WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 13, Issue 13, 206-216. Review Article ISSN 2277–7105

A REVIEW ON ADVANCEMENT OF RIFAMPICIN INTO LIPOSOMAL FORMULATION

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Article Received on
09 May 2024,

Revised on 29 May 2024,
Accepted on 19 June 2024

DOI: 10.20959/wjpr202413-32925

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ABSTRACT

By improving the formulation, an extended release of rifampicin will be achieved. Liposomes have been a capable drug delivery system with flexible drug vesicles. Compared to other drug deliveries they have rapid on-site action, slow or controlled release, protection of drug from degradation. In this review liposomal formulation of rifampicin can obtain higher bioavailability than the traditional one. It is a BCS class 2 drug with lower solubility profile. By advancing this to nano-formulation this can increase the solubility by slowly liberating the drug in the intestine. It can slowly reduce growth or kills the gram-positive bacteria that causes tuberculosis (TB) by releasing the drug into the systemic circulation. It has an antibacterial activity. It is normally given with other drugs or combined with isoniazid, ethambutol. It may increase the side effects or toxicity. Patients administering with this drug can cause more adverse effects like stains in body, anorexia. So due to multiple drugs and its dosage can cause effects. To reduce this liposomal formulation of less dosage can reduce the side effects. To overcome all this toxicity and dosage of drug nano-formulation of rifampicin is brought to an idea. Improved drug formulation can be administered daily with minimum side effects. This review is to obtain an idea for the drug to be effective and give maximum bioavailability inside the body.

KEYWORDS: liposomes, Bioavailability, Nano-formulation.

INTRODUCTION

Rifampicin is an antimicrobial drug that is used to treat contrasting mycobacterial infections and many bacterial infections. The main use of this drug is to reduce or to kill gram positive bacteria. This drug hinders with DNA-dependent RNA polymerase (RNAP). Rifampicin can also be used for treating tuberculosis, leprosy, and methicillin resistant bacteria. Rifampicin is a BCS 2nd class of drug with lower solubility profile.[1] Nausea, vomiting, diarrhea, and appetite loss are typical side effects. It frequently gives tears, sweat, and urine a reddish-orange tint. Allergies or liver issues could happen. Although its safety during pregnancy is unknown, it is part of the recommended treatment for active tuberculosis throughout pregnant. Rifampicin belongs to the class of antibiotics called rifamycin. It functions by reducing the amount of RNA that bacteria produce. Since there are just a few bacteria present, rifampicin can be given alone in individuals with latent tuberculosis infections to stop or postpone the onset of active illness. In patients not infected with HIV, a 3- to 4-month regimen of rifampicin and a 6-month regimen of isoniazid did not vary in efficacy for avoiding active tuberculosis, according to a Cochrane study. Additionally, patients who got rifampicin had a reduced rate of hepatotoxicity. But it was decided that the evidence's quality was inadequate. Because of the high rates of hepatotoxicity, it is no longer suggested to do a shorter 2-month treatment of pyrazinamide and rifampicin.

Liposomes are nano-formulation which can induced to reduce the side effects and reduce the daily dosage of the drug. They exhibit wide variety of properties such as site targeting, sustained release, lower side effects, higher bioavailability inside the body. They have been very promising in the delivery of the drug which can increase its effects inside the body. When they are converted into liposomal formulation they can obtain higher bioavailability with biodegradable liposomal excipients.[2] Phospholipids have been shown to spontaneously form closed structures upon hydration in aqueous solutions. Depending on the type of medication, these vesicles with one or more phospholipid bilayer membranes can carry either lipid or aqueous medications. Lipids' thermodynamic phase qualities and self-assembling traits affect the entropically concentrated arrangement of their hydrophobic sections into spherical bilayers because they are amphipathic (Both hydrophobic and hydrophilic) in aqueous conditions. Lamellae are the names for such layers. Liposomes are characterized as spherical vesicles that typically have particle sizes ranging from several micrometers to 30 nm. The polar head groups of these entities are oriented in the direction of the interior and

exterior aqueous phases, and they are surrounded by one or more lipid bilayers around aqueous units.

Mechanism of action

Rifampicin applies bactericidal effects by inhibiting DNA dependent RNAP. This causes by obstructing the 5^{th} end of elongating RNA and make a short strand of RNAP. Rifampicin distinctively targets microbes of RNA. Rifampicin applies both germicidal properties of both intra and extra cellular M tuberculosis.[1]

Classification of liposomes

Liposomes are distinguished as unilamellar vesicles (ULV), multivesicular liposomes (MVP), oligolamellar liposomes (OLL), small unilamellar liposomes (SUP), large unilamellar liposomes (LUP).[2]

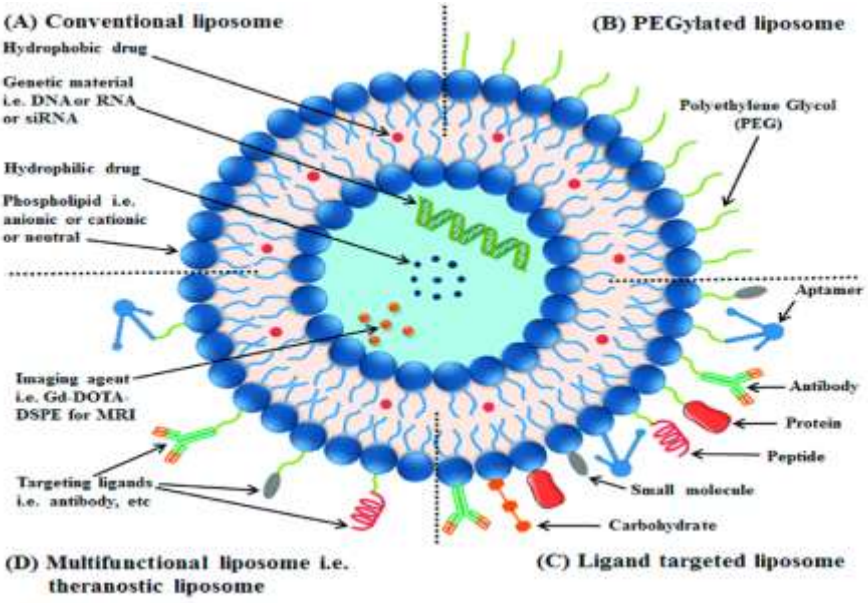
Category	Size (nm)
ULV	20-50 nm
MVP	>500 nm
OLL	100-1000 nm
SUP	20-100 nm
LUP	>100 nm

Merits of liposomes

- They have an increased efficacy and therapeutic index.
- They have higher stability.
- They are non-toxic, biodegradable and nonimmunogenic.
- It reduces the toxicity of the drug due to the encapsulation.
- It has an advanced pharmacokinetic effect.

Components of liposomes

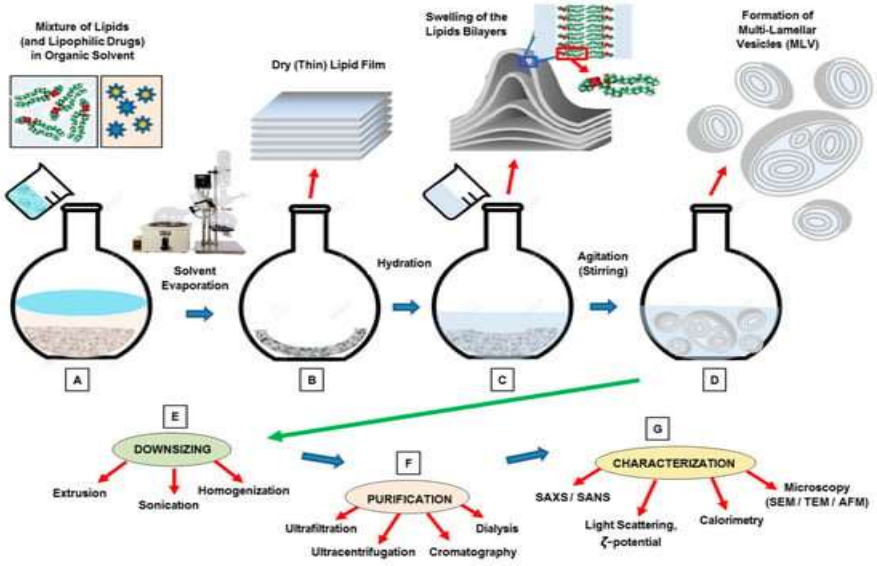
They have a phospholipid layer contains phosphatidylcholine and cholesterol. The phospholipid layer contains the hydrophobic tail and hydrophilic head. They are composed of different size which can encapsulate a wide range of drugs both hydrophilic and lipophilic drugs. With the addition of some excipient's vesicles are formed and drugs are encapsulated inside the vesicles. They have a bilayer containing phospholipid and cholesterol.[3]



Method of preparation

Thin film hydration

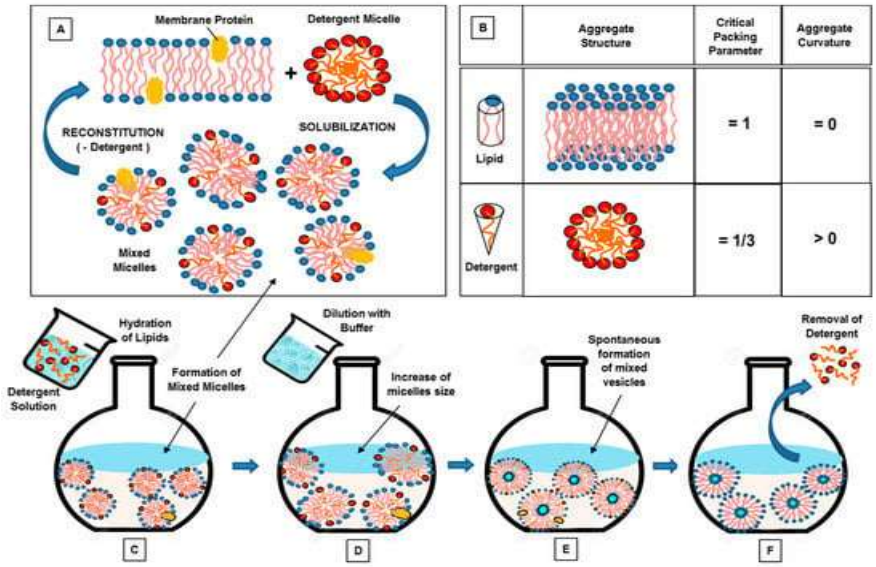
It is conventional technique and favourable for loading the lipophilic drug. A thin film is formed when evaporation of lipid-solvent solution during the process of rotation of flask under vacuum. Multi lamellar liposomes can be obtained by adding aqueous solution into the lipid film. The vesicle size can be reduced further according to the drug encapsulation.[3]



Detergent removal method

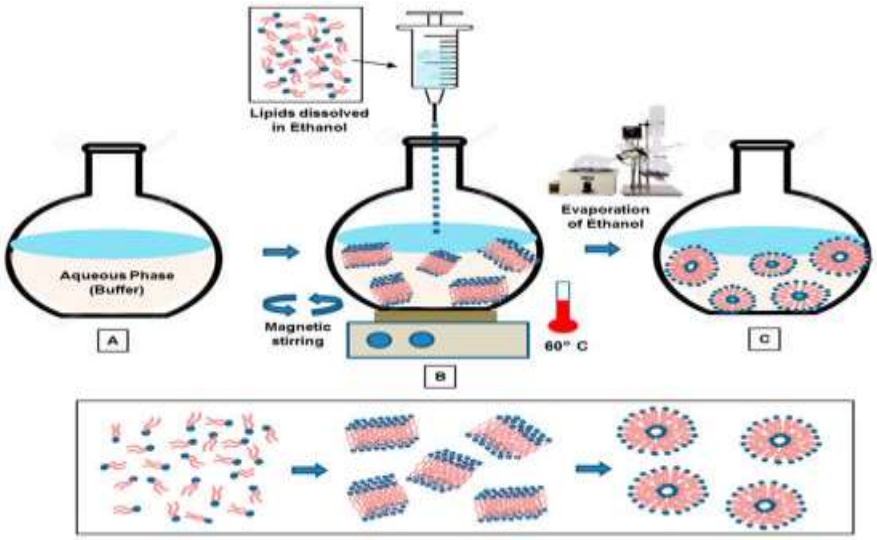
By this method lipid are humidified and solubilized by adding a detergent solution. Detergent will involve in the vesicle formation with the phospholipids that can cause shielding the

hydrophobic portion thus micelles are formed. When removal of detergent the micelles become rich in lipoidal formation. By this technique unilamellar vesicles are formed.[3]



Ethanol injection method

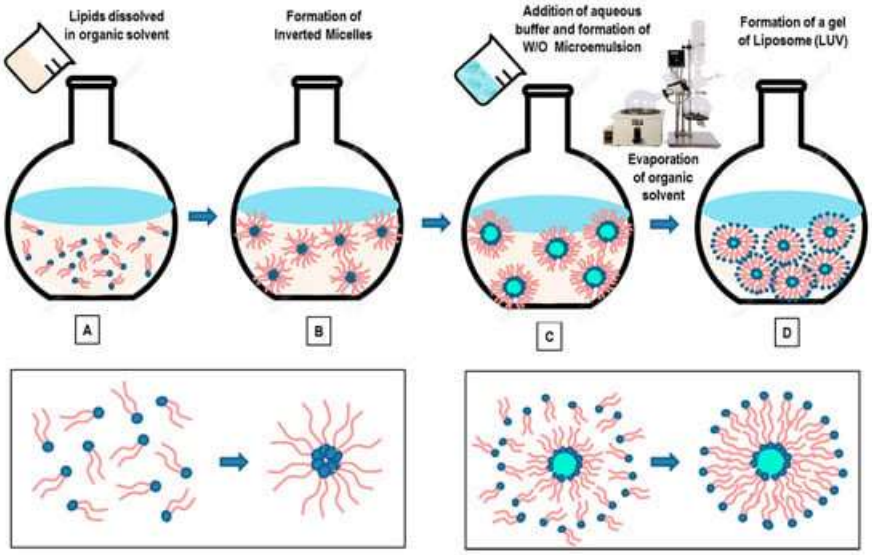
In this method, the phosphatidylcholine is promptly injected to distilled water. Ethanol is diluted into the aqueous solution reproving concentration which helps the lipids inside the buffer which is dissolved. It also helps in the precipitation and consecutive formation of lipid bilayers. This helps in the encapsulation of the drug into the vesicles.[4]



Reverse phase evaporation

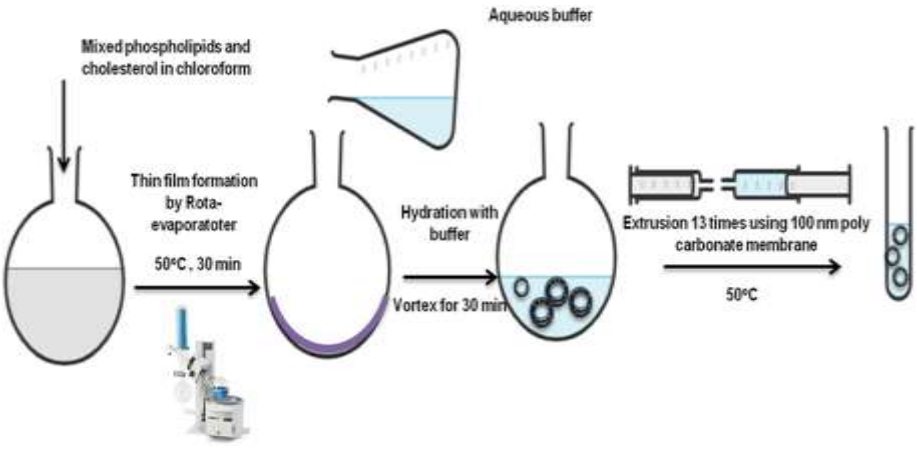
In this process, lipids are incorporated into the organic solvent which contains ether and chloroform. The lipids arrange themselves between water and oil, which is then converted

into a microemulsion. This can be further emulsified by sonication method which helps in the equilibrium dispersion. Due to the continued rotary process organic solvent is thereby removed from the formulation. Formation of inverted micelles is obtained by this kind of technique.



Extrusion method

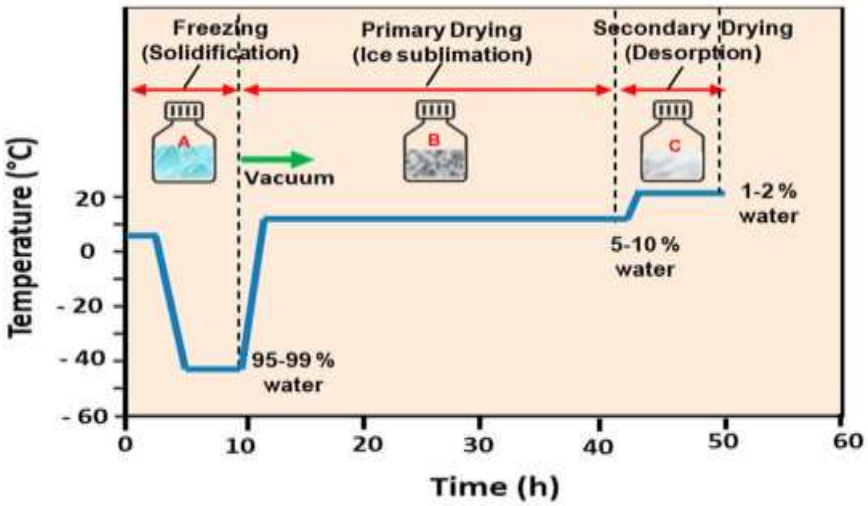
This method consists the discharge through pore which contains membrane. This involves the phase transition of phospholipids. It contains a polycarbonate membrane filters which helps in the formation of large unilamellar liposomes. Due to this process thermos stable vesicles are produced due to the extrusion method.[5]



Freeze drying method

In this method, lipid-based formulation are used for hydrophilic drugs which have low shelf life. Some drugs can be oxidised easily and cause different chemical reaction. So in this

technique water removal is the main process which cause the oxidation of drug. This process involves sublimation under vacuum which favours for the production of anti-oxidative drug formulation which increase shelf life.[5]



Evaluation of liposomes

Physical appearance and pH: Liposomal dispersion was examined visually to assess its appearance, and a digital pH meter was used to record the preparation's pH.

Drug entrapment efficiency: When using the direct method of BCA, EE shows you the percentage of your drug's amount encapsulated or entrapped in all the liposomes or polymers used in your system. The formula for % EE is: total protein-conc of medicines in supernatant ×100/total protein or drug in the system.

Drug content: The amount of medication (mg) found in the entire or half-tablet that was subjected to HPLC analysis. weight is measured.

Optical microscopy: To ensure the formation of liposome vesicles, small amount of liposome dispersion is subjected to simple optical microscopic detection. Sample placed were seen from light background.

In vitro drug release study: The dialysis tube method is used to conduct the drug's in vitro release investigation. Using this technique, a test tube with a dialysis membrane attached is filled with 4 ml of liposomal formulation that contains a known quantity of medication. The sample containing the dialysis membrane is put into a 100 ml PBS 7.4 beaker, which is kept

at 37°C, and stirred using a magnetic stirrer. To keep the sink condition, samples from the receptor compartment are taken out at various times and refilled with brand-new PBS 7.4.

Stability studies: Stability testing is a procedure used in the pharmaceutical industry to assess a drug's or product's quality over a predetermined amount of time in a predetermined environment.

Zeta potential: Using a Malvern zetasizer instrument to measure the zeta potential of the nano emulsion preparation, one may ascertain the surface charge of the particle or globules. The stability of the dispersion and the ways that medications, emulsifiers, coemulsifiers, and other electrolytes affect its value are predicted by the zeta potential. Generally speaking, the nanoemulsion must reach a number larger than thirty in order to prevent the nanodroplets from coalescing and flocculating and to produce a stable nanoemulsion.

CONCLUSION

In this review the main aspect of advancing the liposomal formulation of rifampicin is to increase its bioavailability and reduce the toxicity which can cause higher reduction of adverse reactions and many side effects due to high dosage. Rifampicin is used with isoniazid and pyrazinamide. Due to intake of this as a combination drug, a high risk of adverse effect. Liposomes have higher bioavailability and can be used for less dosage of drug. Thus, drug can release slowly and in a controlled release manner reaching the systemic circulation. It can show its maximum efficacy inside the body. Rifampicin is BCS class 2 drug due to its lower availability. Liposomes are good choice for the production of rifampicin. Liposomes can be obtained in many size according to vesicle formation and easy of encapsulation is applied. Drug with lower bioavailability can be advanced to liposomes. Liposomes can be used for improved drug efficacy with less adverse effects and less dosage.

ACKNOWLEDGEMENT

Firstly, I would like to thank Lord Almighty for his blessings Secondly I would like to give sincere thanks to my guide. Assistant Prof. Shweta Ma’am for her support and involvement in this article. Also, a Huge thanks to Dean DR S K Sharma Sir and all the staff of PDM University Bahadurgarh, Haryana, India for the support.

REFERENCES

1. Ashithkumar Beloor Suresh *Alan Rosani* Preeti Patel* et al, rifampicin medical stats, 2023.
2. Peng Liu,* Guiliang Chen, and Jingchen Zhang* A Review of Liposomes as a Drug Delivery System: Current Status of Approved Products, Regulatory Environments, and Future Perspectives, 2022.
3. Domenico Lombardo* Mikhail A. Kiselev* Methods of Liposomes Preparation: Formation and Control Factors of Versatile Nanocarriers for Biomedical and Nanomedicine Application, 2022.
4. Walhan Alshaer*Hamdi Nsairat* Zainab Lafi*, et al, Quality by Design Approach in Liposomal Formulations: Robust Product Development, 2022.
5. Ji Young Yu* Piyanan Chuesiang * Gye Hwa Shin*, et al, Post-Processing Techniques for the Improvement of Liposome Stability, 2021.
6. Immordino ML, Brusa P, Rocco F, Arpicco S, Ceruti M, Cattel L. Preparation, characterization, cytotoxicity and pharmacokinetics of liposomes containing lipophilic gemcitabine prodrugs. J Control Release.
7. Mamot C, Drummond DC, Hong K, Kirpotin DB, Park JW. Liposome-based approaches to overcome anticancer drug resistance.
8. Alving CR, Steck EA, Chapman WL, Jr, Waits VB, Hendricks LD, Swartz GM, Jr, et al. Liposomes in leishmaniasis: Therapeutic effects of antimonial drugs, 8-aminoquinolines and tetracycline.
9. Rukholm G, Mugabe C, Azghani AO, Omri A. Antibacterial activity of liposomal gentamicin against Pseudomonas aeruginosa.
10. Tadakuma T, Ikewaki N, Yasuda T, Tsutsumi M, Saito S, Saito K. Treatment of experimental salmonellosis in mice with streptomycin entrapped in liposomes.
11. Mohammad Moslehia, S. Ali Reza Mortazavi, ptimization and Characterization of Chitosancoated Liposomes for Solubility Enhancement of Furosemide: A Model BCS IV Drug.
12. Abdul aziz ramadan, hasna mandil, jenan sabouni worked in research article Determination of atorvastatin calcium in pure and its pharmaceutical formulations using iodine in acetonitrile by uv-visible spectrophotometric.
13. Abolfazl Akbarzadeh, 1 Rogaie Rezaei-Sadabady, Soodabeh Davaran, Liposome: classification, preparation, and applications, 1, 2.

14. C.B. Rodell, P. Baldwin, B. Fernandez, R. Weissleder, Quantification of Cellular Drug Biodistribution Addresses Challenges in Evaluating In Vitro and In Vivo Encapsulated Drug Delivery.
15. S.T. Schmidt, D. Christensen and Y. Perrie, Applying Microfluidics for the Production of the Cationic Liposome-Based Vaccine Adjuvant CAF09b.
16. Xiaoxia Li,1, Hong Xiao,1,* Chaowen Lin, Synergistic effects of liposomes encapsulating atorvastatin calcium and curcumin and targeting dysfunctional endothelial cells in reducing atherosclerosis.
17. Eman M. Nour, Salma E. El-Habashy, Michael G. Shehat, Atorvastatin liposomes in a 3D-printed polymer film: a repurposing approach for local treatment of oral candidiasis.
18. Akshay Singha Roy, Sudipta Das, Arnab Samanta, Design, Formulation And Evaluation of Liposome Containing Isoniazid, 2018.
19. Anis Askarizadeh, Alexandra E Butler, Liposomal nanocarriers for statins: A pharmacokinetic and pharmacodynamics appraisal.
20. Reju George Thomas, Ja-hae Kim, Treatment of Ischemic Stroke by Atorvastatin-Loaded PEGylated Liposome.
21. Chimote G, Banerjee R. Evaluation of antitubercular drug-loaded surfactants as inhalable drug-delivery systems for pulmonary tuberculosis. J Biomed Mater Res Part A An Off J Soc Biomater Japanese Soc Biomater Aust Soc Biomater Korean Soc Biomater. Wiley Online Library, 2009.
22. Khadka P, Hill PC, Zhang B, Katare R, Dummer J, Das SC. A study on polymorphic forms of rifampicin for inhaled high dose delivery in tuberculosis treatment. Int J Pharm. Elsevier, 2022.
23. Singh C, Koduri LVSK, Singh A, Suresh S. Novel potential for opti mization of antitubercular therapy: pulmonary delivery of rifampicin lipospheres. Asian J Pharm Sci. Elsevier, 2015.
24. Singh C, Koduri LVSK, Dhawale V, Bhatt TD, Kumar R, Grover V, et al. Potential of aerosolized rifampicin lipospheres for modu lation of pulmonary pharmacokinetics and bio-distribution. Int J Pharm Elsevier, 2015.
25. Changsan N, Chan H, Separovic F, Srichana T. Physicochemi cal characterization and stability of rifampicin liposome dry powder formulations for inhalation. J Pharm Sci Elsevier, 2009.

26. Maretti E, Rustichelli C, Lassinantti Gualtieri M, Costantino L, Siligardi C, Miselli P, et al. The impact of lipid corona on rifampicin intramacrophagic transport using inhaled solid lipid nanoparticles surface-decorated with a mannosylated surfactant. Pharmaceutics.
27. Sharma PR, Dravid AA, Kalapala YC, Gupta VK, Jeyasankar S, Goswami A, et al. Cationic inhalable particles for enhanced drug delivery to M. tuberculosis infected macrophages. Biomater Adv, 2022.
28. Sung JC, Padilla DJ, Garcia-Contreras L, VerBerkmoes JL, Durbin D, Peloquin CA, et al. Formulation and pharmacokinetics of self-assembled rifampicin nanoparticle systems for pulmonary delivery. Pharm Res Springer, 2009.
29. Sharma PR, Dravid AA, Kalapala YC, Gupta VK, Jeyasankar S, Goswami A, et al. Cationic inhalable particles for enhanced drug delivery to M. tuberculosis infected macrophages. Biomater Adv, 2022.
30. Sung JC, Padilla DJ, Garcia-Contreras L, VerBerkmoes JL, Durbin D, Peloquin CA, et al. Formulation and pharmacokinetics of self-assembled rifampicin nanoparticle systems for pulmonary delivery. Pharm Res Springer, 2009.
31. Maretti E, Costantino L, Rustichelli C, Leo E, Croce MA, Buttini F, et al. Surface engineering of solid lipid nanoparticle assemblies by methyl α-d-mannopyranoside for the active targeting to macrophages in anti-tuberculosis inhalation therapy. Int J Pharm Elsevier, 2017.
32. Scolari IR, Páez PL, Sánchez-Borzone ME, Granero GE. Promising chitosan-coated alginate-tween 80 nanoparticles as rifampicin coadministered ascorbic acid delivery carrier against mycobacterium tuberculosis. Aaps Pharmscitech Springer, 2019.
33. Rawal T, Parmar R, Tyagi RK, Butani S. Rifampicin loaded chitosan nanoparticle dry powder presents an improved therapeutic approach for alveolar tuberculosis. Colloids Surfaces B Biointerfaces Elsevier, 2017.
34. Diab R, Brillault J, Bardy A, Gontijo AVL, Olivier JC. Formulation and in vitro characterization of inhalable polyvinyl alcohol-free rifampicin-loaded PLGA microspheres prepared with sucrose palmitate as stabilizer: efficiency for ex vivo alveolar macrophage targeting. Int J Pharm Elsevier, 2012.
35. Mukhtar M, Csaba N, Robla S, Varela-Calviño R, Nagy A, Burian K, et al. Dry powder comprised of isoniazid-loaded nanoparticles of hyaluronic acid in conjugation with mannose-anchored chitosan for macrophage-targeted pulmonary administration in tuberculosis. Pharm, 2022.