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Review of Furosemide Capsule Containing Liquid Crystals

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ABSTRACT: Liquid crystal, substance that blends the structures and properties of the normally disparateliquid and crystalline solid states. Liquids can flow, for example, while solids cannot, and crystalline solidspossess special symmetry properties that liquids lack. Ordinary solids melt into ordinary liquids as thetemperatureincreases—e.g.,icemeltsintoliquidwater.Somesolidsactuallymelttwiceormoreastemperature rises. Between the crystalline solid at low temperatures and the ordinary liquid state at hightemperatures lies an intermediate state, the liquid crystal. Liquid crystals share with liquids the ability to flowbut also display symmetries inherited from crystalline solids.The resulting combination of liquid and solidproperties allows important applications of liquid crystals in the displays of such devices as wristwatches,calculators, portable computers, and flat-screen televisions Nanotechnology, a term derived from the Greekword,,Nano‟‟ meaningdwarf, applies the principles ofengineering,electronics, physical and materialscienceandmanufacturingat amolecularorsubmicronlevel.

Keywords:Liquidcrystal,Nanotechnology,Furosemide.

I. INTRODUCTION

The well-known three states of matter are solid, liquid and gas. When cooled, gas condenses toform a liquid as you see in a warm room in winter where water vapor forms dew on glass windowscooled by the cold air outside. In the gas state, molecules are free to move around pretty muchindependent from each other except for occasional collisions. Molecules in the liquid state are lessmobile and closer to each other. Frequent collisions between molecules make the liquid moreviscous,yetitcanstillflowlike"liquid."Astheliquidisfurthercooled,sayatthefreezingpointofwater 0℃ (32℉), it is transformed to a solid, which is rigid; water freezes to become ice at 0℃(32℉). Until two scientists in Europe, Friedrich Reinitzer and Otto Lehmann, discovered liquidcrystals in the late 19th century, these three were the only states of matter that humans have everknown.

Liquid crystal is the fourth state of matter that occurs between solid and liquid. While studying thefunctionof cholesterolin plants,Friedrich Reinitzer, an Austrian botanist,found an unusualmelting that was always accompanied by the presence of cloudy liquid state before the clear liquidappears. This cloudy liquid is what is now known as "liquid crystal." Intrigued by this unusualobservation, Reinitzer sent the sample 1 to a renowned German crystallographer, Otto Lehmann.Throughhiscarefulobservationsofthemeltingofthesubstanceusinghisstate-of-the-artmicroscope with a gas heating stage, Lehmann was convinced that the cloudy state is truly a newstate of matter that differs from solid, liquid and gas. The year 1888, in which Reinitzer found thisdoublemeltingphenomenon, is officiallyrecognizedastheyearofdiscoveryofliquid crystals.

Liquid crystal, substance that blends the structures and properties of the normally disparate liquidand crystalline solid states. Liquids can flow, for example, while solids cannot, and crystallinesolidspossessspecialsymmetrypropertiesthatliquidslack.Ordinarysolidsmeltintoordinary liquids as the temperature increases—e.g., ice melts into liquid water. Some solids actually melttwice or more as temperature rises. Between the crystalline solid at low temperatures and theordinary liquid state at high temperatures lies an intermediate state, the liquid crystal. Liquidcrystals share with liquids the ability to flow but also display symmetries inherited from crystallinesolids. The resulting combination of liquid and solid properties allows important applications ofliquid crystals in the displays of such devices as wristwatches, calculators, portable computers, andflat-screentelevisions Nanotechnology,atermderivedfromtheGreekword,,Nano‟‟meaningdwarf,appliestheprinciplesofengineering,electronics,physicalandmaterialscienceandmanufacturingatamolecularor

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submicronlevel.Oneofthemostattractiveareasofre searchindrug deliverytodayisthe design of nanosystems that are able to deliver drugs to the right place, at appropriate times andat right dosage (Motwani et al., 2007). Nanotechnology is now being broadly of applied scienceand technology, for manipulating the structure of matter on molecular level at an incredibly smallscale between 1-100nm. Though the unifying theme of nanotechnology is manipulation of matteron atomic and molecular scale but is still not a mature technology and thus, is more appropriatelycalled as "Nanoscience". Drugs with narrow therapeuticindices create a major challenge forpharmaceutical scientists, during their development. Application of nanotechnological principlesfor the delivery of such drugs can significantly rectify this problem. Self-assemble phospholipid,sterically stabilized micelles have numerous advantages as nano drug delivery systems to improvetherapeutic efficacy and reduce toxicity of drugs with narrow therapeutic indices. Liquid crystalsare the state of matter existing between the liquid and the crystalline solid, characterized by thepartial or complete loss of positional order in crystalline solids, while retaining the orientationalorderof constituent moleculeasshow inFigure1(Omray,2013).

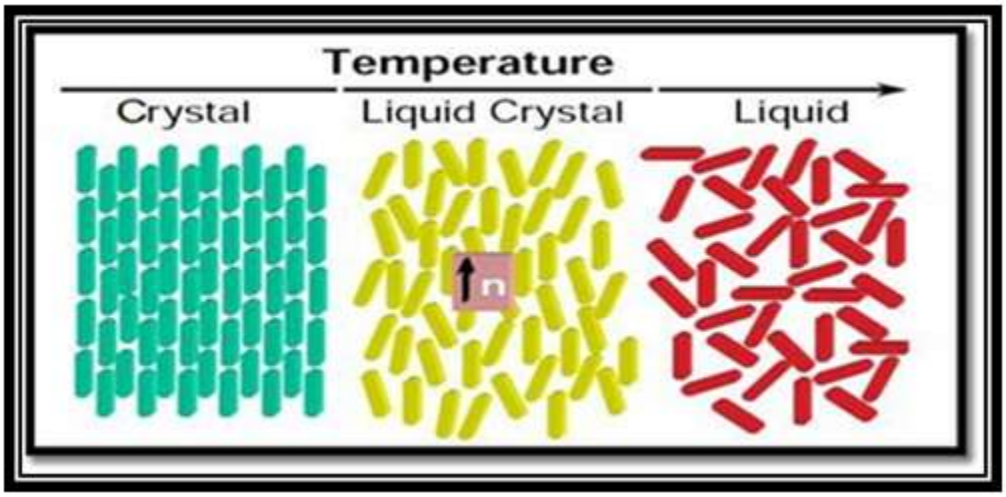

Figure1: Arrangementofmoleculesinthecrystalline,liquidcrystallineandisotropicliquidphases.

Crystallinesolidcharacterizedbylong-rangepositionalandorientationalorderinthreedimensions.Self-assembleamphiphilicmolecules(i.e.,moleculeswithhydrophobicandhydrophiliccharacter)includingsomelipidsinaqueoussystemisknowntoformavarietyofliquidcrystalline phases such as lamellar, inverted hexagonal, and inverted cubic phases (Lai et al.,2009). The structure of cubic phase is unique and consists of two continuous but nonintersectingwater channel separated by a lipid bilayer. Based on X-ray crystallographic studies cubic phasedivided into three types: the double-diamond (Pn3m), gyroid (Ia3d), and primitive (Im3m) phases(Chen et al., 2014). LCs system containing high concentration of amphiphilic surfactant, whichexhibit three-dimensional arrangement of surfactant molecules capable of being transformed intoeach other in a definite sequence under certain circumstances, are termed as lyotropic liquidcrystals. Different lyotropic liquid crystalline phases include lamellar, cubic and hexagonal phase.Cubic phase contains water channels surrounded by saddle-like curved bilayer of the amphiphileextended in three dimensions. The structure is formed separates two continuous networks of waterchannels(Shahetal.,2005).

Lipidhavebeenwidely usedasmainconstituentinvariousdrugdelivery systems,suchasliposome, solid lipid nanoparticles, nanostructure lipid carriers, and lipid based liquid crystals.Amongthem,lipid-basedliquidcrystalshighlyordered,thermodynamically stableinternalnanostructure,therebyofferingthe potentialassustaineddrugreleasematrix(Chenetal., 2014).

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1. ClassificationofLiquidCrystals(Omray,2013;Fongetal,2010)

LCs are differentiated on the basis of positional order (i.e. molecule are arranged in randomlystructure lattice) and orientational order (i.e. molecule are mostly pointed in the same direction).Moreover order can be either short-range (only between the molecule to each other) or long-range(extending to larger, sometimes macroscopic). LCs mainly classified as Lyotropic (LLCs) andThermotropic (TLCs), physicochemical parameters responsible for the phase transitions (Omray,2013;Fongetal., 2010) classificationof liquidcrystalsareasfollowing:

i) Lyotropicliquidcrystals,

a) LamellarLCs
b) HexagonalLCs
c) CubicLCs

ii) Thermotropicliquidcrystals

a) Smecticliquidcrystal
b) Nematicliquidcrystal
c) Cholestericliquidcrystals
d) Discoticliquidcrystals

1.1 Lyotropicliquidcrystal

LLCs (Lyotropic liquid crystals) systems are composed of rod like micelles, and which shows along-range orientational order with respect to symmetry axis of the micelle, but no long-rangpositional order. The three main types of LCs are characterized as being lamellar, hexagonal andcubic. LLCs (Lyotropic liquid crystals) can be formed by certain amphiphilic molecules in thepresenceof solvents;theyareclassifyingasfollows;

a. LamellarLCs
b. HexagonalLCs
c. CubicLCs

1.1.1 StructureofLamellar,HexagonalandCubicLCs

Lamellar LCs known as lamellar mesophase, for hexagonal LCs known as hexagonal mesophaseand cubic LCs known as reverse cubic mesophase, in structure of reverse hexagonal mesophaseand cubic mesophase which existing into the three macroscopic forms are typically encountered:bulkgel and particulatedispersion.

a) LamellarLCs

Lamellar mesophase is generally having bilayer structure as repetition unit, and which shows long-range positional order in one dimension and long-range orientational order within the layer asshowninFigure2.Ifthesurfactantconcentrationof a hexagonalphaseisincreasedaboveacertainthreshold,a sharpdecreaseintheviscosityofthe systemcanbeobservedgenerally.

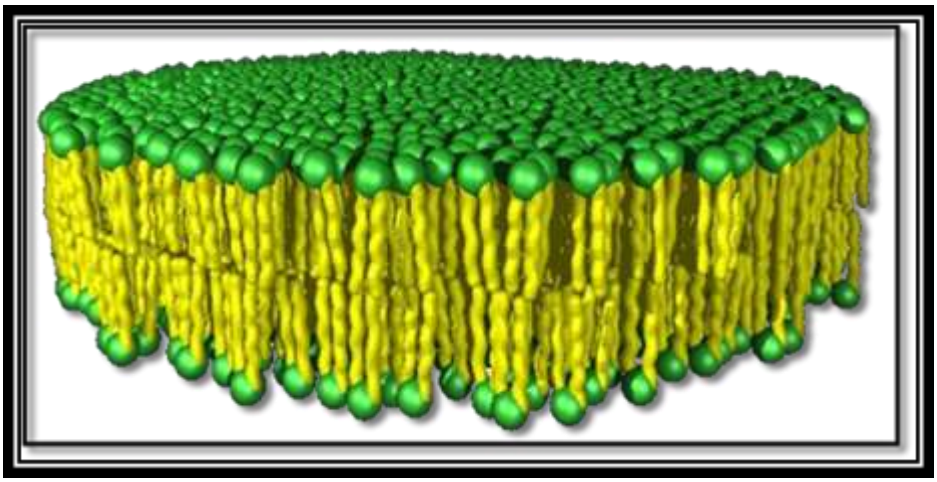

Figure2: Lamellarmesophase

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Openingwiththecrystallinestate,themeso phaseisreachedeitherbyincreasingthetemperature orbyaddingasolvent.Accordinglythermotropicorl yotropicliquidcrystalsformaswiththermotropicliq uidcrystals,variationintemperaturecanalsocausea phasetransformationbetween different mesophases of lyotropic liquid crystals. Lyotropic liquid crystals arise frommesogens that are not the molecules themselves but their hydrates or solvates as well as associatesof hydrated or solvated molecules. Water or a mixture of water and organic solvent are the mostimportant solvents for drug molecules, and the degree of hydration or salvation depends on theamphiphilicpropertiesofadrugmolecule.Hydra tionorsalvationofamostly rod-shapedmolecule results in different geometries, i.e. cone or cylinder. Cylinders arrange in layers. Thisresults in a lamellar phase with alternating polar and nonpolar layers. Water and aqueous drugsolutions can be included in the polar layers, resulting in an increase in layer thickness. Moleculeswith appropriate affinity can be included in the nonpolar layers. In addition to the increased layerthickness of the lamellarphase, lateral inclusion between molecules is also possible with anincreaseinthesolventconcentration,whichtransf ormstherodshape ofthesolvatedmoleculestoacone shape. This leads to a phase change. Depending on the polarity of the solvating agent and themolecule itself, the transition results in a hexagonal or inverse hexagonal phase. Lamellar liquidcrystals identify by polarize light microscope and optical microscope. This lamellar structure isconsidered to be one-dimensional as there is only one parameter that can be quantified, that of therepeat distance between the bilayers. The layers can slide over each other readily; their movementis restricted only in perpendicular direction to the plane of the layers. This property explains thelowerviscosityoflamellarphasecomparedtothe hexagonalarrangement.Inafluidlamellarphase(Lα),whichistheleastorderedofthelamellarphasesmov ementwithinthebilayerisnotrestrained as the alkyl chains are melted and fluid-like. The hydrocarbon tails are thus able to twistaboutwithmovementdrivenbytrans-gaucheisomerization.Collisionswithneighbouring molecules then occuras themolecules are able to undergo rapid rotationaland translationalmotions as well as thermally activated lateral diffusion in the bilayer. Lyotropic liquid crystal(LLC) systems that commonly consist of amphiphilic molecules and solvents can be classified intolamellar(La),cubic,hexagonalmesophases,an dsoon.In recentyears,LLCsystems havereceived considerable attention because of their excellent potential as drug vehicles. Among thesesystems, reversed cubic (Q2) and hexagonal mesophases (H2) are the most important and havebeen extensively investigated for their ability to sustain the release of a wide range of bioactivefrom low molecular weight drugs to proteins, peptides and nucleic acids (Mohammad et al., 2014).Reversedcubicandhexagonalmesophasesar eoftenformedbypolarlipidsinanaqueousenvironm ent.Thestructure-forminglipidscanabsorbacertainamountofwateran dthenspontaneously formgel-likephases withuniqueinternalstructures,into whichdrugs canbeincorporated.Lamellarphasesotherthanthefl uidcasearise:acrystalline(LC),andageltype(Lβ)oc curwiththelatterappearingat atemperaturelower thanthatoftheLαbuthigherthanthatoftheLCs. Thestructures of lamellar phases aresummarizedinFigure3

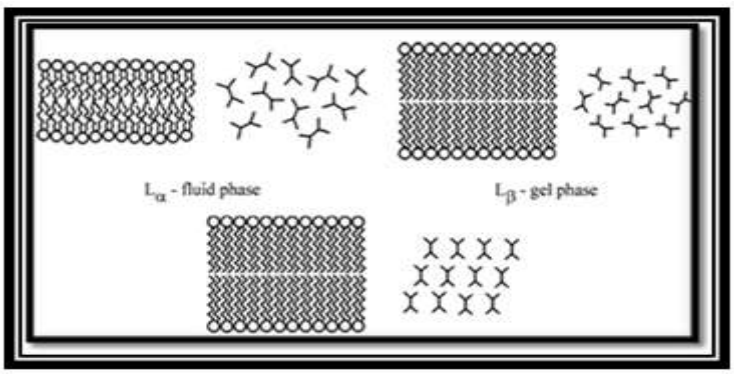

Figure3: Schematicrepresentationofthethreemaintypesoflamellarphases

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b) HexagonalLCs

Hexagonal liquid crystals show long-range positional order in two dimensions. Both the lamellarand hexagonal LCs can be identified using polarized light microscopy as they exhibit a range oftextures that are typical for the corresponding LCs. They also have known as middle phase asshownin Figure4 (Omray,2013).

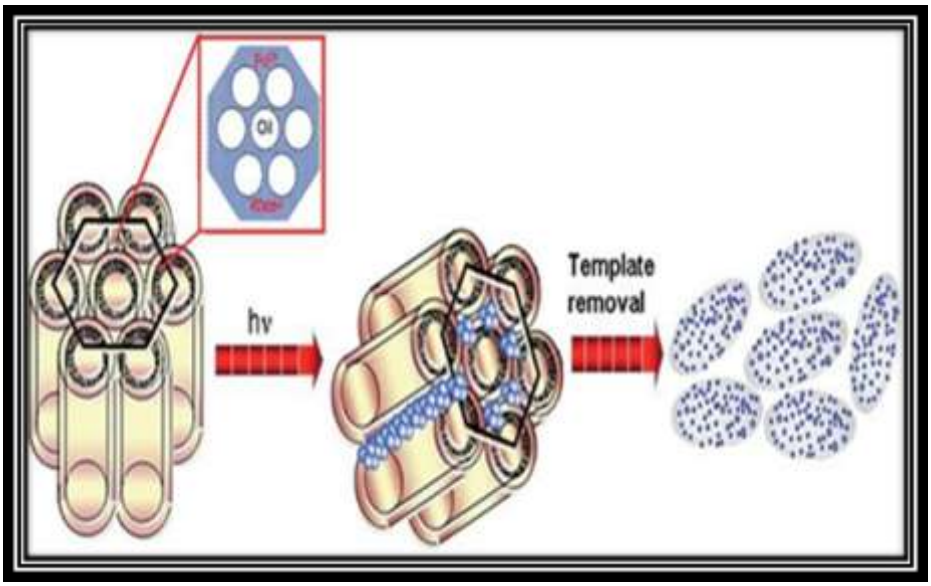

Figure4: Schematicrepresentationofhexagonalmesophase

The liquid crystalline matrices possess distinct lipidic and aqueous domains, and may exhibit anumber of well-defined geometric arrangements depending on the chemical structure of the lipid,the aqueous content of the system, the presence of other additives, and solution conditions such aspH, temperature and pressure. Most often this arrangement consists of lamellar bilayer structures,butforarelativelysmallsubsetoflipids,theexhibitedphasestructuresmayincludetheviscous reversehexagonalphase(HII)orbicontinuouscubic phase(Q)(BoydJ.etal.,2006).

Figure4showhexagonal liquid crystals are often spontaneously formed by the addition of certain amphiphiliclipids in an aqueous environment. When hexagonal mesophase dispersed into nanoparticles withexcess water with an addition of stabilizers such as pluronic copolymers and they form stablecolloidal dispersions which are termed hexosomes either cubosomes (Chen Y. et al., 2014). Thehexagonal mesophases composed of glycerate-based surfactants such as oleylglycerate (OG) andphytanylglycerate(PG)haveshowgreatpotentialindrugdelivery (BoydJ.etal.,2006).Hexosomes are colloidally stabilize by using the tri-block co-polymer Pluronic® F127 and F68.Non-ionic steric stabilizers have been most often employing for the stabilization of the dispersion,as ionic stabilizer typically disrupt the internal nanostructure. A number of stabilizers have beenused in attempt to create stable liquid crystalline dispersion such as beta casein, polyethyleneglycol,hydroxypropylmethylcellulos eacetatesuccinateetc.

- In Figure 5b seen, hydrophilic drugs will be entrapped in the internal water domain,whereas lipophilic drugs will be located within the lipid domain and amphiphilic drugs intheinterface.
- Preparation methods for reversed cubic and hexagonal MesophasesAs a rule, cubic andhexagonal gels can be prepared more easily than their dispersions. For example, liquidcrystal gels could be prepared by simply blending aqueous phase with lipid phase usingvortex or ultrasonication (Boyd et al 2006). The manufacture of cubosomes or hexosomesismorecomplicated,however;therefore,wemainlyconcentrateonthepreparationmethodsofLLCnanoparticles
- Reverse hexagonal mesophases (HII) are characterized by densely packed, straight water-filled cylinders,exhibiting2-

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Dordering.Eachcylinderis surroundedby alayerofsurfactantmoleculesthatareperpendicularto thecylinderinterfacesuchthattheirhydrophobicmoietiespointoutwardfromthewaterrods.

- There is a growing indication that inverse hexagonal mesophases play structural anddynamic roles in biological systems. These systems are assumed to be active as transientintermediates in biological phenomena that require topological rearrangements of lipidbilayers such as membrane fusion/fission and the trans-bilayer transport of lipids andpolarsolutes.
- Theeffectivecriticalpackingparameter(CPP)theorycansupplyareasonableexplanationtothetemperatureinducedstructuralshiftsfromlamellarthroughcubictoreversehexagonal phases, requiring greater curvature than in the lamellar phase. Increasing thethermal motion of both the hydrocarbon chains and the water molecules would increasethe CPP values via expanding the volume of the lipophilic moiety, but decreasing thechainlengthandtheheadgrouparea.

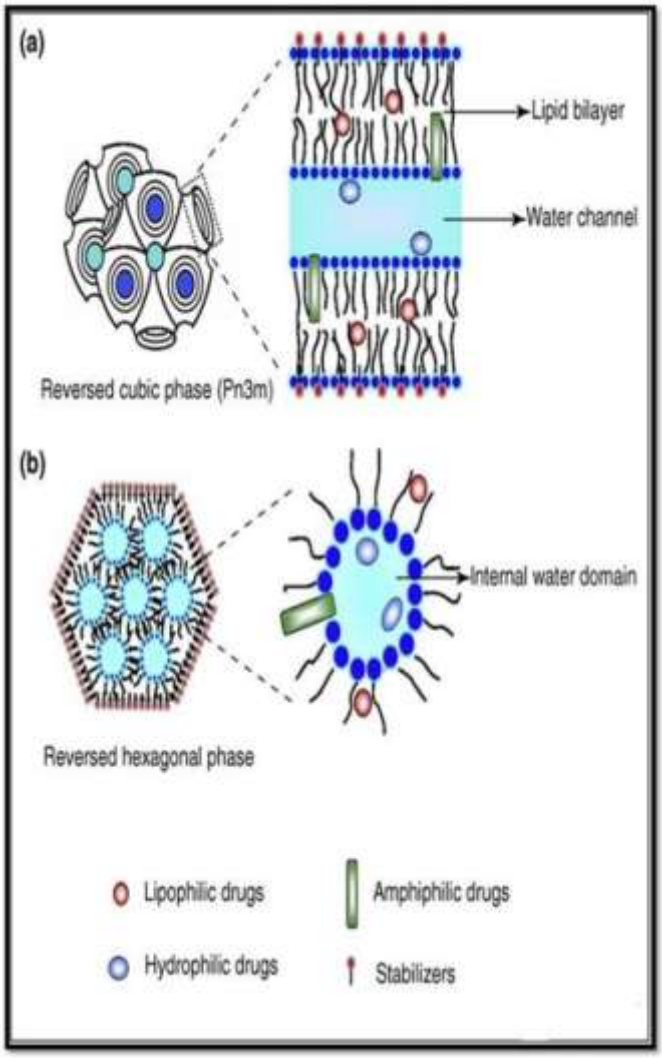

Figure5: Structuresof(a)reversedbicontinuouscubicand(b)hexagonalMesophases.

- In addition, the hexagonal mesophase is characterized by greater packing cost than thecubic phase, but the opposite is true for curvature elastic energy. Therefore, elevatedtemperaturesinducedthetendencyforinterfacialcurvature,

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whichincreasedthecurvatureelasticcostsofthe bicontinuouscubic phase,stabilizinghexagonalsymmetry.

- Systematic research was conducted in our laboratory to decrease the cubic to hexagonaltemperaturetransitionandstabilizet heglycerylmonooleate-basedHII(reversehexagonal)mesophaseat roomtemperature (Libster et al.,2011).

c) CubicLCs

Figure6 describethecubicformofLCs. cubicLCsmainlyshowslong-rangepositionalorderin threedimensions.

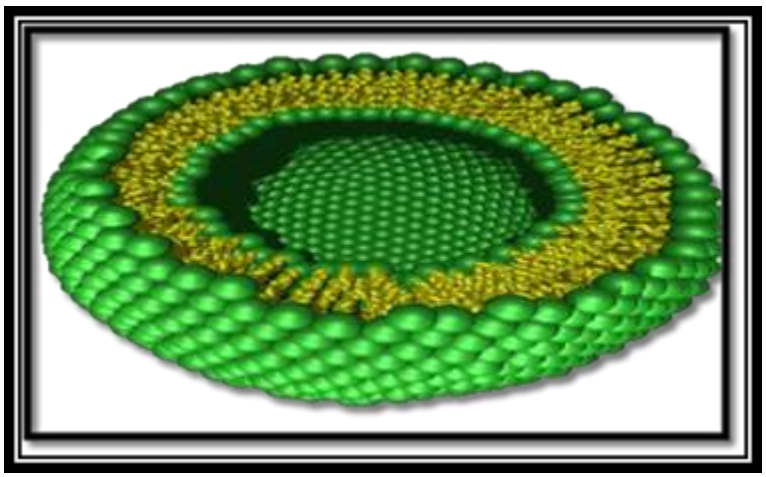

Figure6: Cubicliquidcrystals(Cubosome)

Generally these liquid crystals having cubic packing of the micelles and can not identified usingpolarized light microscopy. Cubic LCs highly viscous and have poor flowing property as comparetolamellarandhexagonalLCs(Shahetal,2005;Omray,2013).Thestructure ofcubicmesophasesis unique and comprises a curved bicontinuous lipid bilayer (with an estimated thickness of 3.5nm) extending in three dimensions and two interpenetrating, but non-contacting, aqueous nano-channels (with a full swollen diameter of approximately 5 nm), with a high interfacial area of 400m²/g (Yaghmur et al.,2009;GuoC.etal2010).

- Cubic phase have been shown to improve the transdermal or topical delivery of relativelysmallmolecule suchasnicotine,acyclovir,salbutamolandaminolevulinicacid.
- Cubic liquid crystals a highly viscous but not injectable, cubic phase with sustainedreleasepropertiesformfromunsaturatedmonoglycerideincontactwithaqueousphase.
- The bulk phase is commonly a clear, viscous, semi solid gel that is similar in appearanceandrheologytocross-linked polymerhydrogel(GuoC.etal2010;Spiceretal.,2001).
- Bicontinuous cubic phases are optically isotropic, very viscous, and solid like liquidcrystals with cubic crystallographic symmetry. Prior to their structural characterization,these phases were termed „„viscous isotropic phases"" and considered quite a nuisance inindustrialprocesses (Spiceretal.,2005).
- X-ray crystallographic studies, three distinct reversed bicontinuous cubic phases can beidentified: the double-diamond lattice (Pn3m, Q224), the body- centered cubic phase(Im3m,Q229)and the gyroid lattice(Ia3d,Q230) (Shah etal.,2001)
- Small-angle X-ray scattering was crucial to the discovery and structural characterizationof bulk cubic phases, cryo-transmission electron microscopy, or cryo-TEM, has beencentraltostudiesof cubosomedispersions(Spicer Pet al.,2005).

1.2 Thermotropicliquidcrystals(TLCs)

Thermotropic LCs formed by heating alone crystalline substance and does not required of solventfor their formation, thermotropic liquid

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crystals unlike lyotropicmesophases. TLCs (Thermotropicliquidcrystals)canbeformedbyheatin ga crystalline solid or by cooling an isotropic melt, theycanfurtheras;

a. Smecticliquidcrystal
b. Nematicliquidcrystal
c. Cholestericliquidcrystals
d. Discoticliquidcrystals

a) SmecticLCs

- SmecticisderivedfromGreekmeaninggreaseorcl ay.
- Thelong axesofallmoleculesinagivenlayerareparallelt ooneanotherandperpendiculartotheplaneofla yers.
- Thelayersarefreetoslipandtravelovereachother.
- Thesmecticstateisviscous.

b) NematicLCs

- NematicisderivedfromGreekmeaningthread-like.
- Itcandetermineunderthepolarizedlightmicros cope.
- NematicLCsarenotextremelyordered,theyma intainedtheirparallelorder.
- Itgenerallyusedinelectronic displayisprimarilyasnematic type.
- LCsshowanisotropicphysicalcharacteristics.

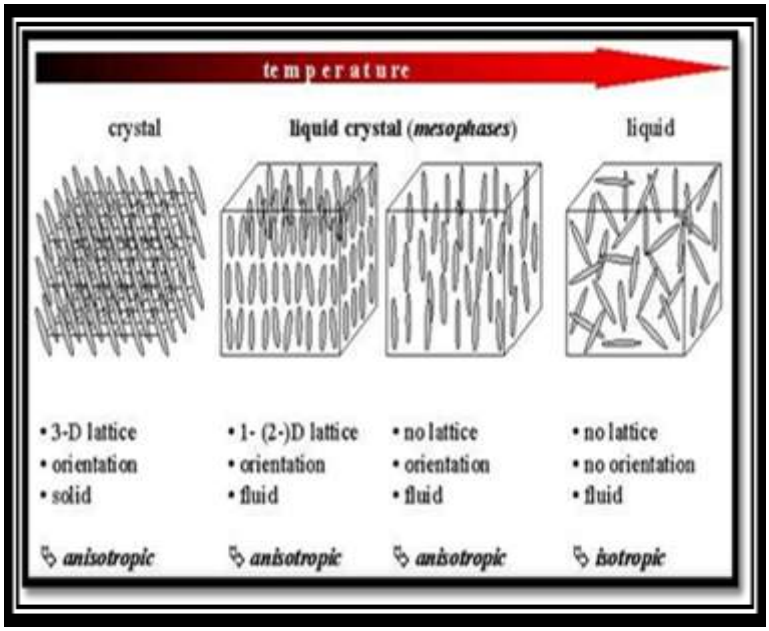

Figure7: Positionandorientationalorderofliquidcrystal

c) CholestricLCs

- CholestericLCsarrangementisextenttocombi nationofnematicandsmectic
- ThemoleculeincholestericLCsarearrangedinl ayersandwithineachlayer,moleculesarealigne din parallel.
- ThemolecularlayersinacholestericLCsarever ythin,withlongaxisofthemoleculesanalogoust oplaneofthelayers.

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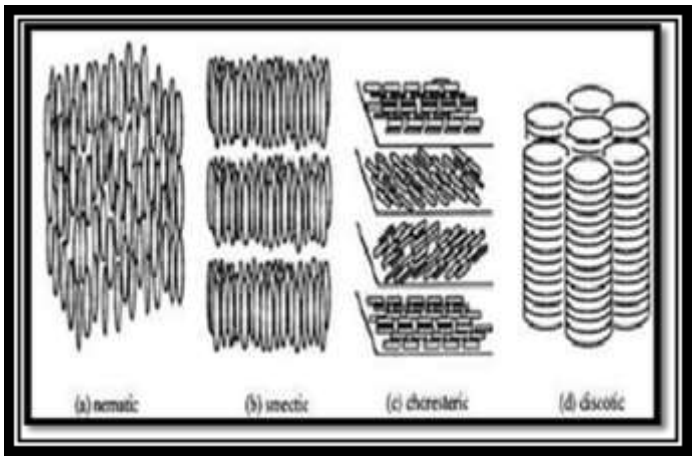

Figure8: Thermotropicliquidcrystalsphases

1.3 MethodofpreparationofLCs(GuoC.etal.,2010).

(a) Top-downapproach

Thisapproachwasprimarilyreportedby(Ljusberg-Wahrenetal.,1996).Theextremeviscousbulkphase is prepared by mixing structure-forming lipids with stabilizers, and then the resultant isdispersedintoaqueoussolutionthroughtheinputof highenergysuchashigh-pressurehomogenization (HPH), sonication or shearing to form LLC nanoparticles. At present, HPH is themostextensivelyusedtechniqueinthepreparation of LLCnanoparticles(Spiceretal.,2005).

Worle et al. 2007; investigated the parameters influencing the properties of glyceryl monooleate(GMO)-basedcubosomes.Basedontheresultsobserved,theconcentrationofF127andtemperatureduring HPHwereregardedas crucially importantparameters.Recently,anovelapproachof shearingwasproposedtofabricateLLCnanoparticlesusingalaboratorybuilt-Shearing apparatus. Compared with the well-established ultrasonication approach, the shearingtreatment could effectively prepare more stable and homogeneous cubosomes or hexosomes withhigh content of the hydrophobic phase (oil + lipophilic additives) within a short time (less than oneminute). It seems that the preparation procedure is simple enough to be realized conveniently. Infact,theoperationunitsinthisprocedurerequireseveralcyclestoachievethedesired

Nanoparticles with appropriate characteristics and the high-energy input is also regarded as abarrier to the temperature resensitive ingredients (Spicer et al., 2005). In addition, the cubosomesprepared through top-down approach are always observed to coexist with vesicles (dispersednanoparticles of lamellar liquid crystalline phase) or vesicle-like structures, which will hamper theinvestigations on plaincubicmesophases.

Advantages:

1) Lowerimpacttooverallorganization.
2) Visibilityofformulationchangesisclear.
3) Noneedoforganicsolvent.
4) Simplemethodascomparetoothermethodsuch asspraydrying.

Disadvantages:

1) Solutionprovideslimitedcoverageinthefirst phase.
2) Highenergyinputrequired.
3) Timeconsumingprocess.

(b) Bottom-upapproach

The key factor in the bottom-up approach is hydrotrope, which can dissolve water- insoluble lipidsto create liquid precursors and prevent the formationof liquid crystals at high concentration(Mezzenga et al., 2005). Compared with the top-down approach, this dilution-based approach canproduce cubosomes without laborious fragmentation. In other words, it needs less energy input.Moreover, this approach is far more efficient at generating small particles. The reason for

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thismightrelatetotheformingmechanismofcubosomes.Thedilution-basedapproachcanberegarded asaprocessofsmallparticles forming big particlesthrough aggregation,which isanalogous to the use of precipitation processes to produce nanoparticles, whereas the top-downapproach is more analogous to the attrition of big particles. In addition, cubosomes preparedthroughdilutionshowlongtermstability,which mightbeattributedtothe homodispersestabilizers onto the surface of cubosomes (Spicer et al., 2005). Indeed, the use of hydrotrope cansimplifythepreparationprocessandproducecubosomespossessingsimilarorevenbetterproperties than those fabricated by the top-down approach. It should be noted, however, that thisprocess via dilution is a pathway by charting trajectories on the ternary phase diagram (lipid andwaterhydrotrope),which

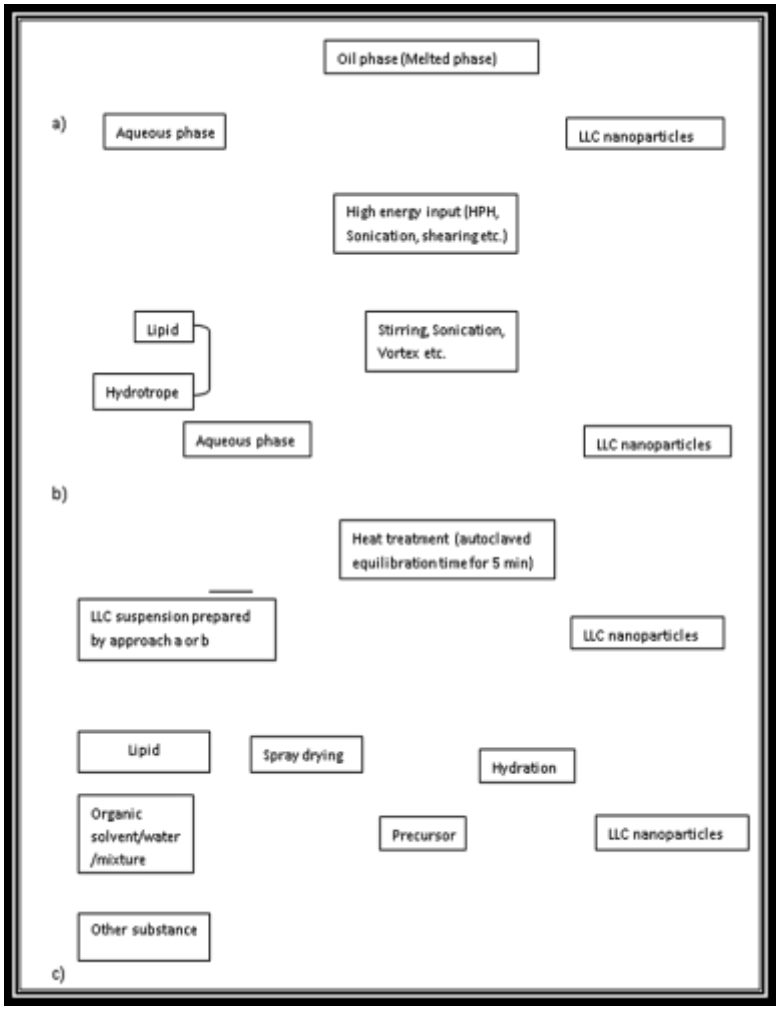

Figure9: Schematicdiagramofpreparationmethodforcubosomeorhexosomesaccordingtotheliterature(a)Top-downapproach(b)Bottom-upapproach(c)Heattreatment(d)Spraydrying

requires knowledge of the full phase behavior; hence, the extent of dilution is difficult to controlprecisely. Owing to the addition of hydrotrope, many issues arise, such as the effects exerted byvaryingconcentrationsofhydrotropeonthephysicochemical properties of LLC nanoparticles and the possible occurrence of irritation and allergic responsewhen the mesophase formulations are administered. Finally, this bottom- up approach cannoteffectively avoid forming vesicles. Through cryo-TEM, many vesicles and vesicle-like structureswerealsoobservedtocoexistwithcubosomes.

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Advantages:

1) Lowerenergyinput.
2) Lesstimeconsumingprocess.
3) AthighconcentrationpreventtheformationofLCs.
4) Noneedthe organic solvent

Disadvantages:

1) Milkywhiteformulationformed.
2) Hydrotropewhichshowsallergicreactionwhen themesophaseformulationadministeredorally .

(c) Heattreatment

The coexistence of cubosomes with vesicles is speculated to provide multiphase manipulation ofthesustainedreleaseofdrugs;hence,tobetterinvestigatethereleasebehaviorof plainmesophases, vesicles should be eliminated as much as possible. In this case, heat treatment can beregarded as a good approach. Note that in the strictest sense, heat treatment is not an integratedprocess for the manufacture of cubosomes because it only promotes the transformation from non-cubic vesicles to well-ordered cubic particles. The dispersed particles, therefore, can be producedby a simple processing scheme comprising a homogenization and heat-treatment step. From thereported studies, heat treatment could cause a decrease in the small particle size fraction thatcorresponded to vesicles and form more cubic phases with narrow particle distribution and goodcolloidalstability(Worleet al.,2007).

Taking the whole process of preparation into account, it is obvious that the transition takes placeduringtheprocedureofheattreatment. Thereasonfortransitioncouldbespeculatedasanelevatedtemperature giving rise to a reduction in solubility and stability. When the temperature was belowcloud point, the surfactant had a high solubility and thus the particles could exist stably and thephenomenon of fusion was hardly observed. Once reaching cloud point, the solubility of surfactantdecreased notably and a notable fast fusion among vesicles would occur. Although masses ofvesicles can transform to cubic nanoparticles through heat treatment, it does not mean that all theLLC systems are suitable for this procedure in particular, the systems loading drugs that cannotprovide sufficient stability under the condition of high temperature (usually above 120°C), such assomeproteinsand temperature-sensitivedrugsarenotsuitable.

Advantages:

1. Itproducedgoodcolloidaldispersion.
2. Itcanreduceparticlesize.

Disadvantages:

1. Degradationofthermosensitivesubstanceduetoformationofaggregate.
2. Reductionofstabilityofformulation.

(d) Spraydrying

To widen the applications of cubosomes in pharmaceutical field, dry powder precursors can befabricated by spray drying and used for the preparation of oral solid formulations and inhalants.This approach was originally proposed and investigated by Spicer et al. (Spicer et al., 2002). In hisresearch, the powder precursor could be prepared through drying a pre-dispersed aqueous solutionthat consisted of GMO, hydrophobically modified starch and water or contained GMO, dextran,ethanol and water, and then the colloidally stable dispersions of nano-structured cubosomes couldbe created by hydration of the precursors. Afterward (Shah et al., 2005) prepared GMO basedcubosomeprecursorcontainingdiclofenacsodiumthroughspraydrying.
Theprecursorwasprovento have more effective and prolonged anti-inflammatory and analgesic activity than pure drugwhen administered per orally; it is noteworthy, however, that residual solvent content is still aproblemthatcannotbeignored.

Advantages:

1. Spraydryingtechniqueisusefulforpowderformulationsuchas DPI(Dry powderinhaler, drysyrup).
2. Thistechniqueusedformicroencapsulation.
3. Organic solventcanuseinthismethod.

Disadvantages:

1. Fromthismethodhaslow yieldofformulationas5-30%outof100%.
2. Spraydryingmethodiscomplicatedascomparetoothermethod.

(e) Ultrasonication/Probesonication

High shear homogenization and ultrasound are dispersing techniques which were

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initially used forthe production of solid lipid nanodispersion. However, its quality is compromised by the presenceof microparticles. A pre-emulsion was obtained under stirring with an Ultra-Turrax T25 by addingmelted lipid to a mixture of surfactants and water. A sonication probe was placed in this pre-emulsion which lead to droplet breakage by acoustic cavitations and subsequent formation of oil inwater (o/w) nanoemulsion which immediately cooled down to room temperature to generate liquidcrystals(Mulleretal.,2010).

Advantages

1. Bothmethodsarewidespreadandeasytohandle
2. Equipmentswhateveruse here areverycommoninevery lab
3. Reducedshearstress

Disadvantages

1. Potentialmetalcontamination
2. Physicalinstabilitylikeparticlegrowthuponsto rage

1.6Applicationsofliquidcrystalssystem(Boydet al.,2007):

Therapeuticcompoundsofdiversephysico chemicalpropertiessuchasanalgesic,antibiotics,an tifungal, anticancer, vitamins, antiasthamatics, immunosuppressive etc. monoglyceride basedcubosome dispersion can be proposed for topical used, such as forprecutaneous or mucosalapplications. Because of the microbicidal properties of monoglycerides, could be used to designintravaginal treatment of sexually transmitted diseases caused by viruses (e.g. HSV, HIV) or bybacteria (e.g. Chlamydia trachomatis and neisseriagenorrticae). The cubosome technology is usedto develop a synthetic venix the chessy white substance that coats infants in late gestation to helppremature infants whoare bornwithoutit.Evernixisacomplexmixtureoflipid(fat),proteinsandwater. Cubosome can also be used for controlled release application. Cubosome particles are usedas oil water emulsion stabilizers and pollutant absorbants in cosmetics. More recent use is aboutpersonalcureproduct areasasvariedasskincare,haircare,cosmeticsandan tiperspirant.

1) Oraladministration

The oral bioavailability of a poorly water-soluble drug, cinnarizine, incorporated in different typesof LLC phases. Through animal experiments, the OG-based hexagonal formulation showed aconsiderably higher relative bioavailability that was almost 3.5 times greater than that of thecontrol suspension of cinnarizine and 3 times greater than the GMO-based cubic formulation. Theoral administration of drugs incorporated into LLC nanoparticles has also been reported, preparedGMO-based cubosomes containing insulin and investigated the hypoglycemic effect generated byoral administration of this formulation. The blood glucose concentration–time profile showed thattheinsulinformulationcouldprovideahypoglyc emiceffectcomparabletointravenousadministratio n of insulin over six hours. Simvastatin incorporated in GMO-based cubosomes wasadministered orally and the relative bioavailability to the control drug crystal powder was 241%.Moreover, the cubosomes showed sustained release of simvastatin over 12 h in beagle dogs. Theauthorpresumedthatthemechanismofenhancin gbioavailabilitymightberelatedtothehydrophilic surface of cubosomes, which stimulated the permeation through the stagnant aqueouslayerof theintestinalmucosa.

2) TopicalAdministration

Topical drug delivery is an attractive alternative to oral administration. Its main drawback is thelimited absorption of drugs through the skin barrier, and investigations on topical drug uptake arenecessary to facilitate the design of efficient topical drug delivery systems. At present, stratumcorneum (SC) is considered to be the rate-limiting barrier in transdermal drug delivery. Manystudies have shown that cubic and hexagonal mesophase formulations are capable of penetratingthroughSCandbecomingcandidatesfor topicaldrugdeliverysystems.CyclosporineAincor poratedinhexosomescomprisingGMO,oleicacida ndwaterwasreportedtobecapableofenhancingdrug permeationwhenappliedtopicallyThereare severalnaturalcharacteristicsthatthereversedcubic andhexagonalphases presenttomakethemsuitablefortopicaldrugdeliver y:

I. Sustainedreleaseofdrugsincorporated,
II. Bioadhesiveproperties,
III. Solubilizationofhydrophilicandlipophilicdru gsandprotectingthemfromphysicalandenzym aticdegradation,and

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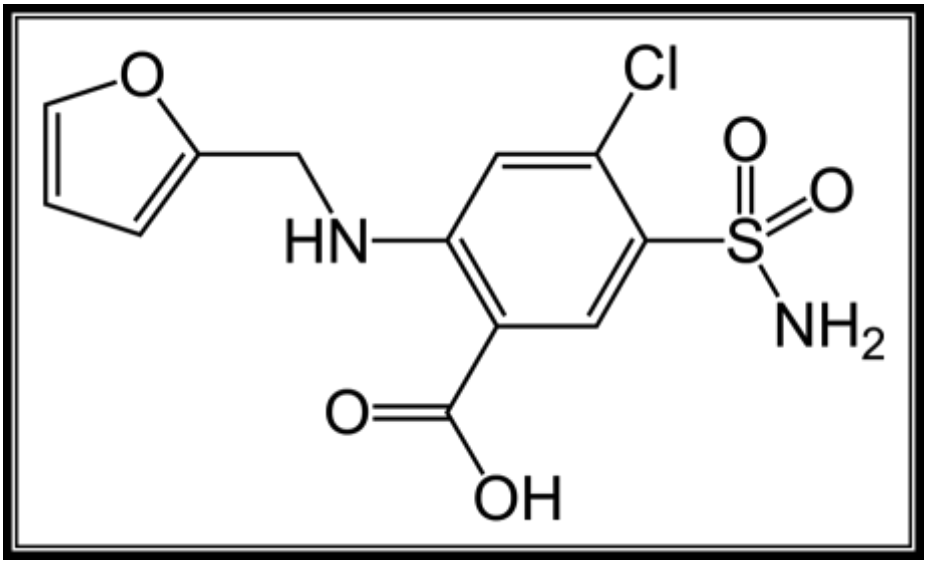
IV. ThenontoxicpermeationenhancersGMOandP Tasstructureformingmaterials.

2.1Furosemide

II. DRUGPROFILE

2..1.2ChemicalStructure



2.1.3 ChemicalFormula-C12H11ClN2O5S

2.1.4 WeightAverage:330.744Monoisotopic: 330.007719869

2.1.5 Indication

Furosemide is indicated forthe treatmentofedema associated withcongestive heartfailure,cirrhosis of the liver, and renal disease, including the nephrotic syndrome, in adults and pediatricpatients. Oral furosemide is indicated alone for the management of mild to moderate hypertensionorseverehypertensionincombination withotherantihypertensive medications.

Intravenous furosemide is indicated as adjunctive therapy in acute pulmonary edema when a rapidonset of diuresis is desired. Subcutaneous furosemide is indicated for the treatment of congestiondue to fluid overload in adults with NYHA Class II/III chronic heart failure. This drug formulationisnotindicatedforemergencysituations or inpatientswithacutepulmonaryedema

2.1.6 Pharmacodynamics

Furosemide manages hypertension and edema associated with congestive heart failure, cirrhosis,and renal disease, including the nephrotic syndrome. Furosemide is a potent loop diuretic thatworks to increase the excretion of Na+ and water by the kidneys by inhibiting their reabsorptionfrom the proximal and distal tubules, as well as the loop of Henle.9 It works directly acts on thecellsofthenephronandindirectlymodifiestheco ntentoftherenalfiltrate.8Ultimately,furosemide increases the urine output by the kidney. Protein-bound furosemide is delivered to itssite of action in the kidneys and secreted via active secretion by nonspecific organic transportersexpressed at the luminal site of action. Following oral administration, the onset of the diureticeffect is about 1 and 1.5 hours 9, and the peak effect is reached within the first 2 hours.10 Theduration of effect following oral administration is about 4-6 hours but may last up to 8 hours.12Following intravenous administration, the onset of effect is within 5 minutes, and the peak effect isreachedwithin30minutes.Thedurationofactionfo llowingintravenousadministrationisapproximatel y 2 hours. Following intramuscular administration, the onset of action is somewhatdelayed.

Furosemideisaloopdiuretic usedtotreathypertensionandedemaincongestivehe artfailure,livercirrhosis,renaldisease,andhyperten sion.

2.1.7 Mechanismofaction

Furosemide promotes diuresis by

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blocking tubular reabsorption of sodium and chloride in theproximal and distal tubules, as well as in the thick ascending loop of Henle. This diuretic effect isachievedthroughthecompetitiveinhibitionofsodium-potassium-chloridecotransporters(NKCC2) expressed along these tubules in the nephron, preventing the transport of sodium ionsfrom the lumenal side into the basolateral side for reabsorption. This inhibition results in increasedexcretion of water along with sodium, chloride, magnesium, calcium, hydrogen, and potassiumions.10Aswithotherloopdiuretics,furosemidedecreasestheexcretionof uricacid.

Furosemide exerts direct vasodilatory effects, which results in its therapeutic effectiveness in thetreatmentofacutepulmonaryedema.Vasodilationleadstoreducedresponsivenesstovasoconstrictors,suchasangiotensinIIandnoradrenaline,anddecreasedproductionofendogenousnatriuretichormones withvasoconstrictingproperties.Italsoleadstoincreasedproduction of prostaglandins with vasodilating properties. Furosemide may also open potassiumchannels in resistance arteries.8 The main mechanism of action of furosemide is independent of itsinhibitoryeffectoncarbonicanhydraseandaldosterone.

2.1.8 Absorption

Following oral administration, furosemide is absorbed from the gastrointestinal tract.12 It displaysvariablebioavailabilityfromoraldosageforms,rangingfrom10to90%.Theoralbioavailabilityof furosemide from oral tablets or oral solution is about 64% and 60%, respectively, of that fromanintravenousinjection ofthedrug

2.1.9 Metabolism

The metabolism of furosemide occurs mainly in the kidneys and the liver, to a smaller extent. Thekidneys are responsible for about 85% of total furosemide total clearance, where about 40%involves biotransformation.5 Two major metabolites of furosemide are furosemide glucuronide,whichispharmacologicallyactive,and saluamine(CSA)or4-chloro-5-sulfamoylanthranilicacid.

2.1.10 Routeofelimination

Thekidneysareresponsiblefor85%oftotal furosemidetotalclearance,whereabout43%ofthedrugundergoesrenalexcretion.Significantlymorefurosemideisexcretedinurinefollowingthe I.V. injectionthanafterthetabletororalsolution. Approximately50%ofthefurosemideloadisexcretedunchangedinurine,andtherestismetabolizedintoglucuronide inthekidney.

III. SUMMARY AND CONCLUSION

Primary objectiveof liquid crystals drug delivery system is to ensure safety and to improveefficacy of drug as well as patient compliance, which can be achieved by better control of lessfrequent dosing. Liquid crystalline drug delivery is very important to use minimum number ofexcipient with minimum processing steps in order to reduce the particle size and drug entrapmentvariation, hence high pressure homogenizer is the most suitable technique.Furosemide is treathypertension and renal disease, which is pale yellow, crystalline powder having 3-4 hrs half-life toBCS class IV. The drug having high dose of frequency, and having poor dissolution rate from itsoralsoliddosageforms.

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