# NANO-EMULSIONS FOR DELIVERY OF BCS CLASS II NSAIDS- A REVIEW

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

Department of Pharmacy
Brac University
February 2021

## Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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# Approval

The thesis/project titled “Use of Nano-emulsion for delivery of NSAID” submitted by Hafiza Khatun (14346011) of Summer, 2014 has been accepted as satisfactory in partial fulfillment of the requirement for the degree Bachelor of Pharmacy (Hons.) on June 2021.

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## Ethics Statement

This study does not involve any kind of animal or human trial.

## Abstract

This review article manifest Non-steroidal anti-inflammatory drug (NSAID) drug delivery system based on nano-emulsified carriers. The main target is to find out a suitable nano-emulsion technique using different types of NSAIDs for their delivery system. Aceclofenac, diclofenac are used as an example of NSAID. This articles briefs mainly about the importance of solubility comparing among their onset of action, solubility, permeability etc. Their mechanism of action, and result will be discussed followed by.

**Keywords:** Nano-emulsion; Drug delivery; Nano-particle; Non-steroidal anti-inflammatory drug (NSAID); Aceclofenac.

## Dedication

Dedicated to my parents, husband and all my respected teachers.

## Acknowledgement

All the praises and thanks be to almighty Allah for giving me patience and knowledge to accomplish my thesis. Therefore, my gratitude for my supervisor Namara Mariam Chowdhury, Lecturer, Department of Pharmacy, Brac University, will never be end for giving me the golden opportunity to work with her. Through the motivation, support and guidance of her I could stay focused and continued my project. Her approach and encouragement towards this project not only allowed me to complete the project on time but also helped me in getting hands on experience better in writing. Last but not the least, I would like to express my whole heartily gratitude towards my parents because of their unconditional faith and support in achieving my goals.

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## List of Acronyms

| | |
|---|---|
| ACF | Aceclofenac. |
| BA | Bioavailability. |
| BCS | Biopharmaceutics classification system. |
| COX | Cyclooxygenase. |
| CXB | Celecoxib. |
| DFS | Diclofenac Sodium. |
| GI | Gastro intestinal. |
| HGC | Hard Gelatin Capsule. |
| NDDS | Novel Drug Delivery System. |
| NE | Nano-emulsion. |
| NEC | Nanoemulsion of Celecoxib. |
| NEG | Nanoemulgel. |
| SC | Stratum Corneum. |
| SNEDDS | Self nano-emulsifying drug delivery system. |

# Chapter 1

# Introduction

Drug delivery system is very important to get highest therapeutic effect but lowest side effect. The touch of advance science and technology introduce us to novel drug delivery system like nanoemulsion. It can protects the drug and even enhance their properties. (Chime et al., 2014)

## 1.1 NSAIDs

NSAIDs are the Non-Steroidal Anti Inflammatory Drugs. They have analgesic, anti-pyretic, anti-inflammatory, anti-arthritis properties. They can also be used to prevent blood clot. They work by inhibiting cyclooxygenase enzyme which target prostaglandin synthesis in two pathways,

- COX-1
- COX-2

There are two types of NSAIDs which are,

- Non selective and
- COX 2 selective

Due to high risk of vascular disease COX-2 inhibitors are no longer used. But because of their various properties they are vastly used in medical field to treat different kind of disease in human and even in veterinary.

Non-steroidal anti-inflammatory drugs are highly permeable but lowly soluble (FDA, 2015) in nature which slow their onset of action and causes more variability in absorption (Dekić & Primorac, 2017). Using nano-emulsifying drug delivery system can be very promising and

creates new era of drug delivery system to avoid these types of problems. Studies are extensively done on Self nano-emulsifying drug delivery system (SNEDDS) because of their advance properties of drug encapsulation though simple preparation but strong physical stability to enhance solubility thus bioavailability (BA).

## 1.2 BCS classification of NSAIDs

BCS classification is known as Biopharmaceutical Classification System. Drug substances are mainly divided based on their solubility and permeability. According to BCS there are four classes of drug substances which are,

- ❒ Class I
  - ✓ High permeability
  - ✓ High solubility
- ❒ Class II
  - ✓ High permeability
  - ✓ Low solubility
- ❒ Class III
  - ✓ Low permeability
  - ✓ High solubility
- ❒ Class IV
  - ✓ Low permeability
  - ✓ Low solubility (Services, 1977)

NSAIDs are known as BCS class II drug as most of the drugs in NSAIDs are lies in BCS class II drugs. Although a little number of them are included in BCS class I but none of them are fall into BCS class III or class IV.

| | High solubility | Low solubility | |
|---|---|---|---|
| | BCS Class I NSAIDs | BCS Class II NSAIDs | |
| **High Permeability** | ▪ Aspirin (Acetyl salicylic acid)<br>▪ Dexketoprofen<br>▪ Ketorolac<br>▪ Loxoprofen<br>▪ Oxaprozin<br>▪ Tolfenamic | ▪ Aceclofenac<br>▪ Celecoxib<br>▪ Clonixin<br>▪ Diclofenac<br>▪ Diflunisal<br>▪ Etodolac<br>▪ Etoricoxib<br>▪ Fenoprofen<br>▪ Flurbiprofen<br>▪ Flufenamic acid<br>▪ Ibuprofen<br>▪ Indomethacin<br>▪ Ketoprofen | ▪ Licofelone<br>▪ Lornoxicam<br>▪ Meclofenamic acid<br>▪ Mefenamic acid<br>▪ Meloxicam<br>▪ Nabumetone<br>▪ Naproxen<br>▪ Nimesulide<br>▪ Piroxicam<br>▪ Phenylbutazone<br>▪ Sulindac<br>▪ Tenoxicam |

*Table. 1. BCS classification of NSAIDs*

## 1.3 Importance of Solubility

A solute dissolve in a solvent is known as its solubility. (Savjani et al., 2012) In GI tract absorption rate is depends on solubility and dissolution rate. Small droplet size of the drug particle increases drug absorption from intestinal tract (Chime et al., 2014). Less soluble NSAIDs required high dose or long period of use which causes more GI problems as they increase permeability of gastrointestinal tract. For example, diclofenac is a NSAID which is naturally insoluble in water with experimental water solubility data of 2.37 mg/L as per DrugBank data (DrugBank, 2015). This less soluble nature causes slow onset of action because as per Barakat, 2009, “For this class of compounds, dissolution in the environmental lumen is

the rate-controlling step in the absorption process". Moreover, to lessen absorption variability and fasten the onset of action it is required to increase solubility and dissolution rate. (Dekić & Primorac, 2017)

## 1.4 Reason for choosing nanoemulsion

Using long period of oral NSAIDs common side effects are GI irritation, GI bleeding, GI ulcer which even lead to anemia. To avoid contact with GI topical nanoemulsion gel could be one of the best solution. Other than nanoemulsion containing oral dosage form also can be more compatible rather than convenient oral formulations. As most of the NSAIDs are in BCS class II drug so they possess high permeability but low solubility which hampered the purpose of drug delivery system. So we have to come up a solution which could enhance the solubility of NSAIDs. Nano emulsion is such a promising drug delivery system which could enhance the solubility of NSAIDs and serve the purpose of drug intake. So that less amount of drug can be enough to show maximum therapeutic effect.

Though there are also many various techniques which are used for the enhancement of the solubility of poorly soluble drugs like,

- ❒ Physical and chemical modifications of drug which include,
  - ✓ Particle size reduction

    E.g. microionization, nanosuspension
  - ✓ Crystal engineering
  - ✓ Solid dispersion
- ❒ Chemical modifications of drug includes,
  - ✓ Salt formation
  - ✓ Use of buffer

- ✓ Complexation etc.

❒ Miscellaneous methods of drug includes,

- ✓ Use of adjuvant

  E.g. surfactant, solubilizers etc.

- ✓ Supercritical fluid process

But the superiority of nanoemulsion contains,

- Intensification of drug loading capacity
- Magnification of drug solubility and bioavilability
- Minimization of patient variability
- Controlling of drug release
- Safeguarding from enzymatic degradation (Chime et al., 2014)

## 1.5 Nanoemulsion

Nanoemulsions can be formulated in both oil in water and water in oil phases. Nanoemulsion can be prepared for both hydrophobic and hydrophilic drugs. (Shaker et al., 2019) NSAIDs are mainly hydrophobic in nature. (Farah et al., 2020)

Methods of nanoemulsion preparation

The preparation of nanoemulsion can be divided into two methods based on the energy. They are also subdivided into different classes which is mention below,

A. High energy method

- ✓ High pressure homogenization
- ✓ Microfluidization
- ✓ Ultrasonication

- ✓ Jet disperser

B. Low energy method

- ✓ Phase inversion temperature
- ✓ Spontaneous emulsification
- ✓ Solvent displacement method (Shaker et al., 2019)

## 1.6 Drug delivery system

Types of drug delivery system

### 1.6.1. Parenteral Drug delivery system

Vascular and lymphatic system are responsible for parenteral drug distribution into tissue which depends on two factors. They are,

- Blood flow and
- Particle size

Size, shape, charge, nature also have effect in parenteral drug delivery system. Smaller particles like 1-20nm has increase circulation half time and do not fall into body's defense trap. In addition, positive charge particles shows wide range of phagocytosis. Therefore, hydrophilicity lessen adsorption of serum proteins. And, Rod shaped and filamentous micelles contains capacity of higher circulation time and increase cellular uptake.(Yukuyama et al., 2016)

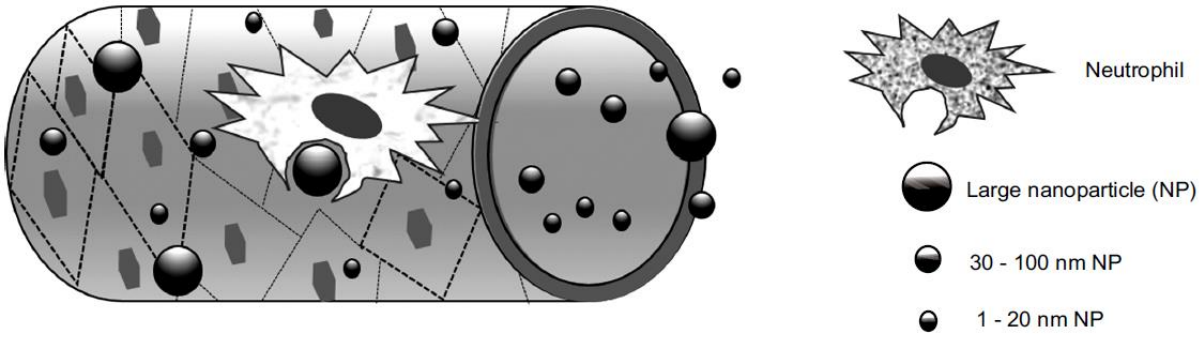


*Figure 1. Natural defense system clearance process cannot phagocyte small size nanoemulsion particle. (Yukuyama et al., 2016)*

Parenteral nanoemulsion formulation can be classified in,

- Non-ionic nanoemulsion
- Polymer associated nanoemulsion
- Drug conjugated nanoemulsion (Yukuyama et al., 2016)

Though IV rout is most convenient rout for quick onset of action with maximum drug efficacy but intravenous NE can be used to improve bioavailability of poorly water soluble drugs. (Norouzi et al., 2020)

### 1.6.2. Oral drug delivery system

The drug uptake pathway nanoemulsion for oral drug delivery system is Lipid delivery system. In GI tract emulsions causes flocculation and coalescence of droplets due to structural modification. The bioavailability is extended due to increase surface area and volume ratio of nanoemulsion. Though liquid state possess increased rate and extent of lipid digestion rather than solid state.

Nanoemulsion for oral drug delivery system can be applied in,

- Non-ionic nanoemulsion
- Polymer associated nanoemulsion (Yukuyama et al., 2016)

### 1.6.3. Topical drug delivery system

Topical NSAIDs work based on their penetration ability of skin's outer barrier SC layer. They have to reach in SC layer in sufficient amount to show their clinical effect. (Isailović et al., 2017)

Topical drug delivery of nanoemulsion is processed in,

- Non-ionic nanoemulsion
- Polymer associated nanoemulsion.

### 1.6.4. Mucosal drug delivery system

It includes natural body cavities like intranasal, ocular rout etc.

For intranasal route

- Nonionic nanoemulsion
- Polymer associated nanoemulsion
- Vaccine adjuvents

For ocular route

- Cationic nanoemulsion (Yukuyama et al., 2016)

| Drug | Rout of administration | Type of NE | Outcome |
|---|---|---|---|
| Meloxicam | Topical | Non-ionic | Lenient, biocompatible, higher therapeutic effect. |
| Aspirin | Oral | Non-ionic | Advance GI tract protection, broad distribution, more drug retention time and greater therapeutic effect. |
| Celecoxib | Imaging guided therapy | Non-ionic | Continuous drug delivery and better monitoring capacity. |

*Table 2. Nanoemulsion drug delivery system application for NSAIDs. (Yukuyama et al., 2016)*

## 1.7 Aim and Objectives

The aim and objective of this review article is to establish a new method delivering drug which will have more advantages and less side effects than the available drugs.

The main objective is improving solubility of drug for the rapid onset of action and increased absorption rate.

# Chapter 2

## Research Methodology

Thorough literature review was done to obtain all the information used in this review paper. The information was collected from various credible sources. Including different peer-reviewed journals, online scholarly database, books and newspaper. Following are the list of some of the many database that were search extensively for the present study.

- ❒ Journal database
- ❒ Library catalogue
- ❒ Subject-specific professional websites
- ❒ Newspaper database

# Chapter 3

# Results and Discussion

Nano emulsion is very important to increase drug solubility and rapid onset of action. So, it is required to use in drug delivery process of NSAIDs. Though it has some advantages but challenges are not minimal. Formulators associated with problems during the development of nanoemulsion with the variables including identification which can create problems regarding therapeutic effect and drug stability.

Through previous years there were many nanoemulsion drugs were available in various country.

For example,

Solufen®, self nanoemulsion of ibuprofen a NSAID is in HGC dosage form by Sanofi-Aventis. (Tran & Park, 2021)

Restasis®, preservative-free non-ionic nanoemulsion of cyclosporine A for dry eye syndrome

Cationorm®, preservative-free cationic nanoemulsion, used in dry eye syndrome.

Neoral®, non-ionic nanoemulsion of cyclosporine used as an oral immunosuppressive agent and

Diprivan®, nanoemulsion of propofol used as an intravenous anesthetic agent. (Yukuyama et al., 2016)

## 3.1 Aceclofenac

Firstly, the most popular drug Aceclofenac. Chronic use of orally intake aceclofenac causes GI bleeding which leads to ulcer followed by anemia. Transdermal delivery of aceclofenac using nanoemulsion drug delivery system lessen these side effects with increase permeability through

skin. This also include patient compliance, could avoid fast pass mechanism and maintains plasma drug level for a longer period of time. Aceclofenac nanoemulsion gel was made in six different formulation where aceclofenac were in same quantity. The following table will show the combination of formulation for Conventional aceclofenac gel (CG).

| 4 Aceclofenac gel | Ingradients for 100g of gel (% wt/wt) |
|---|---|
| Aceclofenac | 2 |
| Carbopol 940 | 1 |
| Isopropyl alcohol | 10 |
| Polyethylene Glycol 400 | 10 |
| Propylene glycol | 10 |
| Triethanolamine | 0.5 g |
| Distilled Water | Qs to 100 |

*Table 3. Preparation of conventional Aceclofenac gel. (Shakeel et al., 2007)*

NG1 was made by converting F1 formulation into nanoemulsion gel formulation in addition with 1% wt/wt Carbopol 940.

For nanoemulsion formulation following components were used,

Oil phase Labrafil and Triacetin (2:1)

Surfactant Tween 80

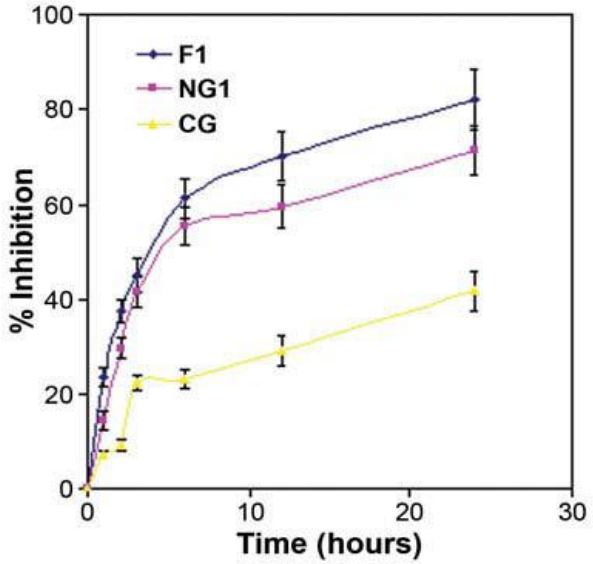
Cosurfactant Transcutol P

Surfactant and cosurfactant mix $S_{mix}$

| Formulation | Oil | Water | $S_{mix}$ | $S_{mix}$ Ratio | Oil:$S_{mix}$ Ratio |
|---|---|---|---|---|---|
| F1 | 15 | 32 | 53 | 2:1 | 1:3.53 |
| F2 | 20 | 27 | 53 | 2:1 | 1:2.65 |
| F3 | 15 | 35 | 50 | 3:1 | 1:3.33 |
| F4 | 20 | 29 | 51 | 3:1 | 1:2.55 |
| F5 | 15 | 35 | 50 | 4:1 | 1:3.33 |
| F6 | 20 | 29 | 51 | 4:1 | 1:2.55 |

*Table 4. % wt/wt Components composition of Nanoemulsion Formulation. (Shakeel et al., 2007)*

Among formulation of aceclofenac F1 contains highest drug permeation capacity, lowest droplet size, polydispersity, viscosity, and optimum surfactant and cosurfactant concentration. On skin irritation test F1 shows value of 2.12±0.45 where according to Van-Abbe et al. non-irritant drug shows value from 0 to 9. Therefore, it also exerts highest permeability capacity in in-vitro skin permeation study. The Nanoemulsion gel also shows greater therapeutic effect in in-vivo study rather than normal aceclofenac gel. (Shakeel et al., 2007)




F1. Nanoemulsion.

NG1. Nanoemulsion gel.

CG. Conventional aceclofenac gel.

*Figure 2. F1 showes highest anti-inflammatory effect. (Shakeel et al., 2007)*

## 3.2 Diclofenac Sodium

Secondly, Diclofenac sodium oral dosage also cause GI bleeding and ulcer. So nanoemulgel is produced using low energy emulsification technique using 64.07±2.65 droplet sized clove oil with 0.238±0.02 polydispersity index along -39.06mV zeta potential to avoid these side effects and increase absorption, efficacy and patient compatibility. The composition of Diclofenac sodium nanoemulgel (DFS-NEG) is given below.

| Ingredients | % Composition (w/w) |
|---|---|
| Diclofenac sodium | 1 |
| Clove oil | 10 |
| Isopropyl myristate | 5 |
| Tween 20 | 31.35 |
| PEG 400 | 14.65 |
| Peppermint Oil | 2.5 |
| Eucalyptus Oil | 2.5 |
| Glycerin | 5 |
| Carbopol 980 | 0.5 |
| Triethanolamine | Qs |
| Distilled water | Qs to 100 |

*Table 5. Composition of DFS-NEG. (Alhakamy et al., 2020)*

The in vitro drug release profile shows higher rate which is $p<0.05$ than available marketed one. The in vivo study also shows higher analgesic and anti-inflammatory property.(Alhakamy et al., 2020)

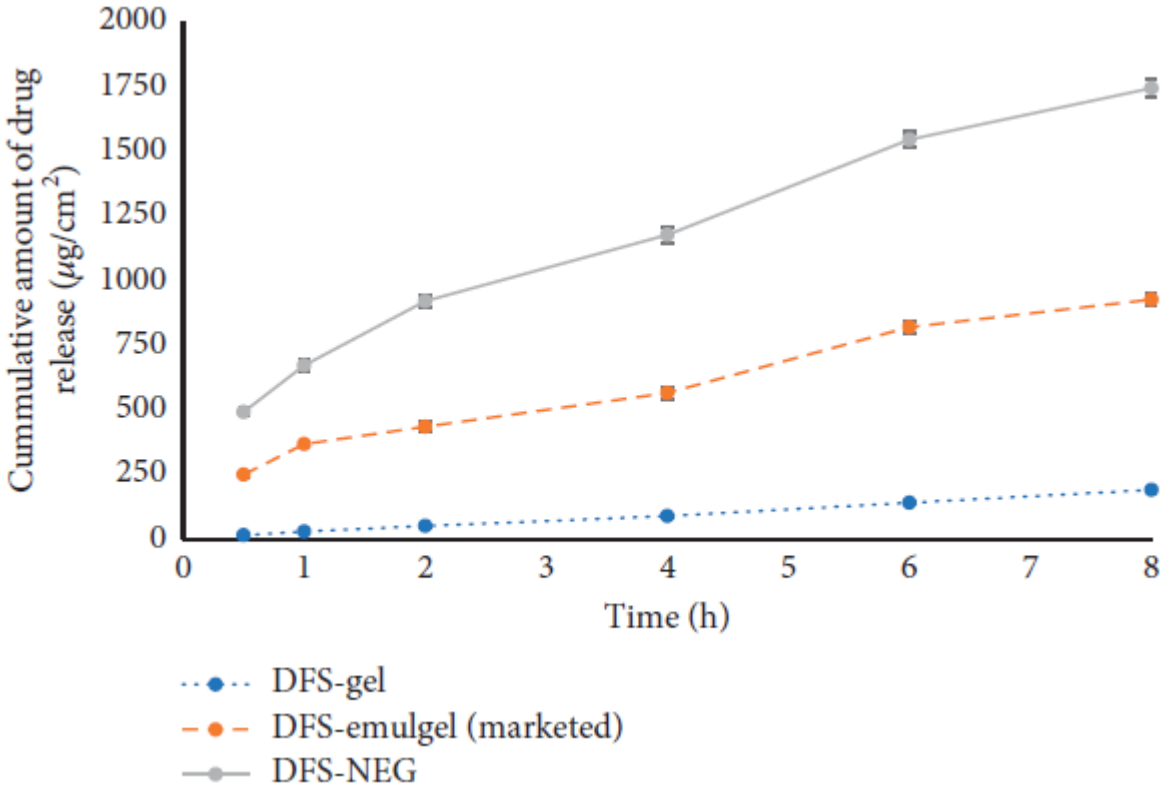



*Figure 3. Comparative curve for in vitro drug release of diclofenac conventional gel, commercialized emulgel and nanoemulsion gel. (Alhakamy et al., 2020)*

## 3.3 Ibuprofen

Thirdly, Ibuprofen shows its poor oral bioavailability due to its less soluble property. To increase solubility thus bioavailability of the drug in the GI tract nanoemulsion is prepared using SNEDDS method. The preparation of nanophase gel (NPG) use following composition,

| | |
|---|---|
| Oil Phase | Olive oil |
| Surfactant | Glycerol |

Cosurfactant Sucrose ester (SE) laurate (L-1695)

| Formulation | Oil:Surfactant | Olive Oil | Glycerol | Sucrose ester Laurate (SE L-1695) |
|---|---|---|---|---|
| A | 3:1 | 60 | 20 | 20 |
| B | 4:1 | 60 | 25 | 15 |
| C | 5:1 | 60 | 28 | 12 |
| D | 6:1 | 60 | 30 | 10 |
| E | 7:1 | 60 | 31 | 8.6 |

*Table 6. Composition of NPG formulations. (Anuar et al., 2020)*

In vitro and in vivo study shows 10.6 times higher and 2.2 folds higher respectively than the control formulation. (Anuar et al., 2020)

| Drug formulation | $C_{max}$ (µg/ml) |
|---|---|
| Control | 23.0±1.4 |
| Nanoemulsion | 53.5±1.9 |

*Table 7. Orally administrated in animal model (rat) pharmacokinetic parameters of ibuprofen (30mg/kg). (Anuar et al., 2020)*

## 3.4 Celecoxib

Finally, Celecoxib an NSAID used for various therapeutic use. Though it has no GI side effects but due to its poor solubility ocular formulation need to be modified. Because poor bioavailability of drug happens due to tear production, less absorption, transient resident time and impermeability of corneal epithelium. So, nanoemulsion of ocular celecoxib dosage form

can make a difference. Eight different celecoxib nanoemulsion, NEC-1 to 8, has prepared to perform the solubility test against control, Celecoxib suspension 1%.

| Formulation | S:C | % Oil | % S+C | % Water |
|---|---|---|---|---|
| NEC 1 | 3:1 | 50 | 40 | 10 |
| NEC 2 | 3:1 | 50 | 45 | 5 |
| NEC 3 | 3:1 | 5 | 85 | 10 |
| NEC 4 | 3:1 | 5 | 90 | 5 |
| NEC 5 | 2:1 | 5 | 85 | 10 |
| NEC 6 | 2:1 | 5 | 85 | 10 |
| NEC 7 | 2:1 | 50 | 45 | 5 |
| NEC 8 | 2:1 | 50 | 40 | 10 |

*Table 8. Composition of Celecoxib nanoemulsion. (Eaga Chandra Mohan*, 2015)*

Rabbit cornea was used as animal model to perform ex vivo cornea permeation studies. The maximum permeation percentage in 5 hours was obtained for NEC-5 which was 15.73% while using control only 1%. In vitro drug release profile shows the highest drug release profile 82.6% for NEC-3 in 24 hours. The diffusivity coefficient and apparent permeability coefficient was 46.62 and 7.23 times higher than control. (Eaga Chandra Mohan*, 2015)

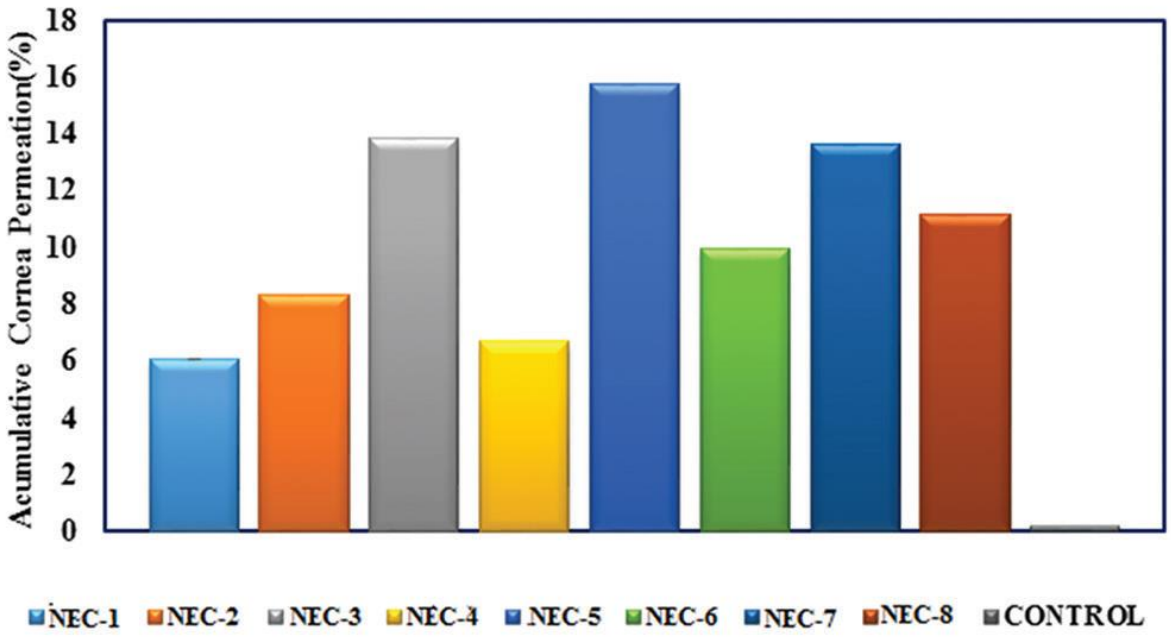



*Figure 4. Comparative permeation percent of different Celecoxib nanoemulsion formulation and control. (Eaga Chandra Mohan*, 2015)*

# Chapter 4

## Future studies

Nanoemulsion is a very promising way to future drug delivery system. They can also be use used in treatment of cancer as they can target tumor cell, macrophages and blood brain barrier due to their higher soluble nature. Though nanoemulsions are kinetically stable but thermodynamically unstable. The main concern is intereaction between drug and the various components that make up the respective nanoemulsion. They can be overcome by advancing formulation composition and other mechanical advancement. (Yukuyama et al., 2016) Self nanoemulsion can be a more advance drug delivery system. (Tran & Park, 2021) It can be more helpful in advancing nanoemulsion technology. Some of the examples are given below,

| Drugs | Oil | Surfactant | Cosurfactan/ Co-solvent | Observation |
|---|---|---|---|---|
| Flurbiprofen | Labrafill M 1944 CS | Labrasol | Transcutol HP | With improve BA the AUC value observed 3-15 times higher than the free drug. |
| Ibuprofen | Lemon essential oil | Cremophor RH 40 | Transcutol HP | In 2 hour in-vitro drug release increased 2 times higher than ibuprofen suspension |
| Indomethacin | Labrafil | Tween 80 | Transcutol HP | Solubility increased 4573 times and in vitro drug release showed approximately 2 times higher than the free drug. |

*Table 4. SNEDDS using drug list. (Tran & Park, 2021)*

# Chapter 5

# Conclusion

NSAIDs are very potent and having variety of therapeutic effect. But side effect of these drugs and solubility causes a lot of difficulties. To avoid these in the delivery of NSAIDs nanoemulsion could be a very promising way. Already there are marketed dosage form and various research also taking place in trial phase. Though it has some difficulties but having proper solution of these problems could open a new era of drug delivery system.

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