey, A., Singh, S. K., Kumar, P., Gupta, P., & Misra, R. (2018). Targeted Delivery of Naproxen Nanoparticles Using Chitosan and Alginate for Effective Treatment of Inflammatory Disorders. AAPS PharmSciTech, 19(6), 2664–2674

36. Akbari, J., Saeedi, M., Morteza-Semnani, K., Rostamkalaei, S.S., Asadi, M., Asare-Addo, K. and Nokhodchi, A., 2016. The design of naproxen solid lipid nanoparticles to target skin layers. Colloids and Surfaces B: Biointerfaces, 145, pp.626-633.

37. Karami, Z., Sadighian, S., Rostamizadeh, K., Hosseini, S.H., Rezaee, S. and Hamidi, M., 2019. Magnetic brain targeting of naproxen-loaded polymeric micelles: pharmacokinetics and biodistribution study. Materials Science and Engineering: C, 100, pp.771-780.

©Daffodil International University

38. Anjum, F., Zakir, F., Verma, D., Aqil, M., Singh, M., Jain, P., Mirza, M.A., Anwer, M. and Iqbal, Z., 2020. Exploration of nanoethosomal transgel of naproxen sodium for the treatment of arthritis. Current Drug Delivery, 17(10), pp.885-897.

39. Yeganeh, F.E., Yeganeh, A.E., Yousefi, M., Farasati Far, B., Akbarzadeh, I., Bokov, D.O., Raahemifar, K. and Soltani, M., 2022. Formulation and Characterization of Poly (Ethylene Glycol)-Coated Core-Shell Methionine Magnetic Nanoparticles as a Carrier for Naproxen Delivery: Growth Inhibition of Cancer Cells. Cancers, 14(7), p.1797.

40.Kim TH, Park IK, Lee ES, Oh KT, Kim DW, Choi YW, Lee KC, Youn YS. Journal:

International Journal of Pharmaceutics. Year: 2011. PubMed ID: 21458543.

41. Alves Rico SR, Abbasi AZ, Ribeiro G, Ahmed T, Wu XY, de Oliveira Silva D. Diruthenium(ii,iii) metallodrugs of ibuprofen and naproxen encapsulated in intravenously injectable polymer-lipid nanoparticles exhibit enhanced activity against breast and prostate cancer cells. Nanoscale. 2017 Aug 3;9(30):10701-10714. doi: 10.1039/c7nr01582h. PMID: 28678269.

42. Li L, Chen Y, Wang Q, Li Z, Liu Z, Hua X, Han J, Chang C, Wang Z, Li D. Albuminencapsulated Nanoparticles of Naproxen Platinum(IV) Complexes with Inflammation Inhibitory Competence Displaying Effective Antitumor Activities in vitro and in vivo. Int J Nanomedicine. 2021 Aug 14;16:5513-5529. doi: 10.2147/IJN.S322688. PMID: 34429597; PMCID: PMC8375242.

43.Yeganeh FE, Yeganeh AE, Yousefi M, Farasati Far B, Akbarzadeh I, Bokov DO,

Raahemifar K, Soltani M. Formulation and Characterization of Poly (Ethylene Glycol)-Coated Core-Shell Methionine Magnetic Nanoparticles as a Carrier for Naproxen Delivery: Growth Inhibition of Cancer Cells. Cancers (Basel). 2022 Apr 1;14(7):1797. doi: 10.3390/cancers14071797. PMID: 35406569; PMCID: PMC8997395.

44.Yeganeh FE, Yeganeh AE, Yousefi M, Farasati Far B, Akbarzadeh I, Bokov DO, Raahemifar K, Soltani M. Formulation and Characterization of Poly (Ethylene Glycol)-Coated

©Daffodil International University

Core-Shell Methionine Magnetic Nanoparticles as a Carrier for Naproxen Delivery: Growth Inhibition of Cancer Cells. Cancers (Basel). 2022 Apr 1;14(7):1797. doi:

10.3390/cancers14071797. PMID: 35406569; PMCID: PMC8997395.

©Daffodil International University

©Daffodil International University