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FORMULATION AND EVALUATION OF CELECOXIB AND CURCUMIN LOADED ETHOSOMAL GEL FOR TOPICAL DRUG DELEIVERY SYSTEM

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1. INTRODUCTION

1.1. NOVEL DRUGDELIVERY SYSTEM[2,14,16]

The aim of the Novel Drug Delivery System is to provide a therapeutic amount of drug to the appropriate site in the body to accomplish promptly and then maintain the desired drug concentration. The drug delivery system should deliver drug at a rate of control by the necessarily of the body over a specified term of treatment.

A number of novel drug delivery systems have emerged encompassing various routes of administration, to achieve controlled and targeted drug delivery. Encapsulation of the drug in vesicular structure is one such system, which can be predicted to prolong the existence of the drug in systemic circulation and reduce the toxicity if selective uptake can be achieved. Consequently, several vesicular drug delivery systems such as liposomes, noisome, transferosome's and pharmacosomes were developed. Advances have since been made in vesicular drug delivery, leading to the development of this system that allows drug targeting and sustained or controlled release of conventional drug medicines.

1.2 NANO TECHNOLOGY[5,17,24]

Nanotechnology can be defined as the science and engineering involved in the design, characterization, production and applications of structures, devices and systems by controlling shape and size at nanometer scale. Nanotechnology provides solutions for several pharmaceutical drug delivery issues. For over 20 years, researchers have appreciated the potential benefits of Nanotechnology in providing vast improvements in drug delivery and drug targeting. Improving delivery techniques that minimize toxicity, improve efficacy, and offer great potential benefits to patients, and new markets for pharmaceutical and drug delivery companies.

1.3. TOPICAL DRUG DELIVERY[5,6,41]

Topical drug delivery system is defined as the application of a drug containing formulation to a skin or mucous membrane, to treat a specific cutaneous disorder (e.g. acne) or cutaneous manifestations of a generalized disease (e.g. psoriasis), with the intent of containing the pharmacological effect of the drug only to the surface or within the layers of skin or mucous membrane.

1.3.1. TYPES OF TOPICAL DRUGDELIVERYSYSTEM

Includes two types of topical drug delivery system

a) Internal- that is applied to the mucous membrane of eye (conjunctiva), ear, oropharyngeal cavity, nasal cavity, vagina or anorectal region for local activity.

b) External– that are spread or dispersed on the cutaneous surface covering the affected area.

1.3.2 CLASSIFICATION–BASEDONPHYSICALSTATE

- SOLID–Powder, Aerosol, Plaster.
- LIQUID–Lotion, Liniment, Solution, Emulsion, Suspension, Aerosol.
- SEMISOLID-Ointment, Cream, Paste, Gel, Jelly, Suppository.

1.3.4 ADVANTAGES OF TOPICAL DRUG DELIVERY SYSTEM[32]

- **Enhanced Skin Permeation:** Ethanol facilitates drug penetration across the stratum corneum18.
- **Sustained Drug Release:** Provides prolonged therapeutic effects, reducing dosing frequency19.

- **Non-Invasive and Patient-Friendly:** Improves patient compliance compared to injections or oral medications20.
- **Encapsulation of Both Hydrophilic and Lipophilic Drugs**: Increases versatility for different drug molecules21.
- **High Encapsulation Efficiency:** Ethosomes can encapsulate drugs of varying solubilities, providing flexibility in formulation.
- **Improved Bioavailability:** By bypassing the hepatic first-pass metabolism, ethosomes enhance systemic drug bioavailability.
- **Controlled Drug Release**: Sustained drug release profiles can be achieved, improving therapeutic outcomes

1.3.5 DISADVANTAGES OF TOPICAL DRUG DELIVERY SYSTEM

- Skin irritation / contact dermatitis due to drug and/or excipients
- Poor permeability of some drugs through the skin
- Possibility of allergic reactions
- Can be used only for those drugs which require low plasma concentration of action
- Enzymes in epidermis may denature the drugs
- Drugs with larger particle size are difficult to get absorbed through the skin

1.4 ETHOSOMAL DRUG DELIVERY SYSTEM[29]

The skin is the most extensive and adaptable route for systemic and topical medication administration. The stratum corneum, the skin's outermost layer, serves as the skin's most durable barrier against drug penetration, limiting medication bioavailability when applied topically. Therefore, it is crucial to research and contrast the various carriers needed for systemic medication delivery to prevent the natural skin barrier. Transdermal drug delivery is a less invasive approach to medication administration that provides controlled drug distribution, less frequent dosing, patient compliance, and prevention of first pass metabolism.[1–3] The development of liposomes heralded a new era in drug delivery research, and a variety of vesicular systems have subsequently been created.[4] Cesc and Blume also discovered transferosomes, which are malleable or elastic liposomes, in 1992. Transferosomes were then followed by the ground-breaking work of Touitou et al. which resulted in the discovery of a unique lipid vesicular system known as ethosomes.[5] The development of modified versions of liposomes was prompted by their lower size, lower entrapment efficiency, and negative zeta potential. Novel modified lipid carriers called ethosomes are made of ethanol, phospholipids, and water. In addition to phospholipids and water, which have been suggested to have improved vesicular properties and skin penetration, ethanol is present in quite high amounts in ethosomes. Ethosomes, are again divided into binary, classical, and trans ethosomes based on their contents like alcohol, have quickly emerged as a unique drug delivery system.

1.4.1 STRUCTURE OF ETHOSOMES

Ethosomes can be subdivided based on their compositions. The major differences between various ethosomes for transdermal drug delivery is shown in.

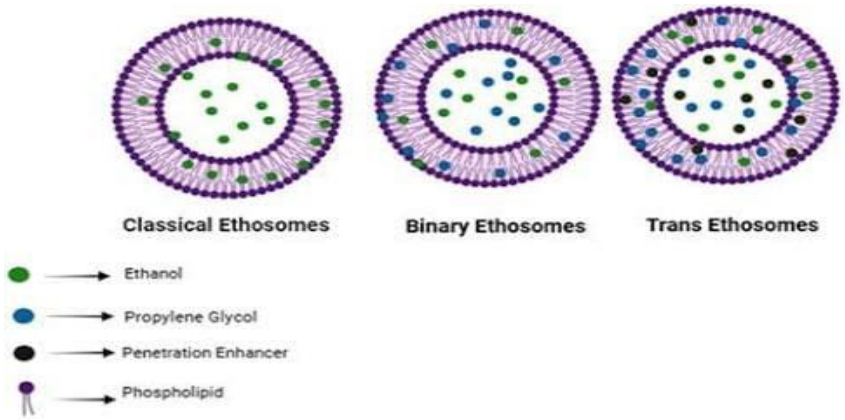


Fig No. 1: Structure Types of Ethosomes.

4.2. ADVANTAGES OF ETHOSOMES[28]

- With this delivery technology, proteins and peptides can be easily supplied
- The raw materials are harmless and readily penetrate the skin.
- This delivery technology is not just useful for pharmaceuticals; it may also be used in other industries, such as veterinary medicine and cosmetics.
- Patient adherence to the ethosomal drug delivery technology is quite high. Because the ethosomal medication is administered in gel or cream in semisolid form for high patient compliance.
- A straightforward drug delivery approach that can be used to contrast complex methods like phonophoresis and iontophoresis.
- The Ethosomal system may be immediately commercialized and is passive and non-invasive.

4.3. DISADVANTAGES OF ETHOSOMES[28]

- It might not be cost-effective.
- A low yield.

- Dermatitis or skin irritation brought on by excipients and enhancers used in medication delivery systems.

1.5 ETHOSOMES: COMPOSITION AND STRUCTURE[28]

Ethosomes are phospholipid-based nanocarriers containing high concentrations of ethanol (20-45%), which enhances skin permeability by disrupting the stratum corneum lipid matrix11. Compared to conventional liposomes, ethosomes offer superior deformability, allowing them to penetrate deeper into the skin, facilitating both topical and systemic drug delivery. Ethosomes consist of three primary components.

Phospholipids: Form the vesicle bilayer and provide biocompatibility.

Ethanol (20-45%): Enhances vesicle flexibility and disrupts skin lipids to facilitate drug penetration.

Water: Acts as a solvent and stabilizer for ethosomal vesicles. This composition allows ethosomes to encapsulate hydrophilic, lipophilic, and amphiphilic drugs, making them versatile carriers for dermatological and transdermal applications.

This composition allows ethosomes to encapsulate a wide range of drugs, including hydrophilic, lipophilic, and amphiphilic molecules, making them versatile carriers for diverse therapeutic applications.

Ethosomes enhance transdermal drug delivery through a dual mechanism:

1.Ethanol Effect: Ethanol increases skin permeability by disrupting intercellular lipid organization in the stratum corneum.

2. Flexible Vesicular System: The deformable ethosomes penetrate through the skin layers and deliver drugs into deeper tissues.

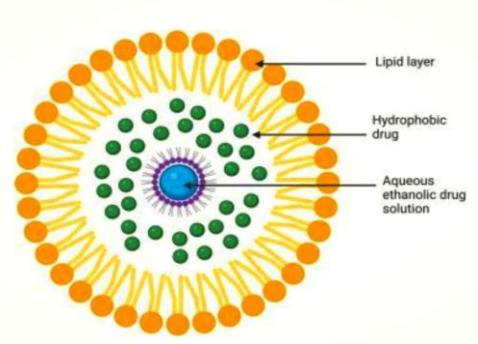


Fig no. 2: Structure Of Ethosomes.

ADVANTAGES OF ETHOSOMES[28]

Ethosomes offer several advantages over conventional drug delivery systems**.**

- **Enhanced Skin Permeation:** Ethanol facilitates drug penetration across the stratum corneum18.
- **Sustained Drug Release:** Provides prolonged therapeutic effects, reducing dosing frequency19.
- **Non-Invasive and Patient-Friendly:** Improves patient compliance compared to injections or oral medications20.
- **Encapsulation of Both Hydrophilic and Lipophilic Drugs:** Increases versatility for different drug molecules21.
- **High Encapsulation Efficiency:** Ethosomes can \encapsulate drugs of varying solubilities, providing flexibility in formulation.
- **Improved Bioavailability:** By bypassing the hepatic first-pass metabolism, ethosomes enhance systemic drug bioavailability.
- **Controlled Drug Release: Su**stained drug release profiles can be achieved, improving therapeutic outcomes.

DISADVANTAGES OF ETHOSOMES[28]

- High ethanol concentration may cause skin irritation, dryness, or erythema in sensitive individuals.
- Ethanol evaporation during storage may reduce formulation stability.
- Drug leakage may occur during prolonged storage.
- Preparation requires careful optimization of formulation variables.
- Phospholipids and other raw materials increase
- production cost.

1.6 THEORIES ON ETHOSOMES PHASE STRUCTURE[28]

A. The Ethanol Effect (Skin Disruption)

This theory focuses on how the high alcohol content in ethosomes changes the outer layer of the skin (the stratum corneum).

1. Lipid Fluidization: Ethanol interacts with polar head groups of skin lipids, reducing their tight packing density and making the lipid matrix more fluid.

2. Barrier Reduction: By lowering the phase transition temperature of skin lipids, ethanol temporarily weakens the skin's barrier function and creates small, flexible pathways.

B. The Ethosomes Effect (Vesicle-Driven Delivery)

This theory describes how the soft vesicles themselves move through the skin after ethanol has altered the barrier.

1. Vesicle Deformability: Because ethosomes contain high levels of ethanol, their own lipid membrane is soft, highly flexible, and malleable.

2. Squeezing Through Pores: Instead of breaking apart immediately, the squishy ethosome vesicles squeeze through the tiny, loosened intercellular spaces in the

3. Fusion and Release: Once deeper inside the skin layers, the vesicles fuse with skin lipids to release their cargo in a slow, controlled manner.

1.7 Method of Preparation[28]

Ethosomal formulations can be prepared using various methods, including the cold method, hot method, classic mechanical dispersion method, and classic method. These techniques are simple, cost-effective, and adaptable for both laboratory-scale preparations and

industrial production, making them a practical option for large-scale pharmaceutical manufacturing.

a) Cold Method

The cold method is the most widely used approach for preparing ethosomal formulations. In this method, phospholipids, the drug, and other lipid components are dissolved in ethanol in a covered vessel at room temperature while being stirred vigorously using a mixer. Propylene glycol or another polyol is added during the stirring process. The mixture is heated to 30°C in a water bath. Separately, water is heated to the same temperature and added to the mixture while stirring for 5 minutes. The size of the ethosomal vesicles can be reduced to the desired level using sonication or extrusion techniques. The final ethosomal formulation is stored under refrigeration to maintain stability.

b) Hot Method

In the hot method, phospholipids are dispersed in water by heating in a water bath at 40°C until a colloidal solution is formed. Separately, ethanol and propylene glycol are mixed and heated to the same temperature. Once both mixtures reach 40°C, the organic phase is added to the aqueous phase. Depending on the hydrophilic or hydrophobic nature of the drug, it is dissolved in water or ethanol before being added. The size of the ethosomal vesicles can be adjusted using probe sonication or extrusion techniques.

c) Classic Mechanical Dispersion Method

In this method, soya phosphatidylcholine is dissolved in a mixture of chloroform and methanol (3: 1 ratio) in a round-bottom flask. The organic solvents are removed using a rotary vacuum evaporator at a temperature above the lipid transition temperature, resulting in the formation of a thin lipid film on the walls of the flask. Residual solvents are further removed by leaving the flask under vacuum overnight. The lipid film is then hydrated by adding a hydroethanolic mixture containing the drug at various concentrations, with the flask rotating at an appropriate temperature to facilitate the formation of ethosomes.

d) Classic Method

In the classic method, the phospholipid and drug are dissolved in ethanol and heated to 30°C ± 1°C in a water bath. Double-distilled water is added in a fine stream to the lipid mixture under constant stirring at 700 rpm in a closed vessel. The resulting vesicle suspension is homogenized by passing it through a polycarbonate membrane using a hand extruder for three cycles, resulting in a stable ethosomal formulation.

1.8 Applications of Ethosomes[28]

a. Dermatological Disorders

- Psoriasis and Eczema: Ethosomes enhance the delivery of corticosteroids and immunomodulators, providing rapid relief and reducing systemic side effects.
- Acne Treatment: Ethosomal formulations of antibiotics like clindamycin improve skin penetration and reduce bacterial resistance.

b. Fungal Infections

- Clotrimazole and Ketoconazole: Ethosomal gels show superior efficacy in treating tinea and candidiasis by delivering antifungal agents to deeper skin layers.
- Terbinafine: Enhanced bioavailability and reduced recurrence rates have been observed with ethosomal delivery.

c. Transdermal Drug Delivery

1. Hormone Replacement Therapy

- Ethosomes effectively deliver estradiol and testosterone, ensuring steady plasma levels.

2. Pain Management

- Drugs like diclofenac and lidocaine exhibit prolonged analgesic effects when delivered via ethosomes.

3. Vaccination

- Ethosomes are being explored as carriers for transdermal vaccines, enhancing immunogenicity and patient compliance.

4. Cosmeceuticals

- Ethosomes are increasingly used in anti-aging, skin whitening, and moisturizing formulations, leveraging their ability effectively to deliver Limitations and Challenges active ingredients.

1.9 SKIN

1. Epidermis- outer layer
2. Dermis-beneath the epidermis
3. Hypodermis- inner layer

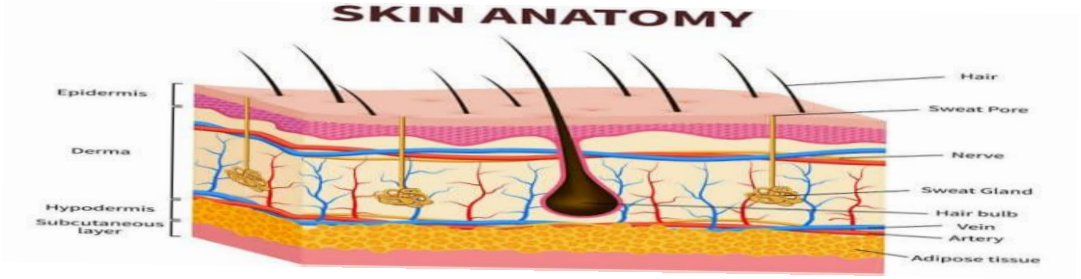


Fig No. 3: The Layers Of The Skin.

1. The epidermis

The epidermis (outer layer) contains no blood vessels and is divided into five layers. Cells move from the base of the epidermis up to the surface, changing shape and structure as they go. The epidermis is made up of stratified squamous epithelium or hardened cells which play a role in the skin's protective function. This is referred to as the stratum corneum. Epidermal cells line the hair follicles, sebaceous glands and sweat glands.

2. The dermis

The main function of the dermis is to provide physical support and nutrients to the epidermis. The two layers identified within the dermis are the papillary layer and the reticular layer. Key substances found in the dermis include elastin, fibrillin and collagen (which helps give support and protection), all of which will decrease with age. The dermis also contains nerve endings, sweat glands, sebaceous gland, hair follicles, and blood vessels. The papillary dermis contains smaller blood vessels which supply oxygen, elastic fibers and nutrients to the lower epidermis.

3. The hypodermis

The skin is supported by a layer of fatty tissue. The fatty area helps to act as a cushion to protect the body and is also important for insulation.

1.9.1 PENETRATION OF DRUG THROUGH HUMAN SKIN

- The skin is the largest organ of the body, with a total area of about 20 square feet. The skin protects us from microbes and the elements, helps regulate body temperature, and permits the sensations of touch, heat and cold.
- Waterproof barrier and creates our skin tone.
- The dermis, beneath the epidermis, contain tough connective tissue, hair follicles, and sweat glands.
- The deeper subcutaneous tissue (hypodermis) is made of fat and connective tissue.

1.9.2 PENETRATIONPATHWAYS

here are three penetration pathways available for topically applied drugs.

- Intercellular
- Intracellular
- Follicular Page

1. Intercellular

It is defined as the transport of drugs through junction between the epithelial cells.

2. Intracellular

It is defined as passage of drugs across epithelial cells.

3. Follicular

Here the hair follicle act as a pathway for penetration of topically applied drugs.

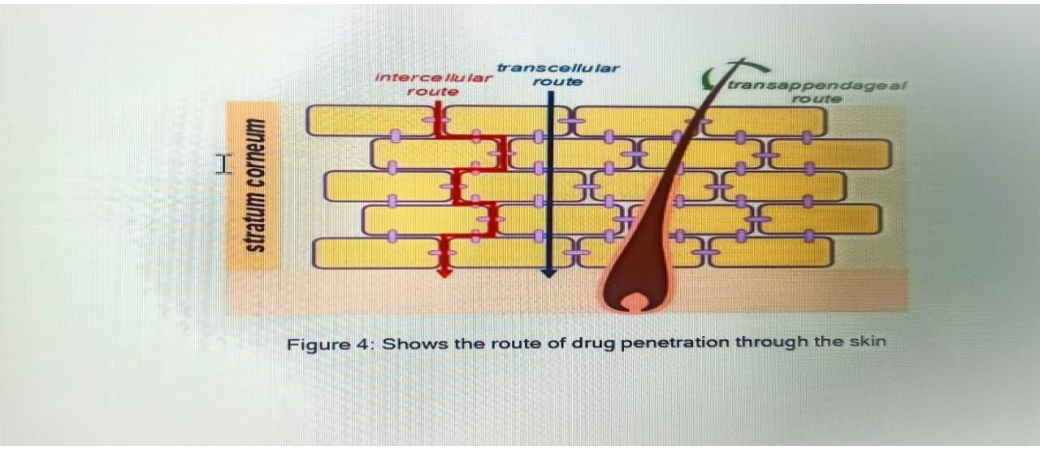


Figure No 4 Shows the route of drug penetration through the skin.

2. EVALUATION OF ETHLSOMAL GEL

1. Appearance
2. PH
3. Viscosity
4. Spreadability
5. Stability studies.
6. Release kinetics

3. DRUGPROFILE[39]

[6.1 CELECOXIB]

celecoxib is a non-steroidal anti-inflammatory (NSAID). This drug is still among the most widely drugs in the world. Celecoxib is used in the treatment of pain and inflammation, associated with rheumatoid arthritis, and several other inflammatory disorders. Celecoxib is a COX-2 specific inhibitor, promoting a reduction of the inflammatory process and maintaining normal physiological levels of proteinoids in the stomach and kidney. It appears to be a gastrointestinal safety profile superior to the traditional NSAID.

A. IUPAC NAME: 4- [5-(4-methyl phenyl)-3-(trifluoro methyl)-1H-pyrazole-1-yl] benzene sulfonamide.

B. Molecular structure

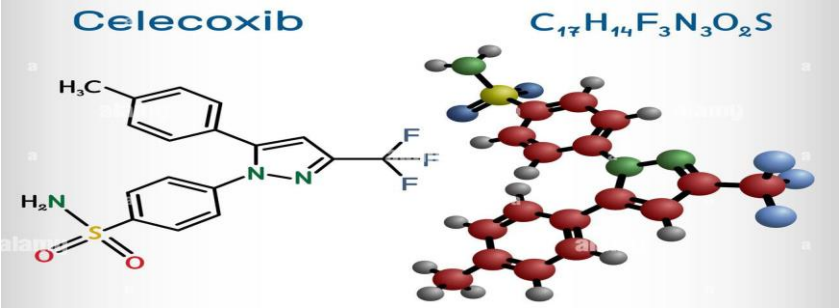


Figure No. 5: Structure Of Celecoxib.

C. Category: Non-steroidal anti-inflammatory drug (NSAID), first specific inhibitors of cyclooxygenase-2(COX)
D. Molecular formula: C17H14F3N7O2S
E. Molecular weight: 381.37
F. Description: white or almost white, crystalline or amorphous powder.
G. Solubility: soluble to freely soluble in methanol, soluble in ethanol, practically insoluble in water.
H. Melting range: 161 to 162 ° C
I. Peak plasma concentration: 3 hours
J**. Recommended daily dose**: 200mg taken once daily or in two divided doses. +
K. Mechanism of Action: Inhibits the cyclooxygenase-2 (COX-2) enzyme, reducing the synthesis of prostaglandins involved in pain and inflammation, while sparing COX-1 (which protects the stomach lining).
L.Indications: •Osteoarthritis •Rheumatoid arthritis •Ankylosing spondylitis •Acute pain •Primary dysmenorrhea •Juvenile idiopathic arthritis (in children ≥2 years)
M. Route of Administration: Oral, topical, Intramuscular, transdermal etc...

Side Effects
- Headache, dizziness
- Hypertension
- Dyspepsia, abdominal pain
- Increased risk of cardiovascular events (e.g., MI, stroke)
- Rare: skin rash, liver enzyme elevation

Contraindications
- Known sulfonamide allergy
- History of cardiovascular disease
- Peptic ulcer or GI bleeding
- Severe hepatic or renal impairment

Precautions
- Monitor BP, renal function
- Use lowest effective dose for the shortest duration
- Avoid in late pregnancy (risk of fetal complications)

4. DRUG PROFILE: CURCUMIN [BCS CLASS 4]
DRUG NAME: Curcumin
BOTANICAL NAME: Curcuma longa L
FAMILY: Zingiberaceae.
Chemical formula: $C_{21}H_{20}O_6$
IUPAC Name: (1E,6E)-1,7-bis (4-hydroxy- 3-methoxyphenyl) -1,6- heptadiene-3,5-dione
Molecular Weight: 368.38 g/mol
Melting Point: 181-183°C
Solubility: Extremely low water solubility and soluble in Ethanol and Acetone

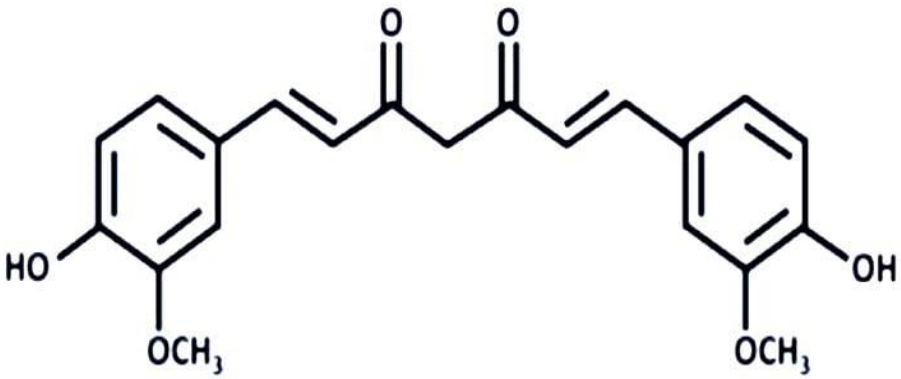


Fig No. 6: Structure Of Curcumin.

5. DISEASE PROFILE
OSTEO ARTHRITIS[27]

- Osteoarthritis (OA) is a chronic degenerative joint disease characterized by progressive cartilage damage.
- It commonly affects the knee, hip, hand, and other weight-bearing joints.
- Major symptoms include joint pain, stiffness, swelling, tenderness, and reduced mobility.
- Treatment includes exercise, physiotherapy, analgesics, NSAIDs such as celecoxib, and surgery in severe cases.

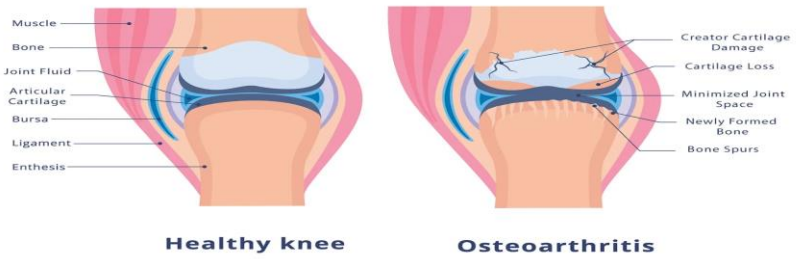


Fig No. 7: Image Of Osteo Arthritis.

6. EXPERIMENTALWORK PRE FORMULATION STUDIES

Pre-formulation testing was an investigation of physical and chemical properties of a drug substance alone. It was the first step in rational development of dosage form.

6.2 IDENTIFICATION OF DRUG[7,32]

A] Identification of drug by FTIR Spectroscopy

The FTIR study was carried out to identify the drug. The infrared spectrum of celecoxib was determined on Fourier transform Infrared Spectrophotometer using the KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was performed by using the FTIR spectrophotometer. Absorption maximum in spectrum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum.

B] Determination of Melting Point[3]

A small amount of drug was loaded in a capillary tube where one of the capillary tubes was closed and kept in the melting point. Apparatus and temperature were noted when drug melts.

6.3 Determination of λ max [Methanol][29]

The stock solution of celecoxib was prepared using methanol. The absorbance of Celecoxib was scanned by a UV-Visible spectrophotometer from a wavelength of 400-200nm. From the standard stock solution, all the required concentrations were prepared using methanol. The spectrum shows maximum absorbance at 254nm, was selected as the wavelength (λ max) and utilized for analysis, in the present investigation. A standard plot was drawn using the data obtained.

6.3.1 Procedure for determination of λ max using methanol

10 mg of celecoxib was weighed accurately and transferred into 100ml(100mcg/ml) volumetric flask and dissolved in methanol. After dissolution, the volume was made up to the mark with methanol. Further dilution was made by Pipetting 10ml into 100 ml (10 mcg /ml) volumetric flask to acquire solution made up of pbs 7.4. The maximum absorption of the standard solution was scanned between the 200-400 nm region on uv spectroscopy.

6.4. Preparation or determination of λ max of phosphate buffer 7.4[38]

1.083g of sodium dihydrogen ortho phosphate and 3.258g of disodium hydrogen phosphate is dissolved with 100 ml of distilled water, stirred continuously until it is completely dissolved. After dissolved, make up 200 ml of distilled water.

6.5. Standard curve of celecoxib in methanol

10 mg of celecoxib was weighed accurately and transferred into 100ml(100mcg/ml) volumetric flask and dissolved in methanol. After dissolution, the volume was made up to the mark with methanol. Further dilution was made by Pipetting 10ml into 100 ml (10 mcg /ml) volumetric flask to acquire solution made up of methanol. Further dilution was made by pipetting 1ml ,2ml, 3ml, 4ml and 5ml into 10mlvolumetric flask acquire solution made up with pbs 7.4. The absorbance measurement of these solutions was carried out against pbs 7.4 as blank at 254 nm. A celecoxib was plotted.

6.6. Standard curve of celecoxib in phosphate buffer 7.4

To establish Celecoxib standard curve, a solution in stock was come about in 10 mg of Celecoxib powder, dissolved in ethanol (50 ml) through the stirring of multiple minutes and accomplishing 100 ml(100mcg/ml)

volume in ethanol further diluted in phosphate buffer contains (pH 7.4). Further dilution was made by pipetting 10ml into 100ml(10mcg/ml) volumetric flask to acquire solution made up with phosphate buffer 7.4. Further dilution was made by pipetting 1ml, 2ml, 3ml, 4ml and 5ml into 10mlvolumetric flask acquire solution made up with pbs 7.4. The absorbance measurement of these solutions were carried out against pbs 7.4 as blank at 254 nm. A celecoxib was plotted.

7. METHOD OF PREPARATION AND EVALUATION OF CELECOXIB AND CURCUMIN LOADED ETHOSOMES[33,28]

COLD METHOD

At room temperature, with vigorous shaking, ethanol is dissolved in the phospholipids, medicine, and other lipid components. The jar is then heated to ±30°C. This is widely used and is referred to as the "cold approach." In another beaker, water is heated to ±30°C before being introduced and continuously swirled into the initial mixture. Vesicles start to emerge after 5 min of churning. It's important to keep produced vesicles cold.

METHOD OF PREPARATION OF CARBOPOL GEL

Preparation of carbopol gel base 1171Carbopol gel was prepared using Carbopol 934 as a gelling agent in 1% w/w concentration with distilled water using mechanical stirrer. Accurately weighed amount of Carbopol 934 was taken, dispersed in distilled water with mild stirring and allowed to swell for 24 hr. To obtain 1% gel. Other excipients were also added with continuous stirring.

INCORPORATION OF ETHOSOMAL SUSPENSION INTO GEL

Incorporation of Ethosomes: The Ethosomal suspension (containing the active ingredients Celecoxib and Curcumin) was introduced into the Carbopol gel base.

Controlled Mixing: The addition was performed slowly with continuous stirring at 700 rpm to ensure uniform distribution within the polymer matrix**.**

Environmental Control: The process was conducted in a closed vessel to prevent solvent evaporation and maintained at a constant temperature of 30°C to preserve the stability of the ethosomes.

Neutralization and Gelation: The acidity of the mixture was adjusted to a neutral Ph by adding triethanolamine, which triggers the thickening of the carbapol gel to get an optimum consistency.

Table No. 4 Formulation chart for celecoxib and curcumin loaded Ethosomal gel.

S.NO	Celecoxib (mg)	Curcumin (mg)	Soya lecithin (gm)	ETHANOL (ml)	PG (ml)	CARBOL 934 (Gm)	MP (mg)	WATER (ml)	TEA (ml)
1.	50	45	0.12	15	5	1	0.10	100	Q.S
2.	50	45	0.10	15	5	1	0.10	100	Q.S
3.	50	45	0.8	15	5	1	0.10	100	Q.S
4.	50	45	0.6	15	5	1	0.10	100	Q.S
5.	50	45	0.4	15	5	1	0.10	100	Q.S
6.	50	45	0.2	15	5	1	0.10	100	Q.S



Figure No: 8 prepared ethosomal gel.

8. Scientific Evaluation of Ethosomal gel[34]

A] Optical Microscopy

The Ethosomal dispersions prepared were observed under binocular compound microscope at 10X and 40X magnification for studying the shape and surface morphology.

B] Particle Size and Polydispersity Index[44]

Particle size (z-average diameter) and polydispersity index (as a measure of particle size distribution) of celecoxib loaded Ethosomal dispersion is performed by dynamic light scattering also known as photon correlation spectroscopy (PCS) using a Malvern Zeta sizer 3000 Nano S (Malvern instruments, UK) at 25°C. Prior to measurements all samples were diluted using

ultra–purified water to yield a suitable scattering intensity. The diluted Ethosomal dispersion was poured into a disposable sizing cuvette which is then placed in the cuvette holder of the instrument and analyzed. Air bubbles were removed before measurement. Monodisperse samples have a lower PDI value, whereas higher PDI value indicates a wider particle size distribution and the polydisperse nature of the sample can be calculated by following equation.

PDI = d/d avg

d is the width of distribution denoted by SD,

d avg is the average particle size denoted by MV (nm) in particle size data sheet.

Table No. 5 Polydispersity Index By Fda.

PARTICLE PDI RANGE	FDA REGULATORY INTERPRETATION	ACCEPTABLE LEVEL
< 0.10	High uniform Monodisperse	Excellent quality
0.10-0.20	Narrow distribution profile	Highly acceptable
0.21-0.30	Moderate/Maximum safe Threshold	Acceptable limit
> 0.30	Heterogeneous/multi-population	Unacceptable/Bad

C] SEM[22,19]

The prepared samples of ethosomes are coated with a gold film under vaccumfor2min. The specimens are transferred to an ISI ABT SX-40A scanning electron microscope and digital images captured.

D] Determination of percentage drug content[44]

5 ml of dispersion was taken and pH7.4 phosphate buffer saline Was used as blank, and the samples were analyzed spectrophotometrically at 254nm.

E] Determination of percentage entrapment efficiency[44]

The %EE of the vesicles was determined using centrifugation technique. The vesicular dispersion was centrifuged for 20 min. Supernatant containing unentrapped drug was withdrawn and measured UV spectrophotometrically at 254nm against phosphate buffer saline pH 7.4. The amount of drug entrapped in Ethosomes was determined by.

$$EE\ \% = \frac{T-C}{T} \times 100$$

were,

Total amount of drug calculated in both supernatant and sediment.

C=Drug in supernatant.

F] In Vitro drug release[18]

In-vitro drug release study was performed by using Modified Franz diffusion cell on egg membrane in phosphate buffer solution (pH 7.4). The egg membrane was mounted horizontally on the receptor compartment of Franz diffusion cell. The effective permeation area of donor compartment exposed to receptor compartment was 2cm2 and capacity of receptor compartment was 30ml of phosphate buffer saline (pH 7.4) maintained at 37± 0.5□C and stirred by a magnetic bar at 100rpm. Transferosomes gel formulation equivalent to 5mg drug was placed on the skin and the top of the diffusion cell was covered. At appropriate time intervals 5ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh phosphate buffer (pH 7.4) to maintain sink conditions. The samples were analyzed at 254 nm.

G] ZETA POTENTIAL[44]

Zeta potential was measured to evaluate the surface charge and stability of Ethosomal vesicles. It indicates the degree of electrostatic repulsion or attraction between particles, Ethosomal systems typically show values in the range of -10 to -20 mV, indicating moderate stability.

8.2. Preparation of Ethosomal gel[28]

The Ethosomal gel was obtained by adding weighted amount of carbomer (1%w/w) in distilled water and kept for half day forgetting to swell of carbomer and the triethanolamine drop by drop up to pH 7. Propylene glycol is added to adjust the consistency. The obtained gel was then diluted with an appropriate amount of ethosomes dispersion in the ratio between the dispersion and the gel was 2: 1 w/w.

9.2.1. Evaluation of Ethosomal gel[40]

A] Appearance[1]

About 1 week after preparation, the gel was visually assessed for optical appearance (e.g., colour, turbidity, homogeneity, presence of macroscopic particles).

B] pH[3,7]

The pH of all formulations is determined by using a digital pH meter by immersing the electrode in gel formulation and pH was measured.

C] Spreadability[31]

A modified apparatus suggested was used for determining spreadability. The spreadability was measured on the basis of slip and drag characteristics of the gels. The modified apparatus was fabricated and consisted of two glass slides, the lower one was fixed to a wooden plate, and the upper one was attached by a hook to a balance. The spreadability was determined by using the formula.

s=ml/t,

Were

s, is spread ability,

m, is weight in the pan tied to upper slide,
t, is the time,
l, is the distance travelled. for the practical purpose the mass, length was kept constant and 't' was determined.

D] Viscosity
Viscosities of the gels were determined by using a Brookfield viscometer. Spindle type, S-64 at 100rpm.

E] Stability Studies[33]
Accelerated stability studies for gel formulation were conducted as per ICH guidelines at 40°C ± 2°C/75% ± 5% RH at sampling intervals of 0, 15, 30, and 60days respectively. The drug content, pH, and drug release are determined periodically.

F] Release kinetics[13]
To study the in vitro release kinetics of the optimized formulation, data obtained from dissolution study were plotted in various kinetics models. Different kinetic models such as zero order (cumulative amount of drug released vs. time), first order (log cumulative percentage of drug remaining vs. time), Higuchi model (cumulative percentage of drug released vs. square root of time), Korsmeyer- Peppas model (Log Cumulative percent drug release versus log time) and Hixson Crowell mode.

9. RESULT AND DISCUSSION

9.1 PREFORMULATION: Pre-formulation testing was an investigation of physical and chemical properties of a drug substance alone. It was the first step in rational development of dosage form.

9.2. IDENTIFICATION OF DRUG

A) FTIR
Spectroscopic studies of FTIR spectroscopy give possible information about the interaction between the drug and polymers. The results are as follows.

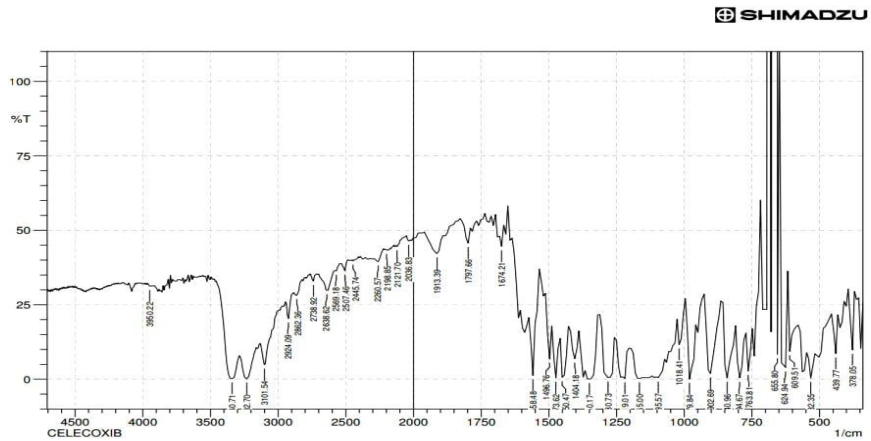


Figure No. 9: FTIR Spectrum of celecoxib drug.

Table No 6: For Interpratation Of Ftir Spectrum.

Wave number (cm-1)	Types of vibrations
794.67 (cm-1)	Aromatic CH Stretching
273.02 (cm-1)	S=O Stretching
1589.34 (cm-1)	N-H Stretching
3505.22 (cm-1)	NH2Stretching

Interpretation of FTIR Spectrum
Major functional groups like NH2 stretching, aromatic CH stretching, and S=O Stretching (sulfonamide group) were present in celecoxib showed characteristic peaks in FTIR spectrum. The Major peaks were identical group of celecoxib. Hence, the sample was confirmed as celecoxib.

B) By melting point
Melting point values of celecoxib drug was found to be in range of 147 to 159 C, which was represent in below table.

1. FOR CELECOXIB

Table 7: Melting Point Of Celecoxib.

S.NO	MELTING POINT	AVERAG E
1	158 º C	
2	157 º C	158º C
3	158 º C	

2. FOR CURCUMIN

Table 8: Melting Point Of Curcumin.

S.NO	MELTING POINT	AVERAGE
1	180º C	
2	179 º C	180 º C
3	180º C	

9.3 PHYSICOCHEMICAL PARAMETERS

A] Organoleptic properties

Table 9: Organoleptic Properties of Celecoxib.

PROPERTY	SPECIFICATION	OBSERVATION
Colour	white or almost white	White color
Nature	Amorphous or crystalline	Amorphous powder
Odour	NA	Odourless

B] Solubility studies of celecoxib

Solubility of celecoxib pure drug in different solvents was represented intable10.

Table no. 10: Solubility of Celecoxib Pure Drug In Various Media.

SOLVENT	SOLUBILITY
Water	Insoluble
Ethanol	Freely soluble
Methanol	Freely soluble
Dichloromethane	Soluble

C) PHYSICAL APPEARANCE

Table No. 10: Shows Physical Appearance.

S.NO	APPEARANCE	PHASE SEPRATION	HOMOGENEITY
F1	SMOOTH, YELLOW	NO SEPERATION	HOMOGENEOUS
F2	SMOOTH, YELLOW	NO SEPERATION	HOMOGENEOUS
F3	SMOOTH, YELLOW	NO SEPERATION	HOMOGENEOUS
F4	SMOOTH, YELLOW	NO SEPERATION	HOMOGENEOUS
F5	SMOOTH, YELLOW	NO SEPERATION	HOMOGENEOUS
F6	SMOOTH, YELLOW	NO SEPERATION	HOMOGENEOUS

INFERENCE

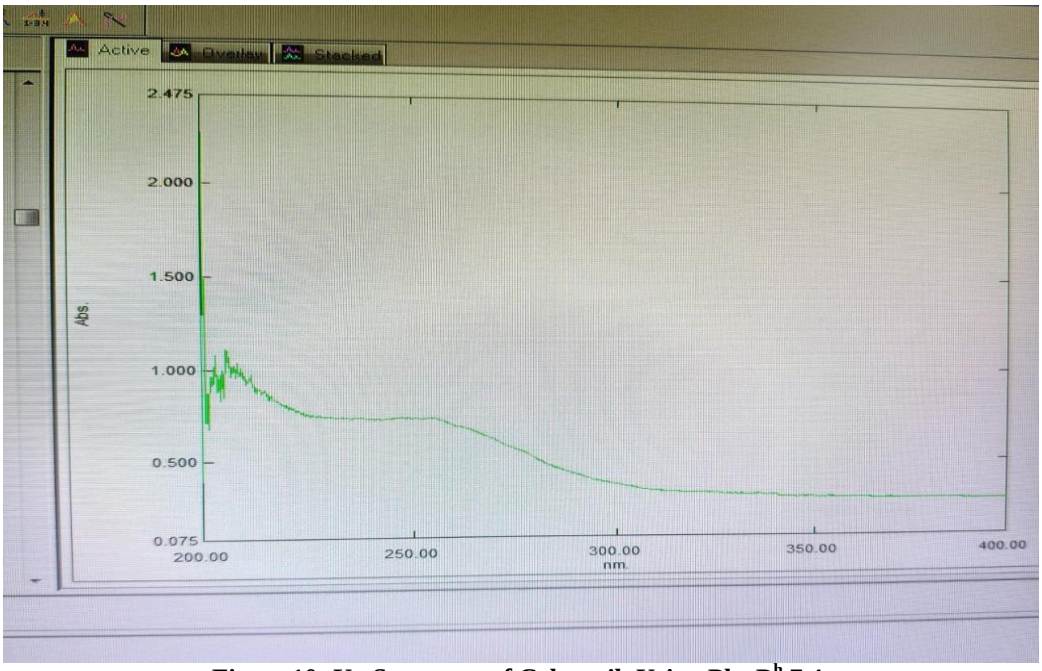
It was determined by visual inspection. All the formulations were found to be homogenous.

9.5. Determination of λ max for celecoxib

The maximum absorbance of the celecoxib was studied. The maximum absorbance of the drug celecoxib was found to be 254nm. Hence the wavelength of 252nm was selected for analysis of drug in dissolution media.

9.5.1 UV spectrum of celecoxib using PBS 7.4

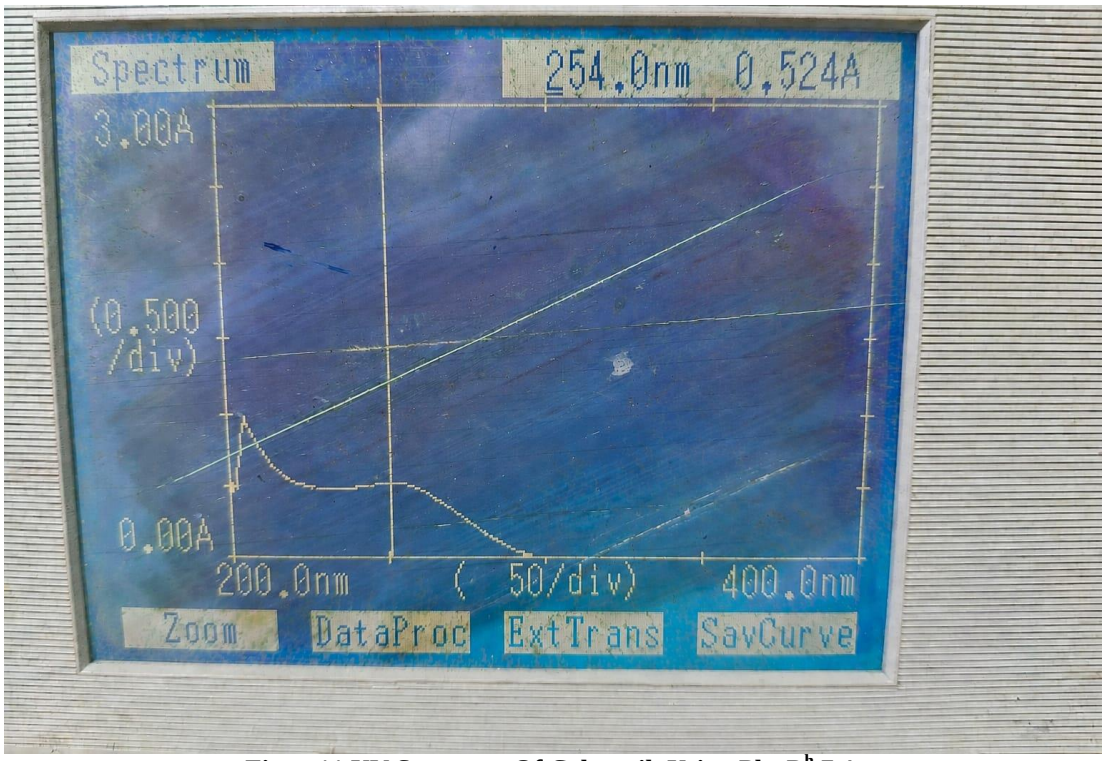
The maximum absorbance of the drug celecoxib was studied at 254nm. The maximum absorbance of the drug celecoxib was found to be 0.735.



Figno. 10: Uv Spectrum of Celecoxib Using Pbs P^{h} 7.4.

9.5.2 UV spectrum of celecoxib using methanol

The maximum absorbance of the drug celecoxib was studied at 254nm. The maximum absorbance of the drug celecoxib was found to be 0.524A.



Figno.11 UV Spectrum Of Celecoxib Using Pbs P^{h} 7.4.

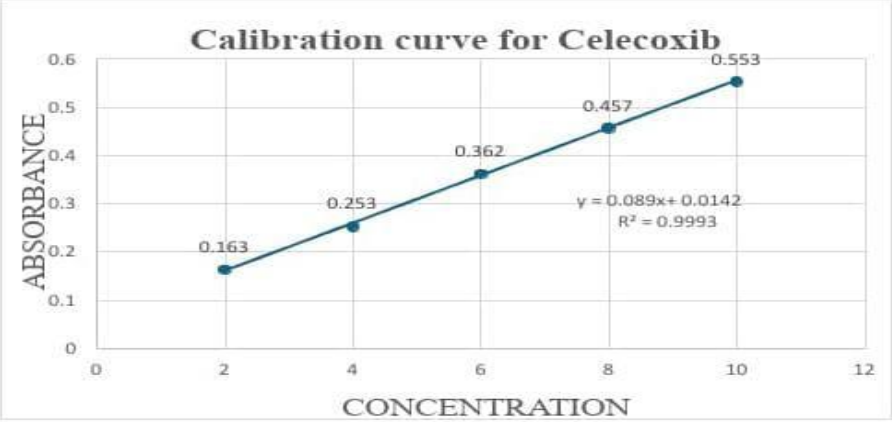
PBS: PHOSPHATE BUFFER SALINE

9.6. Standard Calibration Curve of Celecoxib Using methanol

The Ultraviolet Spectrophotometric method was used to analyze the calibration curve of celecoxib. The absorbance of the drug in of concentration ranging from 2-10 µg/ml was measured at a wavelength of 254 nm against blank.

Table No. 12: "for the calibration curve for celecoxib by methanol.

S.NO	CONCENTRATION	ABSORBANCE
1.	2	0.163
2.	4	0.253
3.	6	0.362
4.	8	0.457
5.	10	0.553



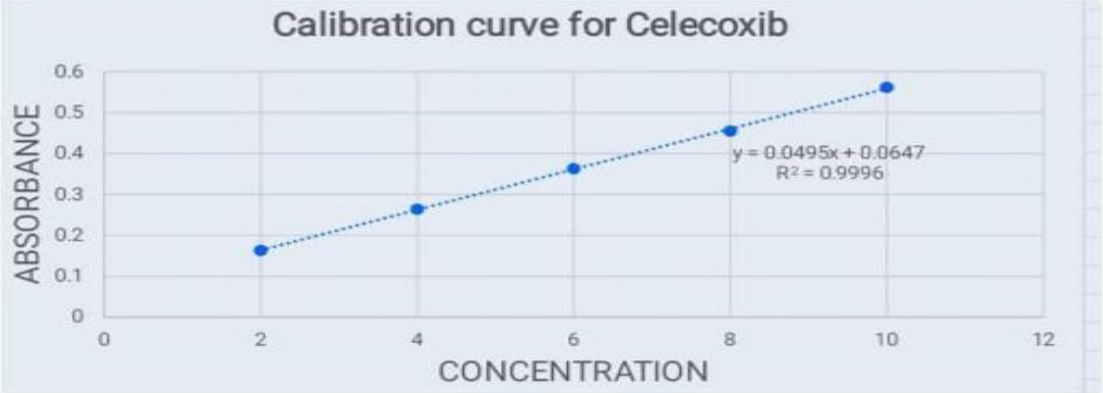
Inference: It was found that the solutions show linearity (R2 = 0.9993) at a concentration of 2-10µg/ml and obeys Beer Lambert's law.

9.7 STANDARD CALIBRATION CURVE OF CELECOXIB IN PHOSPHATE BUFFER PH 7.4

The Ultraviolet Spectrophotometric method was used to analyze the calibration curve of celecoxib. The absorbance of the drug in of concentration ranging from 2-10 µg/ml was measured at a wavelength of 254nm against blank.

Table No. 13: Data for calibration curve of celecoxib in phosphate buffer pH7.4.

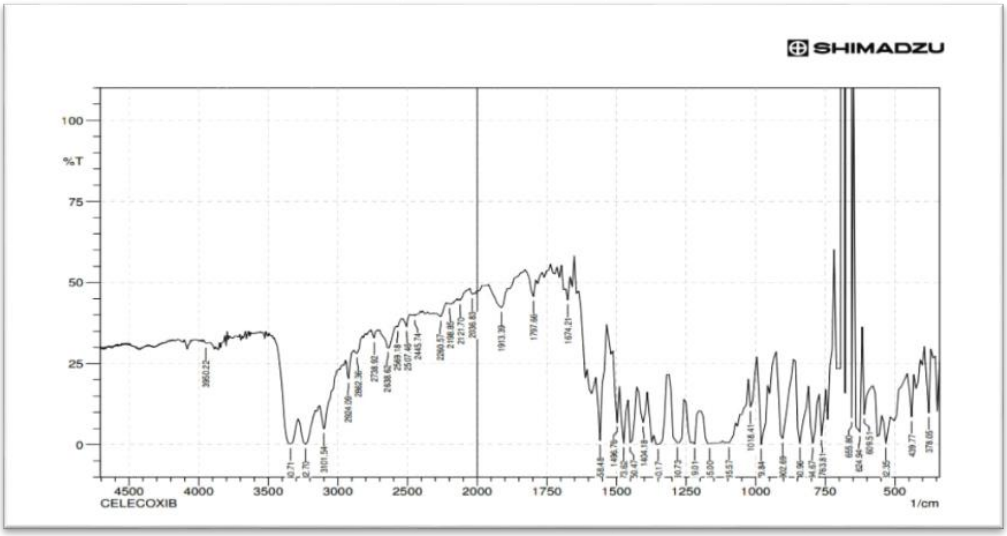
S.NO	CONCENTRATION	ABSORBANCE
1.	2	0.163
2.	4	0.264
3.	6	0.363
4.	8	0.455
5.	10	0.562



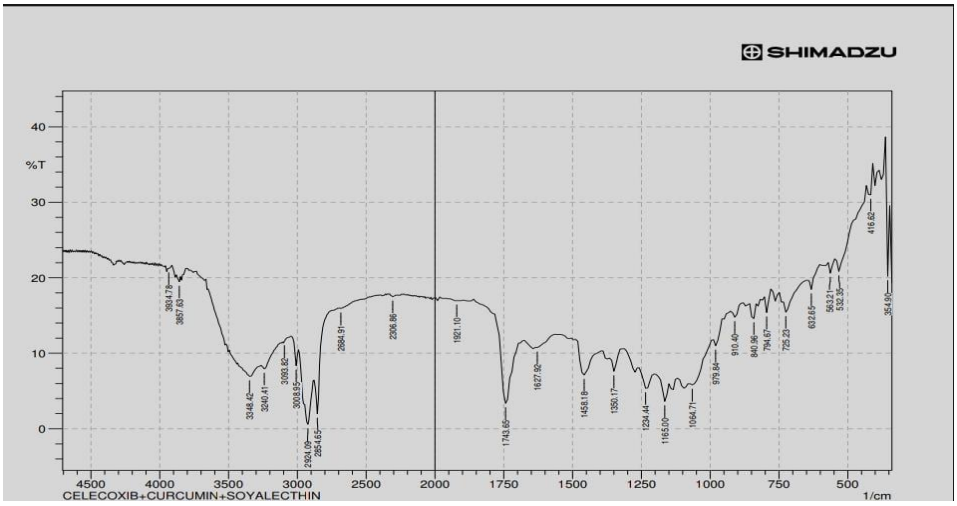
Inference: It was found that the solutions show linearity (R2 = 0.9996) at a concentration of 2-10µg/ml and obeys Beer Lambert's law.

9.8] DETERMINATION OF DRUG-POLYMER COMPATIBILITY

A] By FTIR Spectroscopy



FigNo. 14: FTIR Spectrum of celecoxib drug.



FigNo. 15: FTIR Spectrum of celecoxib +Curcumin+ Soya lecithin.

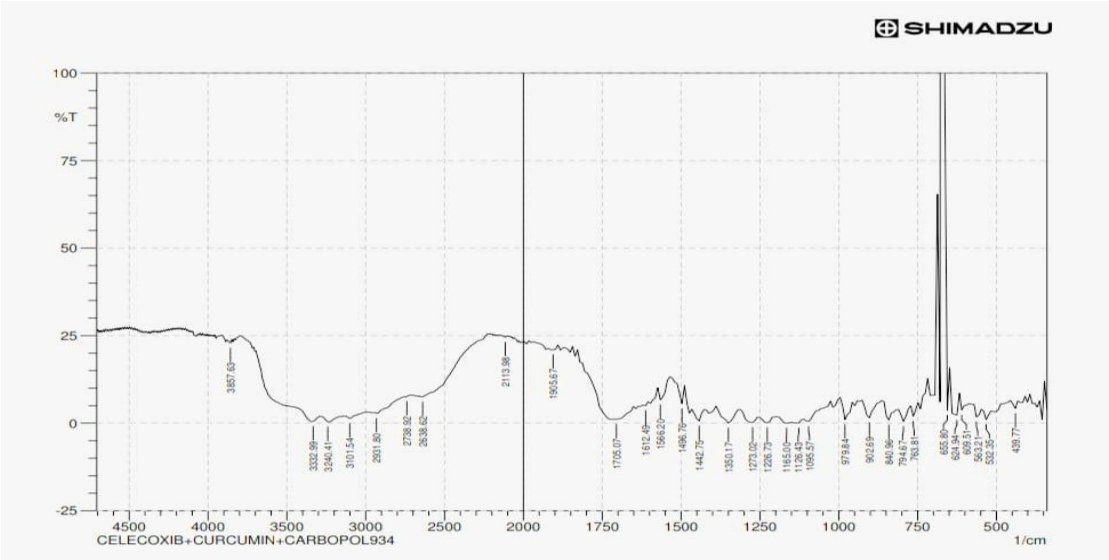


Fig No. 16: FTIR Spectrum of celecoxib +Curcumin +carbopol934.

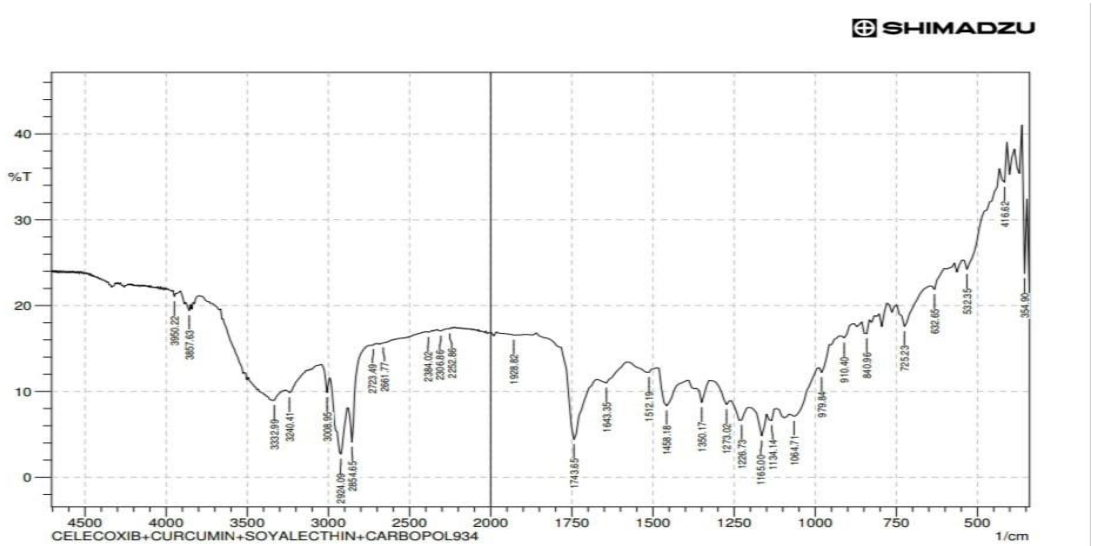


Fig No. 17: FTIR Spectrum of celecoxib + All excipients.

FTIR FOR CURCUMIN

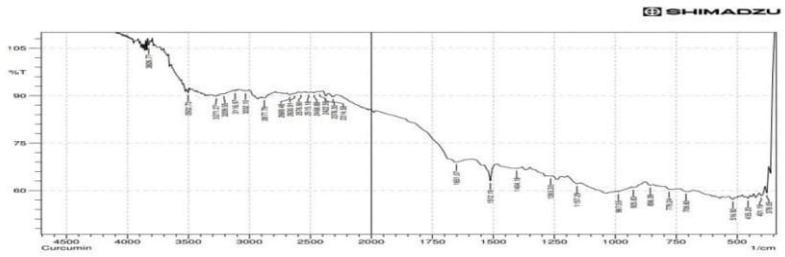


Table 14: Ftir Spectral Interpretation of Drug and Polymers.

Specifiction. (cm^{-1})	Celecoxib	Curcumin	Celecoxib+ curcumin+ soyalecithin	Celecoxib+ curcumin+ Carbopol 934	Celecoxib+ All excipients	Inference
780-820	794.67	800	794.67	794.67	794 .67	**AromaticCH stretching**
1150-1350	1273.02	1274	1234.44	1273.02	1234.44	**S=O stretching**
1550-1650	1589.34	1602	1267.92	1612.20	1643.35	**H stretching**
3200-3500	3505.22	3500	3348.42	3339.99	3332.96	**NH2 stretching**

10. PREPARATION OF ETHOSOMAL GEL

Six different formulations of Ethosomal dispersion were prepared by cold method, by using a drug and with polymers in different concentrations. Polymers, soya lecithin, and Carbopol were used in formulation. The formulation was designed as F1, F2, F3, F4, F5, F6, respectively. All the formulated gels were taken for further evaluation.

10.1 EVALUATION OF ETHOSOMAL GEL

A] Optical microscopy

Image1s obtained under an optical microscope confirmed the formation of crystal ethosomes structures. Showed in figure no.12. It was found that the formed crystals were spherical and some were in cubic.

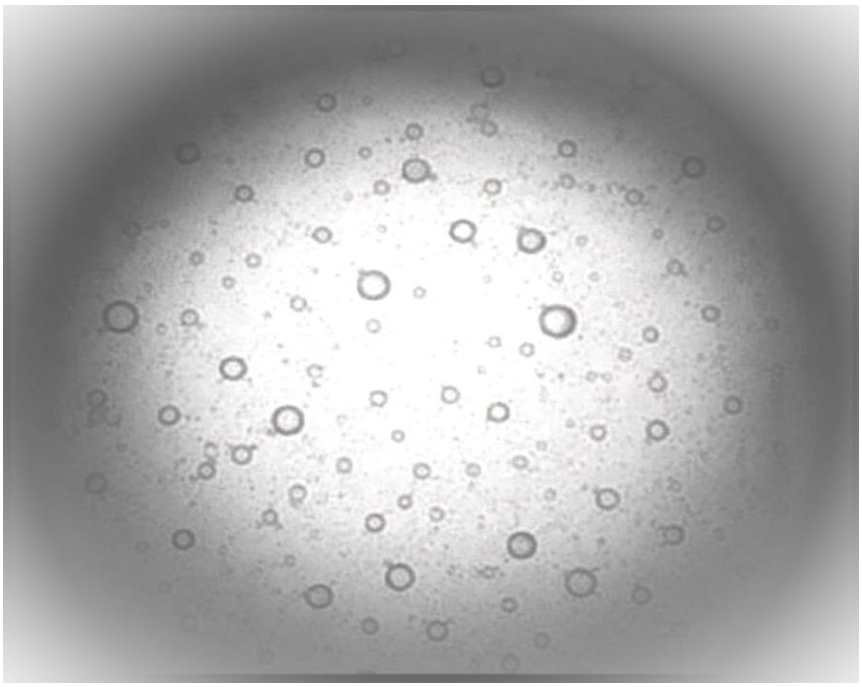


Figure no, 19: optical microscopy of Ethosomal gel.

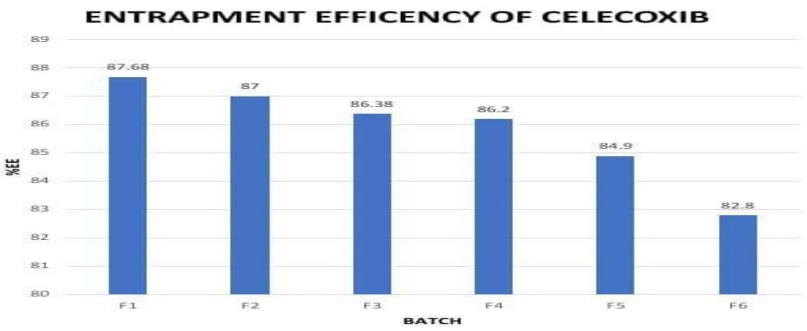
B] DRUG ENTRAPMENT STUDIES

Drug entrapment efficiency was determined to make sure that the added amount of celecoxib is present in the Ethosomes dispersion. The EE of all batches is in the range of 82.8-87.68%. The highest EE was found in batch F1; the result showed that the EE increased, as the amount of lipid and surfactant increased.

B]1. DRUG ENTRAPMENT EFFECIENCY FOR CELECOXIB

Table No. 15 For Entrapment Effeciency % For Celecoxib.

S.NO	FORMULATION	ENTRAPMENT EFFECIENCY PERCENTAGE
1	F1	87.68
2	F2	87.0
3	F3	86.3
4	F4	86.2
5	F5	84.9
6	F6	82.8



Figno 20: Shows Entrapment Effeciency Celecoxib.

C] DRUG ENTRAPMENT EFFECIENCY FOR CURCUMIN

Table No. 16: Drug Entrapment Effeciency For Curcumin.

S.NO	FORMULATION	ENTRAPMENT EFFECIENCY
1	F1	87.42
2	F2	87.0
3	F3	86.69
4	F4	86.33
5	F5	85.53
6	F6	86.09

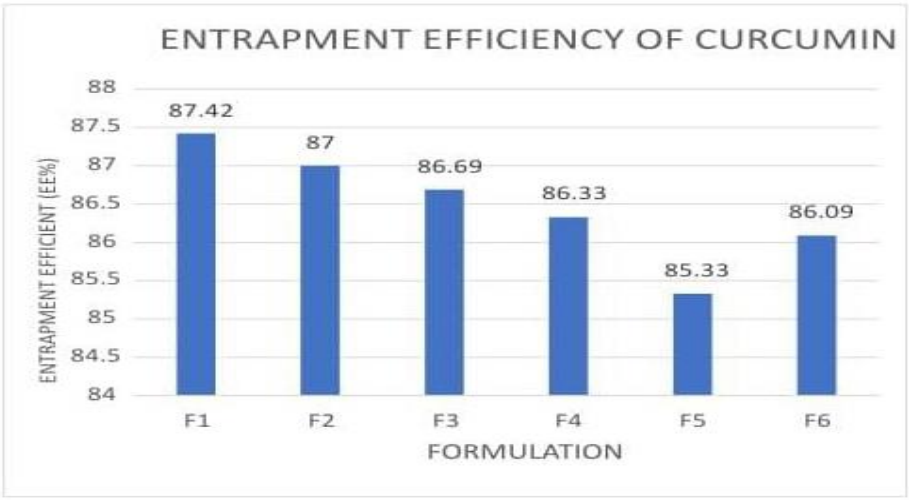


Fig No: 21. Shows Entrapment Effeciency For Curcumin.

C] DRUG CONTENT FOR CELECOXIB

The % drug content in various formulations ranged from [92.04-97.88%]. The drug content data revealed that there was no significant difference in the uniformity of the drug contenting the formulations. So, it indicated that celecoxib was uniformly distributed in vesicular dispersions.

Table No. 17: Percentage Drug Content For Celecoxib.

S.NO	FORMULATION	DRUG CONENT PERCENTAGE
1	F1	97.88
2	F2	90.24
3	F3	93.36
4	F4	96.08
5	F5	95.20
6	F6	92.04

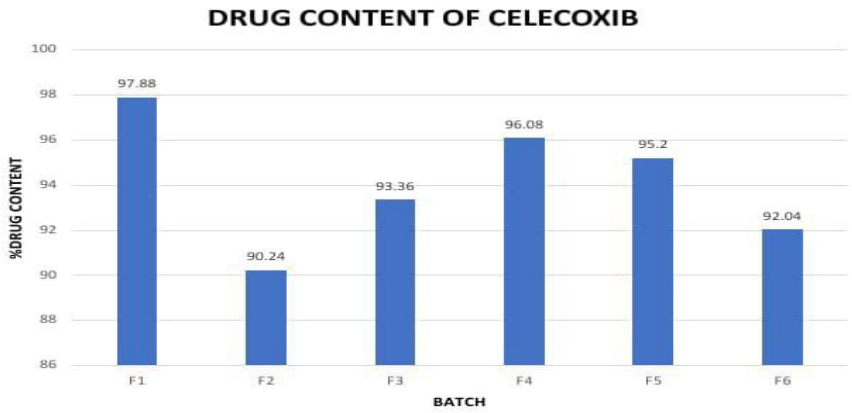


Fig No. 22: Shows Drug Content Percentage For Celecoxib.

C] 2. DRUG CONTENT PERCENTAGE FOR CURCUMIN

The % drug content in various formulations ranged from [94.71-97.87%]. The drug content data revealed that there was no significant difference in the uniformity of the drug contenting the formulations. So, it indicated that curcumin was uniformly distributed in vesicular dispersions.

Table No. 18: Percentage Drug Content For Curcumin.

S.NO	FORMULATION	DRUG CONEN PERCENTAGE
1	F1	97.87
2	F2	97.29
3	F3	95.56
4	F4	96.4
5	F5	96.98
6	F6	94.71

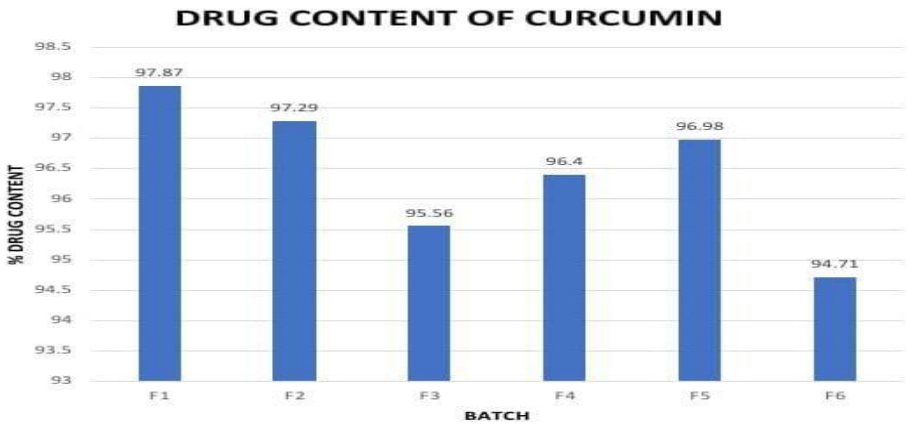


Fig No. 23; Shows Drug Content Percentage For Curcumin.

D] INVITRO DRUG RELEASE DIFFUSION STUDIES:

In-vitro drug release study was performed by using Modified Franz diffusion cell on egg membrane in phosphate buffer saline solution (pH 7.4). Egg membrane was mounted horizontally on the receptor compartment of Franz diffusion cell. The effective permeation area of donor compartment exposed to receptor compartment was 2cm2 and capacity of receptor compartment was 30ml of phosphate buffer (pH 7.4) maintained at 37± 0.5□C and stirred by a magnetic bar at 100rpm. Transferosomes gel formulation equivalent to 5mg drug was placed on the skin and the top of the diffusion cell was covered. At appropriate time intervals 5ml aliquots of the receptor medium were withdrawn and immediately replaced by an equal volume of fresh phosphate buffer (pH 7.4) to maintain sink conditions. The samples were analyzed spectrophotometrically at λ max.

1. FOR CELECOXIB

Table no, 19: Percentage Drug Release Of Ethosomal Gel.

TIME [HRS]	F1	F2	F3	F4	F5	F6
1	13.85%	12.39%	13.07%	13.33%	11.97%	11.99%
2	27.77%	20.66%	24.01%	25.47%	17.89%	18.57%
3	29.69%	28.48%	34.79%	33.86%	26.48%	28.88%
4	49.74%	40.45%	44.68%	47.65%	37.76%	35.73%
5	63.25%	50.67%	62.35%	60.75%	52.00%	51.69%
6	74.61%	65.91%	72.58%	71.84%	63.86%	62.54%
8	94.04%	81.59%	88.45%	85.92%	79.68%	79.12%

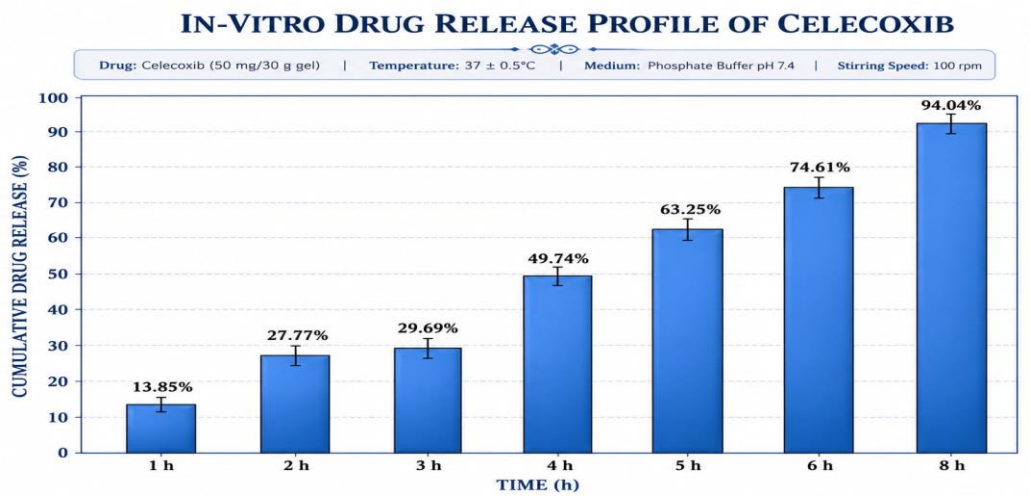


Fig No. 24: Graphical Representation Of % Drug Release Celecoxib.

2. FOR CURCUMIN

Table no: 20 Percentage Drug Release Of Curcumin.

TIME [HRS]	F1	F2	F3	F4	F5	F6
1	11.06%	10.42%	9.65%	8.75%	7.85%	6.95%
2	24.95%	23.15%	21.35%	19.42%	17.36%	15.31%
3	40.00%	38.07%	36.01%	34.08%	32.03%	29.97%
4	55.05%	52.99%	51.06%	49.00%	47.07%	45.02%
5	69.97%	68.04%	65.98%	64.05%	61.99%	60.06%
6	82.06%	81.03%	77.04%	74.08%	68.04%	68.04%
8	95.05%	90.03%	85.02%	80.00%	69.97%	69.97%

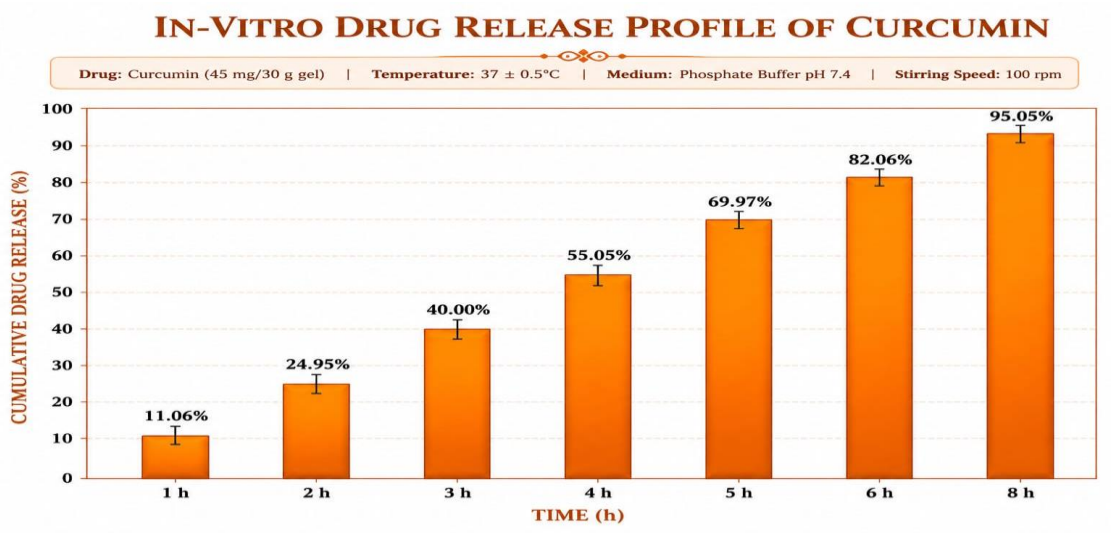


Fig No. 25: Graphical Representation Of % Drug Release Curcumin.

INFERENCE FOR CELECOXIB AND CURCUMIN DRUG RELEASE

- F1 has a higher [SOYA LECITHIN] concentration, so it showed a higher percentage of drug release of celecoxib is 94.04% and curcumin as 95.05%.

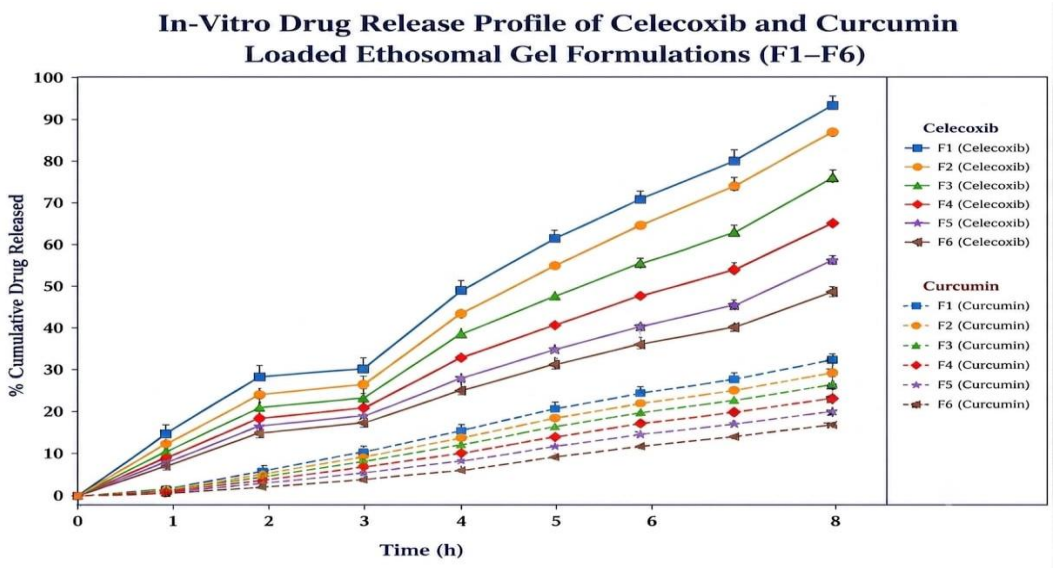


Fig No. 26: Graphical Representation Of Celecoxib And Curcumin.

E] SCANNING ELECTRON MICROSCOPY [SEM]

Surface morphology and shape characteristics of dispersion for formulation F1 were evaluated by means of scanning electron microscopy. The SEM photograph of the dispersion revealed that the dispersion was smooth, hollow surface, cubic in shape, and slightly aggregated. The SEM photographs were provided in figure 18.

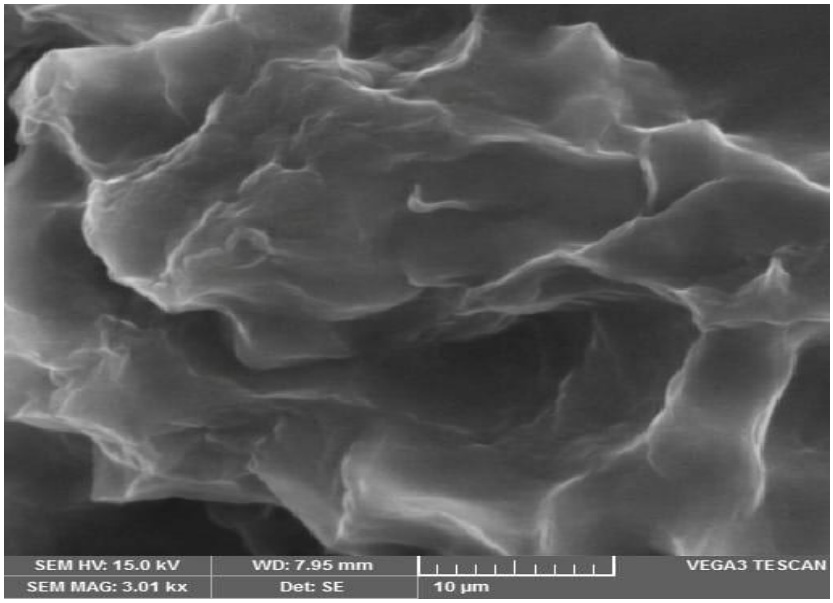


Fig No. 27: Sem Image of Ethosomal Gel.

INFRENCE

The SEM photograph of the dispersion revealed that the dispersion was smooth, hollow surface, cubic in shape, and slightly aggregated. The SEM photographs were provided in figure 18.

F] DETERMINATION OF PARTICLE SIZE AND POLYDISPERSITY OF FORMULATION

PDI indicates the particle size distribution, which ranges from 0 to 1. Theoretically, a monodisperse population indicates PDI equal to zero. The low value of PDI signifies the uniformity of particle size within the formulations.

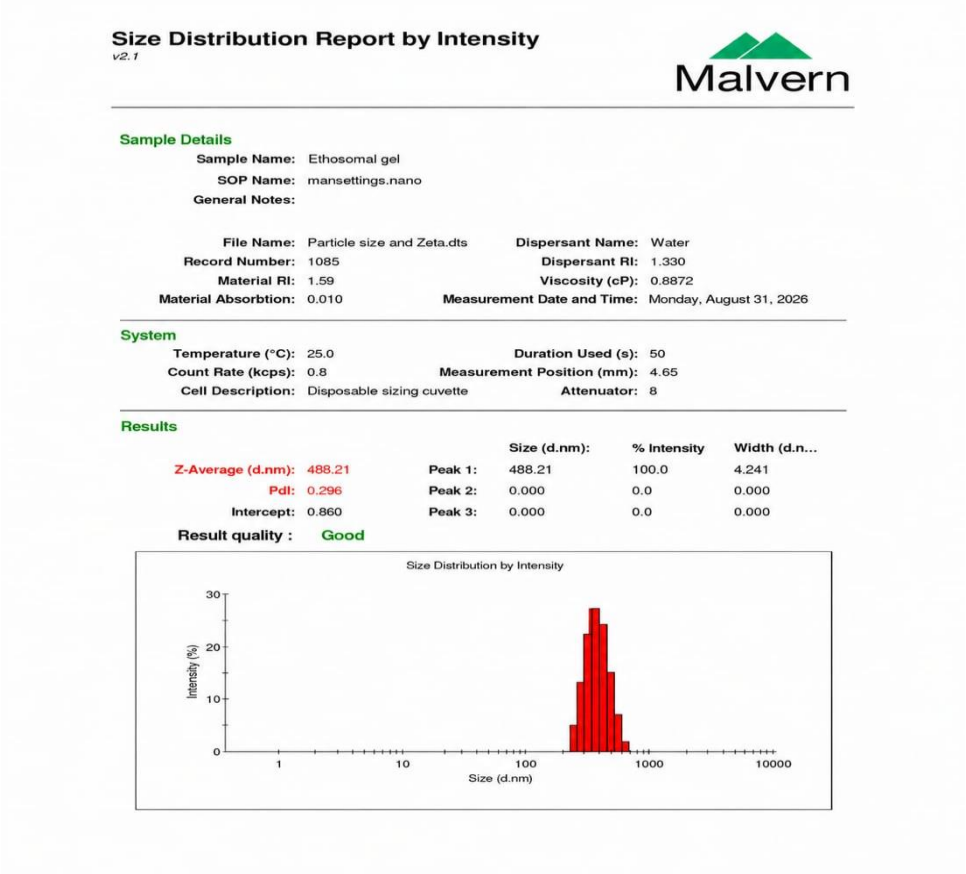


Figure No. 28: Particle Size and Polydispersity of Formulation Inference.

INFERENCE
The Particle Size and Polydispersity of Formulation was found to be 488.21nm and 0.296.

G] ZETA POTENTIAL
Zeta potential was measured to evaluate the surface charge and stability of ethosomal vesicles. It indicates the degree of electrostatic repulsion or attraction between particles, which influences aggregation and dispersion stability. Generally, values above ±30 mV indicate good stability, while lower values may lead to aggregation. The zeta potential of the formulation was determined using a zeta sizer at 25°C. Ethosomal systems typically show values in the range of -10 to -20 mV, indicating moderate stabilit**y.**

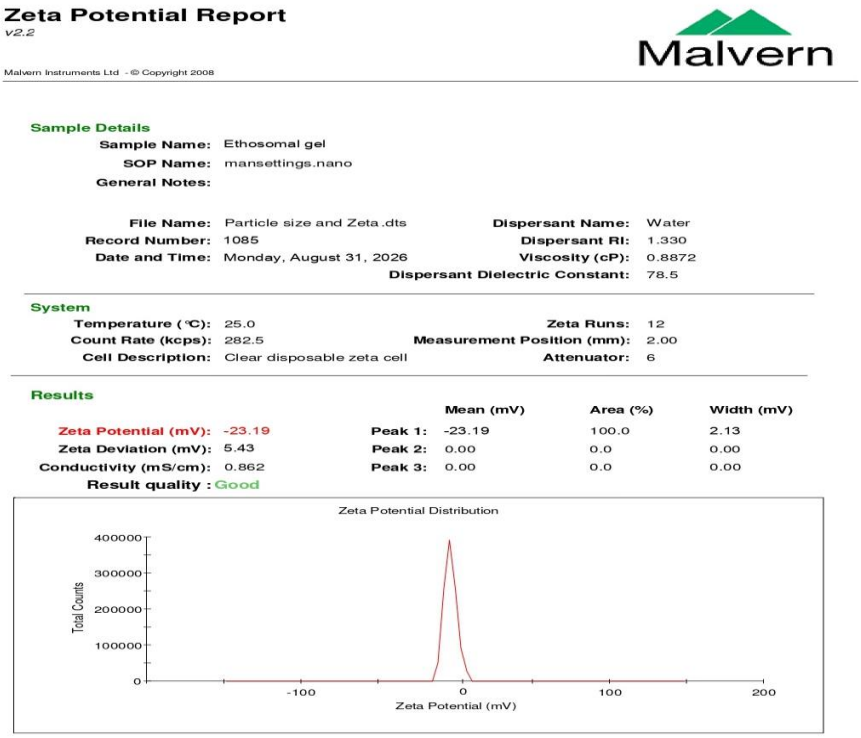


Figure No. 29: Zeta potential of Formulation.

INFERENCE
The zeta potential range is: mv -23.19 and conductivity (MS/cm): 0.862 shows that this range is good.

11.2 EVALUATION OF ETHOSOMAL GEL
From the drug content, entrapment efficiency, and drug release study, it is found that F1 is the best formulation.

A] APPEARANCE
Table No. 21: Data For The Physical Appearance.

S.NO	APPEARENCE	PHASE SEPRATION	HOMOGENEITY
F1	SMOOTH, YELLOW	NO SEPERATION	HOMOGENEOUS
F2	SMOOTH, YELLOW	NO SEPERATION	HOMOGENEOUS
F3	SMOOTH, YELLOW	NO SEPERATION	HOMOGENEOUS
F4	SMOOTH, YELLOW	NO SEPERATION	HOMOGENEOUS
F5	SMOOTH, YELLOW	NO SEPERATION	HOMOGENEUS
F6	SMOOTH, YELLOW	NO SEPERATION	HOMOGENEOUS

INFERENCE: It was determined by visual inspection. All the formulations were found to be homogenous.

B] pH
The pH was found to be 6.2-6.6, which was close to skin pH.

Table No. 22: Data For The Evaluation Of Ph.

S.NO	FORMULATION	P^H
1.	F1	6.6
2.	F2	6.1
3.	F3	6.2
4.	F4	6.5
5.	F5	6.4
6.	F6	6.2

C] SPREADABILITY

A modified apparatus suggested was used for determining spreadability. The spread ability was measured on the basis of slip and drag characteristics of the gels. The modified apparatus was fabricated and consisted of two glass slides, the lower one was fixed to a wooden plate, and the upper one was attached by a hook to a balance. The spreadability was determined by using the formula.

s=ml/t,

s, is spread ability,

m, is weight in the pan tied to upper slide,

t, is the time,

l, is the distance travelled. for the practical purpose the mass, length was kept constant and 't' was determined.

Table No. 23: For The Spreadability Of The Gel.

S.NO	FORMULATION	M (gm)	L (cm)	T(sec)	SPREADABIIY (g.cm/sec)
1.	F1	50	52	198	13.10
2.	F2	50	51	196	13.01
3.	F3	50	47	192	11.97
4.	F4	50	49	194	12.62
5.	F5	50	51	201	12.68
6.	F6	50	50	197	12.70

D] STABILITY STUDIES

P^H and Drug content values are analyzed periodically as per ICH guidelines through accelerated stability studies for optimized gel F1 formulation was shown in Table.

Table no 24: Stability Studyof Ethosomalgel.

Time in days	PH	%Drug content
0	6.6	97.87
15	6.4	97.29
30	6.3	96.04
60	6.1	96.98

INFERENCE

The results show No Significant Change in PH, Drug release and Drug Content of optimized formulation after two months.

E] VISCOSITY

The viscosity of the gels was determined by using a Brookfield viscometer. The range of viscosity for ethosomal gel was found to be 7650-8250cps.

Table No. 25 For The Viscosity For The Ethosomal Gel.

S.NO	FORMULATION CODE	VISCOSITY (cPS)
1.	F1	8250
2.	F2	8100
3.	F3	7950
4.	F4	8020
5.	F5	7780
6.	F6	7650

F] RELEASE KINETICS OF OPTIMIZIED ETHOSOMAL GEL [CELECOXIB]

Table No. 26: Release kinetics [celecoxib]of Optimized Ethosomal gel.

TIME(h)	Log Time	Square root of time	CDR % Release	CDR % Release Drug remaining	Log of CDR % Release	Log of CDR % Release remaiming	Cube root of % remaiming
0	0	0	0.00	100.00	0	2.0000	4.6416
1	0.0000	1.0000	13.85	88.15	1.1414	1.9353	4.4166
2	0.3010	1.4142	27.77	72.23	1.4436	1.8587	4.1646
3	0.4771	1.7321	29.69	70.31	1.4726	1.8470	4.1274
4	0.6021	2.0000	49.74	50.26	1.6967	1.7012	3.6904
5	0.6990	2.2361	63.25	36.75	1.8011	1.5653	3.3247
6	0.7782	2.4495	74.61	25.39	1.8728	1.4047	2.9391
8	0.9031	2.8284	94.04	5.96	1.9733	0.7752	1.8131

F] 2. RELEASE KINETICS OF OPTIMIZIED ETHOSOMAL GEL OF [CURCUMIN]

Table No. 27: Release kinetics [curcumin]of Optimized Ethosomal gel.

TIME(h)	Log Time	Square root of time	CDR % Release	CDR % Release Drug remaining	Log of CDR % Release	Log of CDR % Release remaiming	Cube root of % remaiming
0	0	0	0.00	100.00	0	2.0000	4.6416
1	0.0000	1.0000	13.85	88.94	1.0438	1.9491	4.4637
2	0.3010	1.4142	24.95	75.05	1.3971	1.8754	4.2181
3	0.4771	1.7321	40.00	60.00	1.6021	1.7782	3.9149
4	0.6021	2.0000	55.05	44.95	1.7408	1.6527	3.5556
5	0.6990	2.2361	69.97	30.03	1.8449	1.4776	3.1083
6	0.7782	2.4495	82.06	17.94	1.9141	1.2538	2.6178
8	0.9031	2.8284	95.05	4.95	1.9780	0.6946	1.7043

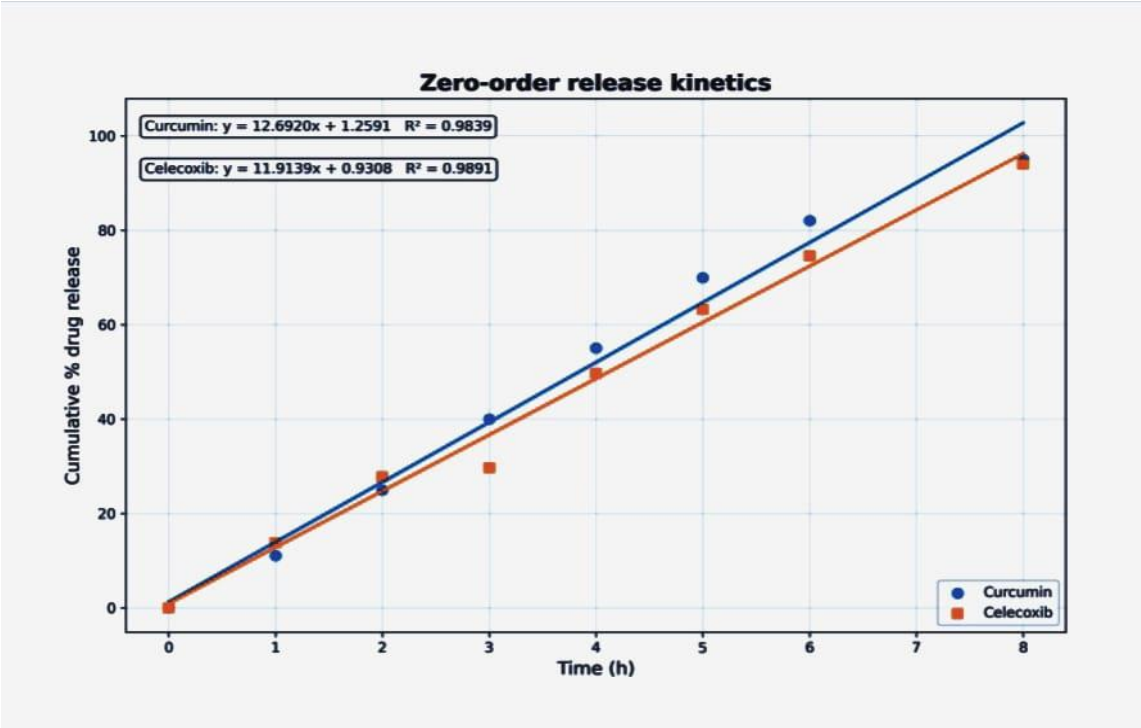


Fig No. 30: A plot for zero order kinetics of optimized Ethosomal gel.

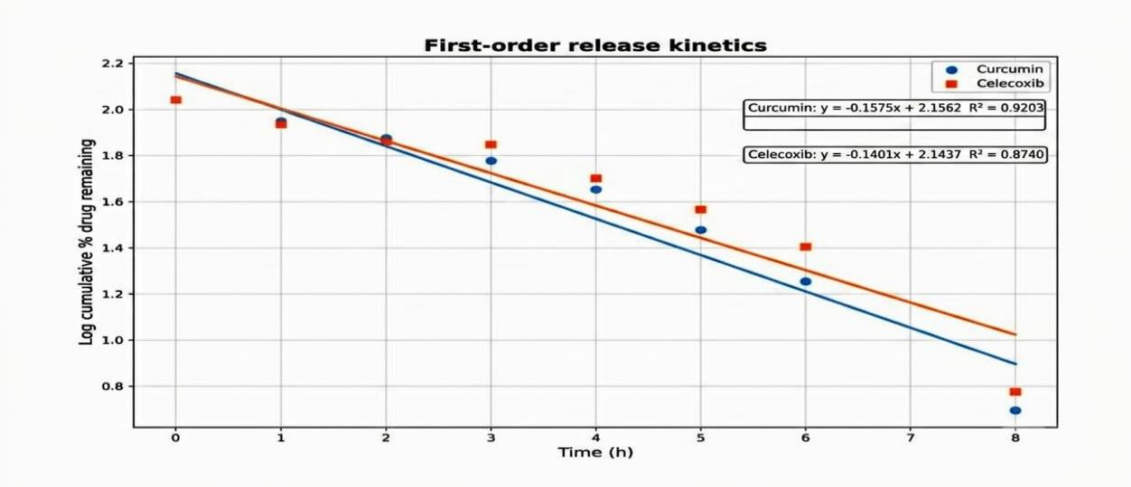


Fig No. 31: A plot for zero order kinetics of optimized Ethosomal gel.

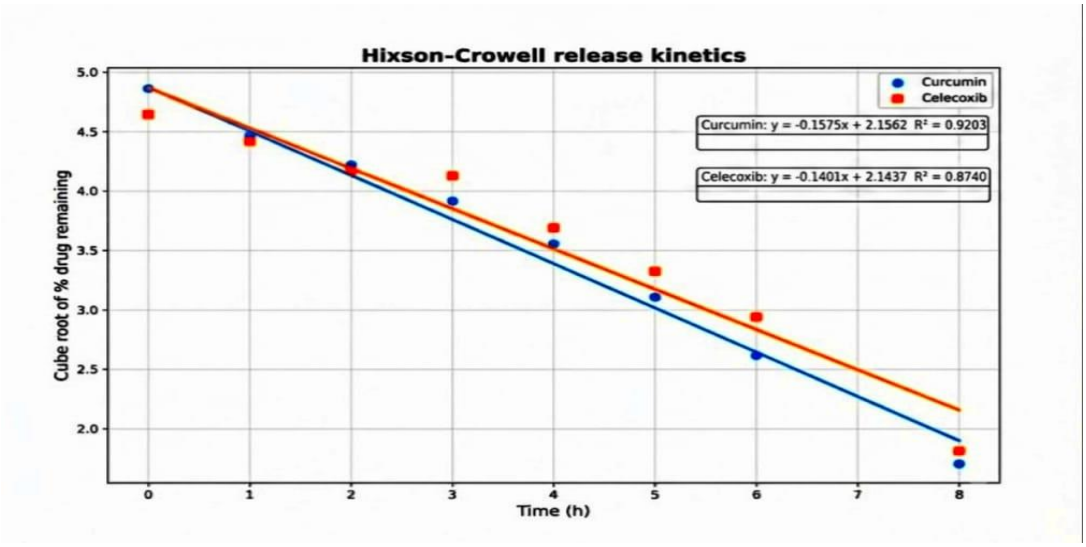


Fig No. 32: A plot for Hixson-Crowell release kinetics of Optimized Ethosomal gel.

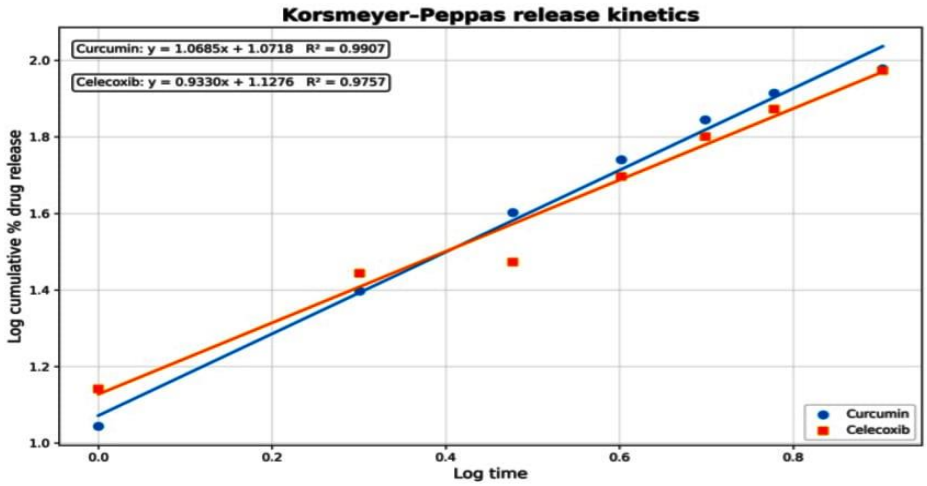


Fig No. 33: A plot for Korsmeyer-Peppas release kinetics of optimized gel.

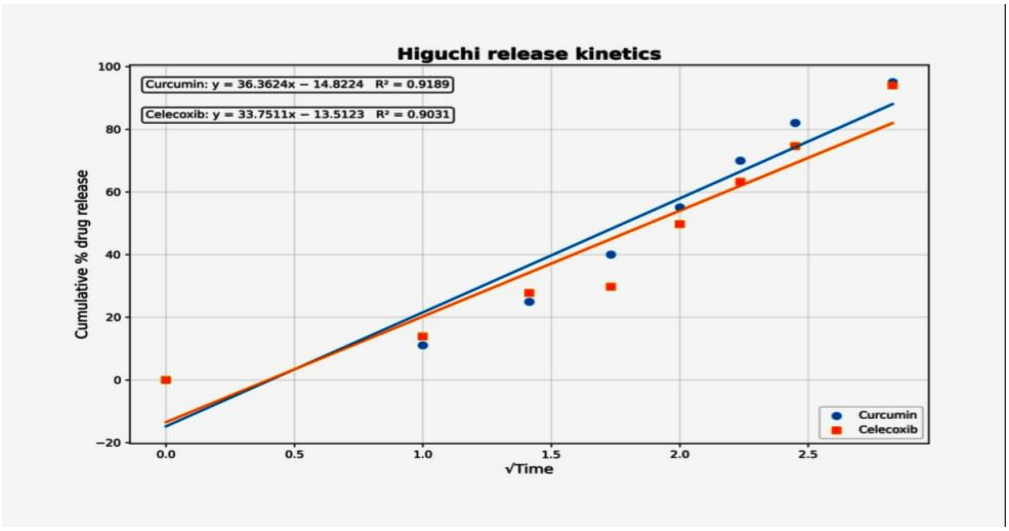


Fig No. 34: A plot for Higuchi release kinetics of optimized Ethosomal gel.

The coefficient of determination (R2) was taken as criteria for choosing the most appropriate model. The R 2 values of various models are given in table.

Table No. 28: kinetics Model and its R2 value.

RELEASE MODEL	CELECOXIB	CURCUMIN
First order	0.9839	0.9891
Zero order	0.9203	0.8740
Higuchi	0.9189	0.9031
Kerseymere Peppas	0.9769	0.9464
Hixson Crowell	0.9907	0.9757

- The data from in vitro release of optimized formulation fit into various kinetic models.
- Good linearity was observed with the First order release kinetics (R2=0.9891) and Hixson Crowell (R2=0.9907)
- Hence the result indicating that the drug release was based on their change in surface area and diameter of the par

11. SUMMARY AND CONCULSION

The present study was carried out with the aim of formulating, optimizing, and evaluating Celecoxib and Curcumin loaded ethosomal gel for effective topical drug delivery. Ethosomes were selected as a vesicular carrier due to their deformability and ethanol content, which may enhance drug penetration across the skin. The prepared ethosomal vesicles were incorporated into a Carbopol 934 gel base to achieve prolonged drug release and suitable topical application properties.

- Celecoxib and Curcumin loaded ethosomes were successfully prepared using soya lecithin and ethanol as the principal components of the vesicular system.
- Carbopol 934 was employed as the gelling agent to obtain the required viscosity, consistency, spreadability and stability of the final ethosomal gel.
- Propylene glycol was incorporated as a co-solvent and humectant, whereas methyl paraben was used as a preservative to enhance the stability of the formulation.
- The prepared formulations were evaluated for various physicochemical and pharmaceutical parameters, including appearance, homogeneity, pH, viscosity, spreadability, drug content, and in-vitro drug release.
- The in-vitro drug release study showed a controlled release pattern for both drugs, with approximately 94.04% Celecoxib and 95.05% Curcumin released at 8 hours.
- The release data were analyzed using Zero-order, First-order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas kinetic models to determine the release pattern and probable mechanism of drug release.
- The incorporation of Celecoxib and Curcumin into an ethosomal gel system may provide the advantages of vesicular drug delivery together with the prolonged-release properties of the Carbopol 934 gel.
- Hence, my thesis shows the F1 Formulation as optimized and best formulation.

CONCLUSION

The present investigation successfully established the potential of Celecoxib and Curcumin-loaded ethosomal gel as a novel topical drug delivery system. The combination of soya lecithin, ethanol and Carbopol 934, along with suitable excipients such as propylene glycol and methyl paraben, produced a formulation with acceptable physicochemical properties and controlled drug release. The optimized formulation therefore shows promise for sustained topical delivery of Celecoxib and Curcumin and may be further investigated through ex-vivo skin permeation, skin-irritation, stability and in-vivo studies to establish its suitability for therapeutic application.

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