Asian Journal of Pharmaceutical Education and Research
Vol -13, Issue-3, July- September 2024
ISSN:2278 7496

REVIEW ARTICLE Impact Factor: 7.014

COMPREHENSIVE REVIEW ON ENHANCING RELEASE RATE OF TOPICAL LIPOSOMAL DICLOFENAC SODIUM FORMULATION

Muhammad Ibrahim Muhammad, Mustapha Abba, Muhammad Salihu Abdullahi, Sandip Prasad Tiwari*

Faculty of Pharmacy, Kalinga University, Naya Raipur, Chhattisgarh India (492101)

*Corresponding Author's E mail: sandip.tiwari@kalingauniversity.ac.in
Received 12 June. 2024; Revised 15 June. 2024; Accepted 21 June. 2024, Available online 10 July. 2024

Cite this article as: Muhammad IM, Abba M, Abdullahi MS and Tiwari SP. Comprehensive review on enhancing release rate of topical liposomal diclofenac sodium formulation. Asian Journal of Pharmaceutical Education and Research. 2024; 13(3): 119-128.

https://dx.doi.org/10.38164/AJPER/13.3.2024.119-128

ABSTRACT

A potential new treatment strategy for treating inflammatory joint diseases, such as rheumatoid arthritis and osteoarthritis, is topical liposomal diclofenac formulations. A summary of current developments, obstacles, and potential paths in the creation and use of these formulations may be found in this comprehensive abstract. The paper talks about the development of liposomal drug delivery methods and emphasizes how they may target tissues with diclofenac while encapsulating it and reducing systemic adverse effects. Personalized medicine techniques, targeted drug delivery systems, and combination therapy are some of the tactics that have been employed in recent research to improve the safety and efficacy of liposomal diclofenac formulations. The creation of customized liposomal formulations based on the unique needs of each patient is a major field of study. Researchers hope to improve treatment results and medication delivery by combining patient-specific factors, biomarkers, and pharmacogenomics data. Furthermore, specific targeting of inflammatory tissues is made possible by tailored drug delivery systems utilizing ligand-functionalized liposomes, which maximize therapeutic efficacy while reducing off-target effects. Personalized medicine through the use of cutting-edge technology, long-term observational studies, and analysis of empirical data are some of the suggested remedies and future research prospects. In conclusion, topical liposomal diclofenac formulations have a bright future ahead of them that might drastically alter the way inflammatory joint illnesses are treated. Researchers seek to provide safe, effective, and customized therapies that increase patient adherence, raise quality of life, and lessen the burden of various chronic disorders through cross-disciplinary collaboration with stakeholders.

Keywords: Topical Liposomal Diclofenac Formulations, Inflammation, Drug delivery systems

INTRODUCTION

Prostaglandins are mediators of fever, pain, and inflammation. Diclofenac sodium primarily acts pharmacologically by inhibiting the cyclooxygenase (COX) enzyme, which reduces prostaglandin production .With a higher affinity for COX-2, it is a non-selective COX inhibitor that inhibits both COX-1 and COX-2. Apart from its antioxidant properties, diclofenac sodium also regulates the release of inflammatory mediators such as cytokines and leukotrienes [1]. Diclofenac sodium is commonly blended into topical treatments, such as gels, lotions, and patches, for the treatment of a range of musculoskeletal disorders, including as osteoarthritis, rheumatoid arthritis, and soft tissue injuries. The advantages of topical diclofenac formulations over oral treatment are limited to localized distribution to the site of pain or inflammation, less systemic side effects, and increased patient compliance. Topical diclofenac has demonstrated efficacy in clinical studies for the treatment of pain and inflammation resulting from disorders such acute musculoskeletal injuries, chronic low back pain, and osteoarthritis of the hand and knee. The aim of this paper is to augment the rate of release of a formulation of topical liposomal diclofenac sodium, with the purpose of enhancing its therapeutic effectiveness and promoting patient adherence in the management of inflammatory disorders, including musculoskeletal disorders and arthritis. On account of the variable drug release kinetics and restricted skin permeation that are currently associated with conventional diclofenac formulations, novel approaches are required to optimize drug delivery to the intended site [2,3].

Challenges associated with conventional topical diclofenac formulations

i. Slow Release

The start of action and duration of impact of conventional topical diclofenac formulations are typically delayed due to sluggish release kinetics .Various reasons, including the drug's lipophilic nature, poor solubility in aqueous fluids, and barrier qualities of the stratum corneum, may be responsible for the delayed release of diclofenac from topical preparations .Diclofenac extended skin residence time can result in systemic absorption and possible systemic adverse effects, especially when used over an extended period of time [4,5].

ii. Limited Penetration

One other concern with traditional topical formulations is the limited penetration of diclofenac into th e skin's deeper layers and underlying tissues.

Diclofenac's ability to reach the site of inflammation or discomfort is limited by the stratum corneum, the skin's outermost layer, which serves as a barrier to drug penetration.Insufficient penetration can l

ead to insufficient drug delivery to target tissues, resulting in less than ideal therapeutic effects and ne cessitating the repeated administration of topical formulations.

Potential of liposomal formulations in enhancing drug delivery

1. **Enhanced Pharmacokinetics**: By changing a drug's distribution, metabolism, and excretion, liposomal formulations can change its pharmacokinetic profile. They have the capacity to extend the bloodstream's circulation duration, which increases bioavailability and decreases systemic toxicity.
2. **Targeted Drug Delivery**: The capacity of liposomal formulations to target certain tissues or cells is one of its most promising features. By selectively interacting with receptors that are overexpressed on target cells by surface modifications using ligands or antibodies, therapeutic efficacy can be maximized and accurate delivery can be achieved while reducing off-target effects.
3. **Combination therapy**: Liposome provide a flexible vehicle for the co-administration of many medications or therapeutic agents with various physicochemical characteristics. This capacity improves treatment results and slows the emergence of drug resistance by enabling synergistic effects, combination therapy, or sequential administration of medications with complimentary modes of action.
4. **Flexibility and Versatility**: A variety of medications, including hydrophilic, hydrophobic, and amphiphilic substances, can be encapsulated in liposomal formulations. Additionally, they may be administered through a variety of methods, such as intramuscular, oral, topical, and intravenous, which makes them appropriate for a wide range of therapeutic uses.
5. **Clinical Translation**: Infectious illnesses, inflammatory disorders, and cancer are only a few of the conditions in which liposomal formulations have shown clinical promise. The fact that several liposomal medication solutions are routinely used in clinical practice and have received approval from regulatory bodies throughout the globe highlights the viability and translational potential of this drug delivery strategy [6,7].

Types of liposome

a. **Niosomes** When non-ionic amphiphiles combine with various lipid surfactant in an aqueous solution, they form niosomes. The primary contrast between niosomes and liposome is their chemical stability and comparatively cheap cost. Aggregation, fusion, and encapsulated drug leakage are hazards that both may encounter. Proniosomes have demonstrated several advantages over noisome in recent times, including the reduction of physical instability problems including

aggregation, fusion, and encapsulated drug leakage. They also provide convenient transportation, distribution, storage, and dosing.

b. **Transferosomes** may be deformed up to 105 times more easily than unmodified liposomes.[8] Particles known as transferosomes,which may penetrate the stratum corneum, have a size of 200–300nm. It has been shown via many study findings that the entrapment effectiveness of liposomes and niosomes is almost identical.

c. Proliposomes are free-flowing particles that, when they are exposed to water, transform into liposomes. Since they are made of porous material that is soluble in water, the medication and phospholipid are deposited in the material's microporous form, maintaining the material's free-flowing properties. Proliposomes can be kept in a dried, sterilized condition or, if desired, dissolved in water to create isotonic multilamellar liposomes.

d. The ethosomes Phospholipid (soy phosphatidylcholine), ethanol, and water make up etherosomes. These are known as multilamellar vesicles, or MLVs, and are acknowledged as permeability enhancers. In Acyclovir, minoxidil, and testosterone are only a few examples of the molecules with greater molecular entrapment efficiency in ethosomes[9-11].

Classification of liposomes

A. Based on structure

1. Unilamellar vesicles(SUVs)

- SUVs, or small unilamellar vesicles, are 2–100nm in size.
- Medium-sized unilamellar vesicles: 40–80nm in size.
- Big unilamellar vesicles: about 100–1000nm in size

2. Oligolamellar vesicles (OLVs)

- OLVs consist of a huge internal volume surrounded by 2-10 lipid bilayers.

3. Multilameller vesicles(MLVs)

- They consist of many bilayers. They are shaped like an onion and include a spherical bilayer of MLV that encloses a huge range of SUVs.

B. **Based on technique of preparation**

1. REV: Reverse-phase evaporation method.

2. DRV: Dehydration rehydration method.

3. VET: Vesicle prepared through extrusion techniques.

METHOD OF LIPOSOME PREPATION

Thin-Film Hydration Method Procedure:

i. Lipid Film Preparation: In a glass vial or round-bottom flask, dissolve lipids (such as phospholipids) in an appropriate organic solvent (such as methanol or chloroform).Utilizing a rotary evaporator or a mild nitrogen gas stream, evaporate the organic solvent until a thin lipid layer forms on the flask's or vial's inside. To avoid residue, make sure all of the solvent is gone by drying at a lower pressure [12-13].

ii. Lipid film hydration involves adding the relevant volume of an aqueous buffer or solution containing the target medication to the lipid film. To guarantee that the water phase uniformly wets the lipid layer, gently swirl the mixture. To help the mixture create liposomes, let it hydrate for a specific amount of time, usually at room temperature.

iii. Liposome Formation: To promote liposome formation, gently agitate the mixture or vortex it once it has been hydrated. To guarantee homogeneity and encourage liposome synthesis even more, you can choose to sonicate the mixture using a probe sonicator or ultrasonic bath. Purification and Characterization: Using methods like size exclusion chromatography, ultracentrifugation, or dialysis, purify the liposome dispersion to get rid of any unencapsulated drug molecules or aggregates.

iv. Utilizing techniques like dynamic light scattering (DLS) for size distribution, transmission electron microscopy (TEM) for shape, and spectroscopic approaches for drug encapsulation efficiency, characterize the produced liposomes [14-16].

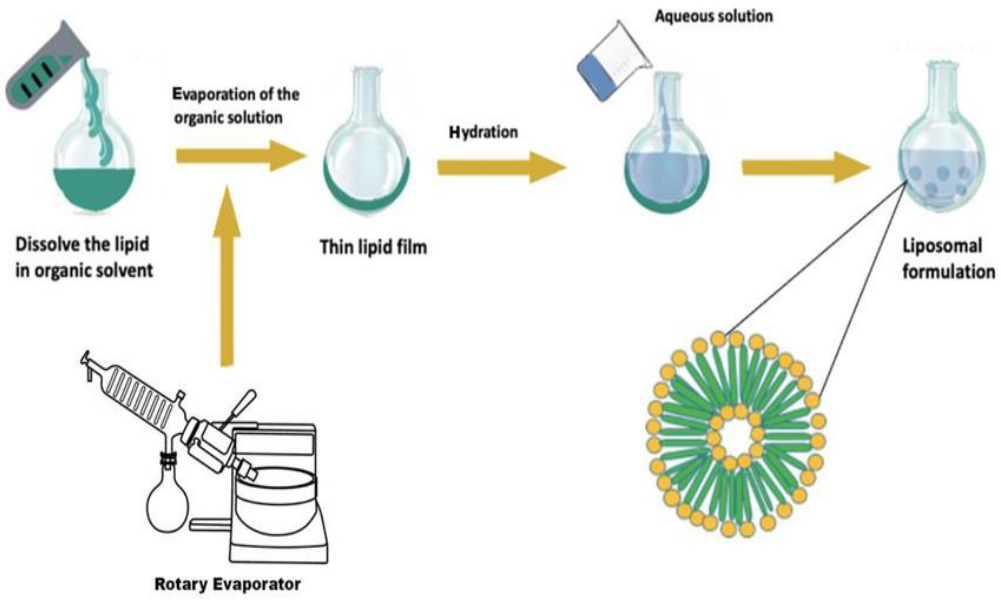


Fig 1: Method of Preparation

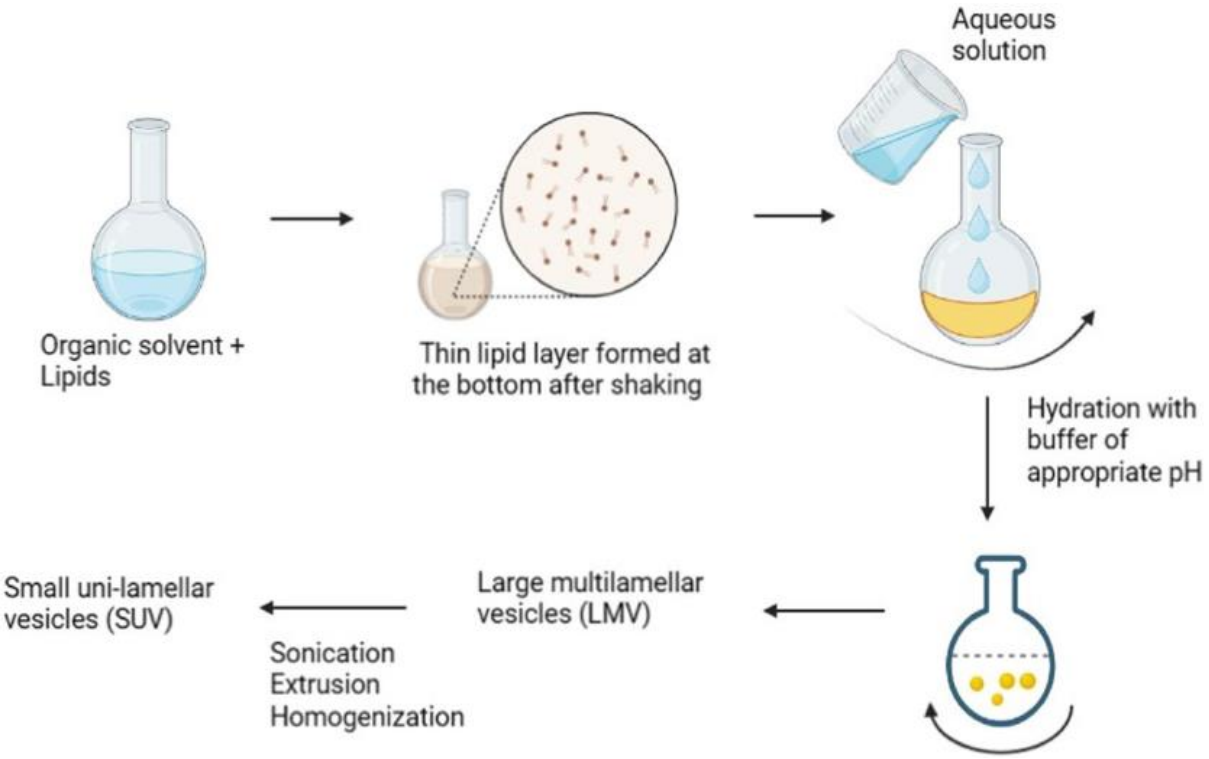
HYDRATION OF LIPID FILM PROCEDURE:

i. Method for Preparing Organic Phase: In a glass vial or round-bottom flask, dissolve lipids (such as phospholipids) in a water-miscible organic solvent (such as ether).Ascertain full dissolution by adding the desired medication to the organic phase

ii. Making a Water-in-Oil Emulsion: Mix the organic phase containing the medication and lipids with an aqueous phase (usually comprising saline solution or buffer).To create a water-in-oil emulsion, homogenize or sonicate the combination. The aqueous phase is contained within lipid vesicles by means of this emulsification procedure.

iii. Solvent Evaporation: Use a rotary evaporator or slightly heat the organic solvent to evaporate it under low pressure. Liposomal formation results from this procedure, which also eliminates the organic solvent.

iv. Characterization and Purification: Using methods like size exclusion chromatography, ultracentrifugation, or dialysis, purify the resultant liposome dispersion to get rid of any unencapsulated drug molecules or aggregates. Use techniques like dynamic light scattering (DLS) to determine the size distribution of the produced liposomes, transmission electron microscopy (TEM) to analyze their shape, and spectroscopic methods to determine the drug encapsulation efficiency [17].



3. Sonication Method:

i. Lipid Dissolution: To create a lipid solution, start by dissolving lipids (such as cholesterol and phosphatidylcholine) in an organic solvent (such as ethanol or chloroform). The stability and membrane fluidity of the liposomes may be controlled by adjusting the lipid content.

ii. Lipid Film Formation: To create a thin lipid coating on the container's surface, evaporate the organic solvent using methods like nitrogen flow or rotational evaporation. Make sure the lipid film is uniformly applied to the whole surface.

iii. Hydration: Drench the lipid film with an aqueous solution that contains the payload (drugs, DNA, or proteins, for example). To guarantee that the lipid layer is evenly hydrated, the aqueous solution must be supplied gradually.

iv. Sonication: Using an ultrasonic probe or bath sonicator, subject the hydrated lipid mixture to sonication. High-frequency sound waves, usually in the 20–100 kHz range, are applied to the mixture during the sonication process.

v. Monitoring: Keep a close eye on the sonication process to avoid overheating and payload or lipid breakdown. To keep the liposomes stable during sonication, temperature management may be

essential.

vi. Post-Sonication Steps: Following sonication, a combination of unilamellar and multilamellar vesicles may be present in the liposomal suspension. Extrusion or centrifugation are two other processing procedures that may be used to produce a more homogeneous population of liposomes with the appropriate properties.

Qualitative Description and Clarification: Examine the size distribution, stability, and encapsulation effectiveness of the resultant liposomal suspension. If required, use methods such as size-exclusion chromatography or ultracentrifugation to purify the liposomal solution [18-20].

CONCLUSION

In conclusion, a viable strategy for the treatment of inflammatory joint diseases including osteoarthritis and rheumatoid arthritis is the creation of topical liposomal diclofenac formulations. By using cutting-edge medication delivery techniques, such as combination medicines, tailored formulations, and targeted delivery systems, researchers hope to maximize treatment results while lowering side effects and boosting patient adherence. Research efforts are still underway to develop the area by assessing long-term safety and efficacy in varied patient groups, understanding underlying mechanisms of action, and investigating new formulations all despite obstacles including scalability and regulatory concerns. Through tackling these obstacles and utilizing cutting-edge technology, such biomarker identification and tracking, scientists can open the door to personalized medicine strategies that customize treatment plans based on unique patient traits and inclinations. As a whole, topical liposomal diclofenac formulations have enormous potential to improve patient outcomes, transform the way inflammatory joint diseases are managed, and raise millions of people's quality of life around the globe. We are able to bring scientific discoveries into clinical practice and take significant steps toward developing safe, efficient, and customized therapies for inflammatory joint disorders by working together with stakeholders and academic disciplines.

REFERENCES:

1. Rainsford KD. Anti-inflammatory drugs in the 21st century. Subcell Biochem. 2007;42:3-27. doi: 10.1007/978-1-4020-5688-6_1. PMID: 17612052.
2. Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA and Vane JR. Nonsteroid drug selectivities for cyclo-oxygenase-1 rather than cyclo-oxygenase-2 are associated with human

gastrointestinal toxicity: a full in vitro analysis. Proc Natl Acad Sci U S A. 1999;96(13):7563-8. doi: 10.1073/pnas.96.13.7563. PMID: 10377451; PMCID: PMC22193.

3. Brune K and Patrignani P. New insights into the use of currently available non-steroidal anti-inflammatory drugs. J Pain Res. 2015;8:105-18. doi: 10.2147/JPR.S75160. PMID: 25759590; PMCID: PMC4341395.
4. Derry S, Moore RA and Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. 2012;9(9):CD007400. doi: 10.1002/14651858.CD007400.pub2. PMID: 22972103; PMCID: PMC6483632.
5. Conaghan PG, Dickson J and Grant RL; Guideline Development Group. Care and management of osteoarthritis in adults: summary of NICE guidance. BMJ. 2008;336(7642):502-3. doi: 10.1136/bmj.39490.608009.AD. PMID: 18309958; PMCID: PMC2258392.
6. Lin J, Zhang W, Jones A and Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. BMJ. 2004;329(7461):324. doi: 10.1136/bmj.38159.639028.7C. PMID: 15217868; PMCID: PMC486249.
7. Derry S, Moore RA, Gaskell H, McIntyre M and Wiffen PJ. Topical NSAIDs for acute musculoskeletal pain in adults. Cochrane Database Syst Rev. 2015;2015(6):CD007402. doi: 10.1002/14651858.CD007402.pub3. PMID: 26068931; PMCID: PMC6483939.
8. Moradi Tuchayi S, Makrantonaki E, Ganceviciene R, Dessinioti C, Feldman SR and Zouboulis CC. Acne vulgaris. Nat Rev Dis Primers. 2015;1:15029. doi: 10.1038/nrdp.2015.29. PMID: 27189621.
9. Williams AC and Barry BW. Penetration enhancers. Adv Drug Deliv Rev. 2012;64:128-37. doi: 10.1016/j.addr.2012.09.012. PMID: 23023058.
10. Luger TA, Barker J, Lambert J, Yang S, Robertson D, Foehl J, et al. Sustained improvements in patients with moderate to severe psoriasis treated with infliximab for up to 1 year: results from the infliximab multinational psoriasis efficacy trial (IMPETU). Eur J Dermatol. 2008;18(1):16-21. PMID: 18031705.
11. Ostro MJ and Cullis PR. Use of liposomes as injectable-drug delivery systems. Am J Hosp Pharm 1989;46:1576-88.
12. Shi J, Xiao Z, Vilos C, Votruba A, Langer R and Farokhzad OC. Lipid-polymer Hybrid Particles. Google Patents; 2017.

13. Uchegbu IF and Vyas SP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharm 1998;172:33-70.

14. Oidu B. Uptake of Liposomes Into Bacterial Cells. South Africa: Nelson Mandela Metropolitan University; 2013.

15. Cosco D, Celia C, Cilurzo F, Trapasso E and Paolino DJ. Colloidal carriers for the enhanced delivery through the skin. Expert Opin Drug Deliv. 2008;5:737-55.

16. Song KH, Chung SJ, Shim CK. Preparation and evaluation of proliposomes containing salmon calcitonin. J Control Release 2002;84:27-37.

17. Uchegbu IF and Vyas SP. Non-ionic surfactant based vesicles (niosomes) in drug delivery. Int J Pharm 1998;172:33-70.

18. Torchilin, V. P. Recent advances with liposomes as pharmaceutical carriers. Nature Reviews Drug Discovery. 2005; 4(2), 145-160.

19. Allen, TM, and Cullis PR. Liposomal drug delivery systems: From concept to clinical applications. Advanced Drug Delivery Reviews. 2013; 65(1), 36-48.

20. Bozzuto G and Molinari A. Liposomes as nanomedical devices. International Journal of Nanomedicine. 2015; 10: 975-999.