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Review Article

Liquid-Crystal and Nano-Crystal Technology for Solubilization of Poorly Water Soluble Drugs

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Abstract

Of all the pharmaceutical compounds, about 40% are considered poorly water soluble and hence, the development of efficacious formulation is being halted. It has been shown that a drug should have a minimum aqueous solubility of 1% to avoid bioavailability problems. During pre-formulation study, sufficient time should be invested in order to improve the solubility of these kinds of drug. At the very beginning when new compounds are screened for bioactivity, it becomes an obstacle for the study. Some technology exists for the enhancement of drug solubility but every technology has some degree of limitations. Hence, there is a need for smart approaches to make such poorly soluble drugs bioavailable. The purpose of this review is to discuss briefly the updates in the liquid crystal and nanocrystal technology for the solubilization of insoluble or poorly soluble drugs.

Keywords: Lyotrpoic liquid crystals, nanocrystals, solubility enhancement, top-down technology, bottom-up technology, nanosuspension

Introduction

The credit of discovery of liquid crystals goes to Austrian botanist Friederich Reinitzer, who in 1988 observed two melting points in cholesterol benzoate, which he extracted from plant. Liquid crystals are state of order between liquids and crystals. They can be fluid like liquid and they can have anisotropic properties like crystals. These are the substances that flow like liquid, but maintain the ordered structure characteristics of crystalline solids (liquid + crystals = liquid crystals).[1]

The distinguishing characteristic of liquid crystalline state is tendency of molecules (mesogens) to point along a common axis, called the director. The characteristic orientation order of liquid crystal state is between solid and liquid phases and this is the origin of the term mesogenic state, used synonymously with liquid crystal state. While the individual molecule will vary slightly in their orientation, on average the molecules will orient in the same general direction.[2]

It is very important to understand properties of liquid crystals and how these relate to molecular structure. Recent issues in liquid crystals sciences are associated with the applications of liquid crystals in area of biology and medicine in which liquid crystals concepts could be useful.

B.D. Fahlman has described a nanocrystal as any nanomaterial with at least one dimension $\leq$100nm and that is single crystalline.[3] In another words, a nanocrystal is a crystalline particle with at least one dimension measuring less than 1000 nanometers (nm), where 1 nm is defined as 1 thousand-millionth of a meter (10^{-9} m). More properly, any material with a dimension of less than 1 micrometre, i.e., 1000 nanometers, should be referred to as a nanoparticle, not a nanocrystal. Crystalline nanoparticles are also of interest because they often provide single-domain crystalline systems that can be studied to provide information that can help explain the behaviour of macroscopic samples of similar materials. NanoCrystal® is also a registered trademark of Elan Pharma International Ltd. (Ireland) for a technology that improves the bioavailability of drugs by rendering them as nanoscale particles that can be suspended in liquids, made into powder, pressed into tablets or encapsulated.[4] More than 40% of pharmaceutical compounds are considered poorly water soluble and hence, their formulation is a challenge to the pharmaceutical scientists. Their formulation development has been halted for several years due to their poor water solubility. Poorly soluble drugs face bioavailability problems. At the pre-formulation stage a great effort should be put to improve the solubility of drugs. It is also an obstacle at the very beginning when screening new compounds for bioactivity. Hence there is a need for smart technological formulation approaches to make such poorly soluble drugs bioavailable.[5] A number of formulation approaches have been adopted for poorly soluble drugs in enhancing water solubility. These approaches include hydroxypropyl beta cyclodextrin complex[6], solid dispersion[7-8], salt formation[9], eutectic mixtures.[10] But It would be much smarter to have a "universal formulation approach[11] applicable to any molecule apart from few exceptions.

Formulating these compounds as pure drug nanoparticles is one

of the newer drug delivery strategies applied to this class of molecules. When the size of the material is reduced to less than 100 nanometers, the realm of quantum physics takes over and materials begin to demonstrate entirely new properties. As decreased size will increase the solubility of drugs hence, this technology is explored to increase oral bioavailability of sparingly water soluble drugs. [11]

On the other hand, engineering of nanocrystals will avoid the use of toxic solvents and surfactants to develop injectable solutions of sparingly water soluble drugs. It is also possible to develop formulations for various routes of administration where size is the critical factor (injectables, ophthalmics and topical preparation). Drug nanocrystals can be used for chemical stabilization of chemically labile drugs. The increased stability can be explained by a shield effect of the surfactants and the drug protection by a monolayer made of degraded drug molecules which reduce the accessibility for destructive agents.

The purpose of this review is to focus on new directions in drug delivery science with especial reference to the improvement of solubility of poorly soluble drugs via nanocrystal and liquid crystals technology.

Type of Liquid Crystals

The liquid crystals can be divided into two classes: thermotropic and lyotropic.[12] Thermotropic liquid crystalline phases are are exhibited by large number of organic compounds whose molecule has anisotropy of shape. This state can be obtained by raising temperature of solids and/lowering temperature of liquid. If temperature increase is too high, thermal motion will destroy ordering of liquid crystal phase, pushing material into isotropic liquid phase. If temperature is too low, most liquid crystal materials will form conventional crystals. Scientists further subdivided thermotropic liquid crystals based on shape of the molecules itself and different variations in ordering of molecules. These can generally be formed by calamitic (rod like) or discotic (disc like) molecules. Smetic liquid crystals have layered arrangement of orientationally ordered rod-like molecules. The simplest liquid crystals phase is called nematic phase and is close to liquid phase. The molecules float around as in liquid phase, but are still ordered in their orientation. The nematic phase is seen as the marbled structure. Columnar liquid crystals are different from previous types because they are shaped like disks instead of long rods. The columns are packed together to form two-dimensional crystalline array.

Lyotropic liquid crystals have several fundamental characteristics that make them dramatically different than thermotropic liquid crystals. First, these types of liquid crystals form in solution rather than in pure substances. Secondly, individual molecules do not align by themselves to create anisotropy instead, the molecules come together to form anisotropic aggregates which themselves align along director. For these reasons, additional conditions besides temperature determine whether the liquid crystals phase forms. Temperature still affects phase in the same way as thermotropic liquid crystals but concentration of substance also has strong effect on liquid crystalline behaviour. Lyotrpoic crystals are formed by the amphiphilic molecules, often known as surfactants.[13]

These two types of liquid crystals are distinguished by mechanisms that drive self-organization, but they are also similar in many ways. Thermotropic phases are initiated by changes in temperature, while lyotropic phases can also be initiated by changes in concentration. Lyotropic liquid crystals occur as a result of solvent-induced aggregation of constituent mesogens into micellar structure.

Liquid Crystals in Enhancement of Drug Solubility

Many substances are more soluble in lyotropic liquid crystals. One exciting example is hydrocortisone.[14] It is often taken in topical applications, but its uses have been limited because highest concentration possible has been only 1%. When hydrocortisone was blended into liquid crystals of lecithin and water, concentration went up to 4%. In time ,liquid crystals may become a primary solvent for topical medications.

Another example for improvement of solubility is pH-induced nano-segregation of ritonavir to lyotropic liquid crystals of higher solubility than crystalline polymorphs.[15] Birefringent spherical vesicles of ritonavir are formed by increasing pH of aqueous solutions from 1 to 3 or to 7 and by addition of water to ethanol solution at room temperature. Increasing pH creates super saturation levels of 30-400. Upon this change in pH, solutions become translucent, implying that some kind of ritonavir assembly was formed. Small spherical vesicles of narrow size distribution are detectable only after a few hours by optical microscopy. Ritonavir self-organizes into various phases (lyotropic crystal form-I, crystal form II) as a result of super saturation created in aqueous solutions. The lyotropic liquid crystal vesicles do not fuse but slowly transform to polymorphs of ritonavir (in days), liquid crystals form I and finally form II liquid crystals. The dissolution and solubility of lyotropic liquid crystals is slightly lower than that of amorphous phase and about 20 times higher than that of form II (amorphous > liquid crystal form I > form II).

Lyotropic liquid crystals can be used for solubility enhancement of poorly soluble drugs, sustained drug release and to modify the stability of drug molecules in gastrointestinal tract. For example, cyclosporine is practically insoluble drug and having toxic side effects. To solve these problems associated with cyclosporine, vitamin E, δ-alpha tocopherol polyethylene glycol -1000 succinate formulations can be utilized.[16-17] It form liquid crystalline structure with gastric fluid to enhance drug solubility and further employs dosage form with impermeable or semi-impermeable barriers to control drug release over time, thereby providing means for lowering dose within therapeutic window.

Amphiphilic substances spontaneously tend to self-associate and with increasing concentration they can form highly ordered aggregates, such as lamellar, hexagonal and cubic phases. The use of lyotropic liquid crystalline phases is favorable in topical drug delivery because of their high solubilization capacity, thermodynamic stability or broad range of rheological property.

A new class of amphiphiles with a glycerate head group is recently found to form reverse hexagonal phase in excess water. The application of these novel materials to the development of a new injectable formulation of irrinotecan was investigated.[18] The formulation of irrinotecan with small percentages of oleic acid in oleylglycerate permitted a clinically relevant dose of irrinotecan to be dissolved in glycerate surfactant and dispersed in aqueous medium to form an injectable particle-based dosage form of irrinotecan. Lyotropic liquid crystals are also used in cosmetic gels and emulsions to stabilize the structure and to retain moisture.

Advantages of Nanocrystals[5, 19, 20]

There are many advantages of nanocrystal formulations designed for oral administration. They are as follows:

1. Increased rate of absorption
2. Increased oral bioavailability
3. Rapid effect
4. Improved dose proportionality
5. Reduction in required dose
6. Applicability to all routes of administration in any dosage form.
7. Reduction in fed/fasted variability
8. Rapid, simple and cheap formulation development
9. Possibility of high amounts (30-40 %) of drug loading
10. Increased reliability
11. Sustained crystal structure
12. Improved stability

Nanocrystal Preparation Methods[21-22]

Several preparation methods for drug nanocrystals have been investigated. Today, implemented preparation methods of nanocrystal formulations can be classified as "bottom up", "top-down", "top down and bottom up" and "spray drying". "Bottom up" technology begins with the molecule; active drug substance is dissolved by adding an organic solvent, and then, solvent is removed by precipitation.

"Bottom up" technology relies on precipitation. The principle of this method is based on the dissolution of the active drug substance in an organic solvent which is then added into a nonsolvent (miscible with the organic solvent). In the presence of stabilizers, thereafter, the nanocrystals are precipitated. Basic advantage of the precipitation technique is that it is simple and has a low cost. Also, scale up is simple in this method.

"Top-down" technology applies dispersing methods by using different types of milling and homogenization techniques. "Topdown" technology is more popular than "Bottom up" technology; it is known as "nanosizing". In other words, it is a process which breaks down large crystalline particles into small pieces. "Top down" technology can be applied by either homogenization or milling. In the milling method; pearl, bead or ball mills can be utilized to prepare a nanocrystal formulation. The other "top down" method is homogenization which can be done by ultra sonification. Homogenization by ultasonification is based on high frequency mechanical vibrations. Liquids are exposed to intense sound waves transmitted with ultrasonification.

Dosage Form Development of Nanocrystals[23-25]

The drug nanocrystals can be transferred into different dosage forms. Nanosuspensions can be directly used as oral suspensions to overcome the difficulties of swallowing tablets by pediatric or geriatric patients. The application of these nanosuspensions can improve the solubility of the drug and the dissolution rate; additionally, suspensions can be applied for reasons of taste-masking. Nanocrystal-loaded tablets can also be produced using direct compression. Using nanosuspensions as granulation fluid for a further tablet production is a very simple approach. The nanosuspension is admixed to binders and other excipients, and the granules are finely compressed into tablets. Nanosuspensions can also be used for the production of matrix pellets or as layering dispersions in a fluidized bed process. After the pellet preparation, the cores can be coated with several polymers in order to modify the release profile of the final formulation. Nanocrystals produced in nonaqueous media, such as liquid PEG or oils can be directly filled into gelatin or HPMC capsules. Nanosuspensions can also be used directly for parenteral drug administration. Although nanosuspensions have shown a sufficient long-term stability without Ostwald ripening, for intravenous products a lyophilization step is recommended in order to avoid aggregation or caking of settled drug nanocrystals. The lyophilized product can be easily reconstituted before use by adding isotonic water, aqueous glucose solution, or other reconstitution media. The first nanocrystal product on the market was Rapamune®, introduced by Elan/Wyeth in 2000. Other Commercial products, which are prepared by nanocrystal technology, are Emend®, Tricor®, Triglide®.

Conclusion

Nanotechnology will affect our lives tremendously over the next decade in very different fields, including medicine and pharmacy. According to literature, about 40% of all synthesized drug candidates are poorly water soluble. Thus, it appears that nanocrystal technology will continue to thrive as a useful tool in pharmaceutics for the improvement of drug solubility, oral absorption, and hence, bioavailability. The fact that this technology

has many advantages; such easy production and scale up, and low cost, make this approach a very attractive means for solving a very serious problem of drugs, poor water-solubility in conjunction with low oral absorption and bioavailability. Transfer of materials into the nanodimension changes their physical properties which were used in pharmaceutics to develop a new innovative formulation principle for poorly soluble drugs: the drug nanocrystals.

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