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LIQUID CRYSTAL AS COLON TARGETED DRUG DELIVERY: A OVERVIEW

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ABSTRACT

Liquid crystals are matter in a state that has properties between those of conventional liquid and those of solid crystals. It is basically a thermodynamic stable phase .The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. Liquid crystals have generated considerable alertness over the years as a potential drug delivery vehicle. The drugs to be used as CTTDS are firstly brought into the LCs stage, then it is coated in the form of microspheres with the help of Eudragit® S100 which is an anionic copolymers based on methacrylic acid and methyl methacrylate . This review article summarizes about liquid crystals and their use as Colon targeted drug delivery system.

Key words: Colon drug delivery system, Liquid crystals, Inflammatory bowel disease, Eudragit.

INTRODUCTION

In 1888, the study of liquid crystals began when an Austrian botanist Friedrich Reinitzer observed that a material named Cholesteryl benzoate had two distinct melting point.

The state of the matter existing between the liquid and the crystalline solid, characterized by anisotropy of properties without the existence of a three dimensional crystal lattice is called liquid crystals. It is basically a thermodynamic stable phase.

A. Properties of liquid crystals:

- Liquid crystal substances are unique in their characteristics and uses.
- Rod like molecular structure .
- Rigidness of the long axis.
- Strong dipole or easily polarisable substituents.
- Tendency of the substances to point along a common axis, called the director.

B. Characterizing of liquid crystals:

There are mainly three parameters which describe structure of the liquid crystalline:

i. Orientational order: Measurement of the tendency of the substances to align along the director on a long range basis is done by orientational order.

ii. Positional order: The extent to which the position of an average substance or group of substances displays translational symmetry.

iii. Bond orientational order: Shows a line joining the centers of nearest neighbour substances without requiring a regular spacing along that line.

C. Phases of liquid crystals

Liquid crystals have mainly two types of phases:

i. Nematic phases

Substances that have no positional order but tend to point in the same direction (along the director) are known as nematic phases. A very special class of nematic liquid crystals are exist called Chiral nematic.

There are mainly two types of nematic phases in the liquid crystals.

- Nematic discotic phase

a. Discs nearly parallel
b. Statistical distribution of centers of molecules.

- Nematic columnar phase

a. Discs columnar orientated
b. No positional order.

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ii. Smectic phases

The term "Smectic" is arises from the Greek word for soap. Another distinct mesophase of liquid crystal substances is called smectic phase. In this phase, substances display a degree of translational order not present in the nematic.

There are mainly three types of smectic phases in the liquid crystals.

- Smectic –A mesophase

Here, director is perpendicular to the smectic plane.

- Smectic –B mesophase

In this mesophase , orientation with the director perpendicular to the smectic plane is occurs.

- Smectic – C mesophase

Substances are arranged as in the smectic-A mesophase.

D. Steric theory of liquid crystals

- Mesogens are modelled as rigid rods ,that is no interpenetration occurs.
- Central objective of this theory is the determination of the number of ways of arranging a population of rods at a particular concentration in a given volume.
- Equation-

$S=k \ln z$

{z= partition function}(1-3).

E. Anisotropy in liquid crystals:

- Anisotropy in liquid crystals include

a. Optical anisotropy

b. Viscosity

- Liquid crystals are the anisotropic substances.
- Their physical characteristics are vary with the average alignment with the director.
- Large alignment – very anisotropic
- Small alignment – almost isotropic(4).

F. Classification of liquid crystals

Liquid crystals are classified into:

- Thermotropics:

Rod like or disk like small organic molecules, which display mesomorphic behaviour as a function of temperature.

- Lyotropics

Mixtures of organic substances which display mesomorphic behaviour as a function of concentration of one or more of the molecular species in the mixture,as well as temperature.

G. Identification of liquid crystals

It includes:

- Optical polarizing microscope
- DSC
- X-ray crystallography
- Miscibility studies
- Neutron scattering studies
- Nuclear magnetic resonance

H. Computer Simulation of liquid crystals:

A well established method to study liquid crystalline mesophase is known as computer simulation. It involves:

- Molecular dynamics technique.(numerical technique)
- Monte carlo technique.

I. Texture and topological defects in liquid crystals

Patterns in the orientation of liquid crystal substances which arise due to their enforced orientation in the vicinity of a surface are known as textures.

There are so many topological defects occur in the liquid crystals. Defects of distortions yielding, are easily produced through control of boundary conditions, surface geometries and external fields.

These defects are imaged optically. Screw dislocations are the simple defect structures in smectic liquid crystals.

J. Applications of liquid crystals:

Applications of liquid crystals are as follows

Fig 1. Liquid crystal displays

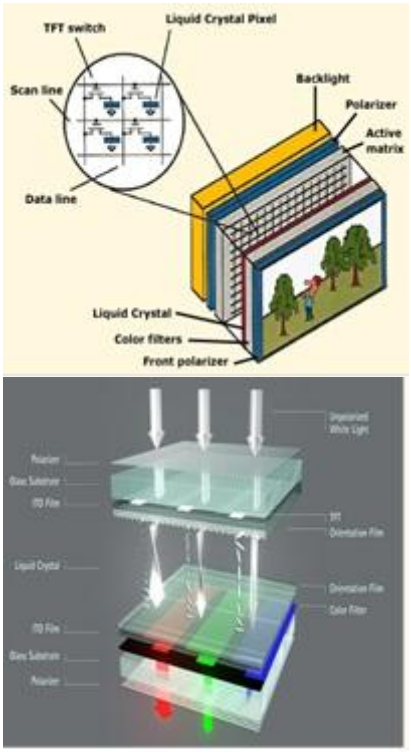


Fig 2. Liquid crystal thermometer

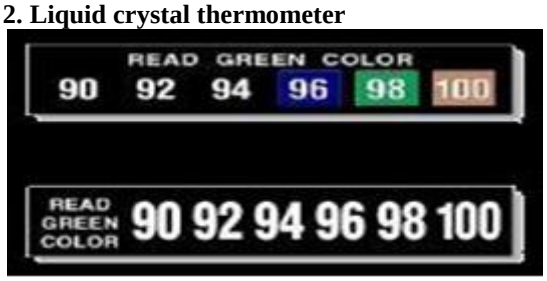


Fig 3. Optical imaging

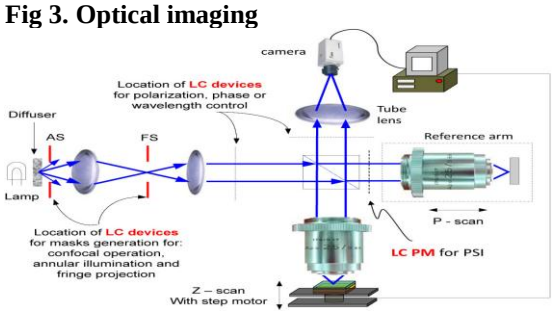
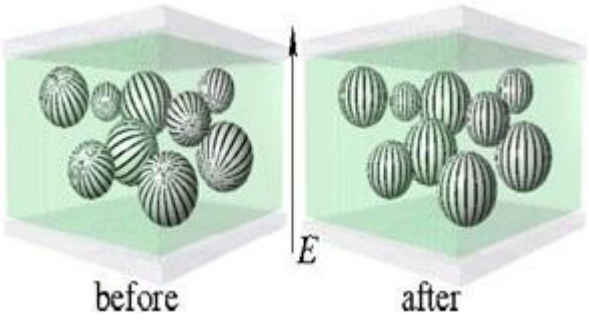


Fig 4. Polymer dispersed liquid crystals



- Other medical applications(5-6).

K. Cubic liquid crystal as drug delivery system:

It includes:

1. Ability to sustain or control drug release.
2. Ability to improve drug bioavailability and reduce drug toxicity.
3. Ability to enhance the stability of drugs.
4. Ability to increase the penetration of drugs.

L. Hexagonal liquid crystals as drug delivery system:

It includes:

1. Applications of OG-Based and PG-Based hexagonal phase
2. Ability to increase the penetration of drugs
3. Application in stimuli responsive drug delivery system(7).

Colon targeted drug delivery

A. General aspect

Aim of any drug delivery system is to supply a therapeutic amount of drug to a target organ, so that the concentration of the drug can be swiftly achieved and then maintained. A targeted drug delivery system is preferred in drugs having low therapeutic index and low solubility.

A drug delivery system which is used to deliver the substances that are degraded by the digestive enzymes in the stomach like-proteins, peptides is known as colon targeted drug delivery system.

B. Advantages of colon targeted drug delivery

- Reduce the side effects in the treatment of colon diseases.
- Minimizes first pass metabolism.
- Enhanced patient compliance.
- Used for chronotherapy.
- Decreases dosage frequency.

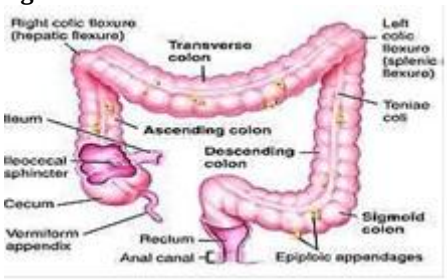
C. Disadvantages of colon targeted drug delivery:

- Manufacturing steps are multiple.
- Drug release incomplete.
- Poor site specificity.

D. Anatomy and physiology of colon:

- Entire colon is about 150 cm long.
- It is divided into five major segments.
- Ascending and descending colon.
- Right colon contains cecum, ascending colon, hepatic flexure and the right half of the transverse colon.
- Left colon consists of the left half of the transverse colon, descending colon , splenic flexure and sigmoid.

Fig 5. Diagram



E. Functions of colon:

- It forms suitable environment for the growth of colonic microorganisms.
- Fecal contents storage reservoir.
- Eviction of the contents of the colon.
- To secrete **k**+ and HCO3-

F. Colon targeted diseases and drugs:(Table-1)

Target sites	Diseases	Drugs
Topical action	Inflammatory& Irritable bowel diseases	Hydro cortisone Mesalazine
Local action	Cystic fibrosis Colorectal cancer	5-fluorouracil
Systemic action	To prevent gastric irritation To prevent first pass metabolism	NSAIDS

G. Factors affecting colon targeted drug delivery

1) Physiologic factors:

- Gastric emptying
- PH of the colon
- Colonic microflora and enzymes

2) Pharmaceutical factors

- Drug candidates
- Drug carriers

H. Approaches for colon targeted drug delivery:

Primary approaches

It includes

- PH sensitive polymer coated drug delivery system
- Delayed release drug delivery system
- Microbially triggered drug delivery

➢ Prodrug approach

➢ Polysaccharide based system

Newer approaches:

It includes:

- Pressure controlled drug delivery system
- CODE

- OROS-CT
- Pulsatile
  - Pulsincap system
  - Port system
- Azo hydrogels
- Multi particulate system based drug delivery.

I. Evaluation of colon targeted drug delivery system:

- In-vitro evaluation:
  - In-vitro dissolution (conventional basket method)
  - In-vitro enzymatic test
- In-vivo evaluation:
  - Animal models (8-10).

Why colon targeted drug delivery?

Colonic delivery offers several potential therapeutic advantages as a site for drug delivery,

(a) The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery.

(b) The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability.

(c) The colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.

(d) Reduced proteolytic activity in the colon may be helpful in achieving reasonable absorption of certain drugs that are enzymatically labile in small intestine.

(e) Reduced fluid motility and motility in the colon when compared with small intestine is advantageous formulation consists of multiple components such as permeation enhancers that must reach epithelial layer to achieve close spatial proximity with each other.

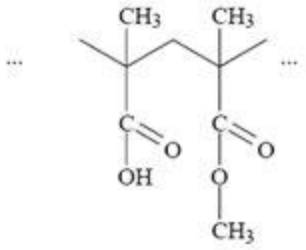
(f) The colonic region has somewhat less hostile environment with less diversity and less intensity of activity as compared to stomach and small intestine.

Application of liquid crystal in CTDDS

LCs have generated considerable alertness over the years as a potential drug delivery vehicle. The coexistence of organic and aqueous phase by means of a structurally well-defined micellar network of surfactants, a large interfacial area, and the possibility to entrap solutes within the gel matrix, along with long-term stability, makes them valuable for a variety of applications. Therapeutic compounds of diverse physicochemical properties such as analgesics, antibiotics, antifungal, anticancer, vitamins, anti asthmatic, immunosuppressive etc. have been either incorporated or itself used for the formation of the LCs with some very encouraging results.

Procedure of preparing LC'S for CTDDS

The drugs to be used as CTTDS are firstly brought into the LCs stage, then it is coated in the form of microspheres with the help of Eudragit® S100 (Strure-1) which is an anionic copolymers based on methacrylic acic and methyl methacrylate



Eudragit® S100.(Structure-1)

Targeted Drug Release Area: Colon delivery

Dissolution: pH 7.0

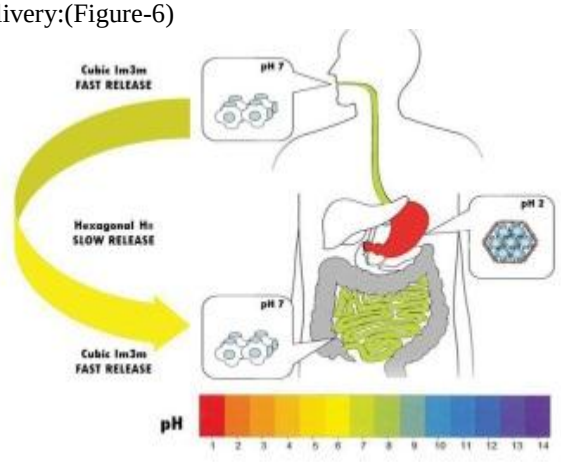
Characteristics:

- Granulation of drug substances in powder form for controlled release
- Effective and stable enteric coatings with a fast dissolution in the upper Bowel
- Site specific drug delivery in intestine by combination with EUDRAGIT® S grades
- Variable release profiles

Coating process

The coating is done basically with the help of emulsion method. The film coated above the microspheres containing the LCs having the thickness of (10-50μm). This helps the microspheres containing the drug in form of LCs to be released in Conlon at pH 7.0 only, after surpassing the acidic environment of the stomach having pH 1.3 for 2 hrs and then staying for sometimes in the small intestine having the pH of 7.4(11-14).

Overall diagram of liquid crystal for colon targeted drug delivery:(Figure-6)



CONCLUSION

Liquid crystalline structures provide a wide varied of structural and functional features. They keep ability to encapsulate hydrophobic and hydrophilic drug(s). It appears that these attributes can be advantageously utilized in colon targeted drug delivery challenges, making surfactant based drug delivery system a successful approach. This are required for drugs currently in use to treat localized diseases of the colon. The advantages of targeting drugs specifically to the diseased colon are reduced incidence of systemic side effects, lower dose of drug, supply of the drug to the

biophase only when it is required and maintenance of the drug in its intact form as close as possible to the target site. Challenges related to manufacturing, stability, and reproducibility has been overcome.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

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