Design And Characterization Of Naproxen Loaded Nanocrystal Gel

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Abstract- *The present study aims to design and characterize Naproxen-loaded nanocrystal gel for topical application. Naproxen, a non-steroidal anti-inflammatory drug (NSAID), is commonly used for pain relief and inflammation but suffer from poor solubility and gastric side effects when taken orally. To overcome these problems, nanocrystals of Naproxen were prepared using the antisolvent precipitation method followed by high pressure homogenization, which helps to reduce particle size and improve dissolution. The prepared nanocrystals were then incorporated into a Carbopol 940 gel base to form a smooth and stable nanocrystal gel. The nanocrystals were evaluated for parameters such as particle size, calibration curve and zeta potential. Nanocrystal gel was evaluated for pH, viscosity, spreadability, drug content and entrapment efficiency. Zeta potential and particle size analysis confirmed the stability of the formulation. The optimised formulation (F3) showed high drug content (92.3%) and high entrapment efficiency (99.9%), confirming the effectiveness of nanocrystal in delivering Naproxen for enhanced therapeutic outcomes. Hence, the present study can be concluded that Naproxen nanocrystal formulation is a promising system for the topical delivery and it enhances the bioavailability by improving the solubility and enhanced bioavailability.*

Keywords- Naproxen, Nanocrystals, Gel, Anti-solvent precipitation, Anti-inflammatory.

I. INTRODUCTION

NAPROXEN

Naproxen is a Non-Steroidal Anti-inflammatory Drug (NSAID) of the propionic acid class that is widely used to relieve pain and inflammation associated with conditions like Arthritis, Muscle Pain, and Menstrual cramps. The NSAIDS has prominent anti-inflammatory, analgesic, and antipyretic properties.[1][2][10]

Naproxen works by inhibiting the **cyclooxygenase 1(cox)** enzymes, especially **cox -2,** for the synthesis of prostaglandins.[3][4] These prostaglandin cause pain, swelling, and inflammation. By blocking their production Naproxen provides relief from pain and inflammation Naproxen has good efficacy, but when taken orally for long duration, it can lead to side effects like gastrointestinal problems. Naproxen is available in tablets (250mg, 375mg, 500mg), suspension for children or those unable to swallow tablets, extended-release tablets for long lasting pain relief, topical gel/cream for local joint or muscle pain. [5][6][9]

- Heart burn
- Constipation
- Diarrhoea
- Ulcers
- Stomach bleeding
- Nausea

Naproxen is also effective in degenerative joint diseases of the hip and knee, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis, juvenile arthritis.[7][8]

NANOCRYSTAL

Nanocrystal are nanoparticles that are fully composed of drugs without any carriers. Drug nanocrystals are pure drug particles, having a particle size range from 1 to 1000nm, which are stabilized by stabilizers (polymeric or surfactant based).[11]Nanocrystals have highest drug loading as compared to other nano-based formulations they are safe for topical use. It is an excellent drug delivery system for BCS Class 2 and BCS Class 4 drugs. Nanocrystals provide numerous benefits such as enhanced solubility and bioavailability; they overcome toxicity problems and inappropriate absorption patterns. [12][13]These nanocrystals have great potential use in various routes such as oral, ophthalmic, dermal, parenteral, pulmonary, etc.[15]

Nanocrystals are pure drug particles suspended in using a suitable stabilizer. Hence, stabilizer is an important excipient for nanocrystal- based formulations.[16][18] They prevent the drug particles from aggregation by adsorbing at the interface. Different types of stabilizers are available. They

can be broadly classified as ionic (sodiumdodecylsulphate), non-ionic (poloxamers, tween, vitamin E ethylene glycol succinate), and polymeric (hydroxypropyl methyl cellulose, polyvinyl pyrrolidone, hydroxypropyl cellulose).[20][21]The nonionic and polymeric stabilisers provide steric hindrance, while ionic stabilizers provide electrostatic repulsion in order to stabilize the nanocrystals.[14]Nanocrystals increase the saturation solubility of the drugs which leads to increase in concentration gradient, thereby showing a potential for passive penetration after topical application, from nanocrystal-based formulations, the molecules penetrating through the skin are quickly recouped by the new molecules dissolving from the nanocrystal depot.[19]

Properties of nanocrystals

- Increased rate of dissolution
- Enhanced saturation solubility
- Enhanced stability
- Enhanced permeability[11]

Composition of nanocrystals:[15][19]

1. Stabilizer

Stabilizer plays a most important role in the nanocrystals. These stabilizers stabilize the nanocrystals and prevent the aggregation of particles. Ex: poloxamer, PVP

2. Polymers

Polymers provide the gel structure, making the formulation more spreadable and application on the skin. Ex: polyethylene glycol, PVP (polyvinylpyrrolidone)

3. Surfactants

They reduce the interfacial tension or surface energy of the nanocrystals. These also helps in maintaining stability of nanocrystals. Ex: tween 80

4. The proper selection of solvent is important for the preparation of nanocrystals

GEL

A gel is a semi solid dosage form that contains a liquid phase within a three-dimensional polymetric matrix. Gels are formed by the entrapment of large amounts of water or alcohol in a network of natural or synthetic polymers. [22] This structure gives gels a soft, jelly-like structure. Gels are prepared using gelling agents like Carbopol, HPMC, or natural gums which help form the structure. They can hold large amount of water or other solvents, making them suitable for delivering drug through the skin, eyes, nose, or vagina. Gels are widely used in pharmaceuticals, cosmetics, and personal care due to their good appearance, spread ability, and patient acceptability. [23] [26] Gel can be designed to encapsulated and release drugs in a controlled manner, either at specific location in the body or in response to certain stimuli Gels can be used as wound dressing Gels are essential in techniques like gel electrophoresis, which is used as separating and analysing DNA and proteins. Gels can be mimic the extra cellular matrix living tissue, providing support for cell growth and tissue repair [24] [25]

Nanocrystal gel is a novel topical drug delivery system in which drug nanocrystal are incorporated into a gel base (like Carbopol or HPMC) to enhance skin penetration and therapeutic effectiveness. Nanocrystals are pure drug particles with a size range of 100-1000nm. These tiny particles have high surface area, leading to faster dissolution and improved bioavailability.[19] [27] When formulation of a gel, the ease of application, patience compliance, and localized drug delivery make it a powerful system, especially for poorly soluble drugs. The combination of nanocrystals technology and gel formulation enhances both solubility and absorption, making it suitable for a wide range of topical treatments.[28] [29]

The aim of this research was to enhance the bioavailability of an anti-inflammatory drug named Naproxen by enhancing its solubility. Thus, this nanocrystal formulation plays a major role in enhancing its solubility.[30]

II. MATERIALS AND METHODS

Materials

Naproxen, ethanol, polyvinyl pyrrolidone(pvp), tween 80, distilled water, Carbopol 934.Preparation of Naproxen Nanocrystals were prepared by anti-solvent precipitation, a bottom-up method, followed by homogenisation. Solution phase was prepared by dissolving naproxen in ethanol, and anti-solvent phase was prepared by dissolving stabilizer in the water. The anti-solvent phase was stirred under homogeniser until the stabilizer dissolves; the solvent phase was added drop by drop by using a needle syringe under stirring. As each drop of naproxen solution hits the large volume of rapidly stirring water, the solubility of the naproxen decreases drastically causing the drug to precipitate as nanocrystals. Stirring is continued for 30mins at high speed to get a homogenous suspension, the suspension is centrifuged

for 15-20mins. The supernatant layer is discarded and the product (nanocrystals) was obtained.

Formulation of Naproxen Nanocrystal using Anti-solvent precipitation method

Table 1. formulation chart

(F1-F4) Ingredients	F1	F2	F3	F4
Naproxen(mg)	500	500	800	800
Tween80 (mg)	5	10	-	10
PVP (mg)	-	-	10	10
Ethanol (ml)	3	13	9	13
Distilled water (ml)	22	25	25	25

Preparation of naproxen loaded nanocrystal gel

We prepared a Carbopol gel base into which naproxen nanocrystals were incorporated. To prepare the gel base, Carbopol 934 (1%w/w) was dispersed in water, stirred for 2hrs and kept overnight for complete. The Ph was adjusted with triethanolamine. A sufficient quantity of the naproxen nanocrystal suspension was mixed in the gel base until homogenous gel is obtained.

III. RESULTS AND DISCUSSION

1. Particle size

The size of nanocrystals is a critical parameter that influences drug release, stability, and cellular uptake. Dynamic Light Scattering (DLS) is typically used to measure nanocrystal size by analysing the scattering patterns of light as it interacts with the particles. This method is especially useful in detecting variations in nanocrystal behaviour caused by Brownian motion. Instruments like the Zetasizer are widely employed in this analysis**.**

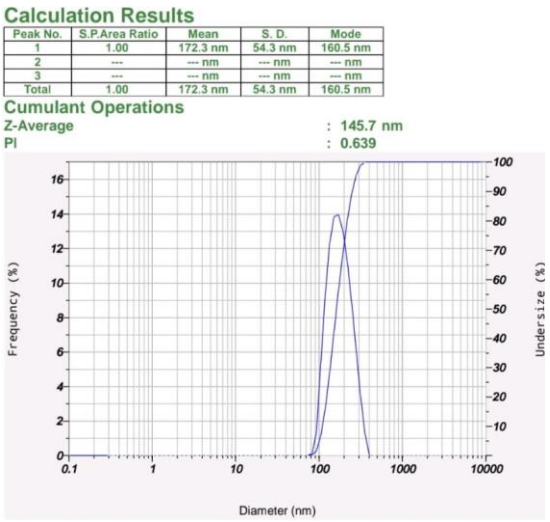
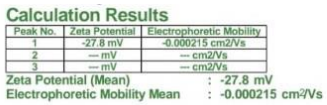


Fig 1:- Particle Size

2. Zeta potential:

Zeta potential measures the surface charge of the nanocrystals, which reflects their electrostatic stability in suspension. A higher magnitude of zeta potential—whether positive or negative—typically means the nanocrystals are less likely to aggregate over time. This parameter is measured using a Zetasizer, which operates based on the principle of electrophoretic mobility in an electric field.



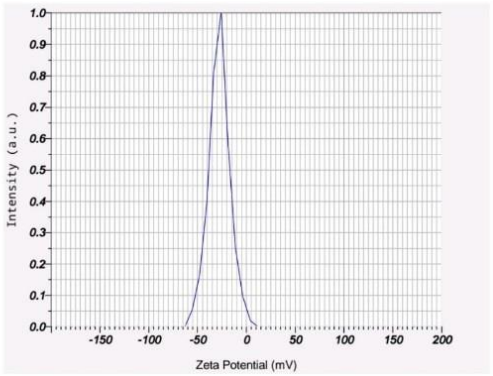


Fig 2 Zeta potential

3.Determination of total drug content

Determining the total drug content involves disrupting the Naproxen Nanocrystals to release the encapsulated drug. Isopropyl alcohol is commonly used to rupture the nanocrystals. The released drug is then quantified

using UV-visible spectrophotometry. This test ensures that the correct dosage has been incorporated in

Table 2: Determination of drug content

FORMULATION	% DRUG CONTENT
F1	91.6%
F2	88.8%
F3	92.3%
F4	90.7

3. ENTRAPMENT EFFICIENCY:

Entrapment efficiency refers to the percentage of drug successfully encapsulated within the nanocrystals compared to the total drug used. After centrifuging the formulation to separate unencapsulated drug, the supernatant is analysed. The amount of drug retained in the nanocrystals is then calculated using the formula

$$\text{Total drug concentration} = \frac{\text{Total amount of drug} - \text{Amount of drug in supernatant}}{\text{Total amount of drug}} X100$$

Table 3:- Entrapment Efficiency

FORMULATION	ENTRAPMENT EFFICIENCY
F1	92.3%
F2	89.6%
F3	99.9%
F4	90.6

4. pH

pH of the formulation was measured using a digital pH meter. The determination of the pH is done by using the glass electrode.The glass electrode is dipped into the solution and the reading which is showing on the display is noted.

Table 4:- Ph

Formulation	Viscosity (cp)
F1	3334
F2	2753
F3	2148
F4	3084

5. Spreadability:

Spreadability is the term expressed to denote the extent of area to the gel readily spreads on application to skin or the affected area. The therapeutic efficiency of the formulation also depends on its Spreadability values.

Spreadability is measured as: SML/T. The Spreadability of each sample was evaluated in triplicate by using fabricated Spreadability apparatus which consists of two glass plates. 0.5 g of sample was placed on the lower plate and the upper plate was placed on the top of the sample. Force was generated by adding increasing weight slowly at I min interval into the pan connected to the upper plate. Each sample was tested at least three times at constant temperature and exerted weight and the mean values of spread surface area on the lower plate were calculated.

Table 5:- Spreadability

Formulation	Spreadability (g.cm/s)
F1	7.15
F2	7.39
F3	6.33
F4	6.62

6. Viscosity measurements:

Viscosity of Nanocrystal gel was determined by using Brookfield viscometer. 20 ml of gel is filled in a 25 ml beaker and the viscosity was measured using spindle number 6 at 10 rpm**.**

Table 6: - Viscosity measurements

Formulation	Viscosity (cp)
F1	3334
F2	2753
F3	2148
F4	3084

IV. CONCLUSION

The present study was designed to improve the solubility of naproxen drug which has low solubility. Nanocrystal drug delivery system was approach Nanocrystals were prepared by anti-solvent precipitation method by using 2 different stabilizers tween 80 and polyvinyl pyrrolidone to know which stabilizer is good for the formulation. The nanocrystal suspension was incorporated in the prepared gel base F1,F2,F3,F4 formulations were prepared to know which

is best formulation. Formulation F3 showed the good results in drug entrapment efficiency, zeta potential, and particle size. The prepared naproxen nanocrystal gel F3 which is evaluated for pH, viscosity, spreadability, and drug content. The formulation was stable, homogenous, and showed excellent consistency without any clumps. Hence the above result we conclude that if it is possible to formulate naproxen nanocrystal for topical use. The prepared naproxen nanocrystal gel enhanced nanocrystal gel enhanced the solubility of the drug thereby leading to its increase bioavailability.

Author contribution:

Shwetha: conceptualized the study. Raghav and Abdul Noor Ulla: conducted the investigation. Mrs. Anju kp: supervised the Manuscript preparation. Balaji k Naidu: Drafted the original manuscript. Anusha E: Reviewed and edited the Manuscript. All authors reviewed and approved the final manuscript.

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