"TO DESIGN LIQUID CRYSTALS CONTAINING APREMILAST REVIEW"

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Abstract

Nanotechnology, a word derived from the Greek word Nano meaning dwarf, applies the principles of engineering, electronics, physical and material science and manufacturing at a molecular or submicron level. one among the foremost attractive areas of research in drug delivery today is that the design of nanosystems that are ready to deliver drugs to the correct place, at appropriate times and at right dosage Nanotechnology is now being broadly of discipline and technology, for manipulating the structure of matter on molecular level at an incredibly small scale between 1-100nm. Though the unifying theme of nanotechnology is manipulation of matter on atomic and molecular scale but remains not a mature technology and thus, is more appropriately called as "Nanoscience". Drugs with narrow therapeutic indices create a serious challenge for pharmaceutical scientists, during their development. Application of nanotechnological principles for 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 boost therapeutic efficacy and reduce toxicity of medication with narrow therapeutic indices.

Keyword: Liquid Crystals, Apremilast, Psoriasis.

1.INTRODUCTION

Liquid crystals are the state of matter existing between the liquid and also the crystalline solid, characterized by the partial or complete loss of positional order in crystalline solids, while retaining the orientational order of constituent molecule as show in Figure 1 Crystalline solid characterized by long-range positional and orientational order in three dimensions. Self-assemble amphiphilic molecules (i.e., molecules with hydrophobic and hydrophilic character) including some lipids in aqueous system is understood to make a spread of liquid crystalline phases like lamellar, inverted hexagonal, and inverted cubic phases. The structure of cubic phase is exclusive and consists of two continuous but nonintersecting water channel separated by a lipid bilayer. supported X-ray crystallographic studies cubic phase divided into three types: the double-diamond (Pn3m), gyroid (Ia3d), and primitive (Im3m) phases LCs system containing high concentration of amphiphilic surfactant, which exhibit three-dimensional arrangement of surfactant molecules capable of being transformed into one another during a definite sequence under certain circumstances, are termed as lyotropic liquid crystals.

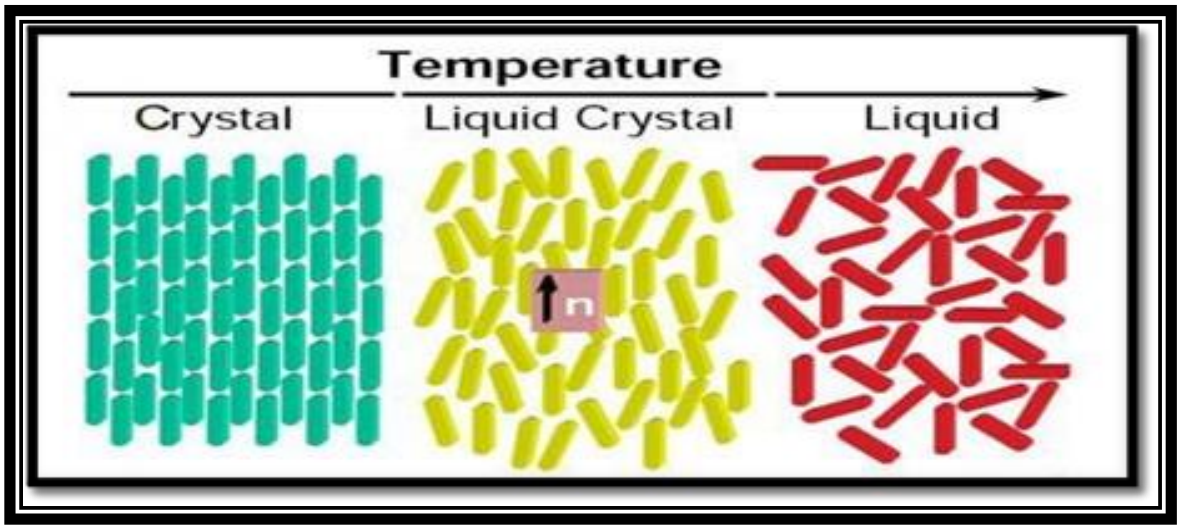

Figure 1: Arrangement of molecules in the crystalline, liquid crystalline and isotropic liquid phases.

1.1. Classification of Liquid Crystals

LCs are differentiated on the idea of positional order (i.e. molecule are settled in randomly structure lattice) and orientational order (i.e. molecule are mostly pointed within the same direction). Moreover order may be either short-range (only between the molecule to every other) or long-range (extending to larger, sometimes macroscopic). LCs mainly classified as Lyotropic (LLCs) and Thermotropic (TLCs), physicochemical parameters accountable for the phase transitions classification of liquid crystals are as following:

1.1.1. Lyotropic liquid crystal

LLCs (Lyotropic liquid crystals) systems are composed of rod like micelles, and which shows a long-range orientational order with relation to symmetry axis of the micelle, but no long-rang positional order. The three main styles of LCs are characterized as being lamellar, hexagonal and cubic. LLCs (Lyotropic liquid crystals) will be formed by certain amphiphilic molecules within the presence of solvents; they're classifying as follows;

1.1.1.1 Structure of Lamellar, Hexagonal and Cubic LCs

Lamellar LCs called lamellar mesophase, for hexagonal LCs called hexagonal mesophase and cubic LCs called reverse cubic mesophase, in structure of reverse hexagonal mesophase and cubic mesophase which existing into the three macroscopic forms are typically encountered: bulk gel and particulate dispersion.

a) Lamellar LCs

Lamellar mesophase is usually having bilayer structure as repetition unit, and which shows long-range positional order in one dimension and long-range orientational order within the layer as shown in Figure 2. If the surfactant concentration of a hexagonal phase is increased above a particular threshold, a pointy decrease within the viscosity of the system will be observed generally.

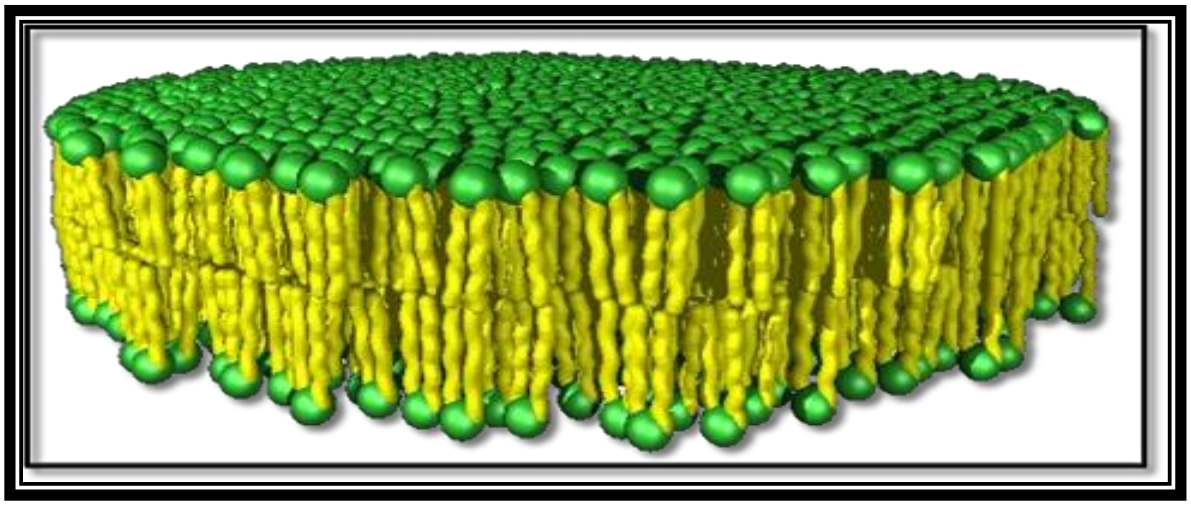

Figure 2: Lamellar mesophase

Opening with the crystalline state, the mesophase is reached either by increasing the temperature or by adding a solvent. Accordingly thermotropic or lyotropic liquid crystals form like thermotropic liquid crystals, variation in temperature may cause a phase transformation between different mesophases of lyotropic liquid crystals. Lyotropic liquid crystals arise from mesogens that don't seem to be the molecules themselves but their hydrates or solvates in addition as associates of hydrated or solvated molecules. Water or a mix of water and organic solvent are the foremost important solvents for drug molecules, and also the degree of hydration or salvation depends on the amphiphilic properties of a drug molecule. Hydration or salvation of a mostly rod- shaped molecule leads to different geometries, i.e. cone or cylinder. Cylinders arrange in layers. This leads to a lamellar phase with alternating polar and nonpolar layers. Water and aqueous drug solutions are often included within the polar layers, leading to a rise in layer thickness. Molecules with appropriate affinity are often included within the nonpolar layers. additionally to the increased layer thickness of the lamellar phase, lateral inclusion between molecules is additionally possible with a rise within the solvent concentration, which transforms the rod shape of the solvated molecules to a round shape. This ends up in a state change. counting on the polarity of the agent and therefore the molecule itself, the transition ends up in a hexagonal or inverse hexagonal phase. Lamellar liquid crystals identify by polarize microscope and optical microscope. This lamellar structure is taken into account to be one-dimensional as there's just one parameter that may be quantified, that of the repeat distance between the bilayers. The layers can slide over one another readily; their movement is restricted only in perpendicular direction to the plane of the layers. This property explains the lower viscosity of lamellar phase compared to the hexagonal arrangement. during a fluid lamellar phase (Lα), which is that the least ordered of the lamellar phases movement within the bilayer isn't restrained because the alkyl chains are melted and fluid-like. The hydrocarbon tails are thus ready to twist about with movement driven by trans-gauche isomerization. Collisions with neighbouring molecules then occur because the molecules are able to undergo rapid rotational and translational motions furthermore as thermally activated lateral diffusion within the bilayer. Lyotropic liquid (LLC) systems that commonly accommodates amphiphilic molecules and solvents may be classified into lamellar (La), cubic, hexagonal mesophases, and so on. In recent years, LLC systems have received considerable attention thanks to their excellent potential as drug vehicles. Amid these systems, inverted cubic (Q2) and hexagonal mesophases (H2) are the primary important and are widely examined for his or her capability to sustain the discharge of a large range of bioactive from low mass drugs to proteins, peptides and nucleic acids (Mohammad et al., 2014).

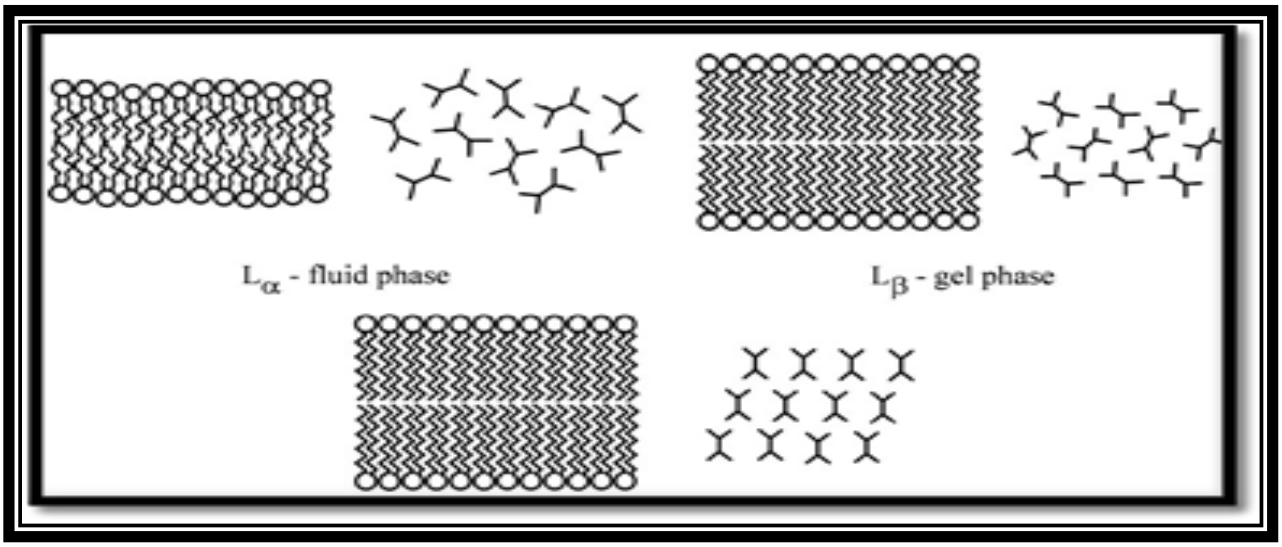

Figure 3: Schematic representation of the three main types of lamellar phases

b) Hexagonal LCs

Hexagonal liquid crystals show long-range positional order in two dimensions. Both the lamellar and hexagonal LCs will be identified using polarized light microscopy as they exhibit a spread of textures that are typical for the corresponding LCs. They even have referred to as middle phase as shown in Figure 4.

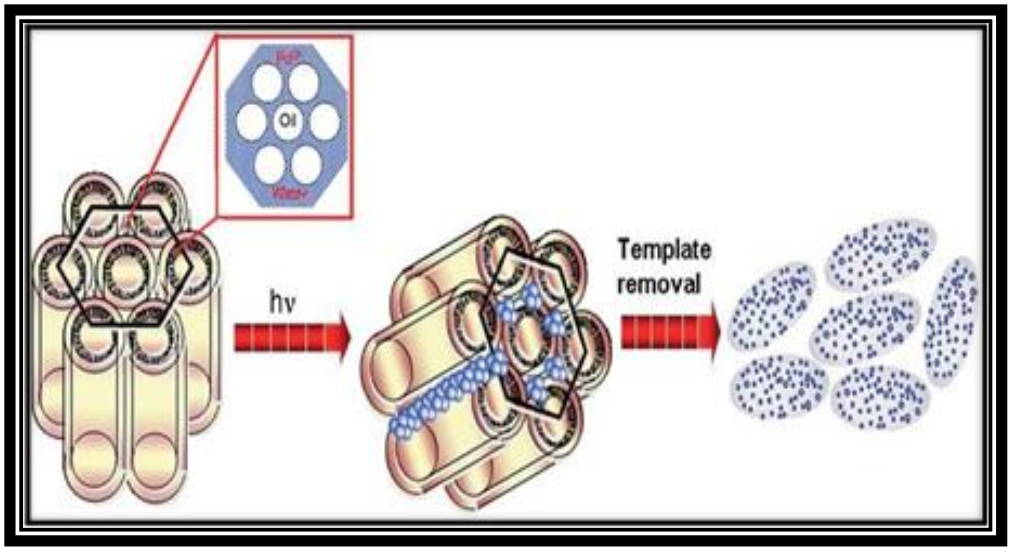

Figure 4: Schematic representation of hexagonal mesophase

The liquid crystalline matrices possess distinct lipidic and aqueous domains, and will exhibit variety of well-defined geometric arrangements counting on the chemical structure of the lipid, the aqueous content of the system, the presence of other additives, and solution conditions like pH, temperature and pressure. most frequently this arrangement consists of lamellar bilayer structures, except for a comparatively small subset of lipids, the exhibited phase structures may include the viscous reverse hexagonal phase (HII) or bicontinuous cubic phase (Q)(Boyd J. et al., 2006). Figure 4 show hexagonal liquid crystals are often spontaneously formed by the addition of certain amphiphilic lipids in an aqueous environment. When hexagonal mesophase

dispersed into nanoparticles with excess water with an addition of stabilizers like pluronic copolymers and that they form stable colloidal dispersions which are termed hexosomes either cubosomes. The hexagonal mesophases consist of glycerate-based surfactants like oleyl glycerate (OG) and phytanyl glycerate (PG) have shown great latent in drug delivery. Hexosomes are colloidally stabilize by using the tri-block co-polymer Pluronic® F127 and F68. Non-ionic steric stabilizers are most frequently employing for the stabilization of the dispersion, as ionic stabilizer typically disrupt the interior nanostructure. variety of stabilizers are employed in try and create stable liquid crystalline dispersion like beta casein, polyethylene glycol, hydroxypropyl methyl cellulose ester succinate etc.

- In Figure 5b seen, hydrophilic drugs are entrapped within the internal water domain, whereas lipophilic drugs are located within the lipid domain and amphiphilic drugs within the interface.
- Preparation methods for reversed cubic and hexagonal Mesophases As a rule, cubic and hexagonal gels may be prepared more easily than their dispersions. as an example, liquid gels can be prepared by simply blending aqueous phase with lipid phase using vortex or ultrasonication The manufacture of cubosomes or hexosomes is more complicated, however; therefore, we mainly consider the preparation methods of LLC nanoparticles
- Reverse hexagonal mesophases (HII) are characterized by densely packed, straight water-filled cylinders, exhibiting 2-D ordering. Each cylinder is surrounded by a layer of surfactant molecules that are perpendicular to the cylinder interface specified their hydrophobic moieties point outward from the water rods.
- The effective critical packing parameter (CPP) theory can supply an affordable explanation to the temperature induced structural shifts from lamellar through cubic to reverse hexagonal phases, requiring greater curvature than within the lamellar phase. Increasing the thermal motion of both the hydrocarbon chains and also the water molecules would increase the CPP values via expanding the amount of the lipophilic moiety, but decreasing the chain length and therefore the headgroup area.

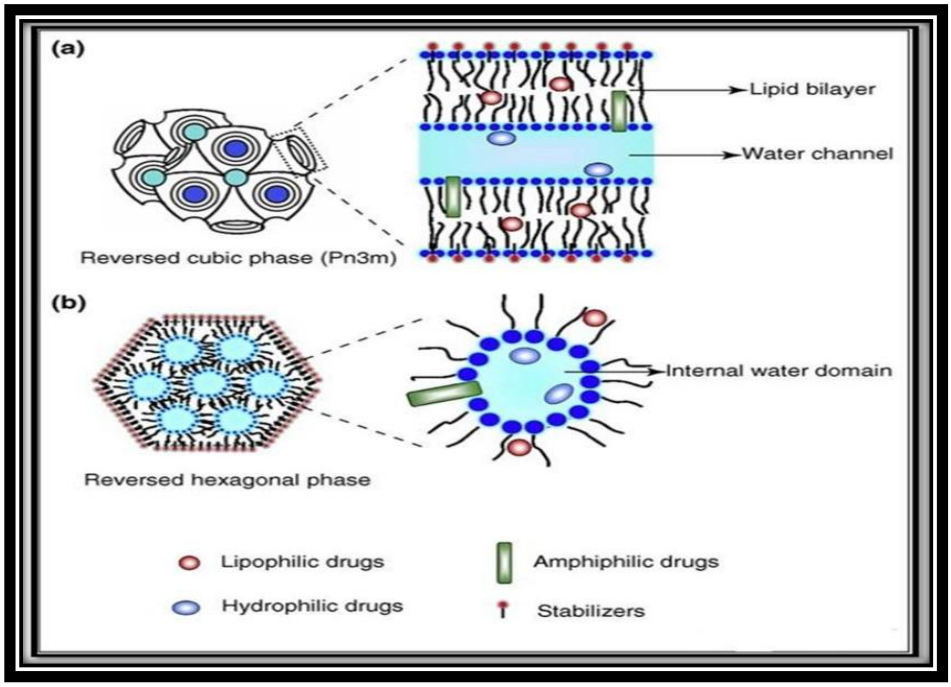

Figure 5: Structures of (a) reversed bicontinuous cubic and (b) hexagonal Mesophases.

- In addition, the hexagonal mesophase is characterized by greater packing cost than the cubic phase, but the other is true for curvature potential energy. Therefore, raised temperatures induced the propensity for interfacial curving, which increased the curving elastic costs of the constant cubic phase, stabilizing hexagonal symmetry.
- Systematic research was conducted in our laboratory to decrease the cubic to hexagonal temperature transition and stabilize the glyceryl monooleate-based HII (reverse hexagonal) mesophase at temperature.

c) Cubic LCs

Figure 6 describe the cubic kind of LCs. cubic LCs mainly shows long-range positional order in three dimensions.

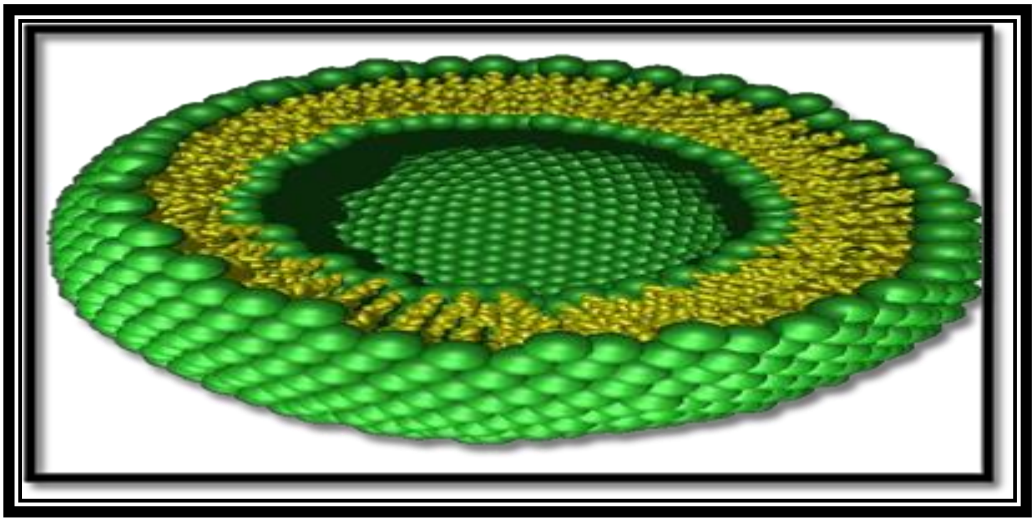

Figure 6: Cubic liquid crystals (Cubosome)

Generally these liquid crystals having cubic packing of the micelles and might not identified using polarized light microscopy. Cubic LCs highly viscous and have poor flowing property as compare to lamellar and hexagonal LCs . The structure of cubic mesophases is exclusive and comprises a curved bicontinuous lipid bilayer (with an estimated thickness of three.5 nm) extending in three dimensions and two interpenetrating, but non-contacting, aqueous nano-channels (with a full swollen diameter of roughly 5 nm), with a high interfacial area of 400 m^2/g

1.1.2 Thermotropic liquid crystals (TLCs)

Thermotropic LCs formed by heating alone crystalline substance and doesn't required of solvent for his or her formation, thermotropic liquid crystals unlike lyotropic mesophases. TLCs (Thermotropic liquid crystals) will be formed by heating a crystalline solid or by cooling an isotropic melt, they'll further as;

a) Smectic LCs

- Smectic springs from Greek meaning grease or clay.
- The long axes of all molecules during a given layer are parallel to 1 another and perpendicular to the plane of layers.
- The layers are liberal to slip and travel over one another.
- The smectic state is viscous.

b) Nematic LCs

- Nematic is derived from Greek meaning thread-like.
- It can determine under the polarized microscope.
- Nematic LCs aren't extremely ordered, they maintained their parallel order.

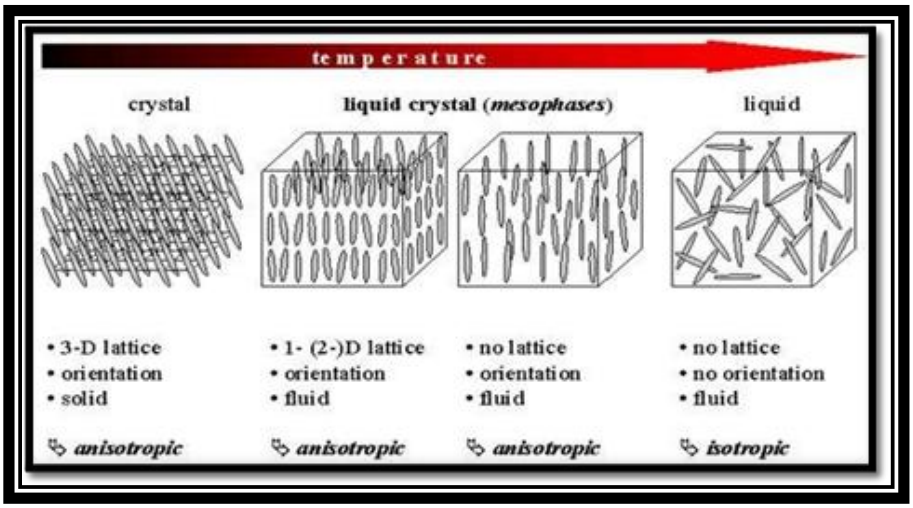

Figure 7: Position and orientational order of liquid crystal

- It generally employed in electronic display is primarily as nematic type.
- LCs show anisotropic physical characteristics.

c) Cholesteric LCs

- Cholesteric LCs arrangement is extent to combination of nematic and smectic
- The molecule in cholesteric LCs are arranged in layers and within each layer, molecules are aligned in parallel.
- The molecular layers in an exceedingly cholesteric LCs are very thin, with long axis of the molecules analogous to plane of the layers.

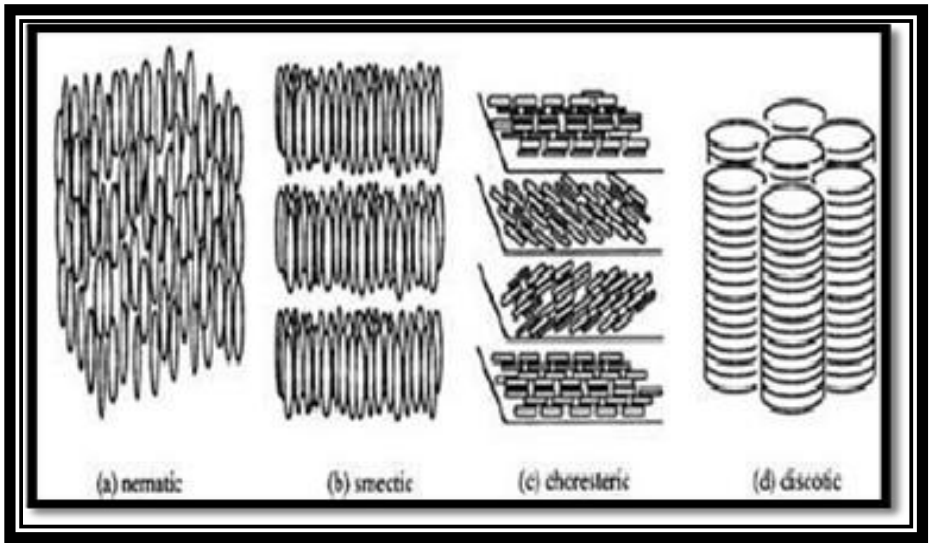

Figure 8: Thermotropic liquid crystals phases

1.1.3 Method of preparation of LCs

(a) Top-down approach

This approach was primarily reported by the acute viscous bulk phase is ready by mixing structure-forming lipids with stabilizers, and so the resultant is dispersed into solution through the input of high energy like high-pressure homogenization (HPH), sonication or shearing to create LLC nanoparticles. At present, HPH is

that the most extensively used technique within the preparation of LLC nanoparticles

Worle et al. 2007; investigated the parameters influencing the properties of glyceryl monooleate (GMO)-based cubosomes. supported the results observed, the concentration of F127 and temperature during HPH were thought to be crucially important parameters. Recently, a unique approach of shearing was proposed to fabricate LLC nanoparticles employing a laboratory built- Shearing apparatus. Compared with the well-established ultrasonication approach, the shearing treatment could effectively prepare more stable and homogeneous cubosomes or hexosomes with high content of the hydrophobic phase (oil + lipophilic additives) within a brief time (less than one minute). It seems that the preparation procedure is easy enough to be realized conveniently. In fact, the operation units during this procedure require several cycles to attain the required Nanoparticles with appropriate characteristics and therefore the high-energy input is additionally thought to be a barrier to the temperature resensitive ingredients additionally, the cubosomes prepared through top- down approach are always observed to coexist with vesicles (dispersed nanoparticles of lamellar liquid crystalline phase) or vesicle-like structures, which is able to hamper the investigations on plain cubic mesophases.

Advantages:

1) Lower impact to overall organization.
2) Visibility of formulation changes is clear.
3) No need of organic solvent.
4) Simple method as compare to other method like spray drying.

Disadvantages:

1) Solution provides limited coverage within the first phase.
2) High energy input required.
3) Time consuming process.

(b) Bottom-up approach

The crucial factor in the bottom- up approach is hydrotrope, which can dissolve water- undoable lipids to produce liquid precursors and help the conformation of liquid chargers at high attention. Compared with the top-down approach, this dilution- grounded approach can produce cubosomes without laborious fragmentation. In other words, it needs lower energy input. also, this approach is far more effective at generating small patches. The reason for this might relate to the forming medium of cubosomes. The dilution- grounded approach can be regarded as a process of small patches forming big patches through aggregation, which is similar to the use of rush processes to produce nanoparticles, whereas the top-down approach is more similar to the waste of big patches. In addition, cubosomes prepared through dilution show long term stability, which might be attributed to the homodisperse stabilizers onto the face of cubosomes. Indeed, the use of hydrotrope can simplify the medication process and produce cubosomes enjoying analogous or indeed better parcels than those fabricated by the top-down approach. It should be noted, still, that this process via dilution is a pathway by charting circles on the ternary phase illustration(lipid and water hydrotrope), which

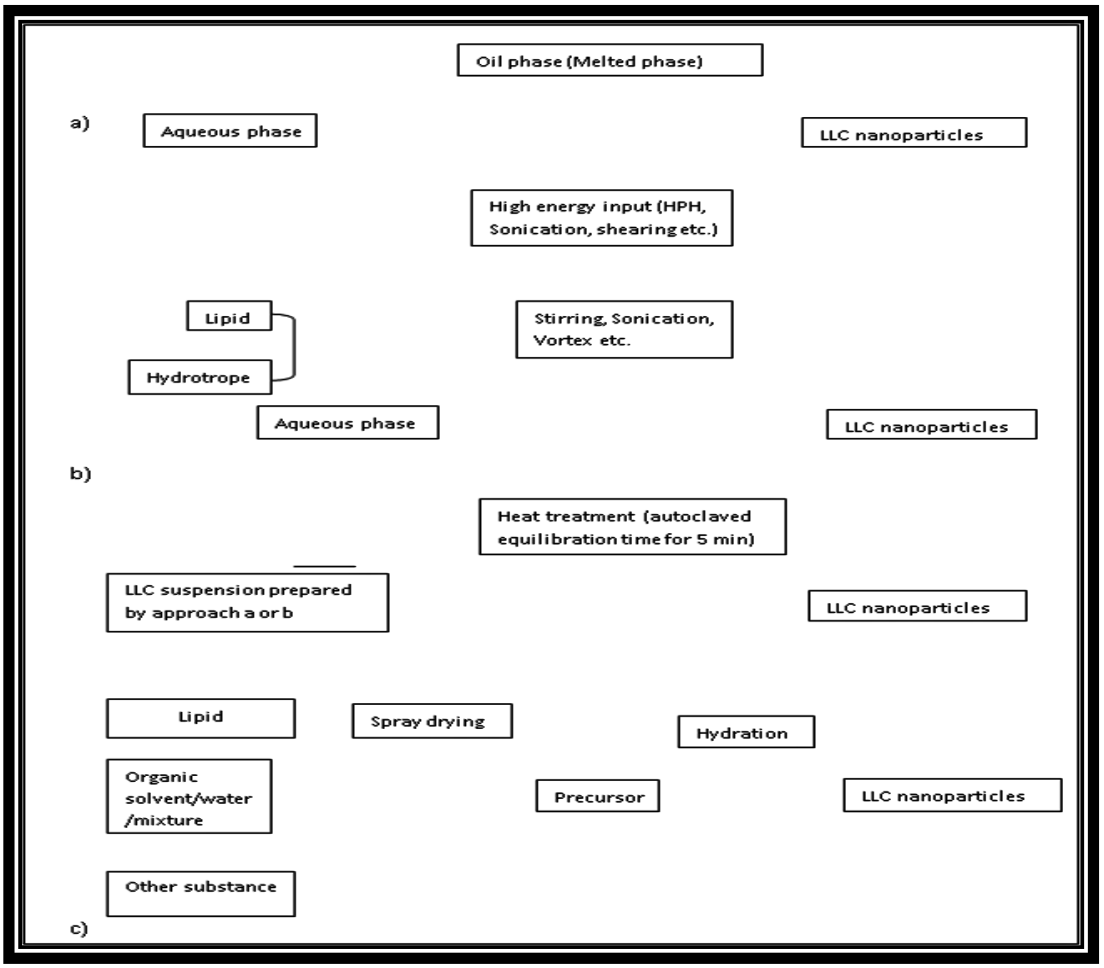

Figure 9: Schematic diagram of preparation method for cubosome or hexosomes according to the literature (a) Top-down approach (b) Bottom-up approach (c) Heat treatment (d) Spray drying.

Requires knowledge of the full phase gets; hence, the extent of dilution is delicate to control precisely. Owing to the addition of hydrotrope, numerous issues arise, similar as the goods wielded by varying attention of hydrotrope on the physicochemical

Properties of LLC nanoparticles and the possible circumstance of vexation and antipathetic response when the mesophase phrasings are administered. Eventually, this bottom- up approach can not effectively avoid forming vesicles. Through cryo- TEM, numerous vesicles and vesicle- suchlike structures were also observed to attend with cubosomes.

Advantages:

1) Lower energy input.
2) Fewer time consuming process.
3) At high attention inhibit the formation of LCs.
4) No need the organic solvent

Disadvantages:

1) Milky white preparation formed.
2) Hydrotrope which appearances allergic reaction when the mesophase preparation administered orally.

(c) Heat treatment

The concurrence of cubosomes with vesicles is suspected to give multiphase manipulation of the sustained release of medicines; hence, to more probe the release geste of plain mesophases, vesicles should be excluded as much as possible. In this case, heat treatment can be regarded as a good approach. Note that in the strictest sense, heat treatment isn't an intertwined process for the manufacture of cubosomes because it only promotes the metamorphosis fromnon-cubic vesicles to well- ordered boxy patches. The dispersed patches, thus, can be produced by a simple

processing scheme comprising a homogenization and heat- treatment step. From the reported studies, heat treatment could beget a drop in the small flyspeck size bit that corresponded to vesicles and form further boxy phases with narrow flyspeck distribution and good colloidal. Taking the whole process of medication into account, it's egregious that the transition takes place during the procedure of heat treatment. The reason for transition could be suspected as an elevated temperature giving rise to a reduction in solubility and stability. When the temperature was below pall point, the surfactant had a high solubility and therefore the patches could live stably and the miracle of emulsion was hardly observed. Once reaching pall point, the solubility of surfactant dropped specially and a notable fast emulsion among vesicles would do. Although millions of vesicles can transfigure to boxy nanoparticles through heat treatment, it doesn't mean that all the LLC systems are suitable for this procedure in particular, the systems lading medicines that can not give sufficient stability under the condition of high temperature(generally over 120 °C), similar as some proteins and temperature-sensitive medicines aren't suitable.

Advantages:

1. It produced good colloidal dispersal.
2. It can decrease particle size.

Disadvantages:

1. Degradation of thermo sensitive material due to development of aggregate.
2. Decrease of stability of formulation.

(d) Spray drying

To widen the operations of cubosomes in pharmaceutical field, dry greasepaint precursors can be fabricated by spray drying and used for the medication of oral solid phrasings and inhalants. This approach was firstly proposed and delved by Spicer etal.(Spicer etal., 2002). In his exploration, the greasepaint precursor could be prepared through drying apre-dispersed waterless result that comported of GMO, hydrophobically modified bounce and water or contained GMO, dextran, ethanol and water, and also the colloidally stable dissipations of nano- structured cubosomes could be created by hydration of the precursors. subsequently set GMO grounded cubosome precursor containing diclofenac sodium through spray drying. The precursor was proven to have further effective and prolongedanti-inflammatory and analgesic exertion than pure medicine when administered per orally; it's noteworthy, still, that residual detergent content is still a problem that cannot be ignored.

Advantages:

1. Spray drying technique is beneficial for powder formulation like DPI (Dry powder inhaler, dry syrup).
2. This system used for microencapsulation.
3. Organic solvent can use during this method.

Disadvantages:

1. From this method has low yield of formulation as 5-30% out of 100%.
2. Spray drying method is complicated as compare to other method.

(e) Ultrasonication / Probe sonication

High shear homogenization and ultrasound are dispersing techniques which were initially used for the assembly of solid lipid nanodispersion. Though, its value is compromised by the existence of microparticles. A pre-emulsion was obtained under stirring with an Ultra-Turrax T25 by adding melted lipid to a mix of surfactants and water. A sonication probe was placed during this pre-emulsion which result in droplet breakage by acoustic cavitations and subsequent formation of oil in water (o/w) nanoemulsion which immediately cooled all the way down to temperature to get liquid crystals

Advantages

1. Both methods are widespread and easy to handle
2. Equipments whatever use here are very common in every lab
3. Reduced shear stress

Disadvantages

1. Potential metal contamination
2. Physical instability like particle growth upon storage

1.1.4 Phase behaviour study:

Generally phase behaviour study important for polymer of drug toxicity or biodegradable properties and during this study we are able to finalist the concentration of polymer either drug.

Phase behavior studies were conducted to work out,

I. The phase progression displayed by the lipid with increasing water content.
II. The water content at the boundary of the lyotropic liquid crystalline innovate contact with excess water.

III. What influenced dissolved drug has on the phase progression displayed by the lipid with increasing water content.
IV. What impact the corresponding fatty alcohol has on the phase behaviour as an indicator of an in vivo hydrolysis of the glycerate surfactant by esterase activity.

Many factors influence the phase behaviors of cubic and hexagonal liquid crystals, like the molecular structures of lipid, pressure, temperature, pH and addition of third substance. Full understanding of those influencing factors on phase change will provide better internal control in addition as expanding the lipid applications in drug development. In Figure 10 conclude that the molecular structure of lipid plays a very important role within the determination of phase behavior.

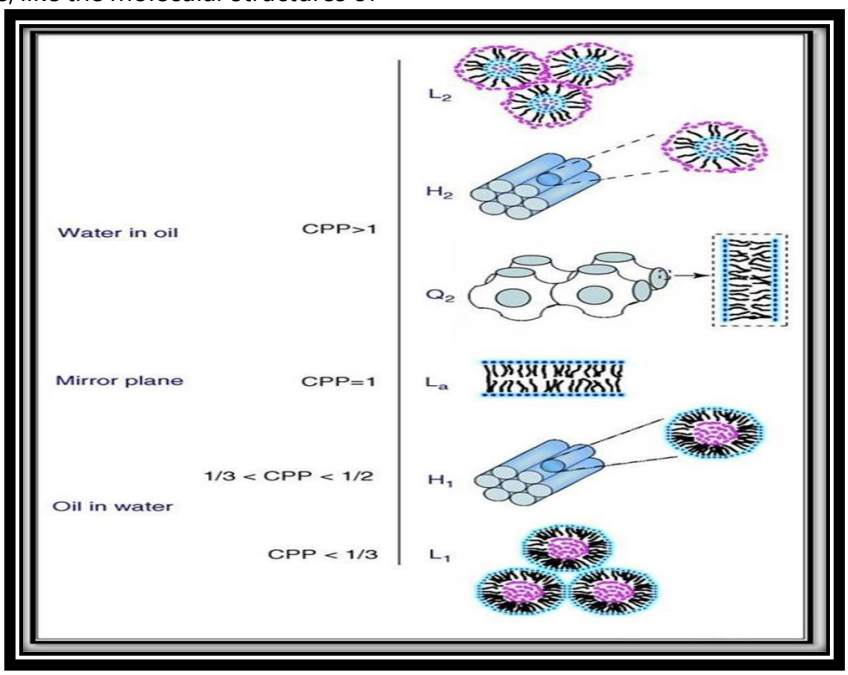

Figure 10: Schematic diagrams of different existing surfactant self-assembly structures & their CPP.

The critical packing parameter (P) is employed to predict nanostructure of formed liquid crystals with formula,

$P = v$ Eq. 1
al —

Where,
P=critical packing parameter,
V=hydrophobic chain volume,
a=cross sectional are of the polar headgroup, and
l=hydrophobic chain length.

t is important to notice that P value (and therefore self-assembled nanostructure) will change together with other parameters like temperature and solvent conditions. reckoning on P, different self-assembled liquid crystalline structures are formed. When P=1, lamellar liquid crystalline structure forms. When P<1, oil-in-water self- assembled structures forms, like normal micelles (L1), normal cubic structure (V1), and normal hexagonal phase (H1). When P>1, water-in-oil self-assembled structures forms, like reverse micelles (L2), reverse cubic structure (V2), and reverse hexagonal structure (H2).

Yaghmur et al. investigate the impact of pressure and temperature on the steadiness of the inverted type discontinuous cubic phase (Fd3m) versus the inverted type hexagonal phase (H2). The result showed that comprising the Fd3m to H2. Interestingly the temperature dependent structural transition demonstrated the other trend where a rise of temperature induced the structural transition from H2 to Fd3m at isobaric condition. Many factors can influence the phase behavior of cubic and hexagonal mesophases. The surface formed by a film between two rings is catenoid, an easy variety of minimal surface

whose principle curvature are equal but opposite in sign at every point, leading to a median curvature of zero and a negative gaussian curvature.

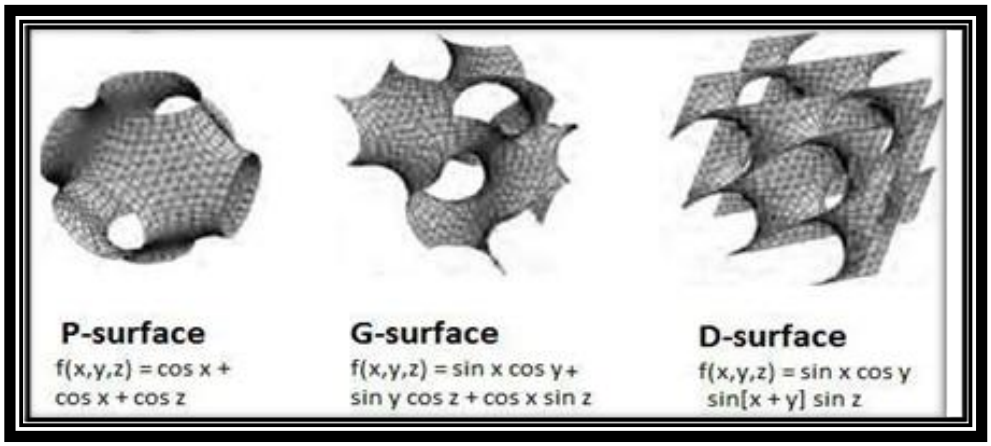

Figure 11: *Unit cubes of the P-surface, G-surface, and D-surface formed in bicontinuous amphiphilic system.*

Figure 11 shows approximate plots of the three most ordinarily studied minimal surfaces in cubic phases. The surfaces in Figure 11 are particularly fascinating because their discovery was purely mathematical, before knowledge of the structure existence in cubic phases. In cubic phases, the minimal exterior is made by the self-assembled bilayer that occurs because the hydrophobic or hydrophilic portions of the surfactant particles line up to decrease their interaction with their opposites. The three structure are all bicontinuous (i.e., they divide space into two continuous but nonintersecting regions); within the case of cubic phases, two separate regions of hydrophilic material (water channels) form. Following suggestion by Scriven that minimal surfaces could explain liquid structure, the minimal surface description to the cubic phase observed within the monoolein-water system and noted the connection to the structures formed in plastid systems. However, Longley and Mcintosh found evidence of an alternate symmetry within the monoolein-water cubic phase, leading Larsson to appreciate that two cubic phases are formed, both with minimal surface structure. The monoolein-water system forms the D-surface at high water levels and therefore the G-surface at lower levels, as shown within the phase diagram. The monoolein-water system forms the D-surface at high water levels and also the G-surface at lower levels,

However, Mcintosh found evidences of another symmetry within the monoolein- water cubic phase, resulting in realize that two cubic phases are formed, both with minimal surface structure. As shown within the phase diagram figure 12.

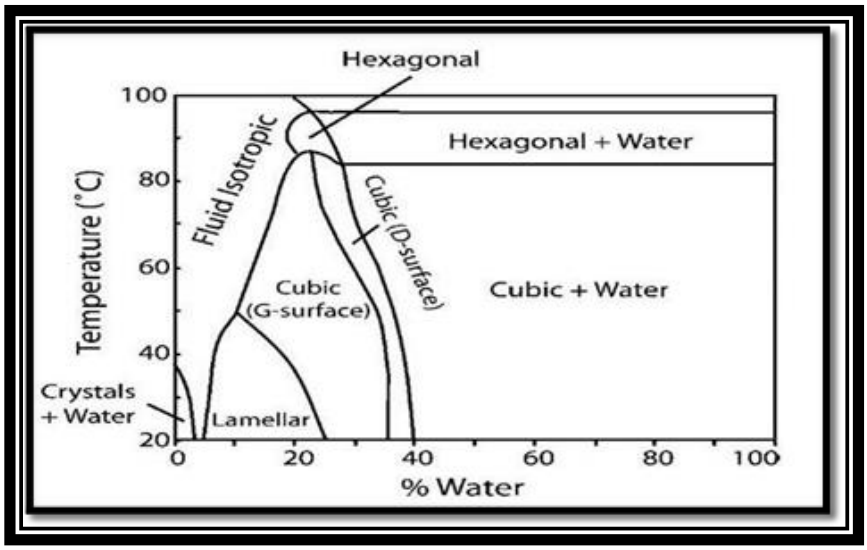

Figure 12: Aqueous stage behavior of the monoolein-water system, updated to reflect the existence of two cubic phases.

1.1.5 Significance

1) LCs enhances the solubility additionally permeability of poorly water soluble drug.
2) LLC shows good compatibility.
3) It is helpful for self-emulsifying drug delivery system (SEDDSs).
4) It gives nano particle size.
5) LCs helpful for oral administration.
6) It helps sustained release for poorly water soluble drugs.
7) Provides maximum drug loading and entrapment efficiency.
8) It is beneficial for amphiphilic drug delivery.

1.6. Applications of liquid crystals system

Therapeutic compounds of diverse physicochemical properties like analgesic, antibiotics, antifungal, anticancer, vitamins, antiasthamatics, immunosuppressive etc. monoglyceride based cubosome dispersion may be proposed for topical used, like for precutaneous or mucosal applications. thanks to the microbicidal properties of monoglycerides, can be used to design intravaginal treatment of sexually transmitted diseases caused by viruses (e.g. HSV, HIV) or by bacteria (e.g. Chlamydia trachomatis and neisseria genorrticae). The cubosome technology is employed to develop an artificial venix the chessy white substance that coats infants in late gestation to assist premature infants who are born without it. E vernix may be a complex mixture of lipid (fat), proteins and water. Cubosome also can be used for controlled release application. Cubosome particles are used as oil water emulsion stabilizers and pollutant absorbants in cosmetics. newer use is about personal cure product areas as varied as skin care, hair care, cosmetics and antiperspirant.

1) Oral administration

The oral bioavailability of a inadequately water-answerable medicine, cinnarizine, incorporated in different types of LLC phases. Through beast trials, the OG- grounded hexagonal expression showed a vastly advanced relative bioavailability that was nearly3.5 times lesser than that of the control suspense of cinnarizine and 3 times lesser than the GMO- grounded boxy expression. The oral administration of medicines incorporated into LLC nanoparticles has also been reported, prepared GMO- grounded cubosomes containing insulin and delved the hypoglycemic effect generated by oral administration of this expression. The blood glucose attention – time profile showed that the insulin expression could give a hypoglycemic effect similar to intravenous administration of insulin over six hours. Simvastatin incorporated in GMO- grounded cubosomes was administered orally and the relative bioavailability to the control medicine demitasse

greasepaint was 241. also, the cubosomes showed sustained release of simvastatin over 12 h in beagle tykes . The author presumed that the medium of enhancing bioavailability might be related to the hydrophilic face of cubosomes, which stimulated the saturation through the stagnant waterless subcaste of the intestinal mucosa.

2) Topical Administration

Topical medicine delivery is an seductive volition to oral administration. Its main debit is the limited immersion of medicines through the skin hedge, and examinations on topical medicine uptake are necessary to grease the design of effective topical medicine delivery systems. At present, stratum corneum(SC) is considered to be the rate- limiting hedge in transdermal medicine delivery. numerous studies have shown that boxy and hexagonal mesophase phrasings are able of piercing through SC and getting campaigners for topical medicine delivery systems. Cyclosporine A incorporated in hexosomes comprising GMO, oleic acid and water was reported to be able of enhancing medicine saturation when applied topically There are several natural characteristics that the reversed boxy and hexagonal phases present to make them suitable for topical medicine delivery

I. Sustained release of drugs incorporated,
II. Bioadhesive properties,
III. Solubilization of hydrophilic and lipophilic medications and protecting them from physical and enzymatic degradation, and
IV. The nontoxic permeation enhancers GMO and PT as structure forming materials.

3) Mucosal drug delivery

Not only the bulk mesophases but also their dissipations could be employed for mucosal medicine delivery. Swarnakar etal. reported that after operation of progesterone loaded hexosomes on the albino rabbit mucosa for 12 h, an obviously enhanced transmucosal flux was observed and that it was fivefold advanced than that of progesterone loaded gel and nearly fourfold advanced than plain progesterone suspension.

4) Rectal administration

Another operation area for system displaying in situ thickening, similar as liquid crystalline phases formed by PEO/ PPO block copolymers, is rectal administration. As an illustration of this, shows results on the rectal administration of indomethacin, the utility of which is oppressively reduced by GIT side goods. Although the bioavailability of the pluronic F127- grounded expression, as determined from the integration of the tube attention over time, is similar to that of suppositories, the Pluronic F127- grounded expression offers several advantages.

5) Parenteral administration

Injectable in situ thickening expression are intriguing also for parenteral administration,e.g., in the form of intramuscular or subcutaneous depot expression with the end of achieving controlled medicine release over a prolonged time. Also in this environment, expression grounded on liquid crystalline phases offer some possibilitiese.g., antitumor treatment using IL- 2 has shown positive results for several cancers in both experimental beast models and in humans. Unfortunately the use of high cure IL- 2 remedy is forestalled due to the toxin associated with it. still, the antitumor goods of IL- 2 have been set up to be identified to the time IL- 2 remains in the serum rather than with the peak serum IL- 2 attention. thus, a sustained release expression of IL- 2 could be anticipated to allow a high remedial effectiveness and at the same time result in reduced poisonous goods. Indeed, pluronic F127/ water expression displaying in situ thickening after intramuscular administration have been set up to affect in a reduced peak serum IL- 2 attention and in a longer rotation of IL- 2 than the corresponding waterless IL- 2 result. similar expression is thus intriguing for IL intramuscular remedy.

1.1.7 Requirements for the formulation of liquid crystals

Ideal distinctness means by means of a prominent or distinctive element of medicine substance which is able of show his significance for the duration of system development similar as demand of liquid chargers, medicine and lipid.

1) Requirement of liquid crystals:

For the medication of liquid chargers necessary as suitable lipid, stabilizer and active pharmaceutical component of any BCS. These entire content affect on the result of expression estimation consideration either finished product properties.

2) Apremilast:

a. Apremilast is treat a certain type of psoriatic arthritis, which is pale unheroic, liquid greasepaint having 3- 4 hrs half- life to BCS class IV.

b. The medicine having high cure of frequence, and having poor dissolution rate from its oral solid lozenge forms.

3) Lipid:

a. Lipids are the category of the biomolecules that's defined by their solubility in organic solvent like methanol, chloroform hexane and their relative solubility in water.
b. Interactions among lipids and of lipid s with other biomolecules arise largely from hydrophobic (water heating) nature.
c. Lipid are often divided in two main categories in keeping with their structure: people who supported carboxylic acid, and people that supported isoprene, a branched five carbon chain.

4) Stabilizer:

a. Stabilizer keeps homogeneity and control crystal growth during the freezing and aeration process.
b. It can help to reduced particle sized in novel drug delivery system like as liquid crystalline system, nanocrystals, solid lipid nanoparticles and nano lipid carrier.
c. Some stabilizer also employed in the foodstuff during to form that food or product i.e. frozen dessert or dairy nutrient

The key factor of stabilizer is that they don't form aggregate in pharmaceutical formulation development.

2. DRUG PROFILE

2.1. Apremilast:

2.2 Structure:

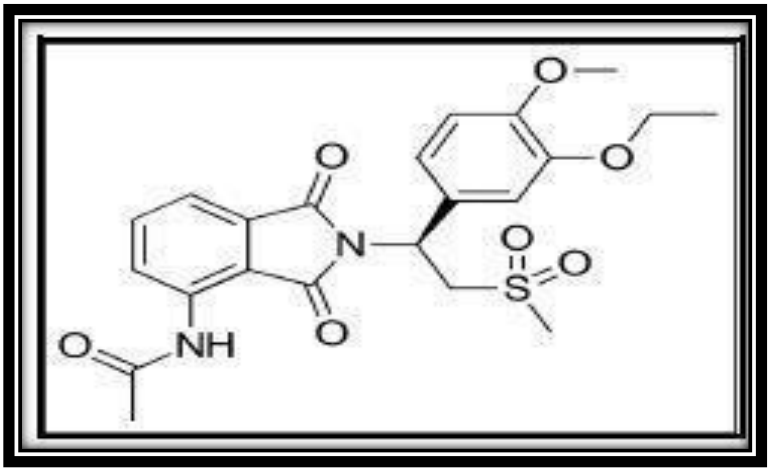

Figure 13: Stucture of Apremilast

2.3 Mode of action:

Apremilast could be a novel, orally available small molecule inhibitor of type-4 cyclic nucleotide phosphodiesterase (PDE-4). PDE-4 could be a cyclic AMP (cAMP)-specific phosphodiesterase that's predominantly located in inflammatory cells. By inhibiting PDE-4, apremilast increases intracellular levels of cAMP and thereby inhibits the assembly of multiple proinflammatory mediators including PDE-4, TNF-alpha, interleukin-2 (IL-2), interferon-gamma, leukotrienes, and gas synthase. By targeting a central component of the inflammatory signaling cascade instead of one inflammatory marker, PDE-4 inhibition may restore the homeostatic balance between pro- and anti-inflammatory signaling.

3. CONCLUSION

Primary objective of liquid crystals drug delivery system is to confirm safety and to boost efficacy of drug furthermore as patient compliance, which may be achieved by better control of less frequent dosing. Liquid crystalline drug delivery is incredibly important to use minimum number of excipient with minimum processing steps so as to cut back the particle size and drug entrapment variation, hence air mass homogenizer is that the most fitted technique.

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