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Research Article

Solubility enhancement of meloxicam by phospholipid complexation

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Abstract

The best solubility enhancement approach is phospholipids complexation. It has been effectively employed by a number of writers to enhance the permeability, oral bioavailability, and solubility of several medicinal substances. The meloxicam is a member of BCS Class II, and because of its poor solubility and high permeability, its clinical application may have been constrained. Therefore, it is necessary to use a method that modifies the biopharmaceutical features. In this work, meloxicam, an NSAID with demonstrated anticancer action, was combined with phospholipid to increase its solubility. Utilizing solvent evaporation, the meloxicam phospholipid complex was produced. Particle size, zeta potential, SEM analysis, in vitro drug release, and solubility were assessed for the produced complex. The results obtained in this study showed the smaller particle size in nanometer range and physical stability with desired zeta potential. Meloxicam's prolonged release from the phospholipid complex is demonstrated by the in vitro drug release investigation. The apparent solubility analysis of meloxicam phospholipid complex. Pure meloxicam showed that the drug's solubility was several times higher than that of the pure form. Hence in conclusion we can say that the phospholipid complexation could be the ideal method for solubility enhancement of drug like meloxicam.

Keyword: Meloxicam, phospholipid complex, solubility, drug release

INTRODUCTION

Meloxicam (MLX) and other non-steroidal anti-inflammatory medicines (NSAIDs) selectively inhibit the COX-2 enzyme's inducible isoform. The catalyst is the prostaglandin synthesis enzyme COX-2, which has been well investigated for its possible connection to the onset of cancer. It influences apoptosis, angiogenesis, and is connected to the creation of carcinogens.[1, 2] MLX which is a member of BCS class II, has demonstrated anticancer efficacy. [3] MLX is a medication that is commonly used to treat inflammation and is taken orally in the form of a regular tablet. The limited aqueous solubility of MLX, however, placed some restrictions on its clinical usage in cancer therapy. Even yet, after the MLX's solubility was improved, the increased permeability might be advantageous. The amount of literature on the use of MLX in cancer treatment was quite restricted. Therefore, it is necessary to investigate MLX's potential as a cancer treatment. Additionally, designing the job is necessary to increase MLX's solubility.

The phospholipids complexation method is the most effective way for increasing solubility[4], and multiple authors have used it to successfully increase the solubility, permeability, and oral bioavailability of plant bioactives and extracts. Phospholipon® 90H, the system's major component, functions in a manner akin to that of plasma membrane phospholipids. [5, 6] The phosphate (+) charged Phospholipon® 90H can successfully interact with any lipophilic drug's polar components to create an amphiphilic molecule.[7]

In the current study, an effort was made to increase the solubility of meloxicam. Based on the phospholipid complex system's beneficial solubility enhancing effects, it is classified as BCS class II. Therefore, the development and evaluation of the meloxicam-phospholipid complex for solubility augmentation was the study's main objective.

MATERIAL AND METHODS

Ramdev Chemicals Pvt. Ltd., Thane, (Maharashtra), India, gave us meloxicam (MLX) as a gift sample. We purchased Phospholipon® 90H from Lipoid GmbH In Ludwigshafen, Germany. Analytical grade chemicals and other reagents were used.

Preparation of MLX-phospholipid Complex

Meloxicam-phospholipid complex was synthesized by modifying a method for solvent evaporation that had previously been described.[7, 8] A solution of 1.5 mL of DMSO and 2 mL of chloroform was used to dissolve about 100 mg of MLX. About 100–300 mg of Phospholipon® 90H were added to this solution, and 1,4-dioxane was then added to further dissolve it. The entire mixture was then refluxed for 4-6 hours on a water bath at 60 to 70 °C. After being heated in a water bath, the reaction mixture was let to condense. Approximately 3–4 mL of n-hexane were added to this saturated mixture. The next day, the supernatant was decanted and dried at room temperature. Stored and used for additional examination.

Physicochemical analysis

Particle size and zeta potential

The formulated MLX phospholipid complex's particle size and size distribution were assessed using the DLS-based technique. .[9] In brief, 5.0 milligram dried MLX phospholipid complex was transferred and distributed using cuvetes-containing de-ionized water. At 25 °C, measurements were taken with this within the Malvern Zetasizer instrument chamber. Using a Malvern Zetasizer nano sizing device, the zeta potential of the MLX phospholipid complex was calculated between the ranges of -200 and +200 mV.[10, 11]

FTIR spectroscopy

In a nutshell, pre-treatment was applied to the MLX and MLX phospholipid complex sample before FTIR analysis. These materials were mixed evenly with potassium bromide (KBr) of FTIR grade in a 1:100 ratio. After that, these were analysed using 45 scans at a resolution of 4 cm-1, covering a range of 4,500 to 400 cm^{-1} .[12]

Scanning electron microscopy

Examining the morphological structural properties has been done using scanning electron microscopy (SEM). On a specimen tab, a little amount of the MLX phospholipid complex was put before being transferred to a slide. The sample was prepared for SEM microscopic examination after palladium coater was applied.[13] Then, SEM images were taken utilising a Carl Zeiss lens and a JEOL scanning electron microscope.

In vitro drug release study

The in vitro drug release study was conducted using the approach outlined in previous publications.[14] In a nutshell, the Franz diffusion cell (donor compartment) was filled with an aqueous suspension of the MLX phospholipid complex. The pH 7.4 phosphate buffer saline was poured into the receptor compartment. The donor and receptor chambers of the diffusion cell were placed apart by the dialysis membrane. An aqueous solution containing 20 mg of MLX phospholipid complex powder, which is equivalent to 10 mg of medicine, was injected into the donor compartment. Periodically, samples from the side arm were taken, and an equivalent volume of pH 7.4 PBS was added to the medium to restore it. The collected samples were measured with a UV spectrophotometer at 362 nm.

Solubility analysis of phospholipid complex

The concentration of the material in the solvent at super-saturation equilibrium is indicated by the apparent solubility. Using a modified approach that was previously published, we investigated the apparent solubility of MLX and the MLX phospholipid complex in this study. .[6, 7] To make a dispersion, approximately 5 mg of MLX and MLX phospholipid complex were combined with 5 mL of clean water and n-hexane. This was centrifuged for 30 minutes at 4000 RPM after being constantly mixed for 24 hours at 25°C. Centrifugation was used to extract the supernatant. The collected supernatant was then filtered using a membrane filter (0.45) to eliminate any insoluble particle debris. After the filtrate was filtered and diluted with DMSO, the concentration of Mlx at 362 nm was measured using a UV-spectrophotometric technique.

RESULT AND DISCUSSION

Physicochemical characterization

Previous studies showed that the micro-sized particles of the original drug or material were substantially less bioavailable than the particles with a size between 200 and 400 nm.[15, 16] Zetasizer measurements showed that the particle size of the MLX phospholipid complex was approximately 122 nm. However, it was found that the zeta potential of the MLX phospholipid complex was 35.8 mV, which is lower than 30 mV. It proved the remarkable physical stability of the MLX phospholipid complex .[17, 18] The zeta potential likewise rises as the surface charge does .[19]

FTIR analysis

The NH_2 scissoring vibrations band is at or near 1619 cm^1, the secondary amine stretching band is at or near 1550.04 and 1530.36 cm^1, the C-N stretching band is at or near 1550.04 and 1530.36 cm^1, and the S-O stretching band is at or near 1346.73, 1265.88, and 1183 cm^1 as shown in figure 1A.

According to figure 1B, FTIR spectrum of MLX phospholipid complex shows peaks with similar stretching frequencies and negligible shifts from 3285.45, 1616.88, and 1061.17 cm^{-1} demonstrated the low intermolecular interaction between MLX and phospholipid. The overall FTIR result was interpreted as indicating that the ingredients used to prepare the MLX phospholipid complex did not interact and found to be compatible.

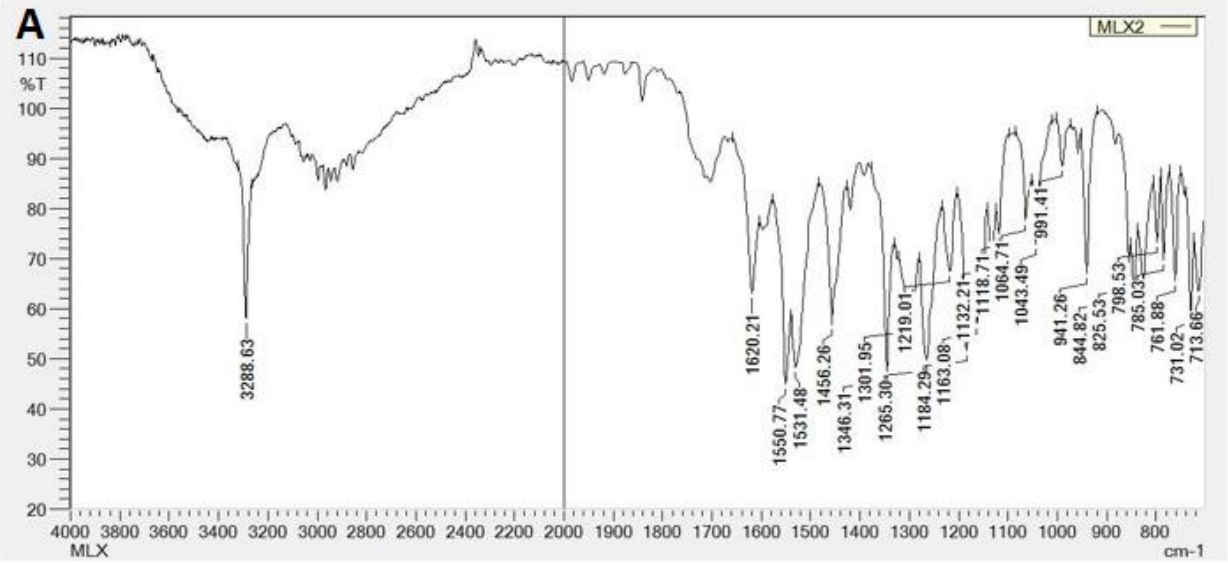

Figure1(A): FTIR spectra of Meloxicam

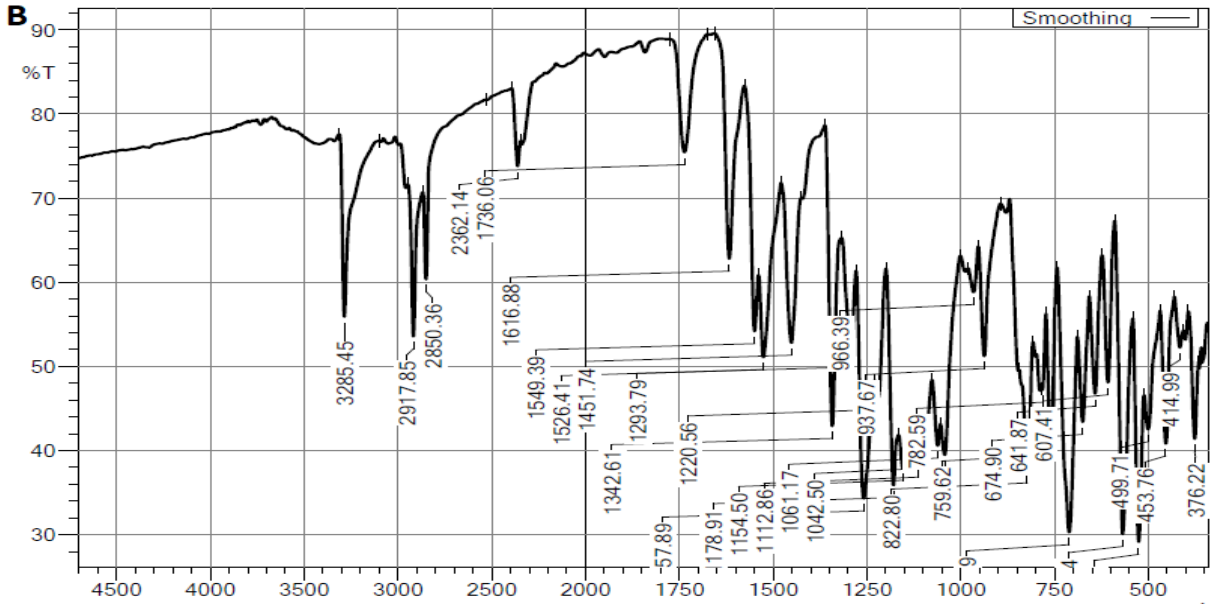

Figure1(B): FTIR spectra of Meloxicam-phospholipid complex

Scanning electron microscopy

SEM was used to study the surface morphology of the MLX phospholipid complex, and structural features were found by looking at SEM pictures, as figure 2 illustrates. The rough surface of the MLX phospholipid complex is shown in this picture. A solvent or other fluid could reach the porous surface of the complex and begin the solubilization process.

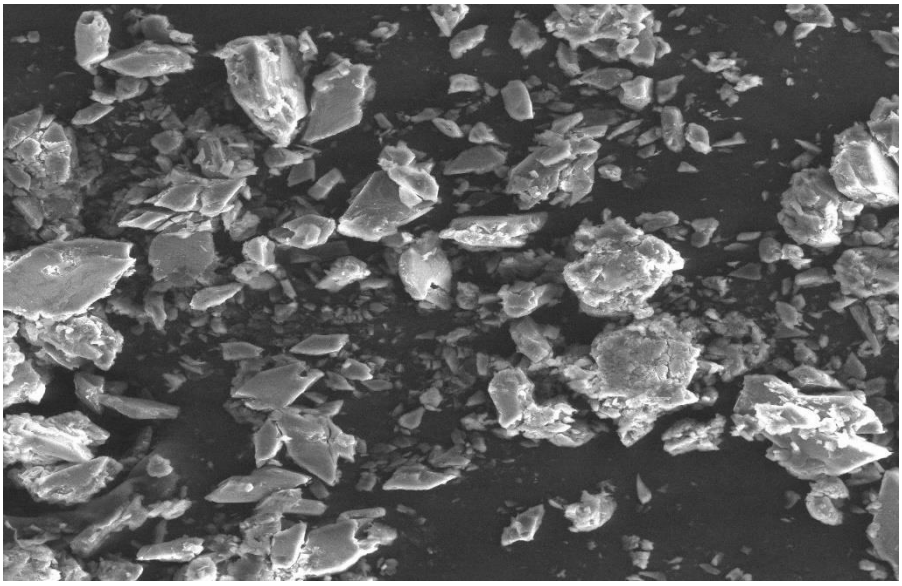

Figure 2: Scanning electron microscopic images of MLX phospholipid complex showing rough surface

***In vitro* drug release study**

A buffer pH 7.4 was used for the drug release study of MLX from the MLX phospholipid complex and MLX solution. The findings of this investigation showed that the initial burst release of MLX was determined to be around 26% in the first two hours, and the 94% release of MLX was recorded after 72 h. However, as seen in the figure 3, MLX solution releases around 94% of the drug in just 6 hours. Therefore, based on these findings, we can say that drugs are released under controlled conditions over a longer period of time .[20, 21]

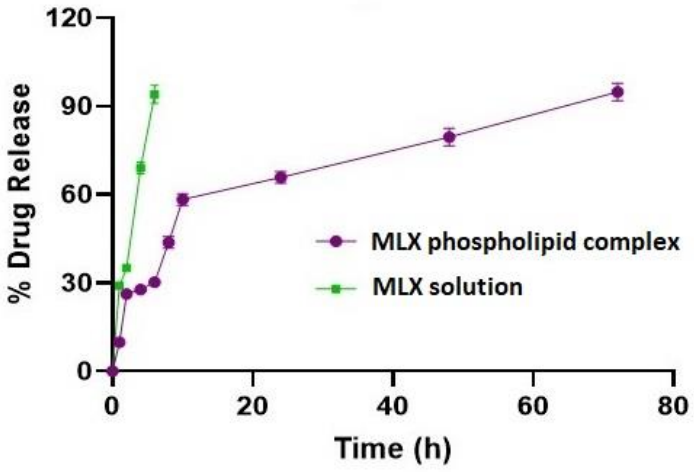

Figure 3: % Drug release from MLX phospholipid complex in 72 h

Apparent solubility analysis

A study on the solubility of MLX and the MLX phospholipid complex in water and other organic solvents revealed improved solubility. In comparison to the MLX, the MLX phospholipid complex exhibits improved solubility and dissolving behavior .[22] After creating the MLX phospholipid complex, the solubility of MLX was shown to have risen many folds.

CONCLUSION

The MLX phospholipid complex was made using the solvent evaporation method. The production of phospholipid complexes may increase a medicine's solubility if it is just marginally soluble in water. Compared to pure MLX, the produced MLX phospholipid complex dissolves more readily in water. The improved MLX phospholipid complex showed reduced particle size and prolonged drug release over a 72-hour period. The overall findings of this investigation demonstrated the superb potential of phospholipid complex for improving solubility.

CONFLICT OF INTEREST

Authors declared no conflict of interest.

REFERENCES

1. Rarokar N, Gurav S, Khedekar P. Meloxicam encapsulated nanostructured colloidal self-assembly for evaluating antitumor and anti-inflammatory efficacy in 3D printed scaffolds. Journal of Biomedical Materials Research Part A. 2021 Aug;109(8):1441-56. https://doi.org/10.1002/jbm.a.37135 PMid:33289225

2. Abdulateef SA, Hussein MH, Al-Saffar AZ. In vitro cytotoxic and genotoxic of lipopolysaccharide isolated from klebsiella pneumoniae as1 on mcf-7 human breast tumor cell line. International Journal of. Drug Delivery Technology. 2021;11(1):184-9.

3. Bolourchian N, Nili M, Shahhosseini S, Nokhodchi A, Foroutan SM. Crystallization of meloxicam in the presence of hydrophilic additives to tailor its physicochemical and pharmaceutical properties. Journal of Drug Delivery Science and Technology. 2021 Dec 1;66:102926. https://doi.org/10.1016/j.jddst.2021.102926

4. Bhange M and Jadhav A. Formulation and Development of Novel Matrix Dispersion System based on Phospholipid Complex for Improving Oral Bioavailability of Ferulic Acid. International Journal of Drug Delivery and Technology. 2022;12(4):1489-1495. https://doi.org/10.25258/ijddt.12.4.01

5. Saoji SD, Raut NA, Dhore PW, Borkar CD, Popielarczyk M, Dave VS. Preparation and evaluation of phospholipid-based complex of standardized centella extract (SCE) for the enhanced delivery of phytoconstituents. The AAPS journal. 2016 Jan;18:102-14. https://doi.org/10.1208/s12248-015-9837-2 PMid:26563253 PMCid:PMC7583548

6. Telange DR, Patil AT, Pethe AM, Fegade H, Anand S, Dave VS. Formulation and characterization of an apigenin-phospholipid phytosome (APLC) for improved solubility, in vivo bioavailability, and antioxidant potential. European Journal of Pharmaceutical Sciences. 2017 Oct 15;108:36-49. https://doi.org/10.1016/j.ejps.2016.12.009 PMid:27939619

7. Rarokar NR, Telange DR, Kalsait RP, Khedekar PB. Solubility enhancement of extract of Lagenariasiceraria by development of Phospholipon® 90 H modulated phospholipid complex employing Box-Behnken design. In Annales Pharmaceutiques Françaises 2022 Nov 11. Elsevier Masson. https://doi.org/10.1016/j.pharma.2022.11.007 PMid:36375530

8. Saoji SD, Rarokar NR, Dhore PW, Dube SO, Gurav NS, Gurav SS, Raut NA. Phospholipid based colloidal nanocarriers for enhanced solubility and therapeutic efficacy of withanolides. Journal of Drug Delivery Science and Technology. 2022 Apr 1;70:103251. https://doi.org/10.1016/j.jddst.2022.103251

9. Zhang Z, Lin Y, Liu F. Preparation and characterization of CdS/ZnS core-shell nanoparticles. Journal of Dispersion Science and Technology. 2020 Apr 15;41(5):725-32. https://doi.org/10.1080/01932691.2019.1611441

10. Rarokar NR, Saoji SD, Raut NA, Taksande JB, Khedekar PB, Dave VS. Nanostructured cubosomes in a thermoresponsive depot system: an alternative approach for the controlled delivery of docetaxel. AAPS PharmSciTech. 2016 Apr;17:436-45. https://doi.org/10.1208/s12249-015-0369-y PMid:26208439 PMCid:PMC4984890

11. Paruchuri VK, Nguyen AV, Miller JD. Zeta-potentials of self-assembled surface micelles of ionic surfactants adsorbed at hydrophobic graphite surfaces. Colloids and Surfaces A: Physicochemical and Engineering Aspects. 2004 Dec 10;250(1-3):519-26. https://doi.org/10.1016/j.colsurfa.2004.04.098

12. Rarokar N, Agrawal R, Yadav S, Khedekar P, Ravikumar C, Telange D, Gurav S. Pteroyl-γ-l-glutamate/Pluronic® F68 modified polymeric micelles loaded with docetaxel for targeted delivery and reduced toxicity. Journal of Molecular Liquids. 2023 Jan 1;369:120842. https://doi.org/10.1016/j.molliq.2022.120842

13. Zeng X, Tao W, Mei L, Huang L, Tan C, Feng SS. Cholic acid-functionalized nanoparticles of star-shaped PLGA-vitamin E TPGS copolymer for docetaxel delivery to cervical cancer. Biomaterials. 2013 Aug 1;34(25):6058-67.

https://doi.org/10.1016/j.biomaterials.2013.04.052 PMid:23694904

14. Rodrigues K, Nadaf S, Rarokar N, Gurav N, Jagtap P, Mali P, Ayyanar M, Kalaskar M, Gurav S. QBD approach for the development of hesperetin loaded colloidal nanosponges for sustained delivery: In-vitro, ex-vivo, and in-vivo assessment. OpenNano. 2022 Jul 1;7:100045. https://doi.org/10.1016/j.onano.2022.100045

15. Wang H, Li Q, Reyes S, Zhang J, Xie L, Melendez V, Hickman M, Kozar MP. Formulation and particle size reduction improve bioavailability of poorly water-soluble compounds with antimalarial activity. Malaria Research and Treatment. 2013;2013. https://doi.org/10.1155/2013/769234 PMid:23766925 PMCid:PMC3666196

16. Freitas C, Müller RH. Effect of light and temperature on zeta potential and physical stability in solid lipid nanoparticle (SLN™) dispersions. International journal of pharmaceutics. 1998 Jun 15;168(2):221-9. https://doi.org/10.1016/S0378-5173(98)00092-1

17. Elnakat H. Distribution, functionality and gene regulation of folate receptor isoforms: implications in targeted therapy. Advanced drug delivery reviews. 2004 Apr 29;56(8):1067-84. https://doi.org/10.1016/j.addr.2004.01.001 PMid:15094207

18. O'Shannessy DJ, Somers EB, Palmer LM, Thiel RP, Oberoi P, Heath R, Marcucci L. Serum folate receptor alpha, mesothelin and megakaryocyte potentiating factor in ovarian cancer: association to disease stage and grade and comparison to CA125 and HE4. Journal of ovarian research. 2013 Dec;6(1):1-6. https://doi.org/10.1186/1757-2215-6-29 PMid:23590973 PMCid:PMC3640997

19. Allard JE, Risinger JI, Morrison C, Young G, Rose GS, Fowler J, Berchuck A, Maxwell GL. Overexpression of folate binding protein is associated with shortened progression-free survival in uterine adenocarcinomas. Gynecologic oncology. 2007 Oct 1;107(1):52-7. https://doi.org/10.1016/j.ygyno.2007.05.018 PMid:17582475

20. Rarokar NR, Khedekar PB, Bharne AP, Umekar MJ. Development of self-assembled nanocarriers to enhance antitumor efficacy of docetaxeltrihydrate in MDA-MB-231 cell line. International journal of biological macromolecules. 2019 Mar 15;125:1056-68. https://doi.org/10.1016/j.ijbiomac.2018.12.130 PMid:30572051

21. Xu Z, Liu S, Kang Y, Wang M. Glutathione-responsive polymeric micelles formed by a biodegradable amphiphilic triblock copolymer for anticancer drug delivery and controlled release. ACS Biomaterials Science & Engineering. 2015 Jul 13;1(7):585-92. https://doi.org/10.1021/acsbiomaterials.5b00119 PMid:33434974

22. Weyna DR, Cheney ML, Shan N, Hanna M, Zaworotko MJ, Sava V, Song S, Sanchez-Ramos JR. Improving solubility and pharmacokinetics of meloxicam via multiple-component crystal formation. Molecular pharmaceutics. 2012 Jul 2;9(7):2094-102. https://doi.org/10.1021/mp300169c PMid:22642304