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Research

Formulation And Evaluation Of Etodolac Nanosponges By Using β-Cyclodextrin As A Polymer For Topical Drug Delivery

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Abstract

Etodolac is an NSAID (Non-steroidal anti-inflammatory drug) used in the treatment of rheumatoid arthritis, osteoarthritis, and other inflammatory conditions. ETO belongs to the Class II of the Biopharmaceutical Classification System (BCS), that is; it shows poor bioavailability and low water solubility in this study, an attempt was made to develop ETO-loaded Cyclodextrin nano sponges to enhanceits topical bioavailability by improving solubility and permeability. Nano sponges are tiny mesh-like structures, capable of carrying both lipophilic and hydrophilic substances and of improving the solubility of poorly water-soluble molecules. β Cyclodextrin based Nano sponges were prepared and loaded with ETO using Diphenyl carbonate (DC) as a crosslinker. Five NS formulations loaded with same amount of ETO, but varying cross linker concentrations with β Cyclodextrin were prepared using melting method. The entrapment efficiency of the favorable Cyclodextrin NS was found to be 65.03 % and in vitro release studies shows 83 % cumulative drug release at the end of 8 hours. The drug-excipient compatibility study of physical mixture and formulation F2 was carried out by FTIR spectroscopy. SEM analysis revealed the size of particles to be around 505 nm. Finally, ETO Nano sponge tablets were formulated for topical therapy and evaluated. These results suggest that the currently formulated Cyclodextrin nanosponge formulation appears to be a preferable drug delivery alternative for augmenting the topical bioavailability of etodolac in topical rheumatoid arthritis therapy.

Keywords: Etodolac, Nanosponges, β-Cyclodextrin, Topical delivery, NSAID.

INTRODUCTION

Drug delivery is administering a pharmaceutical compound to achieve a therapeutic effect in humans or animals[2]. For decades, acute and chronic illnesses are clinically treated through drug delivery to patients in pharmaceutical dosage forms, like tablets, capsules, pills, creams, liquids, ointments, aerosols, injectables, and suppositories, which are referred to as conventional dosage forms. Conventional dosage forms have many

disadvantages. For maintaining the effective concentration of drugs in plasma, it is often necessary to administer the drug several times. Failure in maintaining effective concentration can cause fluctuation in drug levels in plasma and lead to poor patient compliance. The conventional dosage forms delivering the minimal effective concentration of the drug at the required site or organs, sometimes tend to get into general circulation, at higher concentrations leading to unwanted side effects. In order to overcome the drawbacks of the conventional dosage form and to improve the safety and efficacy of drugs, several attempts have been made for delivering this active moiety in the existing desired concentration leading to the development of a drug delivery system. The drug delivery system is the engineered technology for targeting/controlling the release of therapeutic agents to the desired site.

β Cyclodextrin Based Nanospongesystem

The pharmaceutical and healthcare industry has been fabricating and using nanoscale materials for solving many physical, chemical, and biological problems related to disease treatment. So far nanotechnology resulted in variants of formulations like nanoparticles, nanocapsules, nanospheres, nanosuspensions, nanocrystals, nano-erythosomes, etc. Nanoparticles are obtainable in various forms like polymeric nanoparticles, solid-lipid nanoparticles, nanoemulsions, nanosponges, carbon nanotubes, micellar systems, and dendrimers.

Nano sponges are a new class of materials made of microscopic particles with a few nanometers wide cavities, in which many substances can be encapsulated. These particles can carry both lipophilic and hydrophilic substances and of improving the solubility of poorly water-soluble molecules. Nano sponges are tiny mesh-like structures that may revolutionize the treatment of many diseases. Nanosponge technology offers entrapment of ingredients and is believed to contribute towards reduced side effects by controlling the release, improving stability, increasing elegance, and enhancing formulation flexibility. In addition, nanosponges systems are nonirritating, non-mutagenic, nonallergenic, and non-toxic (12)

Cyclodextrin is a class of cyclic oligosaccharides α(1,4)glucopyranosides, and the most common commercially available ones have 6, 7, or 8 (α, β, γ) units. Structurally, CyDs have a hydrophilic outer surface and a considerably less hydrophilic central cavitythat allows them to form complexes with several molecules, thereby modifying their physicochemical properties(6). Nanosponges can be used in topical pharmaceutical products applied to the skin to enhance drug stability, reduce local irritancy, and encourage drug transport. carefully examined the impact of CDs on skin formulations and discovered that CDs are typically able to improve hydrophilic drug penetration.

Cyclodextrin (CD) and its derivatives are widely used to improve the solubilities and dissolution rates of insoluble drugs. The CD is a low molecular weight cyclic oligosaccharide formed by Glucopyranose units through α-1, 4-glycosidic bonds. The most common CD consists of 6, 7 or 8 glucose subunits called α-CD, β-CD, and γ-CD, respectively. The chair structure of the D glucopyranose causes CD to form a truncated cone structure with a hydrophobic inner cavity and a hydrophilic outer surface. The internal cavity structure of CD is composed of the C-H groupand ether oxygen bond, sothe interior is lipophilic (65,66). The primary hydroxyl groups are on the upper edge outside the cavity, and the secondary hydroxyl groups are on the lower edge outside thecavity, so the exterior is hydrophilic. CD and the drug form clathrate compounds, the lipophilic drug combines with the inner cavity, and the hydrophilic outer surface contributes to the dissolution of the drug. CD can encapsulate appropriately sized and molecularly polar compatible compounds in lipophilic cavities, with the exception of some hydrophilic compounds and macromolecules. The β-cyclodextrin (β-CD) is widely used because of its moderate cavity size, good thermal stability, non-toxicity, and low cost (66 Nanosponges (NS) are porous polymer delivery systems with small spherical particles and large porous surfaces. CD and crosslinking agents can form sponge-like porous structures called CD nanosponges (CDNS). CDNS can improve the solubilities of insoluble drugs through inclusion and non-inclusion complexations. The lipophilic inner cavity of CD and the hydrophilic channel of the porous structure of NS can combine more compounds. Compared with natural CD, CDNS have more interaction sites and higher encapsulation efficiency to improve drug solubility and drug permeability and to control drug release.

MATERIALS AND METHODS

Table 1: List of materials

Sl No	Materials	Suppliers
1	Etodolac	Yarrow Chem Pvt Ltd
2	Beta cyclodextrin	Yarrow Chem Pvt Ltd
3	Diphenyl carbonate	Yarrow Chem Pvt Ltd
4	Carbopol 934	Yarrow Chem Pvt Ltd
5	Acetone	Yarrow Chem Pvt Ltd
6	Chloroform	Yarrow Chem Pvt Ltd

7	Deionized water	Yarrow Chem Pvt Ltd
8	Methylparaben	Yarrow Chem Pvt Ltd

Table 2: List of equipment

Sl No	Equipment	Suppliers
1	Electronic balance	shimadzu ay japan 120
2	UV Spectrophotometer	shimadzu uv-1800,japan
3	FTIR Spectrophotometer	Bruker Alpha-E FT-IR, Zn Se
4	Magnetic Stirrer	Remi equipment, India
5	Zeta Sizer	Malvern Instrument
6	pH meter	Hitachi SU6600, FESEM
7	Scanning electron microscope	Hitachi SU6600,FESEM
8	freeze dryer	Alpha 1-2 LD plus

METHODOLOGY

Preformulation studies

Preformulation test is the first step in rational development of dosage forms of a drug substance. Pre-formulation study is the process of optimizing the delivery of a drug through the determination of physicochemical properties of the new compound that could affect drug performance and the development of an efficacious, stable, and safe dosage form. It gives the information needed to define the nature of the drug substance and provides a framework for the drug combination with pharmaceutical excipients in the dosage form. Hence, preformulation studies were performed on the obtained sample of the drug for identification and compatibility studies. The following reformulation studies were performed for etodolac.

Physical appearance of drug

The appearance of the drug sample was inspected and compared with IP standards.

Identification by FT-IR Spectroscopy

The spectrum obtained by infrared absorption spectrophotometry is compared with that of the reference spectrum of Etodolac. The sample is prepared by triturating 10 mg of drug with approximately 300 mg ofdry finely powdered potassium bromide. The mixture is then ground thoroughly and spread uniformly in a suitable die and compressed under vacuum at a pressure of about 800Mpa. The resultant disc is mounted on a suitable holder in the IR spectrophotometer. The spectrum will be scanned in the wavelength range of 400- 4000 cm. -1

Determination of Melting point

The melting point of Doxylamine was determined by a capillary method using melting point apparatus. The drug is placed in a thin-walled capillary tube 10-12 cm long, about 1 mm in inside diameter, closed at one end, and placed into the melting point apparatus. The reading point on providing temperature at which a solid turn into liquid is taken as the melting point of that drug. The obtained melting point is compared with the standard.

Determination of solubility

Solubility is one of the important considerations in the formulation. The solubility test in various solvents such as distilled water, methanol, ether alcohol, dimethyl formamide

Preparation Of Nanosponges Of Etodolac

Formulation of Etodolac Loaded β cyclodextrin Nanosponge Melting With Crosslinker

The cyclodextrin-based nanosponges (NS) are hyper cross-linked sponge-like polymeric structures, derived from β-cyclodextrins with a high capacity to interact with small molecules in their matrix (68). The NS can be obtained by crosslinking different types of cyclodextrin using carbonyl diimidazole, pyromellitic dianhydride, and diphenyl carbonate cross-linkers (83). It exhibits high solubilizing efficiency of hydrophobic drug molecules, and they are proposed to form inclusion and non-inclusion complexes with different drugs. Drug-loaded NS, when dispersed in aqueous vehicle forms colloidalnanosuspension with a tendency to extend drug release.

For the preparation of etodolac loaded β cyclodextrin nanosponge, Diphenyl carbonate is used as a crosslinker. Initially, cyclodextrin nanosponges were prepared with β cyclodextrin by melting at high temperatures. Various molar ratios comprising DPC (cross-linker) and β-CD (polymer) (2:1, 4:1, 6:1, 8:1, and 10:1) were chosen for the nanosponge preparation. Produce NS1, NS2, NS3, NS4, NS5 Different formulation.

Table 3: Composition of CDNS

INGREDIENTS	NANOSPONGE			
	NS1	NS2	NS3	NS4
β CYCLODEXTRIN	1 g	1 g	1g	1g
DIPHENYL CARBONATE	2 g	4 g	6g	8g

Table 4: Composition OF ETO-CDN

INGREDIENTS	FORMULATION				
	F1	F2	F3	F4	F5
Etodolac	500 mg	500mg	500mg	500mg	500mg
NS1	1 g	-	-	-	
NS2	-	1g	-	-	
NS3	-	-	1g	-	
NS4	-	-	-	1g	
NS5					1g

Procedure

Step 1: Preparation Of Nanosponge

Diphenyl carbonate was allowed to melt in a water bath at a temperature of 90^0C. The respective polymer in the correct proportion was added to the above-melted crosslinker and allowed to react for 5 hours at 90^0C in a water bath. β CD starts to meltand form a thick paste. After 5 hours of reaction, a crystalline product is formed which is scrapped off. The solid obtained was ground in a mortar, sieved, and washed with acetone and distilled water several times in order to remove the unreacted crosslinker. The resultant solid was dried at 50°C.

Step 2: Loading Of Etodolac Into Cyclodextrin Nanosponges

The solvent evaporation technique is used for drug loading. The drug became a solution after dissolving in an appropriate solvent. Add placebo nanosponges to the mixture and stir until the solvent is gone. The nanosponges' tufts were created during trituration. To remove any remaining solvent, the solid dispersion was dried in an oven forfour hours at 50 °C. With the aid of the magnetic stirrer operating at 600 rpm for 12 hours,the drug loaded nanosponges were dispersed in deionized water to create a nanosuspension. Aqueous nanosuspension of the nanosponge formulation is homogenized to minimize the particle size. Centrifugation at 2000 rpm for 10 minutes precipitated the medication that had been unloaded. Lyophilizing the supernatant and storing it in a desiccator at 20 °C

Incorporation of Etodolac Loaded Nanosponges into gel formulation

The ETO-loaded nanosponges were dispersed into distilled water with the aid of a mechanical stirrer to form a nanosuspension. For nanosponge gel formulation, a quantifiedamount of carbopol 934 was drenched in water overnight followed by stirring at 800 rpm to obtain a homogeneous dispersion. EN-CDN and methylparaben were incorporated into the carpool 934 solutions with stirring at 500 rpm, to form a smooth dispersion. Stirring was done for 15 min so that the slightest air entrapped, could leak out. Apposite quantities of triethanolamine (2% w/w) and n-methyl2-pyrrolidone (10% w/w) were mixed with this solution and assorted up until the gel was formed. The gel was transferred to a measuring cylinder and the volume was made up to 100 mL with distilled water. The so obtained gelswere filled in collapsible tubes.

Table 5: Master Formula For Gel Formulation

Sl. No	INGREDIENTS	QUANTITY (mg/ml)
1	Carpool 940	35
2	Triethanolamine	2
3	Methylparaben	3
4	Distilled water	q s

Evalution Of Nanosponges Ofetodolac

Drug excipient compatibility studies using FT-IR

The compatibility study of Etodolac with other excipients was done by using Fourier transform infrared spectroscopy (FT-IR). FT-IR spectra of pure drug and mixture of drug and other excipients were measured using

the FT-IR instrument using the KBr method. The samples to be tested were mixed with solid potassium bromide (KBr). The mixture was then pressed into a very thin pellet. The pellets were placed in the holder directly in the IR laser beam. Spectra were recorded using Shimadzu FTIR- 8400s loaded with IR solution version 1.2 software. The FT-IR spectrum of the physical mixture was compared with the standard FT-IR spectrum of the pure drug for any major interaction. The spectrum was observed for the appearance or disappearance of major and minor peaks.

Determination of PercentageYield

The prepared nanosponges of all batches were accurately weighed. The measured weight of prepared nanosponges was divided by the total amount of all the excipients and drug used in the preparation of the nanosponges, which give the total percentage yield of floating nanosponges.
It was calculated by the following equation,
% yield = practical yield/theoretical yield * 100

Determination of Entrapment Efficiency

Nanosponges equivalent to 100mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by dissolving with 100 ml 7.4 phosphate buffer solution with the aid of sonication. The solution was filtered, and the absorbance was measured after suitable dilution spectrophotometrically (UV 1700, Shimadzu, Japan) at 277 nm against the appropriate blank. The amount of drug loaded and entrapped in the nanosponges was calculated by the following formulas:
% entrapment efficiency = amount of drug actually present/theoretical drug loadexpected

Particle size analysis

The particle size distribution of the LPV solid lipid nanoparticles was determined by dynamic light scattering using a zeta sizer (Malvern zeta sizer nano ZS 90)

Morphology study using scanning electron microscopy.

The morphology of ETO-CDN was characterized using a scanning electron microscope.

***In vitro* drug release**

In vitro release studies of pure ETO, ETO loaded Nanosponges were performed using USP dissolution test apparatus II at 37±0.5˚C. 900 ml of phosphate buffer pH 7.4 buffer is taken as the dissolution media at a rotation speed of 50 rpm. ETO-loaded NS (equivalent to 100 mg) was placed into a muslin cloth. For estimation of drug release, 5ml of samples were withdrawn at 15, 30, 60-, 120-, 240-, and 480-min time intervals, replaced by an equal volume of fresh dissolution medium. The sample was filtered and analyzed by UV analysis at 277 nm after suitable dilutions.

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Evaluation Of Etodolac Nanosponges Gel

Visual Inspection

The organoleptic properties such as color, texture, consistency, homogeneity, and physical appearance of gel-containing nanosponges were checked by visual observation.

pH Measurement

Diverse gel formulation pH was recorded using a digital pH meter. 5g gel was dispersed in 45ml distilled water at 27°c and solution pH was measured

Spreadability Studies

The spreadability of etodolac nanosponges gel was measured in terms of thediameter of the gel circle produced when placed between two glass plates of definite weight. A weighed quantity of 0.5 gm gel was placed within a circle of l cm diameter premarked on a glass plate over which a second glass plate was placed. A weight of 500 gmwas allowed to rest on the upper glass plate for 5 minutes. The increase in the diameter due to the spreading of the gels was noted (diameter of the spread circle -initial diameter)

Viscosity measurement

The viscosity of the gel formulation was determined. The Viscosity was determined, by Brookfield digital viscometer (DV-E models) The sample holder taken for the viscosity measurement was filled with the sample and then inserted into a flow jacket mounted on the viscometer. the sample adaptor (spindle), rotated at an optimum speed wasused to measure the viscosity of the preparation.

Drug content

One gram of nanosponges loaded gel was accurately weighed and dissolved in phosphate buffer P^H 7.4

filter and volume was made up to 10ml with buffer solution The drug content was determined by diluting the resulting solution 10 times with phosphate buffer and measuring the absorbance at 277nm using UV spectrophotometer.

***In Vitro* drugrelease**

In-vitro permeation studies using cellophane membrane. 'The in-vitro release of nanosponges containing etodolac from the gel formulation was studied through cellophane membrane using modified apparatus the dissolution medium used was freshly prepared phosphate buffer pH 7.4. The cellophane membrane previously soaked overnight in the dissolution medium, was tied to one end of a specifically designed glass cylinder (open at both ends). 100 mg equivalent gel formulation of etodolac nanosponges was kept in the donor compartment. The cylinder was attached to a stand and suspended in 200ml of dissolution medium maintained at 37#1°C. The membrane just touches the receptor medium surfaces. The dissolution medium was stirred at 100rpm speed 1 using Teflon coated magnetic bead. Aliquots, each of 2ml volumes were withdrawn periodically at a predetermined time interval of 30, 60, 120, 180, 240,300, 360, 420,480, 540, and 600min and replaced by an equal volume of the receptor medium. The aliquots were suitably diluted with the receptor medium and analyzed by UV-Visible spectrometer at 277nm using phosphate buffer.

RESULT

Preformulation Study
Physical appearance

Sl No	Raw Material	Color	Odour
1.	Etodolac	White	Odourless

Solubility

Sl. No	SOLVENT	OBSERVATION
1	Water	Insoluble
2	Chloroform	Soluble
3	Ethanol	Freely Soluble
4	Dimethyl Formamide	Soluble

Meltingpoint

Sl. No	REFERENCE	OBSERVATION
1	145^0C- 150^0C	148^0C

The formulation studies for the drug were conducted. The λ_{max} of etodolac was found at 277 nm. By determining the organoleptic properties, it was observed that the drugwas found to be white in color and odorless. solubility study showed that etodolac is practically insoluble in water. Soluble in methanol, freely soluble in ethanol and dimethyl formamide

Drug -excipient compatibility
A compatibility study by FT -IR spectroscopy
FT-IR spectrum of Etodolac was used to study the possible interaction between Etodolac and excipients. The characteristic peaks of Etodolac with wave number and its corresponding functional group are given below.

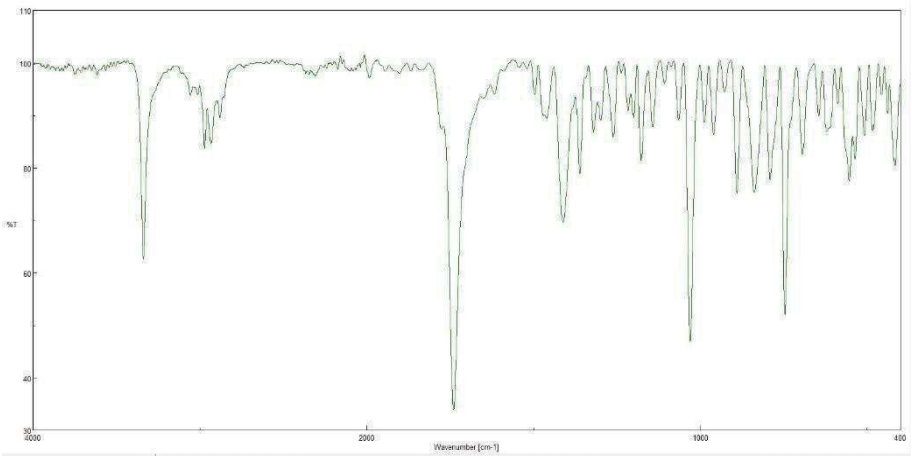

Fig 1: FTIR spectroscopy for Etodolac pure

Table 6: FTIR spectroscopic peaks of Etodolac pure

FUNCTIONAL GROUP	OBSERVED PEAKS (CM^{-1})
N-H STRECHING VIBTATION	**3338.01**
O-H STRECHING VIBTARION	**2878.48**
C=OSTRECHING VIBRATION	**1737.93**
C-H STRECHING VIBRATION	**2929.76**

The FTIR spectrum of ETO was compared with the reference spectrum, and it shows allthe characterize peaks in the relevant region. The identy of the drug was thus confirmed.

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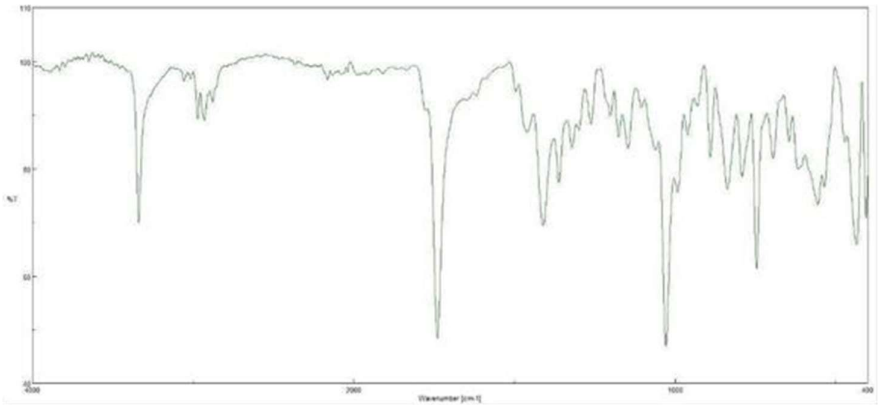

Fig 2: IR spectrum for mixture of ETO and β CD

All the important peaks are present in the FTIR spectra of the drug and excipient. The result of the study indicates no different FT-IR spectrum of drug and excipients.

Formulation Of Etodolac Loaded β Cyclodextrin Nanosponge

The present study aims to formulate drug-loaded CDNS using β CD as polymers and diphenyl carbonate as a crosslinker. Four formulations F1, F2, F3, F4, and F5 were prepared keeping the amount of drug constant while that of the polymer and crosslinker concentration varied molar concentration (1:2,1:4,1:6,1:8,1:10)

Preparation Of Nanosponges By Melting Method

In the initial step blank CDNS was prepared by melting method. When the crosslinker DPC was heated at 90^0 c it begins to melt, to this melted crosslinker polymersβ CD were added. This mixture was heated until homogenous crystalline product was formed. During melting DPC act as carbonyl group donor. The crystalline product is scrapped off sieved, dried and stored.

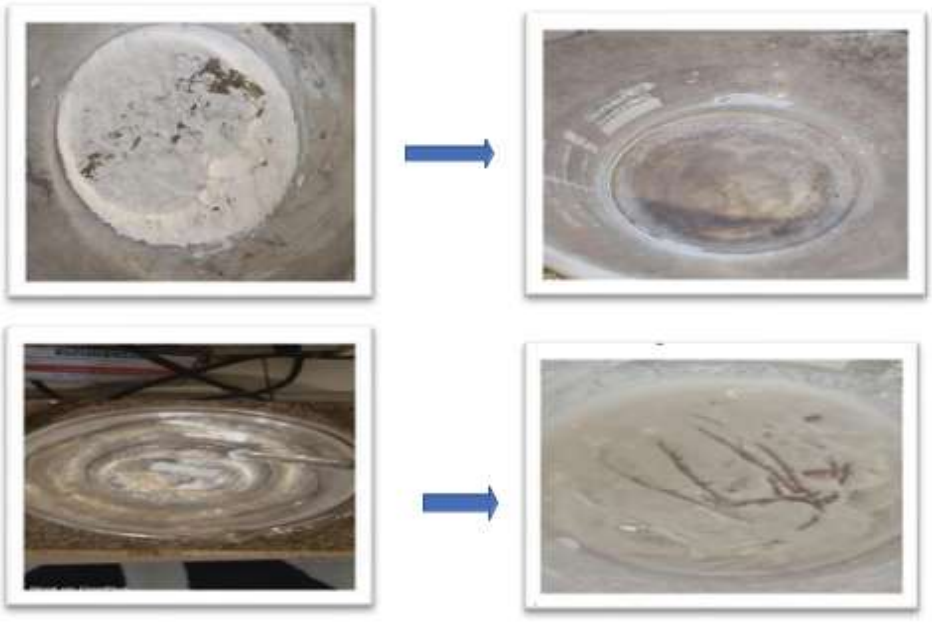

Fig 3: Preparation of CDN by melt method

Loading of the drug to the Nanosponge

In the second step, loading oF ETO was added to the suspension of blank CDNSwith continuous stirring, centrifuged, and the supernatant was freeze-dried.

Fig 4: β CD Nanosponge loaded with ETO

Characterization Etodolac Loaded CyclodextrinNanosponge Product Yield

Table 7: % Product yield of various ETO-CDNS formulations

Formulation	%Product Yield(%W/W)
F1	96.06 ± 0.11
F2	96.08 ±0.21
F3	94.08± 0.10
F4	96.0± 0.11
F5	92.0± 0.12

The product yield of all formulations was calculated**.** Product yield found to be higherfor F2.

Entrapment efficacy

Table 8: %Entrapment efficiency of various ETO-CDNS formulations

Formulation	Entrapment Efficiency (%W/W)
F1	20 ±0.42
F2	65±0.11
F3	55±0.06
F4	50±0.15
F5	17±0.16

The entrapment efficiency of different formulations was carried out, and from the results, it was evident that entrapment efficiency is higher for those Nanesponges prepared with F2 Formulation with a lesser concentration of crosslinker.

Solubility

Table 9: Solubility of various ETO-CDNS formulations

Formulation	Solubility (Mg/Ml)
F1	0.156±0.0005
F2	0.176±0.0006
F3	0.165±0.0006
F4	0.145±0.0004
F5	0.125±0.0004

Solubility of different formulations carried out and find out f2 formulation more solubili**y.**

In-vitro drug release study

In vitro drug release study was performed on four ETO- CDNS formulations F1, F2, F3, F4, and F5. In vitro, drug release studies were carried out in phosphate buffer pH 7.4 with8 hrs and determined the percentage cumulative drug release (% CDR).

Formula Action	%Cdr 0 Min	%Cdr 15 Min	%Cdr 30 Min	%Cdr 60 Min	%Cdr 120 Min	%Cdr 240 Min	%Cd R480 Min
ETO	0	0	0	2.98±0.49	4.12±0.31	6.21±0.25	7.98±0.26
F1	0	11.82±0.51	20.38±0.31	32.68±0.35	51.00±0.21	56.08±0.54	62.29±0.21
F2	0	21.05±0.62	40.65±0.15	61.00±0.14	82.02±0.21	83.12±0.35	83.00.±0.31
F3	0	20.13±0.15	35.12±0.49	58.69±0.65	76.01±	79.08±0.54	79.08±0.31
F4	0	17.13±0.15	30.12±0.49	45.69±0.65	65.01±	75.08±0.54	75.08±0.31
F5	0	13.13±0.15	25.12±0.49	35.69±0.65	55.01±	65.08±0.54	65.08±0.31

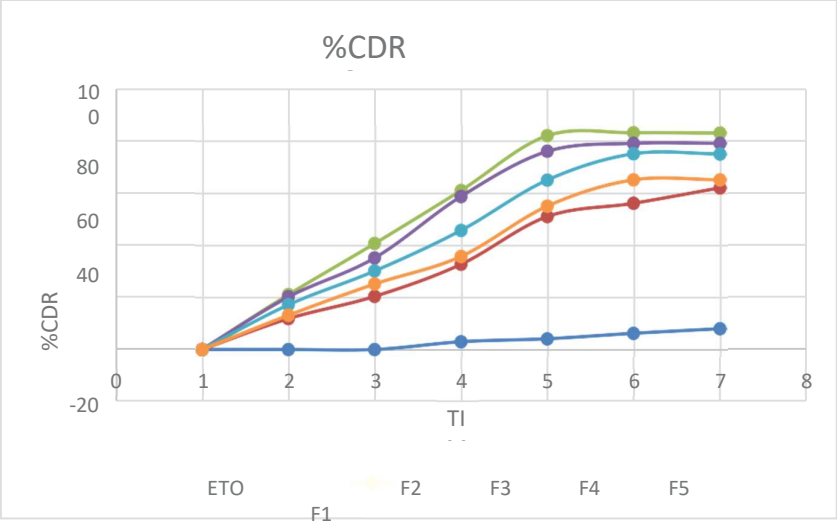

Fig 5: Drug Release

Scanning electron microscopic analysis

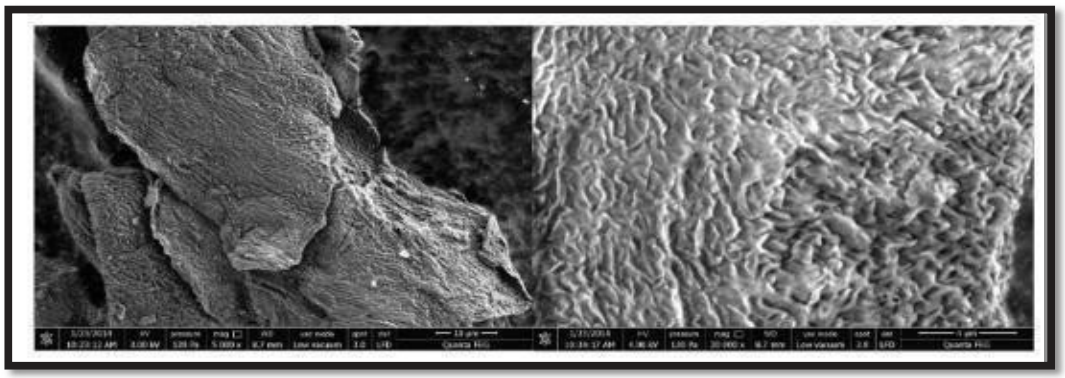

Fig 6: Scanning electron nanosponges of F2 formulation

The SEM image revealed the highly porous structure of L loaded NS formula (F3)indicating sponge-like shape.

Particle size analysis and zeta potential

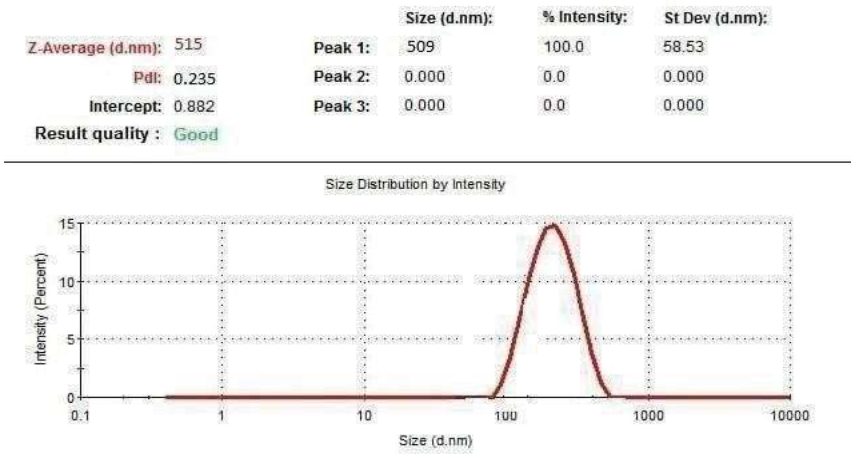

Fig 7: particles

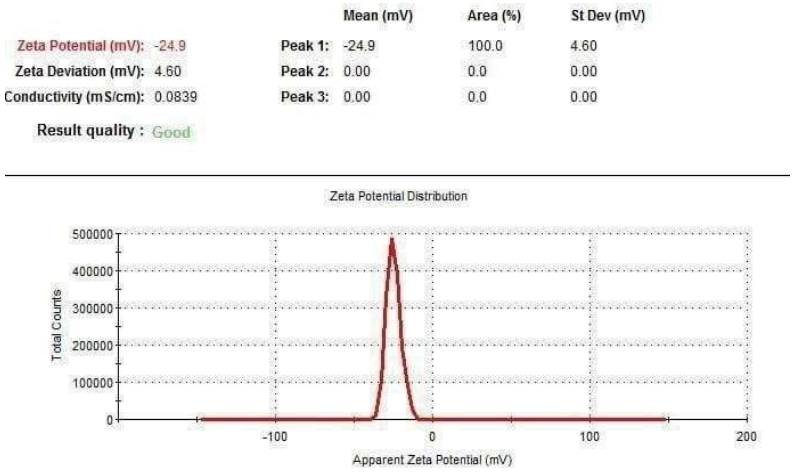

Fig 8: Zeta potential of drug

The particle size of F2 was found to be 515 nm and possessed a zeta potential of -24.9which offers good stability to ETO-CDNS

Evaluation of etodolac nanospongegel

Visual inspection	clear, transparent gel, viscous in nature with smooth texture good homogeneity
spreadability	14.2±0.81
pH	6.5
VISCOSITY	265.5 CPS

Permeability study data of etodolac gel

TIME (hr)	Drug release (%)
0	0
2	7.0312
4	17.1875
6	31.6406
8	49.4140
10	84.5703

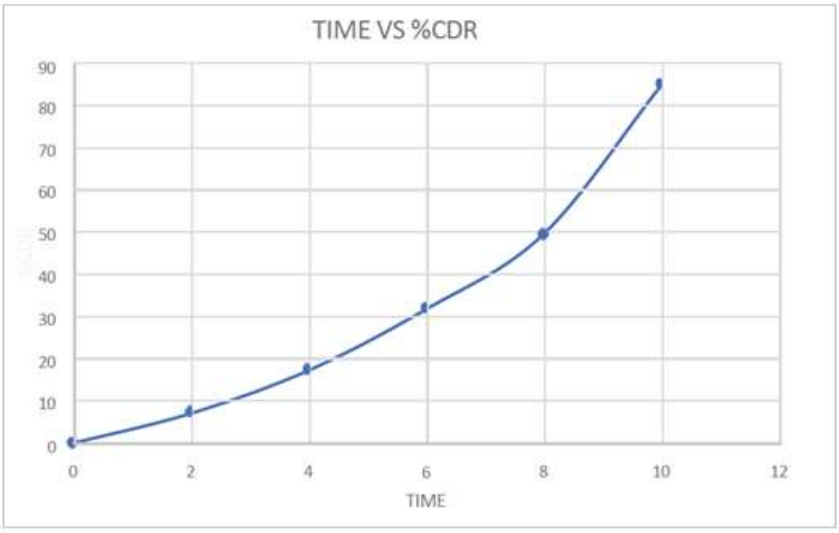

Fig 9: 20% cumulative drug diffused

SUMMARY AND CONCLUSION

Etodolac is an NSAID (Non-steroidal anti-inflammatory drug) used in the treatmentof rheumatoid arthritis, osteoarthritis, and other inflammatory conditions. ETO belongs to the Class II of the Biopharmaceutical Classification System (BCS), that is; it shows poor bioavailability and low water solubility in this study, an attempt was made to develop ETOloaded Cyclodextrin nanosponges in order to enhance its oral bioavailability by improving solubility and permeability. Etodolac's anti- inflammatory effects, like those of other NSAIDs, are caused by suppression of the enzyme cyclooxygenase (COX). This inhibits the development of periphery prostaglandins, which are essential in theregulationof inflammation. Etodolac attaches to the upper portion of the active site of the COX enzyme, preventing arachidonic acid, the enzyme's substrate, from entering the active site.Etodolac, previously assumed to be a non-selective COX inhibitor, is now known for being5–50 times more selective for COX-2 than COX-1β Cyclodextrin based nanosponges were prepared and loaded with ETO using Diphenyl carbonate (DC) as a crosslinker. Five NS formulations loaded with the same amount of ETO, but varying cross-linker concentrations with β CD and were prepared using the melting method. Evaluations like entrapment efficiency, Saturation solubility studies, *in vitro* drug release studies, etc were conducted in order to select a favorable formulation.

In vitro release studies of pure ETO, ETO-loaded Nanosponges were performed in phosphate buffer pH 7.4. After comparing the 5 formulations, F2 was chosen to proceed with further studies. The drug-excipient compatibility study of the physical mixture and formulation F2 was carried out by FTIR spectroscopy. All the major peaks present in the spectrum of pure drug were observed in the spectrum of physical mixture of drug and excipients as well as inthe spectrum of the formulation F2 with only negligible change in the position suggesting that there was no pronounced interaction present. The particle size and zeta potential were found to be 505 nm and –24.9 respectively. The morphological analysis was done for F2 by scanning electron microscopy and revealed the porous structure with a size ranging around 500 nm. Etodolac Nanosponge gel was formulated for topical therapy. *In vitro* drug release data of the formulation F2 gel 82% CDR compared to other formulation.

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