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A Review On liposomes

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ABSTRACT:-

Liposome'sasartificiallypreparedvesicleshavebecomeimportanttoolsforimprovingdelivery of a large number of drugs: antimicrobial agents, drugs against cancer, antifungaldrugs, peptide hormones, enzymes, vaccines and genetic materials. Due to the differences inpreparation methods and lipid compositions, liposomes can be classified according to theirlamellarity, size, charge and application. The flexibility of their behavior can be exploited forthedrugdelivery throughvariousroutesof administrationirrespectiveof theirsolubilityproperties. Encapsulation of drugs in liposomes has provided an opportunity to enhance thetherapeutic indices of many drugs mainly through alteration in their biodistribution, targetingthedrugtoparticulartissues.Theroleofliposomesasdrugdeliverysystemistodeliverdrugin the controlled manner, reducing undesirable side effects improving its in vitro and in vivoactivity,aswellasreducingthetoxicityofthedrugandenhancingtheefficacyoftheencapsulated drug. This article provides an overview of methods for preparation of liposomes,as well as analytical methods for control physical, chemical and biological parameters fordifferent types of drugs. Liposomal drug delivery represents a highly adaptable therapeuticplatformfortreatingawiderangeofdiseases.Naturalandsyntheticlipids,aswellassurfactants, are commonly utilized in the synthesis of liposomal drug delivery vehicles. Themoleculardiversityinthecompositionofliposomesenablesdrugdeliverywithuniquephysiologicalfunctions,suchaspHresponse,prolongedbloodcirculation,andreducedsystemictoxicity.Herein,wediscussstheimpactofcompositiononliposomesynthesis,function,anddclinicalutility.[3.2.1]

Liposome's, sphere-shaped vesicles consisting of one or more phospholipid bilayers, were firstdescribed in the mid-60s. Today, they are a very useful reproduction, reagent, and tool invariousscientificdisciplines,includingmathematics andtheoreticalphysics,biophysics,

Keywords: liposomes,Drug, delivery, Encapsulation, Application,Solubility

I. INTRODUCTION TO LIPOSOME

1.1.Introduction:-

Liposome'shavebeen consideredtobeexcellentmodelsof cellmembranes.They showeffective drug delivery which are commonly used in dermal applications8 .Liposome's aremicroscopic spherical vesicles composed of one or more lipid bilayers with an aqueous core.They are formed when the lipids are dispersed in an aqueous medium by stirring, in turn givingrise to population vesicles which may reach a size range2 . The major structural components ofliposomes are phospholipids and cholesterol. The lipid bilayer is composed of phospholipidswhichhaveahydrophilic headgroupanda hydrophobictailgroup.

SinceAlec D. Bangham's discovery of liposomesin 1965,the lipidvessel hasbecome awidely utilized vehicle to encapsulate and deliver molecules to treat a variety of diseases. Theprimary component of liposomes are lipids and fatty acids that, due to their natural occurrencein cell membranes, are considered inherently biocompatible and biodegradable. Liposomalencapsulation of drugs reduces systemic toxicity and improves tolerable dose regimens foranti-cancer,antibacterial,andanti-fungaltherapies.Thelipidchemistryiscriticalforoptimizingdrugencapsulation,stability,andrelease,andliposomepharmacokineticsandpharmacodynamics.

Herein, we present a review of the literature focused on the rational designofliposomesbasedonchemical,mechanical,andphysiologicalproperties.

Liposome'sareextensivelyusedascarriersfornumerousmoleculesincosmeticandpharmaceutical industries. Additionally, food and farming industries have extensively studiedtheuseofliposomeencapsulationtogrowdeliverysystemsthatcanentrapunstablecompounds (for example, antimicrobials, antioxidants, flavors and bioactive elements) andshield their functionality. Liposome's can trap both hydrophobic and hydrophilic compounds,avoid decomposition of the

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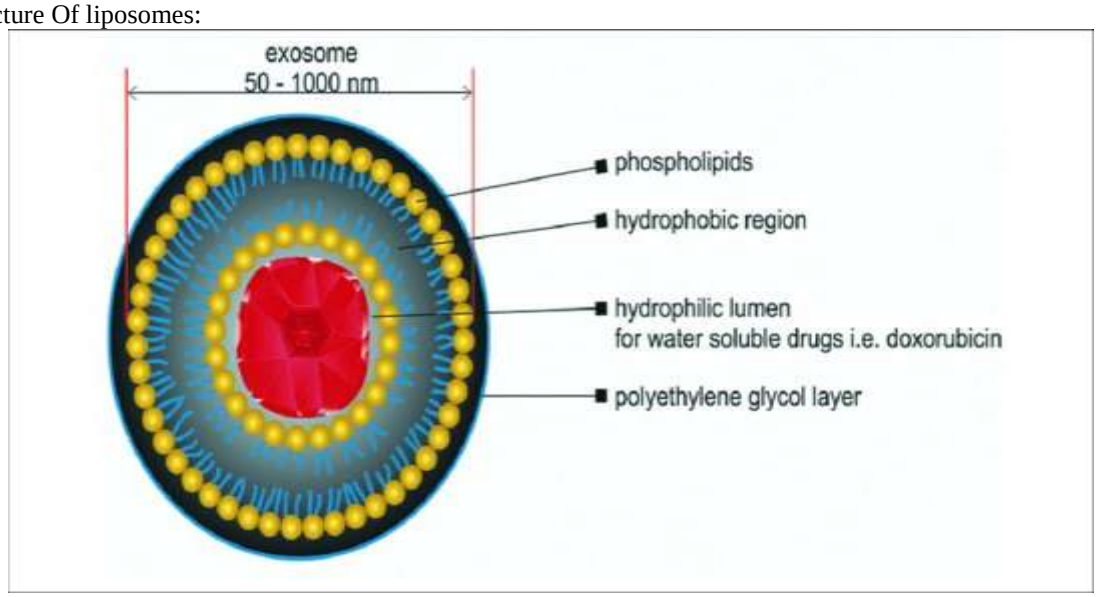
entrapped combinations, and release the entrapped at designatedtargets.
Because of their biocompatibility, biodegradability, low toxicity, and aptitude to trap bothhydrophilic andlipophilic drugs and simplify site-specific drug delivery to tumor tissues,liposomes have increased rate both as an investigational system and commercially as a drug-delivery system. Many studies have been conducted on liposomes with the goal of decreasingdrugtoxicityand/ortargetingspecificcells[1]

Structure Of liposomes:



2.2 Application Of Liposomes [16]
1.Liposomes as drug delivery vehicle
2.Liposome as vaccine carrier
3.Liposome in gene delivery
4.Liposome as artificial blood surrogate
5.Liposome as radio pharmaceutical & radio diagnostic carrier
6.Liposome in tumor therapy
7.Lyososomal storage disease
8.Metal storage disease
9.Cell biological application
10.Liposomes for pulmonary delivery
11.Liposome for topical application
12.Liposome as carrier of drug in oral treatment
13.Metal storage disease
14.Opthalmic delivery of drug
15.AgainstLeishmaniasis

2.3 Main components of liposomes [55]
1. Glycerol phospholipid
2. Cholesterol
3. Hydrophobic fatty acids chain
4. Fatty acids
5. Lauric acids
6. Decanic acids
7. Saturated fatty acids

Structural components of liposome
1. Phospholipid
2. Spingolipid
3. Synthetic phospholipid
4. Polymeric material
5. Polymers bearing lipid

2.4 Advantages of liposomes [31]
1. Lilosomes increased efficacy and therapeutic index of drug
2. Lilosonmescreed stability via encapsulation
3. Lilosomes reduced the toxicity of the encapsulated agent
4. Lilosomes help reduce the exposure of sensetivetissu to toxic drug
5. Flexibility to couple with site specific ligand to achieve active targeting
6. Site avoidance effect

Disadvantages of liposomes
1. Solubility
2. Half Life
3.Leakage And Fusion Of Encapsulated Drug
4. Cost Is High
5.Fever Stable

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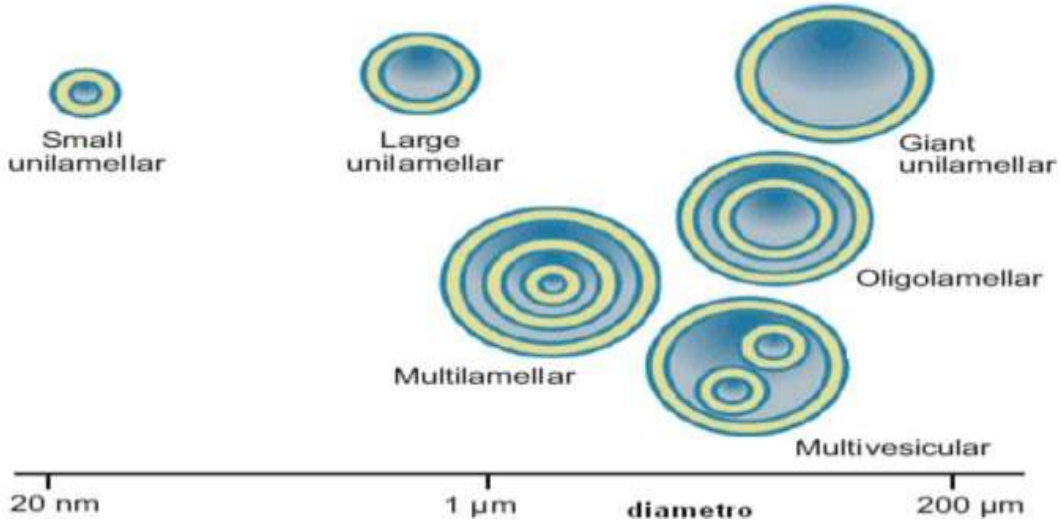
II. CLASSIFICATION OF LIPOSOME [14]



Twoimportantcharacteristicsofliposomalvesiclestha tinfluencedrugencapsulationefficiency and circulation time are size and membrane lamellarity . The method of synthesisdeterminesthetypeofliposomes produced.

Laiposomesareclassifiedas
unilamellarvesicles(ULVs)withone bilayermembrane,oligolamellar vesicles(OLVs)with2–5 bilayermembranes,multilamellarvesicles(MLVs)wit hfiveormorebilayer membranes.

ULVsarefurthercategorizedinto
smallunilamellarvesicles(20–100nmindiameter,SUVs)largeunilamellarvesicles(100 nm1mm,LUVs), andgiantunilamellarvesicles(>1mm,GUVs).

SUVsexhibituniformdrugencapsulationandreleaseki neticsalongwithlongercirculationtimes;therefore,the yarethemostcommonlyusedasdrugdeliveryvehicles

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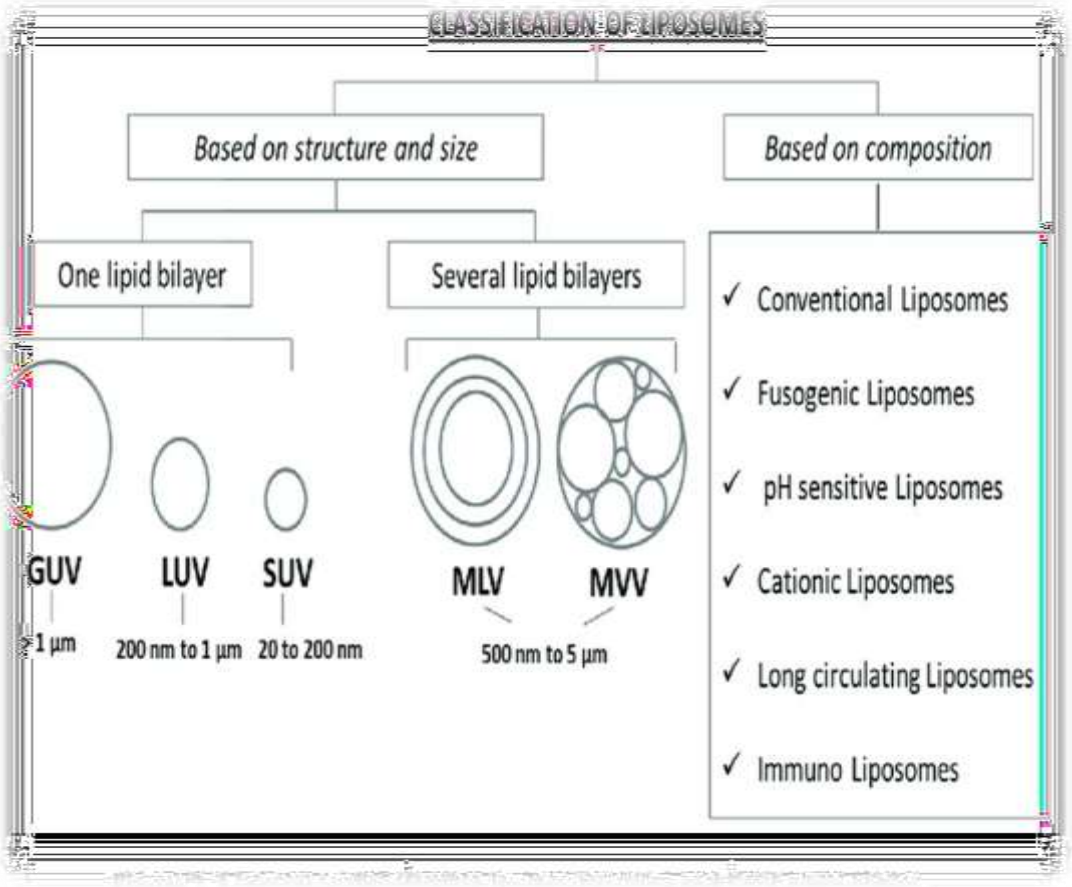

III. DESIGN AND DEVELOPMENT OF LIPOSOMES[3]

Liposome synthesis is a heavily investigated area of research with many recent and modifiedtechniques, including: heating, curvature tuning, localized IR heating, osmotic shock, dualasymmetric centrifugation, spray-drying, lyophilization, gel-assisted hydration, hydration onglass beads, hydration in microfluidics,-electroformation in microfluidics, pulsed microfluidicjetting, transient membrane ejection, continuous droplet interface crossing encapsulation andstationary phase interdiffusion method . Herein, we discuss the most common methods forbenchscalepreparationofliposomes .

3.1.Thinfilmhydration:[3]

The most common method employed for liposome synthesis is thin film hydration . In thismethod, lipids and amphiphilic molecules are solubilized and mixed in an organic solvent. Themixture is then transferred into a round-bottom flask and the solvent is evaporated using arotaryevaporatorundervacuum,leavingathinfilm of lipids.Thethinfilmisthenhydratedina solution that may contain one or more hydrophilic drugs that are desired to be encapsulated.Thetemperatureofthehydrationbuffer mustbeabovethegel-liquidphasetransitiontemperature (Tm)of the lipid.The volume of the aqueous solution used tohydrate the lipidfilm affects the characteristics of the formed liposomes; large volumes lead to the formation ofMLVswhiletherate.ofhydrationdeterminestheefficiencyofdrugencapsulation.
Thesizeandlamellarityofthevesiclesmaybecontrolled byeitherextrusionthroughmembranesofspecificporesizesortheuseofsonicators,wherethefrequencyofthe

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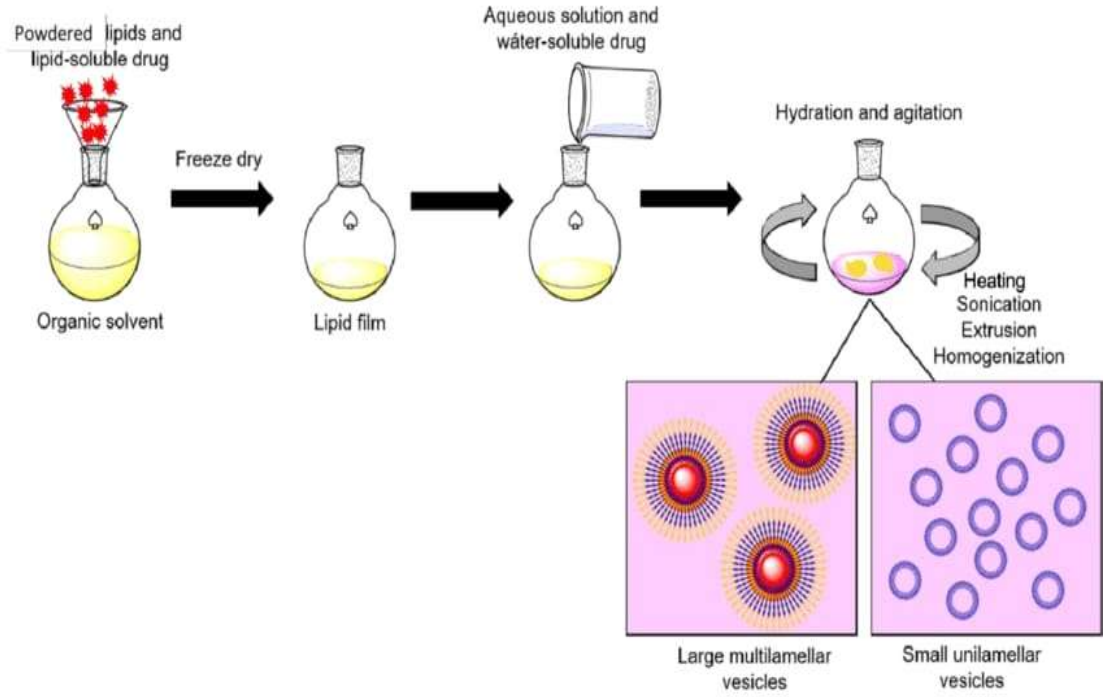

ultrasonicwavesandthedurationoftheproces sdeterminethesizedistributionofthefabricated liposomes . A jacketed extruder or water bath may be used to maintain the solutiontemperature above the Tm of the lipid if necessary. Although sonication is easier and moreconvenient for post-synthesis processing to produce SUVs, especially when large volumes areneeded, it results in less uniform liposomes with lower drug encapsulation efficiency comparedto those produced by extrusion .

3.2Reverse-phaseevaporation [13] [8]

Reverse-phase evaporation produces a mixture of LUVs and MLVs entrapping large aqueousvolumes, which allows for encapsulation of large molecules, such as proteins and nucleic acids.In this method, lipids and amphiphilic molecules are first mixed in an organic solvent , then anaqueous buffer, which may contain a solubilized drug, is added to the mixture. Afterwards, theorganicsolventisevaporatedusingarotaryevaporatorunderlowD.E.Large,R.G.Abdelmessih,E.A.Finke tal.AdvancedDrugDeliveryReviews176(2021)1138512pressure, leaving the lipid vesicles dispersed in the aqueous solution. If an application requiressmaller, more uniform particles, the size ofliposomes may be reduced by extrusion . In thiscase, the pore size of the polycarbonate filter and the number of extrusion cycles will determinethe sizeandpolydispersityofthe synthesizeliposomes.

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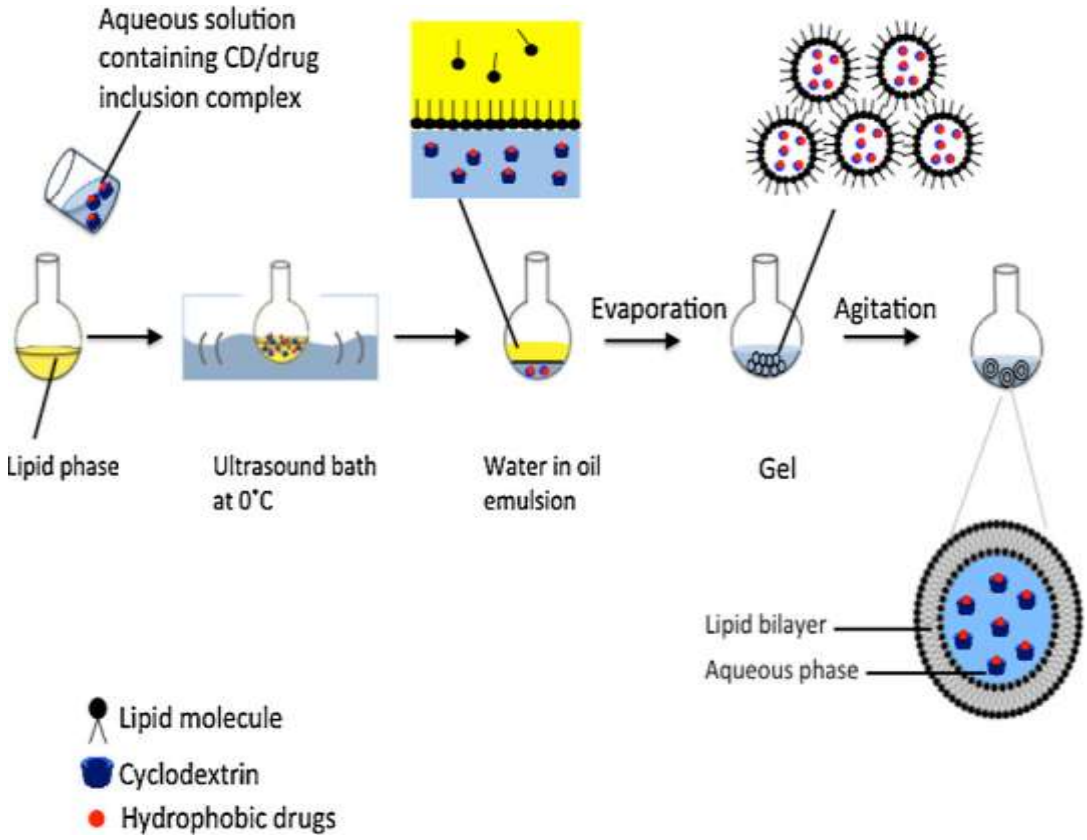
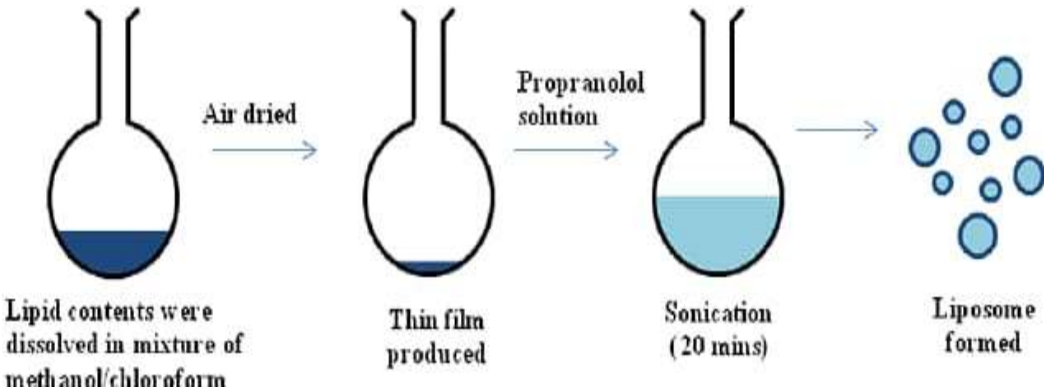


3.3.SonicationMethod [3]

The sonication method is based on size transformation andinvolves the subsequentsonicationof MLVs prepared by thin-film hydration method, using sonic energy usually under an inertatmosphere including nitrogen or argon. The sonication method enables homogenous dispersionof small vesicles using bath type or probe type sonicator with a potential for greater tissuepenetration. The probe tip sonicator delivers high energy to the lipid suspension. The possibilityof overheating of the lipid suspension causes degradation12,22,49 . Sonication tips tend torelease titanium particles into the lipid suspension which must be removed by centrifugationpriortouse.



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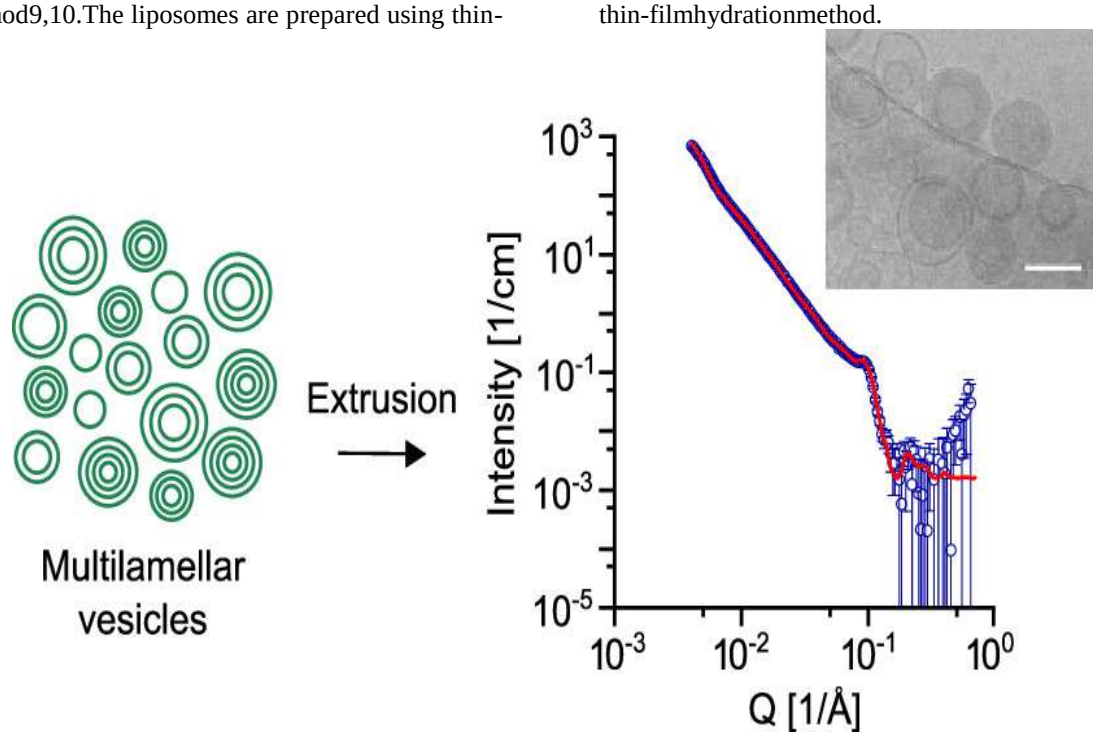
3.4.High-PressuresExtrusionMethod[13,8]

MLVspreparedbythin-filmhydrationmethodarerepeatedlypassedthroughfilterspolycarbonate membranes reducing the liposome size in high-pressure extrusion method9,10.The liposomes are prepared using thin-filmhydration method. MLVs prepared by thin-filmhydration method are repeatedly passed through filters polycarbonate membranes reducing theliposome size in high-pressure extrusion method9,10. The liposomes are prepared using thin-filmhydrationmethod.



3.5 Calcium-InducedFusionMethod

The calcium-induced method is based on adding of calcium to SUV. The formation of multilamellarvesiclesisasresultoffusion.Theaddition ofethylenediaminetetraaceticacid(EDTA)tothepreparations results in the formation of LUV liposomes15. The preparation of LUV liposomes can beobtained only from acidic phospholipids. Fluid from an affected joint is drawn by expert using a needle.The fluid is then tested for inflammation and to determine whether the pain is caused by gout or aninfectionratherthanosteoarthritis.

3.6 Dehydration-RehydrationMethod:-

The method of dehydration-rehydration is used as method for the preparation of liposomes,also44,51. The small unilamellar vesicles which are composed of phosphatidylcholine, 1,2-dioleoyl-3-(trimethylammonium)propane,cholesterolandplasmidDNArepreparedbysonication method51. The obtained formulation is frozen and left freeze-dried overnight. Theformation of multilamellar dehydration-rehydration vesicles containing DNA in their structuredue to the bound of the cationic charges of the inner bilayers is as a result of a controlledrehydrationofthedrypowder

3.7Freeze-ThawsMethod:-[13][16]

Themethod offreezingandthawingisintroducedforincreasingthe trapped volumeofliposomal preparations. The freeze-thaw method is dependent on the ionic strength of themedium and the phospholipid concentration. It influences to a physical disruption of lamellarstructure leading to formation of unilamellar vesicles. The unilamellar vesicles are rapidlyfrozen followed by slow thawing, while the freeze and thawing cycles are repeated. ThepreparationofMLVpropranololliposomesbyfreeze-thawmethodisdescribedintheliterature.Theliposomalpropranololformulationispreparedbyusingdistearoylphosphatidylcholineanddimyristoylphosphatidylcholineasphospholipidsinphosphate buffered salinebuffer,followedbysixfreeze-thaw cycles.

3.8 .Microfluidization:[50]

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Amethodbasedonmicrofluidizationi.e.microemulsificationis usedfor thelargescalemanufacture of liposomes. The preparation of antibiotic liposomes by thin-layer hydrationmethod followed by sonication with a bath-type sonicator and microfluidization in order toachievepartialhomogenizationwasdescribedby.Theprocessofmicrofluidizationisreproducible andyieldliposomeswithgoodaqueousphase encapsulation.

3.9 SupercriticalFluids(SCF) in thePreparationofLiposome's:[13]-

Supercriticalfluidsareintroducedintheprepa rationofliposomestoovercomeexistingproblems with conventional methods such as requiring a high amount of toxic organic solventsandlimitedlaboratory scale production.Themostcommon used supercritical fluidin thepreparation of liposomes in pharmaceutical field is supercritical carbon dioxide. It has severaladvantages:non-toxicity,non-flammability,recyclableandeasy removal from thesolvent,operationatmoderatetemperaturesandavoidingdegradationoftheproductinaninertatmosphere. TheuseofSCFallowscontrollingofextractionconditionbyvariationoftemperature, pressure or adding modifier solvents as cosolvents: acetone, ethanol, methanol,dichloromethane and ethyl acetate. A comparison between thin-film hydration method and SCFmethodisreportedbyKarnetal.,.Amixtureofphosphatidylcholine,cholesterolandcyclosporin A is dissolved in ethanol followed by pumping supercritical carbon dioxide to thereaction vesicle in SCF method. Distilled water in hydration step in thin-film hydration methodisused.

IV. METHODSOFLIPOSOMECHARACTERIZATION[31,19,55]

The key aspects that define the efficacy of a liposome formulation include size, zeta potential,encapsulation efficiency, release, stability, and pharmacokinetics. Size and zeta potential areproperties defined by the liposome preparation method and composition, respectively. Drugencapsulationefficiencyandstabilityarecriticaltoprotectanddeliverthedrugpayload.Inefficient encapsulation can lead to significant waste of expensive drugs. Drug release is desiredin the site of interest; premature drug release may cause undesirable ''off-target" effects. Thepharmacokinetics of the liposome are described by the circulation time and biodistribution of thedrugdeliveryvehicle.Together,encapsulation,stability,release,circulationtime,andbiodistribution characterize the ability of a drug delivery vehicle to achieve the goal of deliveringthe activedrugtothediseasedsite.

4.1 Drugencapsulationefficiencyandrelease:-[55,54,46,3]

The encapsulation efficiency is a measure of the amount of drug incorporated into the liposomeduring formulation. It is defined by subtracting thefree non-incorporated drug from the totaldrug and dividing by the total druginitially added. This can be determined using differentmethods, depending on the chemistry of the drug. The concentration of drug in solution may bedeterminedspectrophotometrically,fluorometrically,orusingradiologicmethods.Characterization of drug release is often performed in vitro using a dialysis method. Liposome'sare placed inside pre-wetted dialysis bags with a selected molecular weight cut-off to entrap theliposomes butallow the drug to permeate across the membrane. The concentration of drugreleased is measured at different time points. This provides a measure of the rate the drug will bereleasedfromliposomeformulations.

4.2 Size,zetapotential,andstability [17]

Liposomal stability is an important indicator of its potential efficacy and utility in clinical use.Often, the stability of a formulation is evaluated by performing physical assessments of theliposomes at multiple timepoints (e.g., days, week, or months) and assessing drug leakage andnanoparticle size. Undesirable changes in the physical characteristics of a liposome formulationinclude aggregation of the particles and physical degradation of the lipid membrane over time.Liposomaldiameterandsurfacechargecanbedetermineusingdynamiclightscattering(DLS)and phase analysis light scattering (PALS), respectively. Liposome's with neutral surface chargeaggregate andare unstablefordrugdeliveryapplications.

4.3 Electronmicroscopy [7]

Electronmicroscopyisthecentraltechniquefor size,morphology,andlamellaritycharacterization of liposomes.While environmental scanningelectron microscopy (SEM)isgood enough to visualize large vesicles, transmission electron microscopy (TEM) is

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normallyrequiredtoresolvethelaminarstructureofsmallvesiclesless than100nm.
However,theuseofanegativestainsuchasuranylacetateorosmiumtetroxideintheconventional To avoid the above problems and to achieve a better differentiation of thelayered structure of liposomes, cryo-transmission electronmicroscopy(cryo-TEM) and freeze-fracture TEM (FF-TEM) which keep the sample at cryogenic temperatures without staining arethe two most frequently used techniques for liposome analysis. By limiting ice crystal formationwithrapidfreezinginliquidnitrogen,proteinsandbiologicalmaterialsintheinnercompartmentsofliposomes canbe preserved.
Cryo-TEM has long been used for liposome analysis since 1980s. There are several reviewarticles illustrating how to use this technology to insight into the size, morphology, and structureoflipidvesicles.Recently,liposomeslabeled withparamagneticlipidsareconsideredaseffectivemagnetic resonanceimaging(MRI)contrastagents.

4.4 Atomicforcemicroscopy [7]

Asamemberofscanningprobemicroscopy,atomicforcemicroscopy(AFM)hasbeenusedinmany research fields since it was developed in 1980s. AFM is a powerful tool to examine severalparameterssuchassize,morphology,andsurfacepropertyofliposomeswithdifferentcompositions.Ruozietal.usedtappingmodeAFMtostudythesurfaceproperties ofconventionalandPEGylatedliposomes.Inthephaseimages,PEGylatedliposomesshowedabrightframeinsharpcontrasttothedarkframeofconventionalliposomeswhichcanbeattributedtothePEGchainonthelipososurface.ThusliposomeswithPEG-graftedorevenothersurfacemodificationcanbeinvestigatedanddistinguishedthroughthisapproach.Therigidityofliposomes,anotherimportantpropertywhichishardlyanalyzedbyothertechniques,can also be measured using AFM. Nakano et al.38 investigated several factors that may influencethe rigidity of liposomes.

4.5 Fluorescencemicroscopy [7,6]

Fluorescence microscopy, including confocal fluorescence microscopy, has been widely used inthe analysis of fluorescently labeled liposomes. Kundinget al.47 immobilized C18-DiO labeledlipid vesicles on a glass slide through biotin-streptavidin interactions. Liposome's were observedunder a confocal laser scanning microscope (CLSM) and the integrated fluorescence intensity ofeach individual vesicle was recorded
the fluorescenceintensity can be converted to sizeby usingfluorescentcolloidal beads ofknown dimension as calibration standards. In contrast to the ensemble averagemeasured with DLS, CLMS enables a faithful reconstruction of size-distribution histograms byanalyzingliposomesatsingle-vesiclelevel.Thismethodiscapableofrevealingthesizedistributionofpolydisperseliposomepopulation.

V. EXAMPLE OF LIPOSOMES:[17]

S.R No	Name of Drug	Name of drug	current status
1	Doxorubicin	Lipodox	Marketed
2	Doxorubicin	Myocet	Marketed
3	Doxorubicin	Doxil	Marketed
4	Mitoxantrone	LEM ETU	Phase1
5	Doxorubicin	MM 302	Phase1

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6	Docetaxel	Doxorubicin	Phase1
7	Anamycin	Liposome Anamycin	Phase2

sr no.	Peptide/Peptide	Preparation Method
1	Admantyltrypepetidase	Dry lipid Hydration
2	Antiovalbumin antibodies	Dry lipid hydration
3	Calcitinine	Dry lipid Hydration
4	Enkephalin	Double Emulsification
5	Hemoglobin	Dry lipid Hydration
6	Insulin	Rever phase evaporation
7	Leridistine	Double Emulsification
8	Leoprolide	Dry lipid Hydration
9	octreotide	Double emulsification
10	Progenipoietin	Double Emulsification

7 Marketed formulation of liposome: [55]

sr no.	Product	Drug	company

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1	Atragen	Tretinoin	Aronex Pharmaceutical Inc
2	Amphotec	Amphotericin B	sequence pharmaceutical inc
3	Ambisome	AmfotericineB	Nexasar pharmaceutical nc
4	Amphocil	Amphotericin B	sequence pharmaceutical inc
5	Abelcer	Dry protein free	Britayniyapharmauk
	Avian	powered of DPPC PG	-
6	Retroviruses.	killed avian retroviruses	vinland lab usk
	Vaccine	-	-
	Depocyte	-	-
7	Doxil	cytrabine	Pacira pharmaceutical inc
8	Topex	Doxorubicin	sequence pharmaceutical Inc
9	Ventus	Terbutalinesulphate	ozone pharmaceutical ltd
10	vinaca zone	Prostaglandin E1	The liposome company
11	Vincristine	-	Nexassarpharmaceutical Inc

sr no.	year of Approval	liposome Product	conduct of liposome product
1	1993	Epaxal	inactivated hepatitis a viruses
2	1995	Abelcet	Amphoterici B

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3	1995	Doxil	Doxorubicin
4	1996	Amphotec	Amphoterici B
5	1996	Ambisome	Amphoterici B
6	1997	InFlecaxal	inactivated influenxa virus
7	1999	Depocyte	cytrabine
8	2000	Myocet	Doxorubicin
9	2000	visudyne	veryeporphine
10	2004	Mepact	Mifamurtide
11	2004	Depodur	Morphine sulfate
12	2012	onivyde	Vincristrine
13	2015	onivyde	Irinoyecan

Examples OfLoposomal Based Protine And Peptide Drug [55]

sr no.	Peptide/Peptide	Preparation Method
1	Admantyltrypepetidase	Dry lipid Hydration
2	Antiovalbumin antibodies	Dry lipid hydration
3	Calcitinine	Dry lipid Hydration
4	Enkephalin	Double Emulsification
5	Hemoglobin	Dry lipid Hydration
6	Insulin	Rever phase evaporation
7	Leridistine	Double Emulsification
8	Leoprolide	Dry lipid Hydration
9	octreotide	Double emulsification
10	Progenipoietin	Double Emulsification

VI. CONCLUSION:

Long circulating liposomes of Capecitabine were successfully formulated, characterized andevaluated in vitro. The DPPC-DSPE sodium (30:25) liposomes were of optimum particle size,Zeta potential, Entrapment efficiency and satisfactory cumulative percent drug release. Theaverage targeting efficiency of drug loaded liposomes was found to be in liver followed byspleen, heart, lungs and kidneys respectively. Stability studies indicated that 4oC is the mostsuitabletemperatureforstorageoflongcirculatin gliposomesofCapecitabine.Thisdrugdelivery is endowed with several exclusive advantages and

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hence holds potential for furtherresearchandclinicalapplication.

Liposome's are highly heterogeneous nanoparticles which exhibit different size, composition,charge,encapsulationamountevenwhen preparedunderthesamecondition.Individualcharacterizationofliposomestogeneratephysicochemicaldistributionsofnanoparticlepreparations is essential to ensure their wide applications in drug development and membranemodeling. In general, any single nanoparticle techniques can be used for the individual analysisof liposomes. However, the fragile structure could cause damage and morphology alteration toliposomesduringtheimmobilizationandvacuuming processesrequiredforelectronmicroscopic studies.

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