TRANSDERMAL DELIVERY OF FEBUXOSTAT USING ELASTIC LIPOSOMES – FORMULATION AND CHARACTERISATION

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CERTIFICATE

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This is to certify that the dissertation entitled **"TRANSDERMAL DELIVERY OF FEBUXOSTAT USING ELASTIC LIPOSOMES - FORMULATION DEVELOPMENT AND CHARACTERISATION"** is a bonafide workdone by **Mr.S.SIVA RAMA KRISHNAN (Reg.No:261711307), Department of Pharmaceutics, College of Pharmacy, Madurai Medical College** in partial fulfillment of The Tamil Nadu Dr.M.G.R Medical University rules and regulations for award of **MASTER OF PHARMACY IN PHARMACEUTICS** under my guidance and supervision during the academic year 2018–2019.

Name & Signature of the Guide

Name & Signature of the Head of Department

Name & Signature of the Dean/Principal

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INTRODUCTION

NOVEL DRUG DELIVERY SYSTEMS :

For many decades treatment of acute disease or a chronic illness has been mostly accomplished by delivery of drugs to patient using various pharmaceutical dosage form includes tablets, capsules, pills, suppositories, cream, gel, injectables and aerosols as drug delivery system are the primary pharmaceutical product common available in the market eventhough this type of delivery system ensure a prompt release of drug but this system had several lack in achieving good therapeutic responses and drug targeting, bioavailability issues are commonly seen in this type of dosage form to overcome this problems several advancement has been done in delivery system.

In the past two decades several new techniques have been developed for drug delivering, these techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and targeting the drug to specific tissues or cell. These Advancement have led to the development of several novel drug delivery system that revolutionise the method of medication and provides a number of therapeutic benefits.

NDDS is the most suitable drug delivery system in which developing the therapeutic efficacy of pre-existing as well as new drugs.

They are mainly classified into two types

1. CONTROLLED RELEASE DRUG DELIVERY SYSTEM
2. SUSTAINED RELEASE DRUG DELIVERY SYSTEM

CONTROLLED RELEASE :

The term controlled release has become associated with those systems from which therapeutic agents may be automatically delivered at a predetermined rate over period of time.

It also implies predictability and reproducibility in the drug release kinetics

SUSTAINED RELEASE :

The term sustain release has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is delayed or prolonged and its plasma profile is sustained in duration.

NDDS has been achieved by various approaches, one such approach is encapsulation of drug molecules in vesicles which can be predicted to prolong the existence of the drug in systemic circulation and also its reduces toxicity.

VESICULAR DRUG DELIVERY SYSTEM :

Vesicular system are highly ordered assembilies of one or more concentric lipid bilayers formed in which hydrophobic , hydrophilic and amphiphillic drug molecules are entrapped inside the vesicles.

Drug delivery refers to approaches, formulations, technologies and systems for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect.

It may involve scientific site-targeting within the body or it might involve facilitating systemic pharmacokinetics; in any case, it is typically concerned with both quantity and duration of drug presence.

Drug delivery technologies modify drug release profile, absorption, distribution and elimination for the benefit of improving product efficacy and safety, as well as patient convenience and compliance. Drug release is from: diffusion, degradation, swelling and affinity-based mechanisms.

Most common routes of administration include the preferred non-invasive peroral (through the mouth), topical(skin),transmucosal(nasal,buccal/sublingual, vaginal,ocular and rectal) and inhalation routes.Conventional dosage forms including prolonged release dosage forms are unable to meet none of these.

At present, no available drug delivery system behaves ideally, but sincere attempts have been made to achieve them through various novel approaches in drug delivery.

Currently, vesicles as a carrier system have become the vehicle of choice in drug delivery and lipid vesicles were found to be of value in immunology, membrane biology and diagnostic technique and most recently in genetic engineering.

Vesicular delivery system provides an efficient method for delivery to the site of infection, leading to reduce the drug toxicity with no adverse effects. Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs.

They can incorporate both by hydrophilic and lipophilic drugs. Different novel approaches used for delivering the drugs by vesicular system include liposomes, niosomes, sphinosomes, transferosomes and pharmacosomes.

The vesicular systems are highly ordered assemblies of one or several concentric lipid bilayer formed, when certain amphiphillic building blocks are confronted with water. Vesicles can be formed from a diverse range of amphiphillic building blocks.

Biologic origin of these vesicles was first reported in 1965 by Bingham, and was given the name Bingham bodies. Drug carrier can be engineered to slowly degrade, react to stimuli and be site-specific.

The ultimate aim is to control degradation of drug and loss, prevention of harmful side effects and increase the availability of the drug at the disease site. Encapsulation of a drug in vesicular structures can be predicted to prolong the existence of the drug in systemic circulation, and perhaps, reduces the toxicity if selective uptake can be achieved.

Lipid vesicles are one type of many experimental models of biomembranes which evolved successfully, as vehicles for controlled delivery. For the treatment of intracellular infections, conventional Chemotherapy is not effective, due to limited permeation of drugs into cells. This can overcome by the use of vesicular drug delivery system

Vesicular drug delivery system has some of the advantages like:

- Prolong the existence of the drug in systemic circulation, and perhaps, reduces the toxicity if selective uptake can be achieved due to the delivery of drug directly to the site of infection.
- Improves the bioavailability especially in the case of poorly soluble drugs.
- Both hydrophilic and lipophilic drugs can be incorporated.

- Delays elimination of rapidly metabolizable drugs and thus function as sustained release systems.

These vesicular systems are accompanied with some problems like drug carriers and externally triggered (eg., temperature, pH, or magnetic sensitive) carriers load drugs passively, which may lead to low drug loading efficiency and drug leakage inpreparation, preservation and transport in vivo.(**Ashara *et .al 2014***)

Why VDDS ..?

Encapsulation of drug into the vesicular structure can be predicted to prolong the existence of drug in the systemic circulation and perhaps, reduces the toxicity if selective uptake is achieved .It has several advantages as mentioned above:

Eventhough it has lot of advantages ,it had some serious disadvantages which restrict their uses,

- Drug passively,which may lead to low drug loading efficiency.
- Drug leakage in the preparation,storage and transportation.
- Stability issues act as a barrier and limit their use.

VESICLES AS DELIVERY SYSTEM FOR THE SKIN :

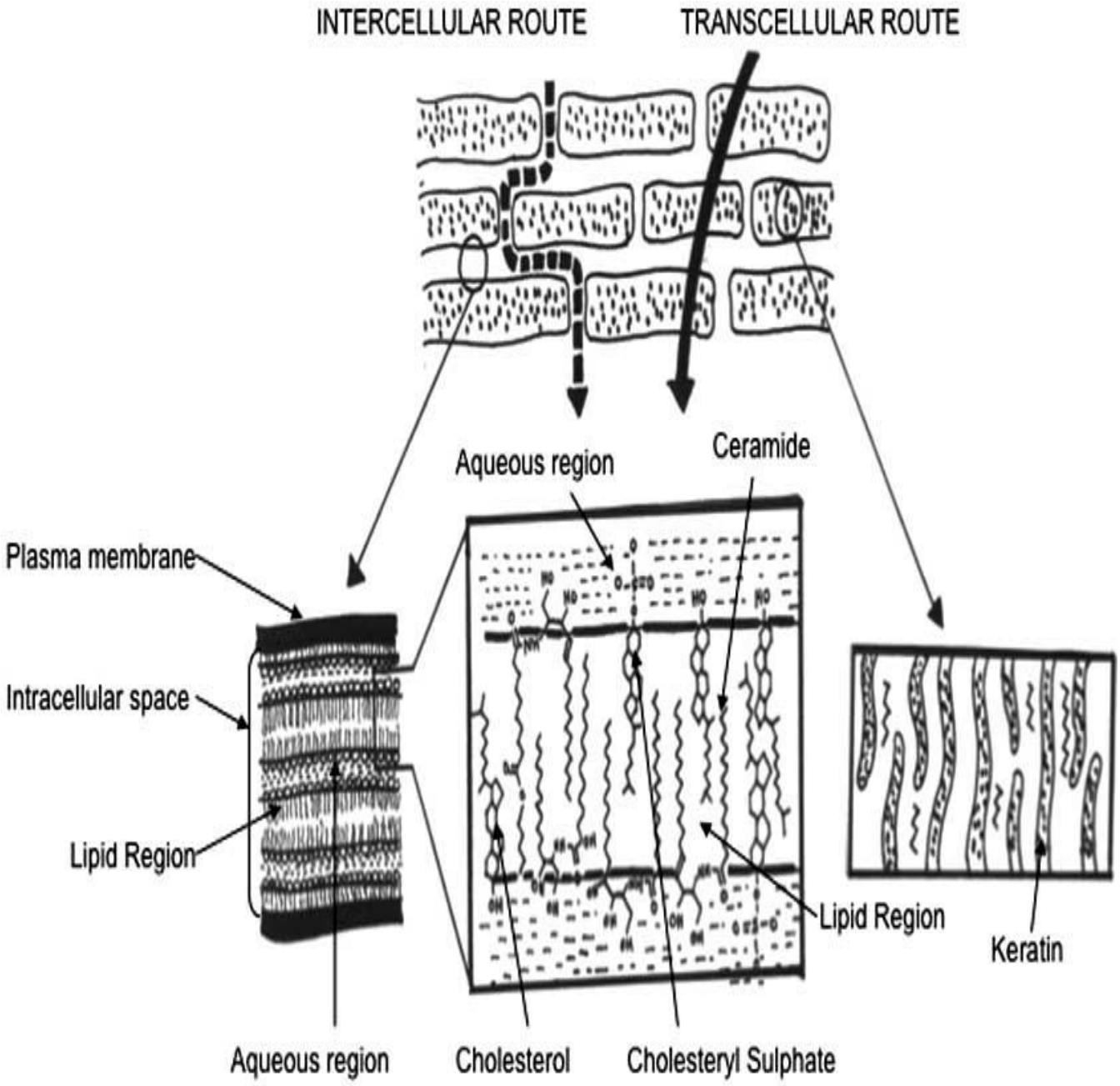
To increase the percutaneous penetration , encapsulation of drug inside the various colloid system like liposomes, niosomes, ethosomes, elastic liposomes, microemulsion. Due to their biocompatibility and capability of incorporating both hydrophilic and lipophilic drugs,liposomes have been investigated as parentral drug and antigen carrier system and more recently as topical /transdermal delivery. Mezei and Gulasekhram first reported their potential use of liposomes as topical delivery.

Conventional liposomes are generally composed of multiple bilayers of phospholipids such as phosphatidylcholine(PC). Cholesterol may be included to enhance the liposome rigidity and stability.

A number of methods of preparation have been described . Following application to the skin surface, conventional liposomes are generally reported to accumulate in the stratum corneum, upper skin layers and in the appendages, with minimal penetration to deeper tissues or the systemic circulation .

Therefore whilst these classical liposomes may have some application for local skin delivery they are not useful as transdermal delivery systems. The first example of a liposomal product for topical application contained the steroid triamcinolone acetonide .

Whilst systemic delivery was lower, drug levels in the epidermis and dermis were four to five-fold greater when applied as a liposomal lotion compared to a conventional formulation. Extensive investigation of conventional liposomal formulations with a wide variety of drugs followed .it increase only the skin deposition not permeation over the skin.



This conclusion leads to the development of various novel vesicular system , In 1990s novel liquid state vesicles were developed these vesicles could better facilitate drug transport across the skin as compared with conventional vesicles.

Novel vesicular system have been recorded to penetrate intact skin if applied non occlusively in vivo ,by virtue of their high and self-optimising deformability.(**Hether A.E.Benson 2009)(Choi.M.J.** and **Maibach 2005)**

TYPES OF VDDS :

There are several types of vdds are formulated

LIPOSOMES :

The Name liposomes is derived from greek words ‘lipos’ meaning fat & ‘soma’ meaning body. Liposomes is simple microscopic vesicules in which an aqueous volume is encapsulated in aqueous space or intercalated lipid bilayer.

Liposomes were first described by british haematologist Dr.Alec D Bangham in 1961 at babrahaminstitute,inCambridge.liposome is a spherical vesicles with a membrane composed of a phospholipid bilayer used to deliver a drug or genetic material into the cell.

CLASSIFICATION :

Liposomes are classified by different methods based on their size ,method of preparation

Classification according to the method of preparation:

- Extraction method VET (vesicles prepared by extraction technique)
- French pressure cell method
- Fusion method
- Reverse phase evaporation method
- Frozen & thawed multilayered vesicles
- Dehydration & rehydration method :DRV
- Stable plurilamellar air vesicles method

Classification according to size :

TYPE	ABBREVIATION	PARTICLE SIZE
MLV	Multilamellar large vesicles	>0.5µm
OLV	Oligo lamellar vesicles	0.1-1µm
UV	Unilamellar vesicles	All size range
SUV	Small unilamellar vesicles	20-100nm
MUV	Medium sized unilamellar vesicles	50-100nm
LUV	Large unilamellar vesicles	>100µm
GUV	Giant unilamellar vesicles	>1µm
MV	Multivesicular vesicles	1µm

ADVANTAGES :

- It provides selective passive targeting to target tissue.
- Increased efficacy and therapeutic index of drug .
- Stable via encapsulation, biocompatible and completely biodegradable.
- Non toxic,flexible and non immunogenic for systemic and non systemic administration.

DISADVANTAGES:

- High production cost.
- Leakage and fusion of encapsulated drug.
- Phospholipid undergoes oxidation and hydrolysis like reaction.
- Short half life.

- Low solubility

NIOSOMES :

Niosomes are microscopic lamellar structure formed on admixture of a non-ionic surfactant,cholesterol,and diethyl ether with subsequent hydration with aqueous media. They can be used as carriers for amphiphilic and lipophilic drugs.

Niosomes are preferred because they exhibit high chemical stability and economy. They improve therapeutic performance of drug molecules by delayed clearance from circulation,

protecting drug from biological environment and restricts to target cells

ETHOSOMES :

Ethosomes are lipid based elastic vesicles ,they are composed of phospholipids,excess concentration of alcohol which make ethosomes unique distribution across the skin layer.lipid membrane packed less tighly than conventional vesicles

hence improved drug distribution through stratum corneum,increase fluidity of cell membrane,increases cell permeability,alters solubility properties of stratum corneum and increase solubility of drug .eg.,levonorgesterol,5-flurouracil.

PHARMACOSOMES :

Pharmacosomes are amphiphilic lipid vesicular system possessing phospholipid complexes of drugs, pharmacon means drug & soma means carrier thus pharmacosomes means drug carrier,system formed by linking drugs to the carrier.colloidal dispersion of drugs covalent bond to the lipids.composed of amphiphilic prodrugs,so high drug entrapment& very low drug leakages occur.increases interfacial tension so increases contact area & finely increases bioavailability.

Eventhough it had lot of advantages ,it having several limitation,covalent bond has to been formed to prevent leakage of drugs,amphiphilic nature is responsible for the synthesis of compounds.on storage undergoes fusion, aggression & chemical hydrolysis.

COLLOIDOSOMES :

Colloidosomes are hollow shell microcapsules consists of coagulated or fused particles at interphases of emulsion droplet,colloidosomes have exciting potential application in controlled release of drugs,proteins,vitamins as well as in cosmetics and food supplements. It have a great encapsulation efficiency with a wide control over size,permeability,mechanical strength and compatability

They were produced first time by encapsulating latex particles adsorbed on the surface of octanol-in-water emulsion drops and removal of oil after fusing monolayers. They can also be template by water in-oil emulsions. The final hollow shells are obtained by removal of central,sacrificial colloidal particles.

Collidosomes assemble polymer latex colloidal particles into shells around water-in-oil emulsion droplets followed by partial fusion of shell and centrifugal transfer into water to yield capsules in which the shell permeability can be controlled by adjacent of partial fusion conditions.

Collidosomes membrane offer great potential in controlling the permeability of the entrapped species and allow the selective & time release.

HERBOSOMES :

The term “herbo” means plant ,while “some” means cell like. The biological active constituent are polar or water soluble phytoconstituents are poorly absorbed of their large molecular size. Herbosomes often called phytosomes.

Exhibit better pharmacokinetic and pharmacodynamic behaviour than conventional herbal extracts . Phospholipids form a molecular layer provides continuous matrix which proteins inserted. It increases the absorption of lipid insoluble polar phytoconstituents through topical as well as oral route thereby increases bioavailability.

SPHINGOSOMES:

Sphingosomes may be defined as concentric, bilayer vesicles in which an aqueous volume is entirely enclosed by a membraneous lipid bilayer mainly composed of natural or synthetic sphingolipid intramuscular, subcutaneous, inhalation. Provide passage for targeting to tumour passively. Improve pharmacokinetic ability.

CUBOSOMES:

Cubosomes are discrete, submicron, nanostructure particles of bicontinuous cubic liquid crystalline phase . Bi continuous water in oil channels are separated by bilayer. The ability of cubic phases to exist as discrete dispersed colloidal particles or phases exist equilibrium with excess water and dispersed.

They are produced by high energy dispersion of bulk cubic phase with colloidal stabilization using surfactants. They possess larger ratio of bilayer and particle volume and large breaking resistance.(**Ashara *et.al.***,)

OVERVIEW OF COLLOIDAL SYSTEMS :

VDDS	SIZE	STRUCTURAL COMPONENTS	TYPES OF DRUG PARTICLES	DRUG LOADING
LIPOSOMES	1-1000nm	Non-ionic surfactant,cholesterol and organic solvent	Lipophilic drug molecules	Low drug loading due to leakage of drug from the phospholipids
NIOSOMES	1-1000nm	Phospholipids,cholesterol and aqueous solvent	Hydrophilic, amphiphilic and lipophilic drug molecules	Drug loading is more than liposomes
TRANSFEROSOMES	1-1000nm	Phospholipids,surfactants,alcohol,and buffering agents	Hydrophilic drug molecules	Drug loading is more than 90% in case of lipophilic drugs
ETHOSOMES	1-1000nm	Phospholipids,ethanol and water	Lipophilic drug molecules	Improved drug loading than liposomes

PHARMACOSOMES	1-1000nm	Phospholipid and organic solvent	Hydrophilic and lipophilic drug molecules	Drug loading is not only high but predetermined because drug itself in conjugation with lipids form vesicles
CUBOSOMES	1-1000nm	Lipids, surfactants(cationic and non-ionic surfactant) and polymers	Lipophilic ,hydrophilic and amphiphilic drug molecules	High drug loading due to stability of the vesicles.

Table :(Harpreet Kaur et.al.,2014)

ELASTIC LIPOSOMES:

It is introduced for the effective transdermal delivery of number of low and high molecular weight drugs. It can penetrate the intact stratum corneum spontaneously along two routes in the intracellular lipid that differ in their bilayers properties.

It consist of both hydrophilic and hydrophobic properties, high deformability gives better penetration of intact vesicles. These elastic liposomes are several orders of magnitudes more elastic than the standard liposomes and thus well suited for the skin penetration. It overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum.

There is provision for this, because of the high vesicle deformability, which permits the entry due to the mechanical stress of surrounding, in a self-adapting manner. Flexibility of elastic liposomes membrane is achieved by mixing suitable surface-active components in the proper ratios.

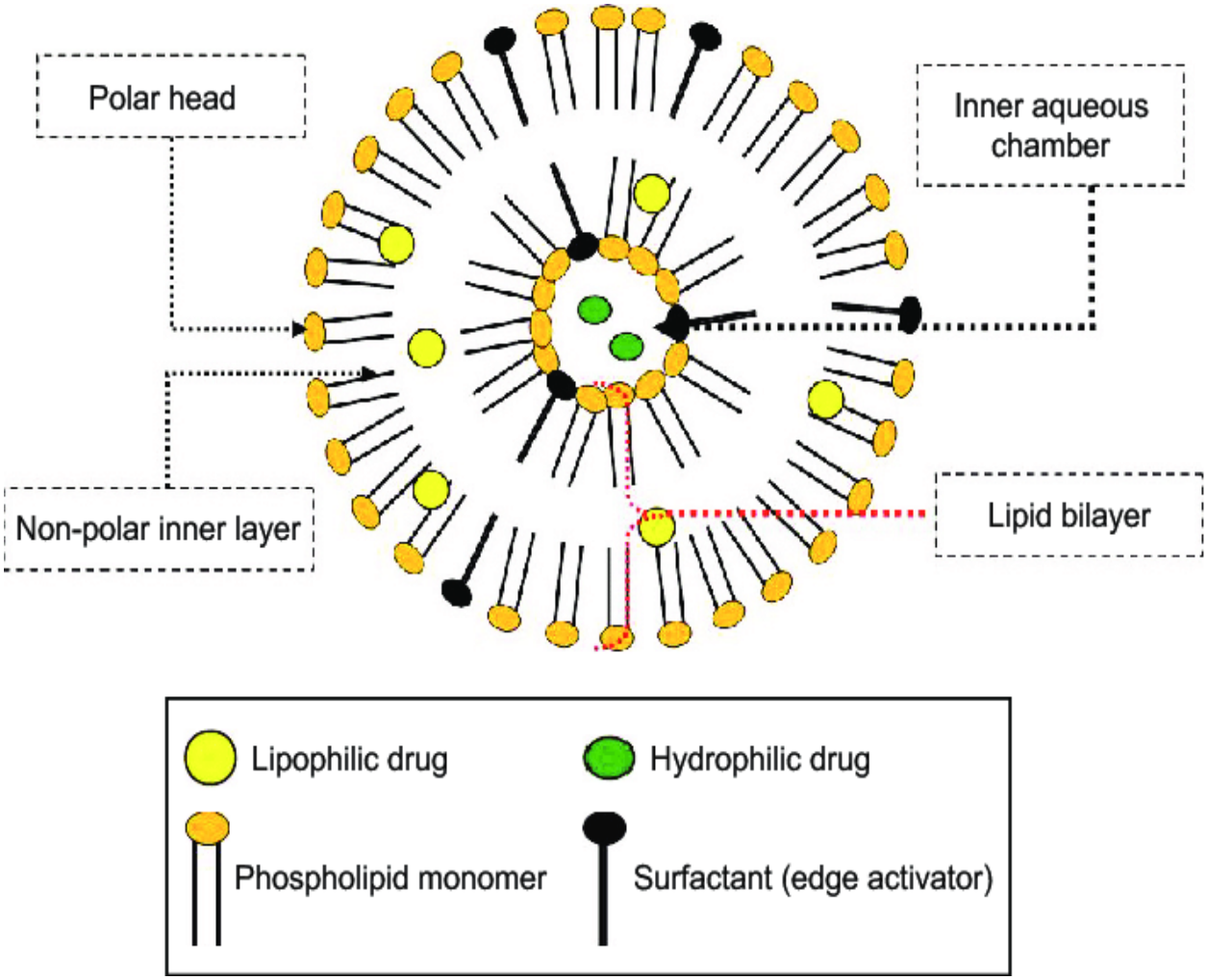
Limitation are chemically unstable because of their predisposition to oxidative degradation, purity of natural phospholipids is another criteria militating against adoption of elastic liposomes as drug delivery vehicles and its formulations.

Elastic liposomes are the most versatile deformable vesicular system that comprise of biocompatabile lipids and surfactants for the delivery of numerous drugs for therapeutic and cosmetic purposes. They are known under different names – deformable liposomes, ultradeformable liposomes, flexible liposomes, ultraflexible liposomes, and transfersomes (pioneered by IDEA AG, Munich, Germany). Such vesicular systems have been developed and reported for topical, nasal, biological (vaccines and toxoids), and transdermal delivery systems comprising hydrophobic and hydrophilic components.

ELs can accommodate challenges faced by traditional drug delivery vehicles due to their improved physicochemical and pharmacokinetic properties.

ELs consist of phospholipids, surfactants such as edge activators (EA), and an inner aqueous compartment enclosed within a lipid bilayer capable of encapsulating hydrophilic (in an aqueous chamber) and lipophilic (in a lipid bilayer) molecules. Moreover, materials such as charged lipids (cationic and anionic), polyethylene glycol (PEG; PEGylation), ethanol, cyclodextrin complexes, and gels have been employed.Its composition influences its physicochemical properties and, subsequently, efficacy by altering skin penetration behavior.

It is note worthy that in vivo skin permeation performance is quite different from in vitro behavior and cannot be justified by in vitro data due to significant differences.The latter mechanism is widely used to determine the permeation behavior of ELs due to convenience.However, comprehensive studies are still needed on ELs to glean sufficient in vivo data.(**Hussain *et.al.*,2017**)



In 1992, Cevc and Blume were first credited with the introduction of this novel alternative to conventional liposomes to facilitate drug passage across the stratum corneum (SC) of skin. ELs are colloidal lipid nanocarriers composed of unique components with characteristic ultra deformability and elasticity to squeeze across microlamellar spaces (which are 1/10th the vesicle diameter) among keratinocytes to pass intact across the skin layer and increase skin hydration to improve transepidermal water loss (TEWL) .

Presently, the enhanced permeability of ELs is generally significant enough due to synergistic effects of ELs acting as a carrier andpenetrant.impressively EL vesicles can penetrate the skin without disintegration.

ELs delivery used for the delivery of hydrophilic ,lipophilic drugs,thermolabile drugs(proteins and peptides),and pH sensitive molecules (enzymes) and chemical sensitive compound, toxoid, nucleic acid, vaccines with more significant outcomes.

MECHANISM OF PERMEATION AND PENETRATION ACROSS THE SKIN :

Skin is the most prominent first line barrier for numerous drugs after topical application several efforts have suggested successful delivery into or across the skin by employing ELs, with or without physical methods.

Topical application of dispersed elastic liposomes in an aqueous suspension on the skin leads to the following sequence of Events . First, the water in suspension starts immediately to evaporate, increasing the concentration of all non-volatile components on the skin.

When saturation is reached, the hydration gradient along the skin barrier becomes available to the elastic liposomes. The water concentration increases from around 10 to 30% at an air-exposed Stratum corneum (SC) surface to around 75% in the viable epidermis.

Based on this transepidermal hydration gradient, the liposome's high elasticity and hydro-affinity allow and prompt the drug-loaded vesicles to'pull' across the skin barrier. The process continues until the vesicle has reached the water-rich viable epidermis.

Then the 'pull' can be replaced by a 'push' on the liposome which already crossed the SC by diffusion-based re-distribution.The 'push' is exerted by the elastic liposomes still sensing the hydration gradient in the SC; intercellular fluid motion in living skin may also be influential.

It should be noted that elastic liposomes do not penetrate the SC without a transcutaneous hydration gradient. Consequently, elastic liposomes should not be applied under occlusion because this would decrease the hydration gradient.

The unique structure of the skin layer is often depicted as the so called " brick and mortar" pattern, which additionally makes the SC ~ 1000 fold more poorly permeable as compared to other biological membranes.

SC is a well known effective barrier to prevent entry of foreign particles into the body .Structurally,the SC has a brick and mortar pattern ,where the corneocytes of hydrated keratin (brick) and flattened keratinocytes (mononucleated) are interspersed in the intercellular matrix of non polar lipids(mortar).

To overcome the aforementioned problem,dosage form has to penetrate through the SC layer,for that addition of Edge Activator (EA) in the elastic vesicles result in deformability to penetrate across the dense SC layer, which contains very small "pores" relative to the vesicle diameter. The SC layer is composed of 15–20 layers with a thickness of 10–15 μm (dry skin) that serves as rate-limiting barrier in transdermal delivery.

Its thickness reaches to 40 μm when swollen on hydration.Researchers have reported that "pores" in the SC barrier are at least 10 times smaller (1/10th of vesicles) than the ultradeformable vesicle diameter (which generally exceeds 100 nm). Moreover, the largest pores on the skin surface are provided by hair follicles and sweat ducts that play insignificant roles in liposomal transdermal drug penetration.

The size obtained from electron microscopy suggests that liposomes up to 600 nm in diameter can penetrate through the skin, whereas sizes >1,000 nm remain in the SC.Thus, the preferred size range of vesicles for topical/transdermal delivery should be 100- 1000 nm**.(Hussain *et.al*.,2017)(Heather A.E.Benson,2009)**

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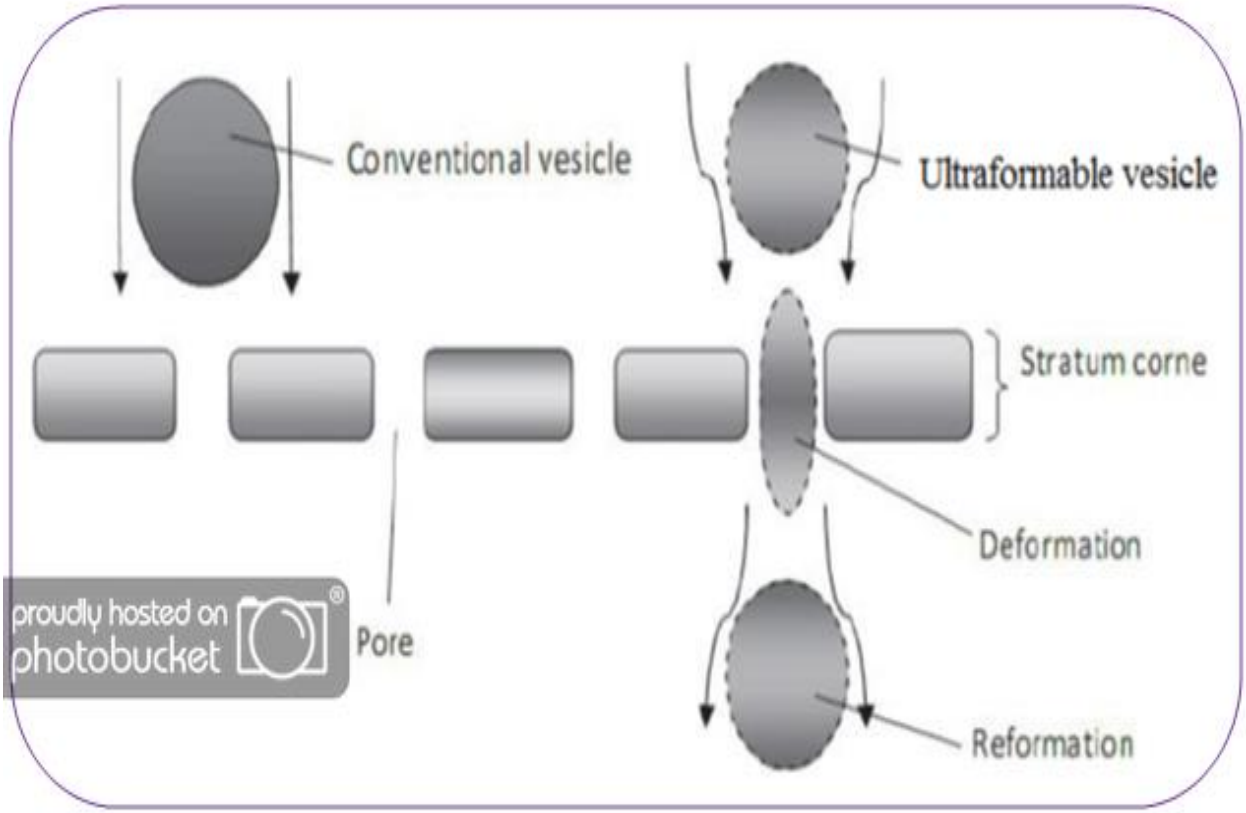
MECHANISM OF ELASTIC LIPOSOMES:

- Elastic liposomes are advantageous as phospholipids vesicles for transdermal drug delivery. Because of their self-optimized and ultra flexible membrane properties

- They are able to deliver the drug reproducibly either into or through the skin, depending on the choice of administration or application, with high efficiency.

- The vesicular liposomes are more elastic than the standard liposomes and thus well suited for the skin penetration.

- Elastic liposomes overcome the skin penetration difficulty by squeezing themselves along the intracellular sealing lipid of the stratum corneum



FORMULATION OF ELASTIC LIPOSOMES:

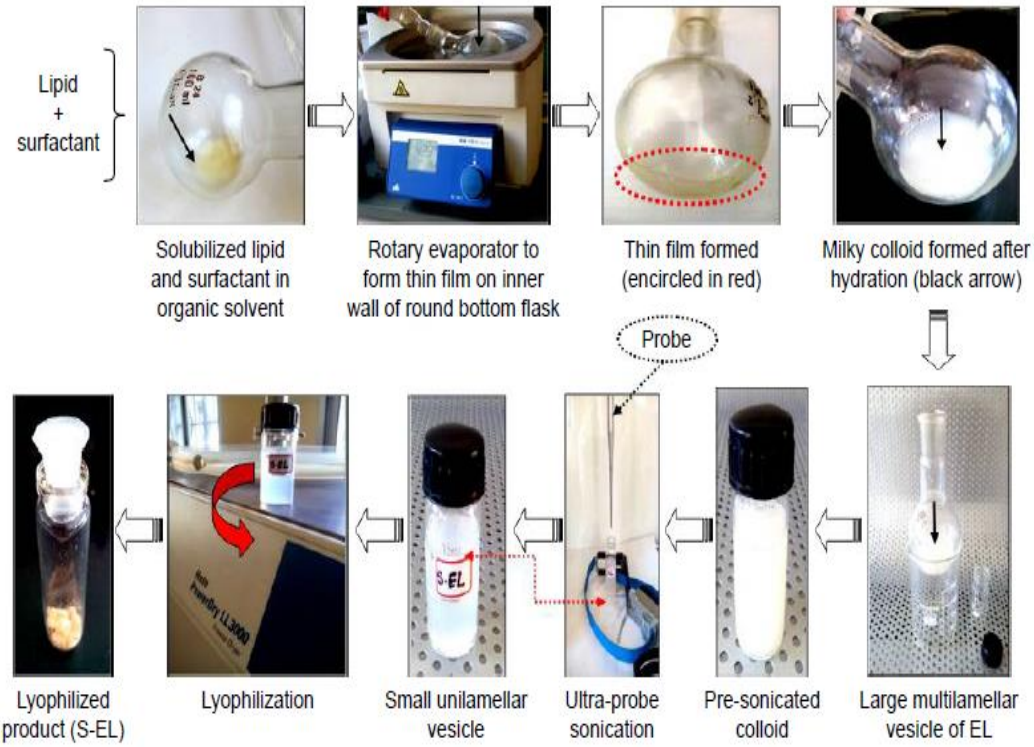
THIN FILM HYDRATION METHOD:

- The elastic liposomes will be prepared by conventional rotary evaporation method, the molar ratio of phospholipids, surfactant will be taken in a clean, dry, round bottom flask and lipid mixture will be dissolved in methanol or chloroform: methanol (2:1 v/v).

- The organic solvents will be removed by rotary evaporation above the lipid transition temperature.

- Final trace of solvent will be removed by vacuum overnight. The deposited lipid film will be hydrated with drug solution in ethanol by rotation at 60 rpm for 1hr at room temperature, the resulting vesicles will be allowed to swollen for 2hrs at room temperature to get large multilamellar vesicles(LMLV).

- To prepare smaller vesicles it will be further sonicated for 20mins at 40W (Probe ultrasonicator)



ADVANTAGES OF ELASTIC LIPOSOMES :

Topical elastic liposomal administration might offer an opportunity for developing a novel delivery system that could overcome these limitations experienced with the systemic and oral liposomal formulation as well as conventional product.the major advantages of topical elastic liposomal formulation include:

1. Reduction of side effects and incompatibilities that may arise from undesirably high systemic absorption of drugs .

2. Marketedly increasing the liposomal drug accumulation in the desired tissue.

3. High penetration ability of formulation increases absorption of drug and avoid degradability of drug via oral route.

4. Capability for incorporation of a wide variety of hydrophobic and hydrophilic part of drug.

BASIC INGREDIENTS OF ELASTIC LIPOSOMES :

PHOSPHATIDYLCHOLINE :

The membrane of liposomes is mainly composed of PC, amphipathic molecules in which a glycerol bridge links a pair of hydrophobic acyl hydrocarbon chains with a hydrophilic polar headgroup of phosphotidylcholine.

The PC acyl chain length and saturation degree have an effect on the phase transition temperature (Tm) of liposomal membrane. Above Tm, lipid chains partially fluidize, owing to their thermally driven conformational isomerization. It is also almost always true that the fluid-chains vesicles with a rather elastic bilayer promote drug transport across skin barrier better than the more rigid liposomes .

Therefore, the most common PC used to prepare elastic liposomes is unsaturated PC (i.e., soybean phosphatidylcholine [SPC] or egg phosphatidylcholine [EPC]) with a much lower Tm (< 0ºC).

PC composition can exert a significant effect on the stabilityof liposomes . For elastic liposomes, the usage of unsaturated PC with lower Tm (< 0ºC) leads to higher fluidity and lower stability of vesicles during storage. In addition, freezedryingis a technique used to dehydrate conventional liposomes to increase stability during storage.

However, it was found that elastic liposomes suffered irreversible aggregation when rehydrated after freeze-drying, even in a high sugar ratio to lipid mass of 4:1 . Therefore, the long-term storage stability problem of elastic liposomes, especially the significant drug leakage from the vesicles, should be given particular
attention.

As the Tm of liposomes can be flexibly modified by changing the ratio of different PCs in the liposomal membrane , the effect of Tm on permeation behaviour and stability of the vesicles should be intensively investigated.

For example, the Tm values can be set as 30ºC. During storage (25ºC), the rigid elastic liposomes are stable because the Tm is higher than storage temperature. Following administration to skin, the liposomal membrane turns into a liquid state due to the skin temperature (32ºC). In this way, both satisfactory stability and elasticity can be obtained simultaneously.

Edge activator:

EA is usually a kind of surfactant, which destabilizes the lipid bilayer of the elastic liposomes and increases elasticity of the bilayer simultaneously. Among EAs, sodium cholate, sodium deoxycholate, Span 80, Tween 80 and Tween 20 were commonly used.

(El Maghraby et al.) showed that incorporation of surfactants into liposomes significantly reduced the mainTm, which induced fluidization of the lipid bilayer. Furthermore,El Maghraby et al. suggested that some chemical penetration enhancers such as oleic acid can also be used as EA to replace the commonly used surfactant

.

The elasticity properties of elastic liposomes depend on the EA. Only at the optimal balance between the amount of EAand the amount of bilayer forming PC, are the vesicles elastic. If the EA level in the vesicles is too low, the vesicles are rigid and if the concentration of EA is too high, most vesicles turn into micelles

TWEEN

It is a non-ionic surfactant,soluble in water.It is distributed between lipid bilayer and aqueous phase when encapsulated in liposome. It enhance the permeation capacity of elastic liposomes when compared to the conventional formulation.

It has mainly two types Tween 20 and Tween 80.Whereas,Tween 80 is mostly applied as an EA. Used extensively for cationic elastic liposomes

SPAN

Span, which is lipophilic in nature, has a high affinity for lipid bilayers. Different Span surfactants have been compared with EA. Elastic liposome formulations of propranolol hydrochloride were prepared using different Span types (Span 80, Span 60 and Span 40) and different concentration levels (SPC: EA = 95:5, 90:10, 85:15, 80:20 and 75:25, w/w) [32]. Transdermal flux first increased with increasing EA concentration (SPC:EA = 95:5 to 85:15) and then decreased (SPC: EA = 85:15 to 75:25), a common phenomenon seen with all three surfactants(**Chen J *et.al*.,2013**)

TRANSDERMAL GEL FORMULATION :

Elastic liposomes has been administered as topical drug delivery system because of its much higher diffusivity in the skin compared to most bare.liposomal formulation are widely used in the pharmaceutical field as drug delivery system due to their versatility and clinical efficacy and they have been used to administer drugs by several routes such as the oral,parentral,and topical.

Among these, topical delivery of drugs carried by liposomes exhibits interesting applications, not only for promoting dermal delivery of drugs which have to act topically, such as

local anesthetics, but also for enhancing topical delivery of drugs intended for systemic use, thus more effectively exploiting this non-invasive alternative route to oral administration.

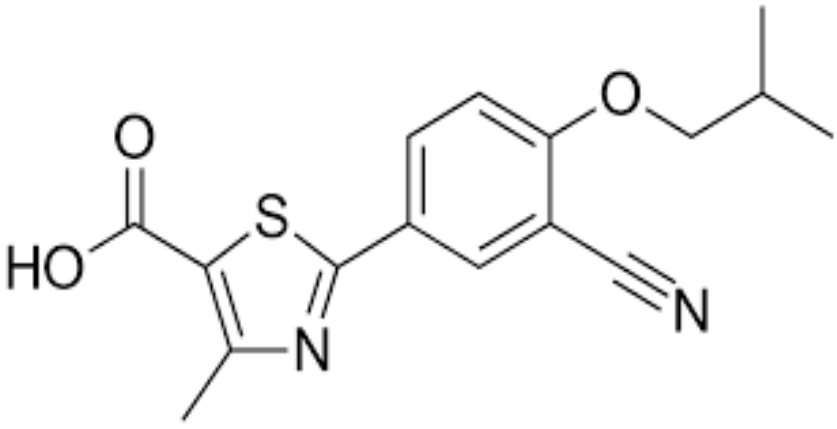
Due to the fore mentioned advantages, in this study liquid-state elastic liposomes were chosen to serve as the drug delivery system. Although liposomes demonstrated promise for Topical drug delivery, the practical application of these formulations onto the skin is less. However, these can be incorporated into the gels than can be applied onto the skin. It has been found that liposomes incorporate into the gels are stable .

However, the major limitation of using liposomes topically is the liquid nature of preparation. That can be overcome by their incorporation in an adequate vehicle where original structure of vesicles is preserved. It has already been shown that liposomes are fairly compatible with gels made from polymers derived from cross linked poly (acrylic acid), such as Carpobol® resins.

Moreover, some Carpobol® has proved excellent bioadhesive properties on the mucosal surface that would increase residence time and at the same time increase absorption of the drug. Therefore, it seemed logical to choose gels prepared from Carbopol 934 as a vehicle for the incorporation of elastic liposomes destined for topical delivery.

FEBUXOSTAT:

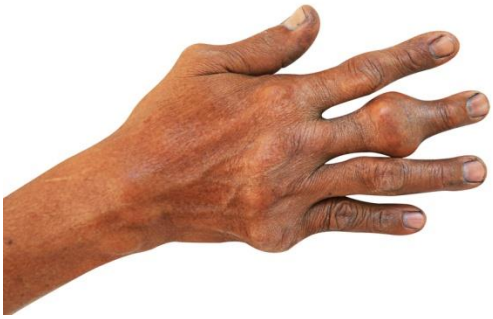
It is an anti-gout drug choosen for formulating elastic liposomes. Because of its oral bioavailability affected by enzymatic degradation, presence of food also decrease its Cmax by38-39% and also it is insoluble in water. It is overcome by this type of formulation and for prolonged therapeutic action.

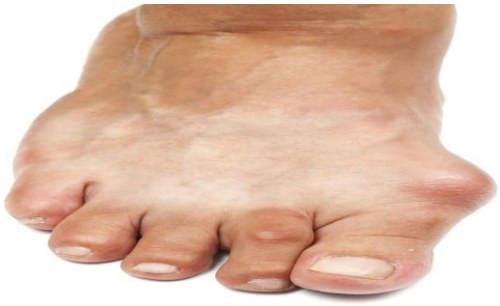


DISEASE –GOUT:

Gout is a kind of inflammatory arthritis characterized by recurrent which is a caused by the formation of monosodium urate crystal in joints.when the concentration of uric acid exceeds the solubility limit i.e. 6.7mg/dl at physiological pH ,It may nucleate to form crystals in tissues and joints.

gout is mainly diagnosed by identification of the pathogenic MSU crystals by joint fluid aspiration or in tophiaspirate.lowering serum uric acid level below deposition threshold either by a dietary modification and using serum uric acid lowering agents is the main goal of gout.





EPIDEMIOLOGY :

The general prevalence of gout is 1–4% of the general population.In western countries, it occurs in 3–6% in men and 1–2% in women. In some countries, prevalence may increase up to 10%. Prevalence rises up to 10% in men and 6% in women more than80 years old.

Annual incidence of gout is 2.68 per 1000 persons.It occurs in men 2–6 folds more than women. Worldwide incidence of gout increases gradually due to poor dietary habits such as fastfoods, lack of exercises, increased incidence of obesity and metabolic syndrome**.**

PATHOGENESIS OF HYPERURICEMIA:

Urate is the ionized form of uric acid present in the body. Uricacid is a weak acid with pH of 5.8. Urate crystals deposition in tissues starts to occur when serum uric acid level rises above the normal threshold. Pathological threshold of hyperuricemia is defined as 6.8 mg/dL.

Some factors may affect the solubility of uric acid in the joint.These include synovial fluid pH, water concentration, electrolytes level, and other synovial components such as proteoglycans an collagen.

SUA level in the body is determined by the balance between its production either from purine intake in diet orendogenous production by cellular turnover and its excretion by the kidneys and GIT.

Increased production of UA is responsible for only 10% of cases of gout while the remaining 90% are caused by its renal under-excretion. Factors which affect SUV level include Age and Gender`,male are prominently affected than female.

OVERPRODUCTION OF URIC ACID :

Deficiency of enzymes involved in purine metabolism leads to over production of UA. For example, Lesch-Nyhan syndrome is an inborn error of metabolism resulting from deficiency of an enzyme involved in UA metabolism named hypoxanthine–guanine phosphoribosyl transferase.

DIET :

Ingestion of foods rich in purines such as cooked or processed food especially from animal and seafood origin is a key element of increasing uric acid precursors Alcohol is a well-known risk factor for gout.

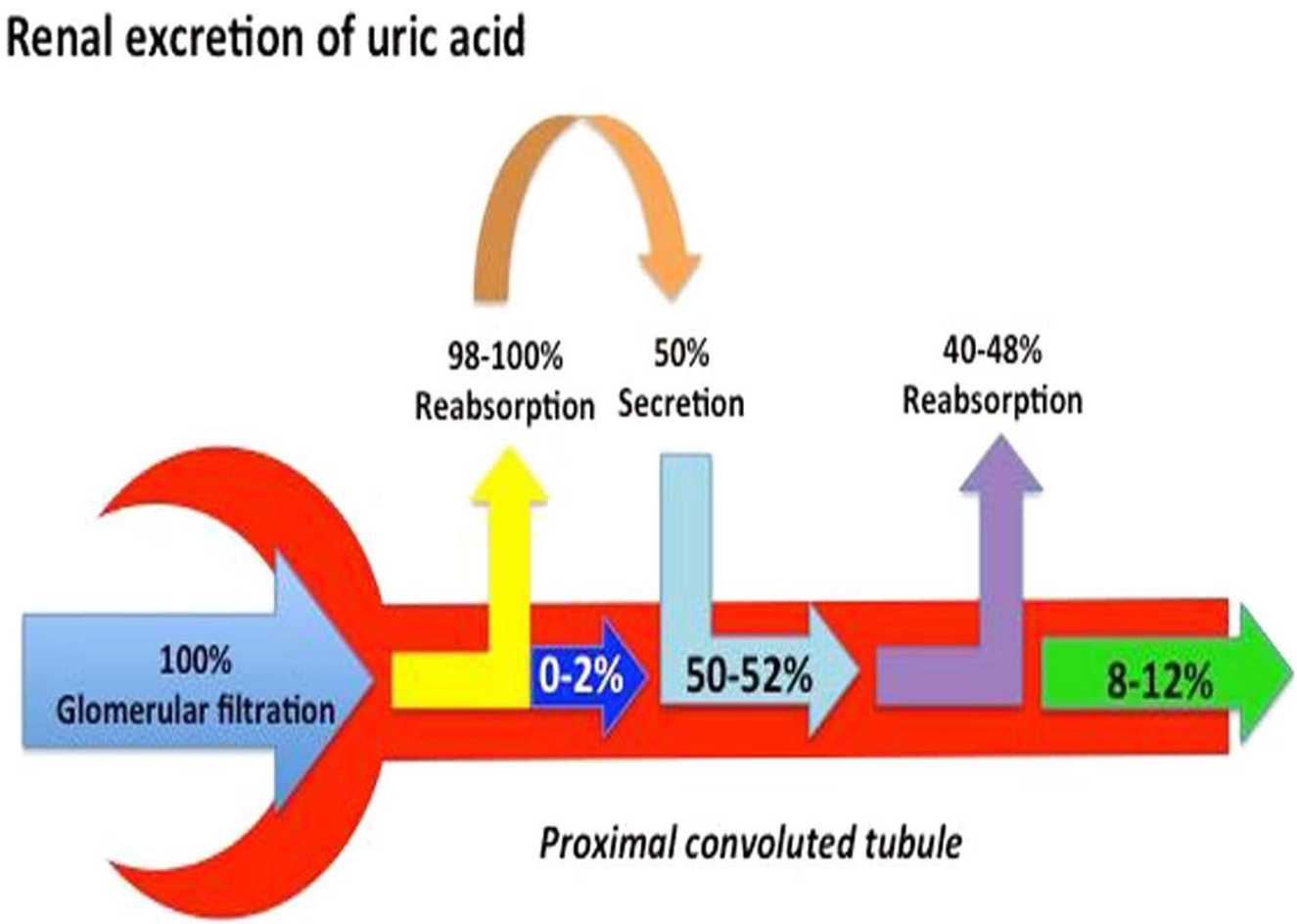
Studies showed that alcohol consumption is related to the amount consumed. Additionally, the risk for gout and hyperuriceamia depends on the type of different alcoholic drinks.

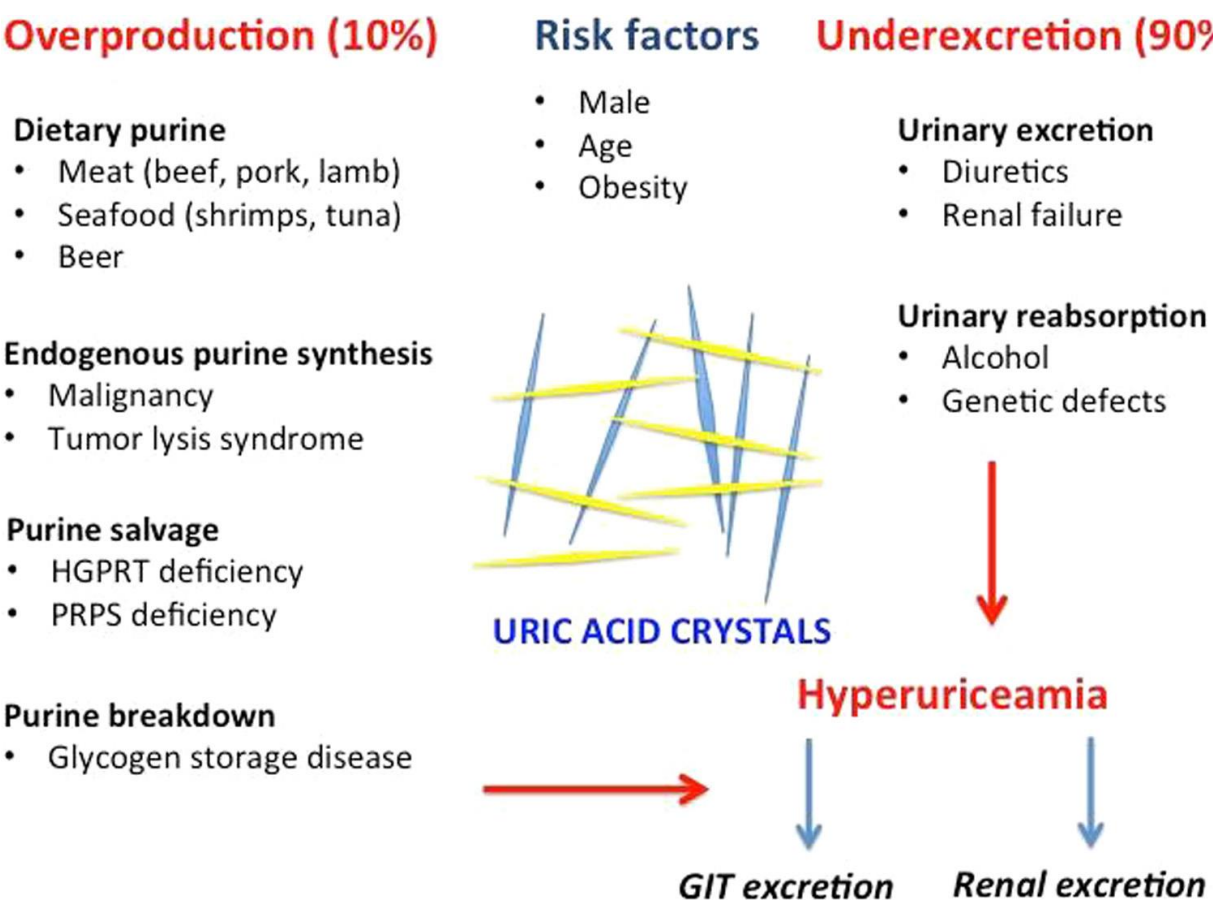
For instance, beer is the worst in increasing the risk for gout compared to liquor. While the lowest risk among alcoholic drinks was for wine

DECREASED EXCRETION OF URIC ACID:

Two thirds of urate excretion occurs in the kidneys while therest is excreted through the gastrointestinal tract (GIT).

Reduced secretory function of the transporter ABCG2 leads to decreased excretion of uric acid through the GIT resulting in rise of serum levels of uric acid and enhanced renal excretion



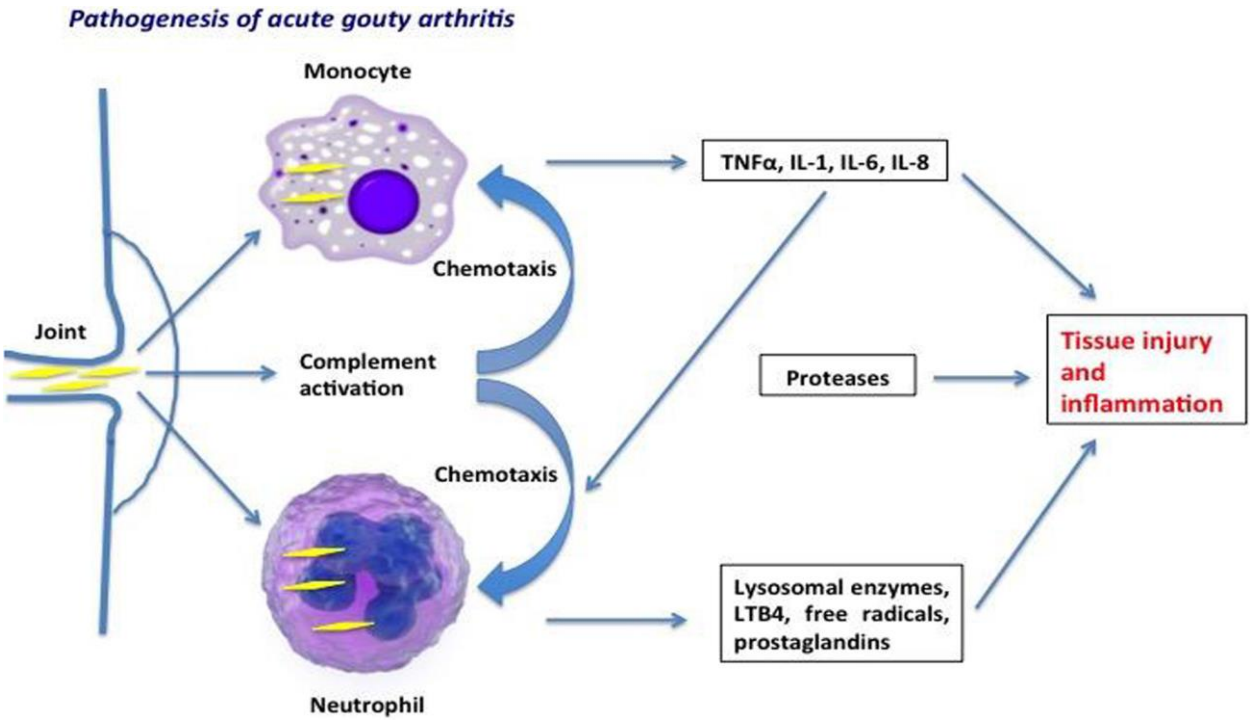


TYPES OF GOUT CONDITION :

- Acute gouty arthritis
- Chronic gouty arthritis

ACUTE GOUTY ARTHRITIS :

Deposition of UA crystals in the joint cavity is the triggering cause of gout. These crystals initiate the inflammatory process by being engulfed by synovial phagocytic cells leading to release of lysosomal enzymes and production of inflammatory chemokines.acute gout condition is also caused by various other mechanism.



CHRONIC GOUT :

Chronicity is a feature of gout. It results from chronic inflammation that follows recurrent attacks of gout. Chronic gout manifests by chronic synovitis, bony erosions, cartilage damage and tophi formation. This can be explained by different mechanisms. (**G.Ragab *et.al*.,2017**)

Presence of urate crystals in the synovium leads to stimulation of chondrocytesto produce inflammatory cytokines, nitric oxide and matrix metalloproteases resulting in cartilage damage.

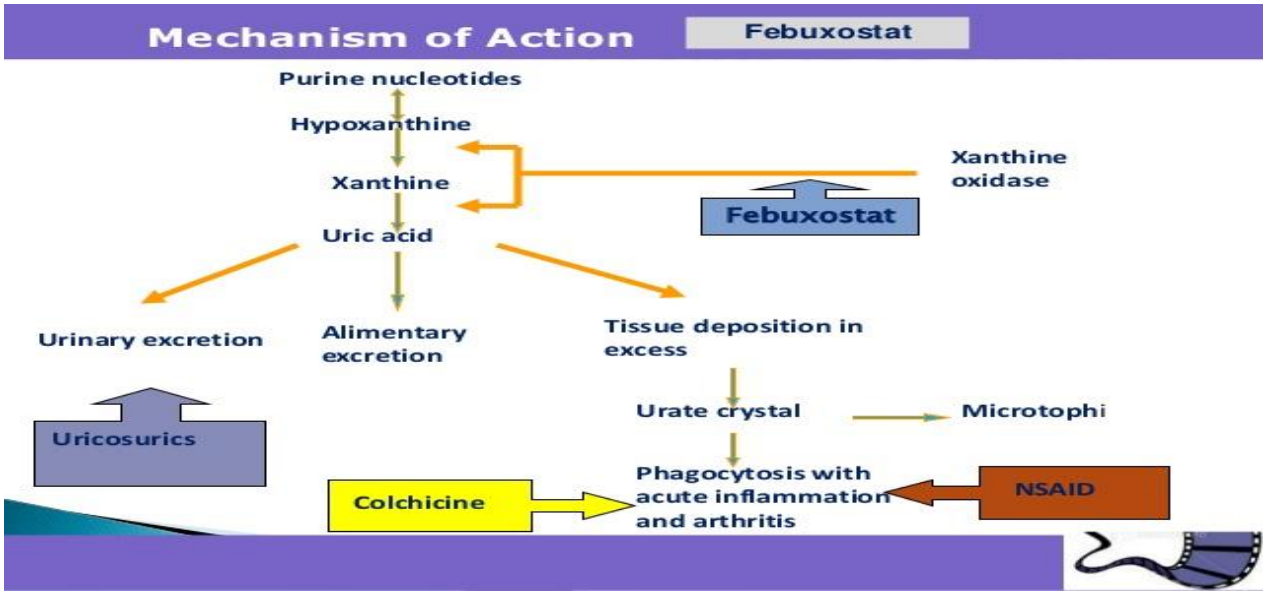
As we know about the pathology of gout,it was treated by two famous pharmacological methods such as

1. Reduction of urate production by the use of xanthineoxidase inhibitor-Allopurinol and ***Febuxostat***

2. Enchancement of uric acid excretion (uricosuric agent) –probenicid

MECHANISM OF ACTION:

It is a xanthine oxidase inhibitor. Inhibits the enzyme and reduce the urate production and inturns gout.



LITERATURE REVIEW

1. **`Singh .*et.al*..,[2016]**

Study is about the formulation of elastic liposome gel on opioid analgesic, optimise the formulation by varying concentration of surfactants. In this work elastic liposome of tramadol were prepared by using a solvent evaporation method with different surfactants like span 80, tween 80,SDC and characterised by using microscopy, particle size, shape, drug content ,drug release and zeta potential. It is further formulated as an transdermal gel.Optimised formulation were found to be in the range of 152. 4nm with a zeta potential of -22.4mV and also it shows better entrapment efficiency(79.71%±0.27%). this results revealed that deformable vesicle is a promising carrier for transdermal delivery.

2. **Huang.Y.B. *et al*.,[2010**]

Elastic liposome of catechin is formulated in this study by thin film hydration method by using tween 80 as surfactant in presence of 15% of ethanol. Increasing in the Tween 80 concentration which decreases the zeta potential of formulation upto -15mV and reduces the particle upto 70nm, More than 80% of (+)catechin was entrapped in the aqueous core of liposome is formulated with 1% of tween 80. In vivo pharmacokinetic study is conducted in rats revealed that elastic liposome of catechin is able to produce 2.7 fold higher (+) catechin accumulation than aqueous solution.

3. **Singh utreja *et a*l.,[2009]**

Topical delivery of colchicine is developed in the form of elastic vesicle in this study and characterised in vivo and in vitro using rat skin .its formulated by conventional rotary sonication method.optimised formul;ation showed 7-11 increase in the transdermal flux in the range of 32.8 to 44.4µgh/cm^2.Skin deposition study showed 12.5 times higher skin deposition as compared to drug solution of colchicines.Antigout activity in rats is assessed by using parameters like reduction in leukocyte count,exudates volume, decreases

in inflammatory cell accumulation and collagen deposition for 24 hrs, result showed better sustained biological effect than drug solution

4. **Hussain *et al*.,[2017]**

This review provides insights into the versatile role that elastic liposomes play in the delivery of numerous drugs and biomolecules by improving drug release, permeation and penetration across the skin as well as stability.this provides an importance of surfactants in the formulation and transdermal delivery of various drugs, furthermore ,it provides future directions that should ensure the widespread use of ELs across the medical fields.

5. **Ming –jun Tsai *et al.,[*2015]**

A potent antioxidant naringenin is developed as elastic liposomes for topical application containing different amounts of tween 80 and cholesterol. It is characterised for vesicle size, surface charge, encapsulation efficeiency, permeability capacity. stability and skin irritation is assessed by clinical utility. optimised formulation shows higher deposition amounts in the skin of naringenin were significantly increased about 7.3-11.8 folds. It also exhibits less irritating compare to that of control group and has potent therapeutic application.

6. **Trotta.M. *et al.,[*2002]**

This study evaluate the skin delivery of dipotassium glycyrrhizinate ,an anti-inflammatory agent employed in treating acute and chronic dermatitis, and of formulating such liposomes in an oil-in-water emulsion (O/W). KG had emulsifying properties and the possibility of producing elastic liposomes was verified. Liposomes containing soya lecithin (PC) or hydrogenated soya lecithin(HPC) mixed with KG in w/w ratios of 2:1, 4:1 or 8:1 were prepared by the solvent evaporation method and then through a high pressure homogeniser.thus, liposome is formed in the size range of 90-120 nm and with

the entrapment efficiency of about 4:1w/w.skin deposition increased 4.5 fold compared with the aqueous solution when KG was formulated in liposomes.

7. **Mishra *et al*.,[2006**]

Ultra deformable elastic vesicles was prepared by incorporating propranalol hydrochloride by conventional rotary evaporation method and characterised for various parameters like vesicles shape,surface morphology,size and size distribution, entrapment efficiency,elasticity,turbidity and in vitro drug release.In vivo study was performed in male albino rats.better permeation through the skin was confirmed by confocal laser scanning microscopy. Results provided that formulation had better transdermal flux,higher entrapment efficiency,ability as a self penetration enhancer and effectiveness for transdermal delivery as compared to liposomes.

8. **Dubey.V. *et al*.,[2006]**

Develop a novel formulation of melatonin which had shorter biological half life,low molecular weight and a variable oral absorption.elastic liposomal formulation of melatonin enchances its efficient transdermal delivery,and its permeation is investigated using franz diffusion cell and permeation potential of the developed formulation was assessed through confocal laser scanning microscopy.It showed enhanced transdermal flux 51.2±2.21µg/cm^2/h. The obtained flux was nearly 5 and 12.3 times higher than conventional liposomal and plain drug solution.

9. **Choi.M.J and Maibach.H.I *et.al*.,[2005]**

Review article provide information about the vesicles –skin interaction and significance of elastic vesicles in the skin permeation.Composition and difference among the transfersomes and ethosomes ,Elastic vesicles Mechanism of action on penetration ,highly deformable vesicles improve the transdermal delivery of low and high molecules in vitro and in vivo system .it

overcomes the limitation of low penetration ability of conventional liposomes across the skin.

10. **Heather A.E.Benson *et al.,[*2009**]**

Elastic liposomes are applied non occluded to the skin and have been shown to permeate through the stratum corneum lipid lamellar regions as a result of the hydration or osmotic force in the skin.This review provides an overview of the development of elastic vesicles for delivery into and via the skin.The deformable vesicle concept can be applied to a variety of compositions with the potential to optimise the skin deposition and permeability of a range of therapeutic molecules.It can deliver enhanced amounts of both small and large therapeutic agents into and through the skin.

11. **Ravikumar *et al.,[*2010]**

Develop and evaluate the elastic liposomes of clotriamazole to provide sustained release and to enhance the antifungal activity of the drug. It was formulated by rotary evaporation method using span 80 as an edge activator.Formed vesicles were evaluated for entrapement efficiency,vesicle size,stability study,in vitro drug release study, ex vivo permeation study and microbiological study.optimised formulation shows better entrapment efficiencies 73.5% ±1.61,vesicles size (100nm) and nominal vesicles distribution ,exvivo study confirmed that it had higher skin permeation property.

12. **Chen.*J et al.,[*2013]**

This review article provides an overview of the formulation ingredient of elastic liposomes and their relationship with skin permeation behaviour. Mainly in this articles it categories basic ingredient and optional ingredients in the formulation. For the choice of ingredients, their effects on drug loading, zeta potential, elasticity and stability of the vesicles is needed to taken into account to obtain satisfactory skin permeation behavior. More attention should be paid

to drug leakage from the vesicles, whether following administration or during long-term storage, for the development of elastic liposomes.

13. **Ragab.G *et al.*,[2017**]

This review states about the epidemiology and pathogenesis of gout.it is considered as nemesis of longevity. it emphasise the identification of MSU crystals in the synovial fluid using polarised light microscopy. it decribes about the various ways of management of disease.

14. **Cereda.C.M. *et al.,[*2013]**

This study developed a elastic and conventional liposomes of butamben .characterised for vesicle size and surface charge, Fluorescence anisotropy, encapsulation efficiency, partition coefficient. Phase separation is used for determining encapsulation efficiencies and membrane water partition coefficient. Elastic liposomal formulation showed better results than conventional formulation thus the anaesthetic access through the skin can be considerably enhanced using liposomal gel formulations compared to plain gel formulations.

15. **Cadena PG *et al.,[*2012]**

This based on the fact that quercitin and resveratrol induce a synergistic inhibition of the adipogenesis and increase apoptosis in adipocytes. It is a new approach for dissolving subcutaneous fat.encapsulation efficiency is almost 97% and zeta potential is slightly negative with a size range of 149nm.It is suitable for delivery in effective way and provides a new strategy for reducing subcutaneous fat.

16. **Utreja.P *et al*.,[2011]**

This study focused on localised delivery of paclitaxel using elastic liposomes. It is extensively characterised in vitro,ex vivo and in vivo.these results were compared against marketed formulation. These studies revealed that transdermal flux is 10.8 folds greater than the marketed form and 15 folds enhanced drug deposition in comparison to drug solution.It demonstrate that elastic liposomes as a carrier is an attractive approach for localised delivery of paclitaxel.

17. **Pinon E *et al*.,[2011]**

The objective of this study was to formulate keterolac tromethamine loaded elastic liposomes and evaluate their in vitro drug release and their ex vivo and in vivo transdermal delivery. It is prepared by flim hydration method. Entrapment efficiency of 73±11% with the vesicle size 127.8±3.4nm and a zeta potential of -12mV.In vitro drug release is determined using franz diffusion cell. These liposomes have the potential to transport the drug through the skin, keep their sizes and drug charge and release the drug into deep skin layers. It hold promise for the effective topical delivery of ketorolac.

18. **Tiwary.A.K *et al*.,[2010]**

This study develop a cyclodextrin colchicine complex and to study its effect on skin permeation and deposition of colchicine. It is prepared by Freeze drying method. It showed 6 fold increase in transdermal flux in comparison to drug solution. Biological evaluation of various vesicular formulations and drug solution was carried out using monosodium urate induced air pouch model. In vivo studies are done using rat and observed for exudate volume, reduction in leukocyte count, decrease in inflammatory cell accumulation and collagen deposition. In conclusion, this approach possess good potential to enhance skin accumulation, prolong drug release and improve the site specifity of colchicine.

19. **Jain S *et al*.,[2008]**

This study developed an elastic liposome of zidovudine for lymphatic targeting .It is prepared and characterised for in vitro,ex vivo and in vivo parameters. Plain and PEGylated elastic liposomal formulation revealed the transdermal flux of 99.8±5.8 and 119.5±5.2µg/cm^2/hr acrossed the rat skin. Results of biodistribution study indicated 27 fold higher accumulation of AZT in lymphoid tissues after application of PEGylated elastic liposomes as compared to free drug. It has better cellular uptake in the form of elastic liposomes.This approach for overcoming the toxicity by its selective uptake in lymphoid organs.This is an attractive approach for sustained and targeted delivery of AZT.

20. **Garg T *et al*.,[2008]**

This study prepared a topical formulation for sustained delivery of rizatriptan and characterised for in vivo and in vitro parameters. In vivo study is done using mice. In vitro skin permeation study is also done using rat skin suggested carrier mediated transdermal permeation for different elastic liposomal formulationto range between 18.1 ±0.6 and 42.7±2.3 µg/h/cm^2 which was approximately 8-19 times higher than that obtained using drug solution. Drug deposition is 10 folds high for elastic liposome than drug solution. biological activity is three folds higher than drug solution.In conclusion, this formulation provides a sustained action of rizatriptan due to depot formation in the deeper layer of skin.

21. **Qiu Y *et a*l.,[2008]**

This study developed an elastic liposomes in a combination method of using micro needle pretreatment and it is mainly developed to increase skin permeation of drugs with high molecular weight and poor water solubility.It is evaluated using rat and porcine skin in vitro .elastic liposomes loaded with docetaxel can enhance transdermal delivery of DTX without microneedle

treatment.This combination of elastic liposomes with microneedle pretreatment can be a useful method to increase skin permeation of drugs with high molecular weight and poor water solubility.

22. **Jain S *K et al.*,[2008]**

This study developed an elastic liposomes bearing acyclovir and it is characterised parameters like vesicle shape and surface morphology, size distribution, entrapment efficiency, elasticity, polydispersity index, turbidity and in vitro release pattern. Using rat skin and artificial membranes permeability studies are performed. It is assessed using confocal laser scanning microscopy it revealed a enhanced transdermal flux nearly 2 to 6.3 folds higher than conventional liposomes. In vivo studies showed the plasma concentration was found to be 105± 9.4 ng/ml. Thus it serves as a promising vehicle for transdermal delivery.

23. Ita K B *et al.*,[2007]

This studied the effect of phospholipid formulation and choice of surfactant on skin permeation of selected hydrophilic drugs from elastic liposomes across human epidermal membrane. To investigate the effect of surfactant liposomes were prepared using different surfactants an dprepared by conventional rotary evaporation technique. Particle size is characterised by transmission electron microscopy. Vertical franz diffusion cell is used for the study of drug delivery through human epidermal membrane.In conclusion, higher transdermal flux was obtained for liposomes containing sodium cholate compared with sodium deoxycholate.

24. Jain S *et al.*,[2005]

The study aimed to prepare novel vesicular elastic liposomes of most commonly used NSAID Diclofenac for its sustained and targeted delivery. Elastic liposomes of diclofenac were prepared in vitro and in vivo. The effect of

different formulation variables like surfactant, concentration of surfactant and dose of drug on transdermal flux,amount of drug deposited into the skin, muscle and plasma concentration are studied.Biological activity is studied using rat paw edema model and results were evaluated and compared with commercial hydrogel formulation.It has two fold increase in the activity. It offers a promising means for the non invasive treatment of local pain and inflammation by topical application.

25. Ita K *et al*.,[2016]

This review examines the use of vesicles elastic liposomes and ethosomes for transdermal drug delivery. Elastic liposomes differ from conventional liposomes because they contain edge activators which impart elasticity and deformability. These are increasingly being used for delivering low and high molecular weight drugs. It shows the usefulness of these vesicles and mechanistic insight of its effectiveness.

26. Desmet E *et a*l.,[2016]

The RNA interference is a rapidly emerging approach for targeted gene silencing to alleviate disease pathology. Interesting target is skin as it allows direct target cells. These are limited to effective skin barrier which hinders penetration. This study explains about the capability of delivering RNAi molecules to the epidermis of impaired and intact skin, without targeting the dermis or circulatory system. Thus these liposomes hold great potential as topical delivery system for RNAi therapeutics in the treatment of numerous skin diseases.

27. Kang M J *et al*.,[2010]

This study develops an elastic liposomes containing oregonin have been formulated and examined for their in vitro skin permeation properties and in vivo therapeutic efficacy assessments. Elastic liposomes consisting of

soybean phosphotidylcholine and tween in the size range of 130nm in size and had a 4 fold higher deformability index than conventional liposomes.The results indicated that it is effective for normalising the immune related responses and alleviating atopic dermatitis evaluated as changes in the levels of inducible nitric oxide synthase,cyclooxegenase-2,interleukin (IL-4), Immunoglobulin E (IgE) and eosinophils in skin or blood.

FEBUXOSTAT

28. Ketan savjini *et.al*.,[2015]

Had developed a modified release formulation of febuxostat that can serve the dual purpose of increasing the efficacy and decreasing the toxicity , thereby improving safety. Pharmacokinetics and pharmacodynamic data , including drug concentration profile, efficacy data and toxicity data have been reviewed thoroughly . Based on available data , target pharmacokinetic profile had been identified as about 50% reduction in Cmax. The developed formulation was a potential candidate for filling to a regulatory agency with the advantage of higher efficacy and less toxicity, which will be beneficial to the patient population and has good commerical visibility.

29. Mukesh sharma *et al*., [2014]

Prepared swellable gastro retentive floating tablet by direct compression technique and evaluated for their swelling characteristics, floating capacity, in-vitro drug release and stability studies. Factorial design was employed to optimise formulation components. The floating lag time and time required for 90%(t90%) of drug release were selected as dependent variables. Polymer with lower viscosity (HPMC K4M) was shown to be beneficial than higher viscosity polymer (K15M and K100M) in improving the floating properties of GRDDS.

30. **Singh.S *et.al*.,**had developed niosomal gel containing febuxostat prepared by using thin film hydration method and evaluated their characteristics of niosomes in-vitro and invivo drug release studies are performed. A 2^3factorial design (DOE analysis) was carried out to reduce the number of experiments. Optimised formulation batch had entrapment efficiency of 73.93+0.75% and percent cumulative drug release of 83.03+0.07%. Invivo study of optimised febuxostat niosomal gel NG (f4) on rabbits revealed better result than the standard febuxostat drug.

31. **Ahuja.B.K *et.al*.,[2014]**

Had developed febuxostat Nano suspension by wet media milling technique. A polymer Hydroxypropyl methyl cellulose (HPMC -E3) and D-alpha tocopherol polyethylene glycol 1000 succinate (TGPS) act as surface stabiliser for formulation. Optimised FNC and oral bioavailability of febuxostat was evaluated in rats. Result shows that it increases relative bioavailability upto 221.6%. It's viable approach to enhance bioavailability of FXT.

32. **Tripura sundari *et al.*,[2016]**

This study attempted to improve the bioavailabilty of febuxostat by solid dispersion technique. This is characterized by Phase solubility studies in liquid state and differential scanning calorimetry, FTIR, X ray diffraction studies and scanning electron microscopy in solid state. These studies indicated the entrapped drug and showed the suitability of carrier polymers which prevents crystallization. The dissolution of drug increases due to lowering of surface tension, results in higher wettability of hydrophobic drugs thus increase the dissolution rate.

AIM AND OBJECTIVE

AIM AND OBJECTIVE

A conventional dosage form can only partly satisfy the therapeutic and biopharmaceutical needs, as it doesn't attain better bioavailability rate to do better pharmacological action, therefore it makes the need of novel approach for increasing bioavailability and to improve its site specific action.

One of the main advantageous approach for increasing bioavailability and easy administration is **Topical/transdermal delivery.** This route of administration has advantages over other pathways including avoiding the hepatic first pass metabolism, continuous drug delivery, fewer side effects and improved patient compliance. A Major obstacle to TT drug delivery is low percutaneous penetration.

To overcome this problem, drug delivery system with vesicular carrier have soft, flexibile self-regulating, self-optimized **elastic vesicles** are to be formulated. its not only act as carrier for topical delivery but also accommodate drug molecules with wide range of solubility, high deformability of these vesicles provide **better penetration** of intact vesicles.

The main purpose of present work is to develop an optimized elastic liposomal gels containing febuxostat anti gout agent.Gout is an collective name for several disorders that are characterised by the formulation and deposition of Monosodium urate (MSUr) crystals. The condition is associated with recurrent episodes of acute joint pain with deposition of MSUr crystals in the synovial fluid.

FEBUXOSTAT is a novel, potent, Non-purine selective xanthine oxidase inhibitor. its a weak acid pka-3.08 and is therefore, practically insoluble in water and vulnerable to enzymatic degradation in both intestine and liver and has a half life of 3 to 5 hrs. hence its oral bioavailability is affected and presence of food also decreases its Cmax by 38-39% which is why its choosen for topical delivery

Elastic liposomes is a good alternative for the combined oral and topical administration of drug for rheumatoid disease, it has been shown that delivery from elastic liposomes caused a sustained prolonged therapeutic action owing to the presence of higher drug concentration in the skin. In this study febuxostat is developed as elastic liposomes and carry out physical evaluation as well as ex vivo drug release studies, stability studies for the prepared formulation.

Aim of the study was to develop the febuxostat loaded elastic liposomes for the effective treatment of gout in the form of transdermal drug delivery.

TRANSDERMAL DELIVERY OF FEBUXOSTAT USING ELASTIC LIPOSOMES – FORMULATION DEVELOPMENT AND CHARACTERISATION

The main objectives are:

- To prepare febuxostat loaded elastic liposomes
- To overcome enzymatic degradation
- To formulate a elastic liposomal gel

PLAN OF WORK

PLAN OF WORK

PREFORMULATION STUDIES:

- Determination of the solubility of febuxostat
- Development of analytical method by UV spectroscopy
- IR spectroscopic analysis

FORMULATION DEVELOPMENT:

- Formulation of elastic liposomes
- Formulation of elastic liposomal gel.

CHARACTERISATION OF PREPARED FORMULATION:

- Determination of particle size, shape, size distribution and zeta potential by using Malvern zeta sizer.
- Measurement of Entrapment efficiency and drug loaded capacity of elastic liposomes
- Visualisation of elastic liposome by Scanning electron microscopy.
- In Vitro drug release studies.

PREPARATION OF GEL:

- Preparation of Hydrogel
- Physiochemical evaluation of gel

CHARACTERISATION OF GEL:

- Homogeneity
- PH
- Viscosity
- Spreadability
- Drug content
- In-Vitro Skin Diffusion studies.

MATERIALS

EQUIPMENTS

S.NO	EQUIPMENTS/INSTRUMENTS	MANUFACTURER/SUPPLIER
1	ELECTRONIC WEIGHING BALANCE	A&D COMPANY HR 200,JAPAN
2	HOT AIR OVEN	RANDS INSTRUMENTS COMPANY,CHENNAI
3	ULTRACENTRIFUGE	EPPENDORF
4	PROBE SONICATOR	VIBRONIC ULTRASONIC PROCESSOR
5	PH METER	MC DALAL CHENNAI
6	MAGNETIC STIRRER	REMI
7	UV VISIBLE SPECTROPHOTOMETER	UV-1700 PHARMASPEC SHIMADZU,JAPAN
8	FOURIER TRANSFORM INFRA RED SPECTROPHOTOMETER	SHIMADZU RXI,JAPAN
9	ROTARY FLASK EVAPORATOR	ROTAVAP

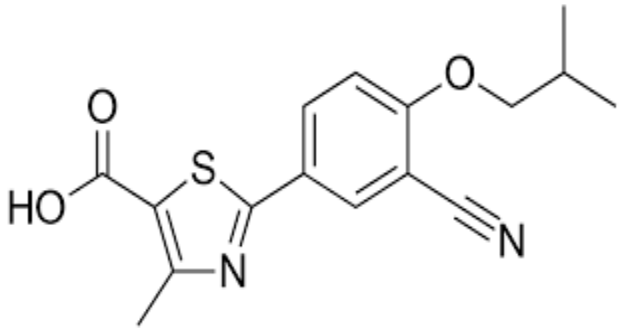
MATERIALS

S.NO	NAME OF THE MATERIAL	USE IN FORMULATION
1	FEBUXOSTAT	ACTIVE INGREDIENT
2	PHOSPHOTIDYL CHOLINE	LIPID
3	TWEEN 80	EDGE ACTIVATOR
4	SPAN 80	EDGE ACTIVATOR
5	CHLOROFORM	DILUENT
6	METHANOL	DILUENT
7	CARBOPOL 934	GELLING AGENT

DRUG PROFILE :

FEBUXOSTAT

Structure :



IUPAC name: 2-[3-Cyano -4-isobutoxyphenyl]-4-methylthiazole-5-carboxylic acid;2-[3-Cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1-3-thiazole-5-carboxylic acid.

Molecular formula : $C_{16}H_{16}N_2O_3S$

Molecular weight :316.37

CAS Registry number :144060-53-7

Solubility: Febuxostat is practically insoluble in water, soluble in methanol, soluble in DMSO, sparingly soluble in acetone

Half-life: Mean elimination half-life of approximately 4-6hours.

Description: Febuxostat is in the crystalline form having off white powder to pale yellow in color

Dose: Suggested dose 40-120 mg daily

Excretion: Febuxostat is eliminated by renal pathway

Storage: Store at controlled room temperature 20-25ºC

Melting point: 238-239ºC

Pharmacokinetic data

Absorption : >49%

Protein binding : 99.2%

Half life : 5-8 hours

pH Range : 1-5

pka value : 3.08

Identification: 317nm in UV spectrophotometer

Route of administration: oral

Dose : 40mg,80mg,120mg

Dosage form : Tablets

Therapeutic categories : xanthine-oxidase inhibitor

Indication :

For the treatment of chronic hyperuricemia in conditions where urate deposition has already occurred (including a history, or presence of ,topus and /or gouty arthritis).it is indicated for the prevention and treatment of hyperuricemia in adult patients undergoing chemotherapy for haematological malignancies at intermediate to high risk of tumor lysis syndrome (TLS).

Febuxostat has therapeutic index in the gout disease and so pharmacokinetically is safe since normal doses can vary from 40-120 mg per day with no substantial difference in acute toxicity or effect.

Volume of distribution : 0.7L/Kg

Time to reach peak plasma concentration : 5hrs

Urinary excretion: approximately 45%

Metabolism :

Febuxostat is extensively metabolised by both conjugation via uridine diphosphate glucoronosyltransferase (UGT)enzymes including UGT1A1,UGT1A3,UGT1A9, and UGT2B7 and oxidation via cytochrome P450 (CYP) enzymes including CYP1A2,2C8 and 2C9 and non P-450 enzymes. The relative contribution of each enzymes isoform in the metabolism of febuxostat is not clear.

The oxidation of the isobutyl side chain leads to the formation of four pharmacologically active hydroxyl metabolites, all of which occur in plasma of humans at a much lower extent than febuxostat.

In urine and feces,acylglucoronide metabolite of febuxostat (~35% of the dose) and oxidative metabolities,67M-1 (~10% of the dose),67M-2(~11% of the dose) ,and 67M-4,a secondary metabolite from 67M-1(~14% of the dose),appeared to be the major metabolites of febuxostat in vivo.

Pharmacodynamic mechanism of action :

Febuxostat is a non-purine selective inhibitor of xanthine oxidase inhibitors.it works by non-competitively blocking the molybdenum pterincentre which is active site on xanthine oxidase. It’s an enzyme needed for oxidize both hypoxanthine and xanthine to uric acid. Hence, febuxostat inhibits xanthine oxidase, therefore reducing production of uric acid.

Febuxostat inhibits both oxidised as well as reduced form of xanthine oxidase because of which febuxostat cannot be easily displaced from the molybdenum pterin site.

Clinical efficacy :

Many long term and short term clinical trials have proved the efficacy of febuxostat in the treatment of your and lowering uric acid levels. Febuxostat was found to be superior to allopurinol in reducing the serum uric acid levels.

Side effects:

The adverse effects of febuxostat are

- ★ Nausea
- ★ Diarrhea
- ★ Arthralgia
- ★ Increased hepatic serum enzyme levels and rash.
- ★ Head ache

Drug interactions :

Drugs metabolised by xanthine oxidase (eg.azathioprine, mercaptopurine, theophylline).plasma concentrations of these agents may be increased, leading to toxicity. Co administration with febuxostat is contra indicated.

Toxicity :

Liver test abnormalities have been reported to occur in 2% to 13%(average-3.5%) of patients receiving Febuxostat, but the levels are generally mild to moderate and self-limited. The height , nature and timing of these abnormalities have not been reported. However , liver test elevation were the major reason for febuxostat discontinuation for adverse events (2%)in clinical trials, despite that fact that no cause of jaundice or acute hepatitis were reported.

The product labelling for febuxostat, however list potential side effects of hepatic steatosis, hepatitis and hepatomegaly. Another unrelated, non-purine xanthine oxidase inhibitor (Benzbromarone) was not approved for use in the United States because of its potential for hepatic toxicity.

EXCIPIENT PROFILE

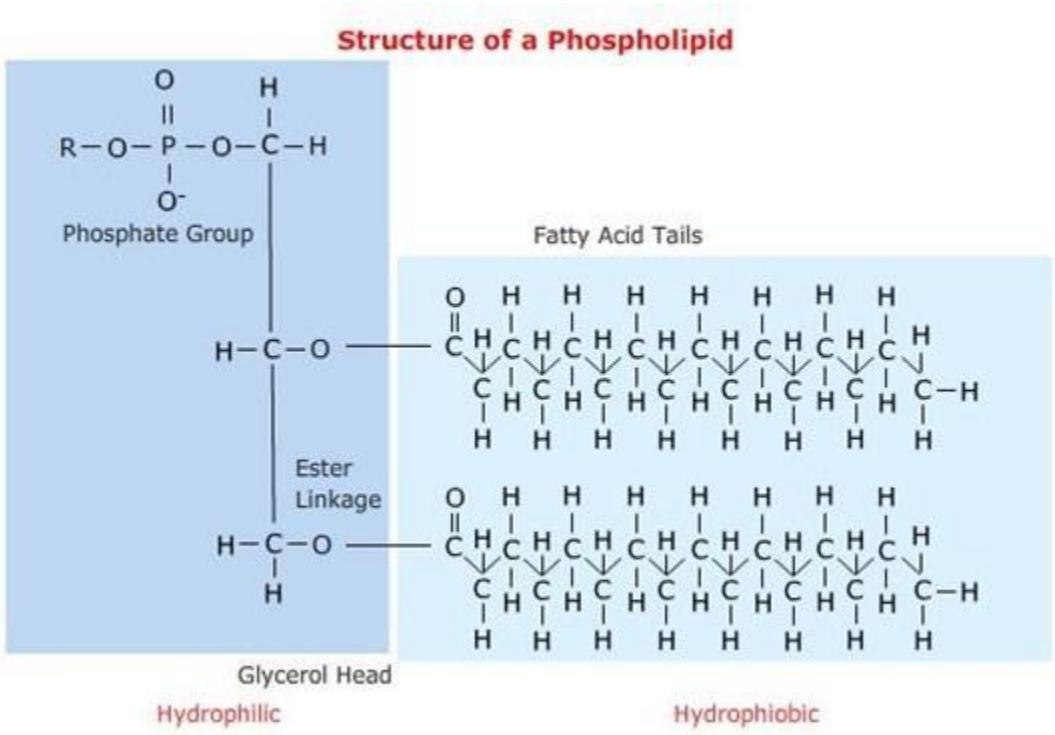
SOY LECITHIN :

Lecithin is a group of yellow-brownish fatty substance occurring in animal and plant tissues, and in egg yolk, composed of phosphoric acid, choline, fatty acids, glycerol, glycolipids, triglycerides, and phospholipids (e.g., Phosphatidylcholine, phosphatidylethanolamine and phosphatidylinositol). However, lecithin is sometimes used as a synonym for pure phosphatidylcholine, a phospholipids that is the major component of its phosphatide fraction.

It may be isolated either from egg yolk (in Greek lekythos or from soy beans, from which it is extracted chemically (using hexane)) or mechanically. Lecithin is used as a food supplement and for medical uses.

CHEMISTRY:

Lecithin used for the study is composed of different type of phospholipids like phosphatidylcholine, phosphatidyletanolamine and phosphotidyl inositol and cholesterol. The structure of basic phospholipids molecule is given below.



DESCRIPTION:

Colour: Yellowish brown

Molecular Formula: $C_{36}H_{72}NO_8P$

Molecular Weight: 677.93gm

Consistency: Agglomerates

Iodine value: 85-95

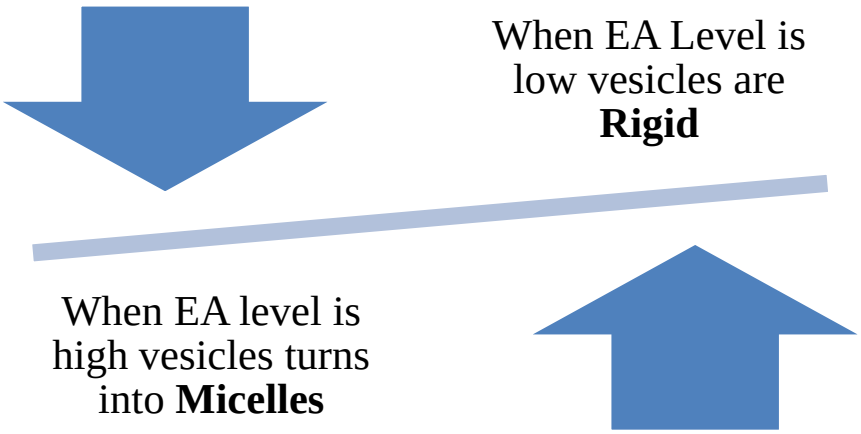
Peroxide value: n.m.t 3

Solubility:

Lecithin is soluble in both aqueous and organic phase. Hence it can be used as emulsifier in food industry and it is also capable of forming vesicles thereby it is used in pharmaceutical industry. It gives clear or slightly opalescent solutions with both phases.

EDGE ACTIVATOR

It is usually a kind of surfactant,which destabilizes the liposomal bilayer and increases elasticity of it. sodium cholate, sodium deoxycholate, Span 80, Tween 80 and Tween 20 were commonly used. The elasticity properties of the elastic liposomes were mainly depends on EA.



EA plays an important role in determining the skin permeation behavior of elastic liposomes. An overview of the difference among EAs is helpful for the selection of an ideal EA for the optimal formulation.

TWEEN 80

Synonyms:

- Armotan PMO 20
- Capmul POE-0
- Cremophor Ps 80
- Montanox 80

Chemical name:

- Polyoxyethylene sorbitan monoleate

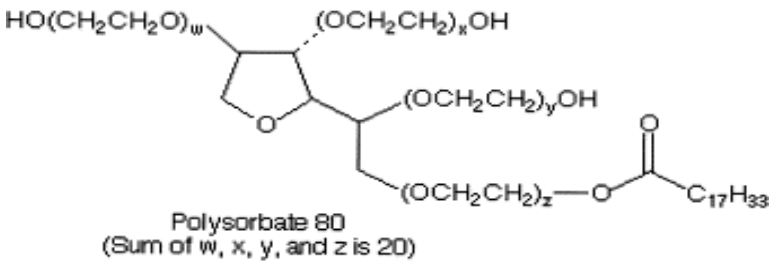
Empirical formula:

- $C_{64}H_{124}O_{26}$

Molecular weight:

- 1310

Structural formula:



Molecular Mass = 1310

HLB value :

- **15**

Functional category:

- Emulsifying agent
- Non-ionic surfactant
- Solubilizing agent
- Wetting agent
- Dispersing / suspending agent

Viscosity at 25$_0$C:

- 425 mPas

Application in pharmaceutical formulation:

- They may be used as solubilizing agents for a variety of substances including essential oils and oil-soluble vitamins and as wetting agents in the formulation of oral and parenteral suspensions.

- They have been found to be useful in improving the oral bioavailability of drug molecules.

- Polysorbates are also widely used in cosmetics and food products.

Description:

- Yellow oily liquid

Melting point:

- -20.556 ^{o}C(-5)

Solubility:

- Soluble in methanol. Easily soluble in cold water .hot water .soluble in toluene ,alcohol .cottonseed oil. Ethyl acetate
- Insoluble in mineral oil.

Stability and storage condition:

- Polysorbates are stable to electrolytes and weak acids and bases.
- Polysorbate should be stored in a well-closed container. Protected from light it should be stored in a cool. dry place.

Incompatibilities:

- The antimicrobial activity of paraben preservatives is reduced in the presence of polysorbates.

Handling Precaution:

- Observe normal precautions appropriate to the circumstances and quality of material handled eye protection and gloves are recommended.

(Hand book of pharmaceutical Excipient by Raymond C Rowe..5th Edition)

SPAN

Synonyms :

- Ablunol S-80
- Arlacel 80
- Sorbitol O
- Campul**S**

Chemical name :

- (Z)-Sorbiton mono-9-octodecanoate

Empirical formula :

- $C_{24}H_{44}O_6$

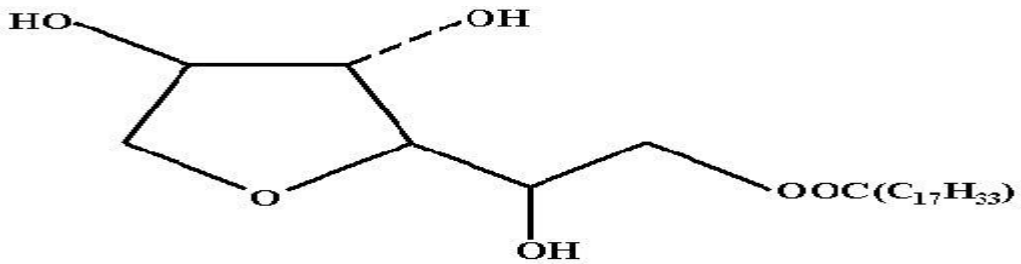
Molecular weight :

- 429

Functional category:

- Dispersing agent
- Emulsifying agent
- Non ionic surfactant
- Solubilising agent
- Wetting agent

Structural formula:



SPAN 80

Application in pharmaceutical formulation:

- Sorbitan esters are widely used in cosmetics, food products,and pharmaceutical formulation as lipophilic non ionic surfactant

- They used as a emulsifying agents in the preparation of creams, emulsion,and ointments for topical formulation.

Descriptions:

- It occurs as amber coloured liquid

HLB value :

- 4.3

Stability and storage condition:

- Polysorbates are stable to electrolytes and weak acids and bases.
- Polysorbate should be stored in a well-closed container. Protected from light it should be stored in a cool. dry place.

Incompatibilities:

- The antimicrobial activity of paraben preservatives is reduced in the presence of polysorbates.

Handling Precaution:

- Observe normal precautions appropriate to the circumstances and quality of material handled eye protection and gloves are recommended.

(Hand book of pharmaceutical Excipient by Raymond C Rowe..5th Edition)

Glyceryl mono oleate

SYNONYMS:

- Aldo MO
- Mono olein
- Stepan GMO

Chemical name:

- 9-octadecenoic acid (Z)

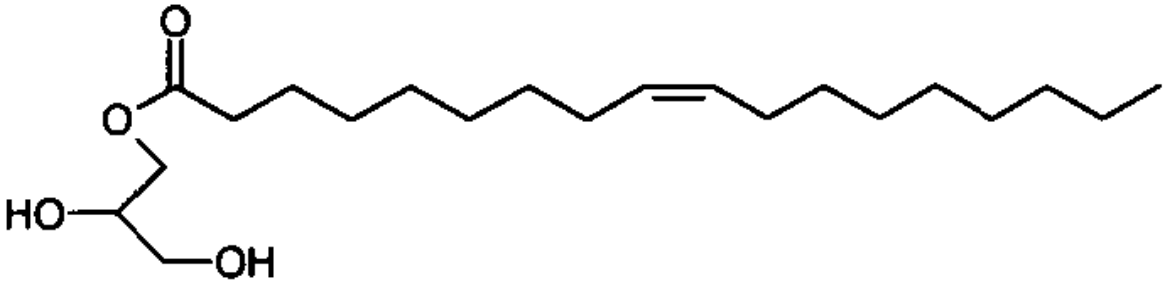
Empirical formula :

- C21H40O4

Molecular weight :

- 356.55

Structural formula:



Functional category :

- Bio adhesive material,
- Emollient
- emulsifying agent
- non-ionic surfactant

Application in pharmaceutical formulation :

- The non emulsifying grade used in the topical formulations as an emollient and as an emulsifying agent
- GMO is reported to enchance the transdermal and buccal penetration.

Description :

- GMO occur as a amber coloured oily liquid ,which may be partially solidified at room temperature.

Melting point :

- 35 ºC

HLB value :

- 3.3

Stability and storage condition :

- GMO should be stored in an air tight container, protected from light in a cool ,dry place.

Incompatibilities :

- GMO is incompatabile with strong oxidising agents.
- The self-emulsifying grade is incomptabile with cationic surfactants.

Safety :

- GMO is used in oral and topical pharmaceutical formulation and is generally regarded as a relatively non irritant and non-toxic excipient.

Carbomer

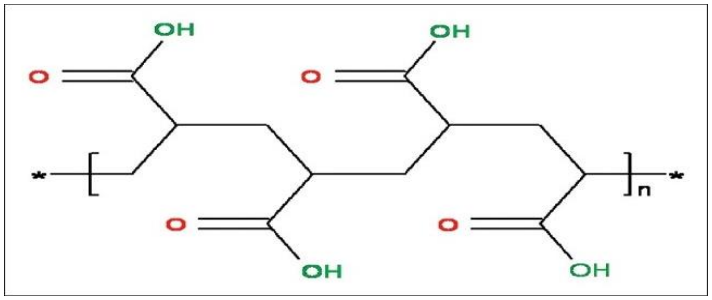
Synonyms :

- Carbopol
- Acrypol
- Carboxy vinyl polymer

Chemical name :

- Carbomer

Structural formula :



Functional category :

- Bio adhesive material
- Controlled release agent
- Emulsifying agent
- Stabilising agent
- Rheology modifier.

Application in pharmaceutical formulation :

- Carbomers are used in liquid or semi solid pharmaceutical formulation as a rheology modifier
- Carbomer polymers have also been investigated in the formulation of sustained release matrix beads.

Description:

- Carbomers are white coloured fluffy hygroscopic powder. with a characteristic odour.

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METHODOLOGY

PROJECT WORK METHODOLOGY

PREFORMULATION STUDY:

- **Solubility study:**

Solubility of the Febuxostat was be tested in various solvents according to the standard procedure.

- **Determination of lambda(λ) max of Febuxostat in phosphate buffer pH 7.4:**

Stock solution was prepared by dissolving 100mg of pure drug in 10 ml methanol and made upto 100 ml with Phosphate buffer pH 7.4. This was designated as stock solution A (1mg/ml). 10ml of the stock solution was taken in 100ml volumetric flask and made upto 100 ml with Phosphate buffer pH 7.4.

This was designated as stock solution B(100 mcg/ml). This stock solution B was further diluted to get 10 mcg/ml. The above solution was scanned between 200-400 nm after suitable dilution.

- **Standard graph of Febuxostat:**

From the above stock solution B' aliquots of 2,4,6,8,10 and 20ml were transferred to 100 ml volumetric flasks and made upto the mark with Phosphate buffer pH 7.4 to get concentration of 2,4,6,8,10 and 20mcg/ml.

The absorbance of this solutionwere measured at 314nm and a graph were plotted with concentration on X axis and absorbance on Y axis.

- **FT-IR compatability studies :**

FTir studies were used to investigate the compatibility between the drug and excipients, Is there any physical or chemical interaction occur between the drug and excipients were determined by shifting or disappearance of functional peak from standard peak.

FTIR spectra of pure drug,excipients and physical mixture were obtained using shimadzu,Japan. sample were prepared by KBr pellet method,one part of the sample and three part of KBr pellet were taken in mortar and triturated .the small amount of sample was taken in pellet maker and compressed at pressure of 10kg\cm^2 using hydraulic press. compressed pellet was scanned at transmittance range of 4000cm^{-1}-400cm^{-1}.ir spectra are recorded of pure drug (febuxostat),excipients –lecithin,span 80,tween 80,GMO,carbol-934 and for physical mixture samples -(drug+lecithin+span-80,drug+lecithin+tween-80,drug +lecithin+GMO).

FORMULATION OF ELASTIC LIPOSOMES:

- **Thin film hydration method:**

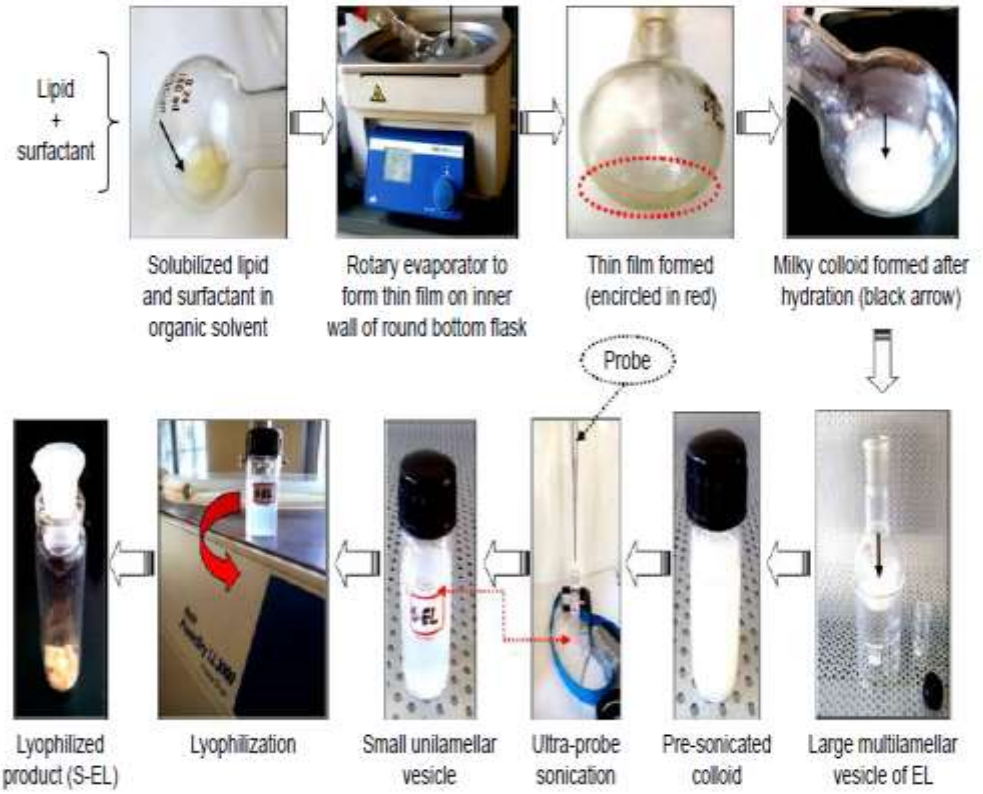
The elastic liposomes was prepared by conventional rotary evaporation method, the molar ratio of phospholipids, surfactant will be taken in a clean, dry, round bottom flask and lipid mixture were dissolved in chloroform: methanol (2:1 v/v)ratio.

The round bottom flask was attached with rotary evaporator by means of plastic clip,it was rotated at 100rpm by maintaining at 60ºC for a few hours through a vaccum pump attached over it.The organic solvents were removed by rotary evaporation above the lipid transition temperature. Final traces of solvent were also removed by vacuum overnight.

The deposited lipid film was hydrated by adding phosphate buffer saline pH-7.4 or 7% ethanol and placing the flask on rotary evaporator for 1hr at room temperature at 60rpm without a vacuum, the resulting vesicles will be allowed to swollen for 2hrs at room temperature to get large multilamellar vesicles(LMLV)

This produces a homogeneous milky suspension. Once a stable MLV was produced , To prepare smaller vesicles it was further sonicated for 20mins at 40W (Probe ultra-sonicator) (**Mishra et al.2006**).

Formulation code	Drug(Mg)	Soya phospholipids (in %)	Span 80 (%)	Tween 80(%)	GMO (%)	Hydration (15ml)
F1	80	95	5	-	-	PBS 7.4
F2	80	90	10	-	-	PBS 7.4
F3	80	85	15	-	-	PBS 7.4
F4	80	80	20	-	-	PBS 7.4
F5	80	95	-	5	-	PBS 7.4
F6	80	90	-	10	-	PBS 7.4
F7	80	85	-	15	-	PBS 7.4
F8	80	80	-	20	-	PBS 7.4
F9	80	95	-	-	5	PBS 7.4
F10	80	90	-	-	10	PBS 7.4
F11	80	85	-	-	15	PBS 7.4
F12	80 .	80	-	-	20	PBS 7.4



CHARACTERISATION OF ELASTIC LIPOSOMES:

Physical characterization of elastic liposomes:

Liposomal formulation were generally evaluated by studying their physiochemical properties like

- Particle size distribution
- Polydispersity index
- Zeta potential analysis
- Microscopic analysis

Particle size distribution :

average particle size, particle size distribution of the elastic liposomes were determined by using Malvern zeta sizer instrument (Malvern,UK).

Polydispersity index:

Polydispersity index was measured by Malvern zetasizer instrument. stability and particle size distribution were measured by standard values such as

- D (0.9) correspond to particle size immediately above 90% of the sample
- D (0.5) correspond to particle size immediately above 50% of the sample
- D(0.1) correspond to particle size immediately above 10% of the sample.

Zeta potential analysis :

Zeta potential is a physical property which is exhibited by any particle in suspension.it can be used to optimize any formulations of suspension and emulsions. knowledge of zeta potential reduces the time needed to produce trial formulation, and also aid to predicting long term stability of suspension.

The magnitude of zeta potential gives an indication of the potential stability of the colloidal system.if all the particles in suspension having large negative or positive zeta potential than they tend to repel each other and there will be no tendency for the particles to come together.however ,if the particles have low zetapotential values then there will be no force to prevent particles coming together and flocculating.

The significance of zeta potential is that its value can be related to the stability of colloidal dispersion.A value of +25 mv to -25mv can be taken as an arbitrary value that separates low charged surface from high charged surface. Zeta potential was analysed by MALVERN ZETASIZER instrument

MICROSCOPIC ANALYSIS :

The surface characteristics of prepared elastic liposomes were characterized for morphology using scanning electron microscope. this image was to further confirm the morphology of the elastic liposomes

For visualizing elastic liposomes under SEM 10 µl was uniformly spread on a glass slide and allowed to dry at room temperature.After gold coating the sample with a Polaron E5100 gold sputter coater, the morphology was observed under a Philips 505 electron microscope at an accelerating voltage of 20 kV.

INVITRO CHARACTERISATION :

Determination of drug content :

Drug entrapped Els formulation 1ml was withdrawn and diluted with methanol made upto.the resultant dispersion was further sonicated for 10 mins and filtered using 0.45µm filter paper.the resultant solution was analysed by using UV spectrophotometer at wavelength of 314nm..the drug content was determined by plotting absorbance value in the standard graph.

Total amount of drug = absorbance X 1/dilution factor X correction factor

$$\text{Drug content} = \frac{\text{experimental drug content X 100}}{\text{theoretical drug content}}$$

Entrapment efficiency :

Entrapment efficiency was determined by ultra-centrifugation method , its done by separation of free drug from entrapped drug . Elastic liposomal suspension was collected in a centrifuge tube and was centrifuged at 14000RPM for 60 minutes at 20 ºC in an ultracold centrifuge (eppendroff centrifuge) to obtain white pellet of SUVs which settled at bottom of centrifuge tube.

The supernatant was separated using a syringe as it contain unentrapped drug ,it was dissolved in PBS pH 7.4 to release unentrapped drug .with this dispersion 1ml of triton-X -100 was added to ensure that the elastic liposomes were lysed completely to release the drug.

This solution was further diluted with PBS pH 7.4 and finally absorbance was determined by UV spectrophotometer at 314nm.

$$\text{Entrapment efficiency} = \frac{\text{total amount of drug} - \text{unentrapped drug}}{\text{Total amount of drug}} \times 100$$

In vitro dissolution studies :

The release of febuxostat loaded ELs from all multilamellar liposomal formulations with different compositions were determined using the membrane diffusion technique. The dialysis tubing membrane (MW cutoff 12000–14000) presoaked overnight in phosphate buffer (pH 7.4) was used.

Accurately measured amount of Febuxostat-ELZ liposomal formulations, equivalent to 40- mg FLZ, was placed in the dialysis tubing membrane and the ends were sealed. The sealed tubings were placed in a beaker containing 250 ml phosphate buffer pH 7.4 and the entire dissolution assembly was placed in a magnetic stirrer and agitated at 100 rpm.

The aliquots of samples were withdrawn from the beaker at specified intervals up to 24hrs and replaced with same volume of fresh solution. The samples were assayed spectrophotometrically for drug content at 314nm. The cumulative drug release was calculated with the help of standard calibration curve of febuxostat.

The experiments were performed in triplicates, and the results were represented as the mean values of three runs. The obtained results were subjected to kinetic treatment to determine the order of release pattern and release rate constant.

Release kinetic studies :

The release data was fitted to various kinetic models like first order mode (equation 1), zero order model (equation 2), Higuchi (equation 3) and Korsemeyer-Peppas (equation 4)

$$\ln\left(\frac{M_1^o}{M_t}\right) = k\,t \longrightarrow \text{equation 1}$$

$$M_O - M_t = k_O t \longrightarrow \text{equation 2}$$

$$M_t = K\sqrt{t} \longrightarrow \text{equation3}$$

$$\frac{M_t}{M_\infty} = kt^n \longrightarrow \text{equation4}$$

where, W_0 and W_t corresponds to the weight of the drug taken initially and at time t, respectively. The terms M_0, M_t, and M_∞ correspond to the amount of dapsone taken at time equal to zero, dissolved at a particular time (t), and at infinite time, respectively. The terms k_1, k_0, , Kt, and k

Represent the release kinetic constants obtained from the linear curves of first –order,zero order, Hixson-crowell cube root law,higuchi model and korsemeyer- peppas respectively.

Stability studies:

The different elastic liposomes will be kept at room temperature and at refrigeration temperature for 45 days. The effects of storage time (0, 15, 30, and 45 days) on the pH, drug content and entrapment efficiency will be determined.

FORMULATION OF GEL:

Optimized elastic liposomal formulation was selected for further gel formulation

Preparation of 1% Carbopol Gel:

Carbopol resin (1%) was dispersed in distilled water 20ML in which glycerol 1ml was previously added. The mixture was stirred until thickening occurred and then neutralized by drop wise addition Triethanolamine until transparent gel appeared.

Incorporation of liposome in 1% Carbopol gel:

Optimized Elastic Liposome containing drug was mixed in to 1% Carbopol gel by an electrical mixer 25rpm/2 min, elastic liposomal gel was formed

EVALUATION OF GEL:

Optimized elastic liposomal enriched hydrogel were characterized for their physiochemical properties such as color, odour, pH, viscosity and drug content.

DRUG CONTENT :

The ELs gel sample 1gm was weighed and it was shaken with sufficient quantity of methanol to extract the drug from gel .for complete lysis of drug it was further sonicated at probe sonicator for 10 mins.

Following solution was further diluted with methanol to analyse by using UV spectrophotometer at 314 nm.the drug content was determined by plotting the absorbance value in the standard graph.

Measurement of pH :

The pH of gel formulation was determined by using digital pH meter.one gram of gel was dissolved in the 100ml distilled water and kept aside for two hours for complete dissolution of gel.the resultant solution was analysed for pH value .

This experiment has to be repeated for triplicate and average value was calculated.

Viscosity studies:

The measurement of viscosity of the prepared gel was done with a brookefield viscometer .the gel was rotated at 1.5 rotations per minute and viscosity was measured in cps.

Spreadability :

Two set of petridish with standard dimension were taken. The elastic liposomal gel formulation was placed over one of the sides.the other slide was placed on the top of the gel,such that the gel was sandwitched between the two slides in an area occupied by a distance of 7.5cm along the slides.

100gm of gel was placed on the upper slide ,so that the gel was between the two slides was pressed uniformly to form a thin layer. The weight was removed and excess of gel adhering to the slides was scrapped off.

The two slides in position were fixed to a stand without slightest disturbance and in such a way that only upper slides to slip off freely by the force of weight tied on it.A 20gm weight was tied to the upper slide carefully.

The time taken for the upper slide to travel the distance of 7.5cm and separated away from the lower slide under the influence of the weight was noted. The experiment was repeated for triplicate and mean time was calculated.

Spreadabaility was calculated by using the following formula :

$$S=m\times l\backslash t$$

Where, S= spreadability,m= weight tied to upper slides(20g),length of the glass slide(7.5cm),t-time taken

Skin permeation studies :

Following procedure were adopted for studying permeating capability of elastic liposomes .

Selection of animal and preparation of skin :

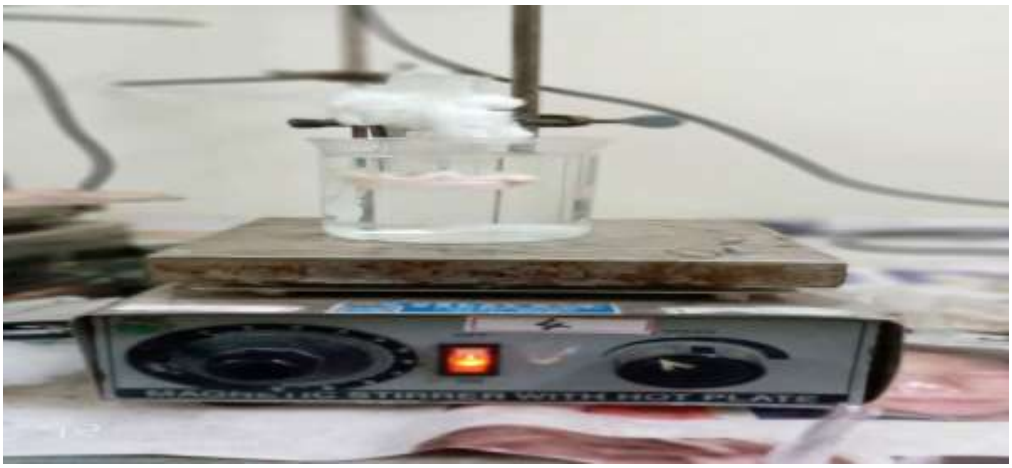
For the present study , goat had choose as an animal.for permeation study only skin part of goat was needed,so it was collected from local slaughter house .

The collected skin was scrapped for removal of hair it would interrupt the permeation of gel inside the skin. Scrapped part of skin was stored in saline solution for 24hrs before the starting of experiment. Excess fat layer and subcutaneous debris are removed by washing with saline

In-Vitro permeation study :

Permeation study was carried out by modified open end test tube method. prepared skin was mounted on the one side of test tube, about 5gm of the gel was applied on the skin in donor compartment and receptor compartment was placed in a beaker containing 250ml of phosphate buffer pH 7.4 Beaker was placed in the magnetic stirrer maintained at 37ºC ±0.5ºC and stirred at 100rpm.

After application of the test formulation on the donor side, at a fixed time intervals for about 12 hours,5ml of aliquots were withdrawn from beaker and analysed by UV spectrophotometer at 314nm.



RESULTS AND DISCUSSION

RESULTS AND DISCUSSION

Febuxostat loaded elastic liposomes were prepared by rotary flask evaporation method and further its sonicated, its choosen as a best method for the formulation from reference articles. formulation was prepared by using different types and concentration of surfactant as listed in the table

A total of 12 batches of elastic liposomes were formulated by varying four independent variables i.e. concentration of soya phosphatidyl choline, surfactant mainly used are tween 80 ,span 80, glycerylmonooleate for all possible combinations (table) in order to evaluate their influence on the dependent variables such as entrapment efficiency, particle size, /zeta potential and drug release. The concentration of independent variable were based on the result obtained from preliminary literature studies.

Before the start of formulation, preformulation studies were done for drug and excipients to find out the characteristic and compatability of drug with excipients and its influence in formulation

Preformulation studies:

Determination of wavelength:

1.STANDARD CALIBRATION CURVE OF FEBUXOSTAT IN UV SPECTROPHOTOMETER:

The λmax of febuxostat was determined by using uv spectrophotometer scanning at range of 100µg/ml solution of drug in phosphate buffer pH 7.4 ,it was found to be 314nm . The absorbance of febuxostat standard solution in the range of 2-20µg/ml measured in uv spectrometer at 314nm.the linearity was plotted against concentration with R^2 value 0.9998 and with the slope equation of Y= 0.9998. The standard curve and absorbance values were shown in the table 1 and plotted in figure 1.

2. SOLUBILITY STUDIES :

The solubility of febuxostat was determined by dissolving in various solvents like distilled water and organic solvents such as methanol, ethanol.in that methanol shows higher solubility range compare to that of other solution.

3.INFRARED SPECTROSCOPIC STUDIES :

Infrared spectroscopic studies (IR) were carried out to confirm the compatability between drug and excipients in the elastic liposomal formulation.The IR studies was performed for febuxostat (pure drug), excipients such as span 80,tween 80, glycerylmonooleate and physical mixture of drug and excipients. The spectra studies are done at range of $4000cm^{-1}$-$400cm^{-1}$.

The principal peak of drug were observed in the wave numbers were shown in the table .there was no appearance or disappearance of characteristic peak of drug in the physical mixture which confirmed the absence of interaction between drug and excipients .The IR results were shown in the (figure 3-9)

Preparation of elastic liposomes:

Elastic liposomes were formulated **by dried thin film hydration method** using rotary evaporator with drug and carrier.

A total of 12 batches of elastic liposomes were formulated by varying type and concentration of surfactant which act as an edge activator ,concentration of other independent variables such as phosphotidyl choline which act as a bilayer forming agent in the formulation. The composition and ratio of compounds showed in the table no 2.

Among these formulation ,optimised batch of formulation was selected based on the evaluations such as zetapotential, entrapment efficiency and particle size.

Physiochemical characterisation :

Particle size and Zeta potential analysis :

Particle size analysis ,polydispertive index and zeta potential of the sonicated elastic liposomes were measured by dynamic light scattering using Malvern zeta sizer instrument.Elastic liposomes were diluted with buffer before measurements.

All measurements were taken at 165º light scattering and temperature 25ºC.the average particle size ,polydispertive index,and at zeta potential of the sonicated elastic liposomes are listed in the table 3

The concentration of soyaphosphotidyl choline seems to be an important factor which affects particle size and also surfactant concentration impart in particle size ,higher surfactant concentration increases particle size ,zeta potential value. Hence optimum concentration of surfactant was required to get an optimum liposomes.

The zeta potential study depicts good stability of the vesicular formulations which lies within the desired millivolt range (-30 mv - +30 mv) ,as high surface charge prevent aggregation of the particles.the higher charge on the surface of vesicles produced a repulsive force between the vesicles which made them stable and devoid of agglomeration.

The reduction in polydispertive index was noticed and this might attributed to the reduction in interfacial tension between the particle which lead very good particle size distribution .

The zeta potential ,polydispertive index, and particle size value of elastic liposomal formulation were listed in the table.from that formulation F3 have value which lies near to arbitrary value which having values of zeta potential (-33.2),polydispertive index (0.532) and particle size (217.3nm).These images were shown in figure 11.

Microscopic analysis:

Scanning electron microscopy:

The determination of shape and surface morphology was done by scanning electron microscope. SEM analysis of sample revealed that elastic liposomal formulation having uniform size, spherical in shape. SEM images were shown in the figure 10.

Drug content :

1ml of elastic liposomal solution was diluted with 10 ml of methanol and further dilution was method upto 10mcg/ml concentration. Absorbance was measured at uv spectrophotometer in the range of 314 nm. drug content was calculated by using formula and listed in the table 5.

Entrapment efficiency :

Entrapment efficiency of elastic liposomes was determined by centrifugation method, which lysis the SUVs in PBS at a pH of 7.4 followed by further treatment with triton –X 100. The drug content in the aqueous phase was measured by uv visible spectroscopy at 314nm.the enhanced EE with a relative increase in surfactant concentration but conversely it also decreases EE of formulation with higher increases in surfactant

Entrapment values of formulation are listed in the table and figure. Formulation F3 and F6 shows good EE compared to that of other formulation. The maximum entrapment efficiency of elastic liposomal formulation was found to be 94.73% for the F3 formulation.it was shown in the table 5 and the figure 14

Stability studies :

Stability of elastic liposomes was main consideration in all step of production and administration, from processing steps to storage to delivery .a stable dosage form has to maintain its physical integrity, and chemical integrity throughout its shelf life.

As elastic liposomes are thermodynamically unstable system, they tend to fuse each other ,grow into bigger vesicles during their storage . for stability analysis entrapment efficienc of drug was noted at different storage condition as given in ICH guidelines at room

temperature (25ºC± 2ºC) and at refrigeration temperature (5ºC± 3ºC),it should not be stored at higher temperature because phospholipid are used for formulation ,it could be Deteriorated.

The stability data of optimised elastic liposomal formulation was given in the table .according to data ,formulation stored in refrigeration temperature (89.78±0.12)showed better entrapment efficiency as compared to that of room temperature(83.68±0.25).

In vitro drug release studies :

In vitro drug release studies were carried by membrane diffusion technique. A measured amount of ELS was placed in dialysis bag and sealed in the ends .the sealing tubes were placed in the 250ml of pbs (pH 7.4) at 37º C± 0.5ºC. The invitro release studies were performed for two formulation F3 and F6 based on the entrapment efficiency values. The surface absorbed drug showing an initial burst release with nearly 25% release within 1hr due to faster diffusion followed by extended release.

Formulation F 3 shows release about 84±1.56 % of the drug after 24hrs ,whereas formulation F6 shows release about 98.7±3.85. from that value it note that formulation F3 shows extended release. The plot of % cum drug release vs time for formulation were plotted in the graph and in table 4 and figure 13.

Thus from above evaluation formulation F 3 could be achieved a depot effect in elastic liposomal formulation and also it shows good EE%,particle size,zetapotential values. Hence it was choosen as an optimised formulation for further formulation and release kinetic studies.

The release kinetic models were further evaluated considering four different mathematical models including zero order,first order,higuchi equation,hixon crowell and korsmeyer's equation and selection was based on the comparison of the relevant coorelation coefficient tand linearity test are mentioned in the table 9 and figure 15-18

Characteristic liposomal gel:

Macroscopic characteristics:

The formulation F3 –ELs Gel formulation were analysed for its macroscopic characters and its qualities such as color, homogeneity, phase separation, and consistency. the gel has a smooth texture, white color, transparent and characteristic odour of gel.

pH of a gel :

The pH value of F3-ELs Gel were found to be in the range from **6.57±0.5** to **7.74±0.2.**this pH value showed that F3 gel probably would not produce any skin irritation .hence it suitable for topical formulation.

Spreadability

The spreadability of F3 ELs Gel was measured high by having low spread of time. The therapeutic efficacy of gel depends upon their spread. The gel spreading helps in uniform application of the gel to the skin, so that prepared gels must have a good spreadability and gratify the ideal quality in topical formulation. result obtained from the experiment shows gel prepared by carbopol 934 have good spreadability value such as **32.9 ±0.36** (±SD value of 3).

Viscosity:

Eventhough spreadability is considered as an essential factor in patient compliance. The uniformity of the substance is one of the most important factors to topical formulations due to being applied to thin layer of the skin so that the gel viscosity plays a vital role in the regulating drug permeation.

The viscosity of the measured ELs gel was measured by brookfield viscometer. polymers were included in the designed topical formulations in order to provide a prompt release of drug and to achieve as well as to maintain the drug concentration within the therapeutically effective range .

As the concentration of the polymer was fixed as1% in all the gel formulation. Further the value between **7325±1.08 centipoise** was reported to be an ideal viscosity value of topical gel formulation. these studies were shown in the table 7

Drug content for ELs Gel

Drug content study was performed for ELs gel formulation by using UV spectrophotometer in the range of 314nm.drug content of ELs Gel formulation was found to be 90 % respectively.

Skin permeation studies :

The in- vitro release profile is an important tool that predicts in advance how a drug will behave in-vivo. The in-vitro permeation of febuxostat ELs Gel using goat skin was done for period of 12 hours. The permeation of febuxostat was calculated in term of the % cumulative drug permeated.

From results the graph was plotted by taking time in x-axis & % cumulative drug release in y- axis.this shows that the permeation across the skin was faster and at the end of 12 hours it shows 80.48 % .it indicates that the release was sustainable and it prolonged the permeability capacity to 12 hours for better therapeutic effect and to reduce the degradability. The results were shown in the table 8 and figure 19.

Table 1: **Calibration curve of Febuxostat**

S.NO	CONCENTRATION (µG\ML)	ABSORBANCE
1	2	0.1403±0.005
2	4	0.2661±0.009
3	6	0.3721±0.003
4	8	0.4863±0.003
5	10	0.5923±0.0037
6	12	0.7192±0.005
7	14	0.8387±0.0.004
8	16	0.9387±0.008
9	18	1.0606±0.0006
10	20	1.1616±0.006

Table 2: **Formulation Ingredients and its Concentration**

Formulation code	**Drug (Mg)**	**Soya phospholipids (in %)**	**Span 80 (%)**	**Tween 80(%)**	**GMO(%)**	**Hydration (15ml)**
F1	80	95	5	-	-	PBS 7.4
F2	80	90	10	-	-	PBS 7.4
F3	80	85	15	-	-	PBS 7.4
F4	80	80	20	-	-	PBS 7.4
F5	80	95	-	5	-	PBS 7.4
F6	80	90	-	10	-	PBS 7.4
F7	80	85	-	15	-	PBS 7.4
F8	80	80	-	20	-	PBS 7.4
F9	80	95	-	-	5	PBS 7.4
F10	80	90	-	-	10	PBS 7.4
F11	80	85	-	-	15	PBS 7.4
F12	80 .	80	-	-	20	PBS 7.4

Table 3: **Particle Size ,Polydispersity Index, Zeta Potential**

FORMULATION CODE	PARTICLE SIZE	POLYDISPERSITY INDEX	ZETA POTENTIAL
F1	225.1	0.390	-29.6
F2	190.6	0.446	-27.4
F3	217.3	0.532	-33.2
F4	280.2	0.362	-34.9
F5	221.6	0.312	-36.3
F6	165.5	0.288	-46.2
F7	163.0	0.244	-38.9
F8	217.3	0.532	-27.4
F9	357.3	0.322	-34.2
F10	226.7	0.642	-22.5
F11	165.0	0.600	-16.6
F12	197.5	0.552	-21.9

Table 4 :**In vitro drug release studies for formulation F3 and F6**

Time (hrs)	Percentage cumulative release*	
	Formulation F3	**Formulation F6**
1	8.5±1.34	4.45±0.87
2	19.34±0.73	8.67±2.52
3	28±0.58	17.71±1.91
4	30.88±2.79	20.95±1.56
5	35±0.57	28.99±2.03
6	36.91±0.09	31.97±0.97
7	41.38±0.64	34.43±1.00
8	44.30±1.59	42.19±1.33
9	47.71±1.84	47.1±1.28
10	50.54±2.45	49.96±1.65
11	52.35±1.62	66.07±4.02
12	73.11±1.48	81.71±3.45
24	84±1.56	98.7±3.85

Note : *average of three determination ±SD

Table 5 : **Drug Content And Entrapment Efficiency**

FORMULATION	DRUG CONTENT (%)	ENTRAPMENT EFFICIENCY (%)*
F1	88.75	60.24±0.85
F2	86.25	46.05±0.78
F3	95	94.73±0.09
F4	92.5	71.05±0.69
F5	81.25	55.21±0.57
F6	92.5	70.27±0.31
F7	75	48.64±0.28
F8	87.5	44.59±0.42
F9	90	45.25±0.35
F10	83.75	54.05±0.18
F11	85	58.10±0.35
F12	76.25	45.94±0.75

Note : *average of three determination ±SD

Table 6: **Composition Of Topical Hydrogel Formulation:**

COMPONENTS	**TOPICAL HYDROGEL FORMULATION (F3)**
ELASTIC LIPOSOME FORMULATION	10ML SUV'S
CARBOPOL 934 (%)	1%
GLYCEROL (ML)	2ML
TRIETHANOLAMINE	2ML
DISTILLED WATER	20ML

Table 7: **Physiochemical Characteristics Of Topical Hydrogel Formulation** :

CHARACTERISTICS	EVALUATION METHOD	RESULT
HOMOGENECITY	VISUAL INSPECTION	GOOD
GRITTINESS	OPTICAL MICROSCOPY	NO
CLARITY	VISUAL INSPECTION	CLEAR
PH	ELECTRONIC PH METER	**7.74±0.2.**
VISCOSITY	BROOKEFIELD VISCOMETER	**7325±1.08 CENTIPOISE**
SPREADABILITY	PETRIDISH METHOD	**32.9 ±0.36**
DRUG CONTENT (%)	SONICATION METHOD	**90%**

Table 8: In vitro skin permeation studies

Time (hours)	Formulation F3 elastic liposomal gel
	% drug permeated through skin
0	0
1	4
2	6.71
3	9.77
4	15.04
5	19.61
6	22.69
7	28.22
8	32.63
9	39.93
10	48.12
11	56.84
12	80.48

Table 9: **Kinetics Studies:**

FORMULATION F3	**KINETIC STUDIES**			
	ZERO	**FIRST**	**KORSMEYER PEPPAS**	**HIGUCHI MODEL**
R^2 value	0.915	0.836	0.836	0.915

Table no : 10 **Stability Data Of Elastic Liposomes Formulation F3**

ENTRAPMENT STUDY (%)*		
DAYS	**5º±3ºC**	**25º±2ºC**
0	94.73±0.09	94.73±0.09
7	93.24±0.15	90.46±0.07
15	91.85±0.07	88.78±0.18
30	89.78±0.12	83.68±0.25

Figure 1:**Standard calibration curve :**

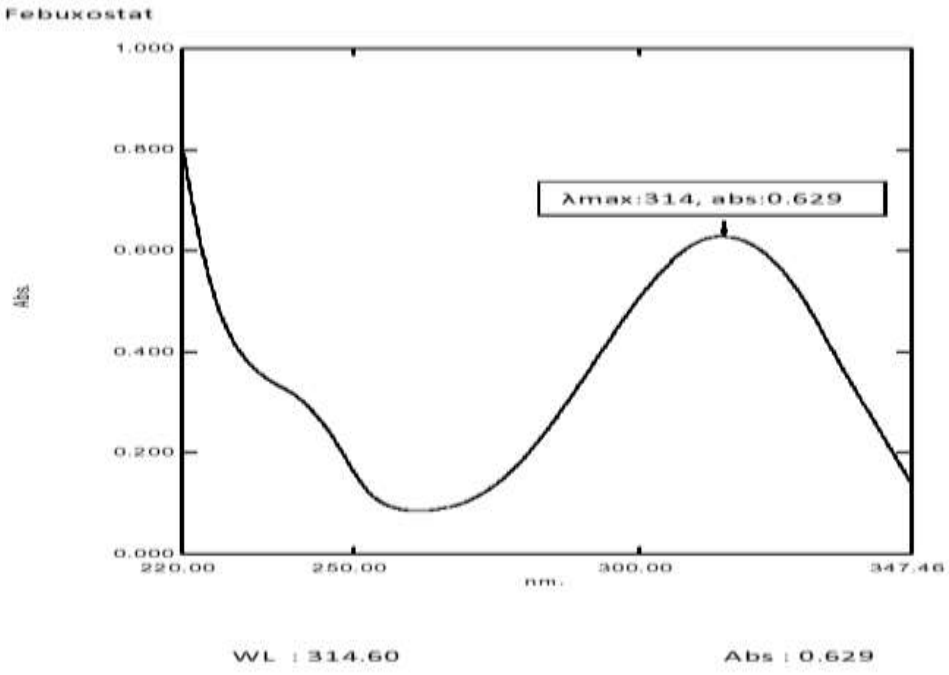


Figure 2: **Calibration curve**

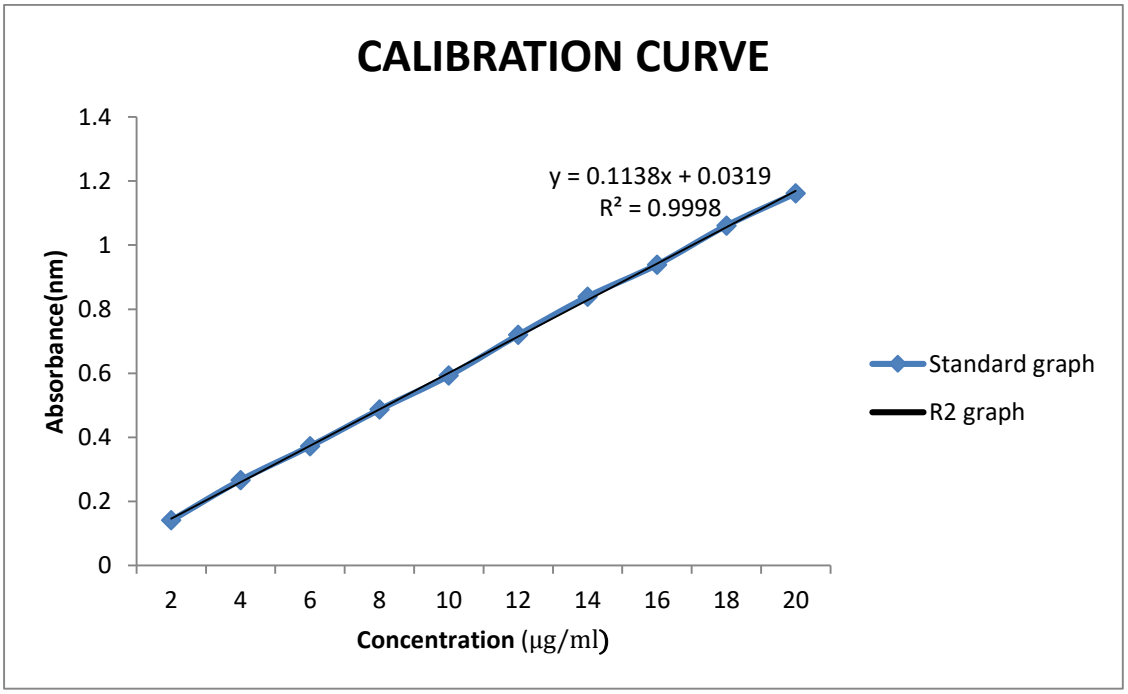
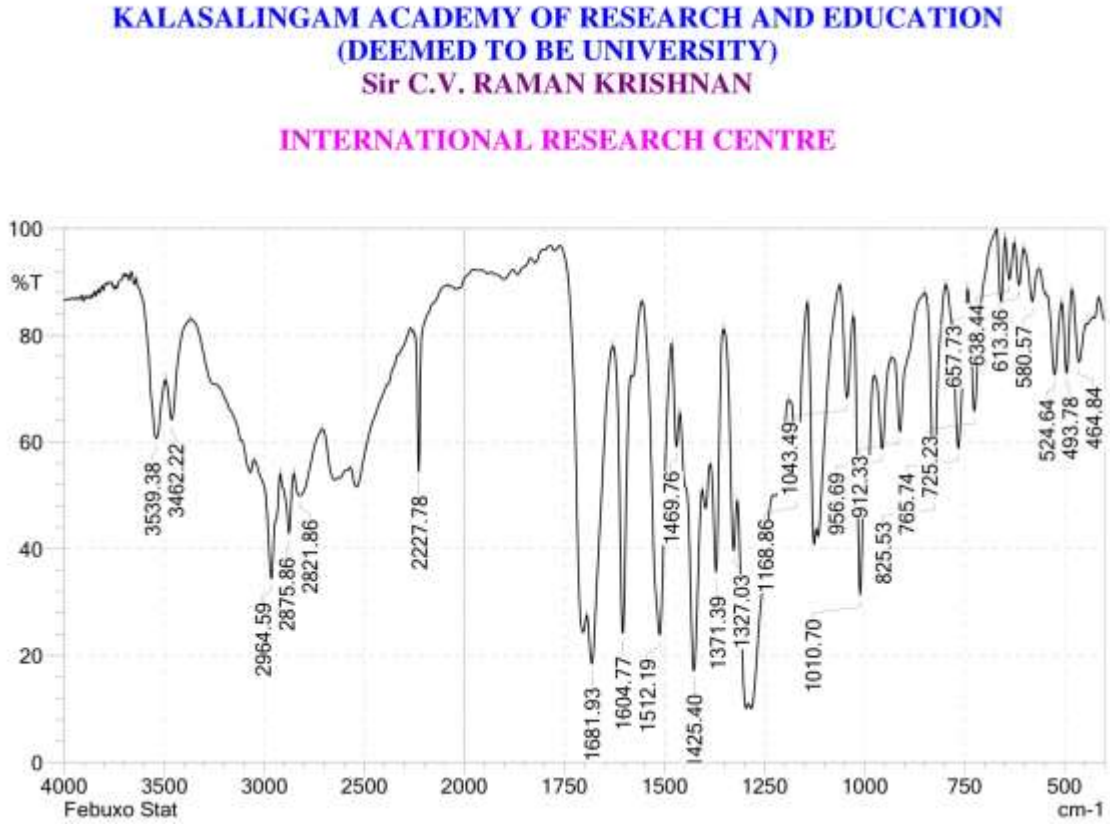
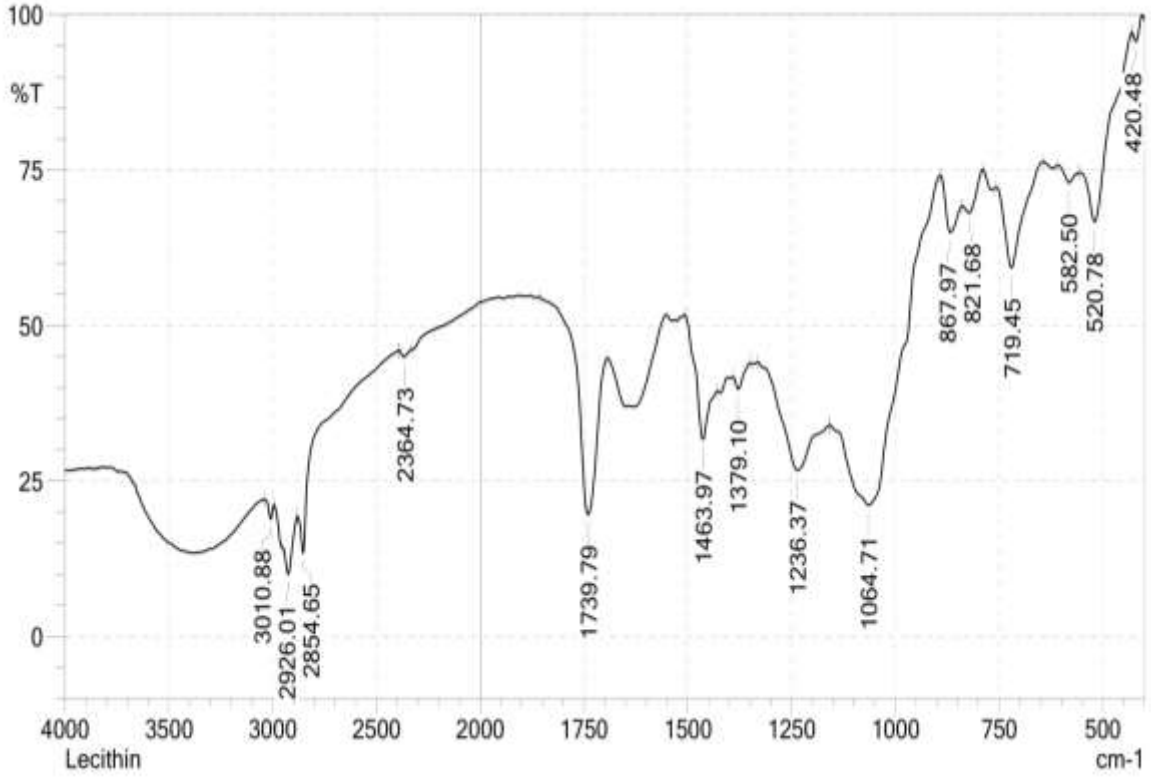


Figure 3: **IR graph of febuxostat**



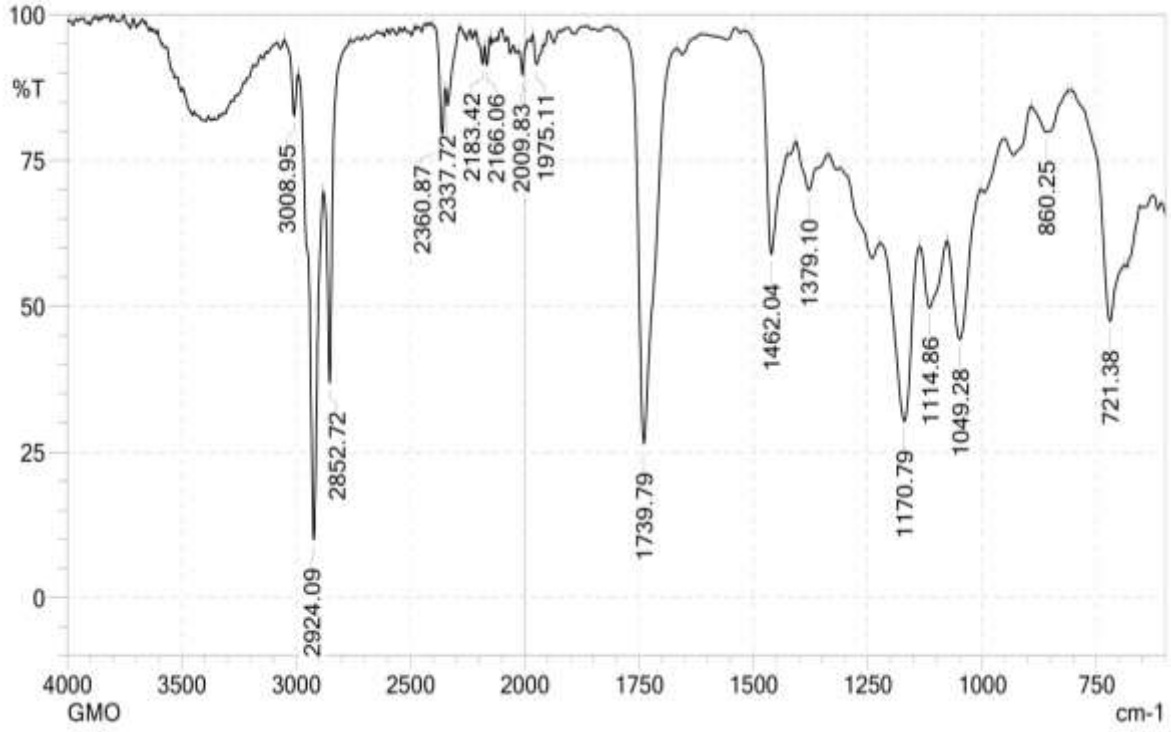
WAVE NUMBER	FUNCTIONAL GROUP
2964.59	C-H STRETCHING
2227.78	C≡N STRETCHING
2875.86	COOH - OH STRETCHING
1512.19	C=C AROMATIC STRETCHING

Figure 4 :**IR graph of lecithin**



WAVE NUMBER	FUNCTIONAL GROUP
3010.88	C-H STRETCHING
2854.65	COOH-OH STRETCHING
1379.10	CH3 BENDING
1739.79	C=O STRETCHING

Figure 5: IR graph of GMO



WAVE NUMBER	FUNCTIONAL GROUP
2852.72	CH2-CH2 STRETCHING
3008.95	OH STRETCHING
1739.75	C=O STRETCHING

Figure 6: **IR graph of tween 80**

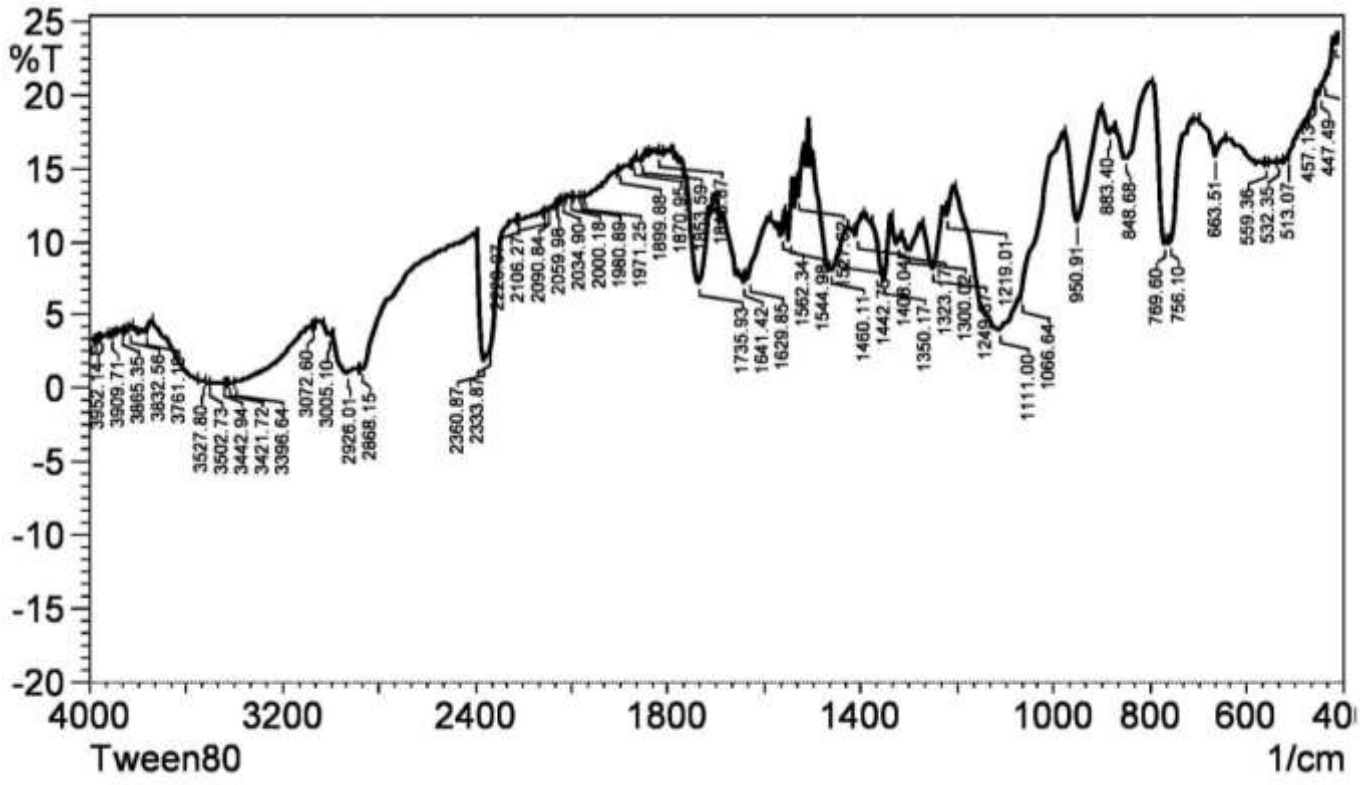


Figure 7: Physical mixture of drug+ span+ lecithin:

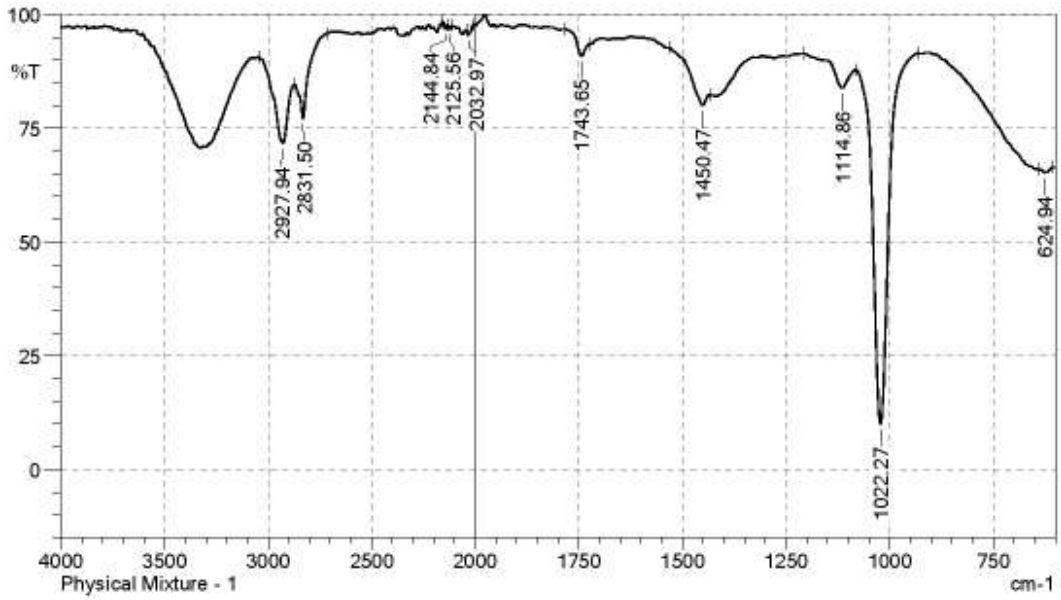


Figure 8: **Physical mixture of drug + tween 80+ lecithin:**

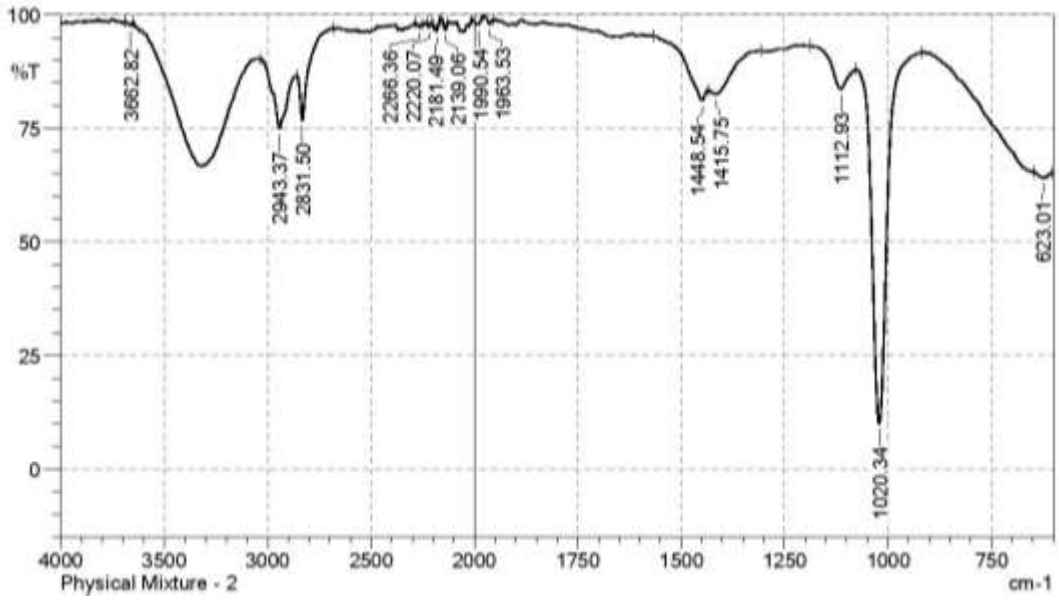


Figure 9: **Drug +Gmo+ lecithin:**

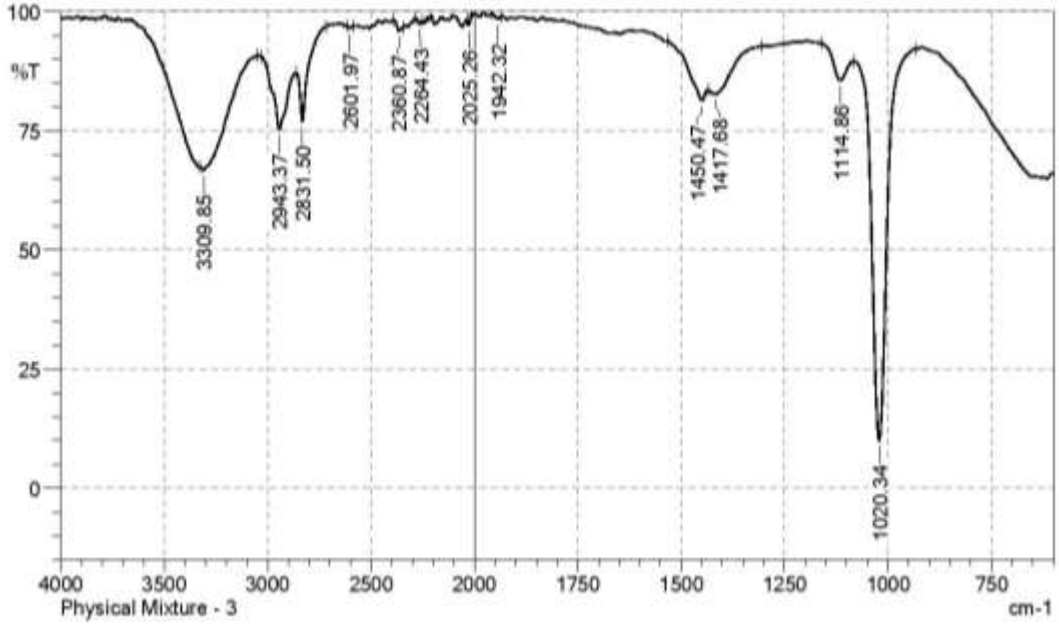


Figure 10: **Scanning electron microscope image of ELs:**

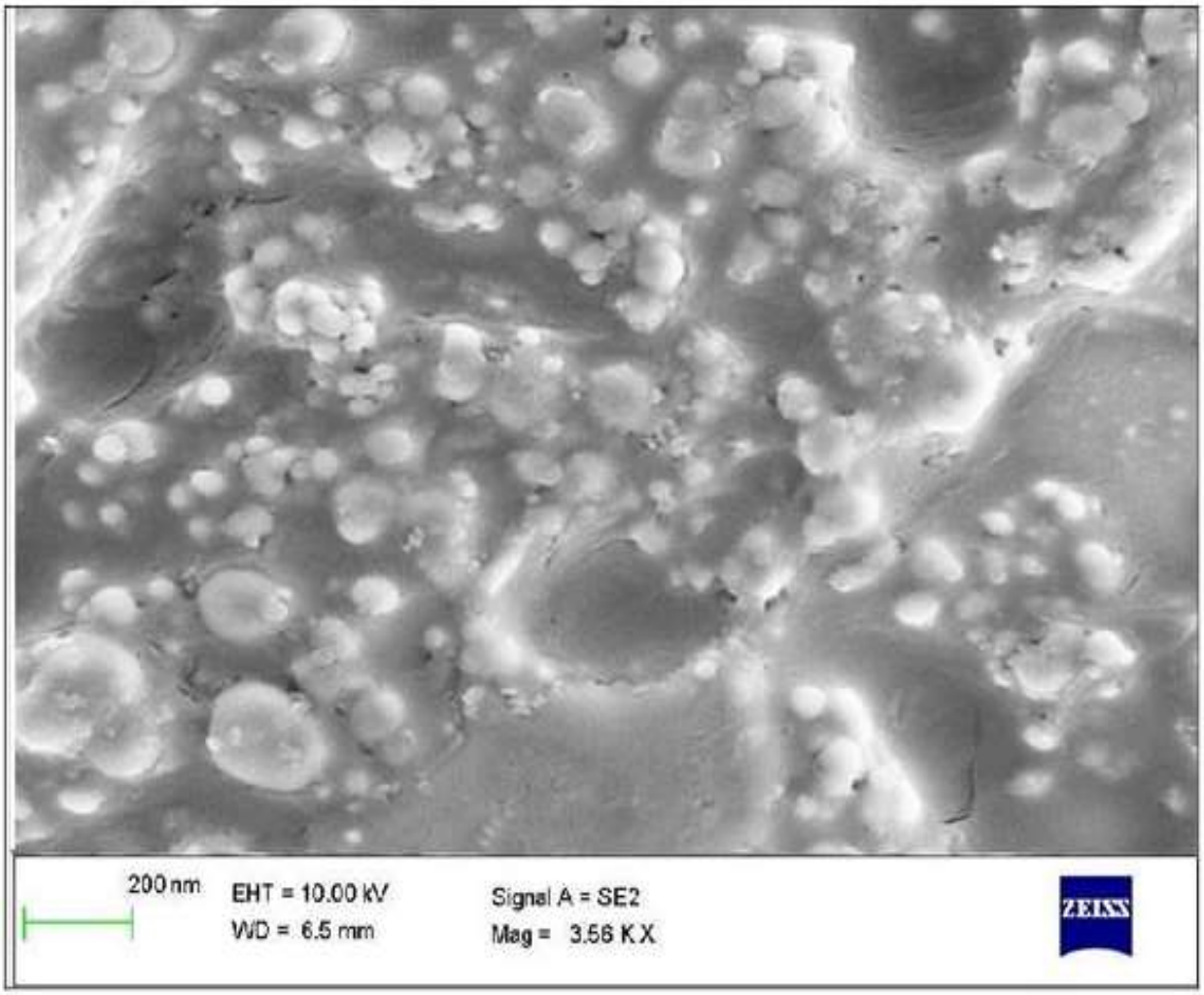


Fig: **Freeze dried Elastic liposomes**

Figure 11: Particle size measurement of formulation f3

Size Distribution Report by Intensity

v2.2

Malvern

Sample Details

Sample Name: F6 1
SOP Name: mansettings.nano
General Notes:

File Name: F3.dts
Record Number: 7311
Material RI: 1.59
Material Absorbtion: 0.010
Dispersant Name: Water
Dispersant RI: 1.330
Viscosity (cP): 0.8872
Measurement Date and Time: Monday, February 25, 2019 2....

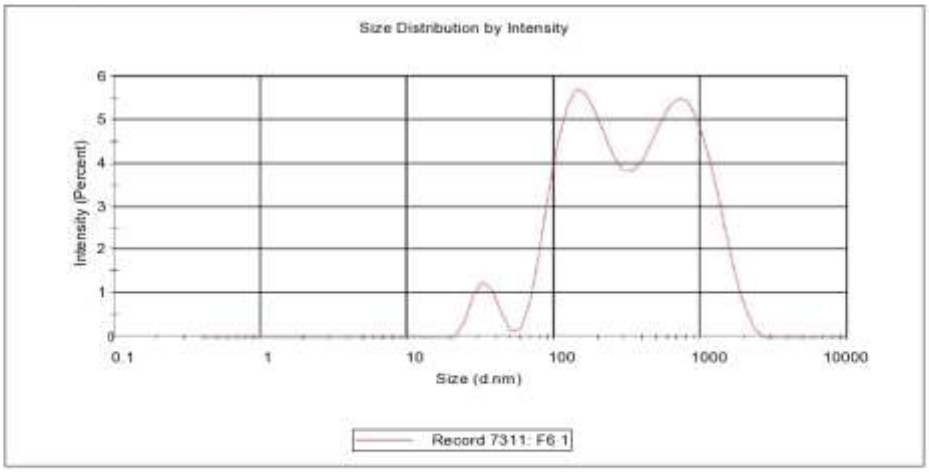
System

Temperature (°C): 25.0
Count Rate (kcps): 255.0
Cell Description: Disposable sizing cuvette
Duration Used (s): 10
Measurement Position (mm): 4.65
Attenuator: 9

Results

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 217.3	Peak 1:	803.1	48.8	386.6
PdI: 0.532	Peak 2:	181.2	47.1	77.51
Intercept: 0.848	Peak 3:	34.31	4.2	6.326

Result quality : Good



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Zetasizer Ver. 7.11
Serial Number: MAL1063602

File name: F3
Record Number: 7311
25 Feb 2019 4:26:08 PM

Figure 12: Zeta potential measurement of formulation f3

Zeta Potential Report

v2.3

Malvern

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Sample Details

Sample Name: F6 Z 1
SOP Name: mansettings.nano
General Notes:

File Name: F3.dts
Record Number: 7312
Date and Time: Monday, February 25, 2019 2:29:...
Dispersant Name: Water
Dispersant RI: 1.330
Viscosity (cP): 0.8872
Dispersant Dielectric Constant: 78.5

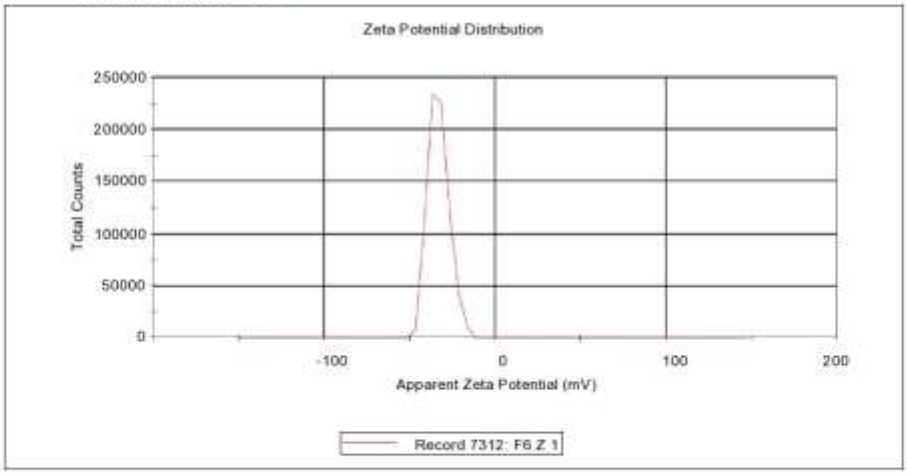
System

Temperature (°C): 25.0
Count Rate (kcps): 246.1
Cell Description: Zeta dip cell
Zeta Runs: 6
Measurement Position (mm): 4.50
Attenuator: 8

Results

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): -33.2	**Peak 1:**	-33.2	100.0	6.02
Zeta Deviation (mV): 6.02	**Peak 2:**	0.00	0.0	0.00
Conductivity (mS/cm): 0.369	**Peak 3:**	0.00	0.0	0.00

Result quality : Good



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Zetasizer Ver. 7.11
Serial Number : MAL1082602

File name: F3
Record Number: 7312
25 Feb 2019 4:29:53 PM

Figure 13: **In vitro drug release:**

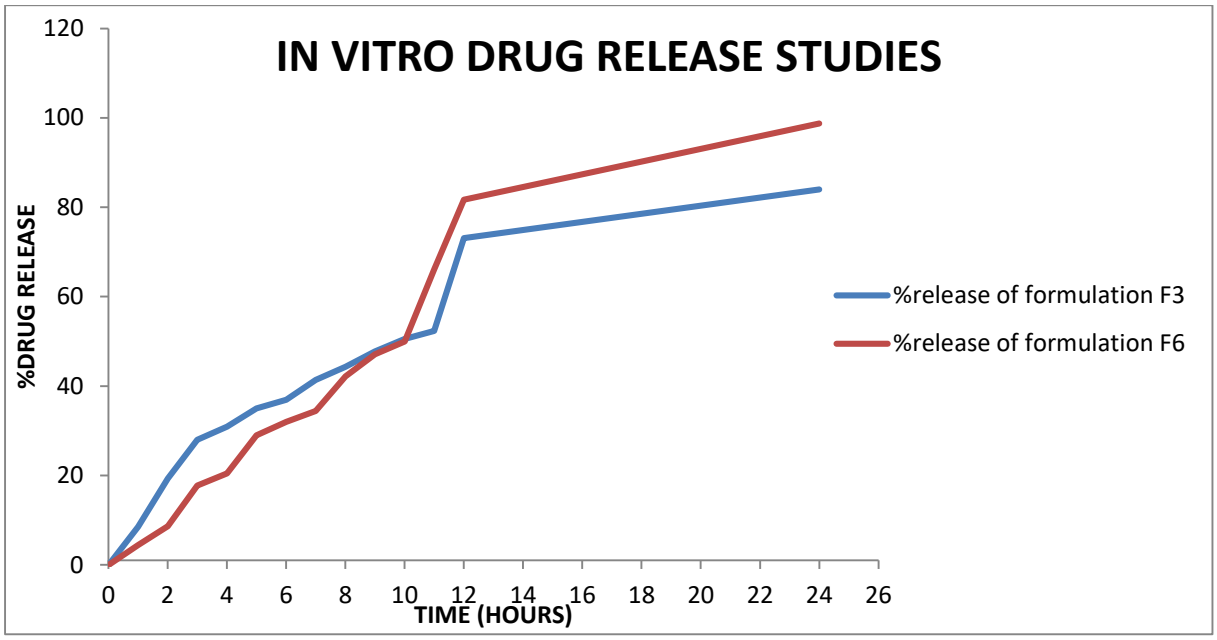


Figure 14: **Entrapment efficiency**:

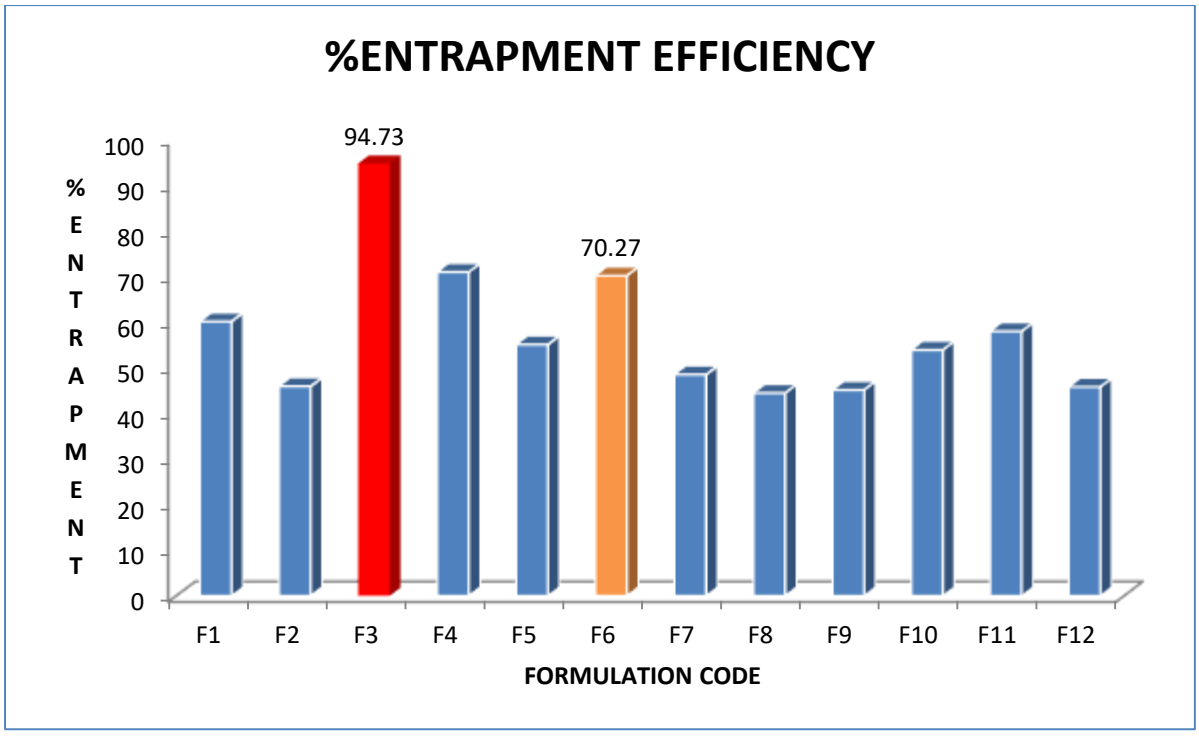


Figure 15: **Zero order studies:**

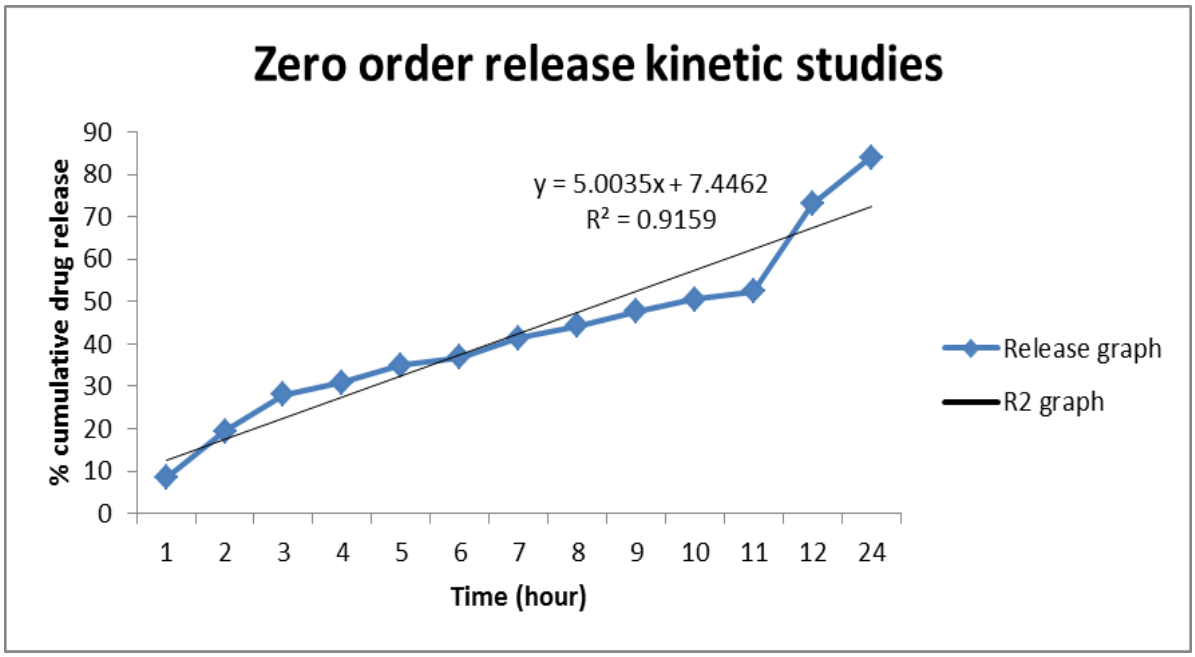


Figure 16:First order release studies:

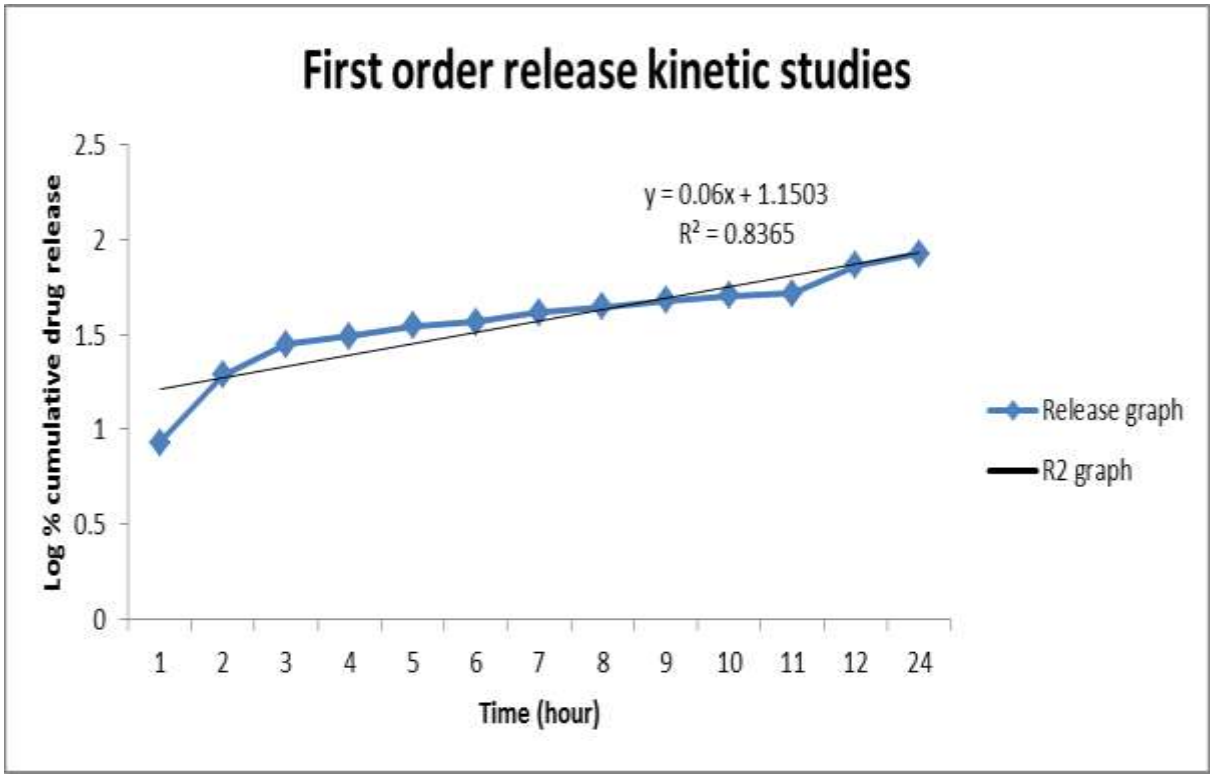


Figure 17: **Korsmeyer peppas model**

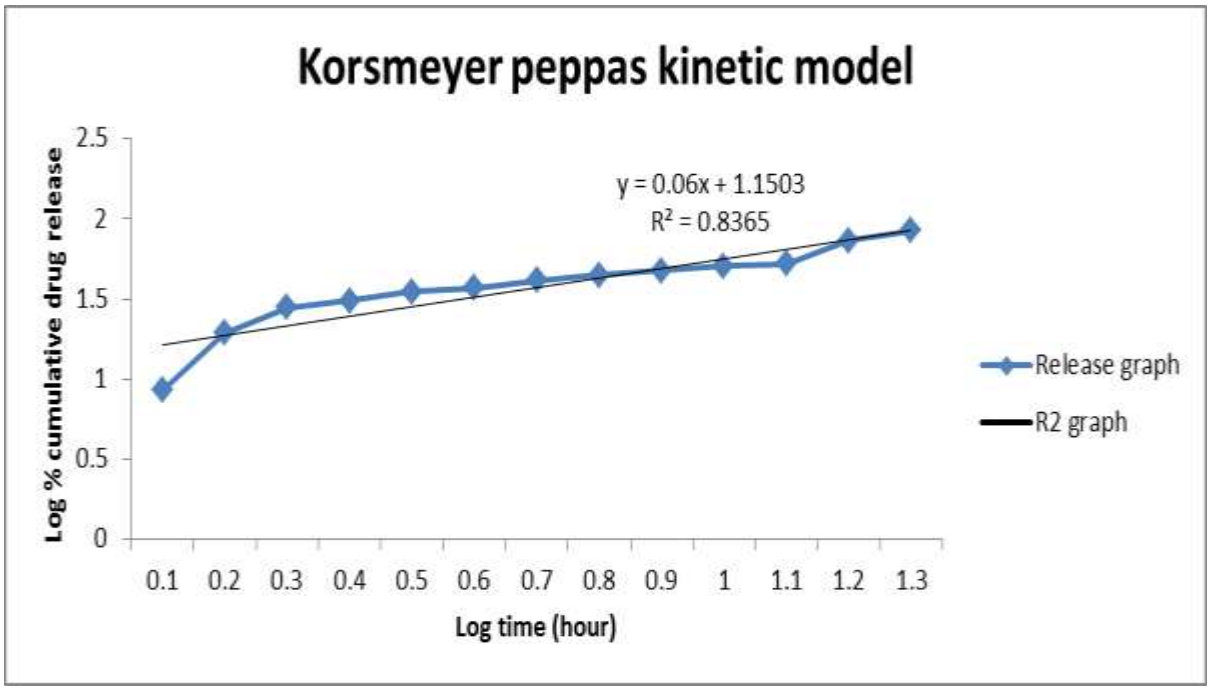


Figure 18: Higuchi release model

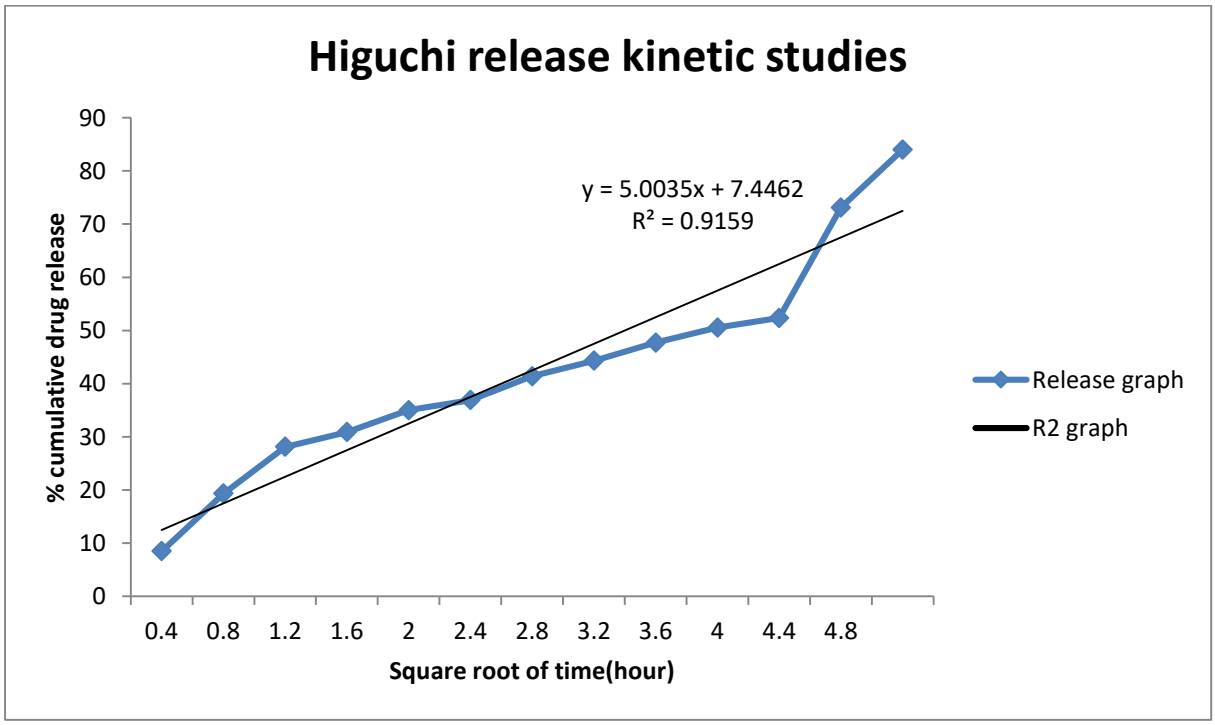
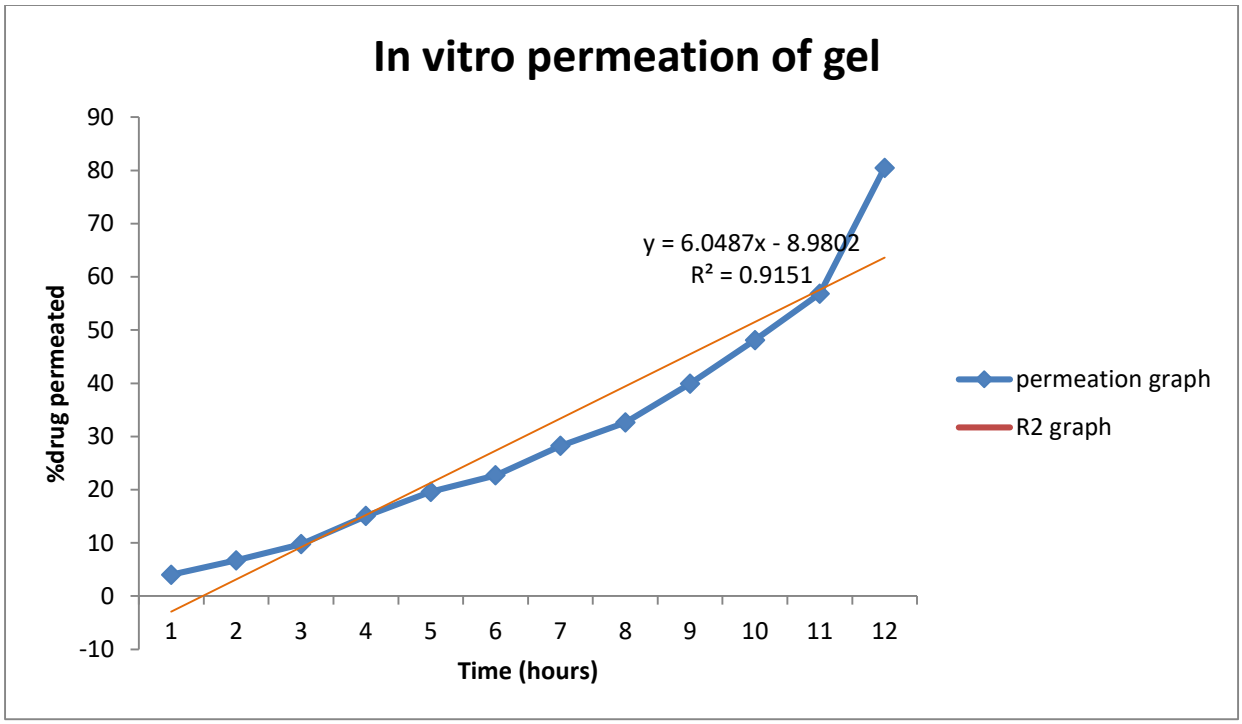


Figure 19: **In vitro permeation gel**



SUMMARY AND CONCLUSION

SUMMARY

The main objective of this work was to formulate and evaluate the febuxostat loaded elastic liposomes. Elastic liposomes increases transdermal efficiency of drug and reduces the drawbacks of febuxostat, it improves bioavailability of drug and avoids enzymatic degradation in stomach., ELs formulation target the site of action by administering via transdermal route and also with effect of edge activator it improves the entrapment efficiency of drug.

Elastic liposomes were prepared by thin film hydration technique using rotary flask evaporator. it was formulated by using soyabean lecithin (phospholipids), edge activators such as tween 80, span 80 and GMO. Concentration of lipid and surfactant set as an dependent variable. based on independent variable values optimised formulation was selected.

These elastic liposomes were obtained by varying surfactant concentration from 5%-20% and phospholipid concentration based on this by varying its concentration about 12 formulations were prepared. From the evaluation of formulation concentration level was optimised.

The prepared ELs of F1 to F12 formulation were evaluated for its physical and chemical characteristics such as particle size, surface morphology, entrapment efficiency, zeta potential .the evaluated batches shows good physio chemical characteristics especially F3 and F6 formulation shows good zeta potential range(-33.2,-46.2) and particle size range(217.3nm,165.5) compared to that of other formulation.

On the basis of these result this selected formulation were chosen for In-vitro dissolution studies .this study was carried out by using dialysis membrane diffusion method by using phosphate buffer pH -7.4.the release of drug from F3 formulation has better sustainable effect compared to that of F6 formulation.so this chosen as an optimised elastic liposomal formulation and release kinetic studies were done for this formulation.

From the results of release studies the data's was fitted into kinetic release models and found out that the release mechanism follows higuchi kinetic model that indicates that the mechanism of release is diffusion.

From these results of this formulation optimised formulation has been selected for formulating a gel.

The stability of ELs formulation was evaluated after stored at room temperature and refrigeration temperature for 30 days. Entrapment efficiency and drug content were calculated at different time intervals. Refrigerated formulation shows better stability compare to that of formulation stored at room temperature.

The optimised F3 formulation was further formulated as a transdermal gel ,it improves patient compliance and permeation capacity of drug. elastic liposomes were already having good permeation ability.by using gel as a carrier it also attenuate its permeability. ELs hydrogel was formulated using carbopol934 as a polymer with addition of triethanolamine which neutralise the gel.

The formulated hydro gel was evaluated for physical and chemical characteristics like morphological characteristics-homogeneity, grittiness, clarity, pH of gel, viscosity and spreadability of gel .visual inspection of gel seems to be good in nature, it was clear , free from grittiness. The pH of gel obtained in the range of 6.5-7.4. its an optimum pH for topical application .Formulated gel had an better spreadability value in lesser time periodand it also had better viscosity value.

In vitro skin permeation studies was done for F3 Els gel formulation by using goat skin as an permeation barrier in an open end test tube method ,it shows good permeability in 12 hours study about 90% of drug was get permeated over the skin

From the result of physiochemical characterisation, In vitro characterisation studies, skin permeation studies, release kinetic studies.it was found that elastic liposomes containing febuxostat shows better permeation, it would increases therapeutic efficacy of drug in the treatment of gout.

CONCLUSION:

Elastic liposomes are especially optimised particles or vesicles which can provide a novel solution for transdermal delivery. febuxostat loaded elastic liposomes were prepared and evaluated for different parameters like microscopy, particle size, zeta potential, in-vitro drug release etc., from the above observation, it can be concluded that sonication is an essential tool for preparation, and while comparing the EE, elastic liposomes containing Phosphotidylcholine(PC): Span 80 at a ratio of 85:15(100%) showed the highest value with respect to all other formulations. The highest sustained action was observed for F3 formulation. The optimised elastic liposomal formulation F3 followed the Higuchi release over the 24 hours. The optimised F3 formulation was further formulated as topical hydrogel and evaluated.this result showed that it shows better skin permeation ability.

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