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# Emerging Trends Of Liquid Crystalline Nanoparticles Drug Delivery For Pulmonary Disorders

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***ABSTRACT***

***In this era of nanotechnology lyotropic liquid crystalline nanoparticles (cubosomes) are relatively less explored lipid-based nanocarriers that can be formulated selectively and specificity for almost all administration routes. The natural compounds are proved to be significantly curative in pulmonary diseases due to reported anti-oxidant, anti-inflammatory and immunomodulatory activities. The natural products have limited bioavailability due to either hydrophilic or low water solubility. These limitations can be overcome by using a novel nanotechnology such as cubosomes or liquid crystalline nanoparticles (LCNs). LCNs can easily encapsulate both hydrophilic and hydrophobic compounds because of the amphiphilic nature of lipid monoolein (MO). LCN can be used to co-deliver synthetic and natural compounds irrespective of their solubility due to multi-compartment structure. We can use LCNs to formulate drugs of synthetic origin with natural one to overcome multidrug resistance (MDR).***

***Keywords: Cubosomes, liquid crystalline nanoparticles, monoolein, pulmonary diseases, multidrug resistance, lipid nanocarrier.***

## 1. INTRODUCTION

The present article focuses on emerging trends in novel drug delivery technologies with special emphasis on lyotropic liquid crystalline nanoparticles (cubosomes). Out of current available novel drug delivery carrierlipid-based nanocarriersare less explored and diverse in term of drug loading of versatile drug molecules. Many aspects of LCNs are still to be clarified related to pharmacokinetics and pharmacodynamics (Murgia, Biffi, & Mezzenga, 2020).

Most of pulmonary diseases lead to death because available allopathic drugs provide symptomatic relief. The natural compounds are proved to be significantly curative due to

reported anti-oxidant, anti-inflammatory and immunomodulatory activities(Sharma *et* al., 2019; Saggu *et al.*, 2014). The natural products have limited bioavailability due to either hydrophilic or low water solubility(M. Mehta et al., 2020; Thakur et al., 2020). The currently available treatments for pulmonary diseases have many limitations such as target delivery, ill-effects. There is a immediate need of emerging novel drug delivery system for target and extended release of anti-inflammatory and antioxidants (Dua, Wadhwa, et al., 2019).

In recent years, various efforts have been taken by researchers in the field pulmonary diseases to target synthetic, natural and biological entities. Nanocarriers such as liposomes and nanoparticles have been encapsulated for target delivery of siRNA and miRNA (oligonucleotides) for respiratory diseases (M. Mehta et al., 2019). In another study on respiratory diseases Dua *et al.* have suggested novel drug delivery systems for tuberculosis regimens to overcome patient compliance and toxicity issues. They proposed use of liposomes and lipid nanoparticles to encapsulate existing drug regimens for extended release drug delivery (Dua et al., 2018).
Despite the promising anticancer potential of curcumin, its therapeutic application has been limited, owing to its poor solubility, bioavailability, and chemical fragility (Yong et al., 2019). Crocins available in saffron have shown many activities for respiratory diseases but limited applications due to hydrophilic nature. These limitations can be overcome by using a novel nanotechnology such as cubosomes or liquid crystalline nanoparticles (LCNs). LCNs can easily encapsulate both hydrophilic and hydrophobic compounds because of the amphiphilic nature of lipid monoolein (MO). The dispersion of MO in aqueous phase lead to self-assemble bicontinuous cubes which are well ordered (Mahesh *et al.,* 2014; Mehta *et al*. 2016, Mishra *et al.*, 2018). Poloxamer (P407) is used to stabilize dispersion of LCNs. LCNs have exceptionally higher drug loading capacity along with bioadhesive nature and extended release properties to encapsulate wide range of drugs(Dua, Malyla, et al., 2019). Further surface modification of LCNs with hydrophilic polymers can also be possible to increase muco adhesion and cellular uptake for enhanced bioavailability (Table 1).

*Evidences supporting need of nanoparticles drug delivery*
Quercetin a natural flavonoid commonly found in many plants, have numerous reported activities such as anti-oxidant, anti-inflammatory, anti-bacterial, anti-diabetic and anti-cancer (D'Andrea, 2015). It has been reported that quercetin significantly reduce LPS- induced inflammation by inhibiting migration and adhesion of macrophages. As quercetin is hydrophobic in nature its applications are limited due to poor intestinal absorption and bioavailability (Cui et al., 2019)**.**
Yong *et al* investigated anti-inflammatory activity of quercetin loaded LCN and sm-LCN using lipopolysaccharide (LPS) induced human primary bronchial epithelial cell line (BCi-NS1.1). The study showed quercetin encapsulated LCNs significantly enhanced anti-inflammatory activity due to bio-adhesive and cell membrane permeability of lipid bilayer of LCNs when compared to quercetin solution in DMSO. The cell membrane permeability in turn resulted in more drug uptake resulted in increased bioavailability (Yong et al., 2019).

Fisetin (FIS) one of the active constituents found in *Cotinus coggygria* tree has various pharmacological activities like anti-oxidant, anti-inflammatory, hypoglycaemic and anti-cancer. FIS has poor bioavailability because of its hydrophobic nature. There are many drug delivery systems have been developed to overcome these limitations, but current study emphasized on LCNs as a drug delivery system for FIS. FIS-LCNs found to have improved pharmacokinetic properties resulted in better bioavailability of active constituent (P. Mehta, Pawar, Mahadik, & Bothiraja, 2018).

Baskaran *et al.* have formulated an aqueous dispersion of curcumin with an MO nanotechnology by dissolving the drug into a solubilizer at the beginning of the preparation procedure, followed by the classic method of preparation of LCN. PEG 400 and RH 40 were found to be best solubilizers because ethylene oxide moiety in both formed hydrogen binding with hydrogens in -OH of the curcumin molecule. This resulted in 100% entrapment of curcumin into an MO-based LCN. The extended release of curcumin was confirmed by stable size and surface charge of LCN dispersion. This study proposed that LCN prepared by MO lead to stable formulation with increased entrapment facilitate cellular uptake for pulmonary drug delivery (Baskaran, Madheswaran, Sundaramoorthy, Kim, & Yoo, 2014).
In another study Abdelaziz *et al*. have prepared LCNs loaded with combination of two anti-cancer drugs, one from natural origin and second from chemical. The LCNs so prepared loaded with resveratrol (RSV) and pemetrexed (PMX) showed improved entrapment efficiency and extended release of active constituents. PMX-RSV-LCNPs release drug upto 24 hours that resulted in reduced systemic toxicity. *In vitro* study showed improved cytotoxic activity due to bioadhesive nature and increased cellular uptake of PMX-RSV-LCNPs by A549 lung cancer cell lines. These effects were confirmed by in vivo experimentation on lung cancer induced mice (Raza *et al*., 2015). The histopathological and immunohistochemical profiles of mice showed reduced toxicity and improved anti-cancer effects of · PMX-RSV-LCNPs as compared to free drugs(Abdelaziz et al., 2019).

Li *et al* have reported oil of *Brucea javanica* (BJO) and doxorubicin (DOX) loaded LCNs as a therapeutic intervention to treat cancer. BJO has been used as traditional herbal medicine to treat various cancer. It arrests proliferation and metastasis of various tumours. Doxorubicin is very effective anti-cancer candidate acts by inhibition of DNA replication and renders protein synthesis. DOX has a limitation of dose-dependent cardiotoxicity which can be checked by targeted and co-delivery with another molecule. BJO and DOX loaded LCNs proved to be more cytotoxic and capable of reversal of DOX resistance when studied using MCF-7 and DOX resistant MCF-7. Furthermore, researchers showed pH induced phase transition of nanocarriers to maximise therapeutic effects (Li et al., 2019).

Polyphenols obtained from Cornelian cherry (*Cornus mas L.*) have reported antioxidant, anti-cancer and anti-inflammatory activities. Various studies showed that most of anthocyanins responsible for activities degrade in gastrointestinal tract only unchanged portion cross intestinal mucosa and reach systemic circulation. These limitations can be overcome by target delivery and LCNs (cubosomes) found to be excellent option. A study has been conducted on *Cornus mas* extract (CME) loaded LCNs and *Cornus mas* extract (CME) to compare antioxidant activity of polyphenols. The Folin Ciocalteu assay showed that CME loaded LCNs have higher content of polyphenols even after storage of 60 days as compared to CME. This study suggested higher antioxidant activity of CME loaded LCNs. Furthermore researchers have reported enhanced anti-cancer activity of CME encapsulated LCNs when tested on HT-29 human colon carcinoma cell line (Radbeh, Asefi, Hamishehkar, Roufegarinejad, & Pezeshki, 2020).

## 2. CONCLUSION

This review mainly considers the latest researches and importance of liquid crystalline nanoparticles as a proficient drug delivery carrier. In addition, it also takes into account the LCNs specific to pulmonary diseases. It has been found from latest literature view that LCNs are very efficient in encapsulation and delivery of natural as well as synthetic molecules. This is the fact that natural products are curative in nature and exert synergistic effects when used in extract form instead of isolated bioactives. In nearest future liquid crystalline

nanotechnology will be the game changer to encapsulate and target delivery of natural products for cure of highly mortal diseases. Furthermore, LCN can be used to co-deliver synthetic and natural compounds irrespective of their solubility due to multi-compartment structure. We can use LCNs to formulate drugs of synthetic origin with natural one to overcome multidrug resistance (MDR). It has been obvious now that LCNs can load wide varieties of compounds to target tissues from almost every route of administration. The latest studies related to LCNs have been compiled in (Table 1.) for further references.

Table 1. Showing latest liquid crystalline nanocarriers studies

| S. No. | Polymers | Active ingredient | Disease | Study | Reference |
|---|---|---|---|---|---|
| 1 | Monoolein | Quercetin | Asthma | Anti-inflammatory activity of quercetin loaded LCN and sm-LCN using lipopolysaccharide (LPS) induced human primary bronchial epithelial cell line (BCi-NS1.1) | (Yong et al., 2019) |
| 2 | PEG 400, RH 40 and MO | Curcumin | Cancer | Curcumin loaded LCNs showed improved cellular uptake by HCT116 in comparison with curcumin dissolved in DMSO. The proposed mechanism was found to be endocytosis. | (Baskaran et al., 2014) |
| 3 | Glyceryl Mono-Oleate (GMO) or MO | Curcumin | NA | Curcumin loaded LCNs improved the extended release properties as compared to curcumin in propylene glycol. Further Cur-LCNs showed 395.56% relative bioavailability when compared to curcumin suspension. | (He, Li, Liu, Wu, & Zhai, 2015) |
| 4 | MO | Gambogenic acid | Cancer | Gambogenic acid loaded LCNs showed improved cellular uptake by SMMC-7721 in comparison with gambogenic solution. Furthermore, GNA-LCNs showed enhanced bioavailability along with extended release *in vitro*. | (Luo et al., 2015) |
| 5 | MO | Pemetrexed (PMX) and resveratrol (RSV) | Lung cancer | Pemetrexed (PMX) and resveratrol (RSV) loaded LCNs have enhanced cytotoxicity due to increased cellular uptake by A549 lung cancer cells. | (Abdelaziz et al., 2019) |
| 6 | MO | Oil of *Brucea javanica* (BJO) and doxorubicin | Cancer | BJO and DOX loaded LCNs proved to be more cytotoxic and capable of reversal of DOX resistance when studied using MCF-7 and DOX resistant MCF- | (Li et al., 2019) |

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|---|---|---|---|---|---|
| | | (DOX) | | 7. | |

## 2. REFERENCES:

[1] Abdelaziz, H. M., Elzoghby, A. O., Helmy, M. W., Samaha, M. W., Fang, J.-Y., & Freag, M. S. (2019). Liquid crystalline assembly for potential combinatorial chemo–herbal drug delivery to lung cancer cells. *International journal of nanomedicine, 14*, 499.

[2] Baskaran, R., Madheswaran, T., Sundaramoorthy, P., Kim, H. M., & Yoo, B. K. (2014). Entrapment of curcumin into monoolein-based liquid crystalline nanoparticle dispersion for enhancement of stability and anticancer activity. *International journal of nanomedicine, 9*, 3119.

[3] Cui, S., Wu, Q., Wang, J., Li, M., Qian, J., & Li, S. (2019). Quercetin inhibits LPS-induced macrophage migration by suppressing the iNOS/FAK/paxillin pathway and modulating the cytoskeleton. *Cell Adh Migr, 13*(1), 1-12. doi:10.1080/19336918.2018.1486142

[4] D'Andrea, G. (2015). Quercetin: A flavonol with multifaceted therapeutic applications? *Fitoterapia, 106*, 256-271. doi:10.1016/j.fitote.2015.09.018

[5] Dua, K., Malyla, V., Singhvi, G., Wadhwa, R., Krishna, R. V., Shukla, S. D., . . . Hansbro, P. M. (2019). Increasing complexity and interactions of oxidative stress in chronic respiratory diseases: An emerging need for novel drug delivery systems. *Chem Biol Interact, 299*, 168-178. doi:10.1016/j.cbi.2018.12.009

[6] Dua, K., Rapalli, V. K., Shukla, S. D., Singhvi, G., Shastri, M. D., Chellappan, D. K., . . . Hansbro, P. M. (2018). Multi-drug resistant Mycobacterium tuberculosis & oxidative stress complexity: Emerging need for novel drug delivery approaches. *Biomed Pharmacother, 107*, 1218-1229. doi:10.1016/j.biopha.2018.08.101

[7] Dua, K., Wadhwa, R., Singhvi, G., Rapalli, V., Shukla, S. D., Shastri, M. D., . . . Chellappan, D. K. (2019). The potential of siRNA based drug delivery in respiratory disorders: Recent advances and progress. *Drug Dev Res, 80*(6), 714-730. doi:10.1002/ddr.21571

[8] He, X., Li, Q., Liu, X., Wu, G., & Zhai, G. (2015). Curcumin-Loaded Lipid Cubic Liquid Crystalline Nanoparticles: Preparation, Optimization, Physicochemical Properties and Oral Absorption. *J Nanosci Nanotechnol, 15*(8), 5559-5565. doi:10.1166/jnn.2015.10311

[9] Li, Y., Angelova, A., Hu, F., Garamus, V. M., Peng, C., Li, N., . . . Zou, A. (2019). pH Responsiveness of Hexosomes and Cubosomes for Combined Delivery of Brucea javanica Oil and Doxorubicin. *Langmuir, 35*(45), 14532-14542. doi:10.1021/acs.langmuir.9b02257

[10] Luo, Q., Lin, T., Zhang, C. Y., Zhu, T., Wang, L., Ji, Z., . . . Chen, W. (2015). A novel glyceryl monoolein-bearing cubosomes for gambogenic acid:

Preparation, cytotoxicity and intracellular uptake. *Int J Pharm, 493*(1-2), 30-39. doi:10.1016/j.ijpharm.2015.07.036

[11] Mahesh, K. V., Singh, S. K., & Gulati, M. (2014). A comparative study of top-down and bottom-up approaches for the preparation of nanosuspensions of glipizide. *Powder technology, 256*, 436-449.

[12] Mehta, C. M., Srivastava, R., Arora, S., & Sharma, A. K. (2016). Impact assessment of silver nanoparticles on plant growth and soil bacterial diversity. *3 Biotech, 6*(2), 254.

[13] Mehta, M., Deeksha, Tewari, D., Gupta, G., Awasthi, R., Singh, H., . . . Satija, S. (2019). Oligonucleotide therapy: An emerging focus area for drug delivery in chronic inflammatory respiratory diseases. *Chem Biol Interact, 308*, 206-215. doi:10.1016/j.cbi.2019.05.028

[14] Mehta, M., Dhanjal, D. S., Paudel, K. R., Singh, B., Gupta, G., Rajeshkumar, S., . . . Dua, K. (2020). Cellular signalling pathways mediating the pathogenesis of chronic inflammatory respiratory diseases: an update. *Inflammopharmacology*, 1-23. doi:10.1007/s10787-020-00698-3

[15] Mehta, P., Pawar, A., Mahadik, K., & Bothiraja, C. (2018). Emerging novel drug delivery strategies for bioactive flavonol fisetin in biomedicine. *Biomedicine & Pharmacotherapy, 106*, 1282-1291.

[16] Mishra, V., Bansal, K. K., Verma, A., Yadav, N., Thakur, S., Sudhakar, K., & Rosenholm, J. M. (2018). Solid lipid nanoparticles: Emerging colloidal nano drug delivery systems. *Pharmaceutics*, *10*(4), 191.

[17] Murgia, S., Biffi, S., & Mezzenga, R. (2020). Recent advances of non-lamellar lyotropic liquid crystalline nanoparticles in nanomedicine. *Current Opinion in Colloid & Interface Science*.

[18] Radbeh, Z., Asefi, N., Hamishehkar, H., Roufegarinejad, L., & Pezeshki, A. (2020). Novel carriers ensuring enhanced anti-cancer activity of Cornus mas (cornelian cherry) bioactive compounds. *Biomed Pharmacother, 125*, 109906. doi:10.1016/j.biopha.2020.109906

[19] Raza, K., Thotakura, N., Kumar, P., Joshi, M., Bhushan, S., Bhatia, A., & Katare, O. P. (2015). C60-fullerenes for delivery of docetaxel to breast cancer cells: a promising approach for enhanced efficacy and better pharmacokinetic profile. *International journal of pharmaceutics*, *495*(1), 551-559.

[20] Saggu, S., Sakeran, M. I., Zidan, N., Tousson, E., Mohan, A., & Rehman, H. (2014). Ameliorating effect of chicory (Chichorium intybus L.) fruit extract against 4-tert-octylphenol induced liver injury and oxidative stress in male rats. *Food and chemical toxicology*, *72*, 138-146.

[21] Sharma, A., Shahzad, B., Kumar, V., Kohli, S. K., Sidhu, G. P. S., Bali, A. S., & Zheng, B. (2019). Phytohormones regulate accumulation of osmolytes under abiotic stress. *Biomolecules*, *9*(7), 285.

[22] Thakur, A. K., Chellappan, D. K., Dua, K., Mehta, M., Satija, S., & Singh, I. (2020). Patented therapeutic drug delivery strategies for targeting pulmonary diseases. *Expert Opin Ther Pat*(just-accepted), 1-13. doi:10.1080/13543776.2020.1741547

[23] Yong, D. O. C., Saker, S. R., Wadhwa, R., Chellappan, D. K., Madheswaran, T., Panneerselvam, J., . . . Pillay, V. (2019). Preparation, characterization and in-vitro efficacy of quercetin loaded liquid crystalline nanoparticles for the treatment of asthma. *Journal of Drug Delivery Science and Technology, 54*, 101297.