

Benefits of Liposomal Nonsteroid-Anti-Inflammatory Drugs

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SUMMARY

Introduction: Liposomes are small, spherical artificial vesicles that can be created from cholesterol and natural non-toxic phospholipids. Due to their size, hydrophobic and hydrophilic character (besides biocompatibility), liposomes are promising drug delivery systems.

Topic: Liposomal formulations of non-steroidal anti-inflammatory drugs (NSAIDs) can be used in all population groups (children, adults, and the elderly) which gives them a wide range of applications. NSAIDs oral administration is associated with severe adverse effects in the gastrointestinal tract such as epigastric pain, heartburn, nausea, diarrhea, vomiting, peptic ulcer, and hepatic impairment. It has been observed in clinical trials, that liposomal formulations enhanced the drug permeability and the percentage of accumulated dose in the skin compared to control conventional gel formulations. Liposomal gel controls ibuprofen release and drug permeability *in vitro* and has shown a permeability pattern conducive to maintaining constant drug levels.

Application: So far, liposomes containing sodium diclofenac, indomethacin, aceclofenac, and related NSAIDs have been produced in laboratory conditions. Liposomal technology is most commonly applied in cosmetology, cancer therapy and yet unexplored application possibilities for liposomes, such as therapy for Alzheimer's disease. Although varying in size and structure, they all possess certain common advantages - increased dermal availability of lipophilic drugs and their targeted delivery onto the required location. Liposomes have been proven highly effective in terms of retaining the NSAIDs in the synovial cavity, mostly because of their size and chemical composition. Undesirable therapy effects, fast clearance, and exposure to nontargeted sites could be minimized by administering NSAIDs using liposomes as carriers. Side effects and complications associated with the long-term oral and intramuscular applications of NSAIDs could especially be avoided using their liposomal formulations. Liposomes can be seen as ideal carriers for anti-inflammatory drugs as their ability to (passively) target sites of inflammation and release their content to inflammatory target cells enables them to increase local efficacy with only limited systemic exposure and adverse effects, improving bioavailability and patient compliance. A few NSAIDs are experimentally formulated in liposomes having improved pharmacokinetic characteristics. Further clinical investigations will show their pharmacodynamic effects. The *in vitro* release and *ex vivo* permeation (permeability) study showed a prolonged diclofenac release with high permeation flux.

Conclusion: The use of liposomes as drug carriers becomes a notable positive step in the treatment of inflammatory, pain-causing, and rheumatic diseases. Liposomes present an

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attractive delivery system due to their flexible physicochemical and biophysical properties, which allow easy manipulation to address the different delivery considerations. The main objectives for the development of NSAIDs in liposomal carriers are deeper penetration of the active substance, fewer side effects, better and longer effect, the ability to change the characteristics of both the drug and the carrier, and adequate dose adjustment. Despite several challenges that accordingly still need to be addressed, liposomal drug formulations have significant health-promoting potential. Despite the encouragement of NSAID development and research studies, it still takes a long time for liposomal NSAID formulations to become available for everyday use.

Keywords: Liposomes, Nonsteroid-Anti-Inflammatory Drugs

INTRODUCTION

Liposomes were discovered by Alec D Bangham in 1961 at the Babraham Institute, University of Cambridge, and consist of single or multiple concentric lipid bilayers encapsulating an aqueous compartment. It took an unexpectedly long period and varying levels of applications and popularity to establish liposomes as a drug delivery platform. With their biocompatibility and well-understood chemistry of encapsulation of a wide variety of active pharmaceutical ingredients (APIs) liposomes make it through the screening process for many potential products [1].

Liposomes are small artificial vesicles of spherical shape that can be created from cholesterol and natural non-toxic phospholipids. Due to their size, hydrophobic and hydrophilic character (besides biocompatibility), liposomes are promising systems for drug delivery [2]. Liposomes are robust drug delivery systems that have been developed into FDA-approved drug products for several pharmaceutical indications. Direct control in producing liposomes of specific dimensions for their distribution is extremely important since their size may impact cellular uptake and biodistribution [3].

TOPIC

Depending on the substance they are intended to carry, the size of these nearly spherical lipid vesicles can range from a few nanometers to several micrometers [3]. However, liposomes applied for specific medical purposes range between 50 and 450 nm [4].

Generally, liposomes could be used for local (topical) and system applications (ampules and pills). The development of liposomal formulations began by studying their

topical application as cosmetics and topical medication carriers (gels, creams, and ointments). Given the relatively new technology in pharmacy and clinical pharmacology, trends of their usage encompass topical application for the most frequent indications of rheumatic degenerative diseases: rheumatoid arthritis, juvenile rheumatoid arthritis, osteoarthritis, tendonitis, ankylosing spondylitis, gout pain, bursitis, as well as other diseases and conditions accompanied by mild to moderate pain and inflammation as backaches, muscle aches, sports injuries/sprains, headaches, fever, dental pain, menstrual cramps. Liposomal formulations of non-steroidal anti-inflammatory drugs (NSAIDs) can be used in all population groups (children, adults, and the elderly) which gives them a wide range of applications [5]. NSAIDs oral administration is associated with severe adverse effects in the gastrointestinal tract such as epigastric pain, heartburn, nausea, diarrhea, vomiting, peptic ulcer, and hepatic impairment [6]. It has been observed in clinical trials, that liposomal formulations enhanced the drug permeability and the percentage of accumulated dose in the skin compared to control conventional gel formulations [7, 8]. Liposomal gel controls ibuprofen release and drug permeability *in vitro* and has shown a permeability pattern conducive to maintaining constant drug levels [9].

The possibility of developing a good formulation of liposomal NSAIDs is being investigated in several research sites worldwide. Due to its clinical significance and financial effect, the development of liposomal drugs is greatest in the field of cytostatics [10]. Until the publication of this paper, no drugs have been registered in the NSAID group [11,12,13].

APPLICATION

Liposomal technology is most commonly applied in cosmetology [14]. Liposomes have a significant perspective in cancer therapy because by targeting the active site, they do not damage the surrounding healthy tissue and thus give fewer side effects. To some extent, there are also yet unexplored application possibilities for liposomes, such as therapy for Alzheimer's disease [15,16].

So far, liposomes containing sodium diclofenac, indomethacin, aceclofenac, and related NSAIDs have been produced in laboratory conditions. Although varying in size and structure, they all possess certain common advantages – increased dermal availability of lipophilic drugs and their targeted delivery onto the required location [17]. Liposomes have been proven highly effective in terms of retaining the NSAIDs in the synovial cavity, most of all because of their size and chemical composition. Undesirable therapy effects, fast clearance, and exposure to nontargeted sites could be minimized by administering NSAIDs using liposomes as carriers. Side effects and complications associated with the long-term oral and intramuscular applications of NSAIDs could especially be avoided using their liposomal formulations [18]. In animal models, liposomes containing NSAIDs have been detected even one week upon injection into the organism, explaining the prolonged action of drugs over this period of time [19]. Liposomes offer the capacity of delivering lower doses of drugs with reduced toxicity, thus improving the risk/benefit ratio of NSAIDs. However, routine clinical applications of liposomal NSAIDs are yet to be developed to their full potential, with improvements required in regards to the stability and efficacy of the specific liposome formulations.

Chronic inflammation is defined as a chronic, low-level inflammation process that can last for months, years, or a lifetime. Constant tiredness, soreness in the mouth, discomfort in the joints, chest or abdomen, rash, and fever are often symptoms or indications of inflammation [18]. To achieve the intended therapeutic effects on inflammatory cells, high doses of drugs are often given, which can have side effects on healthy tissue. Non-steroidal anti-inflammatory drugs (NSAIDs) weaken pain by reversing the action of the enzyme cyclooxygenase (COX). NSAIDs prevent pros-

taglandin synthesis and reduce or eliminate pain. Some of the drugs in this group in widespread use are aspirin, ibuprofen, diclofenac, etc. Since they are among the most commonly used drugs, the study has been conducted to investigate the method to improve their clinical effects by means of using liposomes as NSAID drug delivery systems. Such kind of delivery has a number of advantages related to commonly used methods since liposomes could be specifically designed to gradually release the API, which is especially important for topical applications. Furthermore, liposomes are biocompatible, have the capacity to self-assemble, are able to carry large drug loads, can be functionalized enabling targeted drug delivery, and could be modified in a wide range of physicochemical and biophysical properties controlling their biological characteristics. The advantages of using liposomal NSAIDs are better penetration into the tissue and thus greater efficiency and longer duration of action, the lower dose required to achieve greater therapeutic effects (reduction of pain, swelling, and redness), and the possibility of combining two or more drugs [18,20,21]. Recent studies show that dipalmitoylphosphatidylcholine (DPPC)/Cholesterol spin-labeled liposomes containing NSAIDs penetrate deeply into the skin remaining stable for several hours, making them promising chronic inflammation therapeutics carriers [22]. Global's Burden of Diseases 2000 incidence data on Rheumatoid arthritis (RA) illustrate the significance of a proper therapeutic choice in the treatment of this degenerative painful syndrome. The incidence of RA ranges between 20-300 per 100,000 adults per year. The global average case fatality rate is around 1 per 1,000 prevalent cases in both male and female populations [23]. Treatment of painful conditions with topical preparations is mostly performed as a patient self-treatment, so the drug formulations have to be fast-acting and comfortable for application, especially in the case of sports injuries [24].

The usage of liposomes to assist NSAIDs delivery has a major impact on many biomedical areas (rheumatology, immunology, sport, recreation, physical treatment, etc.). They are biocompatible, biodegradable, and enable the trapping of both hydrophobic and hydrophilic compounds. They increase drug delivery to the tumor site while lowering systemic toxicity [25].

A few clinical trials of transdermal

applications showed the superiority of nanoliposome formulations over non-vesicular ones, and that lipid composition containing a 7/3/1 molar ratio of phosphatidylcholine, cholesterol, and dicetyl phosphate is optimum for nanoliposome preparations, in the cases where controlled delivery of a drug is needed for a sufficient period of time [26].

Liposomes can be seen as ideal carriers for anti-inflammatory drugs as their ability to (passively) target sites of inflammation and release their content to inflammatory target cells enables them to increase local efficacy with only limited systemic exposure and adverse effects [27].

Consequently, for poorly water-soluble drugs, the cationic liposome system was a potential approach to improve ocular bioavailability and patient compliance [26]. A few NSAIDs are experimentally formulated in liposomes having improved pharmacokinetic characteristics. Further clinical investigations will show their pharmacodynamic effects. The *in vitro* release and *ex vivo* permeation (permeability) study showed a prolonged diclofenac release with high permeation flux [29].

Improving modern pharmacotherapy is demanding and is done through the optimal choice of drugs, optimal dosing, control of interactions between drugs, as well as minimizing the occurrence and consequences of drug side effects. In accordance with that, the development of new forms of liposomes as delivery systems could be one of the best solutions. Achieving desired therapeutic effects is a challenging task and a motive for adhering to the highest ethical standards of Good Clinical Practice [30].

The selection of registered NSAIDs is mostly the same worldwide, with some minimal differences [31]. Typical non-selective NSAIDs include Diclofenac, Diflunisal, Etodolac, Fenoprofen, Flurbiprofen, Ibuprofen, Indomethacin, Ketoprofen, Ketorolac, Mefenamic acid, Meloxicam, Nabumetone, Naproxen, Oxaprozin, Piroxicam, Sulindac, Tolmetin. COX-2 Selective NSAIDs: Celecoxib, Rofecoxib, Valdecoxib. NSAIDs are able to prevent prostaglandin synthesis and reduce or eliminate pain. NSAIDs typically relieve pain by reversing the action of the enzyme cyclooxygenase (COX). Some of the drugs in this group that are mostly used are aspirin, ibuprofen, diclofenac, etc. Therefore, investi-

gations should be conducted in way to study the method of improving their clinical effects using liposomes as NSAID drug delivery systems. Such kind of delivery has a number of advantages related to commonly used methods since liposomes could be specifically designed to gradually release the active pharmaceutical ingredients, which is especially important for topical applications [22]. Furthermore, liposomes are biocompatible, have the self-assembling ability, can carry large drug loads and be functionalized enabling targeted drug delivery, and could be modified in a wide range of physicochemical and biophysical properties controlling their biological characteristics. The usage of liposomes to assist NSAIDs delivery has a major impact on many biomedical areas (rheumatology, immunology, sport, recreation, physical treatment, etc.) [22,30].

Liposomes present attractive delivery systems due to their flexible physicochemical and biophysical properties, which allow easy manipulation to address different delivery considerations. The advantage of liposomal-based products is the ability of liposomes to deliver active pharmaceutical ingredients in a targeted manner [1]. The targeting precision of the exterior of the phospholipid/liposome can be readily designed for a wide level of applications. The topical application of liposomes and the final registration of products through all four phases are feasible according to regulations without the special complexity in terms of the research equipment. Without entering into the pharmacoeconomic analysis of consumption and financial share of NSAIDs in the Republic of Serbia, researchers are studying the advantages and specifics of drug-loaded liposome production in laboratory conditions, because they are affordable and convenient to develop, improve and adapt [22,30]. However, in some cases, liposomes' production complexity, deterioration, particle size variability, and distribution make them rather challenging for production, which often turns out to be more of an art than a science. Therefore, the development of liposomes as carriers of the active substances highlights new directions that are being considered for the next generation of therapies [1,32]. More should be discussed related to the advances in liposome-assisted NSAID drug delivery, especially liposome composition, size, control of their degradability, biological challenges, and current clinical and experimental use for bio-

medical applications [22, 33].

CONCLUSION

The use of liposomes as drug carriers becomes a notable positive step in the treatment of inflammatory, pain-causing, and rheumatic diseases. Liposomes present an attractive delivery system due to their flexible physicochemical and biophysical properties, which allow easy manipulation to address the different delivery considerations.

The main objectives for the development of NSAIDs in liposomal carriers are deeper penetration of the active substance, fewer side effects, better and longer effect, the ability to change the characteristics of both the drug and the carrier, and adequate dose adjustment. Despite several challenges that accordingly still need to be addressed, liposomal drug formulations have significant health-promoting potential.

Despite the encouragement of NSAID development and research studies, it still takes a long time for liposomal NSAID formulations to become available for everyday use.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

REFERENCES

1. Bozenhardt HF, Bozenhardt EH. An introduction to liposome processing for drug delivery. Available at: <https://www.pharmaceuticalonline.com/doc/an-introduction-to-liposome-processing-for-drug-delivery-0001> Last updated: June 10, 2020.
2. Akbarzadeh A, Rezaei-Sadabady R, Davaran S, Woo Joo S, Zarghami N, Hanifehpour Y, Samiei M, Kouhi M, Nejati-Koshki K. Liposome: classification, preparation, and applications. *Nanoscale Res Lett*. 2013;8(1):102. doi.org/10.1186/1556-276X-8-102
3. Costa AP, Xu X, Khan MA, Burgess DJ. Liposome formation using a coaxial turbulent jet in co-flow. *Pharm Res*. 2016 Feb;33(2):404-16. doi: 10.1007/s11095-015-1798-8. PMID: 26428671.
4. Bozzuto G, Molinari A. Liposomes as nanomedical devices. *Int J Nanomedicine*. 2015 Feb 2;10:975-99. doi: 10.2147/IJN.S68861. PMID: 25678787; PMCID: PMC4324542.
5. Schenk JM, Calip GS, Tangen CM, Goodman P, Parsons JK, Thompson IM, Kristal AR. Indications for and use of nonsteroidal antiinflammatory drugs and the risk of incident, symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. *Am J Epidemiol*. 2012 Jul 15;176(2):156-63. doi: 10.1093/aje/kwr524. Epub 2012 Jun 28. PMID: 22759721; PMCID: PMC3493197.
6. Goldstein JL, Cryer B. Gastrointestinal injury associated with NSAID use: a case study and review of risk factors and preventative strategies. *Drug Healthc Patient Saf*. 2015;7:31-41. Published 2015 Jan 22. doi:10.2147/DHPS.S71976.
7. Ghanbarzadeh S, Khorrami A, Arami S. Nonionic surfactant-based vesicular system for transdermal drug delivery. *Drug Delivery*, 2015;22(8):1071-1077. DOI: 10.3109/10717544.2013.873837
8. Cvijić S, Parojčić J. Savremeni farmaceutski oblici nesteroidnih antiinflamatornih lekova. *Arh. farm.* 2016;66: 267 - 283
9. Paavola A, Kilpeläinen I, Yliruusi J, Rosenberg P. Controlled release injectable liposomal gel of ibuprofen for epidural analgesia. *Int J Pharm*. 2000 Apr 10;199(1):85-93. doi: 10.1016/s0378-5173(00)00376-8. PMID: 10794930.
10. Panahia Y , Masoud F, Mohammadhosseinid M , Mirahadib M , Khalilov R, Saghfif S, Akbarzadeh A. Recent advances on liposomal nanoparticles: synthesis, characterization and biomedical applications. *Artificial cells, nanomedicine, and biotechnology*, 2017;45(4):788-799. <http://dx.doi.org/10.1080/21691401.2017.1282496>
11. Medicines and Medical Devices Agency of Serbia. Available at: www.alims.gov.rs
12. European Medical Agency. Available at: www.ema.europa.eu/en
13. Food and Drug Administration. Available at: www.fda.gov
14. Rahimpour Y, Hamishehkar H. Liposomes in cosmetics. *Expert Opin Drug Deliv*. 2012 Apr;9(4):443-55. doi: 10.1517/17425247.2012.666968. Epub 2012 Mar 13. PMID: 22413847.
15. Amarandi RM, Ibanescu A, Carasevici E, Marin L, Dragoi B. Liposomal-based formulations: A path from basic research to temozolomide delivery inside glioblastoma tissue. *Pharmaceutics*. 2022 Jan 27;14(2):308. doi: 10.3390/pharmaceutics14020308. PMID: 35214041; PMCID: PMC8875825.
16. Naziris N, Demetzos C. Liposomes: Production Methods and Application in Alzheimer's Disease. *Adv Exp Med Biol*. 2021;1339:385-394. doi: 10.1007/978-3-030-78787-5_48. PMID: 35023130.

17. Puglia C, Tirendi GG, Bonina F. Emerging role of colloidal drug delivery systems (CDDS) in NSAID topical administration. *Curr Med Chem.* 2013;20(14):1847-57. doi: 10.2174/0929867311320140004. PMID: 23410154.
18. Kapoor B, Singh SK, Gulati M, Gupta R, Vaidya Y. Application of liposomes in treatment of rheumatoid arthritis: Quo vadis. *The Scientific World Journal / 2014; Volume 2014, Article ID 978351, 17 pages* doi.org/10.1155/2014/978351 <https://www.hindawi.com/journals/tswj/2014/978351/>
19. Ceponis A, Waris E, Monkkonen J, Laasonen L, Hyttinen M, Solovieva S, Hanemaaijer R, Bitsch A, Konttinen Y. Effects of low-dose, non-cytotoxic, intraarticular liposomal clodronate on development of erosions and proteoglycan loss in established antigen-induced arthritis in rabbits. *Arthritis Rheumatol.* 2001;44(8):1908-1916. doi: 10.1002/1529-0131(200108)44:8<1908::AID-ART329>3.0.CO;2-4. PMID: 11508444.
20. Jogpal V, Sanduja M, Dutt R, Garg V, Tinku. Advancement of nanomedicines in chronic inflammatory disorders. *Inflammopharmacology.* 2022 Apr;30(2):355-368. doi: 10.1007/s10787-022-00927-x. Epub 2022 Feb 25. PMID: 35217901; PMCID: PMC8879181.
21. Musielak E, Feliczak-Guzik A, Nowak I. Synthesis and potential applications of lipid nanoparticles in medicine. *Materials* 2022, 15(2): 682 doi. org/10.3390/ma15020682 ; www.mdpi.com/journal/materials
22. Marković SZ, Mojović MD, Nakarada ĐJ, Kastratović DA. Benefits of liposomal antisteroid drugs - Section of Clinical Pharmacology „dr Srđan Đani Marković”, Serbian Medical Society. Book of abstracts CD rom ISBN 978-86-6061-130-9, XIII Week of the Hospital Clinical Pharmacology. Belgrade, December 11th - 12th, 2021.
23. Symmons D, Mathers C, Pflieger B. The global burden of rheumatoid arthritis in the year 2000, Draft 15-08-06, Global burden of disease 2000. Available at: https://www.who.int/healthinfo/statistics/bod_rheumatoidarthritis.pdf
24. Doomra R, Goyal A. NSAIDs and self-medication: A serious concern. *J Family Med Prim Care.* 2020;31;9(5):2183-2185. doi: 10.4103/jfmpc.jfmpc_201_20. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7380783/>
25. Zabielska-Koczywaś K, Lechowski R. The Use of Liposomes and Nanoparticles as Drug Delivery Systems to Improve Cancer Treatment in Dogs and Cats. *Molecules.* 2017 Dec 7;22(12):2167. doi: 10.3390/molecules22122167. PMID: 29215573; PMCID: PMC6149801.
26. Gaur PK, Bajpai M, Mishra S, Verma A. Development of ibuprofen nanoliposome for transdermal delivery: Physical characterization, in vitro/in vivo studies, and anti-inflammatory activity. *Artif Cells Nanomed Biotechnol.* 2016;44(1):370-5. doi: 10.3109/21691401.2014.953631. Epub 2014 Sep 11. PMID: 25211229.
27. van Alem CMA, Metselaar JM, van Kooten C, Rotmans JI. Recent Advances in Liposomal-Based Anti-Inflammatory Therapy. *Pharmaceutics.* 2021;13(7):1004. Published 2021 Jul 1. doi:10.3390/pharmaceutics13071004
28. Gai X, Cheng L, Li T, Liu D, Wang Y, Wang T, Pan W, Yang X.. In vitro and In vivo Studies on a Novel Bioadhesive Colloidal System: Cationic Liposomes of Ibuprofen. *AAPS PharmSciTech* 19, 700-709 (2018). <https://doi.org/10.1208/s12249-017-0872-4>
29. Zafar A, Alruwaili NK, Imam SS, Yasir M, Alsaidan OA, Alquraini A, Rawaf A, Alsuwayt B, Anwer MK, Alshehri S, Ghoneim MM. Development and Optimization of Nanolipid-Based Formulation of Diclofenac Sodium: In Vitro Characterization and Pre-clinical Evaluation. *Pharmaceutics.* 2022;14(3):507. doi: 10.3390/pharmaceutics14030507
30. Marković SZ, Kastratović DA, Mojović MD, Nakarada ĐJ. The development of new forms of drugs brings improvement to pharmacotherapy. Section of Clinical Pharmacology „dr Srđan Đani Marković”, Serbian Medical Society. Book of abstracts CD rom ISBN 978-86-6061-130-9, XIII Week of the Hospital Clinical Pharmacology. Belgrade, December 11th - 12th, 2021.
31. Ghlichloo I, Gerriets V. Nonsteroidal anti-inflammatory drugs (NSAIDs). Last Update: May 12, 2021. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK547742/>
32. Berger K. NSAIDs: Uses, common brands, and safety info. Available at: <https://www.singlecare.com/drug-classes/nsaids> Last Updated: 03/10/2022
33. Cagdas M, Sezer AD, Bucak S. Liposomes as potential drug carrier systems for drug delivery, In book: Application of nanotechnology in drug delivery 2014; DOI: 10.5772/58459.

Prednosti lipozomalnih nesteroidnih antiinflamatornih lekova

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KRATAK SADRŽAJ

Uvod: Lipozomi su male, sferične, veštačke vezikule koje u svom sastavu mogu imati holesterol i prirodne netoksične fosfolipide. Zbog svoje veličine, hidrofobnog i hidrofilnog karaktera (pored biokompatibilnosti), lipozomi su obećavajući sistemi za isporuku lekova.

Tema: Lipozomalne formulacije nesteroidnih antiinflamatornih lekova (NSAIL) mogu se koristiti u svim populacionim grupama (deca, odrasli i stariji) što im daje širok spektar primene. Oralna primena NSAIL je povezana sa teškim neželjenim efektima u gastrointestinalnom traktu kao što su bol u epigastrijumu, gorušica, mučnina, dijareja, povraćanje, peptički ulkus i oštećenje jetre. U kliničkim ispitivanjima primećeno je da lipozomske formulacije povećavaju propusnost leka i procenat akumulirane doze u koži u poređenju sa kontrolnim konvencionalnim formulacijama gela. Lipozomalni gel kontroliše oslobađanje ibuprofena i permeabilnost leka *in vitro* i pokazuje obrazac permeabilnosti koji pogoduje održavanju konstantnih nivoa leka.

Primena: Do sada su u laboratorijskim uslovima proizvedeni lipozomi koji sadrže natrijum diklofenak, indometacin, aceklofenak i srodne NSAIL. Najčešća primena lipozomalne tehnologije je u kozmetologiji, terapiji raka dok i dalje postoje još uvek neistražene mogućnosti primene lipozoma, kao što je terapija Alchajmerove bolesti. Iako se razlikuju po veličini i strukturi, svi oni poseduju određene zajedničke prednosti - povećanu dermalnu dostupnost lipofilnih lekova i njihovu ciljanu isporuku na potrebnu lokaciju. Lipozomi su se pokazali veoma efikasnim u pogledu zadržavanja NSAIL u sinovijalnoj šupljini, pre svega zbog svoje veličine i hemijskog sastava. Neželjeni efekti terapije, brzo uklanjanje i izlaganje neciljanim mestima mogu se minimizirati davanjem NSAIL koristeći lipozome kao nosače. Neželjeni efekti i komplikacije povezane sa dugotrajnom oralnom i intramuskularnom primenom NSAIL mogu se posebno izbeći upotrebom njihovih lipozomalnih formulacija. Lipozomi se mogu posmatrati kao idealni nosači za antiinflamatorne lekove jer njihova sposobnost da (pasivno) ciljaju mesta upale i otpuštaju svoj sadržaj u ciljane ćelije zapaljenja im omogućava da povećaju lokalnu efikasnost uz samo ograničenu sistemsku izloženost i neželjene efekte, što može poboljšati bioraspodivnost i pridržavanje pacijenata. Nekoliko NSAIL je eksperimentalno formulisano u lipozomima koji imaju poboljšane farmakokinetičke karakteristike. Dalja klinička ispitivanja će pokazati njihove farmakodinamičke efekte. Studija *in vitro* oslobađanja i *ex vivo* permeacije (propustljivosti) pokazala je produženo oslobađanje diklofenaka sa visokim protokom permeacije.

Zaključak: Upotreba lipozoma kao nosača lekova postaje značajan pozitivan korak u lečenju inflamatornih, bolnih i reumatskih bolesti. Lipozomi predstavljaju atraktivan sistem isporuke zbog svojih fleksibilnih fizičko-hemijskih i biofizičkih svojstava, koja omogućavaju laku manipulaciju radi rešavanja različitih razmatranja isporuke. Glavni ciljevi razvoja NSAIL u lipozomalnim nosačima su dublje prodiranje aktivne supstance, manji broj neželjenih efekata, poboljšani i produženi efekat, sposobnost promene karakteristika i leka i nosača, i adekvatno prilagođavanje doze. Uprkos nekoliko izazova koji u skladu s tim tek treba da se reše, formulacije lipozomskih lekova imaju značajan potencijal za unapređenje zdravlja. Uprkos podsticanju razvoja NSAIL i istraživačkih studija, i dalje je potrebno mnogo vremena da lipozomalne formulacije NSAIL postanu dostupne za svakodnevnu upotrebu.

Ključne reči: lipozomi, nesteroidni antiinflamatorni lekovi

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